Peertechz



Global Journal of
Medical and Clinical Case Reports OPEN ACCESS JOURNAL

ISSN: 2455-5282 Journal DOI: https://dx.doi.org/10.17352/gjmccr

Review Article

Cortical Spreading Depression and Migraine: Critical Review of a Neurophysiological Principle in the Third Millennium

Vinod Kumar Gupta*

Physician, Apartment No. 1402, Block A, Anriya Palatial, Bengaluru – 560094, Karnataka, India

Submitted : 09 September, 2026
Accepted : 01 October, 2026
Published : 02 October, 2026

***Corresponding author:** Dr. Vinod Kumar Gupta, MBBS, MD (Internal Medicine), PHYSICIAN, Apartment No. 1402, Block A, Anriya Palatial,,Bengaluru – 560094, Karnataka, India, E-mail: dr_vkgupta@yahoo.com

Keywords: Migraine; Cortical spreading depression; Aura; Headache; Nausea; Vomiting; Vasopressin

Copyright License: © 2026 Gupta VK. This is an open-access article distributed under the terms of the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original author and source are credited.

https://www.clinsurggroup.us

Check for updates

Abstract

Cortical spreading depression (CSD) is implicated in a diverse set of intracranial neurologic diseases and, in the early 21st Century, is generally believed to be the pathogenetic mechanism that underlies migraine. Except for malignant stroke, subarachnoid and intracranial hemorrhage, and traumatic brain injury in humans, CSD has been recorded only in experimental animals. Primary "selfcycling" onset and spontaneous offset, as well as the other characteristic protean features or heterogeneity of migraine phenotype, are inexplicable through CSD. The magnesium-CSD-migraine nexus is untenable. CSD does not generate pain in experimental animals. CSD-induced in dural vasodilatation or neuro-inflammation is highly unlikely to generate lateralizing head or neck pain of migraine (unilateral, bilateral, side-shifting, or side-fixed) confined to the ophthalmic division of the trigeminal nerve (V1). Stress, missing a meal, alcohol consumption, or insufficient sleep are the most common precipitants of migraine but have no link to CSD. Post-stress migraine remains enigmatic with no link to CSD. Migraine selectively involves V1 rather than all three divisions of the trigeminal nerve, a feature inconsistent with generation or propagation, or both, of CSD. Precise and / or circadian onset of migraine attacks is indeterminate, clinically inaccessible, and unlinked to CSD. An initially adaptive, autonomic ocular storm is the apparent pathogenetic mechanism involving systemic and intrinsic brain vasopressinergic-serotonergic-noradrenergic nexus activation. This nexus possibly offers a "protective" effect that significantly delays migraine attacks. Vasopressin (AVP) surges rather than CSD generate early nausea/vomiting in migraineurs. Nausea/vomiting both characteristically release AVP and can, in turn, remit migraine. Photophobia is greater on the side of headache and CSD is unlikely to have a major role in its genesis. Neuroimaging has expanded the radiologic phenotype, but the cause-effect puzzle persists. Migraine with aura (MwA) is not associated with lateralizing abnormalities of cortical grey matter structure or function. Scintillating scotomata (SS) of migraine are not distributed homonymously and do not expand into the nasal visual fields. Eye cover, digital displacement of SS, synchronous movements of SS with the eyes, and determination of selective distribution in visual fields (temporal versus nasal, central versus peripheral) are important tests to determine its source. Displaceable non-homonymous eye movement synchronous nasal-field sparing SS absolutely cannot be cortical in origin or linked to CSD. Typical migraine headache and SS have not been reported after enucleation of eyes in a cohort of migraine patients with prior migraine attacks. Sightlessness markedly attenuates migrainous SS as well as photophobia. Atenolol and nadolol are first-line pharmacologic agents that prevent migraine but do not readily cross the blood-brain barrier (BBB) or affect CSD. Autonomic signs and symptoms are common in migraine but have no link with CSD. CSD has evolved into a landmark CNS physiological experimental phenomenon but has retarded meaningful progress in migraine research. A significant role for retinal spreading depression in SS cannot be excluded. A CNS adaptive or protective role for CSD is distinctly likely in experimental animals as well as in humans.

Abbreviations

AMT: Amitriptyline; AVP: Arginine Vasopressin; BBB: Blood-Brain Barrier; BP: Blood Pressure; BOLD: Blood-Oxygenation-Level-Dependent; CBF: Cerebral Blood Flow; CGRP: Calcitonin-Gene Related Peptide; CNH: Central Neuronal Hyperexcitability; CNS: Central Nervous System; COX: Cyclooxygenase; CSD: Cortical Spreading Depression; DTI: Diffusion Tensor Imaging; EEG: Electroencephalographic; FHM: Familial Hemiplegic Migraine; GTN: Glyceryl Trinitrate; FMRI: Functional Magnetic Resonance Imaging; ICF: Intracellular Fluid; ICHD: International Classification of Headache Disorders; ICU: Intensive Care Unit; MEG: Magnetoencephalography; MCA: Middle Cerebral Artery; Mg^{+2}: Magnesium Ion; $MGSO_4$: Magnesium Sulphate; MMA: Middle Meningeal Artery; MRI: Magnetic Resonance Imaging; MwAL: Migraine With Aura; MwoA: Migraine Without Aura; NO: Nitic Oxide; PET: Positron Emission Tomography; PFO: Patent Foramen Ovale; KCL: Potassium Chloride; RCT: Randomized

Citation: Gupta VK. Cortical Spreading Depression and Migraine: Critical Review of a Neurophysiological Principle in the Third Millennium. Glob J Medical Clin Case Rep. 2026:13(10):228-272. Available from: https://dx.doi.org/10.17352/gjmccr.000273

Controlled Trial; ROSL: Reactive Oxygen Species; RT-PCR: Reverse Transcriptase Polymerase Chain Reaction; SBP: Systolic Blood Pressure; SD: Spreading Depression; SPECTL: Single Photon Emission Computed Tomography; SS: Scintillating Scotomata; TBI: Traumatic Brain Injury; t-TMS: Therapeutic Transcranial Magnetic Stimulation; TNC: Trigeminal Nucleus Caudalis; V 1: Ophthalmic Division of the Trigeminal Nerve; VM: Valsalva Maneuver; WMLs: White Matter Lesions

Introduction

Known since antiquity, migraine is a protean, common, primary, neurologically "self-cycling" (spontaneous onset and offset), lateralizing (unilateral or bilateral, sideshifting or side-fixed) headache with the term 'megrim/hemicrania' (Greek, halfskull) clearly indicating preponderance of half-sided / unilateral or bilateral discrete/episodic headache attacks involving *self-limited* fronto-temporal and / or nuchal pain lasting variably for 4-72 hours (Headache Classification Committee of the International Headache Society-International Classification of Headache Disorders-III (Pearce, 1986; ICHD-III, 2018). In 1597, the Shorter Oxford English Dictionary, even before The Plague and the Great Fire, described migraine as a far wider constellation of symptoms besides headache alone, such as the association with imbalance and motion sickness, including sea-sickness, with 'emotional changes' and 'depression'. (Pearce, 1986) Migraine is one of the most prevalent disorders throughout the world, affecting approximately 1/5th of the adult population, but with widely varying intensity, frequency, social stigma, absenteeism and presenteeism, and largely incomprehensible genetic transmission, as well as varied prevalence in different age groups, including childhood or teenage, adults, trimesters of pregnancy, or advancing age/menopause (ICHD-III, 2018; Bigal and Lipton, 2009). Migraine headache is ranked among the top 10 debilitating diseases worldwide (Leonardi and Raggi, 2013). Prevalence of migraine in the population has remained relatively consistent for the past 30 years, ranging from 11.7% to 14.7% overall, 17.1% to 19.2% in women, and 5.6% to 7.2% in men in the studies reviewed.

(Cohen et al., 2024). Migraine predominantly affects females, and the F:M ratio is 3:1 or 4:1 (Buse et al., 2010). Migraine is far more prevalent among neurologists than in the general population. The 1-year and lifetime prevalences of migraine in a sizable cohort of neurologists is as follows: male neurologists, 34.7%, 46.6%; male headache specialists, 59.3%, 71.9%; female neurologists, 58.1%, 62.8%; and female headache specialists, 74.1%, 81.5% (Evans et al., 2003).

Besides neurological aura and headache, photophobia is another typical feature of migraine headache (Nir et al., 2018) and, along with phonophobia, is included as a diagnostic criterion (ICHD-III, 2018). Nausea and/or vomiting in migraine is a typical, diagnostic, and usually early feature, and can remarkably ameliorate or abort the headache – noted as early as by *Hippocrates (c.460 B.C.-c.370 B.C.)* (Pearce, 1986). The premonitory or prodromal phase of migraine involves tiredness, irritability, reduced concentration, and yawning, and can precede the aura or headache phase by up to 48 hours (Giffin et al., 2003; Kelman, 2007). Most migraine headache attacks are followed by hours or a day of feeling unwell, usually with tiredness, called the postdrome phase (Kelman 2006; Giffin et al., 2016). In one-third of the migraine cohort, headache attacks are associated with neurological phenomena, positive or negative, collectively termed migraine aura (MwA) (Rasmussen and Olesen, 1992). The scintillating scotomata (SS) are regarded as the only truly pathognomonic feature of the disorder (Hupp et al., 1989; Rose, 1995). Comprehension of migraine mechanisms is limited and controversial, despite an elaborate phenotype and sophisticated updated symptomatic classification (Pietrobon and Moskowitz, 2014; Goadsby et al., 2017; Lindquist and Shuttleworth, 2017; Schulte et al., 2017; Youssef et al., 2017; Cozzolino et al., 2018; ICHD-III, 2018). Migraine still does not have a specific diagnostic laboratory or radiologic test (Nalbant et al., 2017). Recurrent migraine headache is usually lateralized to the same side (right or left fronto-temporal region or both or nuchal) in subsequent attacks, or side-locked or side-shifting. Migraine headache is commonly retro-orbital and/or nuchal or, uncommonly, lower-half headache (facial pain) in distribution or location (Campbell 1988, 1990; Blau 1992a; Sjaastad et al., 1992; Constantinides et al., 2015). The protean nature of migraine results in a characteristically varied frequency, differential severity, duration and morbidity, and inconsistent autonomic features in successive headache attacks in the same patient as well as between different patients.

Currently, the migraine attack is regarded as a paroxysmal "self-cycling" alteration in gain, or input-output modulation (Haider and McCormick, 2009) of multiple sensory systems involving multiple cortical, subcortical and brainstem regions with a strong genetic basis to account for the pain and the wide constellation of symptoms characterizing the attack (Ferrari et al., 2015; Goadsby et al., 2017; Brennan and Pietrobon, 2018). Understanding of migraine as disruption in sensory gain and plasticity is an oversimplified completely untested hypothesis (Brennan and Pietrobon, 2018). How a migraine attack starts or stops remains a complete mystery, even in familial hemiplegic migraine (FHM) (Hansen et al. 2011; Burstein et al. 2015). There is almost a complete lack of synaptic, let alone cellular/molecular understanding of "established" phenomena, such as CSD and trigeminovascular system (TVS) sensitization (Brennan and Pietrobon, 2018). Dural TVS nociception is a favoured hypothesis for the genesis of migraine headache involving the largely unmyelinated sensory nerve fibre plexus of the *pan-trigeminal* nerve (Moskowitz et al., 1979; Moskowitz,1990, 1991, 2007a, 2007b, 2008), even though the most typical features of migraine, i.e., lateralization of headache and V1 predominance of distribution of headache cannot be explained by *diffuse* dural activation (Gupta, 2009a, 2019, 2024) (discussed further). Does the dura "self-cycle" in migraine; if so, how? And how does diffuse dural "self-activation" produce lateralizing headache localized to V1?

Cortical spreading depression (CSD) is an electrophysiologic pathological state in which a wave of depolarization in the cerebral cortex is followed by the suppression of spontaneous neuronal activity (Hill et al., 2024). This transient spread

Citation: Gupta VK. Cortical Spreading Depression and Migraine: Critical Review of a Neurophysiological Principle in the Third Millennium. Glob J Medical Clin Case Rep. 2026:13(10):228-272. Available from: https://dx.doi.org/10.17352/gjmccr.000273

of neuronal depolarization on the cortical surface is the hallmark of CSD. Numerous investigations have demonstrated that transmembrane ion transport, astrocytic ion clearing and fatigue, glucose metabolism, certain genetic markers, point mutations, and expression of the enzyme responsible for the production of various arachidonic acid derivatives that participate in the inflammatory response, namely, cyclooxygenase (COX), all influence CSD (Hill et al., 2024). The inflammatory response cannot explain key clinical features of migraine as well as of CSD (Gupta, 2009a, 2019). Since the seminal acknowledgment by Graham (1953) almost eight decades ago that the fundamental reason ("why" and "how") of observed "immediate misbehavior" or "aberration" of cranial vessels in migraine remains a "mystery", nothing substantive has changed. Graham (1953) also elaborated on a peculiar "affinity to stress" and "deficiency in the physiological adaptation to stress" of migraineurs. Graham (1953) additionally conceded that the nature of migraine was elusive, an analysis that seems to have held up to the early 21st century. The neuronal or vascular mechanisms of migraine have been debated vigorously over the last 150 years. In the last decade of the 20th century, a new beginning appeared essential (Edmeads 1991; Blau 1992a).

Migraine pathophysiology has remained impervious to technological advances, nosological "splitting", statistical methods, animal experiments, randomized clinical trials (RCTs) and meta-analyses (Gupta, 2009a, 2010a; Borgdorff, 2018). End-points in migraine research are relatively soft and variable, even in the same patient on different occasions and are difficult to replicate; all therapies, including those linked to RCTs, remain empirical or experiential. Migraine – as well as its relevance to CSD -- stands today where ischemic heart disease stood before the discovery of the atheromatous plaque or diabetes mellitus stood before the discovery of insulin.

Limitations of current understanding of migraine pathogenesis

While the precise aetiology of migraine remains unknown and its genesis is the topic of much controversy and speculation, some researchers underscore seemingly significant progress along the vascular, neurogenic, neurotransmitter, neuroimaging and genetic / molecular biological paradigms (Moskowitz, 2008; Tfelt-Hansen and Koehler, 2011; May, 2013).

Dural TVS nociception – particularly involving the middle meningeal artery (MMA) – has been a compelling influence (Olesen et al., 2009; Akerman et al., 2013; Levy et al., 2019). In humans with inelastic, unyielding dura mater and the bony channels in the inner table of the calvarium, significant and pathogenetic dilatation of such vessels is quite unlikely (Shevel, 2009). In a cohort of 18 healthy volunteers, after correction for placebo-induced dilatation in the MMA, calcitonin-gene-relatedpeptide (CGRP) infusion (1.5 µg/min h-αCGRP over 20 minutes) induced only mild clinically insignificant dilatation in the MMA while there was no change in the middle cerebral artery (MCA) (Asghar et al., 2010). Similar changes were noted after glyceryltrinitrate (GTN)-induced migraine headache (Schoonman et al., 2008). With further studies, a shift from Wolff's concept entrenched for over half a century was recommended (Amin et al., 2017). Two facts, however, ensure that the vascular component of migraine pathophysiology will forever remain relevant: i) GTN consistently causes an early atypical headache and a more delayed more typical headache in migraineurs but without SS or nausea/vomiting (Ashina et al., 2013; Maniyar et al., 2014; Nozaki et al., 2015) and ii) migraine attacks are remitted by triptans (Cameron et al., 2015) and ergotamine (Campbell, 1990). *Another cranial vascular system appears to be involved besides the cerebrovascular system, including the MMA and the MCA* (see below).

A central neuronal dysfunction of the central nervous system (CNS) is generally regarded as the underlying cause of migraine (Burstein et al., 2015; Ferrari et al., 2015; Goadsby et al., 2017; Hougaard et al., 2017; Schulte et al., 2017). Besides CSD (Ayata and Lauritzen, 2015), a "self-cycling" seemingly primary brain stem activation concept (Goadsby and Edvinsson, 1993; Akerman et al., 2011), and the theory of a primary "self-cycling" disorder of sensory processing (Goadsby et al. 2017), with a rhythmic cortical feedback to the thalamus has also been suggested to underlie amplification of thalamocortical oscillations and to influence neuronal excitability, early sensory processing, and multisensory integration (Hodkinson et al. 2016). All CNS theories of migraine, including CSD, suffer from the twin major disadvantages of a plethora of assumptions or arbitrary elements as well as from being unable to explain key phenotypic features of the disorder (Gupta, 2009a, 2019, 2024, 2025; Borgdorff, 2018).

Writing on Airy, Levene (1975) noted the vastness and unmanageability of the migraine literature. Almost fifty years later, the difficulty in assimilating the explosive accretion of data in the absence of an overarching theory is far more profound, a paradox that defies common sense and is very likely to worsen.

Cortical spreading depression (CSD)

In 1944, Leão serendipitously reported, while studying "experimental epilepsy", the ability to produce temporary suppression of electrical activity in the brain of a rabbit under narcosis over areas such as the cerebral cortex, cerebellum, or hippocampus; such stimuli included weak faradic electrical stimulation of the brain surface, application of potassium chloride solution, and slight mechanical deformation (Engelhardt and Gomes, 2015). From these animal experiments, it was inferred that once induced, depression of spontaneous electroencephalographic (EEG) activity travelled slowly and contiguously in all directions into neighbouring regions of cortex – like ripples-in-a-pond. The frontal regions were stimulated more readily than regions near the occipital pole (Leão, 1944a). Leão also reported that CSD was associated with marked dilatation of the pial arteries and increased blood flow; a smaller vasoconstriction sometimes followed (Leão, 1944b). Later, Leão and Morison described a slow, negative-positive potential that accompanied the onset of EEG suppression (Leão and Morison, 1945). CSD, thus, is an electrophysiologic pathological state in which a wave of depolarization in the cerebral cortex is followed by the suppression of spontaneous

Citation: Gupta VK. Cortical Spreading Depression and Migraine: Critical Review of a Neurophysiological Principle in the Third Millennium. Glob J Medical Clin Case Rep. 2026:13(10):228-272. Available from: https://dx.doi.org/10.17352/gjmccr.000273

neuronal activity. *This transient spread of neuronal depolarization on the surface of the cortex is the hallmark of CSD*. Numerous influences on the CSD have been detailed (Hill, 2024); the list is not exhaustive. (see above).

Leão's observations have been repeatedly confirmed in a wide variety of animal species, both vertebrates and invertebrates, including mammals, birds, reptiles, locusts, cephalopods, and *Drosophilia* (Ayata and Lauritzen, 2015; Spong et al., 2016a, 2016b, 2016c). CSD is, thus, a transient wave of intense near-complete neuronal and glial depolarization observed in experimental animals and traumatic brain-injured (TBI) humans as well as in other acute cortical lesions such as malignant stroke, subarachnoid and intracranial hemorrhage (Lauritzen et al., 2011; Lauritzen and Strong, 2017; Hartings et al., 2017). *A working hypothesis for translation to human disease, where complex patterns of depolarizations are observed in acute brain injury and appear to mediate and signal ongoing secondary damage, places CSD in a primary role in acute brain injury, a viewpoint inconsistent with animal experiments* (Gupta, 2009a; Borgdorff, 2018). CSD slowly propagates (≈3-5 mm/min) in grey matter in a characteristic 'creeping' fashion by way of contiguity regardless of functional divisions or arterial territories, followed by hyperpolarization or long-lasting suppression or silence of neural bioelectrical activity, that, in turn, is associated with a dramatic failure of brain ion homeostasis as well as efflux of excitatory amino acids from nerve cells and increased energy metabolism (Pietrobon and Moskowitz, 2014; Somjen, 2001; Lauritzen, 1994, 2001; Lauritzen et al., 2011, see below). Depolarization of both astrocytes and neurons is associated with onset of CSD (Ghaemi et al., 2018). *Following cardiac arrest cerebral ischemia, a protective influence of CSD has been demonstrated, a form of neuronal resistance to ischaemia by preceding spreading depression in Sprague-Dawley rats* (Kawahara et al., 1995) (see below). Other features of a neuronal adaptive / protective role for CSD / SD have been discussed previously (Gupta, 2009a).

CSD in experimental animals is at least a hundred times slower than any other known brain neurological process in humans, vascular or neuronal (Blau 1992a; Kaufman et al., 2017). Since Leão's discovery, CSD has been implicated in migraine due to the presumed similarity in electrophysiological characteristics, in particular the rate of propagation and SS (Milner, 1958; Lauritzen et al., 1985; Bolay et al., 2002). Nevertheless, lateralizing pain of migraine headache is the primary clinical event, although the mechanistic considerations of the SS (Pietrobon and Moskowitz, 2014) appear to have displaced it.

CSD has been maintained in migraine pathophysiology enthusiastically for several decades by a long series of critical omissions and assumptions (see Box 1, Gupta, 2009a). Several major issues, nevertheless, remain unresolved: (i) What triggers CSD itself, in the first instance, in the otherwise normal migraine patient is completely unknown, whereas migraine is triggered by a wide variety of well-known stimuli (Kelman, 2004a, 2004b, 2005, 2006, 2007; Sauro and Becker, 2009; Peroutka, 2014). (ii) CSD appears to arise only in damaged tissues but propagates through uninjured normal tissue (Leão, 1944a). Migraine is not associated with injured brain tissue (Gupta, 2009a). (iii) In contrast to the "wave-in-a-pond" propagation of CSD in rodents, in primates CSD may remain confined to a small local area contiguous with the stimulus, e.g., within one sulcus (Pearce, 1985). (iv) Without violating the principle of contiguity of spread of CSD, the full spectrum of frequently "skipping" migraine aura phenotype cannot be explained (Gupta, 2009a) (see below). (v) Psychogenic stress constitutes the commonest precipitant of migraine (Goadby, 2014; Borkum, 2016; Solotareff et al., 2017; Pellegrino et al., 2018). However, there is no known pathophysiologic link between psychogenic stress and CSD. (Gupta, 2024) (vi) Migraine headache is worsened by increase in heart rate or blood pressure and activities involving the Valsalva maneuver (VM) (Campbell, 1990; Gupta, 2010b), which have no link to CSD (Gupta, 2009a). (vii) In the majority of migraineurs i.e., migraine without aura (MwoA) cohort, the headache is not preceded by an aura – compelling the assumption of a "silent" aura (Moskowitz, 2008; Parisi, 2009; Lambert et al. 2011). (viii) There is a *vast species and factual event gap* between CSD-induced changes of behavior in experimental animals (monkeys or rats/mice) and migraine aura/headache in humans, as reviewed previously (Iadecola 2002; Gupta, 2009a). (ix) Pain of headache is believed, in the absence of definitive evidence, to be linked to CSD through behavioral changes in rats (Pietrobon and Moskowitz, 2014). Single unilateral waves of CSD in rats induce contralateral sensory neglect and motor impairment of the forepaw lasting for 15-30 minutes (Bureš et al., 1974, 1984), both features not unequivocally indicating pain. As reviewed, rats do not experience cortical or hippocampal CSD as aversive (Koroleva and Bures, 1993) (x) *CSD is an all-or-none physiological phenomenon* (Pearce, 1985). In striking contrast, the migraine phenotype is protean with markedly varied frequency, severity, and duration of headaches and strikingly varied accompanying clinical features, including ANS manifestations, disability and morbidity (Gupta 2009a; Borgdorff, 2018). Heterogeneity of CSD in the laboratory has been presumedly linked to clinical variations in the migraine phenotype, in particular the aura (Kaufman et al., 2017).

(see below). (xi) Episodic migraine attacks stop by themselves or remain self-limited (4-72 h) but remain unlinked to CSD, the neurological basis of which cessation is unknown (Houle et al., 2012; Villanueva, 2012) (xii) There is no residual functional neurological impairment after a wave of CSD in experimental animals, maximally observed at one hour (Leão, 1944a). Conversely, persistent neurological deficits and/or prolonged headache over several hours or days, however, are reported in migraine (Hupp et al., 1989; Campbell, 1990; Maxner and Moeller, 2005; ICHD, 2018) (xiii) Migraine-related critical cerebral ischemia, systemic vasculopathy, endothelial dysfunction and a hypercoagulable state are not found with any frequency or consistency in the uncomplicated adult migraine patient (Waters et al., 1983; Kurth et al., 2007; Rambarat et al., 2017). Critical (>75%) ischemia and cerebral infarct have also has not been documented in experimental animals after induction of CSD, as reviewed (Gupta 2009a). Stroke in migraineurs, nevertheless, is believed to be consequent to CSD (Eikermann-Haerter, 2014; Guidetti et al., 2014; Malik

Citation: Gupta VK. Cortical Spreading Depression and Migraine: Critical Review of a Neurophysiological Principle in the Third Millennium. Glob J Medical Clin Case Rep. 2026:13(10):228-272. Available from: https://dx.doi.org/10.17352/gjmccr.000273

et al., 2015). Although migraine attacks can epidemiologically be considered as a risk factor for ischemic or hemorrhagic stroke, the overall clinical impact is limited (Gupta, 2010a, 2017d), and the functional outcome after ischemic strokes is good (Sacco and Kurth, 2014). The key limitation is the plethora of other known vascular risk factors (Eikermann-Haerter, 2014). (xiv) The pathophysiological basis of brain white matter lesions (WMLs) in migraine patients or their link to CSD has not yet been established. (Hamedani et al., 2013; Tana et al., 2013; Montieth et al., 2014; Erdélyi-Bótor et al., 2015). WMLs are always distributed bilaterally; lateralizing WMLs have never been reported in migraine (Gupta, 2009b). (xv) Goadsby et al. (1990) reported non-lateralizing release of calcitonin gene-related peptide (CGRP) in jugular venous blood during migraine attacks. It has been generally accepted that CGRP, expressed throughout the CNS, plays an important role in migraine pathophysiology (Edvinsson, 2008). The *source* of episodic release of CGRP in humans in synchronization with precipitation of migraine headaches and its link to CSD in experimental animals remains speculative (Gupta, 2017c; Gupta, 2019). *No systemic influence (via diffuse release of neuropeptides, including 5-HT or noradrenaline or CGRP or adenosine or oxidants / reactive oxygen species (ROS) or nitric oxide whether released intrinsically in the brain or at the level of the heart – with or without patent foramen ovale (PFO) – or in the circulation can rationally explain the typically recurrent lateralizing headache of migraine* (Gupta, 1996a). *Neuropeptides do not work in splendid isolation in the human body; immediately after secretion or administration of any agent, drug, pharmaceutical, or biological substance into the body or into the brain, another set of counter-regulatory adaptive chemicals are released to maintain homeostasis across the blood-brain barrier (BBB)* (Gupta, 2017e, 2019, 2024). (xvi) BBB issues cloud CSD and pharmacologic absolutes (Borgdorff, 2018; Gupta, 2009a, 2019). One of the key assumptions about BBB disruption during MwA attacks and / or MwoA attacks has been disproved (DosSantos et al., 2014; Amin et al., 2017; Hougaard et al., 2017) (discussed further). (xvii) Tonabersat, an experimental novel benzopyran derivative that serves as a gap-junction modulator and blocks CSD, has not emerged as a useful migraine preventive agent (Hauge et al., 2009; Dodick, 2009; Silberstein et al., 2009; Cao and Zheng, 2014). (xviii) During CSD, influx of Na^{+}, Ca^{++}, and Cl^{-} ions into neuronal cells along with water, causes swelling, which consequently reduces the volume of the extracellular compartment to ~50% of the control value (Hansen and Olsen, 1980; Gorji, 2001). Conversely, significant change in water diffusion during or after spontaneous migraine aura was not demonstrated in a human fMRI study. (Cutrer et al., 1998). (xix) In CSD experiments in rats, cerebral metabolism is distinctly enhanced (Piilgaard and Lauritzen, 2009; Mayevsky and Weiss, 1991) but remained unchanged in MwA patients (Friberg et al., 1994). (xx) EEG activity is depressed to flattened in CSD (Leão, 1944a; Duckrow, 1991, 1993), but EEG depression is not found in migraine aura (Borgdorff, 2018). (xxi) Regular physical activity might reduce migraine attack frequency and pain intensity (Darling, 1991; Linde, 2006; Busch and Gaul, 2008; Irby et al., 2016) but regular physical activity has no known link to CSD. Conversely, intentional avoidance of moderate- and vigorous-intensity physical activity in women is a common migraine management strategy (Farris et al., 2018). (xxii) Perhaps the most significant component of CSD that is also least well understood is the fact that CSD is not an ordinary physiologic action potential but a severe, profound, hyperpolarization following long-lasting suppression or silencing of neuronal bioelectrical activity associated with dramatic failure of brain ion homeostasis, with total neuronal inexcitability resulting from a massive efflux of K^{+} with extracellular potential shift of several millivolts up to 20 mV (Leão 1944a; Pearce, 1985; Borgdorff, 2018). *In the face of such profound neuronal silencing, generation of the well-patterned positive SS or of lateralizing headache of migraine is highly unlikely*.

CSD-Magnesium-Migraine nexus

Magnesium (Mg^{2+}) lies central to the proposed schema for the genesis of CSD and/or vasoconstriction to effect migraine (Welch et al., 1990, see Figure 4). Spreading depression (SD) / CSD can be more readily evoked in Mg^{2+} deficient brain cortex in rat (Mody et al., 1987) and in human (Avoli et al., 1991) cortical slices. The range of pathologies associated with Mg^{2+} deficiency/depletion, acute or chronic, is very wide (Johnson, 2001), but is unlinked to CSD / SD (Gupta, 2024).

Mg^{2+} has differential modulatory effects on vascular tone and reactivity. Lowering Mg^{2+} concentration enhances *in vitro* vascular tone and contractile responses to various agonists (Altura and Altura, 1978; Altura et al., 1987; Laurant et al., 1997). Exogenously administered Mg^{2+} is a systemic vasodilator and a competitive calcium antagonist (Pfefferanferth et al., 1996; Wang et al., 2003). *Vasodilators, generally, precipitate migraine attacks*. Additionally, why migraine patients should primarily or spontaneously become brain Mg2+-depleted or repleted is a far more important issue (Gupta, 2009a, 2017b, 2024).

Mg^{2+} concentration in CSF is significantly greater than in plasma and tends to remain stable or rise mildly and slowly in the face of changing plasma concentration (Watchorn and McCance, 1932; Oppelt et al., 1963). Transport of Mg^{2+} from blood to CSF across the BBB is limited in normal humans and has little effect on post-operative pain scores (Ko et al., 2001; Harris, 2013; Albrecht et al., 2013).

Additionally, in principle (Gupta, 2005c, 2009a) as well as in practice (Mees et al. 2012; Golan et al., 2013; Leijenaar et al., 2015; Dorhout Mees et al., 2015), supplementation or prophylactic use of magnesium sulphate ($MgSO_4$) in subarachnoid hemorrhage to counter delayed cerebral ischemia does not appear useful. In stroke management also, i.v. $MgSO_4$ did not offer significant neuroprotection when administered within two hours of symptom onset (Saver et al., 2015). Intriguingly, exogenous $MgSO_4$ administration itself attenuates enhanced BBB permeability in different experimental models (Esen et al., 2003; Kaya et al., 2004; Esen et al., 2005). *The belief that exogenous Mg^{2+} offers neuroprotection by suppressing development of CSD (Welch et al., 1990; Van Der Hel et al., 1998) does not appear to be tenable any longer in human patients, including in traumatic brain injury (TBI)*.

A low serum Mg^{2+}, as is found in migraine patients, during and between headache attacks, tends to limit or prevent

Citation: Gupta VK. Cortical Spreading Depression and Migraine: Critical Review of a Neurophysiological Principle in the Third Millennium. Glob J Medical Clin Case Rep. 2026:13(10):228-272. Available from: https://dx.doi.org/10.17352/gjmccr.000273

vasodilatation, systemic as well as cranial, thereby restricting the cephalalgogenic effect of various headache triggers. Hypomagnesemia, thus, appears to be a generalizable, logically-defensible, physiological adaptive evolutionary mechanism across the interdisciplinary neurosciences (Gupta, 2004d, 2009a, 2009b) and the cardiovascular sciences (Gupta, 1996b) that enables optimal operation of a host of life-preserving calcium-related cellular-level functions during acute stress of life threatening conditions (such as acute myocardial infarction) or chronic stress of migraine-like conditions. Like all other adaptive functions, e.g., fluid retention, hypomagnesemia is simplistic in nature. Severe hypomagnesemia is linked with hypocalcaemia, refractory arrhythmia, and a poor prognosis. A therapeutic role for i.v. MGSO4 supplementation in refractory atrial fibrillation in combination with other atrio-ventricular nodal blockers is proposed (Bouida et al., 2019).

For almost 100 years, widespread use of MGSO4 has been in practice for pre-eclampsia and eclampsia, based on the premise that it has a powerful central anti-epileptic action (Alton and Lincoln, 1925; Lazard, 1925; Sadeh, 1989). No study of toxemia of pregnancy has found that Mg^{2+} freely, rapidly, or significantly crosses the BBB to prevent convulsions. *Conversely, occurrence of neuromuscular blockade and the resultant potentiation of muscle relaxants during MgSO4 administration has been well-documented* (Giesecke et al., 1968; Skaredoff et al., 1982; Sinatra et al., 1985; Ramanathan et al., 1988). The obstetric anesthesiologist is most concerned about the action of Mg^{2+} at the myoneural junction rather than at the CNS. In addition, during i.v. MGSO4 administration, there is a marked decrease in the serum calcium levels in patients with preeclampsia (Cruikshank et al., 1979). High serum levels of MGSO4 in the range of 12 to 15 mEq/L can cause paralysis and respiratory depression (Sibai, 2004), giving further credence to neuromuscular junction blockade as an alternative or apparent anticonvulsant mechanism in pre-eclampsia/toxemia of pregnancy (Gupta, 2023). The so-called central anti-convulsant action of Mg^{2+} does not support a CNS / brain site of action that might be critical in the genesis of CSD.

A review of the literature from 1990 and of four intervention trials assessing the independent efficacy of oral Mg^{2+} supplementation in the prevention of migraine concluded that the evidence supporting oral Mg^{2+} supplementation is limited (Teigen and Boes, 2015). Coupled with the in-depth evaluation of Mg^{2+} induced cellular, cardiovascular, myoneural, BBB-related kinetics, and basic brain functional aberrations, including CSD, presented in this article, the review of Teigen and Boes (2015) indicates that the concept of a primary aberration of Mg^{2+} in migraine and its correction by exogenous administration of MGSO4 has proved erroneous in migraine therapeutics (Gupta, 2004d, 2009a, 2009b).

CSD and Photophobia

A diagnostic feature of both MwA and MwoA (Drummond, 1986; Vanagaite et al., 1997; ICHD - III, 2018), photophobia is defined as abnormal sensitivity or painful intolerance to light (Miller, 1985). Approximately 80-90% of migraine patients with normal eyesight experience photophobia (Selby and Lance, 1960; Miller, 1985; Drummond, 1986) (see below).

Defining photophobia nearly eight decades ago, Lebensohn and Bellows, (1934) underscored: "exposure" of the eye to light definitely induces or exacerbates pain. The neurobiology of photophobia is important to understand the fundamental basis of migraine (Maniyar et al., 2014a). Exacerbation of headache by light (ambient) or more correctly photoallodynia or photo-oculodynia (Fine and Digre, 1995) is commonly associated with primary intraocular disorders such as corneal abrasion /ulcer, iridocyclitis/uveitis, cone dystrophies, chiasmal compression, psychiatric disorders such as agoraphobia, as well as intracranial pathologies such as essential blepharospasm, almost all forms of migraine, meningitis, subarachnoid haemorrhage, and traumatic brain injury (Kawasaki and Purvin, 2002; Digre and Brennan, 2012; Friedman, 2013; Rossi and Recobar, 2015). Vanagaite et al. (1997) reported that photophobia is reported in 66-88% of migraine patients, and, that 3057% of migraine attacks can be precipitated by different light and glare sources such as sunlight, flicker of moving pictures, or television. Photophobia is more marked on the side of the headache (Drummond, 1986; Lance, 1993). Some regard photophobia as merely a functional symptom (Trobe, 2002). CSD has been suggested to underlie photophobia, through a rather convoluted process that involves activation of peripheral and central trigeminovascular neurons (Noseda and Burstein, 2013).

Painful photophobia depends on the functional integrity of both the optic and the trigeminal nerves (Lebensohn and Bellows, 1934; Maleki et al., 2012).

Photophobia is not associated with "positive" or "negative" migraine aura, and begins with and subsides with episodic migraine headache. Diplopia, palinopsia (illusory rather than hallucinatory), basilar-type migraine, retinal migraine, migraine with unilateral mydriasis, persistent visual aura, visual snow, phosphenes, halos, and migraine with binocular blindness are not associated with photophobia (Hupp et al., 1989; Schwartz and Robbins, 2012; Gersztenkorn and Lee, 2015; Kalita et al., 2016). Similarly, migraine-related vertigo and migraine-associated motion sickness are not associated with photophobia (Crevits and Bosman, 2005).

Usually very uncomfortable and disabling, the exact nature and causative mechanisms of headache-related photophobia in migraine are still uncertain (Chronicle and Mulleners, 1996; Rossi and Recober, 2015). Clinical and preclinical research has identified several potential pathways involved in enhanced light sensitivity. Some of these structures include trigeminal afferents in the eye, second order neurons in the trigeminal nucleus caudalis, third-order neurons in the posterior thalamus, modulatory neurons in the hypothalamus, and fourth order neurons in the visual and somatosensory cortices (Rossi and Recobar, 2015). *The comfort of the dark and that of dark sunglasses afforded to the migraine patient during and inbetween headache attacks suggests a definitive role for miosis in the genesis of dominantly lateralizing photophobia*.

In migraine patients with normal eyesight, green light appears to exacerbate migraine headache significantly less than white, blue, amber, or red lights. (Noseda et al., 2016)

Citation: Gupta VK. Cortical Spreading Depression and Migraine: Critical Review of a Neurophysiological Principle in the Third Millennium. Glob J Medical Clin Case Rep. 2026:13(10):228-272. Available from: https://dx.doi.org/10.17352/gjmccr.000273

Migraineurs experience with colour, and, colour-selective migraine photophobia could originate in cone-driven retinal pathways, fine-tuned in relay thalamic neurons outside the main visual pathway, and preserved by the cortex (Zervas and Smith, 1987; Noseda et al., 2016). *Photophobia of migraine appears to be an "irritability/hyperexcitability" of non-cortical (retinal) origin rather than cortical* (Brennan, 2011). *Importantly, no difference in light sensitivity or photophobia has been found between MwA patients and MwoA patients during attacks as well as between attacks* (Vanagaite et al., 1997). Pain thresholds are generally lower in light sensitive than in non-light-sensitive migraine patients. (Vanagaite et al., 1997)

Remarkably, photophobia, reported by visually impaired adult migraine patients (n=6) in whom the headache preceded the blindness in time, disappeared after the development of the visual impairment (Silva et al., 2014) (see below).

Clearly, the anterior visual pathway rather than the visual cortex-related CSD is predominantly involved in the genesis of photophobia in migraineurs. Pupillary miosis and normal retinal function appear essential in the development of photophobia of migraine.

CSD and meninges

Migraine pain is thought to originate from chemical irritation of the meninges leading to transmission of nociceptive signals from the dura mater to the brain via the TVS (Blau, 1992a; Noseda et al., 2010; Noseda and Burstein, 2013). Such a long-term (frequently over decades), recurrent, episodic, self-limited, non-infective, uncomplicated meningeal activation/irritation is a unique or idiosyncratic, purely arbitrary mechanism or phenomenon that cannot be generalized (Table 1). Given that a far less severe but arbitrary "variant" of meningitis (? meningeal irritation) is prominently proposed to underlie episodic migraine, the concept is presumptive, raises more questions than answers, and encourages further research endeavors in this speculative vein without elucidating the basic neurobiology of CSD or allowing a comprehensive synthesis to emerge. Table 1 presents a comparison between migraine and the long-sought meningitis-like or meningeal "irritation/activation" state to position the discipline in order to confront a mythical neurological concept.

There is, apparently, no link between CSD and meningeal 'irritation', and hence, by extrapolation, between CSD and migraine (Table 1).

CSD and Ophthalmic division of the Trigeminal Nerve (V1)

Migraine is not a pan-trigeminal disorder but primarily affects the ophthalmic division (V 1) of the trigeminal nerve (Gupta, 2009a; Akerman et al., 2013). The pain of migraine headache is not, as has been generally assumed (Moskowitz et al., 1979; Andreou et al., 2010; Edvinsson, 2011), a diffusely distributed involvement throughout the three divisions of the trigeminal nerve. Unilateral or bilateral frontotemporal, parietal, vertex, retro-orbital or nuchal segmental pain is common in many migraine patients (Obermann et al. 2007a; Campbell 1990), and indicates predominant or selective and partial involvement of V 1 (Gupta, 2006b, 2009a, 2019, 2024). Migraine pain uncommonly involves the second (V 2) or maxillary division and generally spares the third (V 3) or mandibular division (Campbell, 1988). However, the pain of migraine may extend to C2 and C3, and neck stiffness is common; also, the pain wanders during individual attacks and in different episodes (Campbell, 1990; Blau and MacGregor, 1994; Bartsch, 2005). In another study with location frequencies, the highest were as follows: eyes (67.1%), temporal (58%), and frontal (55.9%) while the lowest were: diffusely (17.5%) and vertex (24.1%); intermediate frequencies were reported in the occipital (39.8%) and neck areas (39.7%) (Kelman, 2005). Lower-half headache / facial syndrome involving orbital pain spreading into the antral region, lower jaw and upper neck is an uncommon variant, with some patients responding to ergotamine (Campbell 1988; Peñarrocha et al., 2004). There is another variant with atypical pain localization but with typical deep seated unilateral pain, bizarre distribution, and other features of migraine including response to triptan but without V 1 involvement (Obermann et al., 2007a, 2007b).

Spread of pain to the back of the head as well as to the nuchal region has been, again, attributed to a diffuse undifferentiated involvement of all three divisions of the trigeminal nerve and upper cervical spinal segments – "trigeminovascular system" (Bartsch, 2005) or to the hypothetical phenomenon of "convergence" of sensory input (Kelman, 2005). The primary afferent fibres of the three divisions of the trigeminal nerve are arranged in a complex manner at the spinal nucleus with only pain and temperature fibers from the ophthalmic area descending densely to the lower limit of the first cervical spinal segment (Bannister et al., 1995; Bogduk, 1995). It is not possible to conceive that an appropriate V 1 segment or a matching segment of the somatosensory cortex could be selected or activated in isolation, cyclically or periodically or episodically, by any brain neuronal / neuropeptide process, including CSD, to generate neuroanatomically corresponding lateralized/localized cephalic or nuchal pain or both episodically for over decades in any one migraine patient (Gupta, 2009a, 2017e, 2019).

Peripheral sensitization of the trigeminal primary nociceptors via neurogenic inflammation is another favoured pathogenetic hypothesis (Strassman et al., 1996; Olesen et al., 2009; Noseda and Burstein, 2013). While CSD is the prototypic putative central sensitization process, activation of peripheral nociceptors is also believed to underlie neuronal hyperexcitability in migraine. Nociceptive input from perivascular sensory, particularly extracranial, dural, and pial arteries rather than veins, may be responsible for the headache phase of migraine. Such evidences are, however, limited and controversial (Olesen et al., 2009). It is likely, as suggested previously (Olesen et al., 2009), that afferent contributions from all three territories of the trigeminal nerve vary between migraine patients, with a predominant role for V 1 (Gupta, 2009a, 2019, 2024). Nevertheless, *diffuse* peripheral afferent

Citation: Gupta VK. Cortical Spreading Depression and Migraine: Critical Review of a Neurophysiological Principle in the Third Millennium. Glob J Medical Clin Case Rep. 2026:13(10):228-272. Available from: https://dx.doi.org/10.17352/gjmccr.000273

Table 1: Migraine headache versus meningeal activation / irritation-related headache: facts versus belief.

	MIGRAINE	MENINGEAL "IRRITATION" / MENINGITIS
Headache Location, intensity, and duration	Ocular in 67.1% (Kelman, 2005); unilateral (generally) or bilateral (frequently) bitemporal or bifrontal or side-shifting or side-locked with same pattern but differing intensities and durations in subsequent attacks. Always in the distribution of V 1 (partial or segmental, with the full distribution of V 1 rarely involved, commonly fronto-temporal) (Campbell, 1990; Noseda and Burstein, 2013). Atypical facial pain / lower half headache can occur (Campbell 1988; Peñarrocha et al. 2004; Al Balawi et al., 1996; Obermann et al., 2007a). Pain at the back of the head (C 2 segment) is frequent but not lateralized (Bartsch, 2005). Vertex is involved in 24.1% (Kelman, 2005) (see below). Nuchal headache is frequent, unilateral or bilateral (Dewitte et al., 2019).	Always bilateral. Unilateral or partial V1 headache can never be the outcome of diffuse bilateral dural inflammation and nociceptor fibre activation, regardless of the mechanism or etiology involved. Always nuchal with neck rigidity (see below). Meningeal "irritation" has never been definitively documented in migraineurs as part of neurogenic inflammation (Strassman et al., 1996; Noseda et al., 2010; Noseda and Burstein, 2013). Never occurs as discrete attacks or self-limited isolated or recurrent ocular or fronto-temporal or vertex head pain/discomfort.
BBB	The typical localization of headache (as above) is even though meningeal vessels lack BBB and represent much more permeable structures relative to cortical vessels (Edvinsson and Tfelt-Hansen, 2008; Grände et al., 2014).	Meningeal vessels lack BBB compared with cortical vessels (Edvinsson and Tfelt-Hansen, 2008; Grände et al., 2014), leading to diffuse cranial pain rather than neuroanatomically V1-limited pain typical of migraine (see below).
Vomiting	An early feature that can frequently abort episodic migraine headache (Campbell, 1990).	Common feature that never aborts the headache (Juganariu et al., 2012).
Headache Source	Ultimate source is a presumed endogenous repetitive cortical dysexcitability / hyperexcitability – CSD – TVS – EPCS – neurogenic inflammation -- BBB disruption. Pain perception nexus uncertain and unknown (Bolay et al., 2002; Pietrobon and Striessnig, 2003; Coppola et al., 2007; Stankewitz and May, 2009; DosSantos et al., 2014; Lukacs et al., 2017; Russo et al., 2018).	Dural nociceptive nerve fibre activation (Juganariu et al., 2012).
Neck Stiffness / Rigidity	Neck rigidity rarely demonstrated; neck muscle hypersensitivity and hyper-tenderness, restrictions of cervical range of movements (ROM), and hyperalgesia described (Selby and Lance, 1960; Anthony, 1992; Kidd and Nelson, 1993; Goadsby et al., 2002). Benign paroxysmal torticollis is seen in pediatric migraine (Lagman-Bartolome and Lay, 2015).	Neck rigidity defines meningeal irritation/meningitis (Juganariu et al., 2012). Restriction of anterior cervical ROM is characteristic of neck rigidity.
BBB morphology and function	Not disrupted (Edvinsson and Tfelt-Hansen, 2008; Hougaard et al., 2017; Amin et al., 2017). Whereas the trigeminal ganglion (TG) is readily exposed to circulating molecules (Lundblad et al., 2015), it is the presumed CSD-TG nexus operative in migraine genesis for which there is no evidence.	Commonly disrupted (Yang et al., 2023; Putz et. al., 2013)
Fever	Never documented even in most severe and prolonged migraine headaches, including status migrainosus.	Common feature (Burstein et al., 2026)
Consciousness	Never affected, even in the most severe migraine headache attacks. Postural loss of consciousness (LOC) / vasovagal attack discussed below. Non-orthostatic LOC requires reassessment of diagnosis. Mixed picture in migralepsy can involve consciousness (Vercueil, 2022)	Comorbidly impaired (Heckenberg et al., 2014).
Frequency and duration	Recurrent attacks over decades, months, or a lifetime, generally without any permanent neurological consequences. No risk to life. (Campbell, 1990).	Unlikely to occur even once without some neurological consequence or sequela (Juganariu et al., 2012). Serious risk to life (Yang et al., 2023)
Photophobia	Present; worst on the side of the headache (Drummond, 1986).	Present in a diffuse, non-lateralized manner (see above). (Vercueil, 2022)
Cerebrospinal Fluid	Typical normal routine CSF measurements, including CSF pressure (Onderwater et al., 2017)	Unlikely to be clear or acellular. CSF pressure is likely to be elevated. (Pinho-Correia et al., 2025).

Glossary: EPCS – endogenous pain control system; LOC – loss of consciousness; V 1 – ophthalmic division of trigeminal nerve; TVS – trigeminovascular system; TG-- trigeminal ganglion; CSF—cerebrospinal fluid.

trigeminal nociceptor activation, in isolation or in combination with central sensitization, cannot explain persistently or frequently lateralizing headache. *In an exhaustive review of abnormal peripheral sensitization and a discussion of the origin of this input,* (Olesen et al., 2009) *acknowledge that there is little or no evidence with certitude regarding which pain fibers are activated, or how they are activated, or what activates them.*

CSD has no conceivable link with peripheral sensitization of the trigeminal primary nociceptors in migraine whereas there are key limitations for central sensitization of trigeminal primary nociceptors through CSD in the disorder, as further discussed below.

CSD and Migraine Therapies – Major

Pharmacologic-Pathophysiologic Disconnects

A wide spectrum of treatment options is currently available to manage migraine including medical, surgical (Mathew, 2014), and botulinum toxin.

(Ramachandran and Yaksh, 2014; Jackson et al., 2012; Gupta, 2005h, 2006a), closure of patent / persistent foramen ovale (Wilmhurst, 2018; Gupta, 2009c, 2010a), anesthesiologic blockade (Inan et al., 2016; Dilli et al., 2015; Bogduk, 2004), manual (Chaibi et al., 2011), cognitive (Harris et al., 2015),

Citation: Gupta VK. Cortical Spreading Depression and Migraine: Critical Review of a Neurophysiological Principle in the Third Millennium. Glob J Medical Clin Case Rep. 2026:13(10):228-272. Available from: https://dx.doi.org/10.17352/gjmccr.000273

transcranial magnetic stimulation (Kumar et al., 2018; Conforto et al., 2014), acupuncture (Gu et al., 2018), external electrical trigeminal neurostimulation (Schoenen and Coppola, 2018), and noninvasive electrical vagal nerve stimulation (Tassorelli et al., 2018). This list is not exhaustive but underscores the profound confusion in the principles of theory and therapy of migraine. All extant pathogenetic therapies are empirical or experiential, including those supported by RCTs (Gupta, 2009a).

The sustained thrust for CSD is augmented by the assumed potential for development of new therapeutic drugs that could directly act on or modulate CSD to prevent migraine attacks (Kaufman et al., 2017; Galletti et al., 2009; Sanchez-del-Rio et al., 2006; Hadjikhani et al., 2001). It is widely believed that all migraine preventive agents suppress CSD as a common mechanism of action that will eventually lead to targeted and specific therapy (Ayata and Lauritzen, 2015; Ayata, 2010, 2009; Ayata et al., 2006). Widely disparate pharmacologic classes of drugs are used for migraine prevention. (Silberstein, 2015; Bogdanov et al., 2011; Jackson et al., 2015; 2012; 2010; Galletti et al., 2009). To significantly influence the occipital cortex or CSD, the pharmaceutical agent must freely cross the BBB by lipophilicity, carrier mediated influx transport, or receptor- or absorptive-mediated transcytosis (Edvinsson and Tfelt-Hansen, 2008; Gupta, 2019, 2009a). Lipophilicity, significant CSF levels, and prominent CNS side-effects of the pharmaceutical indicate significant BBB and CNS penetration and underscore its potential to influence CSD. While disruption of BBB has been excluded during both MwoA and MwA attacks, respectively, (Amin et al., 2017; Hougaard et al., 2017), penetration of the BBB by the pharmacologic agent inbetween attacks is, intriguingly, not considered important in migraine therapeutics. An assumed combination of peripheral and central sensitization (Goadsby, 2005, 2001; Malick and Burstein, 2000; Burstein et al., 2005; 2000; Knight and Goadsby, 2001) may have theoretically supplanted this pharmacologic absolute (Gupta, 2024, 2019, 2009a). The causal role of CSD appears to be more probable in MwA patients (Bogdanov et al., 2011) but significant limitations persist (see below) (Table 2).

No significant modification of CSD was observed after acute systemic administration of metoprolol, dihydroergotamine, acetylsalicylic acid, lignocaine, clonazepam, and valproate in cat brain (Kaube and Goadsby, 1994), and after acute systemic administration of metoprolol in rat brain (Alemdar et al., 2007). Conversely, chronic daily administration of topiramate, valproate, propranolol, amitriptyline, and methysergide resulted in a dose- and time-dependent suppression of CSD frequency by 40-80% (Ayata et al., 2006). Topical application of propranolol – as well as norepinephrine or clonidine or yohimbine – inhibited migration of a CSD wave in the adult rat grey matter (Richter et al., 2005).

No experimental data have determined definitely the mechanism(s) through which propranolol reduces migraine attack frequency in both MwA and MwoA patients (Weerasuriya et al., 1982; Andersson and Vinge, 1990; Limmroth and Michel, 2001; Gobel and Heinze, 2003; Diener, 2003). The efficacy of propranolol (80-240 mg /day), metoprolol (200 mg/day), and timolol (20-30 mg/day) is supported by clinical studies (Tfelt-Hansen et al., 1984; Tfelt-Hansen, 1986; Linde and Rossnagel, 2004).

While propranolol, metoprolol, and timolol are lipophilic and hence penetrate well into the CNS, atenolol and nadolol are only slightly or not at all lipophilic (Weerasuriya et al., 1982; Cruickshank and Prichard, 1994). Since atenolol (Stensrud and Sjaastad, 1980; Forssman et al., 1983; Johannsson et al., 1987) and nadolol (Ryan et al., 1983; Ryan, 1984; Freitag and Diamond, 1984; Olerud et al., 1986; Sudlikovski et al., 1987) have demonstrated prophylactic efficacy, BBB penetration does not appear to be required for prevention of MWA as well as MwoA (Gupta 2009a; Hougaard et al, 2017; Amin et al, 2017). Atenolol is currently established as a drug of first choice for episodic migraine prophylaxis (Andersson and Vinge, 1990; Emilien and Maloteaux, 1998; Limmroth and Michel, 2001; Edvardsson, 2013; Silberstein, 2015). Atenolol and nadolol are not known to critically alter any brain function possibly related to CSD. Nadolol has shown migraine preventive activity comparable to propranolol (Olerud et al., 1986; Sudlikovski et al., 1987; Andersson and Vinge, 1990). *The concentration in the CSF of propranolol, oxprenolol, and metoprolol approximates that of the free drug concentration in the plasma but appears in brain tissue at concentrations 10-20 times greater than that of the hydrophilic atenolol* (Neil-Dwyer et al. 1981). Remarkably, oxprenolol does not have any migraine preventive activity despite being lipophilic with CSF concentration approximating the plasma concentration and the brain/plasma ratio being higher than that for propranolol (Neil-Dwyer et al., 1981). *This indicates that the pathophysiologic system involved in migraine lies outside the CNS, as is also indicated by other migraine attack-preventive drugs that do not cross the BBB, such as atenolol, nadolol, and verapamil, with no link to CSD* (Gupta, 2004a). Barring insomnia, a side effect that is less often seen than with propranolol users -- as a class effect for ßblockers -- atenolol has no central or brain neuronal side effect (McAinsh and Cruickshank, 1990; Scheer et al., 2012; Chang et al., 2013). All ß-1-selective blockers including hydrophilic atenolol and moderately lipophilic metoprolol and bisoprolol, suppress nighttime melatonin (Stoschitzky et al., 1999; Nathan et al., 1997; Van Den Heuvel et al., 1997; Brismar et al., 1988; Cowen et al., 1985; Arendt et al., 1985). In one polysomnographic study, 100 mg atenolol in healthy volunteers led to decreases in urinary 6-sulphatoxymelatonin and total sleep time, whereas 5 mg of melatonin supplementation while on atenolol restored sleep to baseline levels (Van Den Heuvel et al., 1997). Because the pineal gland lies outside of the BBB, both lipophilic and hydrophilic beta-blockers can selectively suppress melatonin production (Scheer et al., 2012).

Verapamil, a widely used migraine prophylactic agent but with limited evidence of benefit (Solomon, 1989; Andersson and Vinge, 1990; Goadsby et al., 2002), also does not cross the BBB (Agnoli, 1988; Gupta, 2009a). Some therapists prefer to use verapamil prophylactically in MwA patients, with or without headache, particularly when the auras are frequent or associated with hemiparesis, and in sporadic hemiplegic

Citation: Gupta VK. Cortical Spreading Depression and Migraine: Critical Review of a Neurophysiological Principle in the Third Millennium. Glob J Medical Clin Case Rep. 2026:13(10):228-272. Available from: https://dx.doi.org/10.17352/gjmccr.000273

Table 2: Blood-brain barrier permeability of selected anti-migraine agents and their effects on CNS / CSD.

Anti-Migraine Agent	Blood-brain barrier permeability / CNS effects (lipophilicity; influx transport; transcytosis; side- effects)	Cortical Spreading Depression in experimental animals
Propranolol	High lipophilicity; crosses BBB readily; prone to cause depression (Petrie et al., 1982; Agon et al., 1991; Kendall, 1997; Ringoir et al., 2014). 'Gold standard' for prevention of migraine.	Suppresses CSD in rats after chronic administration (Richter et al., 2005; Ayata et al., 2006).
Metoprolol	Moderate lipophilicity; crosses BBB readily (Kendall, 1997). As good as propranolol for prevention of migraine.	Effect of chronic administration on CSD is unknown. Acute administration has no effect on CSD (Alemdar et al., 2007).
Timolol	Moderate lipophilicity; crosses BBB readily (Kendall, 1997). As good as propranolol for prevention of migraine (Tfelt-Hansen et al., 1984; Stellar et al., 1984).	Effect of chronic administration on CSD is unknown.
Atenolol	Hydrophilic (Cruickshank, 1980; Agon et al., 1991; Kendall, 1997). Does not readily cross the BBB. Prevents migraine as effectively as propranolol, both MwA and MwoA (Stensrud and Sjaastad, 1980; Forssman et al., 1983; Johannsson et al., 1987). Regarded by many reviewers also as a drug of first choice (Andersson and Vinge, 1990; Emilien and Maloteaux, 1998; Limmroth and Michel, 2001; Edvardsson, 2013; Silberstein, 2015). Insomnia is the only CNS AE due to pineal melatonin suppression, a class-effect (Van Den Heuvel et al., 1997).	Effect of chronic administration on CSD is unknown.
Nadolol	Hydrophilic (Kendall, 1997; O'Carroll et al., 1999). Does not readily cross the BBB. Prevents migraine as effectively as propranolol, both MwA and MwoA (Ryan et al., 1983; Ryan, 1984; Freitag and Diamond, 1984; Olerud et al., 1986; Sudlikovski et al., 1987).	Effect of chronic administration on CSD is unknown.
Amitriptyline Protriptyline Nortriptyline Venlafaxine Doxepin	Amitriptyline is lipophilic; crosses the BBB readily. Prevents migraine effectively (Couch and Hassanein, 1979; Couch et al., 2011). May cause serotonin syndrome (Sternbach, 1991; Sporer, 1995; Gillman, 1999, 2010; Boyer and Shannon, 2005). Serotonergic agonist action leading to serotonin syndrome. Despite promoting sleep and improving depression, can induce convulsive seizures in overdose (Paksu et al., 2014) and lead to mania when used in combination with MAO inhibitors (de la Fuente et al., 1986) or induced by withdrawal (Dilsaver and Greden, 1986) indicating a well-modulated cortical hyperexcitability. Combination of propranolol and amitriptyline, paradoxically, works very well for migraine prophylaxis (see below). Protriptyline, nortriptyline, and venlafaxine are other antidepressants that prevent migraine (Silberstein, 2015).	Amitriptyline suppresses CSD after chronic administration, an effect similar to that of propranolol (Ayata et al., 2006) despite serotonergic and noradrenergic agonistic effects on the human brain, with AE such as serotonin syndrome.
Topiramate	Appears to readily cross the BBB. Anti-epileptic effect. Probably potentiates the activity of the inhibitory neurotransmitter, gamma-aminobutyric acid (GABA). CNS side-effects like somnolence, dizziness, ataxia, psychomotor slowing, hesitant speech, and word-finding difficulties in doses of 200-400 mg/day in combination with other anti-epileptic drugs (Rosenfeld, 1997; Marmura, 2014). Anti-migraine effect does not appear to be uniform (Lampl et al., 2004; Karadas et al., 2014; Silberstein et al., 2006; Wolthausen et al., 2009; Linde et al., 2013a) with approximately 50% of patients being non-responsive. No dose-response curve.	Suppresses CSD after chronic administration, an effect similar to propranolol (Akerman and Goadsby, 2005; Ayata et al., 2006; Unekawa et al., 2012).
Lamotrigine	Readily crosses the BBB. Selectively prevents migraine aura but not the headache, extrapolation from rats. Believed to have a causal role of CSD in MwA, but not in MwoA (Bogdanov et al., 2011).	Marked suppressive effect on CSD of 37% and 60% at posterior (parieto-occipital) and anterior (frontal) electrodes, respectively, as well as on frontal Fos expression in extrapolation from rats (Bogdanov et al., 2011).
Valproate	Non-selective variable preventive effect on both aura and headache of migraine, extrapolation from rats (Bogdanov et al., 2011, Linde et al., 2013a).	Acute administration has no effect on CSD (Kaube and Goadsby, 1994). Chronic administration suppresses CSD (Ayata et al., 2006). Has no effect on posterior CSD but reduces anterior CSD by 32%, slows propagation velocity, and decreases frontal Fos expression; no effect on triggering of CSD (Bogdanov et al., 2011)
Riboflavine	Does not freely cross the BBB but is tightly regulated by a specialized, high-affinity transport system. Non-selective variable preventive effect on both aura and headache of migraine (Bogdanov et al., 2011; Talebian et al., 2018). No CNS	No effect on suppression or triggering of CSD (Bogdanov et al., 2011). Many studies add to the confusion that prevails in migraine pathophysiology.
	Side effects or physiological alterations of evoked potential abnormalities (Sándor et al., 2000)	Preventive anti-migraine drugs have differential effects on CSD. Lamotrigine has a marked suppressive effect which correlates with its rather selective action on the migraine aura. Riboflavin (and valproate, see above) do not affect the triggering of CSD, although they are effective in migraine without aura. Taken together, these results are compatible with a causal role of CSD in migraine with aura, but not in migraine without aura (Bogdanov et al., 2011).

Citation: Gupta VK. Cortical Spreading Depression and Migraine: Critical Review of a Neurophysiological Principle in the Third Millennium. Glob J Medical Clin Case Rep. 2026:13(10):228-272. Available from: https://dx.doi.org/10.17352/gjmccr.000273

Pregabalin	Appears to cross the BBB readily. Selective ligand of the α2δ subunit of calcium channels and a close analogue of gabapentin (Chizh et al., 2007). Preventive use of pregabalin in migraine is emerging (Calandre et al., 2010; Pizzolato et al., 2011; Linde et al., 2013c; Bakhshandeh Bali et al., 2015). Useful in human peripheral neuropathic pain (Dworkin et al., 2003; Rosenstock et al., 2004).	Increases the threshold for CSD, slows the propagation velocity of CSD, and prevents subcortical propagation of CSD (Cain et al., 2017). Inhibits central sensitization in human volunteers (Chizh et al., 2007).
Methysergide Dihydroergotamine	Not known to cross the BBB (Koehler and Tfelt-Hansen, 2008; Dahlöf and Massen Van den Brink, 2012). Central / brain 5-HT_2 antagonsim is probably not relevant (Koehler and Tfelt-Hansen, 2008; Dahlöf and Massen Van den Brink, 2012).	Suppresses CSD after chronic administration, an effect similar to that of propranolol (Ayata et al., 2006)
Verapamil Nifedipine Amyl Nitrite Isoproterenol	Does not freely cross the BBB and has no CNS neuronal effect. Used preferentially for prevention in MwA, with or without headache, or in aura-associated hemiparesis (Silberstein and Young, 1995). Useful also in hemiplegic migraine, sporadic or familial (Yu and Horowitz, 2003). Nifedipine also aborts migraine aura (Silberstein and Young, 1995). Amyl nitrite (Schumacher and Wolff, 1941) and isoproterenol (Kupersmith et al., 1979) relieve migrainous visual loss.	No known effect on CSD of any drug or on L-type channels (Choudhuri et al., 2002; Akerman et al., 2003) or on N and P/Q type channels (Richter et al., 2002).
Magnesium	Does not freely cross the BBB (discussed above). No definite effect on prevention of migraine attacks (Gupta, 2004d, 2009a; Galletti et al., 2009).	No known effect on CSD (discussed above). No definite CNS effects of exogenous administration, including any anti-epileptic effect in toxemia of pregnancy (discussed above).
Acetyl Salicylic acid	Variable results for prevention of migraine attacks (O'Neill and Mann, 1978; Baldrati et al., 1983; Savi et al., 2013) with small statistically insignificant decreases in women (Benseñor et al., 2001). Particularly useful for preventing MwA (Anoaica et al., 2014), a retrospective study that has not been replicated. Effective first-line treatment for acute migraine headache (Taneri and Petersen-Braun, 1995; Diener et al., 2006; Lampl et al., 2012; Kirthi et al., 2013).	No known effect on CSD (Kaube and Goadsby, 1994). Central CNS effects are well-known, including effects on pain processing centres (Ferreira et al., 1978; Maihöfner et al., 2007; Kröger and May 2014).
Flunarizine	Appears to readily cross the BBB. Can cause drowsiness, parkinsonism, depression, or increased appetite and weight gain (Bono et al., 1985; Micheli et al.,1987; Todd and Benfield, 1989). Drowsiness and weight gain are the most important side effects (Martinez-Lage, 1988). A Parkinsonian syndrome, the incidence of which is 15% in patients over 65 years of age, is the most important and serious side effect on long-term therapy (Centonze et al., 1990). A depressive syndrome might also interrupt therapy (Bono et al., 1985; Micheli et al., 1987; Verspeelt et al., 1996).	No known effect on CSD. Can alleviate cerebral mitochondrial injury induced by CSD under hypoxic conditions (Fengpeng et al., 2011). Exerts vascular effects on arterial resistance by blocking T-type Ca^{2+} channels (Richard, 2005).
Tonabersat	Appears to cross the BBB. Potent anti-convulsant. No effect in acute treatment or in preventing migraine (Goadsby et al., 2009; Hauge et al., 2009; Cao and Zheng, 2014).	Suppresses CSD. Inhibits neurogenic inflammation and CSD-evoked NO release (Smith et al., 2000; Read et al., 2001). Connexin containing gap-junction and nonjunctional connexin-containing hemichannels inhibitor function effective in suppressing CSD (Durham and Garrett, 2009).
Sumatriptan	Relatively hydrophilic triptan. Does not appear to cross BBB – issue under debate (Tfelt-Hansen, 2010). Increased lipophilicity of newer triptans lowers doses with same AE.	Can produce "latent sensitization" and lower threshold for electrically induced CSD (Becerra et al., 2016).
Metoclopramide	Readily crosses the BBB (Peringer et al., 1976) and stimulates AVP release in man (Nomura et al., 1984) independent of osmotic, barometric or volumetric variations (Chiodera et al., 1986; Valiquette, 1987; Gupta, 1997). Can abort episodic migraine attacks (Gupta, 1997, 2019; Eken, 2015).	No known effect on CSD.
Domperidone	Does not readily cross the BBB or possess *in vivo* central dopaminergic activity (Baudry et al., 1979; Laudron and Leysen, 1979). Does not modify AVP levels. Can prevent migraine attack when taken early in the attack (Waelkens, 1982, 1984), an uncontrolled, unreplicated observation.	No known effect on CSD.

Glossary: AE – adverse effect; AVP – arginine-vasopressin; ASA – acetylsalicylic acid

migraine (Silberstein and Young, 1995; Yu and Horowitz, 2003), although verapamil is not known to affect CSD. Nifedipine, like verapamil, does not freely cross the intact BBB, but both drugs can abort migraine aura (Silberstein and Young, 1995; Hupp et al., 1989). Amyl nitrite (Schumacher and Wolff, 1941), isoproterenol (Kupersmith et al., 1979), and glyceryltrinitrate (GTN) are regarded as the best vasodilator drugs to abort migraine aura (Silberstein and Young, 1995) but are *not* known to influence experimental CSD. GTN does not cross the BBB but releases NO radicals that freely cross the BBB. While GTN can precipitate an early and a delayed atypical migraine headache without vomiting (Maniyar et al., 2014), it cannot provoke the SS in MwA patients (Christiansen et al., 1999; Afridi et al., 2004), and is unlikely to affect CSD.

The exclusive focus on brain theories of migraine genesis, including CSD, is not supported by the repeatedly confirmed migraine-preventing action of atenolol, nadolol, and verapamil discovered almost 3-4 decades ago, a feature that remains an enigma. Reduction of intraocular pressure (IOP) likely underlies the anti-migraine effect of beta-blockers and calcium-channel antagonists, a feature that cannot be discussed in detail in this article (Gupta, 2009a, 2019, 2023a, 2024).

Evidence-based guidelines include antidepressants for prevention of migraine.

(Hershey et al., 1999; Colombo et al., 2004; Silberstein et al., 2012; Hershey et al., 2013; Kalita et al., 2013; Hickman et al., 2015). Amitriptyline (AMT) is known to consistently

Citation: Gupta VK. Cortical Spreading Depression and Migraine: Critical Review of a Neurophysiological Principle in the Third Millennium. Glob J Medical Clin Case Rep. 2026:13(10):228-272. Available from: https://dx.doi.org/10.17352/gjmccr.000273

and cumulatively prevent migraine attacks in low doses in placebocontrolled trials (Gomersall and Stuart, 1973; Couch and Hassanein, 1979; Ziegler et al., 1993; Jackson et al., 2015; Silberstein, 2006, 2015). AMT enhances brain intrinsic serotonergic and noradrenergic neuronal activity and can rarely lead to seizure (Andermann et al., 1987, 1987a; Schacter, 1998; Mullins et al., 1999; Reichert et al., 2014). AMT, like cocaine and amphetamine, freely crosses the BBB and stimulates brain noradrenergic and serotonergic function by synaptic reuptake inhibition, as reviewed (Gupta, 2006b; 2006d). In higher doses and in combination with monoamine-oxidase inhibitors (MAOI), like clomipramine, AMT has the potential to cause the serotonin syndrome (Sternbach, 1991; Sporer, 1995; Gillman, 1999, 2010; Boyer and Shannon, 2005). *Development of the serotonin syndrome clearly establishes that AMT is a brain serotonergic agonist. For several decades, AMT has erroneously been regarded as a CNS serotonin antagonist in the migraine literature. The paradoxical combination of propranolol and AMT is also effective for the prevention of migraine attacks* (Ziegler et al., 1987; Ziegler et al., 1993). *Moreover, AMT releases arginine-vasopressin (AVP), the latter, in conjunction with increased migraine attack-related bioavailability of serotonin and noradrenaline within and outside the CNS, possibly maintains ocular vascular integrity, antinociception, and behavior control during early "pre-prodromal" or "pre-premonitory" and prodromal phases of vasodilatory antidromic V 1 nerve discharges* (Gupta, 1997, 2023a, 2024, 2025). *This "adaptive" or "protective" system likely keeps the migraine attack at bay for a limited but variable period of time (post-stress headache) in migraineurs, and, while "stress" is ubiquitous, it possibly offers unlimited neuroendocrine "protection" to the approximately 80% of the general population that does not suffer recurrent migraine attacks – one of the greatest mysteries of migraine* (Gupta, 2024; 2025). *There is no link between this human intrinsic and/or extrinsic eye/brain neuroendocrine adaptive "system" and experimental CSD in lower animals.*

While topiramate at 30 mg kg–1 was able to inhibit both regional CBF changes and cortical depolarization in all rats and in 8 of 13 cats (Akerman and Goadsby, 2005), the drug suppresses migraine aura variably (Lampl et al., 2004; Silberstein et al., 2006; Karadas et al., 2014) or completely (Wolthausen et al., 2009).

Nevertheless, in one study, topiramate was at least as effective as AMT in terms of reducing the rate of mean monthly migraine headache episodes and all prespecified secondary efficacy endpoints (Dodick et al., 2009). In yet another study, topiramate appeared to reduce migraine auras in parallel with headache reductions (Reuter et al., 2010). A recent meta-analysis of placebo-controlled studies also demonstrated that topiramate in a 100 mg/day dosage is effective in reducing headache frequency and is reasonably well-tolerated in adult patients with episodic migraine (Linde et al., 2013a). *Meta-analysis, however, risks drawing the clinician away from clinical reality, clinical judgment, and clinical commonsense* (Horton and Kendall, 1991; Feinstein, 1994). A dose-response association has not been found with use of topiramate in migraine; a dose of 200 mg does not appear to be more effective than 100 mg (Linde et al., 2013a). *Topiramate is a classic example of the difficulty of replicating results in migraineurs and of the variable therapeutic dose paradigm even in the same patient from time to time.*

Lamotrigine, which is selectively effective on the migraine aura but not on the headache, had a suppressive effect on CSD of 37% and 60% at posterior (parieto-occipital) and anterior (frontal) electrodes, respectively, as well as on frontal Fos expression (Bogdanov et al., 2011). Valproate, which has a non-selective effect on both migraine aura and headache, had no effect on posterior CSDs but reduced anterior ones by 32%, slowed propagation velocity, and decreased frontal Fos expression (Bogdanov et al., 2011). Riboflavin also has a non-selective, unpredictable, non-dose-responsive effect in migraine prophylaxis (Schoenen et al., 1998; Colombo et al., 2014; Shaik and Gan, 2015; Namazi et al., 2015) but did not suppress CSD or its propagation (Bogdanov et al., 2011). Valproate and riboflavin have no known effect on the triggering of CSD, although they are seemingly effective in preventing MwoA (see above, Table 2). *These studies highlight the unexpected, unpatterned, differential, inconsistent, irreplicable, and irreconcilable differences between animal experimental CSD results and human pharmacologic evidence.*

Pregabalin is effective in increasing the threshold for CSD in wild-type mice, in slowing the propagation velocity of CSD in familial hemiplegic migraine (FHM)-1 mutant mice, and in preventing CSD subcortical propagation associated with the milder R192Q FHM-1 mutation (Cain et al., 2017). Early reports on the preventive use of pregabalin in migraine are encouraging (Calandre et al., 2010; Pizzolato et al., 2011; Bakhshandeh Bali et al., 2015). In routine clinically efficacious oral doses, chronic administration of pregabalin inhibits measures of central sensitization in the electrical hyperalgesia model in human volunteers (Chizh et al., 2007). Central sensitization is a key in the development and maintenance of chronic pain, particularly neuropathic pain, such as postherpetic neuralgia (Dworkin et al., 2003) and painful diabetic peripheral neuropathy (Didangelos et al., 2014). The pain of migraine, however, is not neuropathic in nature. The precise mechanism(s) of the anti-migraine effect of pregabalin remain unknown.

Acetylsalicylic acid (ASA) prevents migraine attacks, the effects being small, statistically insignificant, not dose-dependent, and variable (Benseñor et al., 2001). In other studies, ASA reduced the attack frequency of migraine to below 50% in relatively large doses (500 mg t.i.d.), the effect being comparable to metoprolol (200 mg daily) (Grotemeyer et al., 1990) or propranolol (O'Neill and Mann, 1978; Baldrati et al., 1983; Savi et al., 2013). ASA (1000 mg) is an effective treatment for acute migraine headaches (Kirthi et al., 2013). In a retrospective study, Anoaica et al., (2014) found ASA to be particularly useful for acute attacks of headache in MwA patients. Both cyclooxygenase-1 and -2 isoenzymes are expressed in peripheral tissues and the CNS. Although a solely peripheral mechanism of action was suggested for several years, various studies have suggested an additional central effect of ASA on the CNS, including pain processing structures (Ferreira et al., 1978; Maihöfner et al., 2007; Kröger and May, 2014).

Citation: Gupta VK. Cortical Spreading Depression and Migraine: Critical Review of a Neurophysiological Principle in the Third Millennium. Glob J Medical Clin Case Rep. 2026:13(10):228-272. Available from: https://dx.doi.org/10.17352/gjmccr.000273

Flunarizine, a Ca++ antagonist (see Table 2), appears to parallel topiramate.

(Kim et al., 2013) and propranolol (Verspeelt et al., 1996) in the prevention of migraine attacks. Following oral administration, flunarizine shows a rise in plasma concentration, reaching the steady state in five weeks. Drowsiness, weight gain, depression (Veerspeelt et al., 1996), and a Parkinsonian syndrome are the most important side effects (Martinez-Lage, 1988; Centonze et al., 1990), none of which can be related to CSD in lower experimental animals.

In summary, BBB penetration and modulation of CSD by migraine preventive drugs is non-uniform, essential, non-dose dependent, and controversial. Drugs that do not cross the BBB significantly have as good migraine preventive action as do drugs that readily cross the BBB. Modulation or abolition of presumed CSD is not an essential prerequisite to prevent MwA or MwoA. The primary site of pathophysiologic aberration in migraine appears to lie outside of the brain / CNS (Gupta, 2023a, 2024, 2025).

CSD, brain cortical excitability, epilepsy, transcranial magnetic stimulation, glyceryl dinitrate, depression, sleep, and anxiety

Central neuronal hyperexcitability (CNH) is regarded as an essential association or precursor / prelude to the presumed spontaneously-generating *idiopathic or de novo* CSD-migraine algorithm (Welch et al. 1990). How or why such CNH should be triggered periodically and result in lateralizing headache as well as non-homonymous SS (see below) in the first place remains unknown.

The link between migraine and epilepsy began with the descriptions of Hughlings Jackson (1834-1911) and later Gowers (Pearce, 1986). The "self-cycling" nature of epilepsy / CNH appeared as the most appropriate model for the CSD-migraine nexus. Childhood epilepsy and migraine are two of the most common conditions seen individually in pediatric neurology and separating the two is not always easy (Oakley and Kossoff, 2014). Despite major phenotypic differences between migraine and epilepsy, the epidemiological bidirectional link in children is overemphasized, especially in those with benign partial epilepsies with occipital paroxysms (Bauer et al., 2013; Oakley and Kossoff, 2014). When either migraine or epilepsy is present in an individual, the other is more likely to be present (Haut et al., 2006; Kelley et al., 2012; Winawer et al., 2013), the reasons for which might vary from a shared genetic susceptibility to "stress" to a shared high commonality in the community. Several clinical observations circumstantially relate migraine to epilepsy, including the following: (i) electroencephalographic (EEG) abnormalities occur in migraineurs who have not had seizures; (ii) patients can have a seizure following onset of migraine; (iii) both conditions may be preceded by an aura, and (iv) anticonvulsants can be effective in both conditions (Andermann, 1987, 1987a; Ottman and Lipton, 1994; Oakley and Kossoff, 2014). Many patients may have both epilepsy and migraine simultaneously (Oakley and Kossoff, 2014). Triggers common to both migraine and epilepsy include sleep deprivation and stress (Neut et al., 2012; Balamurugan et al., 2013). Differentiation between migraine and epilepsy becomes more difficult in individuals whose seizures present with headache or when there is an atypical clinical presentation suggestive of both disorders (Peatfield and Rose, 1981; Gelfand et al., 2013; Bauer et al., 2013; Oakley and Kossoff, 2014). A detailed consideration of the complex and controversial relation between migraine and epilepsy is beyond the scope of this review article. Focal aberrant brain neuronal activation with or without partial or diffuse spread underlies seizure disorder. Migraine headache attacks are, remarkably, generated over a much-slower time framework than epilepsy (hours versus seconds and minutes, respectively). Even the rate of propagation of migrainous SS (discussed below) is at least a hundred times slower, in general, as compared with other neurogenic vascular/neuronal phenomena (Blau, 1992a). The ICHD-II (International Classification of Headache Disorders – II edition--2004) defines "migralepsy", "hemicrania epileptic", and "postictal headache" (Olesen, 2004), while the International League against Epilepsy (ILAE) does not include headache at all (Berg et al., 2010). Key phenomenological and therapeutic differences, nevertheless, exist between epilepsy and migraine (Table 3).

An *idiopathic*, self-generating CNH / hyperresponsiveness of trigeminal neurons is regarded as a pivotal physiological possibility underlying pathogenesis of migraine (Welch et al., 1990, 2005; Aurora et al., 1999; Aurora and Wilkinson 2007; De Simone et al., 2007; Akerman and Goadsby, 2005). Instantaneous but variable responses to therapeutic transcranial magnetic stimulation (tTMS) applied during the aura or headache phase may reflect abnormal impulse activity in cortical pyramidal neurons (outer layers II and III of the cerebral cortex) of migraine patients in the form of a spreading fast oscillatory neuronal activity rather than CSD (Brighina et al. 2004; Fisher, 2004; O'Reardon et al., 2007; McComas and Upton, 2015). It is essential to establish the physiological process(es) that initiate as well as terminate(s) the putative or presumed CNH / trigeminal V1 neuronal hyperresponsiveness. *Moreover, the striking and lateralizing confinement of pain of migraine headache to the trigeminal V1 and/or nuchal region cannot be explained by diffuse CNH or holotrigeminal neuronal hyperresponsiveness* (Gupta, 2024). Finally, while the site of therapeutic transcranial magnetic stimulation (tTMS) is distant from the proposed site of origin of headache (somatosensory area), in a severely affected patient the optimal site for tTMS may move and the "therapy" may eventually lose its efficacy (McComas and Upton, 2015).

Glycerol trinitrate (GTN) precipitates delayed-onset (1.5-6 hours after i.v. administration) migraine-like attacks (Thomsen et al., 1994; Schoonman et al., 2008). *GTN is a nitric oxide (NO) donor, which easily crosses the BBB. GTN (or NO) remarkably, does not generate SS in MwA patients*. Conversely, GTN (0.5 mg sublingually) is the best known treatment to manage SS (Silberstein and Young, 1995).

Additionally, peripheral fronto-temporal scalp application of GTN ointment precipitates fronto-temporal lateralizing migraine attacks, a peripheral feature inexplicable with CNH or CSD or diffuse

Citation: Gupta VK. Cortical Spreading Depression and Migraine: Critical Review of a Neurophysiological Principle in the Third Millennium. Glob J Medical Clin Case Rep. 2026:13(10):228-272. Available from: https://dx.doi.org/10.17352/gjmccr.000273

Table 3: Key Clinical Differences between Epilepsy and Migraine

	Epilepsy	Migraine
Onset	Typically sudden, recurrent, stereotyped attacks (Gelfand et al., 2013; Bauer et al., 2013).	Insidious or subtle in origin; onset cannot be pinpointed in time; also, build-up of headache is generally slow; attacks are protean and "visceral" in nature (Campbell, 1990; Blau, 1992a). Even SS, the shortest component of migraine attacks and its propagation, is about 100 times slower than most neuronal or neurovascular phenomenon (Blau, 1992a).
Stress (Perceived or Subliminal)	Significant contribution of psychodynamic stress and posttraumatic stress disorder (PTSD) (Pepi, et al., 2024; Jhaveri et al., 2023)	Prominent relation to stress and to post-stress circumstances, including post-alcohol consumption, post-GTN challenge (Graham, 1953; Campbell, 1990; Blau, 1992a; TfeltHansen and Tfelt-Hansen, 2009).
Defervescence	Sharp, well-defined (Oakley and Kossoff, 2014)	Poorly defined (Campbell, 1990; Blau, 1992a).
Time framework	Evolves over seconds or minutes (Oakley and Kossoff, 2014)	Evolves over hours and/or days. (Campbell, 1990; Blau, 1992a)
Incidence	More common in infancy and toddlers (Theodore et al., 2006).	More common in school age-children, adolescents, and adults (Theodore et al., 2006).
Prevalence	Not gender specific; slight predominance in boys (0.1-0.2% higher as compared to girls) (Oakley and Kossoff, 2014)	Female predominance, including pediatric population; prevalence rises with age to match and predominate female adult levels (AbuArafeh and Russel, 1994; Sillanpää, 1976; Oakley and Kossoff, 2014; Porreca et al., 2025).
Cognition	Commonly impaired to a variable degree (Bauer et al., 2013; Oakley and Kossoff, 2014).	Rare instances of difficulty with abstract thinking, disorientation, or confusion leading to bizarre disturbances of behavior, especially in children and teenagers (Campbell, 1990).
Remissions & Exacerbations	No well-defined or predictable pattern (Oakley and Kossof, 2014).	Well-defined and predictable pattern (Campbell, 1990).
Pain	Post-ictal non-lateralising headache (35%) and migraine (21%) specifically associated with seizures (Kanemura et al. 2013).	Typically lateralising (unilateral, bilateral, sideshifting, or side-locked) head pain (mild to severe) is the defining primary manifestation, barring atypical presentations (Campbell, 1990; Blau, 1992a).
Vomiting	Rare feature. Present with insular cortical seizure, Lennox-Gastaut and Panayiotopoulous syndromes (Gastaut 1982; Covanis, 2006; Panayiotopoulos et al. 2008; Asadi-Pooya, 2018).	Very common and diagnostic feature. Also relieves migraine headache frequently (Campbell, 1990). Childhood migraine precursors, cyclical vomiting syndrome and benign paroxysmal vertigo may mimic epilepsy but have normal EEG (Panayiotopoulos, 1999; Oakley and Kossoff, 2014).
Loss of Consciousness	Invariable with grand mal tonic-clonic epilepsy; cardiac asystole in complex partial temporal epilepsy (Rubboli et al., 2008; Beal et al., 2011; Kishk et al., 2018). Can fall suddenly or attacks occur during sleep (Rubboli et al, 2008; Oakley and Kossof, 2014).	Orthostatic hypotension; vasovagal syncope with quick recovery after attaining supine position. Always during standing or in upright position; always falls suddenly. Never occurs in sleep (Piovesan et al. 2008; Paisley et al. 2009; Vallejo et al. 2014).
Puberty	May resolve spontaneously around puberty, especially for absence and benign rolandic epilepsy (Sillanpää, et al., 2012; Oakley and Kossoff, 2014).	Tend to worsen with puberty, especially in adolescent girls; post-pubescent young women account for nearly 75% of new migraine patients (Abu-Arafeh et al., 2010; Hershey, 2012; Sillanpää, 1976; Oakley and Kossoff, 2014).
Anti-epileptic agents	Well-defined hallmark role in therapy (Oakley and Kossoff, 2014).	Uncertain consensus as preventive agents. Uncertain differential role between MwA and MwoA (discussed above).
Beta-blockers	No role in therapy.	Well-established role in preventive therapy (discussed above).
Tricyclic-antidepressants	Can precipitate seizures (see above).	Well-established role in preventive therapy, alone or in combination with beta-blockers (discussed above).
Triptans	No role in therapy.	Well-established role in acute/abortive therapy (discussed above).
EEG	Abnormality is hallmark of epilepsy or seizure focus (Bauer et al., 2013;	Incidental abnormalities of EEG, including excessive photic driving, focal slowing,
	Olmez et al., 2006; Chopra et al., 2011).	unrelated epileptiform discharges (Gronseth and Greenberg, 1995).
Premature death and Sudden Unexpected Death (SUD)	Incidence of SUD in children similar to adults (Keller et al., 2018). Well-established increased intrinsic rate of death, possibly due to comorbidities (Holst et al., 2013). Theoretical link of SUD to epilepsy through spreading depression (Cozzolino et al., 2018). Ictal bradycardia / ictal asystole may lead to SUD in epilepsy unconnected to CSD (Hirsh and Hauser, 2004; Bergen, 2005).	Unknown in children. Rare in adults except with arrhythmias (Monroe et al., 2015). SUD is practically unknown (Cozzolino et al., 2018).
Longevity or evolutionary advantage	Not proposed.	Proposed (Blau, 1992 a, b, c; Loder, 2002; Devineni, 2005; Buzzi et al., 2005; Friedman and De ver Dye 2009). Lower all-cause mortality rate amongst more than 23 million individuals, in both patients with status migrainosus and those without status migrainosus (Harnod et al., 2018).
ANS features (conjunctival injection, lacrimation, forehead and facial sweating/flushing, miosis or ptosis or both, hypotension, heart-rate and respiratory-rate variability, tachycardia)	No ANS features.	Prominent cranial ANS features in pediatric/adolescent migraineurs almost as a rule (Gelfand et al. 2013). Frequent in adult migraineurs (27-73%) (Barbanti et al. 2002; Obermann et al. 2007b; Gupta and Bhatia, 2007; Shecter, et al., 2002).

Glossary: SUD – sudden unexpected death; PTSD – post=traumatic stress disorder; GTN-glyceryl trinitrate.

Citation: Gupta VK. Cortical Spreading Depression and Migraine: Critical Review of a Neurophysiological Principle in the Third Millennium. Glob J Medical Clin Case Rep. 2026:13(10):228-272. Available from: https://dx.doi.org/10.17352/gjmccr.000273

trigeminal neuronal hyperresponsiveness. (Bonuso et al., 1989) This experiment underscores the importance of the extracranial fronto-temporal region in genesis of migraine (Bonuso et al., 1989), an importance that is as yet undeciphered but is clearly unlinked to CSD. *While NO does not itself generate CSD, brain tissue NO is increased by CSD; NO is essential for recovery of ionic homeostasis following CSD* (Read et al., 1997; Obrenovitch et al., 2002).

Migraine is comorbid with depression, anxiety, somatic amplification, perceived stress and sleep disorders, and deficiency in problem solving, which observational relationships could be bidirectional (Yavuz et al., 2013; Eskin et al., 2013; Dikmen et al., 2015; Baldacci et al., 2015). A brain cortical hyperactivity has been suggested to underlie the complex neurolimbic dysfunction seen in these comorbid disorders (Baldacci et al., 2015). There is no known parallel or link between CSD in experimental animals and depression, anxiety, or stress generated in humans. The neurocircuitry between migraine and its comorbid neuropsychiatric associations remains unknown (Minen et al., 2016). Sleep can trigger as well as alleviate migraine headache, lending no further clarity to the underlying mechanisms in the current theoretical framework (Bigal and Hargreaves, 2013; Kelman and Rains, 2005). *Regardless of the stage of sleep, AVP is released and can abort migraine headache* (Gupta, 2024). A fuller synthesis of these factors is beyond the scope of this review.

CSD / SD or CNH or trigeminal neuronal hyperresponsiveness have not been linked to the often-lateralizing autonomic nervous system (ANS) dysfunction known to prevail in migraine since approximately 150 years (Hsu et al., 1977; Havanka-Kanniainen et al., 1988; Peroutka, 2004) (discussed further below).

In summary, none of the elaborations of this section clarify the link between migraine and CSD. The extracranial fronto-temporal scalp region appears to have a definitive pathophysiologic significance that needs further elucidation.

CSD, Migraine, Stress, ANS, Adaptation, Stroke

Sudden Death, and Evolution: "Stress" is a ubiquitous clinical influence. While far from fully comprehending the subject and its link to "stress", we have been enabled to visualize its general landscape (Chrousos and Gold, 1995). What was intuitive and remote for many generations of physicians and thinkers, including Hippocrates, Galen, Aristotle,

Sydenham, Bernard, Cannon, and Selye, can now begun to be rationally understood (Goldstein and Kopin, 2007). *The ANS is central to adaptation. Different stressors elicit different patterns of activations of adaptive systems, the outcome of one of such incredibly complex systems concept of ANS adaptation being migraine.*

"Stress is life and life is stress" – *Hans Selye's* words could easily be paraphrased for migraine sufferers – "Stress is migraine and migraine is stress". "Stress" fully pervades our life and influences us as individuals, communities, and humanity. Presently, "stress" serves in migraine, as it does in other medical fields, to confuse and confound rational thought as a "learned" euphemism for scientific ignorance (Charlton, 1992; Chrousos and Gold, 1995; Gupta 2004e, 2004f; 2019; 2024). "Stress" or "tension" and its defervescence (post-stress period) is one of the most commonly cited causes of migraine, and up to two-thirds of migraineurs experience "stress" and its aftermath (Spierings et al., 2014; Kurlander et al., 2014; Lipton et al., 2014; Peroutka, 2014; Goadsby, 2014; Pellegrino et al., 2018). *Whatever cannot be understood in medicine, is attributed to "stress" or "stressors", as if the underlying pathophysiological mechanism thus becomes apparent or that a fundamentally biological or a major therapeutic advance has been attained* (Gupta, 2019; 2024). "Stress" has, however, never been linked to CSD, but migraineurs do indicate a failure to maintain the "milieu intérieur" (Claude Bernard), "homeostasis" or failure of the "fight or flight" response (Cannon) (Goldstein and Kopin, 2007). *The need for near-constant adjustments to maintain physiological, behavioral, cognitive and emotional homeostasis in migraineurs is important.* (Noseda et al., 2014).

Graham (1953) underscored that migraine patients manifest an "undue tendency to seek "stress" and at the same time a deficiency in physiological adaptation to "stress". Graham (1953) also alluded to a mechanistic basis for the self-limited nature of migraine attacks (4-72 hours); he proposed that "they (the migraine attacks) are terminated…when the stress of the attack itself finally stimulates the patient's own adaptation machinery into proper action…". *Graham spoke presciently of "bodily economy", a phrase that can today be interpreted in terms of exhaustion of the entrained physiologic processes, in particular, the proposed vasopressin-serotonin-noradrenaline "system / nexus" and / or ANS as a "limited, variably exhaustible biologic commodity in a large segment of the general population afflicted with migraine attacks"* (Gupta, 2009a, 2019, 2024). *Most importantly*, Graham (1953) *found that migraine attacks were triggered in 75% of patients after the stress / emotion had resolved, a "precipitation-by-exhaustion"* (Gupta, 2009a, 2009b, 2017a, 2024). *A slow, steady draining of physical and psychical energy that could better be termed today as "ANS exhaustion or depletion", appears central to the genesis of episodic post-stress migraine attacks.* A "protective" or "evolutionary defense" or "warning" advantageous role for stress/stressors for a psychosocially-critical but limited-period in migraineurs could thus be postulated (Blau, 1992a, 1992b, 1992c; Loder, 2002; Devineni, 2005; Buzzi et al., 2005), through "physico-psychical collapse" or "enforced rest", including "sleep" or a periodic "upgrading" of the proposed "brain intrinsic vasopressin-serotonergicnoradrenergic" adaptive "system" (Gupta, 2009a, 2017a, 2019, 2024).

Importantly, while fear- or anxiety-related emotional stress may actively *suppress* AVP secretion, sleep *stimulates* AVP release, as reviewed (Gupta,1997). Sleep enhances AVP secretion regardless of EEG sleep stage, remarkably at a time when redistribution of the blood volume from the extremities to the central vessels would otherwise suppress AVP secretion (Valiquette, 1987). AVP effects dose-related moderate to substantial reductions in rapid-eye-movement (REM) sleep, which effects were primary and not mediated by changes in cortisol or blood pressure(Born et al., 1992). *The relationship*

Citation: Gupta VK. Cortical Spreading Depression and Migraine: Critical Review of a Neurophysiological Principle in the Third Millennium. Glob J Medical Clin Case Rep. 2026:13(10):228-272. Available from: https://dx.doi.org/10.17352/gjmccr.000273

between sleep and headache has been known for over a hundred years. Migraine seems to occur in association with REM sleep, and in association with excessive Stage III, IV and REM sleep stages, an association seemingly directly related to the sleep state rather than to circadian rhythmicity (Sahota and Dexter, 1990). Also, preponderance of migraine in women could reflect their need for greater *biological* fitness (Friedman and De ver Dye, 2009). Early and frequent exposure to "visceral" pain of migraine in childhood and adolescence could also prepare females evolutionarily for the most severe "visceral" pain of unassisted cervical/vulval dilatation during parturition, the most vital futuristic adaptive function to the preservation of humans since antiquity.

Migraine could also promote survival (Blau, 1991a, 1992b, 1992c). Normotensive migraineurs maintain a relatively low blood pressure, particularly the diastolic value, before or very early, during, and after migraine attacks (Seçil et al., 2010). Aortic distensibility and aortic stiffness (beta index) were significantly impaired in patients with migraine compared to control subjects (Akturk et al., 2014), indicating a central component to peripheral BP measurements in migraine that limits *antigravity* cranial blood flow. Epidemiological evidence of an inverse relationship between systolic and diastolic blood pressure as well as pulse pressure in a headache-free population at baseline and subsequent development of both migraine and tension-type headache 11 years later has been presented (Fagernæs et al. 2015), in effect confirming that migraine is associated with low blood pressure and low pulse pressure. Migraine patients have fewer than expected cerebrovascular and cardiovascular disease events and fewer electrocardiographic abnormalities (Featherstone, 1986; Waters et al., 1983); an inconsistent statistically heterogeneous outlook expectedly prevails in this comorbidity (Mahmoud et al., 2018). Sudden unexpected death (SUD) in adult migraineurs is rare -- except with arrhythmias (Monroe et al., 2015) -- to practically unknown (Cozzolino et al., 2018) (discussed above). Comorbid depression, fibromyalgia, and severe pain are associated with a high suicide risk. (Breslau et al. 2012; Kim and Park, 2014; Liu et al., 2015) Migraine-associated suicide is not reported in populations where medical needs are comprehensively covered by the Government, such as Taiwan (Harnod et al., 2018). Additionally, the risk of all-cause mortality was not significantly higher in migraineurs (Mahmoud et al., 2018). Finally, the link to ischemic or hemorrhagic stroke is devoid of any defensible mechanistic link to CSD. (Gupta, 2017d, 2024).

The migraineur with frequent attacks remains in a near-constant state of unstable homeostasis or overt/subliminal perception of stress, while the migraine attack reflects an intermittent total failure of homeostasis or adaptive mechanisms. The biology of any disease, including migraine, is the integrated composite of pathogenetic, adaptive, and epiphenomenal features (Gupta 2009a, 2009b, 2017d,2019; 2024). The hyper-focus on biologic "markers" detected in the laboratory over the last several decades has distorted the meaning of the term "biological" in migraine research. The term "biological" is not synonymous with "physiological", "organic", "laboratory" or "non-environmental" (van Pragg et al., 1979). "*Good medicine is indivisible...(has) always (seen) the patient balanced between opposing forces pushing him towards health or disease...*" (Wall and Melzack, 1989). *The concatenation of physiological forces that envelops the migraine patient is not a nihilistic, hopelessly complex obfuscation but a well-orchestrated, intricate combination of opposing influences pushing or pulling the patient towards or away from migraine attacks* (Gupta, 2019, 2024).

Adaptive forces are always generated by the organism itself (Carrel, 1959). Migraine may reflect an evolutionary human ability or "readiness" to always identify and to adapt to a changing environment, albeit with varying success, frequently negative consequences, and comorbidity. Migraine may also be a dynamic psychophysical fulcrum or equilibrium to allow subliminal stress to surface -- an evolutionary "alarm". *Migraine, like life itself, is a high-order dynamic equilibrium that preserves and prepares the patient against many (but not all) odds and offers alarm "systems", enforced rest, and now medications to restore equilibrium. The neuroendocrine adaptive system evolved in migraineurs likely involves a parallel activation of the CNS / extra-CNS "vasopressinergic-serotonergic-noradrenergic" nexus* (Gupta 1997, 2009a). Like all homeostatic systems, however, the adaptive mechanism evolved in migraine has both limitations as well as a distinct biological cost (Gupta, 2024). There appears to be no link between a pathogenetic role for CSD in migraine and this putative adaptive system.

A significant delay (running upto several hours or few days) in onset of migraine attacks, occurs in the following clinical circumstances: (i) stress, exercise or consumption of alcohol (Blau, 1992a); ingestion of tyramine-containing foods, involving a delay of upto 22 hours (Poole, 1986); cocaine abuse or abstinence (Satel and Gawin 1989; Dhuna et al., 1991); caffeine withdrawal over the weekend (Couturier et al., 1992); GTN ingestion or infusion (Thomsen et al., 1994); and, exposure to m-chlorophenylpiperazine (Brewerton et al., 1988). Primary headache associated with catastrophic psychological (non-physical) trauma (Shulman, 1991) or physical trauma (Haas et al., 2004) is similarly associated with a significant delay in onset of migraine (Gupta 2009a, 2009b). In the last 24 hours before headache onset, hypothalamic activity, as seen by MRI as a response to trigeminal nociceptive activity, is altered and increases towards the next migraine attack (Schulte and May, 2016b). Intriguingly, such hypothalamic activity (Maniyar et al., 2014; Schulte et al., 2017) is neither *primary* (Gupta, 2006c) nor *lateralizing* (Gupta, 2004a, 2009a, 2019).

Significant delay in onset of migraine headache encompasses the proposed subliminal "pre-prodromal / pre-premonitory" phase as well as the covert/overt prodromal/premonitory phase of migraine and is entirely analogous to the period after an "acute injury" -- as outlined by Wall and Melzack (1989) -- during which the migraine patient remains largely or completely unaware of the threat of impending painful cephalic disturbance and continues to function appropriately (Gupta 2009a, 2017a, 2019, 2024, 2025). During this "pre-attack" period, a host of linked adaptive physiological features are activated and operate efficiently to keep the pre-attack ("pre-prodromal" / "pre-premonitory") phase, or prodrome, or aura, or headache,

Citation: Gupta VK. Cortical Spreading Depression and Migraine: Critical Review of a Neurophysiological Principle in the Third Millennium. Glob J Medical Clin Case Rep. 2026:13(10):228-272. Available from: https://dx.doi.org/10.17352/gjmccr.000273

or any combination thereof at bay (Gupta, 2019; 2024; 2025). The physiological system(s) *primarily* affected in migraine, therefore, must necessarily be afforded a considerable (but limited and exhaustible) degree of protection by homeostatic defense mechanisms, thereby allowing the subject to continue to function for some considerable time despite exposure to the headache-provoking stimulus or clinical situation. This protection is apparently unlimited or inexhaustible in the majority of the general population who are not susceptible to migraine headaches but are practically exposed to similar stressful situations. Such "adaptive" or "protective" function is liable to fatigue variably both in different migraine patients as well as in the same migraine patient on different occasions. *Onset of primary migraine headache attacks, therefore, likely represents periodic "overwhelming" or "fatigue" of this adaptive "system"* (Gupta, 2024; 2025).

The adaptive role of CSD as a protective biological strategy in the form of vascular preconditioning and consequent delayed intracellular neuronal protection is emerging (Gupta 2005a, 2017a, 2024; Kobayashi et al., 1995; Matsushima et al., 1996; Shen et al., 2016). CSD effects the expression of several potentially neuroprotective genes and induces subsequent or secondary tolerance to permanent focal ischemia in rat brain (Kawahara et al., 1995; Matsushima and Hakim, 1995; Yanamoto et al., 2000; Yanamoto et al., 2004; Yanamoto et al., 2005; Otori et al., 2003). Uncoupling protein 5 (UP-5) is triggered by CSD in rats after 24 hours in the ipsilateral cortex in all cortical strata, suggesting that CSD-stimulated UC-5 can have a neuroprotective effect at this time (Viggiano et al., 2016).

Under conditions of anoxia or high-temperature stress many insects enter a reversible coma, which is protective, a temporary shutdown of neuromuscular systems that prevents irreversible consequences of complete energy loss (Rodgers et al., 2010). SD can be induced in the CNS of the invertebrate, African *Locusta migratoria*, to evoke stress-induced coma as a protective strategy in response to anoxic and other extreme environmental conditions (high ambient temperature, flash floods, and monsoons in their natural habitat) with a silencing of the activity of the nervous and muscular systems until the stress is removed (Rodgers et al., 2010). During stress-induced coma, SD-like events occur in the locust metathoracic ganglion (MTG) that closely resemble CSD in many respects, including mechanisms of induction, extracellular potassium ion changes, and propagation in mammalian grey matter. These locust SD-like events conserve energy and prevent cellular damage (Rodgers et al., 2010). Such coma is associated with dramatic surges of extracellular K^+ and temporary electric silence in the CNS, remarkably bearing all the hallmarks of SD in the vertebrate CNS grey matter. In the locust thoracic nervous system, the SD process can be studied in preparations that have an intact neuronal architecture allowing the simultaneous investigation of cellular and subcellular neuronal responses without anesthetic. After return to normoxia, locusts completely recover from up to at least 6 hours of anoxia-induced coma (Wu et al., 2002; Armstrong et al., 2009). SD was first proposed to occur in insects in the cockroach approximately 50 years ago. (Rounds, 1967).

Neuroimaging "correlates" of Cortical Spreading

Depression in humans: Due to the protean nature of migraine as well as the short duration of the migraine aura, neuroimaging during spontaneous or triggered attacks has proved difficult (Denuelle et al., 2008). Some scientists regard neuroimaging as an exciting development that has provided unprecedented insights and significantly enhanced understanding of migraine as a CNS disorder (Schwedt and Dodick 2009; May, 2013; Lakhan et al., 2013; Schulte and May, 2016a). Descriptions of brain regions and networks that are atypical between migraine attacks are believed to have helped identify the neuroanatomical basis for migraine symptomatology and to bridge the wide gaps between neurophysiological studies and clinical findings (May, 2013; Schwedt and Chong, 2015). It is also firmly believed that functional imaging has confirmed the importance of CSD as the underlying pathophysiological mechanism of migraine aura in human beings (Bogdanov et al., 2011; Lauritzen and Strong, 2017). Mechanisms involved in the transformation of migraine from an episodic disorder to one with near-continuous symptomatology are also believed to have been unveiled through advanced neuroimaging (Maniyar and Goadsby, 2013). Additionally, brain neuroimaging has stoked the hope that novel diagnostic and therapeutic interventions would emerge through further pursuit of CSD (Ayata et al. 2006; Ayata, 2009, 2010; Tedeschi et al., 2012; Costa et al., 2013).

A profound confusion, however, still prevails between CSD-related CBF patterns in experimental animals and altered CBF patterns in humans (Gupta 2009a, 2009b; Charles and Baca, 2013; Borgdorff, 2018). Issues of the basis of "self-cycling", onset and offset of CBF alterations, and other key limitations (see above) critically limit the pathophysiologic validity of the CSD-linked neurovascular theory of migraine (Edmeads, 1991; Blau, 1992a; Gupta, 2009a). Next, the true beginning of a migraine attack remains preclinical and inaccessible to investigators (Friedman, 1985; May, 2013). Moreover, the symptoms and signs of migraine develop at least a hundred times slower than those seen in brain attacks of vascular or epileptic origin (Blau, 1992a) (discussed above). Finally, the notion of clinically "silent aura" for MwoA patients (Moskowitz, 2008) is simply an assumption (Charles and Baca, 2013; Gupta, 2009a).

Localized decrease in cerebral blood flow (CBF) that appeared to spread contiguously along the cerebral cortex was observed in MwA patients (Olesen et al., 1981). This pattern of "spreading oligemia" was confirmed in subsequent studies (Olesen et al., 1982; Lauritzen et al., 1983; Olesen et al., 1990). The "spreading hypoperfusion" in CBF was also seen in MwoA (Gelmers, 1982; Woods et al., 1994).

Whereas an aberrant *hyperemia-oligemia* CBF pattern has been linked to CSD (Leão, 1944b; Lauritzen, 1994), the converse *oligemia-hyperemia* pattern prevails during migraine attacks (Lauritzen and Olesen, 1984; Olsen et al., 1987; Kobari et al., 1989; Olesen et al., 1990). Artifacts related to Compton's scatter (Olsen et al., 1993) and CBF changes induced by carotid artery puncture and catheterization complicated interpretation of such studies. Other studies also demonstrated

Citation: Gupta VK. Cortical Spreading Depression and Migraine: Critical Review of a Neurophysiological Principle in the Third Millennium. Glob J Medical Clin Case Rep. 2026:13(10):228-272. Available from: https://dx.doi.org/10.17352/gjmccr.000273

a noncritical (<25%) oligemia-hyperemia pattern in MwA patients (Andersen et al., 1988; La Spina et al., 1997; Soriani et al., 1997; Sanchez del Rio et al., 1999) and in MwoA patients (Deneulle et al., 2008). In a human model of sildenafil-induced migraine, blood flow velocity in the middle cerebral artery (MCA) as recorded by transcranial Doppler ultrasonography and regional CBF in the territory of the MCA measured using SPECT and xenon-133 inhalation remained unchanged (Kruuse et al., 2003). In these studies in humans, the degree of cerebral oligemia was relatively small and not critical (i.e., not >75%) to affect occipital neuronal function negatively (Gupta, 2009a, 2019). Painful stimulation can itself, on the other hand, induce a robust (22.8%) statistically reliable decrease in global CBF, possibly involving sympathetic nervous system activation (Coghill et al., 1998). It is, therefore, unclear whether the oligemia seen in migraine patients was associated with pain or was a manifestation of CSD (Schwedt and Dodick, 2009).

Cutrer and colleagues studied cerebral hypoperfusion in patients with migraine aura using perfusion- and diffusion-weighted MRI (Cutrer et al., 1998). Decreases in CBF (16-53%) and cerebral blood volume (6-33%) and an increase in tissue mean transit time (10-54%) were seen in the grey matter of the occipital lobe contralateral to the affected visual hemifield (Cutrer et al., 1998). No changes in the apparent diffusion coefficient were observed either while the patients were symptomatic or after resolution of the visual symptoms but before the onset of headache (Cutrer et al., 1998). With a red-green checkerboard stimulus in patients with migraine, the functional MRI-BOLD (blood-oxygenation-level-dependent) technique was used to record the SD of prior activation of BOLD signal before the onset of visual change and headache in migraine patients (Cao et al., 1999). Hadjikhani and colleagues also studied spontaneous visual auras in four migraine patients using BOLD-functional MRI (fMRI) (Hadjikhani et al., 2001). Following a radial flickering checkerboard stimulus, certain CSD-linked CBF characteristics were recorded in migraine patients. Despite direct evidence for the neuronal origin of BOLD-source localized magnetoencephalography (MEG) in resting humans of frequency-specific electrophysiological correlation structure (Hipp and Siegel, 2015), the CSD issue in migraine remains uncertain (Chong et al., 2016).

Structural changes in the brain, using high-resolution cortical measurement and diffusion tensor imaging (DTI), in the visual motion processing network involving bilateral non-lateralizing abnormal thickness in areas MT+ and V3A (both cortical and in the underlying white matter), and, significantly lower fractional anisotropy in subcortical areas (superior colliculus and lateral geniculate nucleus) compared to healthy controls have been detected in some MwA and MwoA patients with longstanding disease (~20 years) that could account for, or be consequent to CNH (Granziera et al., 2006). These and other vascular, morphological, functional, chemical composition, metabolic, and low-frequency oscillatory brain changes in both MwA and MwoA patients suggest a basis for dysfunction between attacks as well as structural and functional plasticity in the "pain matrix", showing reduced cortical thickness and surface area ($P < .01$). These two metrics were increased in regions involved in executive functions and visual motion processing (Messina et al., 2013; Schwedt et al., 2015; Hodkinson et al., 2016; Chong et al., 2016). Questions arise regarding the origin, specificity, selectivity, and duration, as well as the nature of such changes in discrete brain areas such as the hippocampus, anterior insula, and primary somatosensory cortex in different migraine patients with varying (low versus high) frequency of attacks over decades. Furthermore, fMRI detected modular involvement of the salience network in the interictal period, which includes the anterior cingulate cortex, and, the frontoinsular cortex in another cohort of MwoA patients (Yu et al., 2017), and higher amplitude of the resting state fMRI fluctuation in MwA than in MwoA patients in the fronto-parietal and anterior cingulate cortices and the cerebellum (Faragó et al., 2017), again underscoring the variability of the results of neuroimaging between different cohorts and the absence of any functional link between the neuroimaging changes and the neuro-anatomical lateralization of neurologic aura or headache or both (Schmitz et al., 2008). Conversely, other migraine cohorts have an age-related advancing non-headache lateralizing negative and compounding thinning of regions that do not thin in healthy controls, including bilateral postcentral, right fusiform (occipitotemporal gyrus), and right temporal pole areas (Schmitz et al., 2008a; Chong et al., 2014).

The specificity of such non-lateralizing and conflicting functional and structural brain neuronal plasticity changes to migraine attack frequency/duration (DaSilva et al., 2007; Maleki et al., 2011; Messina et al., 2013; Rocca et al., 2014) that may also be conspicuous by their absence (Matharu et al., 2003), the influence of psychological and emotional comorbid factors such as pain, fear, stress, stresssusceptibility, stress-resilience, and helplessness besides anxiety and depression, and their possible link to CSD are other key factors that remain indeterminate. Migraine cohorts differ significantly, as a recent study using highly sensitive surface-based morphometry found no difference in cortical thickness between controls and patients, both in MwA and MwoA (Datta et al., 2011). In still another cohort of MwoA patients, the mean cortical thickness of many brain regions in the frontal lobe, temporal lobe, occipital lobe, parietal lobe, and insula in the migraine patient group was significantly decreased compared with that in the healthy control group (Yu et al., 2016). The mean cortical thickness of the insula anterior was positively correlated with the duration of the disease course, while the mean cortical thickness of insula superior and insula inferior was negatively correlated with the duration of the disease course (Yu et al., 2016). The complex interactive reaction involving many brain regions and many brain network systems in MwoA patients does not clarify the cause-and-effect enigma (Hadjikhani, 2008; Yu et al., 2016). In yet another cohort of MwA patients, sensory migraine aura was not associated with altered grey matter structure, and patients with visual aura had normal cortical structure of areas involved in visual processing; the previously reported decrease in grey matter volume of the cingulate gyrus in patients compared to controls in MwA and MwoA most likely reflects a general clinical bias between patients and healthy controls (Hougaard et al., 2017). Therefore, besides the cause or consequence dilemma that remains unresolved (Hadjikhani, 2008; Yu et al., 2016),

Citation: Gupta VK. Cortical Spreading Depression and Migraine: Critical Review of a Neurophysiological Principle in the Third Millennium. Glob J Medical Clin Case Rep. 2026:13(10):228-272. Available from: https://dx.doi.org/10.17352/gjmccr.000273

a more fundamental limitation of physical measurement and interpretation of cerebral cortex thickness in migraine patients *per se,* besides technical constraints, appears to be involved.

Experience-dependent secondary reactive or adaptive cortical plasticity – thickening or thinning -- is neither unique nor specific to MwA or MwoA patients only, and is quite unlikely to emerge as the long-elusive brain biomarker for the disorder.

Many factors including age (Sowell et al., 2003; Salat et al., 2004; Westlye et al., 2010; Chong et al., 2014; Wierenga et al., 2014), gender (Savic and Arver, 2014), genetics (Fjell et al., 2015), stress-induced alteration of hippocampal neurogenesis and its potential contribution to stress resilience / susceptibility (Levone et al., 2014), perception of pain (Schwedt and Chong, 2014), stress- and hibernation-linked bidirectional neuroplasm fluxes (Sotnikov et al., 2015), attention (Shaw et al., 2012, 2013), state of hydration (Biller et al., 2015), local topological constraints through childhood, adolescence, and young adulthood with white matter organization and expansion driving the thinning of sulcal cortex and synaptogenesis or increases in neuropil causing thickening in gyral cortex (Vandekar et al., 2015), apolipoprotein E genetic variations (Espeseth et al., 2012), influence of medications including opioid dependency in pain-free patients decreasing regional brain volume and connectivity in the amygdala (Upadhyay et al., 2010), cardiovascular fitness improvement (Scheewe et al., 2013), diabetes mellitus (Brundel et al., 2010; Chen et al., 2015; Moran et al., 2015), systemic hypertension (Alosco et al., 2014), and neuropathology and psychopathology influence the thickness of the brain cortex non-specifically (Rosas et al., 2002; Salat et al., 2004; Kuperberg et al., 2003; Rauch et al., 2004; Papagni et al., 2011).

The prevalence of migraine dramatically declines with advancing age (Blau, 1992a), but not necessarily in menopause (Ripa et al., 2015; Carturan et al., 2016); however, the relevance of age-related structural changes in the cerebral cortex to the pathogenesis of migraine appears incredibly complex (see above). Depression appears to be a prominent comorbidity with migraine and affects cortical thickness, with reduced right parahippocampal and fusiform gyrus thickness appearing to serve as a familial trait marker for vulnerability to mood disorders, and with progressive cortical thinning in the left inferior frontal and precentral gyri in subjects who remain well but with an increased risk for mood disorders (Papmeyer et al., 2015; Carturan et al., 2016). Conversely, onset of depression is associated with increasing left inferior frontal and precentral thickness (Papmeyer et al., 2015). With advancing age, increasing local arealization and gyrification occur with decreasing cortical thickness; this pattern of regional "cortical stretching" reflects the well-established phylogenetic principle of maximizing surface area and gyrification rather than increasing thickness to facilitate brain connectivity and functional development (Hogstrom et al., 2013).

Cessation of migraine attack-related pain of headache, i.e., 4-72 hours after onset, does not necessarily indicate a return in the postdrome phase of associated pathophysiologic anomalies to baseline (Gupta, 2005a, 2019). Also, the state of stress-associated arousal accompanying perceptions of challenge, threat, harm/loss, and coping options - primary and secondary appraisals (Schwarzer, 1998) – as well as subliminal stress (Passchier, 1994), besides innate stress-susceptibility or stress-resilience, suggest the operation of a continuum of stress-associated clinical, laboratory, and tissue responses (Gupta, 1997; 2004a; 2009a). Additionally, the prodrome can last several hours to a few days (Kelman, 2004b; Peatfield, 1988), while the postdrome lasts for an average duration of 25.2 hours (Kelman, 2006; Bose et al., 2018; Dodick, 2018). Most neuroimaging studies of migraine patients place a cut-off point of no migraine attack 72 hours before the study session, as well as no migraine attacks during or after scans, as a primary selection criterion (Hodkinson et al., 2015; Youssef et al., 2017). Besides variability between subjects in a cohort (Hodkinson et al., 2015) as well as of the test-retest reliability of CBF measurements in a clinical model of on-going post-surgical pain (Hodkinson et al., 2013), given the characteristically protean nature of migraine, no two attacks in any two migraine patients – and even in the same migraine patient on any two occasions -- would be strictly comparable in terms of length and nature of prodrome, aura manifestation and its attendant morbidity, severity and duration of headache, associated pre-attack and post-attack morbidity, associated symptoms like nausea/vomiting/dizziness, change in systemic BP, postdrome symptoms intensity and duration. (Gupta, 2010a, 2019, 2025) Meta-analyses add to the extant confusion in migraine pathophysiology (Gupta, 2010a; 2018a).

In a typically headache-lateralizing disorder such as migraine (Campbell, 1990), besides non-lateralizing bilateral rCBF increases in the primary somatosensory cortex (Kobari et al., 1989), a chance positive lateralizing correlation was found only within the right primary sensory cortex between rCBF value, migraine attack frequency, and cutaneous allodynia profile (Youssef et al., 2017). *Such neuroanatomically inexplicable and conflicting findings across different investigations deepen the mystery of migraine*. Since no two cohorts of migraine can be identical (Gupta, 2010a), replication of rCBF patterns is rather unlikely, and inexplicable results in neuroimaging are the rule rather than the exception, as the time from onset of migraine attacks to scanning and the quantum of stress-pain neuro-endocrinologic and neuro-psychologic responses will *never* be constant parameters.

In summary, in such a clinical scenario in migraine, statistical significance more often than not does not correlate with biological significance and is clinically misleading (Gupta, 2010a; 2018a; 2019).

Cortical spreading depression and migrainous

Scintillating scotoma: The cardinal attraction of CSD for maintaining the "neuronal" theory of migraine is the presumed ability of the CNS phenomenon (in rabbits and rodents) to explain positive visual aura in humans, in particular the onset and offset of SS and its propagation in MwA patients (Lauritzen, 1985; Vincent and Hadjikhani, 2007; Moskowitz, 2008; Pietrobon and Moskowitz, 2014; DeLange and Cutrer,

Citation: Gupta VK. Cortical Spreading Depression and Migraine: Critical Review of a Neurophysiological Principle in the Third Millennium. Glob J Medical Clin Case Rep. 2026:13(10):228-272. Available from: https://dx.doi.org/10.17352/gjmccr.000273

2014). The pathophysiology of the trigger(s) of CSD in the migraine population, nevertheless, remains unknown. (Charles and Baca, 2013).

Myriad neurological symptoms precede the headache phase in MwA patients (Hupp et al., 1989; Campbell, 1990; Vincent and Hadjikhani, 2007). Visual, sensory, motor, or psychic disturbances in migraine can occur that characteristically last for 10 to 25 minutes, but may be as brief as a few minutes or as long as an hour (Alvarez, 1960; Campbell, 1990; Friedman, 2004, 2008). Positive, negative, autonomic, or efferent ocular symptoms and signs are associated with MwA (Hupp et al., 1989; Friedman, 2004, 2008).

Migraine aura can be stereotyped or can vary greatly in severity on different occasions even in the same patient (Lauritzen, 1994; Schott, 2007; Hansen et al., 2013). Diverse visual (Queiroz et al., 1997), sensory (Jensen et al., 1986), motor (Thomsen and Olesen, 2004), language (Almeida et al., 1999), psychic, bizarre or brain stem disturbances can occur (Hupp et al., 1989; Silberstein and Young, 1995;

Foroozan and Cutrer, 2009), indicating that other areas of the cortex distinct from the occipital lobe must be affected (Vincent and Hadjikhani, 2007). The ability of CSD / SD to originate at discrete "skip" areas of the brain cortical region has been proposed (Vincent and Hadjikhani, 2007) but not established and remains inexplicable as the "dark unknown side of CSD / SD". (Cozzolino et al., 2018) Besides SS, complex visual phenomenon (micropsia, macropsia, altered colour perception), lacrimation, monocular vision loss, diplopia, pupillary abnormalities, ophthalmoplegic migraine, and recurrent facial nerve palsy are also described in migraine (Hupp et al., 1989; Chronicle and Mulleners, 1996; Friedman, 2004; Maxner and Moeller, 2005). Importantly, photophobia, is common to both MwA and MwoA (Chronicle and Mulleners, 1996). The visual aura of migraine is purely symptomatic and is largely inaccessible to others, including investigators (Schott, 2007). C.H. Parry in 1778 described his own scotomas precisely with the phenomenon never being followed by headache (Alvarez, 1960). Fothergill's personal description of the visual aura emphasized movement, brightness, and the angles he likened to a fortification figure (Fox, 1919). Airy, unaware of Fothergill's earlier description (Liveing, 1873), emphasized expansion of his own visual field defect from a "germ" in the paracentral area to a luminous crescent with a "boiling and trembling" motion and coloured angles (Airy, 1870). Individuals, including artists, have been drawing and describing their own migraine visual auras from centuries (Hare, 1966; Wilkinson and Robinson, 1985; Fuller and Gale, 1988; Rose, 2004; Podoll and Robinson, 2008; Schott, 2007; Hansen et al., 2013; Zehentbauer, 2015). Jolly (1902) studied the aura in one eye, the other having been destroyed at the age of nine (Alvarez, 1960).

A positive central scotoma enlarging over 20-30 minutes and then disappearing is probably the only pathognomonic feature of migraine (Fisher, 1980; Rose, 1986). Migraineurs may not be aware of negative scotomata, but the positive and vivid SS cannot fail to be noticed (Fuller and Gale, 1988). The jagged effect of water, silhouette of a man with a spike edge, and a black sun motif intruding into an interior scene are some examples of illustrated migraine attacks by de Chirico (Fuller and Gale, 1988). In a series of paintings, MwA sufferers have shown stars or flashes of light (70%), fortification spectra (48%), and visual loss (16%) illustrated in different styles (Singer, 1928; Wilkinson and Robinson, 1985; Hupp et al., 1989; DeLange and Cutrer, 2014).

Lashley (1941) provided the first quantitative recording of the temporal spread of the migrainous SS completely without headache attacks. Another individual made detailed drawing of his visual percept of migraine aura in real time in over 1000 attacks of migraine aura without headache over 18 years (Hansen et al., 2013). The predominant visual percept was a curvilinear band of flickering (10-15 Hz) colourless brilliant-and-black gridlines, followed by an advancing area of impaired vision (Hansen et al., 2013). Consistent patterns of aura initiation, propagation, and termination were observed in both right and left visual fields. Most aura attacks originated centrally (within 10° eccentricity) but there were also other distinct sites of initiation in the visual fields (Hansen et al., 2013). Auras beginning centrally dominantly propagated first through lower nasal field (69-77% of all auras) before travelling to upper and outer temporal fields. The speed of the visual event was estimated as 2-3 mm/min. Negative visual auras range from tunnel vision and scotomas to homonymous hemianopia and transient cortical blindness (Hupp et al., 1989; Campbell, 1990; Chronicle and Mulleners, 1996; Maxner and Moeller, 2005).

Scintillating scotoma (SS) is characterized most frequently by a wide spectrum of flashes of light or bright zig-zag, positive hemianopic (one sector of the visual field in 79.3% up to of 99% cases at least some of the time), horseshoe-shaped expanding visual perception with the open end of the horse-shoe towards the area of fixation that spreads from the paracentral region towards the peripheral temporal visual field usually in 10-20 minutes, and other less common but equally fascinating symptoms in quality, duration, and distribution i.e., unilateral (uniocular) or bilateral (binocular) (Alvarez, 1960; Manzoni et al., 1985; Hupp et al., 1989; Friedman, 2004). SS and other positive phenomenon possess a brightness that can be seen with eyes either opened or closed (Campbell,1990; Friedman, 2004). The bright positive image of the SS has a zig-zag quality with several short bands of bright colours or white light running parallel to one another (Alvarez, 1960; Hupp et al., 1989; Friedman, 2004). Spreading across the visual field, this positive phenomenon is generally followed by a negative scotoma that creates an area of obscured vision, wherein words are often read incompletely or only half a face might be seen (Hupp et al., 1989; Campbell, 1990; Friedman, 2004). Besides SS, positive visual aura symptoms include phosphenes or photopsiae, heat waves, kaleidoscope effects, and fragmented 'cracked glass' vision (Friedman, 2004). SS and other positive phenomena of the aura are uncertainly declared to be either monocular or binocular in distribution. Many patients will initially maintain that the observed SS was a monocular phenomenon (Hupp et al., 1989; Campbell, 1990) but by suggestion acknowledge a binocular even homonymous SS

Citation: Gupta VK. Cortical Spreading Depression and Migraine: Critical Review of a Neurophysiological Principle in the Third Millennium. Glob J Medical Clin Case Rep. 2026:13(10):228-272. Available from: https://dx.doi.org/10.17352/gjmccr.000273

defect (Campbell, 1990; Friedman, 2004). Bilateral visual field involvement without a definitive homonymous pattern is described in a retrospective study wherein a purely symptomatic phenomenon is complicated unsurprisingly also by passage of time involving memory and introspection (Queiroz, et al., 2011). Central vision disturbances, as is typical of SS, are commonly retinal in origin (Hupp et al., 1989).

Besides important characteristics of SS (Hupp et al., 1989), to further localize its source as being either related either to the anterior or to the posterior visual pathway, the following self-examination maneuvers are essential.

BOX 1. Clinical self-examination by migraine patients in SS / Negative Scotoma

(i) The patient should be instructed to occlude each eye separately and alternatively during an attack of SS or negative scotoma, and, to observe the field of vision of the uncovered eye carefully. Occurrence of a monocular non-homonymous SS is an absolute sign of the retinal origin of the phenomenon.

(ii) Displaceability of the visual phenomenon horizontally or vertically or both offers an absolute clue, with only retinal visual phenomena moving with digital displacement of the eyeball (Hupp et al., 1989). Digital displacement of SS is another absolute proof of its origin in the anterior visual pathway at the level of the retina.

(iii) Movement of the SS synchronously (horizontally or vertically or both) with the movements of the eye is the third absolute proof of the retina being the site of origin of the phenomenon of SS.

(iv)Central vision disturbances, as are common in SS, are retinal in origin.

(v) The MwA patient should be encouraged to draw the SS as a self-perceived visual illustration.

SS is not consistently associated with neuroanatomically lateralizing headache (Pearce, 1985; Blau, 1992a). Macular retinal lesions are well known to be associated with visual distortions (Arndt et al., 2000). Micropsia and macropsia have been described most frequently in the literature (in 58.6% and 45.0% of all patients, respectively), which might indicate that they are the most prevalent types of distortion but also that they are the best known and therefore studied most frequently, including the Alice in Wonderland syndrome (Blom, 2016). A combination of cultural factors and visual distortions at the macula may underlie the Alice in Wonderland phenomenon as part of positive scotomata in migraine.

The high percentage of neurologists and headache-specialists suffering migraine (Evans et al., 2003) or other knowledgeable medical practitioners / scientists are best placed to provide such critical information about migrainous SS. Fisher (1999), a physician, reported his own personal experience with SS in the form of an achromatic zigzag line over 27 years but did not describe a homonymous phenomenon or a simultaneous involvement of either a single or both nasal visual fields. Another neuro-physician with many migraine attacks over seven decades never described a homonymous scintillating / positive visual field defect. (Aring, 1991) Oliver Sachs, a neurologist by profession, described in his foreword for the book by Podoll and Robinson (2008), that he himself suffered left-sided non-homonymous visual phenomena and SS followed by blindness for a few minutes. No artist has as yet drawn their own positive migrainous visual aura to portray a homonymous SS i.e., involvement of both the nasal half of one visual field and the temporal half of the other visual field with lateralizing headache to support the principle of CSD or CSD-like cerebral phenomenon (Chronicle and Mulleners, 1996;

Gupta 2006b; Vongvaivanich et al., 2015). Additionally, the SS of migraine has never been represented diagrammatically by an expanding positive horse-shoe shaped scotoma beginning from the center and occupying the major portion of the nasal half of the visual field, right or left. Even Lashley (1941) did not describe spread of his own SS in the nasal halves of his own visual fields. The patient reported by Hansen et al. (2013) never drew a dominantly nasal expansion of the horse-shoe shaped SS in either right or left visual field. Conversely, migraineurs may experience almost any type of negative scotoma unaccompanied by positive scintillations (Hupp et al. 1989). In order of frequency, these negative scotomata may take the character of homonymous, central, tunnel, or altitudinal visual field defect, and mimics of positive migraine visual aura (see above) (Hupp et al., 1989 (see Table 2, p. 226); Alvarez, 1960; Fisher, 1980; O'Connor, 1981). It is, thus, critical to distinguish between positive and negative scotomata to understand the pathognomonic phenomenon of SS of migraine and to determine its source (retina v/s visual cortex).

Several unresolved issues persist and none of the extant theories offers a defensible hypothesis (Chronicle and Mulleners, 1996). While CSD and its propagation is the favoured theoretical basis for SS (Vincent and Hadjikhani, 2007; Noseda and Burstein, 2013), just like for migraine headache, there is no clue for the nature or basis of "self-cycling" genesis as well as for subsidence of SS. Moreover, there has been a profound conceptual mix-up between the clinical properties of positive and negative visual scotomata in migraine as well as in their neurobiology. Negative homonymous hemianopia of migraine (of cortical origin) must not be confused with positive non-homonymous SS (of retinal origin). Finally, the profound or strong neurosilencing of CSD is not expected to be associated with florid positive symptoms such as SS, flashing lights, castellations or pins and needles (Pearce, 1985; Borgdorff, 2018). In other migraine patients, visual aura symptoms are superimposed on a normal vision or numbness and tingling exist without loss of touch; such preservation of function seems incompatible with CSD that causes a reduction in spontaneous synaptic activity and action potential firing lasting over an hour (Sawant-Pokam et al., 2017). Typical paracentral horse-shoe-shaped expanding positive SS and typical migraine headache and are not reported after enucleation of one or both eyes (Peatfield and Rose, 1981; Nicolodi et al., 1997; Sörös et al, 2003; Noseda et al., 2010). Sightlessness markedly attenuates migrainous SS as well as photophobia (Silva et al., 2014).

Citation: Gupta VK. Cortical Spreading Depression and Migraine: Critical Review of a Neurophysiological Principle in the Third Millennium. Glob J Medical Clin Case Rep. 2026:13(10):228-272. Available from: https://dx.doi.org/10.17352/gjmccr.000273

A migraine-like aura with atypical features in perception and duration is a frequent concomitant or sequela of seizure (Shams and Plant, 2011). Such migraine-like aura is often associated with recurrent non-postular loss of consciousness as in the case-report of Peatfield and Rose (1981), in a woman who underwent bilateral enucleation of the eyes but also developed several episodic unrelated neurological features. Syncopal loss of consciousness in migraine is, conversely, generally orthostatic in origin. (Thijs et al., 2006; Curfman et al., 2012) The migraine aura and / or SS, in general, is much sharper in onset and shorter in duration than the headache. Yet, despite its relatively exceptional clinical pace, the rate of spread of the SS of migraine is remarkably slower than other brain phenomena involving vascular or epileptic / neuronal aberration (Blau, 1992a). Migraine-like visual aura otherwise fulfilling the ICHD (2018) criteria, but not the typical migrainous SS in time, pattern, appearance, or manner of spread -- have been reported to occur with a variety of focal cerebral lesions, i.e., an occipital seizure focus including tumour, arteriovenous malformation or unknown (Wittkowsky, 1952; Battistella et al., 1987; Hupp et al,. 1989; Bruera et al., 1999; Shams and Plant, 2011). Moreover, in six migraine patients with bilateral enucleation of the eyes or damage to the optic nerve due to other illnesses, photophobia was absent (Noseda et al., 2010b), indicating that the postulated image formation input at the level of the central neurons that processes nociceptive signals from meninges is not obligatory for migraine-induced photophobia. Conversely, blind migraineurs with retained eyeballs (i.e., without enucleation), retained light perception, and retained pupillary responses, and with retained circadian photoentrainment reported sensitivity to light (Noseda et al., 2010b), underscoring the link between pupillary responsiveness and photophobia or light sensitivity. In male Sprague-Dawley rats (270-350 g, Harlan, Indianapolis, IN), intense light activates nociceptive neurons in superficial laminae of trigeminal subnucleus caudalis through an intraocular mechanism driven by a luminance-responsive circuit and increased parasympathetic outflow to the eye (Okamoto et al., 2010). Whereas visual pattern perception is not essential to experience photophobia (Amini et al., 2006), a minor or subsidiary central component through optic nerve input is required since intolerance to light due to eye injury is eliminated by enucleation of the eye (Custer and Reistad, 2000).

In summary, the oculo-brainstem-ANS-pupillary nexus in migraine does not appear to have any link to CSD.

⊠Cortical spreading depression, nausea / vomiting of migraine, motion sickness, and cyclic vomiting syndrome

Early nausea and / or vomiting is a cardinal and diagnostic feature of migraine, both in episodic MwA and in MwoA; other forms of primary headache are generally not associated with early or prominent nausea and / or vomiting (ICHD, 2018). In MwA, nausea and / or vomiting, headache, and photophobia generally follow neurological aura symptoms either directly or within an hour (Campbell, 1990). One of the key limitations of the CSD theory appears to be its inability to explain the biology and the mechanism of occurrence of nausea and / or vomiting early in the migraine attack.

Conventionally, early nausea and / or vomiting in migraine attacks is assumed to reflect activation of the same putative pathogenetic cascade in migraine as is for SS or headache or both, with presumed SD-related orbitofrontal cortical, hypothalamic, and brain stem activation along with 5-HT release forming the final common pathway (Willoughby 1981; Welch, 1987; Welch et al. 1990; Schulte and May, 2016a). Nausea and vomiting are among the most frequently occurring symptoms observed by clinicians, a feature that involves vagal sensory inputs to the tractus solitarius that has, in turn, direct or indirect connections with several other hindbrain, midbrain and forebrain structures responsible for coordination of multiple organ systems (Babic and Browning, 2014). Several brain stem nuclei--including the nucleus tractus solitarius, dorsal vagus and phrenic nuclei, medullary nuclei that regulate respiration, and nuclei that control pharyngeal, facial, and tongue movements-coordinate the initiation of emesis. Neurotransmitters postulated to be involved in this coordination include neurokinin-1, serotonin 5-HT_3, and vasopressin (AVP) pathways (Hasler and Chey, 2003). Some believe that nausea and headache, two key symptoms of migraine, interact pathogenetically by reinforcing each other in a vicious circle during attacks (Drummond and Granston, 2004).

Somatic and visceral muscles exhibit stereotypic responses during emesis. Vomiting, coordinated by the brain stem, is effected by neuromuscular responses in the gut, pharynx, and thoraco-abdominal wall across the diaphragm (Hasler and Chey, 2003; Babic and Browning, 2014). The medulla oblongata is phylogenetically the oldest part of the nervous system. The emetic response was selected early in humans for protective purposes and serves as a safeguard against poisoning of the body (Chai et al., 2013). Biologically, nausea and vomiting are important components of an organism's defences against ingested toxins (Andrews and Horn, 2006; Chai et al. 2013). This response gets toxins and drugs out of the body by summoning control over motor neurons either spontaneously or in an induced fashion by reflux gagging (Chai et al., 2013).

Emesis and migraine provoked by unpleasant thoughts or smells is believed to originate in the cerebral cortex (Stankewitz and May, 2001; Friedman and De Ver Dye, 2009; Sjostrand et al., 2010; de Lima et al., 2011). The area postrema, a medullary nucleus, however, responds to bloodborne emetic stimuli and is termed the chemoreceptor trigger zone (CTZ). The area postrema is richly served by nerve fibers acting on 5-HT_3 , muscarinic (M_1), histaminergic (H_1), and dopamine (D_2) receptor subtypes. With the area postrema lying outside the BBB, many drugs and other agents act on the CTZ such as bacterial toxins and metabolic factors produced during uremia, hypoxia, and ketoacidosis. This means that large polar molecules, such as emetic toxins, can diffuse through to and reach the CTZ quite easily (Babic and Browning, 2014). Early adaptive release of AVP that stimulates the CTZ is the likely cause of early nausea and vomiting in migraine (see below) (Gupta, 2004j, 2005b, 2019).

Citation: Gupta VK. Cortical Spreading Depression and Migraine: Critical Review of a Neurophysiological Principle in the Third Millennium. Glob J Medical Clin Case Rep. 2026:13(10):228-272. Available from: https://dx.doi.org/10.17352/gjmccr.000273

Motion sickness represents a condition often associated with migraine that can reduce quality of life (Furman and Marcus, 2012). Motion sickness associated nausea and vomiting is believed to be due to a primary stimulation of the labyrinthine apparatus. Additionally, stress and perceived stress in a wide variety of clinical circumstances e.g., cyclic vomiting syndrome (CVS) (Li and Balint, 2000; Gupta, 2004j, 2005b; McRonald and Fleischer, 2005) also stimulate nausea and / or vomiting in an anticipatory manner to mitigate, alleviate, draw or divert attention from the stressful event. "Anticipatory stress" is a possible mechanism for the occurrence of CVS with migraine (Gupta, 2004g; 2004j). Self-induced vomiting ("gagging") can also be a manipulative event. The pathophysiologic cause-effect mechanisms of "anticipatory stress" remain unknown but is likely linked to AVP secretion early in the course of migraine attack-related stress. The discussion of other clinical circumstances of nausea and / or vomiting are beyond the scope of this review.

As discussed in this review, the term "stress", howsoever generated, does not translate itself into any pathophysiological mechanism. The central processing of signals for nausea and vomiting is particularly problematic in the light of observations that vomiting is more readily amenable to pharmacological treatment than is nausea, despite the assumption that nausea represents "low" intensity activation of pathways that can evoke vomiting when stimulated more intensely (Andrews and Horn, 2006). A central role for AVP in migraine pathophysiology has been suggested (Gupta 1997, 2009a, 2024). Spontaneous migraine-related stress (Hampton et al., 1991; Hasselblatt et al., 1999) and apomorphine-induced nausea (Sørensen and Hammer, 1985) both are powerful stimuli for AVP secretion. Continuous subcutaneous infusion of apomorphine (a classical dopamine receptor agonist with a rapid and powerful emetogenic effect) for three weeks was effective in reducing the frequency and the severity of migraine attacks (Lai et al., 1997).

AVP can itself generate vomiting, while vomiting, in turn, significantly increases AVP secretion resulting in a vicious circle. AVP administered intravenously results in vomiting and retching in humans (Rowe et al., 1979; Kim et al., 1997) and dogs (Carpenter et al., 1984). A low dose of exogenous AVP, which has no effect when given peripherally, causes an emetic response given centrally (Ikegaya and Matsuki, 2002). This suggests that the effects of AVP on nausea and / or vomiting are mediated via the CNS. Plasma AVP concentration is rapidly elevated in response to diverse emetic stimuli such as motion stimuli (Kim et al., 1997), and, apomorphine (Nussey et al., 1988) or cisplatin administration (Edwards, et al., 1989; Cubeddu et al., 1990).

Treatment with antagonists of the AVP receptor efficiently prevents motion sickness (Kohl and MacDonald, 1991; Cheung et al., 1994). *This suggests that endogenous AVP is involved in naturally or spontaneously occurring emesis, including the characteristic nausea and/or vomiting of migraine.* self-limited ressin- One of the most fascinating and vexing issues is how vomiting stops a migraine attack (Chai et al., 2013) and the linked question about how the migraine attacks stop (Villanueva, 2012; Houle et al., 2012). The vasop serotonergic-noradrenergic adaptive "system" apparently is a powerful central brain influence that can have a substantial role in both clinical circumstances(Gupta 19972009a). Intracerebroventricular and intravenous (i.v.) injections of AVP cause opposite effects on intraocular pressure (IOP), with i.v. administration causing a fall in IOP(Gondi M, et al., 2001). (Gondi M, et al., 2001). The central effect of AVP on IOP and the peripheral effects of AVP on IOP and pupil size (miosis) are due to stimulation of the V1 receptors *Negativ e fluid balance, peripheral increase in AVP secretion, and fall in IOP are likely physiological influences that are possibly linked to the mechanisms involved in stopping of migraine attacks with or without nausea and / or vomiting* (Gupta, 2023a). *Moreover, in migraine patients (MwA or MwoA), with or without nausea and / or vomiting, the tamponade effect of the corneoscleral envelope also likely limits ocular distensibility and consequent trigeminal V 1 afferent nociceptive neural traffic, thereby limiting the duration of migraine attacks* (Gupta, 2023a). *in these key*(Gupta, 2019). *In summary, CSD has not been postulated to play a role phenotypic events involving AVP and tamponade effect of the eye(s)* ;

Box 2. Clinical migraine phenomena that cannot be explained by CSD

Spontaneous ("self-cycling") genesis/onset of migraine attacks (both for SS and headache).

Pain/headache of migraine.

Gender asymmetry – female preponderance.

Protean nature of migraine, including predictable (menstrual) as well as unpredictable occurrences.

Prodrome and aura of migraine with multi-faceted "skip" neurological symptoms.

Delayed onset of headache for several hours or even a few days after exposure to triggers, including "stress", significant alcohol consumption, and ingestion of tyramine-containing foods.

Spontaneous defervescence/cessation of migraine attacks (both for SS and headache).

Self-limited duration of migraine headache attacks (4-72 hours).

Variable frequency, severity, and comorbidity of migraine headache in discrete attacks dispersed in time, whereas CSD is an all-or-none physiological phenomenon.

Link to a large number of heterogeneous clinical conditions labelled as migraine triggering factors, particularly "stress" with no commonality of pathophysiologic mechanism(s).

"Post-stress" occurrence of migraine attacks.

Link to migraine remitting factors, particularly sleep, later trimesters of pregnancy. menopause and advancing age.

Citation: Gupta VK. Cortical Spreading Depression and Migraine: Critical Review of a Neurophysiological Principle in the Third Millennium. Glob J Medical Clin Case Rep. 2026:13(10):228-272. Available from: https://dx.doi.org/10.17352/gjmccr.000273

Precipitation of delayed atypical migraine-like headache attacks by GTN (human model) in the absence of aura / SS/ nausea and/or vomiting.

Relief of SS with GTN / isoproterenol without any definitive effect on CSD.

Larger cohort ~66% of MwoA completely unconnected to CSD.

Typical lateralization of migraine headache.

Migraine-linked photophobia.

Similar light-sensitivity between MwA and MwoA.

Greater photophobia and light sensitivity on the side of the headache.

Postdrome of migraine.

Sparing of nasal visual field by SS.

Non-homonymous limited spread by SS in temporal half of visual field.

Markedly slow pattern of development and propagation of SS as well as headache in terms of or in relation to other neurological vascular or epileptic / neuronal disorders.

Loss of migrainous SS in sightless eyes in patients with previous migraine and non-enucleated eyes.

Loss or attenuation of photophobia in sightless eyes in patients with previous migraine and non-enucleated eyes.

Loss of SS, typical migraine headache, and photophobia in enucleated eyes in patients with previous migraine.

Autonomic manifestations of migraine—miosis, mydriasis, ptosis, lacrimation without salivation.

Early nausea / vomiting in migraine attacks.

Frequent abortion / cessation of headache following vomiting.

Link to motion sickness.

Link to cyclical vomiting of migraine.

Maintenance of systemic hypotension, vasovagal attacks with postular syncope, relative tachycardia, beat-to-beat heart rate and respiratory rate variability in between attacks.

Prevention of MwA and MwoA attacks by hydrophilic atenolol, nadolol, verapamil that do not cross the BBB readily.

Relief of migraine attacks by amitriptyline in both MwA and MwoA cohorts, a potentially seizure-inducing drug.

Relief of migraine attacks by a paradoxical combination of propranolol and amitriptyline in both MwA and MwoA cohorts.

Discussion

The chance discovery of CSD in experimental animals by the alert scientist, Leão (1944a; 1944b), the presumed cortical origin of personal experience of SS without headache attacks earlier by another meticulous investigator (Lashley, 1941), and the assumed linkage between these two sets of cross-species events by yet another researcher (Milner, 1958), set the stage for a prolonged philosophic commitment by several migraine researchers to CSD well into the 21st century (Hartings et al., 2017). Another momentous but serendipitous event in migraine research six decades ago was the discovery of the preventive role of beta-blocker drugs (Rabkin et al., 1966), placing the otherwise well-known adaptive function of the ANS into pathophysiologic algorithms (Gupta, 2019; 2024). The bio-behavioral model of migraine emerged in the late 20th century, placing emphasis on aberration of the intrinsic brain noradrenergic function (Welch, 1987). Since the science of migraine has evolved by chance alone, all therapeutic options, including triptans, anti-convulsants, PFO-closure, botulinum toxin, and CGRP-antagonists, remain empirical or experiential (Gupta, 2009a, 2010a; Borgdorff, 2018). Most leading researchers acknowledge large gaps in the "theory" of CSD (and in other braincentric hypotheses including the assumed in vogue but unsustainable "self-cycling" concept), but simultaneously point to incredible and futuristic research progress over the last 100 years.

Do we face a scientific illusion through the lens of CSD or has indeed remarkable progress in the science of migraine been made? Do we know how or why episodes of CSD-linked migraine should start or stop *de novo* in almost one-fifth of humankind? Why is the remaining four-fifths of the human population spared from migraine, although stress is almost ubiquitous? (Gupta, 2019) What tissue or organ determines the typical duration (4-72 hours) of migraine attacks? Or why should vomiting commonly abort migraine attacks? Have we truly defined the biology of migraine? Does the diverse and increasing number of available therapies generate confidence in our comprehension of this discipline? Has the need for an overarching and robust theoretical matrix for migraine, outside of the putative vascular/neuronal hypotheses, become any lesser? (Gupta, 2009a, 2010a). Fundamentally, what is that which makes the CNS in migraine patients intermittently and unpredictably either more or less susceptible to the presumed attack-provoking influence of CSD (or other pathogenetic influences, including stress / stressors)?

(Maagdenberg et al., 2004; Teive et al., 2005; Cozzolino et al., 2018; Borgdorff, 2018).

Genetic mutations and amino acid substitutions in high-voltage sensing calcium channel proteins (Cav.2.1) have generated much excitement and are believed to increase CSD and aura susceptibility (Moskowitz, 2008), but in the context of a comprehensive evolution of the migraine entity, the contribution of these findings is essentially debatable. Several medical illnesses have a geneticpredisposition, such as diabetes mellitus or coronary artery disease, but it is the

Citation: Gupta VK. Cortical Spreading Depression and Migraine: Critical Review of a Neurophysiological Principle in the Third Millennium. Glob J Medical Clin Case Rep. 2026:13(10):228-272. Available from: https://dx.doi.org/10.17352/gjmccr.000273

discovery of insulin and the atheromatous plaque, respectively, that dominates their pathophysiology, management, and research. *In the absence of such a pathogenetic equivalent, migraine pathophysiology will remain rudimentary even with a rapidly increasing data bank, application of futuristic technology, and statistics*. Assumptions and myths sustain CSD as a viable concept for migraine pathophysiology (see Box 2) (Gupta, 2009a).

The need for a major change, and to de-link migraine from both the "vascular" and the "neuronal" theories was perceived almost three decades ago (Edmeads, 1991; Blau, 1992a). *The key to understanding migraine mechanism(s) lies in the unlocking of the physiological processes underlying post-stress headache, an evolutionary protective mechanism* (Graham, 1953; Blau, 1992a). A psychophysiologic and neuroendocrine mechanism underlying an early phase (*preprodromal and prodromal*) "protective" role for stress or emotion was proposed over two decades ago (Gupta, 1997), and further elucidated more recently (Gupta, 2004a, 2009a, 2010a, 2019, 2023a, 2024, 2025). Enhanced migraine attack-related bioavailability of AVP and 5-HT coupled with noradrenergic hyperfunction likely constitutes the adaptive "system" that maintains vascular integrity, antinociception, and behavior control during the early preictal "pre-prodromal / pre-premonitory" phase of stress of migrainous vasodilatory antidromic V1 trigeminal nerve nociceptive discharges (Gupta, 1997, 2009a, 2023a, 2024, 2025). Such an adaptive "system" helps create a conceptual divide between primary and secondary clinical phenomena (Gupta, 2004g, 2009a, 2019, 2024, 2025). The quest for a defensible theoretical matrix to place migraine research data in a logical, increasingly strengthening, robust, and generalizable synthesis appears feasible now.

Whereas CSD / SD has been detected in a few human brain diseases (Strong et al., 2002; Lauritzen et al., 2011; Lauritzen and Strong, 2017) with elements of acute tissue disruption, rheological changes, and pressure alterations such as is found in malignant stroke, subarachnoid and intracranial hemorrhage, and traumatic brain injury, CSD / SD has neither been detected in migraine patients without brain injury nor has any definite pathogenetic role been established for this electrical phenomenon (Gupta 2005a, 2009a; Yanamoto et al., 2000, 2004, 2005; Cozzolino et al., 2018). BBB disruption in migraine has also been practically eliminated in acute attacks of migraine (Hougaard et al., 2017; Amin et al., 2017, see above).

Conversely, the neuroprotective effect of CSD is known for the last three decades. Why might CSD / SD not be viewed as being protective in both children and adult migraineurs, as it is in experimental animals? (Gupta, 2009a; Siniatchkin et al., 2009). The rare clinical presentation of combined seizure-disorder and migraine (migralepsy) must not be allowed to confuse our perception (see above). Recording of primary or causative changes in migraine in the laboratory or by neuroimaging is difficult at present (Danuelle and Fabre, 2013). Since the migraine attack begins well before onset of the prodrome/premonitory phase, as well as the SS/aura, headache, or nausea/vomiting, and an extended postdrome is frequently manifest, researchers are invariably recording secondary changes in the laboratory or by neuroimaging and extrapolating them back to the tenets of experimental CSD / SD or to other central brain theories (Gupta 2009a, 2019, 2024, 2025). The focus on one or two factors recorded in the laboratory or through neuroimaging is generally diversionary as it ignores the whole and limits the perspective (Blau, 1992a).

A large spectrum of factors affects brain function and structure in migraine, and these features cannot be dissociated without insight into the relationship between primary and secondary factors (Gupta, 2019, 2024, 2025). As migraine is a protean disorder, these changes will be reflected variably rather than consistently -- even in the same patient on different occasions -- in advanced neuroimaging, including fMRI and BOLD-related studies, and thus the primary versus secondary or cause-effect debate will persist indefinitely (Gupta 2004a; 2024; 2025). *Paradoxically, with the accumulation of more data in migraine research, pathophysiological confusion will worsen*. SD-like phenomenon (like the CSD of Leão) has also been recorded in the retina, the only other avascular neural tissue (Martins-Ferreira and de Castro, 1966; Wiedemann et al., 1996; Duarte et al., 2003; Dahlem and Müller, 1997; Brand et al., 1998; Weimer and Hanke, 2005). Primary retinal stimulation in migraine patients to generate retinotopic localization of cortical changes cannot be excluded at this stage of our mechanistic comprehension. As discussed in this article, vision as well as the eye appears essential for the generation of typical photophobia, SS, and migraine headache (Gupta, 2019, 2023a, 2024, 2025). Association of low-tension glaucoma and normal-tension glaucoma in migraine (Bar et al., 2025) also has no conceivable link with CSD.

In a broader, more comprehensive, less confused, and more realistic canvas, both CSD in experimental animals and presumed CSD "surrogates" or "homologues" in humans in headache as well as in SS can be discussed afresh in this framework presented to evolve insight into migraine mechanisms. *It is vital to discern the elusive pathophysiological commonality between widely disparate but well-established triggering and remitting factors—one single neurophysiological mechanism*. Such an approach will provide a sound and logical matrix for the extensive and expanding phenotype of migraine. Conceptually, the adaptive "system" of migraine marks the first major defensible distinction between pathogenetic and non-pathogenetic phenomena in migraine (Gupta 2009a, 2023a 2024; 2025).

Remarkably little has been written about nausea and/or vomiting that rapidly follows the migraine attack and can frequently abort the headache. Over 2000 years ago, *Hippocrates* described "...vomiting, when it became possible, was able to divert the pain and render it more moderate" (Allory, 1859). In 1790, Tissot wrote: "...vomiting might herald the termination of the headache" (Pearce, 1986). The final common pathway for vomiting at the level of the brainstem or CTZ remains uncertain (Babic and Browning, 2014). AVP, as a neurotransmitter released in the brain, can itself trigger vomiting (see above) (Mathias and Bannister, 2013). Instantaneous increases in plasma AVP from 100 to 1000 times basal level are not unusual even when

Citation: Gupta VK. Cortical Spreading Depression and Migraine: Critical Review of a Neurophysiological Principle in the Third Millennium. Glob J Medical Clin Case Rep. 2026:13(10):228-272. Available from: https://dx.doi.org/10.17352/gjmccr.000273

the nausea is transient and unaccompanied by vomiting or changes in blood pressure (Valiquette, 1987). Mild nausea can distort physiological AVP responses. because nausea is a more potent and predominating stimulus to AVP release. The onset of the migraine attack possibly represents overwhelming fatigue of the AVP- noradrenergic-serotonin linked adaptive "system" (Gupta 1997, 2009a, 2019, 2024, 2025). Once the migraine attack is triggered, the stress-stimulated release of AVP can trigger nausea or vomiting or both, while migraine attack-related nausea/vomiting may further augment the attack-abortive AVP release associated "system" in an adaptive circle. The tamponade effect of the eye, in the midst of such ANS and neuroendocrinal chaos, probably aids in aborting migraine headache(Gupta, 2009a, 2023, 2025).

While physiological and pharmacological concepts of CSD continue to advance (Spong et al., 2016a, 2016b, 2016c; Wainzstein and Lucci, 2017; Cozzolino et al. 2018; Klass et al. 2018; Close et al. 2019), the connect between CSD and migraine pathophysiology, based as it is on a presumptive link to the SS with many assumptions or arbitrary elements (Gupta 2023a, 2025) has made little progress. "*The specific philosophic approach of the investigator to the problem at hand may itself be(come) one of the critical variables in the design and conduct of a given research strategy*" (Watson, 1968).

In summary, the time to de-link migraine from CSD, a long-sustained mythical scientific connection, has arrived. Given the enormous homeostatic potential of the human body, everything that is recorded in the laboratory or through neuroimaging cannot be simply or simplistically presumed to be pathogenetic.

Methodology

The article is a critical review and not a systematic one. Articles for the critical review have been collected from PubMED; Cochrane database; and, references from selected articles over the last 100 years using the terms "cortical spreading depression; spreading depression; migraine; aura; vomiting; vasopressin; serotonin; catecholamines, traumatic brain injury, photophobia". A synthetic review is presented towards a gestaltic understanding of the disorder.

Conclusion

The role of CSD in migraine pathophysiology is fraught with assumptions and well-entrenched myths, including deeply ingrained link(s) to SS. The neuroanatomic, neurophysiologic, and biologic basis of scotomata / SS cannot be understood without definitive data coming from MwA in a systematic manner, as detailed in this article. Migraine pathophysiology is becoming increasingly blurred when viewed through the lens of CSD with additional data and statistics. This article provides a defensible, robust, generalizable, and progressive concept of the adaptive role of CSD / SD as well as of CNS / extra-CNS pathophysiology surrounding migraine and its main components. It is hoped that this matrix will further evolve the understanding of migraine, and, ultimately, its management and prognosis. The key event in deciphering migraine and creating a primary and secondary (cause / effect) divide is an unravelling of the "vasopressin-serotonin-norepinephrine" nexus and an understanding the fundamental laws that govern migraine pathophysiology and biology, its triggers, its link to stress, and its spontaneous onset, offset, and prevalence.

References

1. Abu-Arafeh I, Razak S, Sivaraman B, Graham C. Prevalence of headache and migraine in children and adolescents: a systematic review of population-based studies. Dev Med Child Neurol 52, 1088-1097, 2010. Available from: https://doi.org/10.1111/j.1469-8749.2010.03793.x

2. Abu-Arafeh I, Russell G. Prevalence of headache and migraine in schoolchildren.BMJ 309, 765-769, 1994. Available from: https://doi.org/10.1136/bmj.309.6957.765

3. Afridi SK, Kaube H, Goadsby PJ. Glyceryl trinitrate triggers premonitory symptoms in migraineurs. Pain 110: 675-680, 2004. Available from: https://doi.org/10.1016/j.pain.2004.05.007

4. Agnoli A. The classification of calcium antagonists by the WHO expert committee: relevance in neurology. Cephalalgia (Suppl 8): 7-10, 1988. Available from: https://doi.org/10.1177/03331024880080s802

5. Agon P, Goethals P, Van Haver D, Kaufman J-M. Permeability of the blood-brain barrier for atenolol studied by positron emission tomography. J Pharm Pharmac 43: 597-600, 1991. Available from: https://doi.org/10.1111/j.2042-7158.1991.tb03545.x

6. Airy H. On a distinct form of transient hemianopia. Philos Trans R Soc 160, 247-264, 1870.

7. AkGerman S, Goadsby PJ. Topiramate inhibits cortical spreading depression in rat and cat: impact in migraine aura. Neuroreport 16: 1383-1387, 2005. Available from: https://doi.org/10.1097/01.wnr.0000175250.33159.a9

8. Akerman S, Holland PR, Goadsby PJ. Diencephalic and brainstem mechanisms in migraine. Nat Rev Neurosci 12, 570-584, 2011. Available from: https://doi.org/10.1038/nrn3057

9. Akerman S, Holland PR, Hoffmann J. Pearls and pitfalls in experimental in vivo models of migraine: dural trigeminovascular nociception. Cephalalgia 33, 577-592, 2013. Available from: https://doi.org/10.1177/0333102412472071

10. Akerman S, Williamson DJ, Goadsby PJ. Voltage-dependent calcium channels are involved in neurogenic dural vasodilation via a presynaptic transmitter release mechanism. Br J Pharmacol 140, 558-566, 2003. Available from: https://doi.org/10.1038/sj.bjp.0705456

11. Akturk F, Erturk M, Topcular B, Altinkaya A, Behrem N, Gul G et al. Impaired aortic elastic properties in young females with migraine. Ideggyogy Sz 67, 201-204, 2014. Available from: https://pubmed.ncbi.nlm.nih.gov/25087380/

12. Al Balawi, Tariq M, Feinmann C. A double-blind, placebo-controlled, crossover, study to evaluate the efficacy of subcutaneous sumatriptan in the treatment of atypical facial pain. Intern J Neurosci 86, 301-309, 1996. Available from: https://doi.org/10.3109/00207459608986720

13. Albrecht E, Kirkham KR, Liu SS, Brull R. Peri-operative intravenous administration of magnesium sulphate and postoperative pain: a meta-analysis. Anaesthesia 68, 79-90, 2013. Available from: https://doi.org/10.1111/j.1365-2044.2012.07335.x

14. Alemdar M, Akman Ö, Selekler HM, Komsuoğlu Ş, Ateş N. Does metoprolol inhibit the cortical spreading depression? Acute effects of systemic metoprolol on CSD in rats. Cephalalgia 27: 1010-1013, 2007. Available from: https://doi.org/10.1111/j.1468-2982.2007.01390.x

15. Allory AL. Concerning migraine. Thesis, Paris, 1859, from Pearce JMS. Historical aspects of migraine. J Neurol Neurosurg Psychiatry 49, 1097-1103, 1986. Available from: https://doi.org/10.1136/jnnp.49.10.1097

Citation: Gupta VK. Cortical Spreading Depression and Migraine: Critical Review of a Neurophysiological Principle in the Third Millennium. Glob J Medical Clin Case Rep. 2026:13(10):228-272. Available from: https://dx.doi.org/10.17352/gjmccr.000273

16. Almeida DB, Arruda WO, Ramina R, Pedrozzo AA, Raskin S. Migrânea com afasia. Relato de uma família. Arq Neuropsiquiatr 57, 111-113, 1999. Available from: https://doi.org/10.1590/s0004-282x1999000100022

17. Alosco ML, Gunstad J, Xu X, Clark US, Labbe DR, Riskin-Jones HH et al. The impact of hypertension on cerebral perfusion and cortical thickness in older adults. J Am Soc Hypertens 8; 561-70, 2014. Available from: https://doi.org/10.1016/j.jash.2014.04.002

18. Alton BH, Lincoln GC. The control of eclampsia convulsions by intraspinal injections of magnesium sulphate. Am J Obstet Gynecol 9: 167-177, 1925.

19. Altura BM, Altura BT. Magnesium and vascular tone and reactivity. Blood Vessels, 15, 5-16, 1978. Available from: https://doi.org/10.1159/000158148

20. Altura BM, Altura BT, Carella A, Gebrewold A, Murakawa T, Nishio A. Mg^{2+}–Ca^{2+} interaction in contractility of vascular smooth muscle: Mg^{2+} versus organic calcium channel blockers on myogenic tone and agonist-induced responsiveness of blood vessels. Can J Physiol Pharmacol 65: 729-745, 1987. Available from: https://doi.org/10.1139/y87-120

21. Alvarez WC. The migrainous scotoma as studied in 618 persons. Am J Ophthalmol 49, 489-504, 1960. Available from: https://doi.org/10.1016/0002-9394(60)91650-0

22. Amin FM, Hougaard A, Cramer SP, Christensen CE, Wolfram F, Larsson HBW, Ashina M. Intact blood-brain barrier during spontaneous attacks of migraine without aura: a 3T DCE-MRI study. Eur J Neurol 24, 1116-1124, 2017. Available from: https://doi.org/10.1111/ene.13341

23. Amini A, Digre K, Couldwell WT. Photophobia in a blind patient: An alternate visual pathway. Case report. J Neurosurg 105, 765-768, 2006. Available from: https://doi.org/10.3171/jns.2006.105.5.765

24. Andermann F. Migraine and epilepsy: an overview. In: Andermann F, Lugaresi E (eds). Migraine and Epilepsy. Boston: Butterworths; pp. 405-422, 1987.

25. Andermann F. Clinical features of migraine-epilepsy syndromes; in Andermann F, Lugaresi E (eds): Migraine and Epilepsy. Boston, Butterworths, pp 3–30, 1987a.

26. Andersen AR, Friberg L, Olsen TS, Olesen J. Delayed hyperemia following hypoperfusion in classic migraine. Single photon emission computed tomography demonstration. Arch Neurol 45, 154-159, 1988. Available from: https://doi.org/10.1001/archneur.1988.00520260040017

27. Andersson KE, Vinge E. Beta-adrenoceptor blockers and calcium antagonists in the prophylaxis and treatment of migraine. Drugs 39: 355-373, 1990. Available from: https://doi.org/10.2165/00003495-199039030-00003

28. Andreou AP, Summ O, Charbit AR, Romero-Reyes M, Goadsby PJ. Animal models of headache from bedside to bench and back to bedside. Expert Rev Neurother 10, 389-411, 2010. https://doi.org/10.1586/ern.10.16

29. Andrews PLR, Horn CC. Signals for nausea and emesis: implications for models of upper gastrointestinal diseases. Autonomic Neuroscience: Basic & Clinical 125, 100115, 2006. Available from: https://doi.org/10.1016/j.autneu.2006.01.008

30. Anoaica M-B, Anoaica PG, Popescu F. Acetylsalicylic acid in migraine with aura prevention - a retrospective study. Curr Health Sci J 40, 126-128, 2014. Available from: https://doi.org/10.12865/chsj.40.02.08

31. Anthony M. Headache and the greater occipital nerve. Clin Neurol Neurosurg 94, 297-301, 1992. Available from: https://doi.org/10.1016/0303-8467(92)90177-5

32. Arendt J, Bojkowski C, Franey C, Wright J, Marks V. Immunoassay of 6-hydroxymelatonin sulfate in human plasma and urine: abolition of the urinary 24-hour rhythm with atenolol. J Clin Endocrinol Metab 60, 1166-1173, 1985. Available from: https://doi.org/10.1210/jcem-60-6-1166

33. Aring CD. Late-life migraine. Arch Neurol 48, 1174-1177, 1991. Available from: Available from: https://doi.org/10.1001/archneur.1991.00530230082027

34. Armstrong GAB, Rodgers CI, Monet TGA, Robertson RM. Suppression of spreading-depression-like events in locusts by inhibition of the NO/cGMP/PKG pathway. J Neurosci 29, 8225-8235, 2009. Available from: https://doi.org/10.1523/jneurosci.1652-09.2009

35. Arndt CF, Seguinet S, Debruyne P, Defoort-Dhelemmes S, Hache JC. Quantitative evaluation of metamorphopsia in macular disease. J Fr Ophthalmol 23, 679-682, 2000. Available from: https://pubmed.ncbi.nlm.nih.gov/10992062/

36. Asadi-Pooya AA. Lennox-Gastaut syndrome: a comprehensive review. Neurol Sci. 2018; 39:403-414. doi: 10.1007/s10072-017-3188-y Available from: https://doi.org/10.1007/s10072-017-3188-y

37. Asghar MS, Hansen AE, Kapijimpanga T, van der Geest RJ, van der Koning P, Larsson HBW, Olesen J, Ashina M. Dilation by CGRP of middle meningeal artery and reversal by sumatriptan in normal volunteers. Neurology 75, 1520-1526, 2010. Available from: https://doi.org/10.1212/wnl.0b013e3181f9626a

38. Ashina M, Hansen JM, Olesen J. Pearls and pitfalls in human pharmacological models of migraine: 30 years' experience. Cephalalgia 33, 540-53, 2013. Available from: https://doi.org/10.1177/0333102412475234

39. Aurora SK, Cao Y, Bowyer SM, Welch KMA. 1999 Wolff Award. The occipital cortex is hyperexcitable in migraine: experimental evidence. Headache 39, 469-476, 1999. Available from: https://doi.org/10.1046/j.1526-4610.1999.3907469.x

40. Aurora SK, Wilkinson F. The brain is hyperexcitable in migraine. Headache Curr 27, 1442-1453, 2007. Available from: https://doi.org/10.1111/j.1468-2982.2007.01502.x

41. Avoli M, Drapeu C, Louvel J, Pumain R, Olivier A, Villemure J-G. Epileptiform activity induced by low extracellular magnesium in the human cortex maintained in vitro. Ann Neurol 30, 589-596, 1991. Available from: https://doi.org/10.1002/ana.410300412

42. Ayata C. Spreading depression: from serendipity to targeted therapy in migraine prophylaxis. Cephalalgia 29: 1097-1114, 2009. Available from: https://doi.org/10.1111/j.1468-2982.2009.01982.x

43. Ayata C. Cortical spreading depression triggers migraine attack: Pro. Headache 50, 725-730, 2010. Available from: https://doi.org/10.1111/j.1526-4610.2010.01647.x

44. Ayata C, Jin H, Kudo C, Dalkara T, Moskowitz MA. Suppression of cortical spreading depression in migraine prophylaxis. Ann Neurol 59: 652-661, 2006. Available from: https://doi.org/10.1002/ana.20778

45. Ayata C, Lauritzen M. Spreading depression, spreading depolarizations, and the cerebral vasculature. Physiol Rev 95: 953-993, 2015 Available from:. https://doi.org/10.1152/physrev.00027.2014

46. Babic T, Browning KN. The role of vagal neurocircuits in the regulation of nausea and vomiting. Eur J Phamacol 722, 38-47, 2014. Available from: https://doi.org/10.1016/j.ejphar.2013.08.047

47. Bakhshandeh Bali M, Rahbarimanesh AA, Sadeghi M, Sedighi M, Karimzadeh P, Ghofrani M. Comparison of propranolol and pregabalin for prophylaxis of childhood migraine: A randomized controlled trial. Acta Med Iran 53, 276-280, 2015 Available from:. https://pubmed.ncbi.nlm.nih.gov/26024701/

48. Balamurugan E, Aggarwal M, Lamba A, Dang N, Tripathi M. Perceived trigger factors of seizures in persons with epilepsy. Seizure 22; 743-747, 2013. Available from: https://doi.org/10.1016/j.seizure.2013.05.018

49. Baldacci F, Lucchesi C, Cafalli M, Poletti M, Ulivi M, Vedovello M, et al. Migraine features in migraineurs with and without anxiety-depression symptoms: a hospitalbased study. Clin Neurol Neurosurg 132, 74-78, 2015. Available from: https://doi.org/10.1016/j.clineuro.2015.02.017

Citation: Gupta VK. Cortical Spreading Depression and Migraine: Critical Review of a Neurophysiological Principle in the Third Millennium. Glob J Medical Clin Case Rep. 2026:13(10):228-272. Available from: https://dx.doi.org/10.17352/gjmccr.000273

50. Baldrati A, Cortelli P, Procaccianti G, Gamberini G, D'Alessandro R, Baruzzi A et al. Propranolol and acetylsalicylic acid in migraine prophylaxis. Double-blind crossover study. Acta Neurol Scand 67, 181-186, 1983. Available from: https://doi.org/10.1111/j.1600-0404.1983.tb04561.x

51. Bannister LH, Berry MM, Collins P, Dyson M, Dussek JE, Ferguson MWJ. Gray's Anatomy, 38th ed. New York, Churchill Livingstone, 1995, p. 1232.

52. Barbanti P, Fabbrini G, Pesare M, Vanacore N, Cerbo R. Unilateral cranial autonomic symptoms in migraine. Cephalalgia 22; 256-259, 2002. Available from: https://doi.org/10.1046/j.1468-2982.2002.00358.x

53. Bar M, Peles I, Ifergane G, Tsumi E, Kratz A. The association between migraine and glaucoma diseases: A retrospective cohort study. Headache. 65: 1-11, 2025. Available from: https://doi.org/10.1111/head.15079

54. Bartsch T. Migraine and the neck: new insights from basic data. Curr Pain Headache Rep 9: 191-196, 2005.

55. Battistella PA, Mattesi P, Casara GL, Carollo C, Condini A, Allegri F et al. Bilateral cerebral occipital calcifications and migraine-like headache. Cephalalgia 7:125-129, 1987. Available from: https://doi.org/10.1046/j.1468-2982.1987.0702125.x

56. Baudry M, Martres MP, Schwartz JC. ^{3}H domperidone: a selective ligand for dopamine receptors. Naunyn-Scheimedeberg's Arch Pharmac 308, 231-237, 1979.

57. Bauer PR, Carpay JA, Terwindt GM, Sander JW, Thijs RJ, Haan J et al. Headache and epilepsy. Curr Pain Headache Rep 17: 351, 2013. Available from: https://doi.org/10.1007/s11916-013-0351-x

58. Beal JC, Sogawa Y, Ceresnak SR, Mahgerefteh J, Moshe SL. Late-onset ictal asystole in refractory epilepsy. Pediatr Neurol 45; 253-255, 2011.

59. Becerra L, Bishop J, Barmettler G, Xie Y, Navratilova E, Porreca F, Borsook D. Triptans disrupt brain networks and promote stress-induced CSD-like responses in cortical and subcortical areas. J Neurophysiol 115, 208-217, 2016.

60. Benseñor IM, Cook NR, Lee I-M, Chown MJ, Hennekens CH, Buring JE. Lowdose aspirin for migraine prophylaxis in women. Cephalalgia 21, 175-183, 2001.

61. Berg AT, Berkovic SF, Brodie MJ, Buchhalter J, Cross JH, van Emde Boas W et al. Revised terminology and concepts for organization of seizures and epilepsies: report of the ILAE Commission on Classification and Terminology, 2005-2009. Epilepsia 51; 676-685, 2010.

62. Bergen DC. In a heartbeat: autonomic changes during seizures. Epilepsy Curr 5; 194-196, 2005.

63. Bigal ME, Hargreaves RJ. Why does sleep stop migraine? Curr Pain Headache Rep 17; 369, 2013.

64. Bigal ME, Lipton RB. The epidemiology, burden, and comorbidities of migraine. Neurol Clin 27; 321-334, 2009.

65. Biller A, Reuter M, Patenaude B, Homola GA, Breuer F, Bendszus M et al. Responses of the human brain to mild dehydration and rehydration explored in vivo by 1H-MR imaging and spectroscopy. Am J Neuroradiol 36, 2277-2284, 2015. Available from: https://doi.org/10.3174/ajnr.A4508

66. Blau JN. The clinical diagnosis of migraine: the beginning of therapy. J Neurol 238 (Suppl 1), S6-S11, 1991. Available from: https://doi.org/10.1007/BF01642899

67. Blau JN. Migraine: theories of pathogenesis. Lancet 339: 1202--1207, 1992a. Available from: https://doi.org/10.1016/0140-6736(92)91140-4

68. Blau JN. Migraine triggers: practice and theory. Pathol Biol 40: 367--372, 1992b.

69. Blau JN. The challenge of unexplained diseases: migraine. J Roy Soc Med 85, 593594, 1992c.

70. Blau JN, MacGregor EA. Migraine and the neck. Headache 34, 88-90, 1994. Available from: https://doi.org/10.1111/j.1526-4610.1994.hed3402088.x

71. Blom JD. Alice in Wonderland syndrome. A systematic review. Neurol Clin Pract. 6: 259-270, 2016. Available from: https://doi.org/10.1212/CPJ.0000000000000251

72. Bogdanov VB, Multon S, Chauvel V, Bogdanova OV, Prodanov D, Makarchuk MY, Schoenen J. Migraine preventive drugs differentially affect cortical spreading depression in rat. Neurobiol Dis 41: 430-435, 2011.

73. Bogduk N. Anatomy and physiology of headache. Biomed & Pharmacother 49, 435445, 1995.

74. Bogduk N. The neck and headaches. Neurol Clin 22, 151-171, 2004.

75. Bolay H, Reuter U, Dunn AK, Huang Z, Boas DA, Moskowitz MA. Intrinsic brain activity triggers trigeminal meningeal afferents in a migraine model. Nat Med 8, 136142, 2002.

76. Bono G, Manzoni GC, Martucci N, Saquegna T, Miceli G, Nappi G et al. Flunarizine treatment in migraine syndrome: long-term follow up in common migraine and preliminary results in migraine with paroxysmal headache. Cephalalgia 5, 538539, 1985.

77. Bonuso S, Marano E, Di Stasio E, Sorge F, Barbieri F, Ullucci EA. Source of pain and primitive dysfunction in migraine: an identical site? J Neurol Neurosurg Psych 52, 1351-1354, 1989.

78. Borgdorff P. Arguments against the role of cortical spreading depression in migraine. Neurol Res 40, 173-181, 2018. Available from: https://doi.org/10.1080/01616412.2018.1428406

79. Borkum JM. Migraine triggers and oxidative stress: a narrative review and synthesis. Headache 56, 12-35, 2016.

80. Born J, Kellner C, Uthgenannt D, Kern W, Fehm HL. Vasopressin regulates human sleep by reducing rapid-eye-movement sleep. Am J Physiol 262 (3 Pt 1): E295-300, 1992.

81. Bose P, Karsan N, Goadsby PJ. The migraine postdrome. Continuum 24; 1023-1031, 2018.

82. Bouida W, Beltaief K, Msolli MA, Azaiez N, Ben Soltane H, Sekma A et al. Low dose magnesium sulfate versus high dose in the early management of rapid atrial fibrillation: randomised controlled double blind study. (LOMAGHI Study). Acad Emerg Med 26: 183-191, 2019. Available from: https://doi.org/10.1111/acem.13522

83. Boyer EW, Shannon M. The serotonin syndrome. N Engl J Med 352, 1112-1120, 2005.

84. Brand S, Fernandes de Lima VM, Hanke W. Pharmacological modulation of the refractory period of retinal spreading depression. Naunyn Schmiedebergs Arch Pharmacol 357, 419-425, 1998.

85. Brennan KC. Turn down the lights!: an irritable occipital cortex in migraine without aura. Neurology 76, 206-207, 2011.

86. Brennan KC, Pietrobon D. A systems neuroscience approach to migraine. Neuron 97: 1004-1021, 2018. DOI Available from: https://doi.org/10.1016/j.neuron.2018.01.029

87. Breslau N, Schultz L, Lipton R, Peterson E, Welch KMA. Migraine headaches and suicide attempt. Headache 52: 723-731, 2012.

88. Brewerton TD, Murphy DL, Mueller EA, Jimerson DC. Induction of migraine-like headaches by the serotonin agonist m-chlorophenylpiperazine. Clin Pharmacol Ther 43: 605-609, 1988.

89. Brighina F, Piazza A, Vitello G, Aloisio A, Palermo A, Daniele O, et al. tTMS of the prefrontal cortex in the treatment of chronic migraine: a pilot study. J Neurol Sci 227: 67-71, 2004.

Citation: Gupta VK. Cortical Spreading Depression and Migraine: Critical Review of a Neurophysiological Principle in the Third Millennium. Glob J Medical Clin Case Rep. 2026:13(10):228-272. Available from: https://dx.doi.org/10.17352/gjmccr.000273

90. Brismar K, Hylander B, Eliasson K, Rössner S, Wetterberg L. Melatonin secretion related to side-effects of beta-blockers from the central nervous system. Acta Med Scand 223: 525-530, 1988.

91. Bruera OC, Lourdes Figuerola M, Gandolfo C, Saggese J, Gilio JA. Status migrainosus: an unusual presentation of a brain abscess. Headache 39: 55-57, 1999.

92. Brundel M, van den Heuvel M, de Bresser J, Kappelle LJ, Biessels GJ; Utrecht Diabetic Encephalopathy Study Group. Cerebral cortical thickness in patients with type 2 diabetes. J Neurol Sci 15, 299, 126-130, 2010.

93. Bureš J, Burešova O, Křivanek J. The mechanisms and applications of Leão's spreading depression of electroencephalographic activity. Prague: Academia, 1974.

94. Bureš J, Burešova O, Křivanek J. The meaning and significance of Leão's spreading depression [review]. An Acad Bras Cienc 56: 385-400, 1984.

95. Burstein R, Cutrer FM, Yarnitsky D. The development of cutaneous allodynia during a migraine attack: clinical evidence for the sequential recruitment of spinal and supraspinal nociceptive neurons in migraine. Brain 123: 1703-1709, 2000.

96. Burstein R, Levy D, Jakubowski M. Effects of sensitization of trigeminovascular neurons to triptan therapy during migraine. Rev Neurol 161, 658-660, 2005.

97. Burstein R, Noseda R, Borsook D. Migraine: multiple processes, complex pathophysiology. J Neurosci 35: 6619-6629, 2015.

98. Burstein B, Waterfield T, Umana E, Xie J, Kuppermann N. Prediction of bacteremia and bacterial meningitis among febrile infants aged 28 days or younger. JAMA 335:425-433, 2026. Available from: https://doi.org/10.1001/jama.2025.21454

99. Burstein R, Yarnitsky D, Goor-Aryeh I, Ransil BJ, Bajwa ZH. An association between migraine and cutaneous allodynia. Ann Neurol 47, 614-624, 2000.

100. Busch V, Gaul C. Exercise in migraine therapy—is there any evidence for efficacy? A critical review. Headache 48, 890-899, 2008.

101. Buse DC, Manack A, Serrano D, Turkel C, Lipton RB. Sociodemographic and comorbidity profiles of chronic migraine and episodic migraine sufferers. J Neurol Neurosurg Psychiatry 81: 428-432, 2010. Available from: https://doi.org/10.1136/jnnp.2009.192492

102. Buzzi MG, Cologno D, Formisano R. Migraine disease: evolution and progression. J Headache Pain 6, 304-306, 2005. Available from: https://doi.org/10.1007/s10194-005-0215-9

103. Cain SM, Bohnet B, LeDue J, Yung AC, Garcia E, Tyson JR, et al. In vivo imaging reveals that pregabalin inhibits cortical spreading depression and propagation to subcortical brain structures. PNAS 114, 2401-2406, 2017. https://doi.org/10.1073/pnas.1614447114

104. Calandre EP, Garcia-Leiva JM, Rico-Villademoros F, Vilchez JS, RodriguezLopez CM. Pregabalin in the treatment of chronic migraine: An open-label study. Clin Neuropharmacol 33, 35-39, 2010. Available from: https://doi.org/10.1097/WNF.0b013e3181bf1dbe

105. Cameron C, Kelly S, Hsieh SC, Murphy M, Chen L, Kotb A, Peterson J, Coyle D, Skidmore B, Gomes T, Clifford T, Wells G. Triptans in the acute treatment of migraine: a systematic review and network meta-analysis. Headache 55 Suppl. 4, 221-35, 2015. Available from: https://doi.org/10.1111/head.12601

106. Campbell JK. Facial pain due to migraine and cluster headache. Semin Neurol 8: 324--331, 1988.

107. Campbell JK. Manifestations of migraine. In: Neurologic Clinics, Headache, ed. Ninan T. Mathew. Philadelphia, W.B. Saunders Company, Vol 8 (4), pp 841-855, 1990.

108. Cao Y, Welch KMA, Aurora S, Vikingstad EM. Functional MRI-BOLD of visually triggered headache in patients with migraine. Arch Neurol 56, 548-554, 1999 Available from: https://doi.org/10.1001/archneur.56.5.548

109. Cao Y, Zheng OJ. Tonabersat for migraine prophylaxis: a systematic review. Pain Physician 17, 1-8, 2014.

110. Carpenter DO, Briggs DB, and Strominger N. Peptide-induced emesis in dogs. Behav Brain Res 11, 277–281, 1984. Available from: https://doi.org/10.1016/0166-4328(84)90220-1

111. Carrel A. Man, The Unknown. Hamish Hamilton Ltd., London, 1959.

112. Carturan P, Scorcine C, Fragoso YD. Migraine in the post-menopausal period is associated with higher levels of mood disorders, disability, and more menopausal symptoms. Arq Neuropsiquiatr 74; 999-1002, 2016. Available from: https://doi.org/10.1590/0004-282X20160153

113. Centonze V, Magrone D, Vino M, Caporaletti P, Attolini E, Campanale G et al. Flunarizine in migraine prophylaxis: efficacy and tolerability of 5 mg and 10 mg dose levels. Cephalalgia 10, 17-24, 1990.

114. Chai NC, Shapiro RE, Rapoport AM. Why does vomiting stop a migraine attack? Curr Pain Headache Rep 17, 362, 2013.

115. Chaibi A, Tuchin PJ, Russell MB. Manual therapies for migraine: a systematic review. J Headache Pain 12, 127-133, 2011. Available from: https://doi.org/10.1007/s10194-011-0296-6

116. Chang JC, Brennan KC, He D, Huang H, Miura RM, Wilson PL, Wylie JJ. A mathematical model of the metabolic and perfusion effects on cortical spreading depression. PLoS One 14;8(8):e70469, 2013. Available from: https://doi.org/10.1371/journal.pone.0070469

117. Chang CH, Yang YH, Lin SJ, Su JJ, Cheng CL, Lin LJ. Risk of insomnia attributable to β-blockers in elderly patients with newly diagnosed hypertension. Drug Metab Pharmacokinet 28, 53-58, 2013.

118. Charles AC, Baca SM. Cortical spreading depression and migraine. Nat Rev Neurol 9, 637-644, 2013. Available from: https://doi.org/10.1038/nrneurol.2013.192

119. Charlton BG. Stress. J Med Ethics 18, 156-159, 1992.

120. Chen Z, Sun J, Yang Y, Lou X, Wang Y, Wang Y et al. Cortical thinning in type 2 diabetes mellitus and recovering effects of insulin therapy. J Clin Neurosci 22; 275279, 2015.

121. Cheung BS, Kohl RL, Money KE, Kinter LB. Etiologic significance of arginine vasopressin in motion sickness. J Clin Pharmacol 34, 664-670, 1994.

122. Chiodera P, Volpi R, Delsignore R, Marchesi C, Salati G, Camellini L, Rossi G et al. Different effects of metoclopramide and domperidone on arginine-vasopressin secretion in man. Br J Clin Pharmac 22, 479-482, 1986.

123. Chizh BA, Göhring M, Tröster A, Quartey GK, Schmelz M, Koppert W. Effects of oral pregabalin and aprepitant on pain and central sensitization in the electrical hyperalgesia model in human volunteers. Br J Anaesth 98, 246-254, 2007.

124. Chong CD, Dodick DW, Schalaggar BL, Schwedt TJ. Atypical age-related cortical thinning in episodic migraine. Cephalalgia 34, 1115-1124, 2014.

125. Chong CD, Schwedt TJ, Dodick DW. Migraine: what imaging reveals. Curr Neurol Neurosci Rep 16; 64, 2016.

126. Chopra SS, Kulkarni SD, Hegde AU, Shah KN. Cyclical vomiting syndrome with bilateral epileptiform discharges. Indian Pediatr 48, 143-145, 2011.

127. Choudhuri R, Cui L, Yong C, Bowyer S, Klein RM, Welck KM et al. Cortical spreading depression and gene regulation: relevance to migraine. Ann Neurol 51, 499-506, 2002. Available from: https://doi.org/10.1002/ana.10158

128. Christiansen I, Thomsen LL, Daugaard D, Ulrich V, Olesen J. Glyceryl trinitrate induces attacks of migraine without aura in sufferers of migraine

Citation: Gupta VK. Cortical Spreading Depression and Migraine: Critical Review of a Neurophysiological Principle in the Third Millennium. Glob J Medical Clin Case Rep. 2026:13(10):228-272. Available from: https://dx.doi.org/10.17352/gjmccr.000273

with aura. Cephalalgia 19, 660-667, 1999. Available from: https://doi.org/10.1046/j.1468-2982.1999.019007660.x

129. Chronicle EP, Mulleners WM. Visual system dysfunction in migraine: a review of clinical and psychological findings. Cephalalgia 16, 525-535, 1996. Available from: https://doi.org/10.1046/j.1468-2982.1996.1608525.x

130. Chrousos GP, Gold PW. In: Stress: Basic Mechanisms and Clinical Implications. Eds. GP Chrousos, R McCarty, K Pacák, G Cizza, E Sternberg, Gold PW, R

131. Kvetňanský. Annals of the New York Academy of Sciences, 771: xv-xviii, 1995.

132. Close LN, Eftekhari S, Wang M, Charles AC, Russo AF. Cortical spreading depression as a site of origin for migraine: role of CGRP. Cephalalgia 2019; 39:428434. Available from: https://doi.org/10.1177/0333102418774299

133. Coghill RC, Sang CN, Berman KF, Bennett GJ, Iadarola MJ. Global cerebral blood flow decreases during pain. J Cereb Blood Flow Metab 18: 141-147, 1998.

134. Cohen F, Brooks CV, Sun D, Buse DC, Reed ML, Fanning KM, et al. Prevalence and burden of migraine in the United States: A systematic review. Headache 64(5):516-532, 2024. https://doi.org/10.1111/head.14709

135. Colombo B, Annovazzi PO, Comi G. Therapy of primary headaches: the role of antidepressants. Neurol Sci 25, S171-S175, 2004.

136. Colombo B, Saraceno L, Comi G. Riboflavin and migraine: the bridge over troubled mitochondria. Neurol Sci 35 Suppl 1, 141-144, 2014.

137. Conforto AB, Amaro E Jr, Gonçalves AL, Mercante JP, Guendler VZ, Ferraira JR, et al. Randomized, proof-of-principle clinical trial of active transcranial magnetic stimulation in chronic migraine. Cephalalgia 34, 464-472, 2014.

138. Constantinides V, Anagnostou E, Bougea A, Paraskevas G, Kapaki E, Evdokimidis I, Kararizou E. Migraine and tension-type headache triggers in a Greek population. Arq Neuropsiquiatr 73: 665-669, 2015. https://doi.org/10.1590/0004-282X20150093

139. Coppola G, Pierelli F, Schoenen J. Is the cerebral cortex hyperexcitable or hyperresponsive in migraine? Cephalalgia 27, 1427-1439, 2007.

140. Costa C, Tozzi A, Rainero I, Cupini LM, Calabresi P, Ayata C et al. Cortical spreading depression as a target for anti-migraine agents. J Headache Pain 14, 62, 2013.

141. Couch JR, for the Amitriptyline Versus Placebo Study Group. Amitriptyline in the prophylactic treatment of migraine and chronic daily headache. Headache 51, 33-51, 2011.

142. Couch JR, Hassanein RS. Amitriptyline in migraine prophylaxis. Arch Neurol 36, 695-699, 1979.

143. Couturier EGM, Hering R, Steiner TJ. Weekend attacks in migraine patients: caused by caffeine withdrawal? Cephalalgia 12, 99-100, 1992.

144. Covanis A. Panayiotopoulos syndrome: a benign childhood autonomic epilepsy frequently imitating encephalitis, syncope, migraine, sleep disorder, or gastroenteritis. Pediatrics 118, e1237-1243, 2006.

145. Cowen PJ, Bevan JS, Gosden B, Elliott SA. Treatment with beta-adrenoceptor blockers reduces plasma melatonin concentration. Br J Clin Pharmacol 19, 258-260, 1985.

146. Cozzolino O, Marchese M, Trovato F, Pracucci E, Ratto GM, Buzzi MG, Sicca F, Santorelli FM. Understanding spreading depression from headache to sudden unexpected death. Front Neurol 9: 19, 2018.

147. Crevits L, Bosman T. Migraine-related vertigo: towards a distinctive entity. Clin Neurol Neurosurg 107, 82-87, 2005. https://doi.org/10.1016/j.clineuro.2004.07.003

148. Cruickshank JM. The clinical importance of cardio-selectivity and lipophilicity in betablockers. Am Heart J 100; 160-178, 1980.

149. Cruickshank JM, Prichard BNC. Beta-Blockers in Clinical Practice. 2. Edinburgh: Churchill Livingstone; 1994.

150. Cruikshank DP, Pitkin RM, Reynolds WA, Williams GA, Hargis GK. Effects of magnesium sulfate treatment on perinatal calcium metabolism. I. Maternal and fetal responses. Am J Obstet Gynecol 134, 243-249, 1979.

151. Cubeddu LX, Lindley CM, Wetsel W, Carl PL, Negro-Vilare A. Role of angiotensin II and vasopressin in cisplatin-induced emesis. Life Sci 46, 699-705, 1990.

152. Curfman D, Chilunga M, Daroff RB, Alsheklee A, Chelimsky G, Chelimsky TC. Syncopal migraine. Clin Auton Res 22, 17-23, 2012.

153. Custer PL, Reistad CE. Enuleation of blind, painful eyes. Ophthal Plast Reconstr Surg 16, 326-329, 2000.

154. Cutrer FM, Sorensen AG, Weisskoff RM, Østergaard L, Sanchez del Rio M, Lee EJ, et al. Perfusion-weighted imaging defects during spontaneous migrainous aura. Ann Neurol 43, 25-31, 1998. https://doi.org/10.1002/ana.410430108

155. Dahlem MA, Müller SC. Self-induced splitting of spiral-shaped spreading depression waves in chicken retina. Exp Brain Res 115, 319-324, 1997.

156. Dahlöf C, Maassen Van Den Brink A. Dihydroergotamine, ergotamine, methysergide and sumatriptan - basic science in relation to migraine treatment. Headache 52, 707-714, 2012.

157. Darling M. Exercise and migraine. A critical review. J Sports Med Phys Fitness 31, 294-302, 1991.

158. DaSilva AF, Granziera C, Snyder J, Hadjikhani N. Thickening in the somatosensory cortex of patients with migraine. Neurology 69, 1990-1995, 2007.

159. Datta R, Detre JA, Aguirre GK, Cucchiara B. Absence of changes in cortical thickness in patients with migraine. Cephalalgia 31,1452-1458, 2011.

160. de la Fuente JR, Berlanga C, León-Andrade C. Mania induced by tricyclic-MAOI combination therapy in bipolar treatment-resistant disorder: case reports. J Clin Psychiatry 47, 40-41, 1986.

161. DeLange JM, Cutrer FM. Our evolving understanding of migraine with aura. Curr Pain Headache Rep 18, 453, 2014.

162. de Lima AM, Sapienza GB, Giraud VD, Fragoso YD. Odors as triggering and worsening factors for migraine in men. Arq Neuropsiquiatr 69, 324-327, 2011.

163. Deneulle M, Fabre N, Payoux P, Chollet F, Geraud G. Posterior cerebral hypoperfusion in migraine without aura. Cephalalgia 28, 856-862, 2008 Available from:. https://doi.org/10.1111/j.1468-2982.2008.01623.x

164. Denuelle M, Fabre N. Functional neuroimaging of migraine. Rev Neurol 169, 380389, 2013.

165. De Simone R, Ranieri A, Marano E, Beneduce L, Ripa P, Bilo L et al. Migraine and epilepsy: clinical and pathophysiological relations. Neurol Sci 28, S150-S155, 2007.

166. Devineni T. Human evolution and the origin of migraine. NHF Headlines 144: 4-5, 2005.

167. Dewitte V, De Pauw R, Danneels L, Bouche K, Roets A, Cagnie B. The interrater reliability of a pain mechanisms-based classification for patients with nonspecific neck pain. Braz J Phys Ther. 23(5); 437-447, 2019. doi: 10.1016/j.bjpt.2018.,2019.

Citation: Gupta VK. Cortical Spreading Depression and Migraine: Critical Review of a Neurophysiological Principle in the Third Millennium. Glob J Medical Clin Case Rep. 2026:13(10):228-272. Available from: https://dx.doi.org/10.17352/gjmccr.000273

168. Dhuna A, Pascaul-Leone A, Belgrade M. Cocaine-related vascular headaches. J Neurol Neurosurg Psychiatry 54, 803-806, 1991.

169. Didangelos T, Doupis J, Veves A. Painful diabetic neuropathy: clinical aspects. Handb Clin Neurol 126, 53-61, 2014. Available from: https://doi.org/10.1016/B978-0-444-53480-4.00005-9

170. Diener HC. Pharmacological approaches to migraine. J Neural Transm Suppl 64: 35-63, 2003.

171. Diener H-C, Lampl C, Reimnitz P, Voelker M. Aspirin in the treatment of acute migraine attacks. Expert Rev Neurother 6, 563-573, 2006.

172. Digre KB, Brennan KC. Shedding light on photophobia. J Neuroophthalmol 32, 6881, 2012.

173. Dikmen PY, Yavuz BG, Aydinlar EI. The relationships between migraine, depression, anxiety, stress, and sleep disturbances. Acta Neurol Belg 115, 117-122, 2015.

174. Dilli E, Halker R, Vargas B, Hentz J, Radam T, Rogers R, et al. Occipital nerve block for the short-term preventive treatment of migraine: A randomized, doubleblinded, placebo-controlled study. Cephalalgia 35, 959-68, 2015.

175. Dilsaver SC, Greden JF. Mania induced by antidepressant withdrawal. Psychosomatics 27, 798-799, 1986.

176. Dodick DW. Tonabersat for migraine prevention: new life or last gasp? Lancet Neurol 8, 693-695, 2009.

177. Dodick DW. A phase-by-phase review of migraine pathophysiology. Headache 58 Suppl 1, 4-16, 2018. doi: 10.1111/head.13300. Available from: https://doi.org/10.1111/head.13300

178. Dodick DW, Freitag F, Banks J, Saper J, Xiang J, Rupnow M et al. CAPSS-277 Investigator Group. Topiramate versus amitriptyline in migraine prevention: a 26week, multicenter, randomized, double-blind, double-dummy, parallel-group noninferiority trial in adult migaineurs. Clin Ther 31: 542-559, 2009.

179. Dorhout Mees SM, Algra A, Wong GK, Poon WS, Bradford CM, Saver JL et al. Early magnesium treatment after aneurysmal subarachnoid hemorrhage: individual patient data meta-analysis. Stroke 46, 3190-3193, 2015. Available from: https://doi.org/10.1161/STROKEAHA.115.010575

180. DosSantos MF, Holanda-Afonso RC, Lima RL, DaSilva AF, Moura-Neto V. The role of the blood-brain barrier in the development and treatment of migraine and other pain disorders. Front Cell Neurosci 8: 302, 2014.

181. Drummond PD. A quantitative assessment of photophobia in migraine and tension headache. Headache 26, 465-469, 1986.

182. Drummond PD, Granston A. Facial pain increases nausea and headache during motion sickness in migraine sufferers. Brain 127, 526-534, 2004.

183. Duarte MA, Almeida AC, Infantosi AF, Bassani JW. Functional imaging of the retinal layers by laser scattering: an approach for the study of Leao's spreading depression in intact tissue. J Neurosci Methods 123, 139-151, 2003.

184. Duckrow RB. Regional cerebral blood flow during spreading cortical depression in conscious rats. J Cereb Blood Flow Metab 11, 150-154, 1991.

185. Duckrow RB. A brief hypoperfusion precedes spreading depression if nitric oxide synthesis is inhibited. Brain Res. 618: 190-195, 1993.

186. Durham PL, Garrett FG. Neurological mechanisms of migraine: potential of the gapjunction modulator tonabersat in prevention of migraine. Cephalalgia 29 Suppl, 2,1-6, 2009. Available from: https://doi.org/10.1179/016164109X12553302210338

187. Dworkin RH, Corbin AE, Young JP Jr, Sharma U, LaMoreaux L, Bockbrader H et al. Pregabalin for the treatment of postherpetic neuralgia: A randomized placebocontrolled trial. Neurology 60, 1274-1283, 2003. Available from: https://doi.org/10.1212/01.WNL.0000076288.93002.92

188. Edmeads J. What is migraine? Controversy and stalemate in migraine pathophysiology. J Neurol 238: S2--S5, 1991.

189. Edvardsson B. Atenolol in the prophylaxis of chronic migraine: a 3-month open label study. SpringerPlus 2: 479, 2013. https://doi.org/10.1186/2193-1801-2-479

190. Edvinsson L. CGRP blockers in migraine therapy: where do they act? Br J Pharmacol 155, 967-969, 2008.

191. Edvinsson L. Tracing neural connections to pain pathways with relevance to primary headaches. Cephalalgia 31, 737-747, 2011.

192. Edvinsson L, Tfelt-Hansen P. The blood-brain barrier in migraine treatment. Cephalalgia 28, 1245-1258, 2008. Available from: https://doi.org/10.1111/j.1468-2982.2008.01675.x

193. Edwards CM, Carmichael J, Baaylis PH, Harris AL. Arginine vasopressin—a mediator of chemotherapy induced emesis? Br J Cancer 59, 467-470, 1989.

194. Eikermann-Haerter, K. Spreading depolarization may link migraine and stroke. Headache 54, 1146-1157, 2014.

195. Eken C. Critical reappraisal of intravenous metoclopramide in migraine attack: a systematic review and meta-analysis. Am J Emerg Med 33, 331-337, 2015. Emilien G, Maloteaux JM. Current therapeutic uses and potential of betaadrenoceptor agonists and antagonists. Eur J Clin Pharmacol 53: 389-404, 1998.

196. Engelhardt E, Gomes MM. Aristides Leão: a birth centennial homage with comments on his spreading depression. Arq Neuropsiquiatr 73, 544-546, 2015.

197. Erdélyi-Bótor S, Aradi M, Kamson DO, Kovács N, Perlaki G, Orsi G et al. Changes of migraine-related white matter hyperintensities after 3 years: a longitudinal MRI study. Headache 55, 55-70, 2015.

198. Esen F, Erdem T, Aktan D, Kalayci R, Cakar N, Kaya M, et al. Effects of magnesium administration on brain edema and blood-brain barrier breakdown after experimental traumatic brain injury in rats. J Neurosurg Anesthesiol 15, 119-125, 2003.

199. Esen F, Erdem T, Aktan D, Orhan M, Kaya M, Eraksoy H, et al. Efficacy of magnesium sulphate administration on blood-brain barrier in a rat model of intraperitoneal sepsis: a randomized controlled experimental study. Crit Care 9, R1823, 2005.

200. Eskin M, Akyol A, Çelik EY, Gültekin BK. Social problem-solving, perceived stress, depression and life-satisfaction in patients suffering from tension type and migraine headaches. Scand J Psychol 54, 337-343, 2013.

201. Espeseth T, Westlye LT, Walhovd KB, Fjell AM, Endestad T, Rootwelt H, et al. Apolipoprotein E ε4-related thickening of the cerebral cortex modulates selective Available from: https://doi.org/10.1016/j.neurobiolaging.2009.12.027

202. attention. Neurobiol Aging 33, 304-322, 2012. Available from: https://doi.org/10.1212/01.WNL.0000090628.46508.D4

203. Evans RW, Lipton RB, Silberstein SD. The prevalence of migraine in neurologists. Neurology 61: 1271–1272, 2003. Available from: https://doi.org/10.1111/ene.12547

204. Fagernæs CF, Heuch I, Zwart JA, Winsvold BS, Linde M, Hagen K. Blood pressure as a risk factor for headache and migraine: a prospective population-based study. Eur J Neurol 22, 156-162, e10-11, 2015. Available from: https://doi.org/10.1186/s10194-016-0716-8

205. Faragó P, Tuka B, Tóth E, Szabó N, Király A, Csete G et al. Interictal brain activity differs in migraine with and without aura: resting state

Citation: Gupta VK. Cortical Spreading Depression and Migraine: Critical Review of a Neurophysiological Principle in the Third Millennium. Glob J Medical Clin Case Rep. 2026:13(10):228-272. Available from: https://dx.doi.org/10.17352/gjmccr.000273

fMRI study. J Headache Pain 18; 8, 2017. Available from: https://doi.org/10.1177/2515816318788284

206. Farris SG, Thomas JG, Abrantes AM, Godley FA, Roth JL, Lipton RB, Pavlovic J, Bond DS. Intentional avoidance of physical activity in women with migraine. Cephalalgia Reports 1; 1-8, 2018.

207. Featherstone HJ. Headache and heart disease: the lack of a positive association. Headache 26, 39-41, 1986. Available from: https://doi.org/10.7326/0003-4819-120-9-199405010-00012

208. Feinstein AR. Clinical judjment revisited: the distractions of quantitative models. Ann Intern Med 120, 799-805, 1994. Available from: https://doi.org/10.1007/s10194-011-0300-1

209. Fengpeng L, Enchao Q, Zhao D, Ruozhuo L, Shiwen W, Shengyuan Yu. Protection of flunarizine on cerebral mitochondria injury induced by cortical spreading depression under hypoxic conditions. J Headache Pain 12, 47-53, 2011. Available from: https://doi.org/10.1016/S1474-4422(14)70220-0

210. Ferrari MD, Klever RR, Terwindt GM, Ayata C, van den Maagdenberg AM. Migraine pathophysiology: lessons from mouse models and human genetics. Lancet Neurol 14: 65-80, 2015. Available from: https://doi.org/10.1016/0014-2999(78)90265-0

211. Ferreira SH, Lorenzetti BB, Corrêa FMA. Central and peripheral antianalgesic action of aspirin-like drugs. Eur J Pharmacol 53, 39-48, 1978.

212. Fine PG, Digre KB. A controlled trial of regional sympatholysis in the treatment of photo-oculodynia syndrome. J Neuroophthalmol 15, 90-94, 1995.

213. Fisher CM. Late-life migraine accompaniments as a cause of unexplained transient ischemic attacks. Can J Neurol Sci. 7, 9-17, 1980. Available from: https://doi.org/10.1046/j.1526-4610.1999.3906391.x

214. Fisher CM. Late life (migrainous) scintillating zigzags without headache: one person's 27 years experience. Headache 39, 391-397, 1999.

215. Fisher MJ. Goodbye headaches: a gun that shoots magnetic pulses puts an end to an age-old scourge. Discover 25, 28-29, 2004. Available from: https://doi.org/10.1073/pnas.1508831112

216. Fjell AM, Grydeland H, Krogsrud SK, Amlien I, Rohani DA, Ferschmann L et al. Development and aging of cortical thickness correspond to genetic organization patterns. Proc Natl Acad Sci U S A 112: 15462-15467, 2015. doi: 10.1073/pnas.1508831112.

217. Foroozan R, Cutrer FM. Transient neurologic dysfunction in migraine. Neurol Clinics 27; 361-378, 2009. Available from: https://doi.org/10.1111/j.1526-4610.1983.hed2304188.x

218. Forssman B, Lindblad CJ, Zbomikova V. Atenolol for migraine prophylaxis. Headache 23, 188-190, 1983.

219. Fox RH. Dr. John Fothergill and His Friends. London, Macmillan and Co., 1919, p. 61.

220. Freitag FG, Diamond S. Nadolol and placebo comparison study in the prophylactic treatment of migraine. J Am Osteopath Assoc 84; 343–347, 1984. Available from: https://doi.org/10.1161/01.STR.25.5.974

221. Friberg L, Olesen J, Lassen NA, Olsen TS, Karle A. Cerebral oxygen extraction, and regional cerebral blood flow during the aura phase of migraine. Stroke 25; 974979, 1994.

222. Friedman AP. Headache. eds. AB Baker, RJ Joynt, in: Clinical Neurology, Harper & Row. Philadelphia, 1985, pp.1-50.

223. Friedman DI. The eye and headache. Ophthalmol Clin N Am 17; 357-369, 2004. Available from: https://doi.org/10.1007/s11916-008-0050-1

224. Friedman DI. Headache and the eye. Curr Pain Headache Rep 12; 296-304, 2008. Available from: https://doi.org/10.1111/head.12228

225. Friedman DI. Unanswered questions in headache: so what is photophobia, anyway? Headache Currents 53; 1675-1676, 2013. https://doi.org/10.1111/j.1526-4610.2009.01443.x

226. Friedman DI, De ver Dye T. Migraine and the environment. Headache 49, 941-952, 2009. Available from: https://doi.org/10.1136/bmj.297.6664.1670

227. Fuller GN, Gale MV. Migraine aura as artistic inspiration. BMJ 297; 1670-1672, 1988. Available from: https://doi.org/10.1212/01.CON.0000421621.18407.96

228. Furman JM, Marcus DA. Migraine and motion sensitivity. Continuum 18; 11021117, 2012. Available from: https://doi.org/10.1016/j.pneurobio.2009.07.005

229. Galletti F, Cupini LM, Corbelli I, Calabresi P, Sarchielli P. Pathophysiological basis of migraine prophylaxis. Prog Neurobiol 89; 176-192, 2009. Available from: https://doi.org/10.1177/155005948201300102

230. Gastaut H. A new type of epilepsy: benign partial epilepsy of childhood with occipital spike-waves. Clin Electroencephalogr 13; 13-22, 1982. https://doi.org/10.1212/WNL.0b013e31829d872a

231. Gelfand AA, Reider AC, Goadsby PJ. Cranial autonomic symptoms in pediatric migraine are the rule, not the exception. Neurology 81: 431-436, 2013. https://doi.org/10.1046/j.1468-2982.1982.0201029.x

232. Gelmers HJ. Common migraine attacks preceded by focal hyperemia and parietal oligemia in the rCBF pattern. Cephalalgia 2: 29-32, 1982. Available from: https://doi.org/10.1016/j.survophthal.2014.06.003

233. Gersztenkorn D, Lee AG. Palinopsia revamped: a systematic review of the literature. Surv Ophthalmol 60; 1-35, 2015.

234. Ghaemi A, Alizadeh L, Babaei S, Jafarian M, Khaleghi Ghadiri M, Meuth SG, Kovac S, Gorji A. Astrocyte-mediated inflammation in cortical spreading depression.

235. Cephalalgia. 38(4):626-638, 2018. doi: 10.1177/0333102417702132.

236. Giesecke AH, Morris RI, Dalton MD, Stephen CR. Of magnesium, muscle relaxants, toxemic parturients and cats. Anesth Analg 47, 689-695, 1968.

237. Giffin NJ, Ruggiero L, Lipton RB, Silberstein S, Tvedskov JF, Olesen J, Altman J, Goadsby PJ, Macrae A. Premonitory symptoms in migraine: an electronic diary study. Neurology 60: 935-940, 2003. Available from: https://doi.org/10.1212/01.WNL.0000052998.58526.a9

238. Giffin NJ, Lipton RB, Silberstein SD, Olesen J, Goadsby PJ. The migraine postdrome. An electronic diary study. Neurology 87: 309–313, 2016. https://doi.org/10.1212/WNL.0000000000002789

239. Gillman PK. The serotonin syndrome and its treatment. J Psychopharma 13, 100109, 1999. Available from: https://doi.org/10.1177/026988119901300111

240. Gillman PK. Triptans, serotonin agonists, and serotonin syndrome (serotonin toxicity): A review. Headache 50; 264-272, 2010. https://doi.org/10.1111/j.1526-4610.2009.01575.x

241. Goadsby PJ. Stress and migraine. Something expected, something unexpected. Neurology 82, 1388-1389, 2014. Available from: https://doi.org/10.1212/WNL.0000000000000349

242. Goadsby PJ. Migraine, aura, and cortical spreading depresssion: why are we still talking about it? Ann Neurol 49(2): 4-6, 2001. https://doi.org/10.1002/1531-8249(200101)49:1%3C4::AID-ANA3%3E3.0.CO;2-W

243. Goadsby PJ. Migraine pathophysiology. Headache 45; S14-S24, 2005. Goadsby PJ, Charbit AR, Andreou AP, Akerman S, Holland PR. Neurobiology of migraine. Neuroscience 161, 327-341, 2009.

244. Goadsby PJ, Edvinsson L. The trigeminovascular system and migraine:

Citation: Gupta VK. Cortical Spreading Depression and Migraine: Critical Review of a Neurophysiological Principle in the Third Millennium. Glob J Medical Clin Case Rep. 2026:13(10):228-272. Available from: https://dx.doi.org/10.17352/gjmccr.000273

studies characterizing cerebrovascular and neuropeptide changes seen in humans and cats. Ann Neurol. 33:48-56, 1993. doi: 10.1002/ana.410330109. Available from: https://doi.org/10.1002/ana.410330109

245. Goadsby PJ, Edvinsson L, Ekman R. Vasoactive peptide release in the extracerebral circulation of humans during migraine headache. Ann Neurol. 28: 183-187, 1990. https://doi.org/10.1002/ana.410280213

246. Goadsby PJ, Holland PR, Martins-Oliveira M, Hoffmann J, Schankin C, Akerman S. Pathophysiology of Migraine: A Disorder of Sensory Processing. Physiol Rev. 97(2):553-622, 2017. Available from: https://doi.org/10.1152/physrev.00034.2015

247. Goadsby PJ, Lipton RB, Ferrari MD. Migraine--current understanding and treatment. N Engl J Med. 24;346(4):257-70, 2002. doi: 10.1056/NEJMra010917.

248. Gobel H, Heinze A. Prophylactic drug management of migraine. Nervenarzt 74: 915-934, 2003.

249. Golan E, Vasquez DN, Ferguson ND, Adhikari NK, Scales DC. Prophylactic magnesium for improving neurologic outcome after aneurysmal subarachnoid hemorrhage: systematic review and meta-analysis. J Crit Care 28, 173-181, 2013. https://doi.org/10.1016/j.jcrc.2012.07.001

250. Goldstein DS, Kopin IJ. Evolution of concepts of stress. Stress 10; 109-120, 2007. Available from: https://doi.org/10.1080/10253890701288935

251. Gomersall JD, Stuart A. Amitriptyline in migraine prophylaxis. Changes in pattern of attacks during a controlled clinical trial. J Neurol Neurosurg Psychiatry 36; 684-690, 1973. https://doi.org/10.1136/jnnp.36.4.684

252. Gondim EL, Liu JH, Costa VP, Weinreb RN. Exogenous vasopressin influences intraocular pressure via the V (1) receptors. Curr Eye Res 22(4):295-303, 2001. https://doi.org/10.1076/ceyr.22.4.295.5508

253. Gorji A. Spreading depression: a review of the clinical relevance. Brain Res Brain Res Rev 38(1-2):33-60, 2001. https://doi.org/10.1016/S0165-0173(01)00081-9

254. Graham JR. The natural history of migraine: some observations and a hypothesis. Trans Am Clin Climatol Assoc 64: 61--74, 1953.

255. Grände G, Labruijere S, Haanes KA, Maassenvandenbrink A, Edvinson L. Comparison of the vasodilator responses of isolated human and rat middle meningeal arteries to migraine-related compounds. J Headache Pain 15; 22, 2014. https://doi.org/10.1186/1129-2377-15-22

256. Granziera C, DaSilva AF, Snyder J, Tuch DS, Hadjikhani N. Anatomical alterations of the visual motion processing network in migraine with and without aura. PLoS Med 3; e402, 2006. Available from: https://doi.org/10.1371/journal.pmed.0030402

257. Gronseth GS, Greenberg MK. The utility of the electroencephalogram in the evaluation of patients presenting with headache: A review of the literature. Neurology 45; 1263-1267, 1995. Available from: https://doi.org/10.1212/WNL.45.7.1263

258. Grotemeyer KH, Scharafinski HW, Schlake HP, Husstedt IW. Acetylsalicylic acid vs. metoprolol in migraine prophylaxis--a double-blind cross-over study. Headache 30; 639-641, 1990. https://doi.org/10.1111/j.1526-4610.1990.hed3010639.x

259. Gu T, Lin L, Jiang Y, Chen J, D'Arcy RCN, Chen M, Song X. Acupuncture therapy in treating migraine: results of a magnetic resonance spectroscopy imaging study. J Pain Res 11; 889-900, 2018. https://doi.org/10.2147/JPR.S162696

260. Guidetti D, Rota E, Morelli N, Immovilli P. Migraine and stroke: "vascular" comorbidity. Front Neurol 5; 193, 2014. https://doi.org/10.3389/fneur.2014.00193

261. Gupta R, Bhatia MS. A report of cranial autonomic symptoms in migraineurs. Cephalalgia 27; 22-28, 2007.

262. Gupta VK. Nitric oxide and migraine: another systemic influence postulated to explain a lateralizing disorder. Eur J Neurol 3; 172-174, 1996a.

263. Gupta VK. Does magnesium supplementation have any role in acute myocardial infarction? No. Cardiovasc Drugs Ther 10; 303-305, 1996b.

264. Gupta VK. A clinical review of the adaptive potential of vasopressin in migraine. Cephalalgia 17; 561-569, 1997.

265. Gupta VK. Non_lateralizing brain PET changes in migraine: phenomenology versus pharmacology? Brain e12, 2004a. https://doi.org/10.1093/brain/awh182

266. Gupta VK. White matter hyperintensities: pearls and pitfalls in interpretation of MRI abnormalities. Stroke 35: 2756-2757, 2004c.

267. Gupta VK. Magnesium therapy for migraine: do we need more trials or more reflection? Headache 44, 445-446, 2004d.

268. Gupta VK. Sympathetic nervous system dysfunction in migraine: pearls and pitfalls in the theorizing process. Headache 44: 841--842, 2004e.

269. Gupta VK. Stress, adaptation, and traumatic event headaches: pathophysiologic and pharmacotherapeutic insights. BMC Neurology. Published online 26 November 2004f. Archived comment available at: Stress, adaptation, and traumatic-event headaches: pathophysiologic and pharmacotherapeutic insights. (Researchgate)

270. Gupta VK. Conceptual divide between adaptive and pathogenetic phenomena in migraine: nausea and vomiting. Brain 127; E18, 2004g.

271. Gupta VK. Intravenous magnesium for neuroprotection in acute stroke: clinical hope versus basic neuropharmacology. Stroke 35, 2758-2759, 2004h.

272. Gupta VK. Cyclic vomiting syndrome: anticipatory stress response in migraine? Headache 106-107, 2004j.

273. Gupta VK. Cortical spreading depression is neuroprotective: the challenge of basic sciences. Headache 45, 177-178, 2005a. https://doi.org/10.1007/s10194-010-0287-z

274. Gupta V. Cyclical vomiting syndrome – migraine – vasopressin nexus: a new hypothesis for anticipatory nausea and vomiting. BMC Pediatrics 2005b. Available at: Available: http://www.biomedcentral.com/1471-2431/5/3/comments (Researchgate)

275. Gupta VK. Magnesium for delayed cerebral ischemia in aneurysmal subarachnoid hemorrhage: time for a paradigm shift? Stroke 36, 2530, 2005c. Magnesium for Delayed Cerebral Ischemia in Aneurysmal Subarachnoid Hemorrhage: Time for a Paradigm Shift? | Stroke

276. Gupta VK. Botulinum toxin type A therapy for chronic tension-type headache: fact versus fiction. Pain 116, 166-167, 2005h.

277. Gupta VK. Botulinum toxin: a treatment for migraine? A systematic review. Pain Med 7, 386-394, 2006a.

278. Gupta VK. Migrainous scintillating scotoma and headache is ocular in origin: A new hypothesis. Med Hypotheses 66, 454-460, 2006b. https://doi.org/10.1016/j.mehy.2005.11.010

279. Gupta VK. MRI imaging in primary headaches. Radiology 238, 754-755, 2006c. https://doi.org/10.1148/radiol.2382051007

280. Gupta VK. Pharmacotherapeutics of migraine and the blood-brain barrier: serendipity, empiricism, hope, and hype. MedGenMed 8, 89, 2006d.

281. Gupta VK. Adaptive Mechanisms in Migraine. A Critical Conceptual hiatus. In: Progress in Migraine Research. Ed. Amadeo O. Fernandez. Nova Science Publishers, New York, 109-169, 2007.

Citation: Gupta VK. Cortical Spreading Depression and Migraine: Critical Review of a Neurophysiological Principle in the Third Millennium. Glob J Medical Clin Case Rep. 2026:13(10):228-272. Available from: https://dx.doi.org/10.17352/gjmccr.000273

282. Gupta VK. CSD, BBB and MMP-9 elevations: animal experiments versus clinical phenomena in migraine. Expert Rev Neurother 9: 1595–1614, 2009a. https://doi.org/10.1586/ern.09.103

283. Gupta VK. Adaptive Mechanisms in Migraine. A Comprehensive Synthesis in Evolution. Breaking the Migraine Code. Nova Science Publishers, Inc. New York, 2009b.

284. Gupta VK. Closure of PFO: science, quasi-science, or empiricism. Cardiology 113: 108–110, 2009c.

285. Gupta VK. Patent foramen ovale closure and migraine: science and sensibility. Expert Rev Neurother 10: 1409-1422, 2010a. https://doi.org/10.1586/ern.10.125

286. Gupta V. Constipation-related Migraine Is linked to the effect of the Valsalva maneuver on the eye: A case report and a mechanistic review. WebmedCentral NEUROLOGY 1(12):WMC001433, 2010b.

287. Gupta VK. Cortical spreading depression: at the razor's edge of scientific logic. J Headache Pain 12: 45–46, 2011. https://doi.org/10.1007/s10194-010-0287-z

288. Gupta VK. Stress: Adaptive mechanisms in migraine. Neurology. Epub September 7, 2017a. Letter to the Editor. Available at: http://n.neurology.org/content/stress-adaptivemechanisms-migraine

289. Gupta VK. Serum magnesium and all-cause dementia including Alzheimer disease. Neurology Epub 27 September, 2017b. Letter to the Editor. Available at: http://n.neurology.org/content/serum-magnesium-and-all-cause-dementia-includingalzheimer-disease

290. Gupta VK. Calcitonin-gene related peptide antagonism to prevent migraine: hope, hype, and hokum. Neurology Epub September 07, 2017c. Letter to the Editor. Available at: http://n.neurology.org/content/89/12/1237.long#comments

291. Gupta VK. Re: Migraine and stroke. Stroke Vasc Neurol, Published Online Response 9 September, 2017d. Letter to the Editor. Available at: https://svn.bmj.com/content/2/3/160.responses#re-migraine-and-stroke

292. Gupta VK. Migraine: a lateralizing disorder with onset before aura/headache? Neurology. Epub September 19, 2017e. Letter to the Editor. Available at: http://n.neurology.org/content/migraine-lateralizing-disorder-onset-auraheadache

293. Gupta VK. Vagaries of meta-analysis: migraine attacks increase with high and low BMI. Neurology Epub Rapid Response April 29, 2018a. Letter to the Editor. Available at: http://n.neurology.org/content/vagaries-meta-analysis-migraine-attacks-increasehigh-and-low-bmi

294. Gupta VK. What is the practical value of genetic analysis to comprehension of migraine? Neurology Published April 01, 2018b. Letter to the Editor. Available at: http://n.neurology.org/content/what-practical-value-genetic-analysis-comprehensionmigraine

295. Gupta VK. Pathophysiology of migraine: an increasingly complex narrative to 2020. Fut Neurol 2019, FNL 13, 10.2217/fnl-2019-0003. https://doi.org/10.2217/fnl-2019-0003

296. Gupta VK. Eclampsia in the 21st century: Paradigm shift from empirical therapy with magnesium sulfate. Basic science synthesis vs. current WHO-recommended pharmacotherapeutic practice. J Brain and Neurological Disorders. 6(2): 2023. https://doi.org/10.31579/2642-973X/045

297. Gupta VK. Bimatoprost Ophthalmic Solution (BOS) 0.3 mg w/v for 1 open trial of long-term preventive therapy of migraine in 3 patients with pathophysiologic shift from brain to eye. Journal of Neuroscience and Neurological Disorders, 7(2), 134–154, 2023a. https://doi.org/10.29328/journal.jnnd.1001087

298. Gupta VK. Laws of pathophysiology of migraine in the third millennium. J Neurosci Neurol Disord. 8: 024-032, 2024.

299. Gupta VK. The 'pre-prodromal' or 'pre-premonitory' phase holds the key to the cause-effect basis of migraine buried over 25 centuries: Continuum of the confusion surrounding allodynia-randomized controlled trials-stress-intraocular pressuremigraine nexus. J Neuroscience and Neurological Surgery, 18(1); 2025. https://doi.org/10.31579/2578-8868/382

300. Hadjikhani N. Relevance of cortical thickness in migraine sufferers. Expert Rev Neurother 8(3):327-329, 2008. https://doi.org/10.1586/14737175.8.3.327

301. Hadjikhani N, Sanchez del Rio M, Wu O, Schwartz D, Bakker D, Fischl B, Kwong KK, Cutrer FM, Rosen BR, Tootell RBH, Sorensen AG, Moskowitz MA. https://doi.org/10.1073/pnas.071582498

302. Mechanisms of migraine aura revealed by functional MRI in human visual cortex. Proc Natl Acad Sci USA 98: 4687-4692, 2001. https://doi.org/10.1073/pnas.071582498

303. Haider B, McCormick DA. Rapid neocortical dynamics: cellular and network mechanisms. Neuron 62(2):171-89, 2009. doi: 10.1016/j.neuron.2009.04.008. https://doi.org/10.1016/j.neuron.2009.04.008

304. Hamedani AG, Rose KM, Peterlin BL, Mosley TH, Coker LA, Jack CR et al. Migraine and white-matter hyperintensities. The ARIC MRI study. Neurology 81, 1308-1313, 2013. https://doi.org/10.1212/WNL.0b013e3182a8235b

305. Hampton KK, Esack A, Peatfield RC, Grant PJ. Elevation of plasma vasopressin in spontaneous migraine. Cephalalgia 11, 249-250, 1991. https://doi.org/10.1046/j.1468-2982.1991.1106249.x

306. Hansen JM, Baca SM, VanValkenburgh P, Charles A. Distinctive anatomical and physiological features of migraine aura revealed by 18 years of recording. Brain 136, 3589-3595, 2013. https://doi.org/10.1093/brain/awt309

307. Hansen JM, Hauge AW, Ashina M, Olesen J. Trigger factors for familial hemiplegic migraine. Cephalalgia 31: 1274-1281, 2011. https://doi.org/10.1177/0333102411415878

308. Hansen AJ, Olsen CE. Brain extracellular space during spreading depression and ischemia. Acta Physiol Scand 108, 355-365, 1980. https://doi.org/10.1111/j.1748-1716.1980.tb06544.x

309. Hare EH. Personal observation on the spectral march of migraine. J Neurol Sci 3, 259-264, 1966.

310. Harnod T, Lin C-L, Kao C-H. Survival outcome and mortality rate in patients with migraine: a population-based cohort study. J Headache Pain 19; 57, 2018. https://doi.org/10.1186/s10194-018-0889-4

311. Harris B. Magnesium sulphate and postoperative pain. Anaesthesia 68(8):875-6, 2013. https://doi.org/10.1111/anae.12313

312. Harris P, Loveman E, Clegg A, Easton S, Berry N. Systematic review of cognitive behavioural therapy for the management of headaches and migraines in adults. Br J Pain 9, 213-224, 2015. https://doi.org/10.1177/2049463715578291

313. Hartings JA, Shuttleworth CW, Kirov SA, Ayata C, Hinzman JM, Foreman B et al. The continuum of spreading depolarizations in acute cortical lesion development: Examining Leão's legacy. J Cereb Blood Flow Metab 37, 1571–1594, 2017. https://doi.org/10.1053/j.gastro.2003.09.040

314. Hasler WL, Chey WD. Nausea and vomiting. Gastroenterology 125, 1860-1867, 2003. https://doi.org/10.1186/1471-2377-4-17

315. Hass DC. Traumatic-event headaches. BMC Neurology. 2004; 4:17. https://doi.org/10.1097/00001756-199902050-00039

316. Hasselblatt M, Köhler J, Volles E, Ehrenreich H. Simultanous monitoring of endothelin-1 and vasopressin plasma levels in migraine. Neuroreport 10, 423-425, 1999. https://doi.org/10.1016/S1474-4422(09)70135-8

Citation: Gupta VK. Cortical Spreading Depression and Migraine: Critical Review of a Neurophysiological Principle in the Third Millennium. Glob J Medical Clin Case Rep. 2026:13(10):228-272. Available from: https://dx.doi.org/10.17352/gjmccr.000273

317. Hauge AW, Asghar MS, Schytz HW, Christensen K, Olesen J. Effects of tonabersat on migraine with aura: a randomized, double-blind, placebo-controlled crossover study. Lancet Neurol 8, 718-723, 2009. https://doi.org/10.1016/S1474-4422(06)70348-9

318. Haut SR, Bigal ME, Lipton RB. Chronic disorders with episodic manifestations: Focus on epilepsy and migraine. Lancet Neurol 5, 148-157, 2006. https://doi.org/10.1111/j.1526-4610.1988.hed2807465.x

319. Havanka-Kanniainen H, Tolonen, Myllylä VV, Autonomic dysfunction in migraine: A survey of 188 patients. Headache: 28: 465-470, 1988.

320. Headache Classification Committee of the International Headache Society (IHS). The International Classification of Headache Disorders (ICHD, III edition. [No authors listed] Cephalalgia. 38(1): 1-211, 2018. doi: 10.1177/0333102417738202.

321. Heckenberg SG, Brouwer MC, van de Beek D. Bacterial meningitis. Handb Clin Neurol. 121: 1361-75, 2014. https://doi.org/10.1016/B978-0-7020-4088-7.00093-6

322. Hershey AD, Powers SW, Bentti A-L, deGrauw TJ. Standardized dosing of amitriptyline is highly effective in a pediatric headache center population. Headache 39, 357-358, 1999.

323. Hershey AD, Powers SW, Coffey CS, Eklund DD, Chamberlin LA, Korbee LL; CHAMP Study Group. Childhood and Adolescent Migraine Prevention (CHAMP) study: a double-blinded, placebo-controlled, comparative effectiveness study

324. of amitriptyline, topiramate, and placebo in the prevention of childhood and adolescent migraine. Headache. 53, 799-816, 2013. https://doi.org/10.1111/head.12105

325. Hickman C, Lewis KS, Little R, Rastogi RG, Yonker M. Prevention for pediatric and adolescent migraine. Headache 55, 1371-1381, 2015.

326. Hill A, Amendolara AB, Small C, Guzman SC, Pfister D, McFarland K, et al. Metabolic pathophysiology of cortical spreading depression: A review. Brain Sci 14(10):1026, 2024. doi: 10.3390/brainsci14101026

327. Hipp JF, Siegel M. BOLD fMRI correlation reflects frequency-specific neuronal correlation. Curr Biol 25:1368-74, 2015. doi: 10.1016/j.cub.2015.03.049.

328. Hirsh LJ, Hauser WA. Can sudden unexplained death in epilepsy be prevented. Lancet 364, 2157-2158, 2004.

329. Hodkinson DJ, Veggeberg R. Wilcox SL, Scrivani S, Burstein R, Becerra L, Borsook D. Primary somatosensory cortices contain altered patterns of regional cerebral blood flow in the interictal phase of migraine. PLoS One 10(9):e0137971, 2015. doi: 10.1371/journal.pone.0137971.

330. Hodkinson DJ, Wilcox SL, Veggeberg R, Noseda R, Burstein R, Borsook D, Becerra L. Increased amplitude of thalamocortical low-frequency oscillations in patients with migraine. J Neuroscience 36, 8026-8036, 2016.

331. Hodkinson DJ, Krause K, Khawaja N, Renton TF, Huggins JP, Vennart W, et al. Quantifying the test-retest reliability of cerebral blood flow measurements in a clinical model of on-going post-surgical pain: A study using pseudo-continuous arterial spin labelling. Neuroimage Clin. 3:301-310, 2013. doi: 10.1016/j.nicl.2013.09.004.

332. Hogstrom LJ, Westyle LT, Walhovd KB, Fjell AM. The structure of the cerebral cortex across adult life: age-related patterns of surface area, thickness, and gyrification. Cereb Cortex 23; 2521-30, 2013. doi: 10.1093/cercor/bhs231.

333. Holst AG, Winkel BG, Risgaard B, Nielsen JB, Rasmussen PV, Haunsø S et al. Epilepsy and risk of death and sudden unexpected death in the young: a nationwide study. Epilepsia 54, 1613-1620, 2013.

334. Horton RC, Kendall MJ. Clinical pharmacology and therapeutics. Postgrad Med J 67, 1042-1054, 1991.

335. Hougaard A, Amin FM, Christensen CE, Younis S, Wolfram S, Cramer WSP, Larsson HPW, Ashina M. Increased brainstem perfusion, but no blood-brain barrier disruption, during attacks of migraine with aura. Brain 140: 1633-1642, 2017.

336. Houle TT, Turner DP, Penzien DB. How does the migraine attack stop? It is NOT the trigger: common headache triggers do not predict cessation of pain. Headache 52, 189-190, 2012.

337. Hsu LKG, Crisp AH, Kalucy RS, Koval J, Chen CN, Carruthers M et al. Early morning migraine. Nocturnal plasma levels of catecholamines, tryptophan, glucose and free-fatty acids and sleep encephalographs. Lancet ii, 447-451, 1977.

338. Hupp SL, Kline LB, Corbett JJ. Visual disturbances in migraine. Surv Ophthalmol 33: 221-236, 1989.

339. Iadecola C. From CSD to headache: a long and winding road. Nat Med 8: 110-112, 2002.

340. Ikegaya Y, Matsuki N. Vasopressin induces emesis in Suncus murinus. Jpn J Pharmacol 89, 324-326, 2002.

341. Inan N, Inan LE, Coşkun Ö, Tunç T, Ilhan M. Effectiveness of greater occipital nerve blocks in migraine prophylaxis. Noro Psikiyatr Ars 53, 45-48, 2016.

342. Irby MB, Bond DS, Lipton RB, Nicklas B, Houle TT, Penzien DB. Aerobic exercise for reducing migraine burden: mechanisms, markers, and models of change processes. Headache 56, 357-369, 2016.

343. Jackson JL, Cogbill E, Santana-Davila R, Eldredge C, Collier W, Gradall A, et al. A comparative effectiveness meta-analysis of drugs for the prophylaxis of migraine headache. PLos ONE 10; e0130733, 2015.

344. Jackson JL, Kuriyama A, Hayashino Y. Botulinum toxin A for prophylactic treatment of migraine and tension headaches in adults: a meta-analysis. JAMA 307, 1736-1745, 2012.

345. Jackson JL, Shimeall W, Sessums L, DeZee KJ, Becher D, Diemer M et al. Tricyclic antidepressants and headaches: systematic review and meta-analysis. BMJ 2010; 341; c5222, 2010. doi: 10.1136/bmj.c5222.

346. Jensen K, Tfelt-Hansen P, Lauritzen M, Olesen J. Classic migraine. A prospective recording of symptoms. Acta Neurol Scand 73, 359-362, 1986.

347. Jhaveri DJ, McGonigal A, Becker C, Benoliel JJ, Nandam LS, Soncin L, Kotwas I, Bernard C, Bartolomei F. Stress and epilepsy: Towards understanding of neurobiological mechanisms for better management. eNeuro. 2023 10(11):ENEURO.0200-23.2023. doi: 10.1523/ENEURO.0200-23.2023.

348. Johannsson V, Nilsson LR, Widelius T, Jäverfalk T, Hellman P, Åkesson J-Å, Olerud B, Gustafsson C-L, Raak A, Sandahl G, Tilling B, Almkvist G, Troein M. Atenolol in migraine prophylaxis: a double-blind cross-over multicenter study. Headache 27: 372-374, 1987.

349. Johnson S. The multifaceted and widespread pathology of magnesium deficiency. Med Hypotheses 56, 163-170, 2001.

350. Jolly F. Ueber flimmersktom und migraine. Berl Klin Wochenschr 42, 973-976, 1902.

351. Juganariu G, Miftode E, Teodor D, Leca D, Dorobăţ CM. Clinical features and course of bacterial meningitis in children. Rev Med Chir Soc Med Nat Iasi 116, 722726, 2012.

352. Kalita J, Bhoi SK, Misra UK. Amitriptyline vs divalproate in migraine prophylaxis: a randomized controlled trial. Acta Neurol Scand 128; 65-72, 2013.

353. Kalita J, Uniyal R, Bhoi SK. Is palinopsia in migraineurs an enhanced physiological phenomenon? Cephalalgia 36; 1248-1256, 2016.

354. Kanemura H, Sano F, Ishii S, Ohyama T, Sugita K, Aihara M. Characteristics of headache in children with epilepsy. Seizure 22; 647-650, 2013.

Citation: Gupta VK. Cortical Spreading Depression and Migraine: Critical Review of a Neurophysiological Principle in the Third Millennium. Glob J Medical Clin Case Rep. 2026:13(10):228-272. Available from: https://dx.doi.org/10.17352/gjmccr.000273

355. Karadas O, Gul HL, Ozturk B, Eroglu E, Demirkaya S. The effects of topiramate therapy on cerebral metabolism in migraine with aura patients. Turk Neurosurg 24; 704-709, 2014.

356. Kaube H, Goadsby PJ. Anti-migraine compounds fail to modulate the propagation of cortical spreading depression in the cat. Eur Neurol 34; 30-35, 1994.

357. Kaufmann D, Theriot JJ, Zyuzin J, Service CA, Chang JC, Tang YT, Bogdanov VB, Multon S, Schoenen J, Ju YS, Brennan KC. Heterogeneous incidence and propagation of spreading depolarizations. J Cereb Blood Flow Metab 37; 1748-1762, 2017.

358. Kawahara N, Ruetzler CA, Klatzo I. Protective effect of spreading depression against neuronal damage following cardiac arrest cerebral ischaemia. Neurol Res 17; 9-16, 1995.

359. Kawasaki A, Purvin VA. Photophobia as the presenting visual symptom of chiasmal compression. J Neuroophthalmol 22; 3-8, 2002.

360. Kaya M, Gulturk S, Elmas I, Kalayci R, Arican N, Kocyildiz ZC, Kucuk M, Yorulmaz H, Sivas S. The effects of magnesium sulphate on blood-brain barrier disruption caused by intracarotid injection of hyperosmolar mannitol in rats. Life Sci 76; 201-212, 2004.

361. Keller AE, Witney R, Li S-A, Pollanen MS, Donner EJ. Incidence of sudden unexpected death in epilepsy in children is similar to adults. Neurology 2018; 10;91: e107-e111.doi: 10.1212/WNL.0000000000005762.

362. Kelley SA, Hartman AL, Kossoff EH. Comorbidity of migraine in children presenting with epilepsy to a tertiary care center. Neurology 79; 468-473, 2012.

363. Kelman L. Osmophobia and taste abnormality in migraineurs: a tertiary care study. Headache 44; 1019-1023, 2004(a).

364. Kelman L. The premonitory symptoms (prodrome): a tertiary care study of 893 migraineurs. Headache 44, 865-872, 2004(b).

365. Kelman L. Migraine pain location: a tertiary care study of 1283 migraineurs. Headache 45, 1038-1047, 2005.

366. Kelman L. The postdrome of the acute migraine attack. Cephalalgia 26: 214-220, 2006.

367. Kelman L. The triggers or precipitants of the acute migraine attack. Cephalalgia 27, 394-402, 2007.

368. Kelman L, Rains JC. Headache and sleep: examination of sleep patterns and complaints in a large clinical sample of migraineurs. Headache 45; 904-910, 2005.

369. Kendall MJ. Clinical relevance of pharmacokinetic differences between beta blockers. Am J Cardiol 80; 15J-19J, 1997.

370. Kidd RF, Nelson R. Musculoskeletal dysfunction of the neck in migraine and tension headache. Headache 33; 566-569, 1993.

371. Kim H, Byun SH, Kim JS, Lim BC, Chae JH, Choi J et al. Comparison of flunarizine and topiramate for the prophylaxis of pediatric migraines. Eur J Paediatr Neurol 17; 45-49, 2013.

372. Kim MS, Chey WD, Owyang C, and Hasler WL. Role of plasma vasopressin as a mediator of nausea and gastric slow wave dysrhythmias in motion sickness. Am J Physiol Gastrointest Liver Physiol 272; G853– G862, 1997.

373. Kim S-Y, Park S-P. Suicidal ideation and risk factors in Korean migraine patients. J Clin Neurosci 21; 1699-1704, 2014.

374. Kirthi V, Derry S, Moore RA. Aspirin with or without an antiemetic for acute migraine headaches in adults. Cochrane Database Syst Rev 4; CD008041, 2013.

375. Kishk N, Nawito A, El-Damaty A, Ragab A. Ictal asystole: a case presentation. BMC Neurology 18; 100, 2018. https://doi.org/10.1186/s12883-018-1105-5

376. Klass A, Sánchez-Porras R, Santos E. Systematic review of the pharmacological agents that have been tested against spreading depolarizations. JCBFM; 38(7); 1149-1179, 2018. DOI: 10.1177/0271678X18771440

377. Knight YE, Goadsby PJ. The periaqueductal grey matter modulates trigeminovascular input: a role in migraine? Neuroscience 106; 793-800, 2001.

378. Ko S-H, Lim H-R, Kim D-C, Han Y-J, Choe H, Song H-S. Magnesium sulfate does not reduce postoperative analgesic requirements. Anesthesiology 95; 640–646, 2001.

379. Kobari M, Meyer JS, Ichijo M, Imai A, Oravez WT. Hyperperfusion of cerebral cortex, thalamus and basal ganglia during spontaneously occurring migraine headaches. Headache 29; 282-289, 1989.

380. Kobayashi S, Harris VA, Welsh FA. Spreading depression induces tolerance of cortical neurons to ischemia in rat brain. J Cereb Blood Flow Metab 15; 721-727, 1995.

381. Koehler PJ, Tfelt-Hansen PC. History of methysergide in migraine. Cephalalgia 28; 1126-1135, 2008.

382. Kohl RL, MacDonald S. New pharmacologic approaches to the prevention of space/motion sickness. J Clin Pharmacol 31; 934-946, 1991.

383. Kröger IL, May A. Central effects of acetylsalicylic acid on trigeminal-nociceptive stimuli. J Headache Pain 15; 59, 2014.

384. Kruuse C, Thomsen LL, Birk S, Olesen J. Migraine can be induced by sildenafill without changes in middle cerebral artery diameter. Brain 126; 241-247, 2003.

385. Kumar S, Singh S, Kumar N, Verma R. The effects of repetitive transcranial magnetic stimulation at dorsolateral prefrontal cortex in the treatment of migraine comorbid with depression: A retrospective open study. Clin Psychopharmacol Neurosci 16; 62-66, 2018.

386. Kuperberg GR, Broome MR, McGuire PK, David AS, Eddy M, Ozawa F et al. Regionally localized thinning of the cerebral cortex in schizophrenia. Arch Gen Psychiatry 60; 878-888, 2003.

387. Kupersmith MJ, Hass WK, Chase NE. Isoproterenol treatment of visual symptoms in migraine. Stroke 10; 299-305, 1979.

388. Kurlander DE, Punjabi A, Liu MT, Sattar A, Guyuron B. In-depth review of symptoms, triggers, and treatment of temporal migraine headaches (Site II). Plast Reconstr Surg 133; 897-903, 2014.

389. Kurth T, Gaziono JM, Cook NR, Bubes V, Logroscino G, Diener HC, Buring JE. Migraine and risk of cardiovascular disease in men. Arch Intern Med 167; 795-801, 2007.

390. Lagman-Bartolome AM, Lay C. Pediatric migraine variants: a review of epidemiology, diagnosis, treatment, and outcome. Curr Neurol Neurosci Rep 15; 34, 2015. doi: 10.1007/s11910-015-0551-3.

391. Lakhan SE, Avramut M, Tepper SJ. Structural and functional neuroimaging in migraine: insights from 3 decades of research. Headache 53; 46-66, 2013.

392. Lai M , Loi V , Pisano MR , Del Zompo M. Therapy of migraine by modulating dopamine hypersensitivity: its effect on mood and pain. Int J Clin Pharmacol Res 17; 101-103, 1997.

393. Lambert GA, Truong L, Zagami AS. Effect of cortical spreading depression on basal and evoked traffic in the trigeminovascular sensory system. Cephalalgia 31; 1439-1451, 2011.

394. Lampl C, Bonelli S, Ransmayar G. Efficacy of topiramate in migraine aura

Citation: Gupta VK. Cortical Spreading Depression and Migraine: Critical Review of a Neurophysiological Principle in the Third Millennium. Glob J Medical Clin Case Rep. 2026:13(10):228-272. Available from: https://dx.doi.org/10.17352/gjmccr.000273

prophylaxis: preliminary results of 12 patients. Headache 44; 174-176, 2004.

395. Lampl C, Voelker M, Steiner TJ. Aspirin is first-line treatment for migraine and episodic tension-type headache regardless of headache intensity. Headache 52; 4856, 2012.

396. Lance JW. Mechanism and management of headache. 5th ed. Oxford: Butterworth-Heinemann Ltd. 1993, pp 74-75.

397. Lashley KS. Patterns of cerebral integration indicated by the scotomas of migraine. Arch Neurol Psychiatry 46; 331-339, 1941.

398. La Spina I, Vignati A, Porazzi D. Basilar artery migraine: transcranial Doppler EEG and SPECT from the aura phase to the end. Headache 37; 43-47, 1997.

399. Laudron PM, Leysen JE. Domperidone, a specific in vitro dopamine antagonist, devoid of in vivo central dopaminergic activity. Biochem Pharmac 28; 2161-2165, 1979.

400. Laurant P, Touyz RM, Schiffrin EL. Effect of magnesium on vascular tone and reactivity in pressurized mesenteric resistance arteries from spontaneously hypertensive rats. Can J Physiol Pharmacol 75; 293-300, 1997.

401. Lauritzen M. On the possible relation of spreading cortical depression to classical migraine. Cephalalgia 5; 47-51, 1985.

402. Lauritzen M. Pathophysiology of the migraine aura. The spreading depression theory. Brain 117; 199-210, 1994.

403. Lauritzen M. Cortical spreading depression in migraine. Cephalalgia 21; 757-760, 2001.

404. Lauritzen M, Drier JP, Fabricius M, Hartings JA, Graf R, Strong AJ. Clinical relevance of cortical spreading depression in neurological disorders: migraine, malignant stroke, subarachnoid and intracranial hemorrhage, and traumatic brain injury. J Cereb Blood Flow Metab 31; 17-35, 2011. doi: 10.1038/jcbfm.2010.191.

405. Lauritzen M, Olesen J. Regional cerebral blood flow during migraine attacks by Xenon-133 inhalation and emission tomography. Brain 107; 447-461, 1984.

406. Lauritzen M, Skyhøj Olsen T, Lassen NA, Paulson OB. Changes in regional cerebral blood flow during the course of classic migraine attacks. Ann Neurol 13; 633-641, 1983.

407. Lauritzen M, Strong AJ. 'Spreading depression of Leão' and its emerging relevance to acute brain injury in humans. J Cereb Blood Flow Metab 37; 1553-1570, 2017.

408. Lazard EM. A preliminary report on the intravenous use of magnesium sulphate in eclampsia. Am J Obstet Gynecol 9; 178-188, 1925.

409. Leão AAP. Spreading depression of activity in cerebral cortex. J Neurophysiol 7; 359-390, 1944a.

410. Leão AAP. Pial circulation and spreading depression of activity in cerebral cortex. J Neurophysiol 7; 391-396, 1944b.

411. Leão AAP, Morison RS. Propagation of spreading cortical depression. J Neurophysiol 8; 33-45, 1945.

412. Lebensohn JE, Bellows J. The nature of photophobia. Arch Ophthalmol 12; 380390, 1934.

413. Leijenaar JF, Dorhout Mees SM, Algra A, van den Bergh WM, Rinkel GJ; MASHII Study Group. Effect of magnesium treatment and glucose levels on delayed cerebral ischemia in patients with subarachnoid hemorrhage: a substudy of the Magnesium in Aneurysmal Subarachnoid Haemorrhage trial (MASH-II). Int J Stroke 10 Suppl A 100;108-112, 2015.

414. Leonardi M, Raggi A. Burden of migraine: international perspectives. Neurol Sci 34(Suppl. 1); S117–S118, 2013.

415. Levene JR. Sir G.B. Airy F.R.S. (1801-1892) and the symptomatology of migraine. Notes Rec R Soc London 30; 15-23, 1975.

416. Levone BR, Cryan JF, O'Leary OF. Role of adult hippocampal neurogenesis in stress resilience. Neurobiol Stress 1; 147-155, 2014. doi: 10.1016/j.ynstr.2014.11.003.

417. Levy D, Labastida-Ramirez A, MassenVandanVanDenBrink. Current understanding of meningeal and cerebral vascular function underlying migraine headache. Cephalalgia 39; 1606-1622, 2019 doi: 10.1177/0333102418771350.

418. Li BU, Balint JP. Cyclic vomiting syndrome: evolution in our understanding of a brain-gut disorder. Adv Pediatr 47; 117-160, 2000.

419. Limmroth V, Michel MC. The prevention of migraine: a critical review with special emphasis on beta-adrenoceptor blockers. Br J Clin Pharmacol 52; 237-243, 2001.

420. Linde M. Migraine: a review and future directions for treatment. Acta Neurol Scand 111; 71-83, 2006.

421. Linde M, Mulleners WM, Chronicle EP, McCrory DC. Topiramate for the prophylaxis of episodic migraine in adults. Cochrane Database Syst Rev, Issue 6: Art. No.: CD010610, 2013a. doi: 10.1002/14651858.CD010610.

422. Linde M, Mulleners WM, Chronicle EP, McCrory DC. Valproate (valproic acid or sodium valproate or a combination of the two) for the prophylaxis of episodic migraine in adults. Cochrane Database Syst Rev 6; CD010611, 2013b.

423. Linde M, Mulleners WM, Chronicle EP, McCrory DC. Gabapentin or pregabalin for the prophylaxis of episodic migraine in adults. Cochrane Database Syst Rev 4, CD010609, 2013c.

424. Linde K, Rossnagel K. Propranolol for migraine prophylaxis. Cochrane Database Syst Rev 2; CD003225, 2004.

425. Lindquist BE, Shuttleworth CW. Evidence that adenosine contributes to Leao's spreading depression in vivo. J Cereb Blood Flow Metab 37; 1656-1669, 2017.

426. Lipton RB, Buse DC, Hall CB, Tennen H, Defreitas TA, Borkowski TM et al. Reduction in perceived stress as a migraine trigger. Testing the "let-down" hypothesis. Neurology 82; 1395-1386, 2014.

427. Liu H-Y, Fuh J-L, Lin Y-Y, Chen W-T, Wang S-J. Suicide risk in patients with migraine and comorbid fibromyalgia. Neurology 85; 1-7, 2015.

428. Loder E. What is the evolutionary advantage of migraine? Cephalalgia 22; 624-632, 2002.

429. Lukacs M, Tajti J, Fulop F, Toldi J, Edvinsson L, Vecsei L. Migraine, neurogenic inflammation, drug development - pharmacochemical aspects. Curr Med Chem 24; 3649-3665, 2017. doi: 10.2174/0929867324666170712163437.

430. Lundblad C, Haanes KA, Grände G, Edvinsson L. Experimental inflammation following dural application of complete Fruend's adjuvant or inflammatory soup does not alter brain and trigeminal microvascular passage. J Headache Pain 16; 91, 2015.

431. Maagdenberg AMJM, Pietrobon D, Pizzorusso T, Kaja S, Broos LAM, Cesetti T, van de Ven RCG, Tottene A, van der Kaa J, Plomp JJ, Frants RR, Ferrari MD. A Cacna1a knockin migraine mouse model with increased susceptibility to cortical spreading depression. Neuron 41; 701-710, 2004.

432. Mahmoud AN, Mentias A, Elgendy AY, Qazi A, Barakat AF, Saad M et al. Migraine and the risk of cardiovascular and cerebrovascular events: a meta-analysis of 16 cohort studies including 1 152 407 subjects. BMJ Open 2018: 8, e020498, 2018. doi:10.1136/bmjopen-020498.

433. Maihöfner C, Ringler R, Herrndobler F, Koppert W. Brain imaging of

Citation: Gupta VK. Cortical Spreading Depression and Migraine: Critical Review of a Neurophysiological Principle in the Third Millennium. Glob J Medical Clin Case Rep. 2026:13(10):228-272. Available from: https://dx.doi.org/10.17352/gjmccr.000273

analgesic and antihyperalgesic effects of cyclooxygenase inhibition in an experimental human pain model: a functional MRI study. Eur J Neurosci 26;1344-1356, 2007.

434. Maleki N, Becerra L, Nutile L, Pendse G, Brawn J, Bigal M et al. Migraine attacks the basal ganglia. Mol Pain 7; 71, 2011.

435. Maleki N, Becerra L, Upadhyay J, Burstein R, Borsook D. Direct optic nerve pulvinar connections defined by diffusion MR tractography in humans: implications for photophobia. Hum Brain Mapp 33; 75-88, 2012. doi:10.1002/hbm.21194.

436. Malick A, Burstein R. Peripheral and central sensitization during migraine. Funct Neurol 15; (Suppl 3), 28-35, 2000.

437. Malik R, Freilinger T, Winsvold VS, Anttila V, Heiden JV, Traylor M, et al. Shared genetic basis for migraine and ischemic stroke. A genome-wide analysis of common variants. Neurology 84; 2132-2145, 2015.

438. Maniyar FH, Goadsby PJ. Functional imaging in chronic migraine. Curr Pain Headache Rep 17; 333, 2013.

439. Maniyar FH, Sprenger T, Monteith T, Schankin C, Goadsby PJ. Brain activations in the premonitory phase of nitroglycerin-triggered migraine attacks. Brain 137; 232241, 2014.

440. Maniyar FH, Sprenger T, Schankin C, Goadsby PJ. Photic hypersensitivity in the premonitory phase of migraine – a positron emission tomography study. Eur J Neurol 21; 1178–1183, 2014a.

441. Manzoni GC, Farina S, Lanfranchi M, Solari A. Classic migraine - Clinical findings in 164 patients. Eur Neurol 24; 163-169, 1985.

442. Marmura MJ. Safety of topiramate for treating migraines. Expert Opin Drug Saf 13; 1241-1247, 2014.

443. Martinez-Lage JM. Flunarizine (Sibelium) in the prophylaxis of migraine. An open, long-term, multicenter trial. Cephalalgia 8 (Suppl 8); 10-15, 1988.

444. Martins-Ferreira H, de Castro GO. Light-scattering changes accompanying spreading depression in isolated retina. J Neurophysiol 29; 715-726, 1966.

445. Matharu MS, Good CD, May A, Bahra A, Goadsby PJ. No change in the structure of the brain in migraine: a voxel-based morphometric study. Eur J Neurol 10, 53-57, 2003.

446. Mathew PG. A critical evaluation of migraine trigger site deactivation surgery. Headache 54, 142-152, 2014. doi: 10.1111/head.12218

447. Mathias CJ, Bannister R. Autonomic Failure. A Textbook of Clinical Disorders of the Autonomic Nervous System. Oxford University Press, 5 th Edition, 2013.

448. Matsushima K, Hakim AM. Transient forebrain ischemia protects against subsequent focal cerebral ischemia without changing cerebral perfusion. Stroke 26; 1047-1052, 1995.

449. Matsushima K, Hogan MJ, Hakim AM. Cortical spreading depression protects against subsequent focal cerebral ischemia in rats. J Cereb Blood Flow Metab 16; 221-226, 1996.

450. Maxner CE, Moeller JJ. Visual disturbances and migraine. Curr Neurol Neurosci Rep 5; 376-381, 2005.

451. May A. Pearls and pitfalls: neuroimaging in headache. Cephalalgia 33; 554-565, 2013.

452. Mayevsky A, Weiss HR. Cerebral blood flow and oxygen consumption in cortical spreading depression. J Cereb Blood Flow Metab 11; 829-836, 1991.

453. McAinsh J, Cruickshank JM. Beta-blockers and central nervous system sideeffects. Pharmacol Ther 46; 163-197, 1990.

454. McComas AJ, Upton ARM. Cortical spreading depression in migraine--time to reconsider? Arch Neuropsiquiatr 73; 714-721, 2015.

455. McRonald FE, Fleisher DR. Anticipatory nausea in cyclical vomiting. BMC Pediatrics 55; 3, 2005.

456. Mees SM, Algra A, Vandertop WP, van Kooten F, Kuijsten HA, Boiten J et al. MASH-2 Study Group: Magnesium for aneurysmal subarachnoid haemorrhage (MASH-2): a randomised placebo-controlled trial. Lancet 380; 44-49, 2012.

457. Messina R, Rocca MA, Colombo B, Valsasina P, Horsfield MA, Copetti M et al. Cortical abnormalities in patients in migraine: a surface-based analysis. Radiology 268; 170-180, 2013.

458. Micheli F, Pardal MF, Gatto M, Torres M, Paradiso G, Parera IC et al. Flunarizine and cinnarizine induced extrapyramidal reactions. Neurology 37; 881-884, 1987.

459. Miller NR. Photophobia. In: Miller NR, editor. Walsh and Hoyt's Clinical Neuroophthalmology, vol. 2. Baltimore: Williams & Wilkins; 1985. P. 1099-1106.

460. Miller NR. Photophobia. In: Miller NR, editor. Walsh and Hoyt's clinical neuroophthalmology. 4th ed., vol. 2. Baltimore: Williams and Wilkins, 1985, pp 1099-1106.

461. Milner PM. Note on a possible correspondence between the scotomas of migraine and spreading depression of Leão. Electroencephalogr Clin Neurophysiol 10 (4); 705, 1958.

462. Minen MT, De Dhaem OB, Van Diest AK, Powers S, Schwedt TJ, Lipton R et al. Migraine and its psychiatric comorbidities. J Neurol Neurosurg Psychiatry 87; 741-749, 2016.

463. Mody I, Lambert JDL, Heinemann V. Low extracellular magnesium induces epileptiform activity and spreading depression in rat hippocampal slices. J Neurophysiol 57; 869-888, 1987.

464. Monroe DJ, Meehan JT 4th, Schandl CA. Sudden cardiac death in a young man with migraine-associated arrhythmia. J Forensic Sci 60, 1633-1636, 2015.

465. Monteith T, Gardener H, Rundek T, Dong C, Yoshita M, Elkind MSV, DeCarli C, Sacco RL, Wright CB. Migraine, white matter hyperintensities, and subclinical brain infarction in a diverse community: The NOMAS Study. Stroke 45; 1830-1832, 2014.

466. Moran C, Beare R, Phan TG, Bruce DG, Callisaya ML, Srikanth V; Alzheimer's Disease Neuroimaging Initiative (ADNI). Type 2 diabetes mellitus and biomarkers of neurodegeneration. Neurology 85; 1123-30, 2015.

467. Moskowitz MA. Basic mechanisms in vascular headache. Neurol Clin 8; 801-815, 1990.

468. Moskowitz MA. The visceral organ brain: implications for the pathophysiology of vascular head pain. Neurology 41; 182-186, 1991.

469. Moskowitz MA. Genes, proteases, cortical spreading depression and migraine: impact on pathophysiology and treatment. Funct Neurol 22; 133-136, 2007a.

470. Moskowitz MA. The 2006 Thomas Willis Lecture. The adventures of a translational researcher in stroke and migraine. Stroke 38; 1645-1651, 2007b.

471. Moskowitz MA. Defining a pathway to discovery from bench to bedside: the trigeminovascular system and sensitization. Headache 48; 688-690, 2008.

472. Moskowitz MA, Reinhard JF Jr, Romero J, Melamed E, Pettibone DJ. Neurotransmitters and the fifth cranial nerve: is there a relation to the headache phase of migraine? Lancet ii; 883-885, 1979.

Citation: Gupta VK. Cortical Spreading Depression and Migraine: Critical Review of a Neurophysiological Principle in the Third Millennium. Glob J Medical Clin Case Rep. 2026:13(10):228-272. Available from: https://dx.doi.org/10.17352/gjmccr.000273

473. Mullins ME, Cristofani CB, Warden CR, Cleary JF. Amitriptyline-associated seizures in a toddler with Munchausen-by-proxy. Pediatr Emerg Care 15; 202-205, 1999.

474. Nalbant E, Nalbant H, Eruyar E. Is migraine related to medial meningeal artery and spinous foramen caliber? J Clin Anal Med 8; 252--256, 2017.

475. Namazi M, Heshmati J, Tarighat-Esfanjani A. Supplementation with riboflavin (Vitamin B2) for migraine prophylaxis in adults and children: a review. Int J Vitam Nutr Res 85, 79-87, 2015.

476. Nathan PJ, Maguire KP, Burrows GD, Norman TR. The effect of atenolol, a beta1adrenergic antagonist, on nocturnal plasma melatonin secretion: evidence for a dose-response relationship in humans. J Pineal Res 23:131-5, 1997.

477. Neil-Dwyer G, Bartlett J, McAinsh J, Cruickshank JM. β-adrenoceptor blockers and the blood-brain barrier. Br J Clin Pharmac 11; 549-553, 1981. doi: 10.1111/j.1365-2125.1981.tb01169.x.

478. Neut D, Fily A, Curvellier JC, Vallée I. The prevalence of triggers in pediatric migraine: a questionnaire study in 102 children and adolescents. J Headache Pain 13; 61-65, 2012.

479. Nicolodi M, Frezzotti R, Diadori A, Nuti A, Sicuteri F. Phantom eye: features and prevalence. The predisposing role of headache. Cephalalgia 17; 501-504, 1997.

480. Nir R-R, Lee AJ , Huntington S, Noseda R, Bernstein CA, Fulton AB et al. Bertisch SM, Hovaguimian A, Buettner C, Borsook D, Burstein R. Colorselective photophobia in ictal vs interictal migraineurs and in healthy controls. Pain 159: 2030-2034; 2018. doi: 10.1097/j.pain.0000000000001303.

481. Nomura K, Kurimoto F, Demura H, Sakurai H, Nomura T, Zibiki K, Naruse M, Kanai N, Shisume K. Effect of metoclopramide on plasma vasopressin in man. Clin Endocrinol 21; 117-121, 1984.

482. Noseda R, Bernstein CA, Nir R-R, Lee AJ, Fulton AB, Bertisch SM et al. Migraine photophobia originating in cone-driven retinal pathways. Brain 139; 19711986, 2016.

483. Noseda R, Burstein R. Migraine pathophysiology: anatomy of the trigeminovascular pathway and associated neurological symptoms, CSD, sensitization and modulation of pain. Pain 154 Suppl 1; S44-S53, 2013.

484. Noseda R, Constandil L, Bourgeais L, Chalus M, Villanueva L. Changes of meningeal excitability mediated by corticotrigeminal networks: a link for the endogenous modulation of migraine pain. J Neurosci 30; 14420-14429, 2010.

485. Noseda R, Kainz V, Jakubowski M, Gooley JJ, Saper CB, Digre K, Burstein R. A neural mechanism for exacerbation of headache by light. Nat Neurosci 13; 239-245, 2010b.

486. Noseda R, Kainz V, Borsook D, Burstein R. Neurochemical pathways that converge on thalamic trigeminovascular neurons: potential substrate for modulation of migraine by sleep, food intake, stress and anxiety. PLoS One 9; e103929, 2014. doi: 10.1371/journal.pone.0103929.

487. Nozaki C, Markert A, Zimmer A. Inhibition of FAAH reduces nitroglycerininduced migraine-like pain and trigeminal neuronal hyperactivity in mice. Eur Neuropsychopharmacol 25; 1388-1396, 2015.

488. Nussey SS, Hawthorn J, Page SR, Ang VT, Jenkins JS. Responses of plasma oxytocin and arginine vasopressin to nausea induced by apomorphine and ipecacuanha. Clin Endocrinol (Oxf) 28; 297-304, 1988.

489. Oakley CB, Kossoff EH. Migraine and epilepsy in the pediatric population. Curr Pain Headache Rep 18; 402, 2014. doi: 10.1007/s11916-013-0402-3.

490. Obermann M, Mueller D, Yoon M-S, Pageler L, Diener HC, Katsarava Z. Migraine with isolated facial pain: a diagnostic challenge. Cephalalgia 27; 1278-1282, 2007a.

491. Obermann M, Yoon MS, Dommes P, Kuznetsova J, Maschke M, Weimar C, et al. Prevalence of trigeminal autonomic symptoms in migraine: a population-based study. Cephalalgia 27; 504-509, 2007b.

492. Obrenovitch TP, Urenjak J, Wang M. Nitric oxide formation during cortical spreading depression is critical for rapid subsequent recovery of ionic homeostasis. J Cereb Blood Flow Metab 22; 680-688, 2002.

493. O'Carroll RE, Drysdale E, Cahill L, Shajahan P, Ebmeier KP. Memory for emotional material: a comparison of central versus peripheral beta blockade. J Psychopharmacol 13; 32-39, 1999.

494. O'Connor PJ. Acephalgic migraine. Ophthalmology 88, 999-1003, 1981.

495. Okamoto K, Tashiro A, Chang Z, Bereiter DA. Bright light activates a trigeminal nociceptive pathway. Pain 149; 235-242, 2010.

496. Olerud B, Gustavsson CL, Furberg B. Nadolol and propranolol in migraine management. Headache 26; 490-493, 1986.

497. Olesen J. The International Classification of Headache Disorders. Headache 24; s1, 1-150, 2004.

498. Olesen J, Burstein R, Ashina M, Tfelt-Hansen P. Origin of pain in migraine: evidence for peripheral sensitization. Lancet Neurol 8; 679-690, 2009.

499. Olesen J, Friberg L, Skyhøj Olsen T, Iversen HK, Lassen NA, Andersen AR et al. Timing and topography of cerebral blood flow, aura, and headache during migraine attacks. Ann Neurol 28, 791-798, 1990.

500. Olesen J, Larsen B, Lauritzen M. Focal hyperemia followed by spreading oligemia and impaired activation of rCBF in classic migraine. Ann Neurol 9; 344-52, 1981. https://doi.org/10.1002/ana.410090406

501. Olesen J, Lauritzen M, Tfelt-Hansen P, Henriksen L, Larsen B. Spreading cerebral oligemia in classical- and normal cerebral blood flow in common migraine. Headache 22; 242-248, 1982. https://doi.org/10.1111/j.1526-4610.1982.hed2206242.x

502. Olmez A, Köse G, Turanli G. Cyclic vomiting with generalized epileptiform discharges responsive to topiramate therapy. Pediatr Neurol 35; 348-51, 2006. https://doi.org/10.1016/j.pediatrneurol.2006.06.014

503. Olsen TS. Spreading oligemia in the migraine aura – most likely an artifact due to scattered radiation. Cephalalgia 13; 86-88, 1993. https://doi.org/10.1046/j.1468-2982.1993.1302086.x

504. Olsen TS, Friberg L, Lassen NA. Ischemia may be the primary cause of the neurological deficits in classic migraine. Arch Neurol 44; 156-161, 1987. https://doi.org/10.1001/archneur.1987.00520140028013

505. Onderwater GLJ, Van Dongen RM, Zielman R, Terwindt GM, Ferrari MD. Primary headaches. Handb Clin Neurol 146: 267-284, 2017. https://doi.org/10.1016/B978-0-12-804279-3.00016-2

506. O'Neill BP, Mann JD. Aspirin prophylaxis in migraine. Lancet ii; 1179-1181, 1978. https://doi.org/10.1016/S0140-6736(78)92159-1

507. Oppelt WW, MacIntyre I, Rall DP. Magnesium exchange between blood and cerebrospinal fluid. Am J Physiol 205, 959-962, 1963. https://doi.org/10.1152/ajplegacy.1963.205.5.959

508. O'Reardon JP, Fontecha JF, Christancho MA, Newman S. Unexpected reduction in migraine and psychogenic headaches following rTMS treatment for major depression: a report of two cases. CNS Spectr 12; 921-925, 2007. https://doi.org/10.1017/S1092852900015716

509. Otori T, Greenberg JH, Welsh FA. Cortical spreading depression causes a longlasting decrease in cerebral blood flow and induces tolerance to permanent focal ischemia in rat brain. J Cereb Blood Flow Metab 23; 43-50, 2003. https://doi.org/10.1097/01.WCB.0000035180.38851.38

510. Ottman R, Lipton RB. Comorbidity of migraine and epilepsy. Neurology 44; 2105– 2110, 1994. https://doi.org/10.1212/WNL.44.11.2105

Citation: Gupta VK. Cortical Spreading Depression and Migraine: Critical Review of a Neurophysiological Principle in the Third Millennium. Glob J Medical Clin Case Rep. 2026:13(10):228-272. Available from: https://dx.doi.org/10.17352/gjmccr.000273

511. Paisley RD, Arora HS, Nazeri A, Massumi A, Razavi M. Migraine and vasodepressor syncope in a large family. Tex Heart Inst J 36, 468-469, 2009.

512. Paksu S, Duran L, Altuntas M, Zengin H, Salis O, Ozsevik SN , Albayrak H, Murat N, Guzel A, and Paksu MS. Amitriptyline overdose in emergency department of university hospital: evaluation of 250 patients. Hum Exp Toxicol 33; 980-990, 2014. https://doi.org/10.1177/0960327114527918

513. Panayiotopoulos CP. Elementary visual hallucinations, blindness, and headache in idiopathic occipital epilepsy: differentiation from migraine. J Neurol Neurosurg Psychiatry 66; 536-40, 1999. https://doi.org/10.1136/jnnp.66.4.536

514. Panayiotopoulos CP, Michael M, Sanders S, Valeta T, Koutroumanidis M. Benign childhood focal epilepsies: assessment of established and newly recognized syndromes. Brain 131; 2264-2286, 2008. https://doi.org/10.1093/brain/awn162

515. Papagni, SA, Benetti S, Arulanantham S, Mccrory E, Mcguire P, Mechelli A. Effects of stressful life events on human brain structure: A longitudinal voxel-based morphometry study. Stress 14; 227-232, 2011. https://doi.org/10.3109/10253890.2010.522279

516. Papmeyer M, Giles S, Sussmann JE, Kielty S, Stewart T, Lawrie SM et al. Cortical thickness in individuals at high familial risk of mood disorders as they develop major depressive disorder. Biol Psychiatry 78; 58-66, 2015. https://doi.org/10.1016/j.biopsych.2014.10.018

517. Parisi P. Why is migraine rarely, and not usually, the sole ictal epileptic manifestation? Seizure 18; 309-312, 2009. https://doi.org/10.1016/j.seizure.2009.01.010

518. Passchier J. A critical note on psychophysiological stress research into migraine patients. Cephalalgia 14; 194-198, 1994. https://doi.org/10.1046/j.1468-2982.1994.014003194.x

519. Pearce JMS. Is migraine explained by Leão's spreading depression? Lancet ii; 763-766, 1985. https://doi.org/10.1016/S0140-6736(85)90639-7

520. Pearce JMS. Historical aspects of migraine. J Neurol Neurosurg Psychiatry 49, 1097-1103, 1986. https://doi.org/10.1136/jnnp.49.10.1097

521. Peatfield R. Drugs and the treatment of migraine. Trends Pharmacol Sci 9; 141-145, 1988. https://doi.org/10.1016/0165-6147(88)90197-6

522. Peatfield RC, Rose FC. Migrainous visual symptoms in a woman without eyes. Arch Neurol 38, 466, 1981. https://doi.org/10.1001/archneur.1981.00510070100024

523. Pellegrino ABW, Davis-Martin RE, Houle TT, Turner DP, Smitherman TA. Perceived triggers of primary headache disorders: a meta-analysis. Cephalalgia 38; 1188-1198, 2018. https://doi.org/10.1177/0333102417727535

524. Peñarrocha M, Bandrés A, Peñarrocha M, Bagán JV. Lower-half facial migraine: a report of 11 cases. J Oral Maxillofac Surg 62; 1453-1456, 2004. https://doi.org/10.1016/j.joms.2004.01.027

525. Peringer EP, Jenner P, Donaldson IM, Marsden CD. Metoclopramide and dopamine receptor blockade. Neuropharmacology 15; 463-469, 1976. https://doi.org/10.1016/0028-3908(76)90056-3

526. Peroutka SJ. Migraine: a chronic sympathetic nervous system disorder. Headache 44, 53-64, 2004. https://doi.org/10.1111/j.1526-4610.2004.04011.x

527. Peroutka SJ. What turns on a migraine? A systemic review of migraine precipitating factors. Curr Pain Headache Rep 18, 454, 2014. https://doi.org/10.1007/s11916-014-0454-6

528. Petrie WM, Maffucci RJ, Woosley RL. Propranolol and depression. Am J Psychiatry 139; 92-94, 1982. https://doi.org/10.1176/ajp.139.1.92

529. Pffafenrath V, Weseley P, Meyer C, Isler HR, Evers S, Grotemeyer KH et al. Magnesium in the prophylaxis of migraine: a double-blind placebo-controlled trial. Cephalalgia 16; 336-340, 1996. https://doi.org/10.1046/j.1468-2982.1996.1606436.x

530. Pietrobon D, Moskowitz MA. Chaos and commotion in the wake of cortical spreading depression and spreading depolarizations. Nat Rev Neurosci 15; 379-393, 2014. https://doi.org/10.1038/nrn3770

531. Pietrobon D, Striessnig J. Neurobiology of migraine. Nat Rev Neurosci 4; 386-398, 2003. https://doi.org/10.1038/nrn1102

532. Piilgaard H, Lauritzen M. Persistent increase in oxygen consumption and impaired neurovascular coupling after spreading depression in rat neocortex. J Cereb Blood Flow Metab 29; 1517-1527, 2009. https://doi.org/10.1038/jcbfm.2009.73

533. Pinho-Correia LM, McCullough SJC, Ghanizada H, Nedergaard M, Rustenhoven J, Mesquita SD. CSF transport at the brain-meningeal border: effects on neurological health and disease. Lancet Neurol 24: 535-547, 2025. https://doi.org/10.1016/S1474-4422(25)00115-2

534. Piovesan EJ, Sobreira CF, Scola RH, Lorenzoni PJ, Lange MC, Werneck LC et al. Episodic migraine associated with postural orthostatic tachycardia syndrome and vasovagal syncope. Arq Neuropsiquiatr 66; 77-79, 2008. https://doi.org/10.1590/S0004-282X2008000100018

535. Pizzolato R, Villani V, Prosperini L, Ciuffoli A, Sette G. Efficacy and tolerability of pregabalin as preventive treatment for migraine: A 3-month follow-up study. J Headache Pain 12; 521-525, 2011. https://doi.org/10.1007/s10194-011-0338-0

536. Podoll K, Robinson D. Migraine Art. The Migraine Experience from Within. North Atlantic Books, Berkely, California, 2008.

537. Poole CJM. Migraine. Br J Hosp Med 36, 90-93, 1986.

538. Putz K, Hayani K, Zar FA. Meningitis. Prim Care 40(3):707-26, 2013. https://doi.org/10.1016/j.pop.2013.06.001

539. Queiroz LP, Friedman DI, Rapoport AM, Purdy RA. Characteristics of migraine visual aura in Southern Brazil and Northern USA. Cephalalgia 31; 1652-1658, 2011. https://doi.org/10.1177/0333102411430263

540. Queiroz LP, Rapoport AM, Weeks RE, Shefftel FD, Siegel SE, Baskin SM. Characteristics of migraine visual aura. Headache 37; 137-141, 1997. https://doi.org/10.1046/j.1526-4610.1997.3702137.x

541. Rabkin R, Stables DP, Levin NW, Suzman MM. The prophylactic value of propranolol in angina pectoris. Am J Cardiol 18; 370-383, 1966.

542. Ramachandran R, Yaksh TL. Therapeutic use of botulinum toxin in migraine: mechanisms of action. Br J Pharmacol 171; 4177–4192, 2014. https://doi.org/10.1111/bph.12763

543. Ramanathan J, Sibai BM, Pillai R, Angel JJ. Neuromuscular transmission studies in preeclamptic women receiving magnesium sulfate. Am J Obstet Gynecol 158; 4046, 1988. https://doi.org/10.1016/0002-9378(88)90772-7

544. Rambarat CA, Elgendy IY, Johnson BD, Reisb SE, Thompson DV, Sharaf BL et al. Migraine headache and outcomes: an extended follow-up of the women's ischemia syndrome evaluation. Am J Med 130; 738-743, 2017. https://doi.org/10.1016/j.amjmed.2017.02.008

545. Rasmussen BK, Olesen J. Migraine with aura and migraine without aura: an epidemiological study. Cephalalgia 12; 221-228, 1992. https://doi.org/10.1046/j.1468-2982.1992.1204221.x

546. Rauch SL, Wright CI, Maetis B, Busa E, McMullin KG, Shin LM et al. A magnetic resonance imaging study of cortical thickness in animal phobia. Biol Psychiatry 55; 946-952, 2004. https://doi.org/10.1016/j.biopsych.2003.12.022

Citation: Gupta VK. Cortical Spreading Depression and Migraine: Critical Review of a Neurophysiological Principle in the Third Millennium. Glob J Medical Clin Case Rep. 2026:13(10):228-272. Available from: https://dx.doi.org/10.17352/gjmccr.000273

547. Read SJ, Hirst WD, Upton N, Parsons AA. Cortical spreading depression produces increased cGMP levels in cortex and brain stem that is inhibited by tonabersat (SB220453) but not sumatriptan. Brain Res 891; 69-77, 2001. https://doi.org/10.1016/S0006-8993(00)03191-7

548. Read SJ, Smith MI, Hunter AJ, Parsons AA. The dynamics of nitric oxide release measured directly and in real time following repeated waves of cortical spreading depression in the anaesthetized cats. Neurosci Lett 232; 127-130, 1997. https://doi.org/10.1016/S0304-3940(97)00604-

549. Reichert C, Reichert P, Monnet-Tschudi F, Kupferschmidt H, Ceschi A, RauberLüthy C. Seizures after single-agent overdose with pharmaceutical drugs: analysis of cases reported to a poison center. Clin Toxicol 52; 629-634, 2014. https://doi.org/10.3109/15563650.2014.918627

550. Reuter U, Del Rio MS, Diener HC, Allais G, Davies B, Gendolla A et al. Migraines with and without aura and their response to preventive therapy with topiramate. Cephalalgia 30; 543-551, 2010.

551. Richard S. Vascular effects of calcium channel antagonists: new evidence. Drugs 65; S1-S10, 2005.

552. Richter F, Ebersberger A, Schaible HG. Blockage of voltage-gated calcium channels in rat inhibits repetitive cortical spreading depression. Neurosci Lett 334; 123-126, 2002.

553. Richter F, Mikulik O, Ebersberger A, Schaible HG. Noradrenergic agonists and antagonists influence migration of cortical spreading depression in rat—a possible mechanism of migraine prophylaxis and prevention of postischemic neuronal damage. J Cereb Blood Flow Metab 25; 1225-1235, 2005.

554. Ringoir L, Pedersen SS, Widdershoven JWMG, Pouwer F, Keyzer JML, Romeijnders AC, Pop VJ. Beta-blockers and depression in elderly hypertension patients in primary care. Fam Med 46; 447-453, 2014.

555. Ripa P, Ornello R, Pistoia F, Carolei A, Simona Sacco S. Spreading depolarization may link migraine, stroke, and other cardiovascular disease. Headache 55; 180-182, 2015.

556. Rocca MA, Messina R, Colombo B, Falini A, Comi G, Filippi M. Structual brain MRI abnormalities in pediatric patients with migraine. J Neurol 261, 350-357, 2014.

557. Rodgers CI, Armstrong GAB, Robertson RM. Coma in response to environmental stress in the locust: a model for cortical spreading depression. J Insect Physiol 56, 980-990, 2010.

558. Rosas HD, Liu AK, Hersch S, Glessner M, Ferrante RJ, Salat DH et al. Regional and progressive thinning of the cortical ribbon in Huntington's disease. Neurology 58; 695-701, 2002.

559. Rose FC. The history of migraine from Mesopotamian to Medieval times. Cephalalgia 15; 1–3, 1995.

560. Rose FC. The neurology of art: an overview. In: Rose FC, editor. Neurology of the arts. London: Imperial College Press; 2004, pp. 43-76.

561. Rose FC. Headache: definition and classification. In: Vinken PJ, Bruyn GW, Klawans HL, Rose FC, eds. Handbook of Clinical Neurology. Amsterdam: 4(48), 1986, pp 483-486.

562. Rosenfeld WE. Topiramate: A review of preclinical, pharmacokinetic, and clinical data. Clin Ther 19; 1294-1308, 1997.

563. Rosenstock J, Tuchman M, LaMoreaux L, Sharma U. Pregabalin for the treatment of painful diabetic peripheral neuropathy: a double-blind, placebo-controlled trial. Pain 110; 628-638, 2004.

564. Rossi HL, Recober A. Photophobia in primary headaches. Headache 55; 600-604, 2015.

565. Rounds HD. KCL-induced "spreading depression" in the cockroach. J Insect Physiol 13; 869-872, 1967.

566. Rowe JW, Shelton RL, Helderman JH, Vetal RE, Robertson GL. Influence of the emetic reflex on vasopressin release in man. Kidney Int 16; 729-735, 1979.

567. Rubboli G, Bisulli F, Michelucci R, Meletti S, Ribani MA, Cortelli P, et al. Sudden falls due to seizure-induced cardiac asystole in drug-resistant focal epilepsy. Neurology 70; 1933-1935, 2008.

568. Russo A, Coppola G, Pierelli F, Parisi V, Silvestro M, Tessitore A et al. Pain perception and migraine. Front Neurol 9; 576, 2018 doi: 10.3389/fneur.2018.00576.

569. Ryan RE. Comparative study of nadolol and propanolol in prophylactic treatment of migraine. Am Heart J 108; 1156–1159, 1984.

570. Ryan RE, Sr, Ryan RE, Jr, Sudilovski A. Nadolol: its use in the prophylactic treatment of migraine. Headache 23; 26–31, 1983.

571. Sacco S, Kurth T. Migraine and the risk for stroke and cardiovascular disease. Curr Cardiol Rep 16; 524, 2014.

572. Sadeh, M. Action of magnesium sulphate in the treatment of pre-eclampsiaeclampsia. Stroke 20; 1273-1275, 1989.

573. Sahota RK, Dexter JD. Sleep and headache syndromes: a clinical review. Headache 30; 80-84, 1990.

574. Salat DH, Buckner RL, Snyder AZ, Greve DN, Desikan RSR, Busa E et al. Thinning of the cerebral cortex in aging. Cereb Cortex 14; 721-730, 2004.

575. Sanchez del Rio M, Bakker D, Wu O, Agosti R, Mitsikostas DD, Østergaard L et al. Perfusion weighted imaging during migraine: spontaneous visual aura and headache. Cephalalgia 19; 701-707, 1999.

576. Sanchez-del-Rio M, Reuter U, Moskowitz MA. New insights into migraine pathophysiology. Curr Opin Neurol 19; 294-298, 2006.

577. Sándor PS, Áfra J, Ambrosini A, Schoenen J. Prophylactic treatment of migraine with beta-blockers and riboflavin: differential effects on the intensity dependence of auditory evoked cortical potentials. Headache 40; 30-35, 2000.

578. Satel SL, Gawin FH. Migraine-like headache and cocaine use. JAMA 261, 29952996, 1989.

579. Sauro KM, Becker WJ. The stress and migraine interaction. Headache Currents 49; 1378-1386, 2009.

580. Saver JL, Starkman S, Eckstein M, Stratton SJ, Pratt FD, Hamilton S et al., FAST-MAG Investigators and Coordinators. Prehospital use of magnesium sulfate as neuroprotection in acute stroke. N Eng J Med 372; 528536, 2015.

581. Savi LT, Condello V, Bert F, Pinessi L. Prophylaxis of migraine with aura: a place for acetylsalicylic acid. J Headache Pain 14 (Suppl 1); P195, 2013.

582. Savic I, Arver S. Sex differences in cortical thickness and their possible genetic and sex hormonal underpinnings. Cereb Cortex 24; 3246-3257, 2014.

583. Sawant-Pokam PM, Suryavanshi P, Mendez JM, Dudek FE, Brennan KC. Mechanism of neuronal silencing after cortical spreading depression. Cereb Cortex 27; 1311-1325, 2017.

584. Schacter SC. Iatrogenic seizures. Neurol Clin 16; 157- 170, 1998.

585. Scheer FAJL, Morris CJ, Garcia JI, Smales C, Kelly EE, Marks J, Malhotra A, Shea SA. Repeated melatonin supplementation improves sleep in hypertensive patients treated with beta-blockers: a randomized controlled trial. Sleep 35; 13951402, 2012.

586. Scheewe TW, van Haren NE, Sarkisyan G, Schnack HG, Brouwer RM, de Glint M et al. Exercise therapy, cardiorespiratory fitness and their effect on brain volumes: a randomised controlled trial in patients with schizophrenia and healthy controls. Eur Neuropsychopharmacol 23; 675-85, 2013.

Citation: Gupta VK. Cortical Spreading Depression and Migraine: Critical Review of a Neurophysiological Principle in the Third Millennium. Glob J Medical Clin Case Rep. 2026:13(10):228-272. Available from: https://dx.doi.org/10.17352/gjmccr.000273

587. Schmitz N, Admiraal-Behloul F, Arkink EB, Kruit MC, Schoonman GG, Ferrari MD, van Buchem MA. Attack frequency and disease duration as indicators for brain damage in migraine. Headache 48; 1044-1055, 2008.

588. Schmitz N, Arkink EB, Mulder M, Rubia K, Admiraal-Behloul F, Schoonman GG et al. Frontal lobe structure and executive function in migraine patients. Neurosci Lett 440; 92-96, 2008a.

589. Schoenen J, Coppola G. Efficacy and mode of action of external trigeminal neurostimulation in migraine. Exp Rev Neurother 18; 545-555, 2018. doi.org /10.1080/14737175.2018.1488588.

590. Schoenen J, Jacquy J, Lenaerts M. Effectiveness of high-dose riboflavin in migraine prophylaxis: a randomized controlled trial. Neurology 50; 466-470, 1998.

591. Schoonman GG, van der Grond J, Kortmann C, van der geest RJ, Terwindt GM, Ferrari MD. Migraine headache is not associated with cerebral or meningeal vasodilatation – a 3T magnetic resonance angiography study. Brain 131; 2192-2200, 2008.

592. Schott GD. Exploring the visual hallucinations of migraine aura: the tacit contribution of illustration. Brain 130; 1690-1703, 2007.

593. Schulte LH, Allers A, May A. Hypothalamus as a mediator of chronic migraine: evidence from high resolution fMRI. Neurology 88; 2011-2016, 2017.

594. Schulte LH, May A. The migraine generator revisited: continuous scanning of the migraine cycle over 30 days and three spontaneous attacks. Brain 139; 1987-1993, 2016a.

595. Schulte LH, May A. Functional neuroimaging in migraine: chances and challenges. Headache 56, 1474-1481, 2016b.

596. Schumacher GA, Wolff HG. Experimental studies on headache. Arch Neurol Psychiatry 45; 199-214, 1941.

597. Schwartz DP, Robbins MS. Primary headache disorders and neuro-ophthalmologic manifestations. Eye and Brain 4; 49-61, 2012.

598. Schwarzer R. Stress and coping from a social-cognitive perspective. Ann N Y Acad Sci 851; 531-537, 1998.

599. Schwedt TJ, Berisha V, Chong CD. Temporal lobe cortical thickness correlations differentiate the migraine brain from the healthy brain. PLoS One 10; e0116687, 2015.

600. Schwedt TJ, Chong CD. Correlations between brain cortical thickness and cutaneous pain thresholds are atypical in adults with migraine. PLoS ONE 9; e99791, 2014. https://doi.org/10.1371/journal.pone.0099791

601. Schwedt TJ, Chong CD. Functional imaging and migraine: new connections? Curr Opin Neurol 28, 265-270, 2015. https://doi.org/10.1097/WCO.0000000000000194

602. Schwedt TJ, Dodick DW. Advanced neuroimaging of migraine. Lancet Neurol 8; 560-568, 2009. https://doi.org/10.1016/S1474-4422(09)70107-3

603. Seçil Y, Ünde C, Beckmann YY, Bozkaya YT, Özerkan F, Başoğlu M. Blood pressure changes in migraine patients before, during and after migraine attacks. Pain Practice 10; 222-227, 2010. https://doi.org/10.1111/j.1533-2500.2009.00349.x

604. Selby G, Lance JW. Observations on 500 cases of migraine and allied vascular headache. J Neurol Neurosurg Psychiat 23; 23-32, 1960. https://doi.org/10.1136/jnnp.23.1.23

605. Shaik MM, Gan SH. Vitamin supplementation as possible prophylactic treatment against migraine with aura and menstrual migraine. BioMed Research International Article ID 469529, 2015. http://dx.doi.org/10.1155/2015/4695529

606. Shams PN, Plant GT. Migraine-like visual aura due to focal cerebral lesions: case series and review. Surv Ophthalmol 56; 135-161, 2011. https://doi.org/10.1016/j.survophthal.2010.07.005

607. Shaw P, Malek M, Watson B, Greenstein D, de Rossi P, Sharp W. Trajectories of cerebral cortical development in childhood and adolescence and adult attentiondeficit/hyperactivity disorder. Biol Psychiatry 74; 599-606, 2013. https://doi.org/10.1016/j.biopsych.2013.04.007

608. Shaw P, Malek M, Watson B, Sharp W, Evans A, Greenstein D. Development of cortical surface area and gyrification in attention-deficit / hyperactivity disorder. Biol Psychiatry 72; 191-197, 2012. https://doi.org/10.1016/j.biopsych.2012.01.031

609. Shecter A, Stewart WF, Silberstein SD, Lipton RB. Migraine and autonomic nervous system function: a population-based, case-control study. Neurology 58; 422427, 2002. https://doi.org/10.1212/WNL.58.3.422

610. Shen P-p, Hou S, Ma D, Zhao M-m, Zhu M-g, Zhang J-d, Feng L-s, Cui l, Feng J-c. Cortical spreading depression-induced preconditioning in the brain. Neural Regen Res 11; 1857-1864, 2016. https://doi.org/10.4103/1673-5374.194759

611. Shevel E. Middle meningeal artery dilatation in migraine. Headache 49; 1541-1543, 2009. https://doi.org/10.1111/j.1526-4610.2009.01495.x

612. Shulman BH. Psychiatric aspects of headache. Med Clin North Am 75; 707-715, 1991. https://doi.org/10.1016/S0025-7125(16)30444-8

613. Sibai BM. Magnesium sulphate prophylaxis in preeclampsia: lessons learnt from recent trials. Am J Obstet Gyne 190; 1520-1526, 2004.

614. Silberstein SD. Preventive treatment of migraine. Trends Pharmacol Sci 27; 410-415, 2006. https://doi.org/10.1016/j.tips.2006.06.003

615. Silberstein SD. Preventive migraine treatment. Continuum 21; 973-989, 2015. https://doi.org/10.1212/CON.0000000000000199

616. Silberstein SD, Holland S, Freitag F, Dodick DW, Argoff CE. Ashman E. Evidence-based guideline update: pharmacologic treatment for episodic migraine prevention in adults: report of the Quality Standards Subcommittee of the American Academy of Neurology and the American Headache Society. Neurology 78; 13371345, 2012. https://doi.org/10.1212/WNL.0b013e3182535d20

617. Silberstein SD, Hulihan J, Karim MR, Wu SC, Jordan D, Karvois D, Kamin M. Efficacy and tolerability of topiramate 200 mg/d in the prevention of migraine with/without aura in adults: a randomized, placebo-controlled, double-blind, 12 week pilot study. Clin Ther 28; 1002-1011, 2006. https://doi.org/10.1016/j.clinthera.2006.07.003

618. Silberstetin SD, Schoenen J, Göbel H, Diener HC, Elkind AH, Klapper JA, Howard RA. Tonabersat, a gap-junction modulator: efficacy and safety in two randomized, placebo-controlled, dose-ranging studies of acute migraine. Cephalalgia 29 (Suppl 2); 17-27, 2009. https://doi.org/10.1111/j.1468-2982.2009.01974.x

619. Silberstein SD, Young WB. Migraine aura and prodrome. Semin Neurol 15; 175182, 1995.

620. Sillanpää M. Prevalence of migraine and other headache in Finnish children starting school. Headache 15; 288-290, 1976.

621. Sillanpää M, Saarinen M, Schmidt D. Long-term risks following first remission in childhood-onset epilepsy. A population-based study. Epilepsy Behav 25; 145-149, 2012.

622. Silva GCC, Góes CPQF, Vincent MB. Aura-like features and photophobia in sightless migraine patients. Arq Neuropsiquiatr 72; 949-963, 2014.

623. Sinatra RS, Philip BK, Naulty JS, Ostheimer GW. Prolonged neuromuscular blockade with vecuronium in a patient treated with magnesium sulfate. Anesth Analg 64; 1220-1222, 1985.

Citation: Gupta VK. Cortical Spreading Depression and Migraine: Critical Review of a Neurophysiological Principle in the Third Millennium. Glob J Medical Clin Case Rep. 2026:13(10):228-272. Available from: https://dx.doi.org/10.17352/gjmccr.000273

624. Singer C. The visions of Hildegard of Bingen. In: From Magic to Science. London: Ernest Benn, 199-239, 1928.

625. Siniatchkin M, Reich AL, Shepherd AJ, van Baalen A, Siebner HR, Stephani U. Peri-ictal changes of cortical excitability in children suffering from migraine without aura. Pain 147; 132-140, 2009.

626. Sjaastad O, Bovim G, Stovner LJ. Laterality of pain and other migraine criteria in common migraine. A comparison with cervicogenic headache. Funct Neurol 7; 289-294, 1992. https://doi.org/10.1016/j.pain.2009.08.028

627. Sjöstrand C, Savic I, Laudon-Meyer E, Hillert L, Lodin K, Waldenlind E. Migraine and olfactory stimuli. Curr Pain Headache Rep 14; 244-251, 2010. https://doi.org/10.1007/s11916-010-0109-7

628. Skaredoff MN, Roaf ER, Datta S. Hypermagnesemia and anaesthetic management. Can Anaesth Soc J 29; 35-41, 1982.

629. Smith MI, Read SJ, Chan WN, Thompson M, Hunter AJ, Upton N, Parsons AA. Repetitive cortical spreading depression in a gyrencephalic feline brain: Inhibition by the novel benzoylamino-benzopyran SB-220453. Cephalalgia 20; 546-553, 2000.

630. Solomon GD. Verapamil in migraine prophylaxis—a five-year review. Headache 29; 425-427, 1989. https://doi.org/10.1111/j.1526-4610.1989.hed2907425.x

631. Solotareff L, Cuvellier J-C, Duhamel A, Vallée L, The Tich SN. Trigger factors in childhood migraine: a prospective clinic-based study from North of France. J Child Neurol 32; 754-758, 2017. https://doi.org/10.1177/0883073817717528

632. Somjen GG. Mechanisms of spreading depression and hypoxic spreading depression-like depolarization. Physiol Rev 81, 1065-1096, 2001. https://doi.org/10.1152/physrev.2001.81.3.1065

633. Sørensen PS, Hammer H. Vasopressin in plasma and ventricular cerebrospinal fluid during dehydration, postural changes, and nausea. Am J Physiol 248; R78-83, 1985.

634. Soriani S, Feggi L, Battistell PA, Arnaldi C, De Carlo L, Stipa S. Interictal and ictal phase study with Tc 99m HMPAO brain SPECT in juvenile migraine with aura. Headache 37; 31–36, 1997.

635. Sörös P, Vo O, Husstedt I-W, Evers S, Gerding H. Phantom eye syndrome. Its prevalence, phenomenology, and putative mechanisms. Neurology 60; 1542-1543, 2003.

636. Sowell ER, Peerson BS, Thompson PM, Welcome SE, Henkenius AL, Toga AW. Mapping cortical change across the human life span. Nat Neurosci 6, 309-315, 2003. https://doi.org/10.1038/nn1015

637. Sotnikov OS, Vasyagina NY, Krasnova TV. [Isometric retraction and the invisible processes of nerve cells] [Article in Russian] Morfologiia 148; 9-17, 2015.

638. Spierings EL, Donoghue S, Mian A, Wöber C. Sufficiency and necessity in migraine: how do we figure out if triggers are absolute or partial and, if partial, additive or potentiating? Curr Pain Headache Rep 18; 455, 2014.

639. Spong KE, Mazzetti TR, Robertson RM. Activity dependence of spreading depression in the locust CNS. J Exp Biol 219; 626-630, 2016a.

640. Spong KE, Andrew RD, Meldrum Robertson XR. Mechanisms of spreading depolarization in vertebrate and insect central nervous systems Kristin E. J Neurophysiol 116; 1117–1127, 2016b.

641. Spong KE, Rodriguez EC, Robertson RM. Spreading depolarization in the brain of Drosophilia is induced by inhibition of the Na+/K+-ATPase and mitigated by a decrease in activity of protein kinase G. J Neurophysiol 116; 1152-1160, 2016c.

642. Sporer KA. The serotonin syndrome. Implicated drugs, pathophysiology, and management. Drug Safety 13; 94-104, 1995.

643. Stankewitz A, May A. Increased limbic and brainstem activity during migraine attacks following olfactory stimulation. Neurology 77; 476-482, 2001.

644. Stankewitz A, May A. The phenomenon of changes in cortical excitability in migraine is not migraine specific: a unifying thesis. Pain 145; 14-17, 2009.

645. Stellar S, Ahrens SP, Meibohm AR, Reines SA. Migraine prevention with timolol. JAMA 252; 2576-2257, 1984. https://doi.org/10.1001/jama.1984.03350180030025

646. Stensrud P, Sjaastad O. Comparative trial of tenormin (atenolol) and Inderal (propranolol) in migraine. Headache 20; 204-207, 1980. https://doi.org/10.1111/j.1526-4610.1980.h2004006.x

647. Sternbach H. The serotonin syndrome. Am J Psychiatry 148; 705-713, 1991. https://doi.org/10.1176/ajp.148.6.705

648. Stoschitzky K, Sakotnik A, Lercher P, Zweiker R, Maier R, Liebmann P, Lindner W. Influence of beta-blockers on melatonin release. Eur J Clin Pharmacol 55; 111-115, 1999. https://doi.org/10.1007/s002280050583

649. Strassman AM, Raymond SA, Burstein R. Sensitization of meningeal sensory neurons and the origin of headaches. Nature 384; 560-564, 1996. https://doi.org/10.1038/384560a0

650. Strong AJ, Fabricius M, Boutelle MG, Hibbins SJ, Hopwood SE, Jones R, Parkin MC, Lauritzen M. Spreading and synchronous depressions of cortical activity in acutely injured human brain. Stroke 33, 2738-2743, 2002. https://doi.org/10.1161/01.STR.0000043073.69602.09

651. Sudlikovski A, Elkind AH, Ryan RE, Sr, Saper JR, Stern MA, Meyer JH. Comparative efficacy of nadolol and propranolol in the management of migraine. Headache 27; 421–426, 1987. https://doi.org/10.1111/j.1526-4610.1987.hed2708421.x

652. Talebian A, Soltani B, Banafshe HR, Moosavi GA, Talebian M, Soltani S. Prophylactic effect of riboflavin on pediatric migraine: a randomized, doubleblind, placebo-controlled trial. Electron Physician 10; 6279-6285, 2018. https://doi.org/10.19082/6279

653. Tana C, Tafuri E, Tana M, Martelletti P, Negro A, Affaitati G et al. New insights into the cardiovascular risk of migraine and the role of white matter hyperintensities: is gold all that glitters? J Headache Pain 14; 9, 2013. https://doi.org/10.1186/1129-2377-14-9

654. Taneri Z, Petersen-Braun M. Double blind study of intravenous aspirin vs placebo in the treatment of acute migraine attacks. Schmerz 9; 124-129, 1995. https://doi.org/10.1007/BF02530130

655. Tassorelli C, Grazzi L, de Tommaso M, Pierangeli G, Marteletti P, Rainero I, Dorlas S, Geppetti P, Ambrosini A, Sarchielli P, Liebler E, Barbanti https://doi.org/10.1212/WNL.0000000000005857

656. P; PRESTO Study Group. Non-invasive vagus nerve stimulation as acute therapy for migraine. The randomized PRESTO study. Neurology 91; e364-e373, 2018. https://doi.org/10.1007/s10072-012-1049-2

657. Tedeschi G, Russo A, Tessitore A. Functional neuroimaging in migraine: usefulness for the clinical neurologist. Neurol Sci 33 (Suppl 1); S91-S94, 2012. https://doi.org/10.1177/0333102414564891

658. Teigen L, Boes CJ. An evidence-based review of oral magnesium supplementation in the preventive treatment of migraine. Cephalalgia 35; 912-922, 2015. https://doi.org/10.1212/01.wnl.0000183281.12779.cd

659. Teive HAG, Kowacs PA, Filho PM, Piovesan EJ, Werneck L. Leão cortical spreading depression: from experimental "artifact" to physiological principle. Neurology 65; 1455-1459, 2005. https://doi.org/10.1177/03331024860060S502

Citation: Gupta VK. Cortical Spreading Depression and Migraine: Critical Review of a Neurophysiological Principle in the Third Millennium. Glob J Medical Clin Case Rep. 2026:13(10):228-272. Available from: https://dx.doi.org/10.17352/gjmccr.000273

660. Tfelt-Hansen P. Efficacy of beta-blockers in migraine. A critical review. Cephalalgia 6; S15-S24, 1986.

661. Tfelt-Hansen PC. Does sumatriptan cross the blood–brain barrier in animals and man? J Headache Pain 11; 5–12, 2010.

662. Tfelt-Hansen PC, Koehler PJ. One hundred years of migraine research: major clinical and scientific observations from 1910-2010. Headache 51: 752–778, 2011.

663. Tfelt-Hansen P, Standnes B, Kangasniemi P, Hakkarainen H, Oleson J. Timolol vs. propranolol vs. placebo in common migraine prophylaxis: a double-blind multicenter trial. Acta Neurol Scand 69; 1-8, 1984.

664. Tfelt-Hansen PC, Tfelt-Hansen J. Nitroglycerin headache and nitroglycerin-induced primary headaches from 1846 and onwards: a historical overview and an update. Headache 49; 445-456, 2009.

665. Theodore WH, Spencer SS, Wiebe S et al. Epilepsy in North America: a report prepared under the auspices of the global campaign against epilepsy. The

666. International Bureau of Epilepsy, the International League Against Epilepsy, and the World Health Organization. Epilepsia 47; 1700-1722, 2006.

667. Thijs RD, Kruit MC, van Buchem MA, Ferrari MD, Launer LJ, van Dijk JG. Syncope in migraine. The population-based CAMERA study. Neurology 66, 10341037, 2006.

668. Thomsen LL, Kruuse C, Iversen HK, Olesen J. A nitric oxide donor (nitroglycerine) triggers genuine migraine attacks. Eur J Neurol 1; 73-80, 1994. https://doi.org/10.2165/00003495-198938040-00004

669. Thomsen LL, Olesen J. Sporadic hemiplegic migraine. Cephalalgia 24; 1016-1023, 2004.

670. Todd PA, Benfield P. Flunarizine: a reappraisal of its pharmacological properties and therapeutic use in neurological disorder. Drugs 38; 481-499, 1989. https://doi.org/10.1177/0333102412442718

671. Trobe JD. Photophobia in anterior visual pathway disease. J Neuroophthalmol 22; 12, 2002. https://doi.org/10.1093/brain/awq065

672. Unekawa M, Tomita Y, Toriumi H, Suzuki N. Suppressive effect of chronic peroral topiramate on potassium-induced cortical spreading depression in rats. Cephalalgia 32; 518-527, 2012.

673. Upadhyay J, Maleki N, Potter J, Elman I, Rudrauf D, Knudsen J et al. Alterations in brain structure and functional connectivity in prescription opioid-dependent patients. Brain 133; 2098-2114, 2010. https://doi.org/10.1016/j.ijcard.2013.11.132

674. Valiquette G. The neurohypophysis. Neurol Clin 5; 291-331, 1987. https://doi.org/10.1046/j.1468-2982.1997.1707733.x

675. Vallejo M, Martínez-Martínez L-A, Grijalva-Quijada S, Olguín-Ruvalcaba H-M, Salas E, Hermosillo AG, Cárdenas M. Frequency of migraine in patients with vasovagal syncope. Int J Cardiol 171; e14-e15, 2014. https://doi.org/10.1523/JNEUROSCI.3628-14.2015

676. Vanagaite J, Pareja JA, Storen O, Whit LR, Sand T, Stovner LJ. Light-induced discomfort and pain in migraine. Cephalalgia 17; 733-741, 1997. https://doi.org/10.1016/S0031-9384(97)00103-7

677. Vandekar SN, Shinohara RT, Raznahan A, Roalf DR, Ross M, DeLeo N et al. Topologically dissociable patterns of development of the human cerebral cortex. J Neurosci 35; 599-609, 2015. https://doi.org/10.1097/00001756-199807130-00006

678. Van Den Heuvel CJ, Reid KJ, Dawson D. Effect of atenolol on nocturnal sleep and temperature in young men: reversal by pharmacological doses of melatonin. Physiol Behav 61; 795-802, 1997.

679. Van Der Hel WS, Van Den Bergh WM, Nicolay K, Tulleken KAF, Dijkhuizen RM. Supression of cortical spreading depressions after magnesium treatment in the rat. Neuroreport 9; 2179-2182, 1998. https://doi.org/10.1016/j.neurol.2022.01.006

680. Van Praag HM, Lader HM, Rafaelsen OJ, Sachar EJ (eds). Handbook of Biological Psychiatry. Marcel Dekker, INC, New York/Basel, 1979, Part 1, pp 166-167.. https://doi.org/10.1046/j.1468-2982.1996.1605328.x

681. Vercueil L. Migralepsy, what it is and what it is not. Rev Neurol (Paris). 178: 654658; 2022. https://doi.org/10.2147/NDT.S107074

682. Verspeelt J, De Locht P, Amery WK. Post-marketing cohort study comparing the safety and efficacy of flunarizine and propranolol in the prophylaxis of migraine. Cephalalgia 16, 328-336, 1996.

683. Viggiano E, Monda V, Messsina A, Moscatelli F, Valenzano A, Tafuri D et al. Cortical spreading depression produces a neuroprotective effect activating mitochondrial uncoupling protein-5. Neuropsychiatr Dis Treat 12; 1705-1710, 2016. https://doi.org/10.1046/j.1468-2982.2007.01404.x

684. Villanueva L. How does migraine attack stop? Headache 52; 188, 2012. https://doi.org/10.1177/0333102414560635

685. Vincent M, Hadjikhani N. Migraine aura and related phenomena: beyond scotomata and scintillations. Cephalalgia 27; 1368-1377, 2007. Available from: https://doi.org/10.1136/bmj.284.6325.944

686. Vongvaivanich K, Lertakyamanee P, Silberstein SD, Dodick DW. Latelife migraine accompaniments: A narrative review. Cephalalgia 35; 894-911, 2015. Available from: https://doi.org/10.1046/j.1468-2982.1984.0402085.x

687. Waelkens J. Domperidone in the prevention of complete classical migraine. BMJ 284, 944, 1982. Available from: https://doi.org/10.1016/j.ncl.2017.06.006

688. Waelkens J. Dopamine blockade with domperidone: bridge between prophylactic and abortive treatment of migraine? A dose-finding study. Cephalalgia 4, 85-90, 1984.

689. Wainsztein N, Lucci FR. Cortical spreading depression and ischemia in neurocritical patients. Neurol Clin 35; 655-664, 2017. Available from: https://doi.org/10.1046/j.1526-4610.2003.03102.x

690. Wall PD, Melzack R. Textbook of Pain. 2nd ed. New York, Churchill Livingstone, 1989.

691. Wang F, Van Den Eeden SK, Ackerson LM, Salk SE, Reince RH, Elin RJ. Oral magnesium oxide prophylaxis of frequent migrainous headache in children: a randomized, double-blind, placebo-controlled trial. Headache 43; 601-610, 2003.

692. Waters WE, Campbell MJ, Elwood PC. Migraine, headache, and survival in women. Br Med J 287; 1442-43, 1983.

693. Watchorn E, McCance RA. Inorganic constituents of cerebrospinal fluid. The ultrafiltration of calcium and magnesium from human sera. Biochem J 26; 54-64, 1932.

694. Watson JD. The Double Helix. Signet Books, New American Library, New York, 1968. Available from: https://doi.org/10.1007/s00221-005-0014-7

695. Weerasuriya K, Patel L, Turner P. β-adrenoceptor blockade and migraine. Cephalalgia 2; 334-45, 1982. Available from: https://doi.org/10.1001/archneur.1987.00520150063024

696. Weimer MS, Hanke W. Propagation velocity and triggering threshold of retinal spreading depression are not correlated. Exp Brain Res 164; 185-193, 2005. Available from: https://doi.org/10.1111/j.1526-4610.2005.4501008.x

697. Welch KMA. Migraine. A biobehavioral disorder. Arch Neurol 44; 323-327, 1987. https://doi.org/10.1016/S0733-8619(18)30319-0

Citation: Gupta VK. Cortical Spreading Depression and Migraine: Critical Review of a Neurophysiological Principle in the Third Millennium. Glob J Medical Clin Case Rep. 2026:13(10):228-272. Available from: https://dx.doi.org/10.17352/gjmccr.000273

698. Welch KMA. Brain hyperexcitability: the basis for antiepileptic drugs in migraine prevention. Headache 45 [Suppl 1]: S25-S32, 2005. https://doi.org/10.1016/j.neuroimage.2010.03.056

699. Welch KMA, D'Andrea G, Tepley N, Barkley G, Ramadan NM. The concept of migraine as a state of central neuronal hyperexcitability. Neurol Clin 8; 817-828, 1990. Available from: https://doi.org/10.1007/BF00371317

700. Westlye LT, Walhovd KB, Dale AM, Bjørnerud A, Due-Tønnessen P, Engvig Available from: https://doi.org/10.1016/j.neuroimage.2013.10.005

701. A et al. Differentiating maturational and aging-related changes of the cerebral cortex by use of thickness and signal intensity. Neuroimage 52; 172-185, 2010. Available from: https://doi.org/10.1016/j.neuroimage.2010.03.056

702. Wiedemann M, de Lima VM, Hanke W. Effects of antimigraine drugs on retinal spreading depression. Naunyn Schmiedebergs Arch Pharmacol 353; 552-556, 1996. Available from: https://doi.org/10.1007/bf00169175

703. Wierenga LM, Langen M, Oranje B, Durston S. Unique developmental trajectories of cortical thickness and surface area. Neuroimage 87; 120-126, 2014. Available from: https://doi.org/10.1016/j.neuroimage.2013.11.010

704. Willoughby JO. The pathophysiology of vegetative symptoms in migraine. Lancet ii (8244); 445-446, 1981. Available from: https://doi.org/10.1016/s0140-6736(81)90777-7

705. Wilkinson M, Robinson D. Migraine art. Cephalalgia 5; 151-157, 1985.

706. Wilmhurst PT. Migraine with aura and persistent foramen ovale. Eye (Lond.) 32, 184-188, 2018. Available from: https://doi.org/10.1038/eye.2017.269

707. Winawer MR, Connors R; EPGP Investigators. Evidence for a shared genetic susceptibility to migraine and epilepsy. Epilepsia 54; 288-295, 2013. Available from: https://doi.org/10.1111/epi.12072

708. Wittkowsky L. Ophthalmic migraine in arteriovenous aneurysm: symptoms of hemicranias. Nervenarzt 23; 140-143, 1952. Available from: https://pubmed.ncbi.nlm.nih.gov/14947912/

709. Wolthausen J, Sternberg S, Gerloff C, May A. Are cortical spreading depression and headache in migraine causally linked? Cephalalgia 29; 244-249, 2009. Available from: https://doi.org/10.1161/01.STR.0000169903.09253.c7

710. Woods RP, Iacoboni M, Mazziotta JC. Bilateral spreading cerebral hypoperfusion during spontaneous migraine headache. NEJM 331; 1689-1692, 1994. Available from: https://doi.org/10.1056/nejm199412223312505

711. Wu BS, Lee JK, Thomson KM, Walker VK, Moyes CD, Robertson RM. Anoxia induces thermotolerance in the locust flight system. J Exp Biol 205; 815-827, 2002. Available from: https://doi.org/10.1242/jeb.205.6.815

712. Yanamoto H, Miyamoto S, Tohnai N, Nagata I, Xue JH, Nakano Y, Nakajo Y, Kikuchi H. Induced spreading depression activates persistent neurogenesis in the subventricular zone, generating cells with markers for divided and early committed neurons in the caudate putamen and cortex. Stroke 36; 1544-1550, 2005. Available from: https://doi.org/10.1161/01.str.0000169903.09253.c7

713. Yanamoto H, Xue JH, Miyamoto S, Nagata I, Nakano Y, Murao K et al. Spreading depression induces long-lasting brain protection against infarcted lesion development via BDNF gene-dependent mechanism. Brain Res 1019; 178-188, 2004. Available from: https://doi.org/10.1016/j.brainres.2004.05.105

714. Yanamoto H, Mizuta I, Nagata I, Xue J, Zhang Z, Kikuchi H. Infarct tolerance accompanied enhanced BDNF-like immunoreactivity in neuronal nuclei. Brain Res 877; 331-344, 2000. Available from: https://doi.org/10.1016/s0006-8993(00)02718-9

715. Yang R, Wang J, Wang F, Zhang H, Tan C, Chen H, Wang X. Bloodbrain barrier integrity damage in bacterial meningitis: The underlying link, mechanisms, and therapeutic targets. Int J Mol Sci 24: 2852, 2023. Available from: https://doi.org/10.3390/ijms24032852

716. Yavuz BG, Aydinlar EI, Dikmen PY, Insesu C. Association between somatic amplification, anxiety, depression, stress and migraine. J Headache Pain 14; 53, 2013. Available from: https://doi.org/10.1186/1129-2377-14-53

717. Youssef AM, Ludwick A, Wilcox SL, Lebel A, Peng K, Colon E, Danehy A, Burstein R, Becerra L, Borsook D . In child and adult migraineurs the somatosensory cortex stands out…again: an arterial spin labelling investigation. Hum Brain Mapp 38; 4078-4087, 2017. Available from: https://doi.org/10.1002/hbm.23649

718. Yu D, Yuan K, Luo L, Zhai J , Bi Y , Xue T et al. Abnormal functional integration across core brain networks in migraine without aura. Mol Pain 13; 1-10, 2017. Available from: https://doi.org/10.1177/1744806917737461

719. Yu W, Horowitz SH. Treatment of sporadic hemiplegic migraine with calciumchannel blocker verapamil. Neurology 60; 120-121, 2003. Available from: https://doi.org/10.1212/01.wnl.0000042051.16284.70

720. Yu ZB, Peng J, Lv YB, Zhao M, Xie B, Liang ML et al. Different mean thickness implicates involvement of the cortex in migraine. Medicine (Baltimore) 95; e4824, 2016. Available from: https://doi.org/10.1097/md.0000000000004824

721. Zehentbauer, JY. Scintillating Scotoma: Migraine, Aura, and Perception in European Literature, 1860-1900, 2015. Electronic Thesis and Dissertation Repository. 2694.

722. Zervas JP, Smith JL. Neuro-ophthalmic presentation of cone dysfunction in the adult. J Clin Neuroophthalmol 7; 202-218, 1987. Available from: https://pubmed.ncbi.nlm.nih.gov/2963026/

723. Ziegler DK, Hurwitz A, Hassanein RS, Kodanaz HA, Preskorn SH, Mason J. Migraine prophylaxis. A comparison of propranolol and amitriptyline. Arch Neurol 44; 486-489, 1987. Available from: https://doi.org/10.1001/archneur.1987.00520170016015

724. Ziegler DK, Hurwitz A, Preskorn S, Hassanein R, Seim J. Propranolol and amitriptyline in prophylaxis of migraine. Pharmacokinetic and therapeutic effects. Arch Neurol 50; 825-830, 1993. Available from: https://doi.org/10.1001/archneur.1993.00540080036010

Discover a bigger Impact and Visibility of your article publication with Peertechz Publications

Highlights

- Signatory publisher of ORCID
- Signatory Publisher of DORA (San Francisco Declaration on Research Assessment)
- Articles archived in worlds' renowned service providers such as Portico, CNKI, AGRIS, TDNet, Base (Bielefeld University Library), CrossRef, Scilit, J-Gate etc.
- Journals indexed in ICMJE, SHERPA/ROMEO, Google Scholar etc.
- OAI-PMH (Open Archives Initiative Protocol for Metadata Harvesting)
- Dedicated Editorial Board for every journal
- Accurate and rapid peer-review process
- Increased citations of published articles through promotions
- Reduced timeline for article publication

Submit your articles and experience a new surge in publication services
https://www.peertechzpublications.org/submission

Peertechz journals wishes everlasting success in your every endeavours.

Citation: Gupta VK. Cortical Spreading Depression and Migraine: Critical Review of a Neurophysiological Principle in the Third Millennium. Glob J Medical Clin Case Rep. 2026:13(10):228-272. Available from: https://dx.doi.org/10.17352/gjmccr.000273