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Cortical spreading depression—new insights and persistent questions

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Abstract

Since its original extensive description by Leao in 1944, thousands of publications have characterized the phenomenon of cortical spreading depression (CSD). Despite the attention that CSD has received over more than six decades, however, many fundamental questions regarding its initiation, propagation, functional consequences, and relationship to migraine and other human disorders remain unanswered. Advances in genetics and cellular imaging have led to important insights into the basic mechanisms of CSD, with increasing attention focused on specific neuronal ion channels, neurotransmitters and neuromodulators. In addition, there is growing recognition that astrocytes and the vasculature may play an active, rather than simply a passive or reactive role in CSD. Several recent descriptions of CSD in humans in the setting of brain injury provide definitive evidence that this phenomenon can occur and have important functional consequences in the human brain. Although the exact role of CSD in migraine has yet to be conclusively established, there is strong evidence that the investigation of CSD in animal models can provide meaningful information about migraine that can be translated into the clinical setting. This review will briefly address the extensive work that has been done on CSD over more than half a century, but focus primarily on more recent studies with a particular emphasis on relevance to migraine.

Keywords

Spreading depression; migraine; prophylaxis

INTRODUCTION

Spreading depression (SD) is a slowly propagated wave of depolarization of neurons and glial cells, followed by a subsequent sustained suppression of spontaneous neuronal activity, accompanied by complex and variable changes in vascular calibre, blood flow, and energy metabolism. Although SD has been most extensively studied in the cortex [i.e. cortical spreading depression (CSD)], the phenomenon may occur in all neural tissues. In addition to the cortex, it has been well-characterized in the hippocampus, cerebellum, and retina, among other regions (for recent reviews, see (1–3)). CSD is associated with cellular swelling, the release of multiple neurotransmitters and neuromodulators, and dramatic fluxes of ions into and out of cells. Some of these neurochemical and ionic changes may be responsible for the

initiation and propagation of the event, whereas others may be compensatory and play a greater role in recovery from CSD. As discussed in the accompanying paper in this issue (by C. Ayata), the cellular ion channels, membrane pumps, neurotransmitter release mechanisms, neurotransmitter receptors, and vascular signalling pathways that are involved in CSD may each represent individual therapeutic targets for conditions in which CSD could play a role. These conditions include not only migraine, but also haemorrhagic and ischaemic stroke, subarachnoid haemorrhage, traumatic brain injury, and epilepsy. The distinctive features of CSD may also provide important insights into novel mechanisms of signalling between neurons, astrocytes, and vascular cells that are involved in normal brain function.

LEAO'S ORIGINAL DESCRIPTION OF CSD

Leao's initial four papers on CSD in 1944–1947 are rich with information, and it is worth reviewing these papers in detail because they continue to provide a foundation for ongoing studies. The first paper reported the basic phenomenon of a slowly propagated depression of spontaneous electrical activity in the rabbit, pigeon and cat cortex triggered by tetanic electrical or mechanical stimulation (4). Interestingly, CSD was more difficult to elicit in the visual cortex, despite the fact that it consistently travelled to this region when triggered elsewhere. He also reported that CSD could occur in the opposite hemisphere if the stimulus intensity was increased. He found that sensory and visual evoked potentials were reduced in association with the depression of spontaneous activity, as were discharges typically evoked by direct cortical stimulation or application of excitatory compounds. In a second paper, he reported that CSD was associated with marked dilation of pial arteries, in some cases followed by a sustained smaller constriction (5). In a third paper, he reported that CSD could be evoked in all regions of cortex except the retrosplenial gyrus (6). He found that the propagation of CSD within a single hemisphere did not require subcortical connections or the lower three layers of grey matter, but that inter-hemispheric propagation of CSD could occur via the corpus callosum and could be triggered by stimulation of the white matter. He also reported that tetanic stimulation was more effective in eliciting CSD when it was applied closer to the surface of the cortex, compared with deeper cortical layers. Finally, he reported that cocaine applied near branches of the middle cerebral artery was capable of blocking the electrical and vascular propagation of CSD, even when the cocaine was applied at a distance from the path of CSD propagation. In his fourth paper (7), he reported that slow changes in direct current (D.C.) potential occurred in association with CSD. There was a large negative shift in D.C. potential lasting 1–2 min, followed by a positive deflection lasting 3–5 min, followed by return to baseline. The initial negative shift was sometimes preceded by a brief, low-amplitude, positive deflection. Brief ischaemia induced by arterial occlusion resulted in cessation of spontaneous cortical activity and increased the amplitude of the d.c. potential changes associated with CSD, whereas more sustained ischaemia resulted in a d.c. potential shift that occurred without CSD. Leao's wide-ranging experimental observations underscored the anatomical and physiological complexity of the phenomenon of CSD, and highlighted the involvement of distinct parenchymal and vascular mechanisms. The similarity between the characteristics of CSD propagation and the spread

of the cortical representation of the migraine visual aura immediately gave rise to the hypothesis that CSD is the cause of migraine aura (6).

CSD IN HUMANS

Although CSD has been studied in a wide variety of animal models over more than decades, it is only relatively recently that its occurrence in humans has been definitively demonstrated (8, 9). Mayevsky et al. used an invasive multiparametric monitoring system to record D.C. shift, reduction of electroencephalogram (EEG) amplitude, and an increase in extracellular K^+ in a patient with severe head injury (8). Strong and colleagues (10) used electrodes placed near foci of damaged cortical tissue in patients with intracranial or subarachnoid haemorrhage to record propagated depressions of electrocorticographic (ECoG) activity whose rate of spread (0.6–5 mm/min) was the same as that of CSD. Fabricius et al. (9) then reported accompanying propagated slow potential changes in similar patients, leading them to the conclusion that the ECoG depressions in patients were identical to CSD observed in animal models. Dreier et al. (11) found that repeated spreading depolarizations with prolonged depression periods were associated with delayed ischaemic neurological deficits following subarachnoid haemorrhage. In addition to subarachnoid haemorrhage, it has now also been reported that ischaemic stroke is commonly associated with clusters of CSD events (12). Further work has shown that vasoconstriction associated with CSD may contribute to ischaemic damage in stroke and brain injury (13). This important series of studies, and ongoing studies by the same groups, have shown unequivocally that CSD can occur in the human brain, and that it may be a key therapeutic target in the setting of acute brain injury resulting from multiple different pathological conditions.

Although these observations provide strong circumstantial support for the hypothesis that CSD could occur in patients with migraine, there has as yet been no definitive electrophysiological demonstration of CSD in a migraine patient. This may be because non-invasive EEG recording techniques have not been sensitive enough to capture CSD. Magnetoencephalography techniques have demonstrated d.c. potential changes that are suggestive of CSD (14). Functional imaging studies of migraine patients have shown dramatic changes in blood flow and brain activity whose temporal and spatial characteristics are similar to those of CSD (15–18). Whether these phenomena are the same as the CSD seen in humans with brain injury or in animal models of CSD remains to be determined. Regardless, however, there is growing evidence that the study of CSD can provide information that can be directly translated into the understanding of migraine mechanisms, and that CSD in animal models represents a platform for identification of new migraine therapies.

WHAT TRIGGERS CSD AND HOW DOES IT PROPAGATE?

Basic mechanisms involved in the initiation and propagation of CSD are summarized schematically in Fig. 1. In human or animal tissue *in vitro*, or in animal models *in vivo*, CSD can be evoked by a wide variety of stimuli. These include local mechanical stimulation or injury, tetanic or D.C. electrical stimulation, KCl, hypo-osmotic medium, metabolic inhibitors, ouabain, glutamate receptor agonists, and endothelin. Of these, stimulation with

KCl has been the most widely used, and most models of CSD include elevations in extracellular K^+ as a critical event in the initiation of CSD (for recent reviews, see (19, 20)). The inhibition of CSD by N-methyl-D-aspartate (NMDA) receptor antagonists in most preparations also suggests a key role for activation of neuronal glutamate receptors in the initiation of CSD (21–24). However, tetrodotoxin, which blocks neuronal action potentials in spontaneous synaptic activity, does not consistently block CSD (25–28). It is important to recognize that there may be sequential mechanisms leading to CSD, some of which are ‘upstream’ and lead to shared final common ‘downstream’ events involved in the initiation and spread of CSD. For example, the firing of action potentials and associated synaptic transmitter release may initiate CSD by increasing extracellular K^+ and glutamate. Tetrodotoxin might therefore block the events that lead to CSD under some conditions, but it may not block the occurrence and propagation of CSD that is stimulated, for example, by direct application of KCl, which may evoke CSD by depolarizing neurons and glial cells without requiring the firing of neuronal action potentials.

Leao’s original papers raised the prescient concept that the propagation of CSD probably occurs via non-synaptic mechanisms. He stated that ‘electrical stimulation may initiate the depression by exciting neurons in the immediate vicinity of the stimulating electrodes but that the subsequent spread of the phenomenon is in all probability independent of synaptic activity’. The slow rate of CSD propagation, its predilection for superficial cortical layers, and its occurrence in the face of ischaemia or pharmacological inhibition of synaptic neuronal activity are all consistent with a mechanism of propagation that does not require synaptic signalling. A number of recent studies have confirmed earlier observations that SD may involve distinct activation of neuronal apical dendrites (as opposed to cell bodies or axons). Canals et al. (29) reported that there were cellular gradients of changes in CA1 neuronal activity associated with SD in the hippocampus, with apical dendrites showing localized changes in membrane potential that were different from those observed in the neuronal cell body. Henning et al. (30) reported that manganese-enhanced magnetic resonance imaging (MRI) changes evoked by CSD showed particular involvement of cortical regions with dense apical dendrites, again suggesting an important role for dendritic activation in CSD. Localized increases in glutamate or K^+ in the extracellular spaces could allow for a slowly propagated dendritic depolarization that does not require involvement of neuronal cell bodies or normal synaptic signalling. There is also evidence that cortical dendrites, particularly the dendrites of interneurons, may be electrically coupled (31, 32). This could represent a potential mechanism for a slowly propagated dendritic wave that does not necessarily spread to deeper neuronal layers. Signalling within a syncytium of cortical astrocytes could also play a significant role in this type of non-synaptically propagated change in the composition of the extracellular space (see below)

A key unresolved question is what evokes the spontaneous occurrence of CSD in the injured or non-injured brain. The lowered threshold for induction of CSD in mice expressing mutations associated with familial hemiplegic migraine type 1 (33, 34), and in female vs. male mice (33, 35), indicates that alterations in the functions of calcium channels and the hormonal modulation of brain excitability can influence the propensity to CSD. However, what actually triggers and propagates CSD under these conditions of genetic or hormonal predisposition remains uncertain. As discussed above, elevations in extracellular K^+ or

glutamate above certain threshold levels are likely candidates as final common steps in the process, but again, there may be multiple distinct processes that can lead to these steps.

An important related question is why specific brain locations may be sites of initiation of CSD, or whether it may in fact be multifocal. In the setting of a focal brain injury in humans, it is clear that the site of brain injury acts as the point of initiation for CSD, but in the non-injured brain it is possible that a generalized reduction in threshold could lead to induction of CSD at multiple sites, as can be seen with the sustained application of KCl or ouabain in different preparations. While the classically described propagation of the migraine visual aura is consistent with the initiation of CSD at a single site, the more complex pattern of sensory, motor, language, and/or cognitive dysfunction in migraine patients raises the possibility that it could be a multifocal event.

ION CHANNELS AND MEMBRANE PUMPS

CSD involves the orchestrated function of a wide variety of cellular ion channels and pumps (36), and specific channels have received considerable recent attention for their potential role in migraine. One such channel is the P/Q type calcium channel. Mutations in the CACNA1A P/Q type calcium channel have been identified as the cause of familial hemiplegic migraine type 1 (37). Mice expressing two of these mutations show a reduced threshold for induction of CSD, and an increased rate of CSD propagation (33, 34). The inhibition of CSD *in vitro* by P/Q channel blockers (38) supports the concept that these channels play an important role in CSD, as do studies of different mutations of P/Q channels that indicate that they also alter the susceptibility to CSD (39). Although studies of the functional consequences of these mutations in different cellular expression systems have yielded variable results (40), studies of channels in cells from knock-in mice are all consistent with the concept that these mutations result in changes in the function of the channel that cause increased calcium influx and increased excitatory neurotransmitter release, thereby leading to an increased propensity to CSD (34, 41, 42).

The roles of sodium channels and potassium channels in CSD have also been investigated using pharmacological modulators of these channels (43). As mentioned above, the sodium channel blocker TTX does not inhibit CSD evoked by a variety of stimuli. It has been reported, however, to block the cerebral blood flow response associated with CSD evoked by mechanical stimulation (43), and in some cases inhibit CSD evoked by hypoxia (26). Although a direct role for familial hemiplegic migraine SCN1A Na⁺ channel mutations in CSD has not yet been demonstrated, two SCN1A mutations were recently reported to be responsible for the phenotype of elicited repetitive daily blindness (44). The characteristics of this phenotype are strongly suggestive of a process involving retinal SD, suggesting that increased excitability resulting from Na⁺ channel mutations associated with FHM3 could predispose not only to CSD, but to retinal SD as well. Openers of KCNQ (Kv7) potassium channels have been reported to inhibit CSD (45), whereas inhibitors of Kv1.1 and 1.2 potassium channels (dendrotoxin and titustoxin) have been shown to activate SD in the cerebellum (46). The KATP channel blocker glibenclamide has been found to increase the hyperaemic response to CSD in rat evoked by KCl (47), but not by mechanical stimulation (43), whereas the K_{Ca2+} channel blocker charybdotoxin was reported to have no effect. Thus,

different types of Na⁺ and K⁺ channel may play distinct roles in the initiation and propagation of CSD evoked by different stimuli, and may have specific effects on CSD-evoked vascular responses.

It is likely that glial and potentially neuronal Na⁺/K⁺ pumps play a significant role in CSD. Mutations in a Na⁺/K⁺ ATPase expressed primarily in astrocytes in adults have been identified as the cause of FHM2 (48). Although there is as yet no direct evidence that this mutation is involved in CSD, it seems likely based on indirect evidence that this will be the case, since dysfunction of the Na⁺/K⁺ ATPase would be expected to increase extracellular K⁺. Na⁺/K⁺ ATPase activity has been reported to play a key role in the clearance of K⁺ from the extracellular space (49). Oubain, an inhibitor of Na⁺/K⁺ ATPases, has been shown to evoke CSD in brain slice preparations (50, 51). Reduced function of the Na⁺/K⁺ ATPase has also been suggested as a mechanism for CSD evoked by energy failure (11, 13). Studies of transgenic mice expressing FHM2 mutations have the potential to yield important new insight into the specific roles that the Na⁺/K⁺ pump plays in SD.

GLUTAMATE

Substantial evidence supports a key role for the excitatory neurotransmitter glutamate in the initiation and propagation of CSD. Significant release of glutamate occurs with CSD both *in vivo* and *in vitro* (52, 53). Application of glutamate or NMDA can evoke CSD, whereas NMDA receptor antagonists (but not other glutamate receptor subtype antagonists) have been shown to inhibit CSD in a variety of different preparations (21–24). Recent studies indicate that antagonists of NMDA receptors containing the NR2-B subunit may selectively inhibit CSD (24, 54). Some of these agents are receiving attention as potential migraine preventive therapies. Memantine, a pan-NMDA receptor blocker with an activity-dependent mechanism of action, inhibits susceptibility to CSD and reduces CSD amplitude (54). Initial clinical studies of memantine as a migraine preventive agent have yielded encouraging results (55, 56), suggesting that inhibition of CSD with well-tolerated inhibitors of NMDA receptors may be an achievable goal.

NITRIC OXIDE

A variety of previous studies have implicated nitric oxide (NO) as at least one of multiple potential mediators of the vasodilation associated with CSD (57–59), and conversely have suggested that inhibition of NO synthesis leads to hypoperfusion associated with CSD (60). Recent evidence suggests that NO may be involved not only in the vascular response to CSD, but also in its initiation, propagation and resolution (61). Studies by Petzold et al. (62) resulted in a number of interesting observations. They found that NO is produced by both neurons and endothelial cells during CSD. Surprisingly, they also found that inhibition of NO synthesis reduced the threshold for CSD, an effect that is abolished by inhibitors of P/Q calcium channels or NMDA receptors (62). Since NO produced by endothelial cells may diffuse into the surrounding brain parenchyma, these findings raise the possibility that endothelial NO synthesis may be a mechanism by which the vasculature conditions the response to CSD (see below). In addition, they found that under conditions of low NO levels, CSD was associated with spreading ischaemia (62). These findings may at first seem

inconsistent with the observations that NO donors or guanylate cyclase inhibitors are known to trigger migraine. However, these drugs are known to evoke migraine after a significant delay (63, 64), so it is possible that NO levels or cyclic guanosine monophosphate levels have fallen by the time that migraine occurs. It is also possible that drugs that increase NO levels or potentiate its effects are working on pain mechanisms that are downstream from any CSD event (65).

ATP AND ADENOSINE

Substantial release of ATP has been shown to occur with CSD (66). As discussed below, one potential source of this ATP may be astrocytes, which release large amounts of ATP in association with intercellular calcium signalling (67, 68). It has been suggested that ATP may mediate ischemic tolerance—i.e., an increased resistance to ischaemic insult that has been observed following CSD (66). Also, since ATP is well known as a nociceptive messenger (69), it is possible that ATP released with CSD could activate nociceptive afferents and thereby mediate headache. In addition to activating multiple types of purinergic receptors directly, ATP is rapidly metabolized in the extracellular space to adenosine (69). Adenosine is a potent inhibitory transmitter in addition to a vasoactive substance, and could thereby mediate multiple downstream effects of CSD.

CALCITONIN GENE-RELATED PEPTIDE (CGRP)

CGRP has been implicated as a modulator of the vascular response to CSD in multiple animal models (19). CGRP receptor antagonists inhibit CSD-associated vasodilation in rabbit, cat and rat (57, 70, 71) consistent with CGRP release, although one study did not find measureable increases in CGRP in the jugular vein of cat with CSD (72). As with ATP, CGRP may also act as a nociceptive messenger, and could thereby activate pain pathways in addition to mediating vascular effects associated with CSD.

METABOLIC CHANGES WITH CSD

Dramatic changes in brain metabolism occur during and after CSD. *In vivo* imaging approaches have been recently used to confirm a variety of previous studies showing that significant tissue hypoxia can occur during CSD (73). In addition, CSD has been reported to result in sustained depletion of brain glucose (74). These effects could play multiple roles in the generation of migraine symptoms, but also may be particularly important with CSD that occurs in the setting of subarachnoid haemorrhage, stroke and brain injury in humans (11, 13).

GLIAL CELLS

Early studies by Sugaya and colleagues found that the D.C. potential changes of CSD were correlated to a greater degree with astrocyte membrane potential than with neuronal membrane potential (28). These studies suggested a primary role for astrocytes in the physiological readout of CSD. Nonetheless, it has been widely assumed that astrocytes play primarily a passive role in the phenomenon, acting as a sink for extracellular K^+ and in general as a buffer for the ionic and neurochemical changes that initiate and propagate CSD.

Recent studies indicate that astrocytes may in fact be actively involved in the initiation and propagation of CSD, as well as the accompanying vascular response. As discussed above, the fact that mutations in an astrocyte Na^+/K^+ pump are responsible for FHM2 suggest that alterations in astrocyte function could lead to conditions that predispose to CSD (48, 75). Furthermore, calcium imaging studies indicate that CSD is consistently associated with waves of increased intracellular Ca^{2+} concentration that spread widely between astrocytes (50, 76–78). These astrocyte Ca^{2+} waves, which have temporal and spatial characteristics that are remarkably similar to those of CSD, can be triggered independently of CSD (79). Astrocyte Ca^{2+} waves are associated with the active release of adenosine triphosphate (ATP), glutamate, K^+ , and eicosanoids (80). Although inhibition of astrocyte Ca^{2+} waves does not inhibit the occurrence of CSD, in the absence of pharmacological manipulation they are consistently observed in conjunction with CSD. Thus, astrocyte Ca^{2+} waves and CSD appear to be two distinct but inter-related phenomena that may have overlapping mechanisms and functional consequences.

Astrocyte Ca^{2+} waves have been shown to propagate beyond the extent of a CSD wave in brain slice preparations (77). This observation raises the possibility that a spatially limited SD event could lead to more extensive propagation of an astrocyte wave. There is growing evidence that astrocytes play a key role in coupling between neuronal activity and vascular tone (80). On one hand, astrocytes have processes in contact with synapses and along neuronal processes such that they are in a position to ‘listen’ to neuronal activity. On the other hand, they are in close contact with blood vessels via endfeet that enwrap arterioles and capillaries. Activation of astrocytes (as evidenced by increases in intracellular calcium concentration) can evoke either vasoconstriction or vasodilation, via release of K^+ or eicosanoids (81–86). One recent two-photon microscopy study of CSD in rat *in vivo* showed that although inhibition of astrocyte Ca^{2+} waves did not inhibit the propagation of CSD, it abolished the associated vasoconstriction (78). Thus, astrocytes may be important mediators of the vascular responses associated with CSD.

VASCULAR RESPONSES TO CSD

The vascular responses to CSD are complex and variable, depending on preparation and the experimental conditions. The different vascular responses that have been observed are comprehensively summarized in the review by Busija et al. (19). Leao’s original paper describing CSD in rabbit reported a transient vasodilation with CSD, followed in some cases by a more sustained and less pronounced vasoconstriction (5). In both mouse and rat, there is an initial dilation of arterioles with CSD, and accompanying increase in blood volume (59, 87). In mouse, this initial dilation is followed by a profound constriction of vessels throughout subsequent phases of CSD, whereas in rat the initial dilation is sustained (59, 87, 88). With recovery of the DC potential, the calibre of vessels and blood volume returns toward baseline, although there may be sustained oligoemia or hyperaemia that continues following the electrophysiological recovery from CSD (89). Thus, under some conditions, the predominant vascular response may be vasodilation and hyperaemia, whereas under other conditions it may be vasoconstriction and oligoemia. The variability of the vascular responses to CSD may depend on a number of factors including resting vascular tone (90),

sensitivity of the vessels to extracellular K^+ (87), tissue oxygenation (84, 91), and basal and evoked levels of NO (62, 92).

Studies of CSD in humans following subarachnoid haemorrhage suggest that the vascular response to CSD may show a similar variability depending on the metabolic state of the brain at the time that it occurs. As in animal models, CSD in humans was found in some cases to be associated with an increase in blood flow, whereas in others it caused a spreading oligoemia or ischaemia (13). The ischaemic response occurred primarily under conditions of metabolic stress, suggesting an important role for energy depletion (13). This variability in the vascular response to CSD raises the intriguing possibility that the clinical manifestations of CSD could vary depending on the accompanying vascular response, which in turn could vary depending on a number of genetic, metabolic or hormonal factors in a given individual at a given time.

Similar to concepts regarding astrocytes, it has long been presumed that the vasculature responds only passively to CSD. However, even some of the earliest studies by Leao indicated that vessels might play an active role in CSD propagation (6). Leao's observation that the propagation of CSD was inhibited by application of cocaine to vessels at a location that was not in the path of the CSD wave led him to conclude: 'It seems well to consider therefore that, however brought about, vascular changes may precede and condition the cortical depression' (6).

We found that vasodilation of cortical surface arterioles travelled ahead of the CSD wavefront with characteristics that are consistent with an intrinsic vascular mechanism of propagation, and that vasodilation could be propagated into regions of cortex that were not reached by the CSD wave (59). Given that vascular cells release diffusible factors such as NO, K^+ and ATP, it is possible that vascular signalling ahead of the CSD wavefront could influence CSD propagation or recovery from a CSD event.

SEX, HORMONES AND CSD

Growing evidence suggests that an increased propensity to CSD could be a mechanism involved in the increased prevalence of migraine in women. Both oestrogen and progesterone have been reported to increase the frequency of CSD and its amplitude in rat cortical slices (93). We found that the threshold for induction of CSD by either KCl injection or tetanic electrical stimulation was significantly reduced in female vs. male wild-type mice (35). Eikermann-Haerter et al. similarly reported an increased susceptibility to CSD in female mice, but only in transgenic mice expressing an FHM1 mutation and not in wild types (33). Differences between these results and ours are probably related to methodological differences—we quantified CSD thresholds based on the magnitude of transient stimulations, whereas Eikermann-Haerter et al. determined CSD susceptibility by quantifying the number of CSD events evoked by a continuous stimulus. They found that the increase in CSD susceptibility in female mice expressing the FHM1 mutations was abolished by ovariectomy and by senescence, and partially restored by supplemental oestrogen, indicating a primary role for ovarian hormones in the modulation of CSD susceptibility (33). Although specific mechanisms by which gonadal hormones may

modulate CSD remain uncertain, these results indicate that modulation of cortical excitability underlying CSD may be a primary mechanism for gender differences in migraine prevalence.

MRI FINDINGS IN CSD

MRI is proving to be a useful tool in the visualization of CSD in animal models. Initial studies in rats using multiple different MRI techniques revealed slowly propagated changes in signal in the cortex consistent with CSD (reviewed in (94)). Gradient echo sequences revealed a propagated increase in signal (possibly caused by increased vascular oxyhaemoglobin) (95), diffusion-weighted images showed signal changes indicating changes in apparent tissue coefficient (ADC) of tissue water (96), and manganese-enhanced MRI showed extensive propagated uptake of Mn^{2+} (a marker of neuronal activity) associated with CSD (30). Interestingly, the latter studies indicate extensive propagation of CSD-associated activation throughout the cortex of the stimulated hemisphere in rat, as well as into the hippocampus and thalamus. Diffusion-weighted MRI studies in cat, whose gyrencephalic brain more closely resembles that of human than the lissencephalic rodents, also showed propagated decreases in ADC associated with CSD evoked by KCl (97–100). These ADC changes could involve the entire stimulated hemisphere, but did not cross to the opposite hemisphere. Transient or sustained KCl application evoked repetitive CSD events; the ADC change associated with the first event had a higher amplitude, and spread faster and farther than those associated with subsequent CSD events (100). Measurement of blood oxygen level-dependent (BOLD) signals revealed increases that correlated well with ADC changes, suggesting increased venous oxygenation associated with CSD (97). Whereas some patients with migraine with aura show BOLD signal changes consistent with those found in animals and some patients with aura show FLAIR changes consistent with vasogenic oedema, most patients with migraine with aura have no clear changes in MRI signal. More sensitive MRI technologies have the potential to yield much more information about the process by which CSD is initiated and propagated in animals, and to what extent it may be occurring in patients with migraine.

CSD IN MIGRAINE?

Despite the longstanding assumption that CSD is the primary mechanism underlying the migraine aura, there has as yet been no definitive demonstration of the electrophysiological features of CSD in a migraine patient. The spatial and temporal characteristics of migraine aura symptoms and of the propagated changes in blood flow and functional MRI signal observed with functional imaging in migraine patients are certainly consistent with CSD. However, surface EEG recordings in migraine patients, including a few documented patients with migraine with aura, have not demonstrated the classical electrophysiological features of CSD (101). This may be because surface EEG does not have the sensitivity to detect CSD. Although it is not surprising that EEG would not detect the D.C. potential changes of CSD, it is less clear why the depression of spontaneous activity for which CSD was named would not be detected. It is also not clear how CSD could produce only minor neurological symptoms, or even none at all. The study by Woods et al. (18) describes dramatic and sustained propagated oligoemia in a migraine patient whose only neurological symptom was

mild blurring of vision. It is difficult to explain how CSD, a profound neurophysiological event, could involve this amount of cortex for this duration without resulting in more significant neurological deficits. One possible explanation is that waves of glial and/or vascular activity could spread beyond a spatially limited CSD event, or even occur in the absence of CSD, to produce dramatic changes in functional images without associated symptoms.

SUMMARY

CSD is an extremely robust and reproducible phenomenon that is triggered by a variety of stimuli in multiple preparations of neural tissue *in vitro*, as well as in multiple animals and humans *in vivo*. It involves distinct neuronal, glial and vascular mechanisms, each of which may be targets for therapy in migraine and other neurological disorders. Although its specific role in migraine has yet to be definitively established, there is strong evidence that CSD in rodent models represents a valid platform for increasing our understanding of human migraine mechanisms, and for the identification and characterization of migraine therapies. It may be another 60 years before we have a complete understanding of CSD and its role in migraine. Nonetheless, it is likely that the ongoing investigation of CSD will continue to yield important information about the function of the nervous system, including the pathways that lead to migraine and their potential modulation by new migraine therapies.

Video sequences of CSD and related astrocytic, neuronal signalling can be viewed on our website, <http://hartp.neurology.ucla.edu>.

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Figure 1. Schematic representation of the basic mechanisms of CSD and its functional consequences.