Interplay between Cortical Spreading Depolarization and Seizures

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Cortical spreading depolarization · Spreading depression · Epileptiform activity · Epilepsy · Vasospasm · Electrocorticography

Abstract

Cortical spreading depolarization (CSD) is an electrophysiologic phenomenon found mostly in the setting of neurologic injury resulting in the disturbance of ion homeostasis and leading to changes in the local vascular response. The bioelectric etiology of CSD shares similarities to those in epileptic disorders, yet the relationship between seizures and CSD is unclear, with several studies observing cortical depression before, during, and after seizure activity, thus obscuring our understanding of whether CSD activity potentiates or limits seizures and vice versa. Cortical sampling has exhibited how the redistribution of ion concentrations in the intra- and extracellular environments interplay between the excitation of seizures and the electrical depression of CSD. Modeling of both environments has suggested that CSD synchronizes the affected tissue, creating a favorable environment for seizure activity; however, other studies have demonstrated the opposite: epileptiform activity initiating waves of CSD. Further studies have underscored the role of the vascular response and subsequent ischemia in CSD that contributes to epileptogenesis. Investigations in migraine, traumatic brain injury, and other neurologic injuries suggest that several drugs may target CSD. Manipulations in the occurrence and

nature of CSD can potentially alter the threshold for seizure activity, and perhaps minimize immediate and long-term sequelae associated with epilepsy.

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Introduction

Cortical spreading depolarization (CSD), at its most fundamental level, is a pathologic disruption of cortical electrical activity resulting from a spreading loss of ion homeostasis. Since its discovery by Leao in 1944, this phenomenon has been studied extensively in both animal and, more recently, human models [1, 2]. From this work, we now understand that cortical excitation seen in CSD can occur from a variety of insults, and the subsequent depression of electrical activity that follows leads to secondary changes in blood flow as well as neuronal and astrocyte damage.

Mechanism of CSD and Vascular Response

A variety of biological states, such as hypoxia, hypoglycemia, subarachnoid hemorrhage, traumatic brain injury, stroke, and seizures, has been shown to initiate the onset of CSD [2–6]. It is believed that the blood-brain barrier is disrupted by this inciting insult, allowing for changes in extracellular concentrations of ions including

a decrease in magnesium concentrations and elevation in potassium levels [7–9]. Such changes alter the local neuronal microenvironment and trigger a cascade of cellular events ultimately leading to glutamate-induced toxicity [10]. Glutamate release, in turn, activates both sodium and calcium channels via N-methyl-D-aspartate (NMDA) receptors. This results in a rapid influx of large cations down their concentration gradient, leading to the loss of the normal membrane potential [2, 11]. Mechanisms to restore membrane potentials, such as the sodium-potassium pumps, fail to counter this disruptive change, and the affected neurons begin to swell from the osmotic shift associated with the influx of cations [2]. These damaged neurons no longer permit electrical activity and an overall depression in cortical activity is observed. This sequence of depolarization and depression spreads slowly at a rate on the order of 2–6 mm/min with a predilection for surrounding injured tissue [12].

In addition to the changes in electrical activity, a vascular response is seen with CSD that leads to secondary injury in injured brain states. In healthy brains, depolarization leads to the release of glutamate and nitric oxide, a crucial signaling molecule, allowing for local vasodilation and increased blood flow [13, 14]. Hyperemia and improved oxygen delivery meets the demand of energy expenditure required for the repolarization of the neuron [15]. In damaged tissue, however, the loss of ion homeostasis manifests in an acidic microenvironment with elevated levels of potassium, both of which promote vasoconstriction [16–18]. With this pathological decrease in blood flow, the necessary hyperemic response cannot be achieved and energy demands to restore membrane potential are not met. The result is a vicious cycle; these areas become ischemic from perfusion-demand mismatch due to this altered vascular response, and are further susceptible to the ongoing spread of CSD, perpetuating the cellular damage caused by the inciting insult to the brain.

Neuronal Injury Leading to CSD

CSD was first described in humans through cerebral blood flow studies of migraines capturing the oligemia consistent with the scale and timing of CSD as described above [12, 19, 20]. It was initially difficult to study the electrical disruption of CSD through the use of scalp electroencephalography, as it is believed that the scalp, calvarium, and meninges filter out the low frequency changes [2, 19]. In the preceding decades, invasive techniques, such as electrocorticography using subdural electrodes,

have allowed for in vivo observation of the CSD phenomenon. In doing so, the occurrence of CSD has been observed in the setting of a variety of central nervous system injuries.

In traumatic brain injury, several studies have utilized electrocorticography in patients who require craniotomy as part of their acute management [21, 22]. These studies have found worse outcomes in patients whose electrocorticography recordings showed the occurrence of CSD following the inciting trauma. Moreover, the presence of CSD correlated with low blood pressure, abnormal cerebral pressure, and fever, all of which have been associated with increased morbidity in trauma patients [23].

Similarly, in cases of malignant strokes, studies have found a high incidence of CSD occurrence, varying from 35 to 88% of patients. The frequency and duration of these CSD events are significantly associated with the size of the infarct [19, 24–30]. As described above, the pathologic vascular response in relation to the distorted electrochemical signaling of CSD correlates with ischemic damage in the peri-infarct region leading to expansion of the affected area [29, 31–34].

This oligemic response becomes increasingly important in the case of aneurysmal subarachnoid hemorrhage. One of the most concerning complications of this type of hemorrhage is the cerebral ischemia brought on by delayed cerebral ischemia (DCI) [35, 36]. Recently, the term DCI has been used more extensively given that only half of the cases of radiographic vasospasm are associated with ischemia [37]. The cause of the vascular change associated with DCI remains relatively unknown, yet our understanding of the abnormal vascular response in the setting of CSD makes it a plausible mechanism. In experiments using subdural electrodes, the cortical regions in which CSD electrical activity have been recorded correlate strongly with arteriolar vasoconstriction, which is angiographically occult [2, 35]. In animal models, nimodipine and increased fluids, both treatments for vasospasm, were shown to reverse the reduced perfusion seen with CSD [38]. CSD events also aligned consistently with areas of DCI [2, 35]. The current evidence is compelling regarding CSD as a mechanism for the observed secondary ischemic damage in subarachnoid hemorrhage.

CSD and Epilepsy

Current research reveals a complex and ambiguous relationship between seizures and CSD. Excitotoxic states are a common mechanism to both seizures, with neuro-

nal activation, and CSD, with neuronal deactivation. Seizures have been seen prior to, during, and following CSD [39–44]. Additionally, the individual states themselves appear to be interrelated.

Seizures have been known to create an environment conducive to CSD. In the human hippocampal slices of epileptic patients, the neurons appear to be primed for CSD; with mere blockage of T-type calcium channels or adding enough extracellular potassium to the microenvironment, investigators were able to induce CSD [45]. Koroleva and Bures [44] administered sodium-penicillin to rat cortex, which induced seizures; however, they also noted occasional CSD occurring after the ictal activity. After several minutes, when the tissue recovered, the first spike produced another CSD event, which continued for up to 20 cycles. Similarly, pentylentetrazol, a drug known to cause seizures at high doses, was seen to cause cortical depression at low doses in rats [46]. In recent animal models, CSD activity was seen to reverberate for several cycles and last for durations of up to four and a half minutes following epileptiform activity (EA) [47]. Given the depression of electrical activity accompanying CSD, it may be the cause of the postictal state. Koroleva and Bures [44] noted that an increase in spreading depression occurred during postictal depression, with repetitive cycles occurring for several minutes. Slow recovery of focal and global cognitive states is an unexplained phenomenon of seizures and the occurrence of a depressive process following EA may explain the loss of function.

Contrarily, CSD may lead to EA. The presence of cortical depression in rat cortex led to states of excitability similar to that seen just prior to seizures [40]. During a later phase, after cortical depression, a neuronal state of hyperexcitability with less hyperpolarization may prime it for EA [48, 49]. Cellular swelling, noted as a prominent feature in CSD, increases EA. It is thought that the expansion of the intracellular space leads to generation of a slow inward current and the generation of action potentials through NMDA receptors [50]. Following induction of spreading depression, enhanced NMDA, α -amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA), and kainate receptor-binding sites were noted in rat hippocampus, which may lower the threshold for EA [51]. The addition of the GABA receptor antagonist bicuculline to rat and human cortices at both low and high concentrations induced seizures in chronically epileptic rat and human slices; however, low doses induced cortical spreading depression but not EA in nonepileptic rat slices [52]. Researchers using human

models of hippocampal slices have postulated that CSD results in a synchronizing effect, setting the stage for a hyperexcitable state conducive for increased frequency and amplitude of spontaneous seizure activity [39]. This may be reflective of the upregulation of excitatory receptors like NMDA [51]. Spikes are seen to return immediately following a CSD event, and these tissues may be susceptible to synchronization for a long period of time [44]. Additionally, low concentrations of extracellular magnesium and high extracellular potassium seen in CSD have also been shown to produce seizure-like activity [42, 53].

Given that CSD results in depolarized neurons, it is reasonable to infer that a wave of CSD would interrupt a seizure. Indeed, in rat cortex, the induction of seizures led to some CSD activity, which halted the seizures [44]. Similarly, a depression in absence seizures occurring in a rat model was noted after induction of CSD with mechanical stimulation; the cessation of seizures lasted up to an hour [54, 55]. The opposite interaction has also been noted; repetitive stimulation produced EA, which blocked cortical depression in rats [56]. However, most studies suggest CSD and EA potentiate each other. Overall, no clear relationship has been observed between CSD and etiology, type, or location of epilepsy. A link has been seen between posttraumatic and postaneurysmal subarachnoid hemorrhage-related seizures and CSD [40, 43, 57]. In familial hemiplegic migraine, shared genetic mutations in voltage-gated channels lead to both epilepsy and migraine, with a proposed underlying mechanism of CSD leading to hypersynchronization leading to either seizure or spreading depression and migraine [58].

Several therapeutic agents used experimentally have shown promise for treating both seizures and CSD, again suggesting a common mechanism. A derivative of valproic acid, an antiepileptic agent, called *sec*-butylpropylacetamide reduced CSD events through GABA-mediated potentiation and reduction in NMDA receptor activity [59]. Likewise, eugenol, an aromatic molecule, has been previously described to have both antiepileptic and antiheadache properties. In animal models, systemic introduction of eugenol was shown to reduce both EA and spreading depression [60]. Mechanistically, NMDA receptors play a central role in both EA and CSD. Antiepileptic antagonists of the NMDA receptors, such as ketamine, were shown to halt CSD activity; however, antiepileptics without NMDA properties, such as diazepam, did not affect CSD activity [61].

Conclusion

The association between CSD and seizure activity has been investigated in both animal and human studies over the past several decades. Although the excitotoxic mechanisms of CSD are similar to those seen in epileptic disorders, the exact relationship between these 2 phenomena has yet to be elucidated. Seizures seem to result in reverberating CSD, and CSD has been shown to prime damaged

neurons for further seizure activity. Other studies have shown that depolarized neurons in CSD are capable of interrupting the wave of seizures. With greater understanding from future studies, manipulations in the occurrence and duration of CSD can potentially alter the threshold for seizure activity, and perhaps minimize secondary damage and long-term sequelae associated with a variety of neurological injuries. This complex relationship deserves further research with the hopes of diminishing both disorders.

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