REVIEW ARTICLE

Spreading Depolarization Waves in Neurological Diseases: A Short Review about its Pathophysiology and Clinical Relevance

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Abstract: Lesion growth following acutely injured brain tissue after stroke, subarachnoid hemorrhage and traumatic brain injury is an important issue and a new target area for promising therapeutic interventions. Spreading depolarization or peri-lesion depolarization waves were demonstrated as one of the significant contributors of continued lesion growth. In this short review, we discuss the pathophysiology for SD forming events and try to list findings detected in neurological disorders like migraine, stroke, subarachnoid hemorrhage and traumatic brain injury in both human as well as experimental studies. Pharmacological and non-pharmacological treatment strategies are highlighted and future directions and research limitations are discussed.

1. INTRODUCTION

Spreading Depolarization (SD) is a phenomenon that occurs in brain tissue and is recognized as an important contributor in the pathophysiology of several neurological diseases. It is a propagating depolarization wave of neurons and glial cells in the cerebral gray matter, followed by transient suppression of electrical activity. It was first described by the Brazilian neurophysiologist Aristides Leão [1]. Now it is recognized as a universal way of cortical lesion development in several neurological disorders [2, 3].

First evidence for SD as a relevant pathological mechanism for neurological diseases was a report about the symptoms of migraine aura. An excitation-depolarization wave that propagated across the human primary visual cortex was described and attention drawn to the similarity of wave front move velocity with depolarization waves observed in animal experiments [4-6].

Its importance for human brain physiology and pathophysiology has emerged in the last decade [2, 3] and aim of this review is to give a brief idea about the relation of SD waves and neurological diseases. Mainly, the mechanisms for SD generation and its probable role in migraine, stroke, subarachnoid hemorrhage, and traumatic brain injury will be discussed.

1.1. Mechanisms of Spreading Depolarization and Its Importance as a Pathological Mechanism in Human Neurological Conditions

For many years, the difficulty and inadequacy of detecting SD in routine scalp EEG recordings led scientists to think that SD was just an artifact, which occurs in the rodent brains and during experimental conditions. Hence, its significance and translation to human pathological conditions were obscure and there were opponent arguments about its presence and implication for neurological diseases especially for migraine. Unfortunately, the routine scalp EEG was not sensitive enough due to the high impedance of dura and skull to record SD waves from a relatively narrow cortical area. With the development of new imaging technologies, first clues about its presence and the role in disease pathophysiology, especially for migraine aura, have emerged. A wave of reduced blood flow propagation across the brain during an attack of a patient with migraine aura has been elegantly demonstrated by Hadjikhani *et al.* *via* blood flow changes detected with BOLD magnetic resonance imaging and travel velocity of blood flow changes over cortex was similar to the SD waves observed in experimental animals [7]. Later on, studies of several clinical and preclinical groups clearly demonstrated that SD waves can occur in several pathological conditions in humans like migraine, stroke, subarachnoid hemorrhage, trauma, *etc* [2, 3, 8-12]. These researchers recorded SD waves through cranial windows or with direct electro-corticographic (ECoG) recordings and laser speckle imaging. Additionally, ECoG recordings of operative pa-

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tients with acute brain injury obtained during intensive care suggest that SD waves play a role in the deterioration of cognitive functions and promote lesion progression [13].

SD waves can occur in both physiological and pathological conditions. They usually start from a point on the cortex and travel through with a velocity of 2 to 5 mm/min and the length of travel depends on the severity or amplitude of depolarization waves as well as origin [1]. In healthy brain tissue, as the SD propagates, both the spontaneous and the evoked synaptic activity is silenced for 5-15 minutes, then it spontaneously returns to normal; whereas in pathological conditions (such as head trauma, hypoxia-ischemia, hypoglycemia) depolarization waves start spontaneously and the recovery period is prolonged [14].

Spreading depolarizations of neurons and glial cells on the cortical surface are preceded by propagated field oscillations that create a brief moment of hyperexcitability that covers distances up to 1 mm [15]. There is a complete silence of electrical activity after these oscillations and this electrical silence turns back to normal in 5 to 10 minutes [1]. The silencing of the neurons is accompanied by perturbations in ionic homeostasis and increased release of excitatory amino acids from neurons [16].

Events leading to initiation of SD waves are not clearly understood yet, but increased extracellular levels of K^+ [17] and excitatory amino acids especially glutamate are proposed as triggers for SD occurrence [18]. Moreover, depolarization of neurons removes the voltage-sensitive Mg2+ block of the N-methyl-D-aspartate (NMDA) receptors, and makes the receptor more sensitive to fluctuations of interstitial glutamate levels [19]. Interactions between glutamate and NMDA receptors trigger further K^+ and glutamate release hence increase the excitability of brain tissue and make the neuronal depolarization pass through to neighboring regions [17].

During the passage of spreading depolarization waves, extracellular K^+ levels increase, whereas Ca^{+2}, Cl^- and Na^+ levels significantly decrease [14, 20]. At the same time, pH declines from 7.3 to 6.9 and extracellular space shrinks due to increased water uptake into neurons [21]. This event leads to reversible neuronal swelling while the volume of astrocytes remains stable as they express significant amounts of volume sensitive channels that allow rapid efflux of taurine, aspartate and glutamate [22-25]. There is also a massive efflux of glutamate and aspartate from the neurons during the depolarization wave [26, 27]. Recently, neuronal swelling was found to be associated with a novel chloride channel SLC26A11 mutation leading to Na^+ and Cl^- influx, but it was independent of Ca^{+2} influx leading to cytotoxic neuronal edema [28].

SD is also associated with an increased synthesis of matrix metalloproteinase-9 (MMP-9) [29] Fig. (**2**). Increased MMP-9 activity causes opening of the blood-brain barrier and results with vasogenic edema formation [30]. Other pro-inflammatory cytokine pathways are also found to be upregulated [31]. There are also signs of immediate early gene expression in response to SD [32].

1.2. Effects on Blood Flow and Energy Metabolism: Accompanying Conditions

Inside the depolarized tissue, cerebral blood flow briefly decreases just before the onset of depolarization [33]. As the ionic changes are restored, cerebral blood flow (CBF) increases by approximately 100% to 200% in anesthetized animals [34], which lasts for 1 to 2 minutes. This period is called hyperemic phase of SD. It is followed by a persistent blood flow reduction of 20% to 30% of baseline value that lasts 1 to 2 hours, termed as oligemic phase. However, this pattern of brief hyperperfusion followed by hypoperfusion is mainly observed in healthy and energetically stable brain tissue. Recovery from SD and normalization of membrane potentials and extracellular as well as intracellular ionic hemostasis requires optimum amount of energy. Hence, during pathological conditions accompanied by energy deprivation like stroke and trauma, SD is observed to trigger a cortical spreading ischemia [35, 36], and in stroke patients the cerebrovascular changes triggered by SD vary greatly in the penumbra depending on the distance to the infarct core [37]. The regional CBF changes might also create a mismatch between oxygen demand and supply for the already energetically compromised tissue, which may lead to tissue hypoxia [23, 38]. Recovery of the ionic homeostasis after SD is an energy demanding process and metabolic rate rises significantly during this process [39]. For this reason, continuity of normal blood flow supply is critical to guarantee the brain's needs of glucose and oxygen during this high-energy requiring period.

Main energy consuming enzyme during SD is Na^+/K^+-ATPase. This pump restores extracellular K^+ levels using ATP [40]. During an SD wave, extracellular K^+ levels rises up to 60-100 mmol/L and Na^+/K^+-ATPase tries to drop it to around 3 mmol/L. Re-establishment of ionic hemostasis enables neurons to repolarize. The rise in cytosolic Ca^{+2} during SD depolarizes neuronal mitochondria and increases the oxygen use through the Ca^{+2} uniporter that is located in the inner mitochondrial membrane [24]. A recent study in mice demonstrated that the disruption of mitochondria in ischemic and traumatic injuries is reversible and can be a possible therapeutic target [41]. Additionally, presynaptic NMDAR activation creates a positive feedback loop of glutamate induced glutamate release *via* both Ca^{+2} influx from extracellular space and mitochondria by mitochondrial Na^+ / Ca^{+2} exchanger [42]. Takano *et al.* observed that even when there are no significant changes in cerebral perfusion, or at the hyperemic phase, local tissue hypoxia occurred during SD due to the increased metabolic rate and energy demand [23]. This prolonged mismatch between oxygen demand and supply has been suggested to contribute to the pathogenesis of some other neurodegenerative diseases [43]. Takano *et al.* also pointed out that there are transient morphological changes in dendritic structures accompanying SD such as spine loss, that are comparable to the ones observed during anoxic depolarization [23]. A recent *in vivo* experiment also showed that there is dendritic beading during SD and this beading was strictly dependent on the presence of chloride ions, and the blockage of all chloride coupled transporters

significantly reduced dendritic beading but did not have any effect on the SD waves [44]. SD also activates glycolytic pathways leading to an increase in brain lactate levels and reduction in brain glycogen. On the other hand, the concentration of energy-rich phosphate compounds remains the same in normal brains [45, 46]. There are also reports suggesting that depolarizations are associated with progressive reduction in brain tissue glucose *via* monitoring of extracellular brain glucose concentration with microdialysis in patients with traumatic brain injury [46, 47]. Whether this state of energy depletion delays the recovery of cortical function or not, depends on the persistence of oxygen and glucose supply. Acute CBF responses during SD waves are also found to be varying between species [48].

All of these listed evidences for SD induced blood flow, metabolic and enzymatic changes point out the importance of spreading depolarization in nervous tissue and SDs may have a significant role in several neurological diseases as a main mechanism or as secondary conditions leading to detrimental effects in tissue. Some examples of aforementioned neurological conditions are discussed below in regard to pathophysiological effects of spreading depolarizations.

1.2.1. Migraine

Migraine is a common neurological disorder and an important health care problem. It is characterized by recurrent attacks of headache variable in intensity, frequency and duration and has two major subtypes, with or without aura. Its prevalence is around 10 percent per year (changes between 3 and 11.2 according to region; [49]). The migraine aura is a transient neurological disturbance that occurs 10-20 minutes before the migraine headache. In humans, visual auras are the most commonly observed ones and mostly present with scintillating scotomas or visual field defects. But auras with different clinical presentations are also recorded suggesting that various brain regions might be involved in other kinds of migraine auras like tingling sensations, talking difficulties, *etc* [9, 50]. It is demonstrated that migraine aura induced blood flow changes and speed of spread is very similar to SD waves [7]. Visual auras originate from Broadmann area 17 at occipital cortex, a region with the highest neuronal density. It is speculated that high density of neurons compared to astrocytes makes this region a poor K^+ ion buffering area, hence an increased susceptibility to SD [51]. Intrinsic brain activity triggering SD waves that occur in cortex can lead to headache generation. It is proven that SD generated in the cortex led to activation of both brain stem trigeminal nuclei as well as trigeminal nerve endings around dural vessels and hence pain generation [11, 52]. Later on, Karatas *et al.* demonstrated the pathway from SD to pain generation (Fig. **1**). Wave front of SD, as an intrinsic brain activity, opens neuronal Pannexin1 (Panx1) mega-channels [53] and this induces activation of inflammasome complex and caspase-1 and release of pro-inflammatory mediators such as high-mobility group box 1 (HMGB1) from neurons and IL-1β from glia limitans. Those proinflammatory cytokines in turn stimulate trigeminal nerve endings around pial vessels leading to headache generation. Moreover, neuronal HMGB1 release was found to be positively correlated with the number of the SDs, and multiple SD waves induced a robust HMGB1 release [54]. This robust HMGB1 release subsequently causes microglial activation by acting on the TLR2/4 receptors. The significance of microglial activation is controversial. It may contribute to neuroprotection by getting involved in synaptic repair on dendritic spines of the cortical neurons [54], or it might be causing detrimental effects on the tissue [55]. The major component of these activated mi-
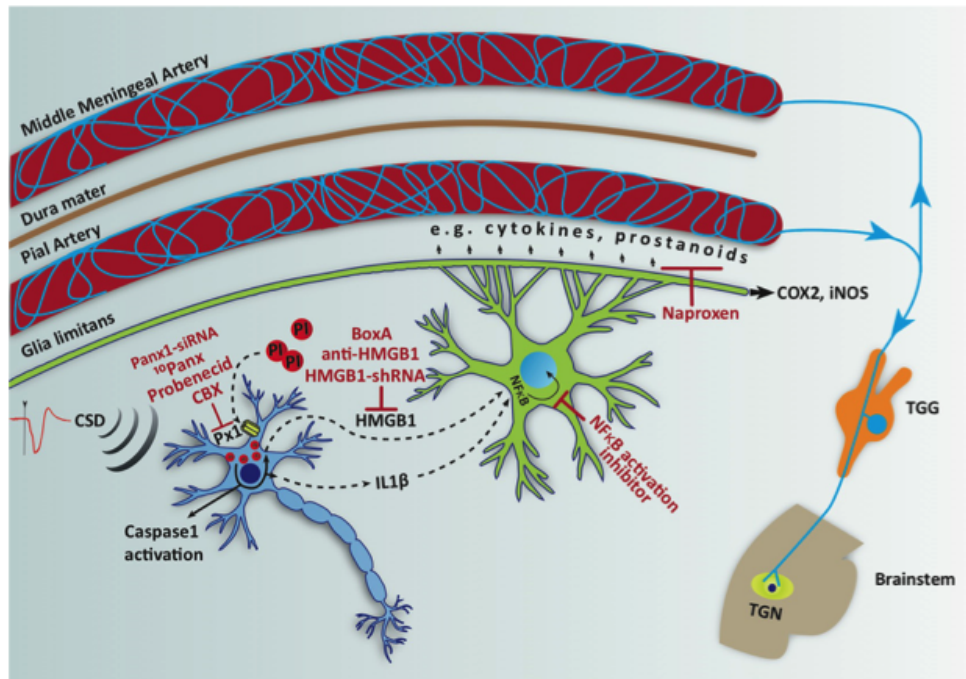

Fig. (1). Cascade of events leading to trigeminal activation and headache generation after SD. Reproduced from Karatas *et al.* 2009, Science; with permission.

croglias was immunoreactive for Catepsin D, which suggested enhanced lysosomal activity and active phagocytosis [56].

Genetic factors are also known to increase susceptibility to SD occurrence. Familial hemiplegic migraine is a genetic form of migraine, which includes defects in neuronal sodium (SCN1A, FHM3), calcium channels (CACNA1A, FHM1) or in the glial Na^+-K^+ pump (ATP1A2, FHM2) [57, 58]. Transgenic mice models like the mutation of pore-forming subunit of neuronal Ca(V)2.1 channels present sensitivity to SD, has a reduced threshold for SD generation and increased propagation velocity [59]. These genetic factors may increase the brain tissue's sensitivity to external stimulation and hence generation of SD waves. It has also been shown that in these genetically susceptible brains, SDs also propagate to subcortical regions such as basal ganglia, diencephalon and hippocampus, which might explain the prolonged hemiplegia, coma and seizure phenotypes in patients experiencing migraine with aura [60]. Animal experiments also pointed out that potassium and glutamate clearance was also impaired in cortical astrocytes during neuronal activity in FHM2 knockin mice [61].

Studies in transgenic mouse models with human monogenic-migraine-syndrome gene mutations pointed out that SD waves increased the sensitivity to focal ischemia and the suppression of SD waves in this model improved stroke outcome [62]. A recent study revealed a positive correlation between migraine and risk of perioperative ischemic stroke [63] and a recent meta-analysis has concluded that migraine with aura, can be also considered an overall risk factor for cardiovascular diseases [64].

Recently, Schain *et al.* demonstrated that SD waves close to the paravascular space can impair glymphatic flow in mice [65]. This might also be a novel therapeutic target in the future.

1.2.2. Ischemic Stroke

Stroke is one of the leading causes of mortality and morbidity worldwide. In addition to developing secondary preventive strategies, decreasing tissue damage after occlusion of cerebral vessels is also an important therapeutic approach. SD waves can also be called as peri-infarct or peri-lesion depolarization waves (PID) occur in ischemic brain tissue and may cause metabolic derangements leading to secondary tissue damage around the ischemic area. SD waves may lead to enlargement of energetically compromised peri-lesion tissue at early hours *via* supply-demand mismatch [38], and at late hours with the effect of continuing SDs through blood-brain barrier disruption that occurs due to increased matrix metalloproteinase (MMP) activity [29] (Fig. **2**). Subsequent edema formation and neuronal death might happen if the tissue is already energetically compromised.

Presence of SD waves has been described in the penumbra in a primate model of stroke induced by occlusion of the middle cerebral artery (MCAO) [66]. Similar events were noted after MCAO in humans [67, 68] and in rat, cat and mouse experimental ischemia models [69]. These PIDs appeared spontaneously in the ischemic 'penumbra', adjacent to the acute ischemic tissue that was not irreversibly dama-

ged yet, but was functionally and metabolically compromised [70, 71]. Later, it was confirmed that there is directly proportional relationship between the number of PIDs and infarct size [72]. These experimental studies demonstrated that the infarcted tissue enlargement is correlated with the PID frequency [73-75]. Recently, it is demonstrated that PID waves occur due to supply-demand mismatch around ischemic penumbral area [38]. Although experimental studies informed us about the mechanisms and pathophysiology of PIDs, studies performed by COSBID research group involving multimodal monitoring of patients at neurocritical care units demonstrated that SDs or PIDs occur in humans after stroke, hemorrhage or trauma and are correlated with lesion enlargement [2, 3, 38, 76-78].

There is difference between blood flow responses to depolarization waves after SDs and PIDs in ischemic tissue compared to uninjured, metabolically non-demised tissue and this phenomenon is called "pathological inverse coupling". In the uninjured brain which has enough energy, huge metabolic and blood flow changes can be restored. SD induces a wave of spreading hyperaemia (physiological neurovascular coupling) that supplies the tissue with the necessary energy to restore ionic equilibrium [77, 79-82] However in the ischemic or injured tissue, depolarization waves induce a microvascular constriction that leads to a transient hypoperfusion instead of hyperemia [35, 83]. Furthermore, around the ishemic core area where there has normal or minimally decreased blood flow, changes in glutamate levels and glucose are detected. Pinczolits *et al.* measured minor glutamate elevations and slight glucose decrease at 5 mm from the infarct [84], which is consistent with other microdialysis measurements of perilesional SDs [85] which may add to progression of lesion enlargement.

Another recent study pointed out that neocortical stroke in rats causes BBB impairment in the ipsilateral hippocampal area, and this BBB opening is associated with SDs and subsequent epileptiform activity [86], similar to the one reported in SAH patients [87]. Lapilover *et al.* also showed that both *in vivo* and *in vitro* exposure of albumin lowered the threshold for SDs [86].

Another important tissue is the age. Although stroke symptoms may occur at any age, the mean age of stroke is 71 years in the United States [88]. Elder stroke patients also have higher mortality and comorbidity rates and cardiovascular dysfunctions [89-96]. It has been found that age is an accelerating factor in the conversion of ischemic tissue into infarction [90, 91]. There are several studies implying that occurrence of prolonged SDs and different number of SD waves is detected according to the age. In animal studies, aged rats had fewer SDs than young ones, but these waves were prolonged and effective in larger areas [94]. Menyhart *et al.* suggested that SDs increase the acidic load in the already acidic ischemic penumbra thereby extending tissue acidosis and causing delayed call death, even more in elderly patients [97].

1.2.3. Subarachnoid Hemorrhage (SAH)

Even though the clinical management of aneurysmal subarachnoid hemorrhage significantly improved over the last decade, delayed cerebral ischemia (DCI) is the most com-
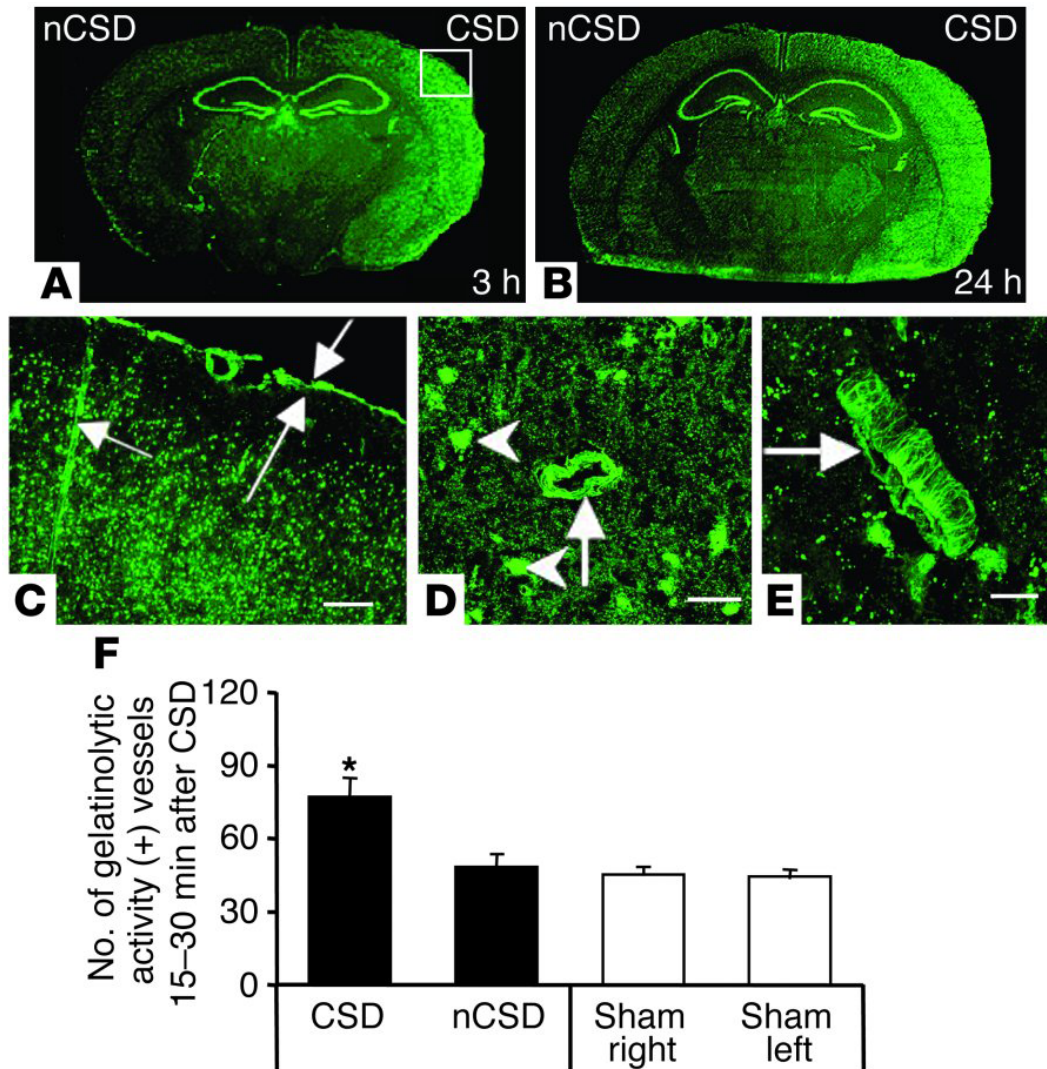
Fig. (2). Increased MMP-9 activity after SD induction as early as 3 hours after insult was detected with *in-situ* gel zymography. Contralateral hemisphere denoted as nCSD. Blood brain barrier opening and leakage demonstrated with Evans blue leakage also correlates with MMP-9 activity (bottom graph). Reproduced from Gursoy-Ozdemir *et al.* 2004, JCI; with permission.

mon cause of morbidity and mortality in patients with SAH. Delayed cerebral ischemia (DCI) is a clinical syndrome that consists of delayed ischemic neurological deficits (DINDs) and/or ischemic lesions and it occurs unpredictably in ∼30% of patients, 3-14 days after primary hemorrhage [98]. The occurrence of DINDs is correlated with the amount of the primary bleeding. Due to the fact that DINDs and hemolysis of the blood clot appear concurrently, it has been suggested that erythrocyte products such as hemoglobin (Hb) and potassium ions may take part in its pathology [68, 99]. Sakowitz *et al.* demonstrated that clusters of SD waves can occur after SAH and compared to single SDs, clusters are more difficult for the tissue to manage or to re-establish metabolic changes occurred after SAH [68].

In the normal brain tissue, the reaction between nitric oxide (NO) and oxyhemoglobin (oxyferrous Hb) creates methemoglobin (ferric Hb) [100]; whereas in the SAH since there is excess amount of blood, the reaction between NO and deoxyhemoglobin (ferrous Hb) forms NO-hemoglobin

[101-104]. The decline of NO levels in patients with DINDs [105] also proves that NO is an important factor for normal blood flow supply to brain tissue leading to vasodilation. Hence, depletion of NO may lead tissue to hypoxia and ischemia [106, 107].

The first evidence of SD waves that occur in SAH was the experiments using intracortical K^+ and Ca^{+2} sensitive microelectrodes on cats [108, 109], but these studies gave limited information because the experiments were conducted in the initial hours after hemorrhage. To observe the delayed conditions and what happens during and after the subarachnoid hemolysis, rat models were used, and the phenomenon of spreading ischemia was only discovered then [35]. In a recent article, spreading depolarization waves were not detected in experimental SAH model until 72 hours and SD waves were recorded after DINDs occurred and it was argued that depolarization waves occur in SAH only after tissue ischemia occurs [110]. A recently published retrospective study pointed out that higher CSF pH and lower CSF

PCO2 might contribute to the development of DCI, possibly due to ineffective CSF drainage resulting from the inefficient removal of blood clot [111, 112]. Sakowitz *et al.* also demonstated that SDs can propagate in nonischemic brain tissue and metabolic changes related to SD waves might be the sign of secondary damage in healthy brain tissue [113] and this may add to the enlargement of the affected tissue after SAH and may be an important target for the correct management of the SAH patients at neurointensive care units.

1.2.4. Traumatic Brain Injury (TBI)

The pathophysiology of TBI in humans is extremely complex due to the heterogeneity of the lesions. Primary injury may include mixtures of parenchymal contusion, intracerebral hemorrhage, SAH, extraparenchymal hematoma, and diffuse axonal injury [114], and is frequently complicated with secondary insults such as hypotension, hypoxia, fever and brain edema that leads to high intracranial pressure. These factors increase the possibility of a breakdown in ionic homeostasis that may increase susceptibility to occurrence of SDs in TBI. A recent study demonstrated that sensory cortical areas are more susceptible to SD occurrences in both mice and human brains and it was argued that this difference may be related to the complexity of cortical areas as well as differences in potassium buffering capacity [115].

In clinical studies of patients with TBI that underwent neurosurgery, by using different monitoring techniques, 50% to 60% of the patients showed depolarization waves [116], although they were rare compared to ischemic stroke [77, 117-119]. In these patients, it was observed that the patterns of depolarization waves differed extensively. They could be rare, single waves in some patients or they could be progressive clusters of waves that repeat frequently. Also, Vespa *et al.* using cerebral microdialysis found that low glucose levels (<0.2 mmol/L) and increased lactate-pyruvate ratio (LPR) were common in severe TBI and low glucose levels were linked to poor outcome [120]. Similarly, Hinzman *et al.* showed abnormal glutamate and LPR levels (>10 μmol/L and >40 μmol/L, respectively) are correlated with increased SD occurrence rate in TBI patients [121]. This elevated LPR levels in TBI patients are also shown to be predictive of frontal lobe tissue atrophy at 6 months [122]. PIDs were also found to be associated with the secondary insults after TBI such as hyperthermia, hypotension and increased intracranial pressure (ICP) [119].

In animal models of cerebral contusion, it was observed that only a single depolarization wave was triggered by the primary insult. They have recorded only a few or even no spreading depolarization waves in subsequent hours after primary insult [123, 124]. Results from animal models of TBI should be assessed with caution because they rarely replicate the complexity of primary and secondary injuries in TBI patients.

1.3. Previously Tested Therapeutic Approaches

As SD clusters are proven to play a significant role in the pathogenesis of aforementioned neurological diseases, prevention of recurring SD waves in acutely injured brain tissue has been an intriguing and challenging subject. Studies made

in gyrencephalic swine brain have shown that NMDAR antagonist ketamine decreases speed, duration, spread of SDs in low-dose infusion (2 mg/kg/h), and inhibits induction and expansion of SDs in high-dose infusion (4 mg/kg/h) [125]. Similar results were obtained in rats [126], swine [127] and human patients [128, 129]. There are studies suggesting that low dose of ketamine (2 mg/kg/h) in swine brain was not effective at preventing the hemodynamic response in the oligemic phase, but reduced the initial hyperemic response to SDs [127]. Sedatives that are frequently used in intensive care units such as isoflurane, sevoflurane and propofol have been studied as potential therapeutic agents. Takagaki *et al.* has shown that isoflurane is more effective than propofol in preventing SDs and suggested isoflurane to be preferred as the sedative agent in acute ischemic stroke and trauma patients [130]. Animal experiments also show that isoflurane reduces the frequency of SDs during focal cerebral ischemia in rats and therefore have neuroprotective effects [131]. Another study of isoflurane shows that it prevents acquired epilepsy in rat models of temporal lobe epilepsy [132]. Experiments on pentobarbital have conflicting results [131, 133]. Chronic administration of migraine prophylactic drugs such as topiramate, valproate, amitriptyline, and methysergide has also shown to suppress SDs in a dose dependent manner, but chronic D-propranolol treatment was found to be ineffective at suppressing SDs [134]. Tonabersat is another promising SD inhibitor drug with potential uses in migraine prevention. It has been shown to reduce the median frequency of aura attacks by 71%, but has no effect on non-aura attacks [135]. Pregabalin, a GABA analogue, has also been shown to be effective at suppressing the initiation, wave speed and subcortical propagation of SDs *in vitro* [136]. Although there are many different experimental therapeutic agents (Fig. **3**), there is no consensus on a particular agent in humans to be used.

1.4. Non-pharmacological Management Options of SDs at Intensive Care Units

In addition to pharmacologic agents, there are several clinically relevant applications that might inhibit the occurrence of SD waves and stabilize the perilesional tissue [13]. Normobaric hyperoxia [137], temperature control [138] and glucose management [139-141] have been shown to decrease the rates of SD waves and they must be considered as important management points for the patients followed in intensive care units.

SD stimulates fast glucose consumption leading to glucose depletion within minutes [39, 46, 142-147] and hypoglycemia prolongs the recovery period from SD, suggesting that glucose is essential in restoring the transmembrane ionic gradients after SD [39, 144, 148]. It has been shown that peri-infarct SDs can be suppressed in hyperglycemic patients [140, 149, 150]. Hoffmann *et al.* demonstrated hyperglycemia in rats elevated electrical thresholds for triggering SD, and reduced frequency of KCl-induced SD [139].

SDs are shown to increase brain temperature in intracerebral hemorrhage and TBI patients [119, 138, 151]. Hartings *et al.* also discussed that high core temperatures were associated with higher risk of depolarization, suggesting
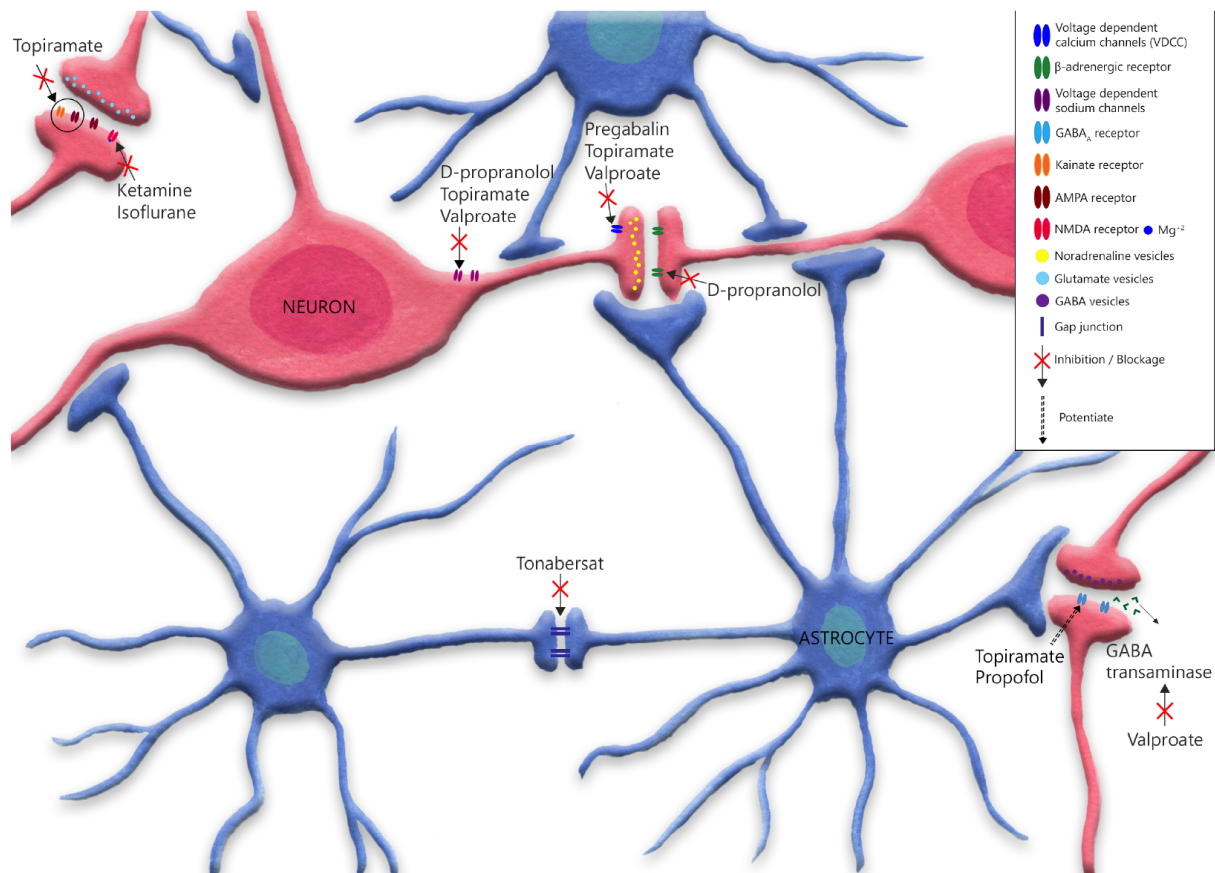
Fig. (3). Proposed effects of possible therapeutic agents that may be used in either occurrence or progression of SD waves. Topiramate may inhibit AMPA and kainate receptors and voltage dependent sodium channels while potentiating GABA$_A$ receptors. Ketamine and isoflurane inhibit NMDA receptors. D-propranolol inhibits both voltage dependent sodium channels and β-adrenergic receptors. Valproate inhibits voltage dependent sodium and calcium channels and also inhibits GABA transaminase therefore increases GABA in the synaptic cleft. Pregabalin inhibits voltage dependent calcium channels. Tonabersat inhibits astrocytic gap junctions. Propofol potentiates GABA$_A$ receptors.

temperature control as a potential preventative measure for secondary insults [119].

Several studies have also shown that personalized management of cerebral perfusion pressure (CPP) is beneficial to patients with TBI [152, 153], and low CPP values are known to increase depolarization risk [154, 155] and reduce the neurovascular responses to depolarization [119, 156, 157].

Altogether, if the factors listed above may be followed and/or managed closely at intensive care units, morbidity and mortality of patients with stroke, SAH and traumatic brain injury may decrease significantly and may help to limit secondary tissue damage.

1.5. Future Directions and Research Limitations

In the last 15 years, monitorization of SDs in patients after stroke and brain trauma at intensive care units has been established in multiple centers under the framework of Co-Operative Studies on Brain Injury Depolarizations (COSBID). More than 500 patients have been monitored in multiple centers in various countries, and multiple trials are currently in process, such as DISCHARGE-1, Invasive and Non-Invasive Monitoring of Spreading Depolarization by Electrocorticography in Trauma and Stroke (INSPECT),

NEWTON trial (Nimodipine microparticles to Enhance recovery While reducing TOxicity after subarachNoid hemorrhage) and MHS trials [158]. Although the monitorization of the actual patients pointed out some pathological pathways, there have also been some limitations of human trials of SDs. As ECoG is an invasive technique that requires electrode strips placed directly on top of the cortical surface, it can only be done in patients who are in need of neurosurgery, and as the level of consciousness alters in these patients, it is difficult to assess clinical symptoms of SD waves. More importantly, there is no clinical trial that demonstrates a benefit on the patient outcome. Secondly, initial lesions differ between patients and the location of the electrode and its distance to the lesion are also factors that might alter the results. The question that arises from these limitations is, how can SDs be identified in the absence of cortical strips. Marching pattern and transient nature of neurological deficits might make a physician assume that there are SDs, but forming a noninvasive diagnostic method is still an intriguing research subject. There have been some attempts of imaging SDs noninvasively. Previously, voxel based morphometry in high-resolution, three dimensional magnetic-resonance imaging was found to be effective in measuring learning induced brain plasticity [159]. A recently published article

also suggested that structural MRI might also be used in monitoring functional changes like blood volume, blood flow and tissue oxygenation [160]. BOLD-fMRI has also been proposed as an alternative to gadolinium contrast agent-based perfusion assessment in acute stroke as it can significantly identify microvascular hypoperfusion in severely hypoperfused tissue in acute stroke [161].

While SDs are present as aggravating factors in many pathological conditions such as migraine, ischemic stroke, trauma and subarachnoid hemorrhage, there is also evidence suggesting that they might have neuroprotective effects [162]. It has been discussed that these neuroprotective properties may be due to uncoupling protein-5 (UCP-5) trigger [162], which is known to have a long-term effect upon neuron protection [163]. Also, brief acidosis in ischemic conditions are considered neuroprotective, which is called "pH paradox" [164-170]. This brief acidosis period was also reported to reduce stroke infarct size [164, 169]. Additionally, studies show that pre-conditioning cortex with SDs provides neuroprotection against subsequent ischemia which is characterized by decrease in final cell death and infarct size [171-175], and is thought to act likely by upregulation of cytokines and growth hormones [171, 176, 177], as well as down regulation of metabolism [178] and altered neurotransmission [179]. Also SDs potentially have a role in induction of neurogenesis and plasticity [180-182]. Therefore, it is still a topic of debate whether SDs should be considered completely pathological, or sometimes beneficial, and whether these two properties are mutually exclusive and if so how to distinguish them.

Another important issue is the translation of the knowledge gathered through experimental animals to humans. Humans, swine and cats have a highly folded and more complex cortex, termed as 'gyrencephalic' compared to small animals that are widely used in research, such as mice and rats (lissencephalic brains). They have much less cortical foldings. A recent study compared SDs in swine, rat and human brains and observed that in addition to the differences in the propagation patterns due to anatomical differences, both lissencephalic and gyrencephalic brains exhibit heterogeneous propagation of SD waves [183]. Furthermore, Santos *et al.* described these heterogeneous SD propagation patterns in gyrencephalic brains [184], and suggested using movement-compensated intrinsic optical signal imaging (IOS) for the analysis of haemodynamic responses to SDs during secondary brain damage [185]. In the light of these findings, researchers must be cautious when translating research findings and observations on lissencephalic brains to human.

CONCLUSION

As an important contributor to the expansion of acutely injured brain tissue, SD waves point to new therapeutic targets and grant future studies. Especially prevention of recurring SD waves may provide protection to metabolically demised but functionally normal tissue around the lesion and may be a novel treatment option especially for stroke, SAH and traumatic brain injury.

CONSENT FOR PUBLICATION

Not applicable.

CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

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