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Spreading depolarization: A phenomenon in the brain

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A B S T R A C T

In 1944, the physiologist Leão while studying epilepsy in the rabbit noticed a sudden temporary cessation of electrocorticographic (ECoG) activity accompanied with a large negative slow potential change recorded by extracellular electrodes, that is later known as spreading depolarizations (SDs). The depression of the brain electrical activity was slowly propagating through the cerebral cortex. The mechanism of propagation is still controversial. SDs and seizures are following each other interchangeably, yet the puzzle needs more investigation to be clarified. SDs have an obvious effect on blood-brain barrier integrity mainly through transcellular and paracellular routs, but not much known about that especially following traumatic brain injury (TBI). The cortical spreading depolarization (CSD) and the depression of brain activity have been recognized following a variety of neurological diseases and brain injuries. CSD has been studied in animal models and recently in humans, and it has been recognized and described as a massive neuronal depolarization accompanied with high level of disturbances in transmembrane ion gradients and significant changes in cerebral blood flow[1-3]. Although there is a considerable amount of literatures on SD have been done since 1944, but the biophysical mechanism of SD, the long term effect on the brain structures and functions, and it is role in different disorders are still incompletely understood.
Here, we summarize the history of spreading depolarization and the most accepted hypothesis for mechanism of initiation and propagation of that phenomenon. Most importantly, we present the most updated research on the relationship and interaction between spreading depolarization and traumatic brain injuries, seizure, blood-brain barrier, neurovascular coupling, and other neurological conditions. Learning more about the spreading depolarization will increase our understanding about that phenomenon and may explain its association with different clinical presentations.

Key words

Spreading depolarization • spreading depression • concussion • traumatic brain injury • blood-brain barrier

Abbreviations

***SD** = spreading depolarization • **TBI** = traumatic brain injury • **NVC** = neurovascular coupling • **BBB** = blood-brain barrier*

Part I

Definition and Characteristics of SDs

Spreading depolarizations is a generic term for the spectrum of waves initiated and propagated in the central nervous system (CNS), characterized by abrupt and near-complete sustained neuronal depolarization[1,4], observed as a large slow potential change in the extracellular space[5,6] and propagate at 1-9.5 mm/min across the brain[7,8]. During SDs, neurons cannot fire action potentials, as the sustained depolarization is above the threshold, and the

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membrane channels that generate action potentials are inactivated[9]. The propagation of SD waves in the gray matter of the CNS causes swelling of neurons, distortion of dendritic spines[1], and silencing of the brain electrical activity (spreading depression)[10].
SDs were previously implicated as the relevant pathological waves propagated across migrainous brain[11]. In 2002, Anthony Strong and colleagues recorded SDs for the first time from human brain following traumatic brain injury (TBI)[12] and intracerebral hemorrhage[13], and in a rodent model immediately following mild traumatic brain injury[14]. Furthermore, SDs occur abundantly in individuals with aneurismal subarachnoid hemorrhage (ASH), delayed ischemic stroke, subarachnoid hemorrhage (SAH)[5], and malignant hemispheric stroke[15].

Mechanism of Initiation and Propagation

SDs can be triggered experimentally in animal model using mechanical or electrical methods beside also using various noxious conditions; such as potassium, glutamate, sodium pump inhibitors, hypoxia, and ischemia[1,16-19]. However, it is unclear if there is any difference between SDs initiated spontaneously following TBI and other neurological disorders and those triggered experimentally in labs. Grafstein in 1956 established a proposed mechanism for SDs, suggested that during SDs there is a liberation of K^+ from depolarized neurons beyond the critical value, and until these days, it is the most acceptable hypothesis[19]. On the other hand, assuming that K^+ is the major player in this process is at odds with decreasing extracellular K^+ during the time course of SDs[20]. There are extreme changes in different ion concentrations and neurotransmitters, most importantly glutamate, during SDs[21,22]. There is an implicit assumption that during SDs there is a near complete neuronal depolarization accompanied by a loss of an electrical activity[23]. The assumption was disputed by a recent rodent study recorded intrasomatic and intradendritic at the same time from a hippocampal pyramidal neuron. The study revealed that not all parts of neuron are inactivated during SDs, and neurons can maintain their integrity and electrical function. Even at the level of dendrite, just a specific part of its membrane depolarized during SD. Furthermore, the electrical response may still intact in some parts of pyramidal cells engaged in SDs even if electrical activity not detected in soma[4].
When brain tissue is exposed to stimuli that is enough to initiate SDs, neurons will be depolarized, and the concentration of K^+ in the extracellular space will increase[24,25]. The minimum extracellular $[K^+]$ at which SDs could be induced is 15 mM[26]. It had been hypothesized that high extracellular $[K^+]$ will activate and increase net inward current, resulting in a vicious circle that increases neuronal depolarization and extracellular $[K^+]$. While K^+ is released from cells to the extracellular space[19], positive ions such as Na^+, Ca^{2+}, and Cl^- will enter cells followed by water influx, that cause cell swelling (Figure 1). The extracellular $[K^+]$ rapidly

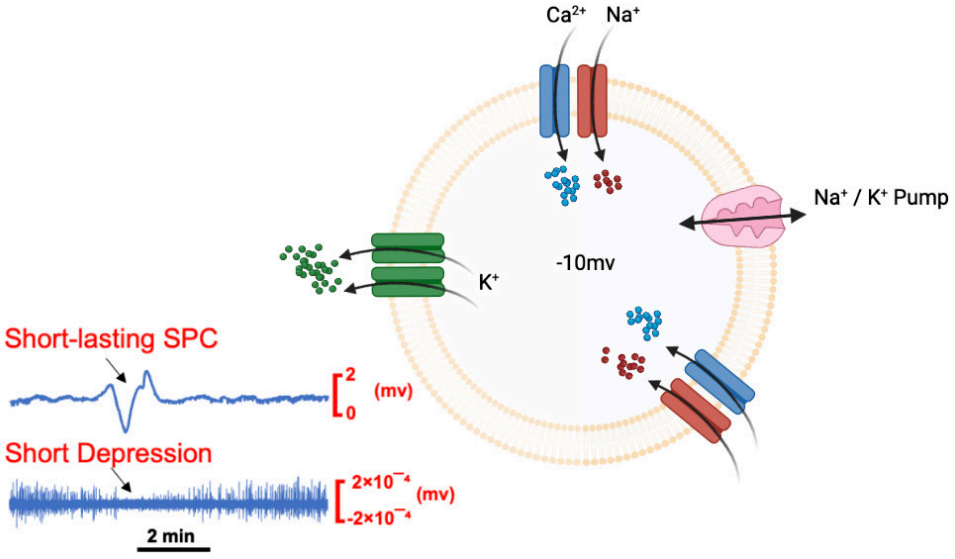

Fig. 1 - Mechanism of spreading depolarization in the neuron.

increased within 2-3 second to 55 mM, whereas extracellular [Na^+] rapidly decreased to 60 mM, [Cl^-] decreased to 75 mM, and [Ca^{2+}] also decreased to 0.08 mM[27]. Activation of voltage-gated Ca^{2+} channels in presynaptic terminals will enhance releasing of glutamate from cortical pyramidal cells synapses[28,29] (Figure 2).

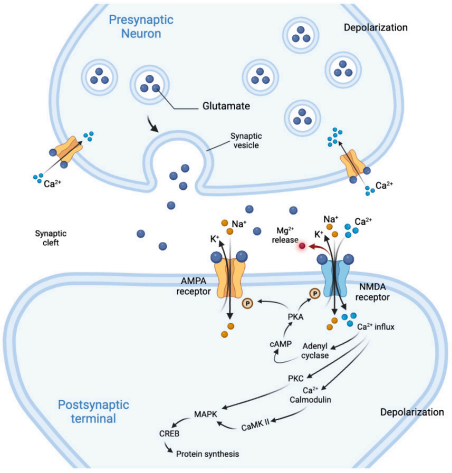

Fig. 2 - Appearance of increased glutamate release from cortical pyramidal cell synapses due to activation of voltage-gated Ca^+ channels at presynaptic terminals.

During SD, there is an abrupt-near complete sustained massive neuronal depolarization, observed as a slow potential change (SPC) in extracellular space (ECs). Neuron cannot fire action potentials (AP), as the sustained depolarization is above the inactivation threshold, at which the membrane channels that generate AP are inactivated.

Glutamate is well known as the main excitatory neurotransmitter activating N-methyl-D-aspartate receptors (NMDARs), leading to increase of a net inward current and exacerbate neuronal depolarization[21,30,31] (Figure 2). It is worth noting that activation of NMDARs will sustain and prolong the duration of the increase in dendritic Ca^{2+} following SDs. It is well known that the increase in the intracellular [Ca^{2+}] will initiate an acute neuronal injury and even a neuronal death[32]. The intracellular [Ca^{2+}] increased first in distal dendrites then propagated toward the soma, but the intracellular [Ca^{2+}] returned to baseline first in soma then after 2 minutes in dendrites[33].

Although it is not clear how astrocyte can contribute to the occurrence of SDs, glial reuptake mechanism has a role in this process performed primarily by astrocyte. Glial Na^+-K^+ pump and inward rectifier K^+ channels (Kir) have a role in buffering the increase in extracellular [K^+][34]. Furthermore, glutamate transporters on astrocytic endfeet are efficiently remove glutamate from synapses[35]. On the other hand, swelling of astrocyte is another contribution and response to SD manifested by brain edema, mainly due to K^+ uptake and water movement that follows Cl^- uptake[24].

As mentioned previously, SDs can be triggered and blocked experimentally. However, SDs can be initiated by activation of NMDARs, and it was identical to that electrically triggered[17]. On the other hand, NMDAR antagonists can block SDs triggered in cerebral cortex using KCl or electrical stimulation[25,30,36]. This may indicate that NMDARs are crucial for initiation of SDs[37], and at the same time they affect SDs propagation[36,38].

The depolarization waves spread throughout the brain cells, causing a neuronal swelling, an acidic environment, and a global loss of hyperpolarization in a disorganized abnormal manner[10,39]. The propagation of SDs across the cerebral cortex and the brain as a general is still a controversy. However, many hypotheses had been suggested to explain this process, but the diffusion of chemical substances was the most acceptable one that explained the slow propagation of SDs across the brain through diffusion of K^+ to the interstitial space[19,27]. Thus, the increase in concentration of K^+ and glutamate[21,28-31] in extracellular space during SDs will cause excitability in neighboring neurons and enhance propagation of SDs to the surrounding tissue across the brain[1,39]. Recently, it has been found that SDs initiated immediately following mild traumatic brain injury (TBI) within around 2 minutes in multisite pattern at the same time[14,40]. The simultaneous arrest of spontaneous brain activity at different brain regions at the same time is describing what is known as nonspreading depression[1,8,10,14,41,42]. The idea of connecting the term of nonspreading depression to the simultaneous arrest of brain activity is no more can be generalized for all cases, as a simultaneous spreading depolarization of brain activity at different cortical brain regions was recorded in a rodent model of a mild TBI as described previously[14]. However, the mechanism of SDs initiation in multifocal cortical pattern following TBI is unknown.

Part II

SDs in Traumatic Brain Injury

Traumatic brain injury (TBI) is an insult to the brain from an external mechanical force, and it can result in temporary or permanent impairment of cognitive and psychosocial functions (Figure 3)[43]. Mild traumatic brain injury (mTBI) is very common. The global population incidence of mTBI has been estimated to be 42 million people annually[44,45]. TBI can be related to different mechanical forces including direct physical insults, falls, motor vehicle collisions and sport injuries. It has been found that TBI is associated with neurophysiological and neurochemical changes lasting for days, months and even years post-trauma. These changes vary in severities and include dysregulation of neurotransmitters, releasing of inflammatory molecules and brain cellular death[46]. TBI has adverse clinical outcomes affect all ages; including the increase in risk of developing post traumatic epilepsy (PTE)[47], Alzheimer's disease[48,49], chronic traumatic encephalopathy (CTE)[50,51], permanent disability, and even death[52].

Spontaneous CSD have been described in sedated patients after severe injuries to the brain, including TBI[6,53,54], SAH[5,55] and malignant stroke[7,56]. Under these conditions, CSD may be associated with an impaired vascular response[7,57] and worse clinical outcome[58,59]. SDs were recorded in 53% of TBI patients underwent craniotomies for hematoma evacuation and decompression through 1-week post-trauma[53]. It had been suggested that prolonged duration of SDs is one of the major factors that stands behind forming cortical lesions, that might be attributed to hypoperfusion and impaired neurovascular coupling during SDs[6]. However, monitoring and blockade of SDs will be one of the major steps to assess patients progress and avoiding secondary brain injury[41,53,57].

Although there is still a considerable controversy surrounding the definition of concussion, but there is a general consensus that concussion term represents different kinds of head trauma associated with pathophysiological changes[60,61]. Concussion seen with variable clinical and cognitive signs and symptoms. It may with or without loss of consciousness, seizures, confusion, dizziness, and sometime normal structural imaging[62,63].

Many hypotheses were suggested, but none of them explained all the signs and symptoms following

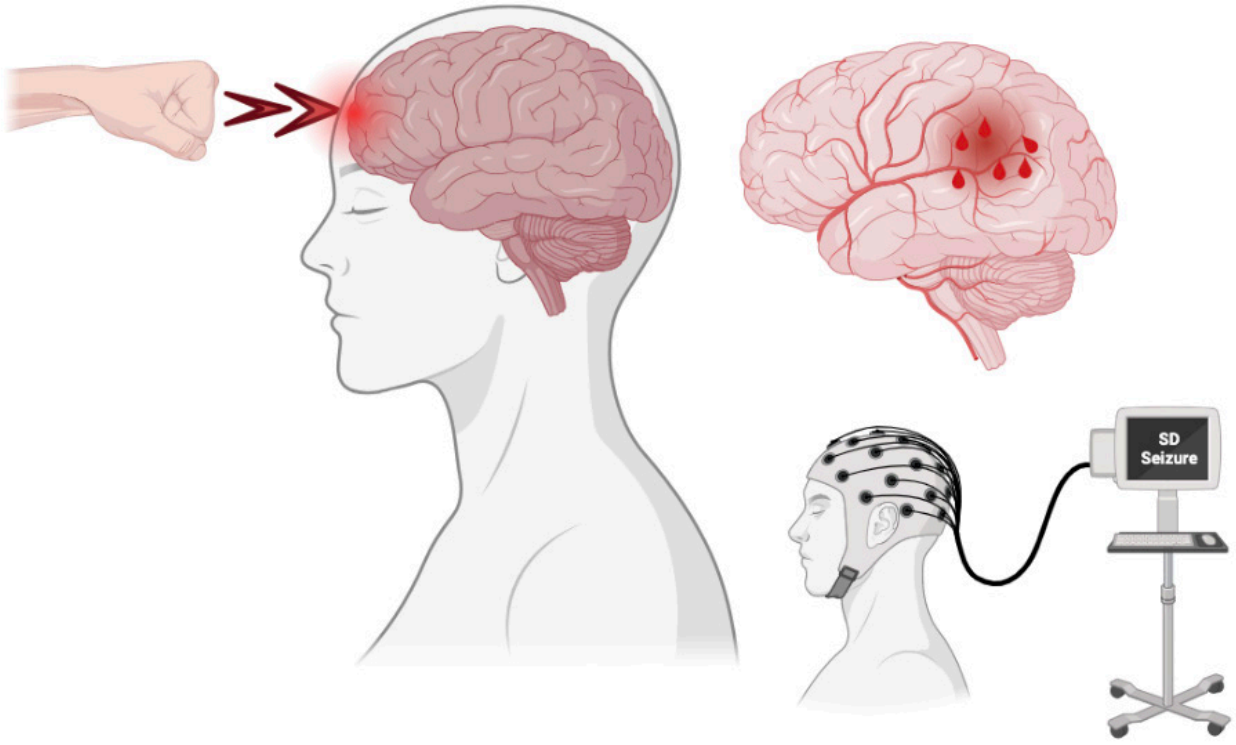

Fig. 3 - Traumatic brain injury.

concussion, especially alteration of consciousness after TBI.

Electroencephalography (EEG) has been used to study the effect of TBI on the electrical activity of the brain, and immediate depression of EEG has been reported after TBI impact[64-66]. Due to the methods used, spreading depolarization was not identified as the mechanism of silencing of the electrical activity of the brain.

Recently, electrophysiological recordings confirming that SDs are common early cortical electrophysiological events in a rodent model of mild TBI[14]. SDs were recorded in around 50% of injured animals immediately within ~ 2 minutes following a direct impact to the closed-head model of TBI. The study showed that most rats with SDs required a longer time to resume spontaneous locomotion compared to injured animals with no SDs or sham controls [14,40]. This may explain side of the incomplete understanding of the etiology of signs and symptoms after TBI. Still there is a gap between the unexplained signs and symptoms of concussion and the humbled data revealed in the literatures. Further studies needed to investigate the involvement of subcortical structures including basal ganglia.

Part III

SDs and Seizures

The relationship and interaction between SDs and seizures are still a controversy. Hyperexcitable state and firing of groups of neurons during seizures and neuronal deactivation state during SDs make the relationship more complex, especially since they are following each other interchangeably. While neurons fire action potentials synchronously during epileptic activity[67], spreading waves of electrical brain silence (spreading depression) are observed during SD[14,53,58,68]. Seizures and CSD were reported following acutely injured human brain, and they have a role in the exacerbation of tissue damage[12,69,70]. Electrocorticographic (ECoG) recordings from patients with ASH and TBI demonstrated that SDs are more frequent compared to seizures[12,58], and are associated with worse outcomes[58,59]. Seizures were very rare compared to animals showing SDs following mild TBI induced in a rat model[14]. The high occurrence of SDs within minutes following head injury could be related to the significant acute ionic disturbance in the brain following the moments of impact, that is severely affects the neurons and depolarize them massively, exceeding seizure level to triggering spreading depolarization. In contrast to chronic epilepsy that favors the episode of ictal epileptic events over that of SDs, patients with acute brain injury and ASH were found to favor the occurrence of SDs over ictal epileptic events[12,58]. Interrelation between SDs and seizures had noticed previously, in which SDs were preceded or followed seizures[14,71]. However, triggered SDs were found enhancing the neuronal excitability and facilitate the seizure activity in epileptic human brain tissues[72-74]. On the other hand, and in anesthetized rats, triggering of seizure activity can lead to a single and repetitive SDs[74].

It is worth noting that, mechanistically, NMDARs have an important role in both epileptiform activity and SDs. Antiepileptic antagonists of the NMDARs, such as ketamine (Figure 4), were found to halt SD activity; however, antiepileptics without NMDA properties, such as diazepam, did not affect SD activity[75].

Further studies needed to improve our knowledge about the relationship between these two depolarization phenomena.

Part IV

SDs and Blood-Brain Barrier

Blood-brain barrier (BBB) is a unique anatomical and physiological selective protective barrier, formed and exist in the CNS and separating the CNS from the systemic circulation[76] (Figure 5). The existence of this barrier in the brain was described for the first time by Paul Ehrlich in 1885. The BBB is formed by endothelial cells (ECs) that act as a principal barrier unit; which are connected to each other via tight junctions[77]. Cell to cell interaction together with other cellular elements such as astrocytes, pericytes, and neurons that are surrounding and close to endothelial cells, BBB preserves the brain and maintains normal neuronal functions [78]. The ECs and the surrounding cellular elements form a barrier and neurovascular unit that have many functions such as: (1) regulate and maintain the ionic and the molecular components of the extracellular environment in the brain. (2) maintain the transport of oxygen and other

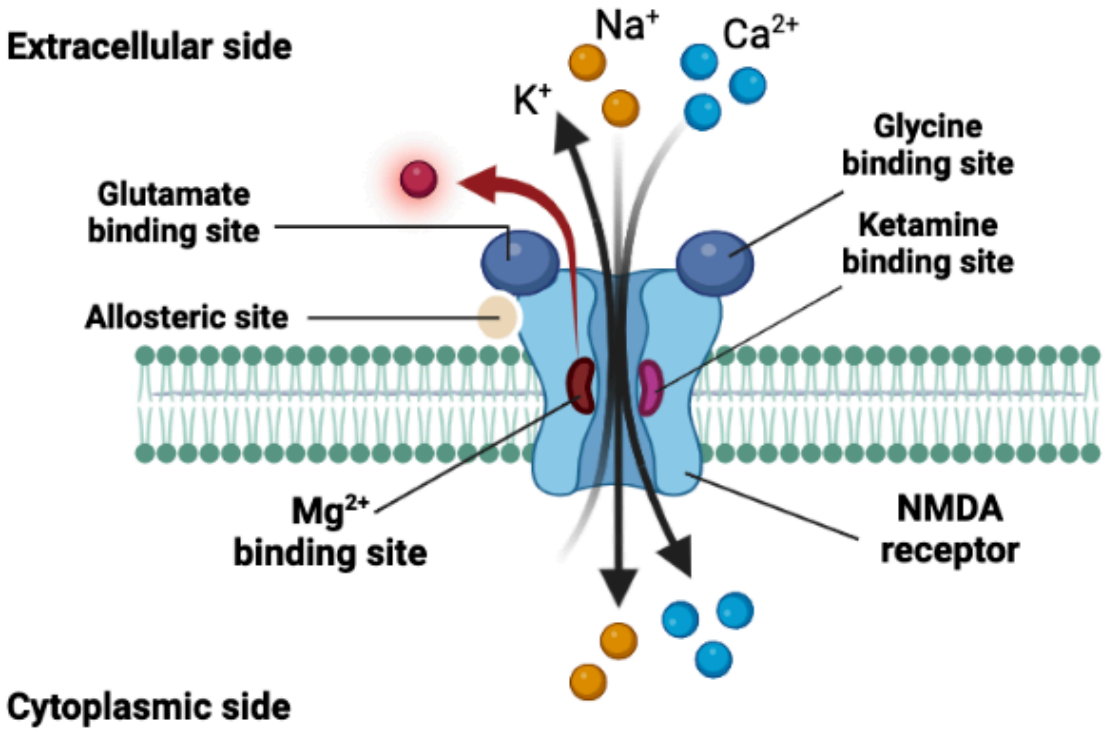

Fig. 4 - Schematic view of NMDA receptor.

nutrients between the brain and the blood stream. (3) protect the brain from different pathogens and toxins[77,79].

The relationship between SDs and BBB changes is not well known. Recently, it has been suggested that there is a relationship between SDs and BBB, and it is mediated by a family of proteolytic enzymes called matrix metalloproteinases (MMPs)[80]. MMPs are members of an enzyme family (proteolytic enzymes) that digest components of the extracellular matrix (ECM) such as the interstitial and basement membrane collagens and cell surface receptors[81-83]. The effect of release and activation of MMPs were observed following intracerebral hemorrhage, stroke, brain tumor and TBI[81,84-87] with an obvious effect on the integrity of BBB. MMPs had been injected into the rat brains, and an increase in capillary permeability was observed[84]. The change in the BBB permeability was attributed to the destruction of collagen in the basal lamina, and the damage is proportional to the amount of enzyme activation and the plenty of MMPs inhibitors that reduce extracellular matrix proteolysis and protect the BBB[84]. It has been suggested that CSD cause prolonged MMP-9 activity that leads to BBB dysfunction and vascular leakage that can be suppressed by an MMPs inhibitor. In the previous study, following 3-6 hours of triggered SDs, the level of MMP-9 was increased, reaching the maximum at 24 hours and lasting at least for 48 hours. Cerebral vascular leakage of plasma protein was detected after 3 hours of SDs. Protein leakage from cerebral vessels was not detected in MMP-9-null mice, indicating that MMPs was a predisposing factor for the late initiation of BBB dysfunction, suggesting that loss of the basement membrane (type IV) collagen and tight junction protein (Zonula occludens 1) are the main mechanisms by which MMP-9 activation disrupts the BBB[80]. In another study, after 30 minutes of intracortical injection of KCl, C-sucrose leaked to the cortex, and resolved within 6 hours, while there was no change observed in tight junction proteins (occludin or claudin-5) expression, a tight junction proteins localization has been suggested as presumptive cause for the increase in BBB permeability[88]. In another study, KCl-triggered SDs increased endothelial transcytosis starting between 3-6 hours and lasting for 24 hours, but tight junction, pericyte and basement membrane

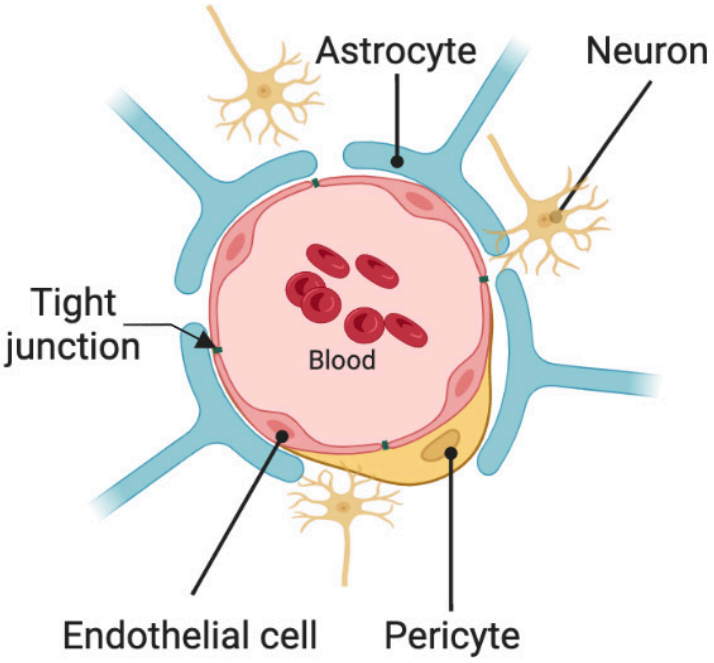

Fig. 5 - Schematic view of the blood-brain barrier.

remain preserved after SDs[89]. Furthermore, an increase in the number of pinocytic vesicles in endothelial cells and swelling of the end feet of astrocyte were reported following KCl-triggered CSD, that it could be another mechanism by which SDs contribute to BBB dysfunction[90]. However, the increase in extravasation of plasma protein as a result of topical KCl itself was not excluded[91].

The permeability of the BBB was increased following activation of NMDARs and excessive glutamate release in a rodent model[92]. While SDs are accompanied by massive increase in glutamate level, NMDAR antagonists had reduced the BBB permeability by decreasing the number of SDs[91]. The extracellular concentration of glutamate was raised immediately and peak within 4-5 minutes following TBI[93]. In another study, the concentrations of glutamate and aspartate in cerebrospinal fluid (CSF) of patients with head injuries were 2 to 8-fold higher than control, measured after an hour of injuries and continued for 3 days[94] and up to 9 days[95]. In a rat model, the rise in extracellular glutamate level was reported immediately and lasted up to 9 days following TBI[96]. This may indicate that the increase of glutamate following head injury and SDs occurrence has an obvious effect on BBB permeability with unclear mechanism. In a recent study, an increase in BBB permeability was noticed within an hour of triggering SDs in TBI animals, suggesting that there may be a fast mechanism by which SDs affect BBB integrity following TBI[40]. Further work needed to investigate the rapid mechanisms by which TBI-induced SDs affect the BBB integrity and cause further brain injury.

Part V

SDs and Neurovascular Coupling

The phenomenon of increased in regional cerebral blood flow (rCBF) in response to physiological neuronal activation and decreased rCBF in response to neuronal deactivation is known as the neurovascular coupling (NVC)[98-101]. The coupling process accomplished by different components link and maintain dynamic interactions with each other, including neurons, astrocytes, pericytes, and vascular smooth muscle cells (VSMC)[102,103] (Figure 6). All these components form a neurovascular unit (NVU). One of the most important functions of the NVU is to regulate the transport and diffusion of different substances and molecules across the endothelial cells of BBB depending on the energetic and metabolic statuses[104].

SDs abundantly and ictal epileptic activities to less extent were recorded in acutely injured human

brains and ASH[5,105], suggesting that SDs have a role in neuronal death, increasing the metabolic demands, and inversing NVC. Both SDs and ictal epileptic events were seen accompanied by increase in cerebral blood flow to compensate the increase in energy demands, and sometime reverse in NVC and a decrease in cerebral blood flow. The changes in cerebral blood flow whether hyperemia or oligemia in response to SDs were studied before[98,106-112]. The response of cerebral vessels to SDs is varied between normal healthy and pathological tissue. In healthy tissue, physiological hemodynamic response (hyperemia) was the dominant, but oligemia in tissue at risk for progressive damage was the inverse hemodynamic response[1,57,113-115]. NVC was varied between TBI patients depending on the severity of the injuries. The variations in NVC response were physiological hyperemic, pathological inverse, and sometime switch from physiological to pathological coupling[57]. However, a decrease the cerebral blood flow and inverse NVC were recorded with SDs following subarachnoid hemorrhage, TBI, and injured human brain[6,116-118], suggesting that the inverse NVC leads to exacerbate existing ischemic condition and increases the duration of SDs. SDs were seen accompanied by release of glutamate, arachidonic acids, and production of NO, that ultimately leading to vasodilation[119,120]. Furthermore, during SD, glucose and energy consumption are increased three times, tissue ATP abundance falls, and the extracellular concentration of sodium, chloride, and calcium ions are decreased[120-122]. Although there is an increase in rCBF during the early phase of SD to supply the tissue with the energy necessary to restore ionic equilibrium[54], but tissue hypoxia still can be detected in brain regions that are away from capillary supply[123,124]. A rodent study monitored the blood flow in cortical cerebral vessels, and hyperemia during SDs was obvious in small vessels and to less extent in arterioles and venules[111].

Part VI

Summary and Conclusion

Many studies demonstrated the involvement of spreading depolarization after severe injuries to the brain including traumatic brain injuries, subarachnoid hemorrhage, and stroke. Spreading depolarizations were recorded as the early cortical electrophysiological events following mild and severe traumatic brain injury in rodents and human. Prolonged duration of spreading depolarization can cause hypoperfusion and impaired neurovascular coupling, that may lead to form cortical lesions. Spreading depolarizations and seizures were following each other interchangeably after traumatic brain injury, subarachnoid hemorrhage, and epilepsy without an understandable explanation, and more investigations needed to explain part of that controversy. Following different neurological conditions, spreading depolarizations have an

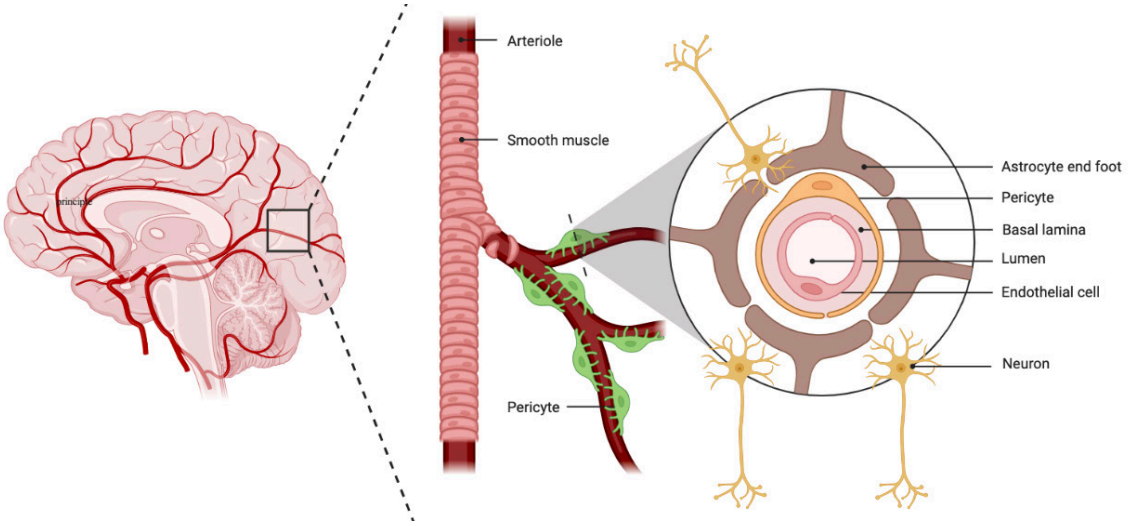

Fig. 6 - Semantic representation of the Neurovascular unit.

obvious effect on the integrity of BBB by different mechanisms. Better understanding of spreading depolarization will lead to novel therapeutic intervention to prevent occurrence of spreading depolarization and prevent its adverse effect on the brain.

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