How Spreading Depolarization Can Be the Pathophysiological Correlate of Both Migraine Aura and Stroke

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Abstract The term spreading depolarization describes a mechanism of abrupt, massive ion translocation between neurons and the interstitial space, which leads to a cytotoxic edema in the gray matter of the brain. In energy-compromised tissue, spreading depolarization is preceded by a nonspreading silencing (depression of spontaneous activity) because of a neuronal hyperpolarization. By contrast, in tissue that is not energy compromised, spreading depolarization is accompanied by a spreading silencing (spreading depression) of spontaneous activity caused by a depolarization block. It is assumed that the nonspreading silencing translates into the initial clinical symptoms of ischemic stroke and the spreading silencing (spreading depression) into the symptoms of migraine aura. In energy-compromised tissue, spreading depolarization facilitates neuronal death, whereas, in healthy tissue, it is relatively innocuous. Therapies targeting spreading depolarization in metabolically compromised tissue may potentially treat conditions of acute cerebral injury such as aneurysmal subarachnoid hemorrhage.

Keywords Aneurysmal subarachnoid hemorrhage • Spreading depression • Delayed cerebral ischemia

Introduction

Spreading depolarization is characterized by (1) extensive breakdown of transmembrane ion gradients [16, 35], (2) extreme shunting of neuronal membrane resistance [2], and (3) transient neuronal swelling with dendritic spine distortion [31, 37]. In 1945, the Brazilian neurophysiologist

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Aristides Leão proposed that spreading depolarization is the pathophysiological correlate of the migraine aura [22], and, in 1947, he linked migraine aura and stroke to spreading depolarization as their common mechanism [21].

Spreading Depolarization may Be a Common Mechanism of Migraine Aura and Stroke Although Their Clinical Symptoms Are Different

Most neurologists today agree that spreading depolarization is likely the pathophysiological correlate of the migraine aura [30] and contributes to the cellular injury in stroke even though migraine aura and stroke typically have different medical histories. This applies particularly to the temporal pattern of the initial symptoms and to the fact that migraine with aura is usually a harmless disease in contrast to stroke [17]. It is therefore counterintuitive that spreading depolarization is a mechanism of stroke, which initiates and facilitates neuronal injury in energy-depleted tissue, and, on the other hand, can be the pathophysiological correlate of the migraine aura. However, Leão provided a plausible explanation for this paradox when he discovered that the energy state of the tissue determines both (1) the duration of the spreading depolarization and (2) the depression (silencing) pattern of spontaneous activity that accompanies the depolarization. The two major types of silencing of spontaneous activity which can co-occur with spreading depolarization are nonspreading depression and spreading depression of spontaneous activity [21]. Nonspreading depression describes a sudden silencing of spontaneous activity that is simultaneously observed in different brain regions wherever brain perfusion drops below ~20 ml/100 g/min [12]. When spreading depolarization develops in such electrically silent tissue, it cannot cause spreading depression of activity because the spontaneous activity has already ceased.

But, unless spreading depolarization is preceded by arrest of spontaneous activity, it initiates spreading depression of activity because the near-complete depolarization is above the inactivation threshold for the action potential-generating ion channels [13]. Spreading depression of activity thus requires a grossly intact energy supply in stark contrast to nonspreading depression of activity. Thus, both spreading and nonspreading depression of activity can occur in stroke where there is a gradient of energy depletion from the core to adjacent watershed and healthy regions of cortex. In the ischemic core, where nonspreading depression of activity has already developed, spreading depolarizations are ignited and propagate into adjacent tissue with preserved spontaneous activity, which is then depressed in a spreading manner.

Nonspreading depression of activity caused by occlusion of blood flow is assumed to be the pathophysiological correlate of the sudden and simultaneous neurological deficits of transitory ischemic attacks, nonmigrainous stroke, and cardiac arrest. The spreading depression of spreading depolarization that occurs in these conditions may have additional clinical correlates, but these would be subtle and difficult to detect on a baseline of obtundation and major widespread deficits [6]. In contrast, the creeping neurological deficits of migraine aura and migrainous stroke are obvious to patients and clinicians in the context of intact neurologic function and are thought to be mediated by the spreading depression of brain electrical activity. Thus, the depression patterns caused by disruption of energy supply and by spreading depolarization determine the clinical symptoms of these diseases. The existing energy supply, such as the level of perfusion [5] and the level of blood glucose [15], for example, largely determine whether spreading depolarization initiates a countdown to neuronal death. The tissue fate is reflected by the duration of spreading depolarization, because neuronal survival depends on rapid repolarization, which is energy dependent. Notably, if, in experiments, spreading depolarization is markedly prolonged by other means than energy shortage, for example, by a long-lasting artificial increase in the baseline potassium concentration, neurons will eventually also die although the energy supply is normal. However, under such conditions, the time period from the onset of spreading depolarization to the neuronal death will be longer than under conditions of energy depletion [5]. For a more comprehensive account of the signals in relation to migrainous stroke, we refer the reader to a former review [4].

Processes Leading Up to Spreading Depolarization: Potential Targets for Therapeutic Intervention

The abrupt near-complete breakdown of neuronal ion homeostasis characterizes spreading depolarization. Spreading depolarization could contribute significantly to the higher vulnerability of neurons to ischemic stress compared with other cells of the body. This raises important questions: (1) which neuron-specific channels and processes in the membrane are large enough to allow for such a rapid influx of cations and water and (2) might it be possible to block them pharmacologically to protect the cells and delay the cell death?

The experimental study of the membrane channels participating in spreading depolarization has been hindered by their mixed contribution and the heterogeneous subcellular distribution over the anatomy of neurons. Of note, the channels that contribute to the initiation or propagation of spreading depolarization could be different from the major carriers

of electric charge during the sustained phase of depolarization. Thus, the massive ion translocation across the membrane occurs during the first 2–3 s, in close time association to the initial DC shift. Thereafter, the ions remain stable at this new plateau or drift slightly [11, 16], indicating that conditions close to a new steady state have been achieved. Channels contributing to initiation of spreading depolarization may include voltage-gated cation channels and *N*-methyl-D-aspartate (NMDA) receptor-controlled channels [1, 8, 10, 19, 20, 25, 38]. Nevertheless, the question of which channels contribute specifically to the initiation or propagation processes seems to depend largely on the conditions present immediately before the spreading depolarization. This is reflected by the notion that the propagation of spreading depolarization can be blocked by NMDA receptor antagonists in healthy, naïve tissue [8, 20, 25], whereas this is not possible under hypoxic or ischemic conditions [1, 10, 19, 26] or when the baseline extracellular potassium concentration is artificially increased [28].

The process of massive ion translocation is even less understood than the processes of initiation or propagation. In a pioneering study, a large voltage-independent current was identified using whole-cell recordings during ongoing spreading depolarization [3]. The large voltage-independent current flows inward through membrane channels that stay open during spreading depolarization and are mostly localized in dendritic regions [2]. A wealth of pharmacological data has not singled out one membrane channel that is involved but it has pointed to a combination [29]. In a realistic neuron model aiming to replicate the subcellular changes of membrane resistance during spreading depolarization, it was found that in addition to standard potassium-, sodium-, and glutamate-mediated conductances, the initial opening and gradual closing of an as yet undetermined large conductance is required [24]. So far there are no hints regarding the nature of such spreading depolarization-specific conductance. It may be a known channel with modified kinetics produced by the severe chemical changes imposed during spreading depolarization, or it may be a totally different channel. New families of neuron membrane channels are being discovered. Among possible candidates, gap junction hemichannels have a variable pore aperture that would permit the passage of common ions. However, although gap junction blockers halt spreading depolarization in some experimental settings [18], they do not in others [27, 33]. In a similar fashion to that described for gap junctions, pannexin hemichannels could contribute as major carriers of electric charge during spreading depolarization [32]; interestingly, recent evidence also points to a role for pannenxins in the release of factors triggering pain after spreading depolarization [14]. Other putative candidates are transient receptor potential (TRP) channels [23] and tandem pore domain potassium (2PK) channels [7], but their distribution and kinetics are largely unknown. It is therefore not yet possible to analyze their contribution in the realistic neuron model. Finally, low calcium-activated cation channels are possible candidates [9, 36], because they are gated by external calcium reduction and appear to be voltage independent, two conditions found during spreading depolarization. Last but not least, the caveat must be added that space clamp problems associated with voltage-clamping central nervous system neurons [34] mean that a number of voltage-dependent channels expressed on distal dendrites cannot be completely excluded as contributors, including NMDA receptor-controlled channels.

Conclusion

Spreading depolarization is an important phenomenon of cerebral pathology. Notably, it occurs in patients with stroke including subarachnoid hemorrhage. Its pharmacology is very complex as it changes with the conditions under which it occurs.

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Conflict of Interest Statement We declare that we have no conflict of interest.

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