Spreading Depression and Neurovascular Coupling

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Spreading depression, discovered by Leao in 1944,1 is an intense depolarization wave that slowly propagates (=3 mm/min) in gray matter by way of contiguity, regardless of functional divisions or arterial territories. The depolarization is associated with massive transmembrane ionic and water shifts coupled to a surge in extracellular K+ and neurotransmitter levels, including glutamate. Transmembrane ionic gradients are restored within less than a minute in otherwise normal tissue without causing permanent injury.

Dating back to Leao’s discovery, spreading depression has been implicated in migraine because of the similarities between electrophysiological characteristics of spreading depression and symptomatology of migraine aura.2-5 Although it has been known that ischemia could also trigger spreading depression,6 it was not until the 1980s that recurrent spreading depression-like depolarization waves were demonstrated in focal ischemic brain.7 Often termed peri-infarct depolarizations, or simply injury depolarizations, these recurrent waves seem to originate at the junction between the severely ischemic core (ie, tissue that has developed anoxic depolarization) and the moderately ischemic penumbra where all synaptic activity has ceased, but membrane potentials are preserved. Once initiated, injury depolarizations propagate along the infarct rim and often into the nonischemic tissue, and exert profound metabolic and hemodynamic effects to acutely exacerbate the supply–demand mismatch and worsen the ischemic tissue outcome. Over the past decade, injury depolarizations have been detected in human brain not only after ischemic stroke but also after subarachnoid hemorrhage, intracerebral hemorrhage, and traumatic brain injury, raising their pathophysiological profile as a novel therapeutic target.8

In most species, spreading depression triggers a pronounced hyperemic response. Because spreading depression strongly stimulates ATP consumption, presumably to restore the transmembrane ionic gradients, it has been assumed that the large hyperemic response is simply driven by the increased metabolic need for oxygen and glucose. Yet, providing a surplus of oxygen and glucose did not seem to diminish the response,9 nor did oxygen or glucose shortage augment it,10 casting some doubt over this view. Evidence accumulated over the past decade suggests a more complex picture, in which the hemodynamic response to spreading depression is composed of multiple vasomotor components; some components exert a dilator influence, whereas others are constrictive.

At least 3 vasomotor elements are discernible based on available data (Figure). The first is a vasoconstrictive tone that temporally overlaps with the depolarization, possibly induced by the very high extracellular K+ levels and vasoactive mediators released from parenchymal neurons, astrocytes, and perivascular nerves during the depolarization. This vasoconstrictive component is most prominent in mice, but can be augmented or unmasked in other species as well by, for example, nitric oxide synthase inhibition11-13 and tissue ischemia (see below). The second and most conspicuous component is a profound hyperemia that starts at or soon after the depolarization onset. It gains momentum during the repolarization phase, but often does not reach a peak until after complete recovery of spreading depression. This hyperemic phase usually lasts up to a few minutes, and has attracted the most attention as being arguably the most potent hyperemic response to any physiological stimulus.14 Multiple vasodilator molecules have been implicated, including nitric oxide and calcitonin gene–related peptide; however, it is not clear whether these directly mediate the hyperemia or play a permissive role. In the wake of hyperemia, blood flow usually drops below baseline for up to an hour. This third and longest-lasting phase is often called postspreading depression oligemia, and can be modulated by mitochondrial permeability transition pore and calcineurin.15 Although undoubtedly oversimplified, this is still a helpful conceptual framework to characterize the dilator and constrictor mechanisms and mediators of the vascular response to spreading depression.

The magnitude and timing of each vasomotor element seem to be species dependent, and can be modulated by systemic and tissue physiological state and by pharmacological interventions, changing the shape of the blood flow response. For example, in mice the vasoconstrictive components are much stronger than in other species. Therefore, the predominant blood flow response is a pronounced hyperfusion that coincides with the depolarization, followed by a transient normalization of flow and a severe postspreading depression oligemia.16 As such, the blood flow response sets a sharp contrast with the monophasic hyperemia in rats.17 The vasomotor response also differs in different arterial segments. Vasoconstriction during the depolarization is more pronounced in deep cortical arteries compared with larger pial arteries.18 Capillary flow arrest is frequently observed, which is curious because capillary compression or focal constrictions have never been observed during spreading depression.
or injury depolarizations. Interestingly, the vasoconstrictive components are most conspicuous during the first spreading depression in naïve tissue, and rapidly diminish with recurrent spreading depolarizations triggered in closed succession (eg, within <30 minutes of each other).

Intravascular perfusion pressure is a major factor determining the shape of the hemodynamic response to spreading depression. For example, systemic hypotension can transform the monophasic hyperemic response in rats into a biphasic response by unmasking an initial vasoconstriction and diminishing the subsequent dilation. Consistent with this, peri-infarct depolarizations predominantly cause vasoconstriction in ischemic penumbra in all species studied to date, including mice, rats, and cats. The more severe the perfusion deficit is (ie, deeper into the ischemic territory), the stronger the vasoconstrictive response and loss of perfusion are, as elegantly demonstrated by high-spatiotemporal resolution optical imaging technologies. Because more severe perfusion deficits in penumbra are also associated with longer-lasting peri-infarct depolarizations, their vasoconstrictive effect is also prolonged, creating a vicious cycle. In other words, peri-infarct depolarization worsens the perfusion deficit, which slows down and sometimes prevents repolarization. Indeed, when a peri-infarct depolarization fails to recover in critically hypoperfused penumbra (ie, when a portion of penumbra is incorporated into the core), its vasoconstrictive effect also becomes permanent. Because anoxic depolarization is a permanent (or at least a very long-lasting) spreading depression-like state, it is associated with persistent vasoconstriction and loss of perfusion in ischemic core.

In summary, spreading depression and related injury depolarizations have complex vasomotor effects on cerebral vasculature, consisting of multiple components presumably with distinct mediators and modulators. Although the profound hyperemia is considered as the prototypical hemodynamic response to intense depolarizations in normal brain, vasoconstriction and hypoperfusion become more pronounced under pathological conditions, such as ischemic or hemorrhagic stroke. As such, recurrent injury depolarizations have been shown to worsen tissue perfusion in animal as well as human brain as a potential mechanism, leading to detrimental outcomes in stroke, subarachnoid hemorrhage, and other brain injury states. Therefore, suppression of injury depolarizations and their vasoconstrictive effects may improve outcome in ischemic, hemorrhagic, and traumatic brain injury by enhancing tissue perfusion.

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References

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