Age-related impairment of metabo-vascular coupling during cortical spreading depolarizations

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Running headline: Cortical spreading depolarizations in aging

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Abstract

Cortical spreading depolarizations (SDs) may lead to long-lasting alterations in cerebral blood flow (CBF), which contribute to neuronal dysfunction and hypoxic tissue injury. There is growing evidence to suggest that age-related structural and functional alterations of the neurovascular unit significantly increase both the incidence of SDs and aggravate their functional consequences. Recent studies suggest that metabolic signaling plays a major role in modulating cerebral blood flow responses evoked by SDs and provide critical evidence that aging considerably weakens metabovascular coupling with SD. As a consequence, the aged brain becomes increasingly more vulnerable to the deleterious effects of SDs.
Clinical relevance of cortical spreading depolarizations

Spreading depolarizations (SDs) are waves of massive cellular depolarization travelling within the brain at a speed of 2-4 mm/min, characterized by sustained near-complete depolarization of neuronal cells, a massive depolarization of glial cells, and a negative deflection of the extracellular DC potential. In addition to temporarily shutting down neuronal function and information processing within neuronal networks SDs represent an important metabolic challenge for the brain parenchyma due to the large energy demand for repolarizing neuronal and glial cells. Importantly, SDs that propagate in the cortex also trigger rapid vasoconstriction, followed by a significant hyperemic response and then a long-lasting oligemic phase(2, 3, 7, 8, 11, 21, 28, 36, 57). Clinical observations and strong experimental evidence suggest that SDs occur after a diverse range of injury types, including intracerebral hemorrhages, ischemic strokes, migraine, subarachnoid hemorrhages, as well as traumatic brain injuries and correlate with poor outcome (2, 3, 5, 14-16, 25, 27, 29, 31, 34, 41, 43, 44, 58-60). Injury-induced SDs (e.g. in stroke) can propagate along ischemic, but viable areas adjacent to the damaged brain regions, and repetitive occurrence and especially long lasting SD episodes exacerbate neuronal lesions and thereby worsen the clinical outcome (19, 26).

Importantly, there is increasing evidence that age-related structural and functional alterations of the cerebral circulation (18, 20, 42, 51) significantly increase both the incidence of SDs and aggravate their functional consequences (11, 21, 28, 36). Despite their importance, the mechanistic effects of aging on SDs and the cellular and molecular mechanisms by which SDs can exacerbate brain injury are still largely unknown.

Age-related impairment of metabo-vascular coupling during SDs

pH is often a neglected aspect of brain metabolism. Brain energy state is most often studied by measuring glucose, lactate and/or pyruvate levels, but pH also offers useful insights into cell metabolism. Increased carbohydrate metabolism results in CO$_2$ and/or lactate production that contribute to interstitial fluid acidification. In addition, exocytosis of highly acidic synaptic vesicles can induce acidosis in response to increased neuronal activity. These acidic shifts can be mitigated by the buffering capacity of the interstitial fluid and especially, the activity of the enzyme carbonic anhydrase that accelerates CO$_2$ hydration into carbonic acid, as well as a number of proton pumps that help equilibrate intra- and extracellular pH (10). Despite this high buffering capacity, brain pH is known to change transiently in response
to sustained neuronal activity or pathological states like ischemia. Such pH changes can have profound effects on neuronal excitability by modulating a variety of ion channels, or even lead to cell death when pH deviates too much and/or too long from its physiological value (45).

In this article, published as part of the special collection of papers “Advances in Cardiovascular Geroscience”(4, 12, 13, 17, 22, 23, 35, 39, 46, 47, 52, 54, 56, 61), and in a previous study from the same authors, Menyhárt et al. have monitored pH changes evoked by SDs in control animals, as well as in aged or ischemic rats (37, 38). While SD induced transient acidic shifts in the order of 0.1-0.2 pH units in young healthy animals, pH shifts were considerably larger (about 0.4 pH units) after ischemia or in aged animals. In addition, the correlation between pH shifts, hyperemia and the amplitude of depolarization typically observed in young healthy animals was absent after ischemia or aged animals. These observations were made possible by small pH microelectrodes that could monitor the pH of the interstitial fluid with minimal perturbation of the brain parenchyma. Such pH electrodes were initially developed in the 1980s(1, 30, 40), but remain extremely difficult to handle reliably. The present work by Menyhárt et al. illustrates the power of this brain monitoring technique. The discrepancy between the pH signature of an SD in a healthy brain and that in an ischemic or aged brain could provide a basis for understanding why such events are usually harmless in young animals or patients, but aggravate neuronal lesions in an already injured or aged brain.

The results of Menyhárt et al.(37), corroborate the notion that metabolic signaling plays a major role in the mediation of hyperemia in response to SD. They provide convincing evidence that hyperemic element of the cortical blood flow response to SDs is effectively modulated by tissue pH. The authors put forward the hypothesis that on a hyperemia spectrum with functional and reactive hyperemia as its two end points, the nature of the SD-coupled hyperemic response falls closer to reactive than to functional hyperemia (Figure 1). This would be especially relevant for SD events, which produce a sudden, transient drop of perfusion prior to the evolution of hyperemia. Importantly, Menyhárt et al., also provide critical evidence that aging considerably weakens metabovascular coupling with SD and that tissue acidosis lasts disproportionally longer in the aged cortex, making the tissue increasingly more vulnerable. This important observation can have far-reaching consequences. The results of Menyhárt et al.(37) open exciting new perspectives for improved neuroprotective strategies based on improving the buffering capacity of the brain extracellular fluid by targeting, for example, lactic acid production and clearance. This study illustrates how chemical monitoring
of brain molecules using minimally invasive real-time sensors and/or imaging techniques can reveal physiological or pathological mechanisms, improve our understanding of cellular and molecular brain processes, and guide the development of new therapeutic strategies.

Growing evidence from epidemiological, clinical and experimental studies indicate that aging-induced cerebromicrovascular dysfunction plays a critical role in the pathogenesis of various types of dementia and brain damage in the elderly (9, 24, 32, 33, 48, 54-56). Importantly, there is strong evidence demonstrating that functional hyperemia/neurovascular coupling is impaired in aging both in humans and laboratory animals (6, 42, 53, 62), which likely contributes to the development of vascular cognitive impairment (49, 50). The study of Menyhárt et al. has important relevance for cerebrovascular geroscience, as it also highlights a novel age-related mechanism by which cerebromicrovascular reactivity and thereby normal neurovascular coupling responses may be altered in the elderly.

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Figure 1. Conceptual overview of the type of coupling between spreading depolarization (SD) and the associated hyperemia in the context of aging (see text for details).