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A Postictal Traffic Jam

Seizure-Induced Neutrophil Adhesion in Brain Capillaries Leads to a Decrease in Postictal Cerebral Blood Flow

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Cerebral hypoperfusion has been proposed as a potential cause of postictal neurological dysfunction in epilepsy, but its underlying mechanism is still unclear. We show that a 30% reduction in postictal cerebral blood flow (CBF) has two contributing factors: the early hypoperfusion up to ~30 min post-seizure was mainly induced by arteriolar constriction, while the hypoperfusion that persisted for over an hour was due to increased capillary stalling induced by neutrophil adhesion to brain capillaries, decreased red blood cell (RBC) flow accompanied by constriction of capillaries and venules, and elevated intercellular adhesion molecule-1 (ICAM-1) expression. Administration of antibodies against the neutrophil marker Ly6G and against LFA-1, which mediates adhesive interactions with ICAM-1, prevented neutrophil adhesion and recovered the prolonged CBF reductions to control levels. Our findings provide evidence that seizure-induced neutrophil adhesion to cerebral microvessels via ICAM-1 leads to prolonged postictal hypoperfusion, which may underlie neurological dysfunction in epilepsy.

Commentary

It is not over till the postictal state ends. It may last from minutes to days and could be associated with neurological and/or psychiatric symptoms, from confusion and memory impairment to sudden unexpected death in epilepsy. A hallmark of the postictal state is alterations in regional cerebral blood flow (CBF), although the direction of change may vary across patients and brain regions and over time. Hyperperfusion, which is often documented during seizures, has been observed during the postictal state. More typically, though, the postictal blood flow drops below baseline levels up to an hour after seizure termination to the point that assessment of postictal hypoperfusion has been suggested as a tool to identify the seizure-onset zone.[1] Because the energy storage capacity of the brain is limited, even a short disruption of oxygen and glucose supply as a result of severe hypoperfusion may cause irreversible damage to brain cells.[2] Hypoperfusion can contribute to epileptogenesis (e.g., as a result of oxidative stress) and might underlie to some extent the postictal symptoms.[3] In the case of SUDEP, it has been suggested that repeated seizures with postictal hypoperfusion could lead to an accumulating damage to the brainstem respiratory centers until the terminal event.[3]

Research into the mechanisms of reduced CBF has mostly focused on vasoconstriction.[1,3] The study by Lim et al[4] now introduces new players in this process—neutrophils, which enter the game beginning ~30 minutes after the end of acute seizures in mice and obstruct capillaries. In line with this phenomenon, the investigators identified vascular stalls in the cortex, which were 2.3-fold more abundant than in saline-treated mice. The neutrophil-specific antibody anti-Ly6C/G pinpointed neutrophils as a component of ~60% of the postictal stalls. Moreover, when this antibody (which can prevent neutrophil adhesion) was administered preemptively, it reduced capillary stalling and recovered the CBF levels starting 40 minutes into the postictal period. Neither the antibody nor its isotype control affected the early component of vasoconstriction, suggesting that hypoperfusion is mediated by multiple mechanisms.

In search of a potential culprit among vascular adhesion molecules, the investigators identified a specific, 1.22-fold increase in the expression of intercellular adhesion molecule-1 (ICAM-1). This appears to be a small change, but the western blot analysis was conducted without prior isolation of blood vessels, suggesting that the actual magnitude of ICAM-1 induction was underestimated. Indeed, antibodies against the neutrophilic integrin receptor leukocyte function associated antigen-1 (LFA-1), which interacts with endothelial ICAM-1, recapitulated the effects of the Ly6C antibody. The latter finding supported the role of ICAM-1 in vascular clogging.

A limitation acknowledged by the authors was the selection of an acute seizure model which does not mimic chronic epilepsy. Yet it is plausible that the chronic inflammation of epilepsy would be associated with activation of vascular endothelial cells, thereby potentially leading to overexpression of vascular adhesion molecules.

Vascular clogs are not the only mischief of adhered neutrophils: in a previous study, neutrophil infiltration worsened hippocampal neurodegeneration in kainic acid-treated mice lacking adaptive immune cells (T- and B-cells). Moreover, invading neutrophils were engulfed by activated microglial cells, suggesting a neuroprotective role of both lymphocytes and microglia against neutrophil infiltration into the epileptic focus.[5] The neutrophil adhesion could be the first step of their invasion into the brain parenchyma in these mice. Whether a similar process could take place in epilepsy patients whose immune system is dysfunctional is unknown.

Go With the Flow

The diminished postictal CBF is expected to affect to the greatest extent the blood–brain exchange of compounds whose cerebral kinetics are flow-limited. Because the structural features of most anti-seizure medications (ASMs) allow them to cross the blood–brain barrier rapidly by passive diffusion,[6] they fall into this category. It is therefore expected that the target concentrations of ASMs given as rescue therapies would be higher if their maximal concentrations in plasma coincides with the phase of enhanced CBF during a seizure. Accordingly, the faster the drug is administered after seizure onset, the better the likelihood of its rapid and appropriate distribution within the seizure focus. This also holds true for intranasal therapies, whose distribution into the brain involves absorption from both the nasal cavity and the systemic circulation.

Lost in Translation?

The novel postictal neutrophil clogs, which have also been detected in preclinical models of Alzheimer's disease and stroke, are a good starting point for the development of new epilepsy therapies. Yet in translation from both rodents to humans and across diseases, better understanding of the novel target role in epilepsy and how therapies would affect it can minimize the risk of neutral or negative results of clinical trials. For instance, in the Enlimomab Acute Stroke Trial (EAST), an anti-ICAM-1 antibody was associated with increased patient mortality. In a post-trial study in a rat post-stroke model, administration of the antibody led to the production of host antibodies against ICAM-1 and activation of an inflammatory response.[7]

Misplaced leukocytes appeared in this journal 2 decades ago, with the seminal commentary by Annamaria Vezzani on brain inflammation and seizures.[8] Research has since advanced, with better understanding of the role of monocytes, T-cells, and other blood–borne components in epileptogenesis. Unfortunately, translation of this knowledge to effective therapies is complex because neuroinflammation is a heterogenous and dynamic process, which can vary from one condition, patient, or time point to the others. A recent example is the failure of the multiple sclerosis drug natalizumab to reduce seizure frequency in patients with drug-resistant focal epilepsy in the Phase 2 OPUS trial.[9] Natalizumab disrupts the interaction between the leukocytic α4-integrin and vascular cell adhesion molecule 1 (VCAM-1), which is likely more central in the pathophysiology of multiple sclerosis than in epilepsy.[10] The case of natalizumab suggests that in drug repurposing, initial comparative assessment across the respective diseases of drug targets and their mechanisms would support estimation of realistic efficacy endpoints and harm: benefit ratios. This should be kept in mind before established neutrophil-targeting drugs, from N-acetylcysteine to monoclonal antibodies, are considered for patients with epilepsy.

The study by Lim et al supports the notion that the end of the postictal state of a single seizure event may be just the beginning of a hazardous cascade. It is fascinating that novel pathways can still be discovered after 2 decades of research into the role of neuroinflammation in epileptogenesis. As with any other target, we need to well-understand what we do and why we do it before the assessment of neutrophil-modulating therapies in human epilepsy, to maximize success.

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Declaration of Conflicting Interests

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