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Potential implications of HCN channel dysfunction after subarachnoid hemorrhage

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Subarachnoid hemorrhage (SAH) most commonly occurs due to rupture of a cerebral aneurysm, and it is responsible for approximately a quarter of all cerebrovascular deaths. Although considerable advances have been made in the understanding of the pathophysiology of SAH and its complications, it is still associated with significant mortality (40% at 30 d) and morbidity (50% of survivors have long-term neurologic deficits). This high morbidity and mortality can be attributed to two distinct yet similar phenomena: early brain injury and delayed cerebral ischemia (DCI). Early brain injury occurs <72 h after SAH and is characterized by pathophysiological changes that result in global hypoperfusion, blood–brain barrier breakdown, cerebral edema, and neuronal cell death. DCI begins several days after the ictus and peaks ~7 d after SAH. DCI was initially attributed to vasospasm, a phenomenon characterized by delayed narrowing of large cerebral arteries. More recently, it has been recognized that in addition to vasospasm, several other factors, including cortical spreading depolarization (CSD), microvascular dysfunction, and microthrombosis, are important contributors to DCI and subsequent neuronal cell death (Macdonald et al., 2008).

Among the non-vasospasm contributors to DCI, much evidence from animal and human studies supports a critical role for CSDs (Dreier, 2011). In brief, CSDs are characterized by spreading waves of sustained depolarization in neurons that is initiated by a disturbance of the cellular electrochemical gradient. CSDs are normally accompanied by a hemodynamic response consisting of microvascular dilatation that aims to increase tissue perfusion and meet the energy demands of the cell. However, in damaged regions of the cerebral cortex, neuronal depolarization and blood flow become inversely coupled, leading to microvascular spasm instead of dilatation. This phenomenon exacerbates the energy crisis in neurons and ultimately results in cell death.

In an article recently published in *The Journal of Neuroscience*, Li et al. (2012) examined the contribution of hyperpolarization-activated cyclic nucleotide-gated (HCN) channels to neuronal hyperexcitability after SAH. The HCN channel family is comprised of four homologous members (HCN1–4) that differ functionally in their current activation kinetics and response to cAMP. Li et al. (2012) focused on the HCN1 subtype because CSDs are easily provoked in the neocortex and hippocampus, where HCN1 channels are abundant. They performed whole-cell clamp recordings on pyramidal neurons from CA1 in hippocampal slices to examine HCN channel activity, and they mimicked SAH by adding oxyhemoglobin to the perfusate. The authors also assessed the expression of HCN1 channels in tissue obtained from a rat SAH model involving endovascular perforation.

A principal finding of Li et al. (2012) was that infusion of oxyhemoglobin induced firing of pyramidal neurons in CA1, and that this neuronal hyperexcitability was mediated by oxyhemoglobin-induced inhibition of HCN channels. These findings are important for several reasons. First, this *in vivo* model builds upon previous *in vivo* studies (Dreier et al., 2000), which demonstrated that superfusion of hemoglobin onto the cortical surface in rats induced CSDs and neuronal death in the presence of high extracellular K+ or low glucose. The study by Li et al. (2012) is therefore an important addition to the growing body of evidence supporting neuronal hyperexcitability and CSD after SAH. Second, the finding is important because a significant proportion of long-term disability in patients who survive after SAH is related to cognitive impairment. Although the etiology of SAH-induced cognitive impairment is likely multifactorial and cognitive impairment in different domains may be observed in SAH patients (Mayer et al., 2002), altered spatial memory has been demonstrated in both humans and rat models of SAH (Mayer et al., 2002; Jeon et al., 2010). Given that the hippocampus (especially the CA1 region) plays a critical role in spatial memory, it is plausible that HCN channel dysfunction after SAH might contribute to cognitive impairment in SAH patients. This notion is supported by the findings that long-term potentiation in the hippocampal Schaffer collateral pathway is impaired after experimental SAH (Tariq et al., 2010), and that, under normal conditions, pharmacological blockade of HCN channels impairs long-term potentiation in this pathway (He et al., 2010). Nevertheless,
It is also important to understand the limitations of the work of Li et al. (2012). First, the authors used oxyhemoglobin to mimic the effect of SAH. It would be interesting to see whether similar results are obtained when the slice preparation is perfused with ACSF containing red blood cell lysate, an experimental paradigm that would more closely mimic the CSF milieu in SAH. Performing such an experiment is critical given that HCN currents (Ih) are increased with increasing extracellular K+ (Biel et al., 2009), and a perfusate containing red blood cell lysate would contain high levels of K+. An in vivo model would be even more likely to replicate events occurring during SAH. For example, one could perform electrophysiology on hippocampal slices obtained after induction of SAH in rats via endovascular perforation or other methods. Another improvement would be to perform intracellular recording in vivo after induction of experimental SAH. A second limitation of the study by Li et al. (2012) is that the authors examined only pyramidal neurons in the hippocampus. Although the hippocampus is important for learning and memory, a larger proportion of the long-term morbidity after SAH is due to cortical infarcts and subsequent sensorimotor deficits. Because several studies have demonstrated spreading depolarizations on the cortical surface in SAH patients, a logical next step would be to examine the function of HCN channels in pyramidal neurons of the cerebral cortex and understand their role in SAH-induced neuronal hyperexcitability and CSD. Examination of cortical neurons is also important given that alteration of HCN channel activity can have different consequences depending on the brain region and the net effect of different types of ion channels present in that particular neuronal population (Postea and Biel, 2011). A third limitation is that all the electrophysiology studies by Li et al. (2012) were performed on hippocampal slices from neonatal rats. However, SAH occurs primarily in adults, with a peak incidence of 45–55 years. Since it is well recognized that neural circuits and activity are different in adults than neonates, it is essential to examine whether the findings of this study are applicable to adults.

In summary, Li et al. (2012) provide compelling evidence to suggest that dysfunction of neuronal HCN channels may occur after SAH. Future studies need to be performed to establish this in an in vivo model of SAH, to characterize the subtype of HCN channels and brain regions involved, and to identify the functional consequences of HCN channel dysfunction. If the aforementioned studies are realized and cross-validated in different experimental models of SAH, modulation of HCN channel function may emerge as a new therapeutic strategy to attenuate SAH-induced neurovascular dysfunction.

References


