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EDITORIAL COMMENT

Targeting Muscles in the Brain to Enhance Cerebral Perfusion*

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Pound for pound, the brain is the most energy-consuming organ in the human body, requiring 20% of cardiac output but only weighing in at 3% of body weight. The energy demands of brain metabolism combined with its low intrinsic energy reserves impose a requirement of steady and constant blood supply to the brain as a whole, regardless of natural variations in arterial blood pressure. The homeostatic process by which arterioles dilate or constrict to maintain constant cerebral blood flow (CBF) over a large range of blood pressures is termed cerebral autoregulation. When this process is impaired, consequences can be dire (e.g., brain perfusion rises or falls at the mercy of systemic blood pressure fluctuations), leading to cerebral ischemia under conditions of relative hypotension, or blood-brain barrier breakthrough and cerebral edema under conditions of relative hypertension.

Cerebral autoregulation is regulated in part by passive mechanisms involving intrinsic responses of the smooth muscle cells (SMCs) to changes in transmural pressure in brain arterioles, termed the "myogenic response." Cerebral arterioles constrict by way of SMC contraction to increases in transmural pressure or dilate by way of SMC relaxation in response to decreases in transmural pressure. They are regulated by a variety of molecular signaling pathways, including cellular mechanosensors sensitive to stretch, intracellular ion levels, and second messenger systems.

Scores of disorders can impair cerebral autoregulation, leading to reduced CBF and varying degrees of brain injury. One such condition of immense public health significance is chronic heart failure (HF), the most common cardiovascular disease in the elderly, which results in decreases in cardiac output affecting all organs in advanced stages. The brain is particularly vulnerable for reasons discussed earlier but also because autoregulatory mechanisms may be affected by chronic HF. HF is associated with increases in cerebrovascular myogenic tone, resulting in decreased global CBF (1). This pathophysiological mechanism may in part explain the increasingly recognized complication of neurocognitive impairment in patients with HF (2).

Rodent models of ischemic HF have revealed some clues regarding the cellular and molecular mechanisms involved in this autoregulatory disruption. HF results in increased circulating levels of tumor necrosis factor (TNF), an inflammatory cytokine, with a strong inverse correlation with survival. Moreover, TNF expression is also increased in SMCs within the cerebral vasculature. TNF, in turn, triggers a cascade of signaling, including increased local bioavailability of sphingosine-1-phosphate (S1P), which signals via G-protein-coupled S1P receptors to release calcium from the sarcoplasmic reticulum and increase sensitivity to calcium signaling via RhoA/Rho kinase activation. These cascades augment myogenic response to a given transmural pressure, leading to an

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exaggerated autoregulatory curve and potentially compromised CBF. An important regulator of S1P metabolism in the cerebral vasculature is the cystic fibrosis transmembrane regulator (CFTR), better known for its role in chloride secretion in lung epithelium, which enhances S1P transport across the plasma membrane leading to its intracellular degradation and prevents it from engaging S1P receptor signaling (3). Indeed, down-regulation of CFTR has been identified as a critical mediator of TNF-α–induced increases in cerebrovascular myogenic tone in animal models of chronic HF.

SEE PAGE 940

It is difficult to conceive that chronic HF has common pathobiology with acute subarachnoid hemorrhage (SAH). However, in this issue of *JACC: Basic to Translational Science*, Lidington et al. (4) report not only a common pathobiology but a novel therapeutic target to treat cerebrovascular complications of these 2 very different diseases. In contrast to chronic HF, SAH is an acute emergency resulting from the rupture of a cerebral aneurysm and bleeding into the subarachnoid space surrounding the brain. This uncommon cause of stroke has a mortality rate of 30%, and 50% of survivors have long-term cognitive deficits. The largest treatable cause of poor SAH outcome is delayed cerebral ischemia (DCI), the development of new focal neurological deficits or deterioration in level of consciousness that results from a variety of causes, including vasospasm, microthrombi, and autoregulatory failure.

Previous work from Lidington et al. (5) has shown a remarkable similarity between cerebrovascular mechanisms leading to DCI after SAH and that observed after chronic HF in rodent experimental models. These studies have shown enhanced cerebrovascular myogenic response due to decreased CFTR expression, reversible by blocking TNF-α signaling. However, to avoid the wide-ranging side effects of TNF-α blockade, the authors (4) chose to target CFTR for several reasons: 1) its selective expression in cerebrovascular SMCs, making it a specific target for cerebrovascular myogenic tone; and 2) the availability of numerous drugs approved by the US Food and Drug Administration (FDA) that increase CFTR expression/activity with a favorable side-effect profile.

To demonstrate a causal link between CFTR activity and cerebrovascular myogenic tone, Lidington et al. (4) compared ex vivo posterior cerebral artery (PCA) myogenic tone between CFTR mutant mice ($CFTR^{\Delta f508}$) and wild-type mice. As expected, they found that PCAs in the mutant mice had augmented myogenic tone compared with PCAs in wild-type mice. In contrast, arteries derived from cremasteric muscles were unaffected by the CFTR mutation, suggesting that cerebrovascular arteries were selectively regulated by CFTR. Bulk blood flow measures confirmed this result in vivo: CBF was significantly reduced in CFTR mutant mice, whereas total peripheral resistance (mainly mediated by skeletal muscle vascular tone) and cardiac output were unchanged. These data suggest that CFTR activity is a selective driver of cerebrovascular myogenic tone, without apparent effect on other vascular beds.

To examine the efficacy of CFTR-targeted therapies on preclinical models of HF and SAH, the authors used 2 different small molecule CFTR interventions: 1) C18, a "CFTR corrector" that increases CFTR cell surface expression; and 2) lumacaftor, a C18 analogue that is FDA approved for the treatment of cystic fibrosis (4). After inducing ischemic cardiomyopathy and HF with permanent left anterior descending coronary artery occlusion resulting in myocardial infarction in mice, CFTR expression was decreased in the PCAs; this outcome was in parallel with augmentation in ex vivo PCA myogenic tone. In HF mice treated with C18, CFTR expression in PCAs was restored, as was ex vivo PCA myogenic tone. C18 had no effect on PCAs derived from CFTR knockout mice, confirming that CFTR was the target for the effect of C18. In vivo hemodynamic assessment showed a decrease in cardiac output and a small drop in arterial pressure following HF induction, as well as a marked reduction in CBF. C18 treatment increased CBF to levels comparable to those of sham-operated control mice. Again, this effect was exclusive of any effect on cardiac output or total peripheral resistance. Consistent with the salutary effects of C18 on CBF, mice also exhibited improvement in neurobehavioral tests; in particular, their performance on a novel object recognition task was restored to a level similar to that of sham-operated control mice. Morphometry of pyramidal neurons in the frontal cortex revealed that C18 attenuated dendritic atrophy and reduced dendritic spine density in the HF mice, providing histopathological correlates of the improved neurobehavioral tests.

A similar benefit was seen in a mouse model of SAH, induced by arterial blood injected into the chiasmatic cistern (4). In this model, cerebral artery myogenic tone increases and is maximal 2 days after ictus, mimicking the DCI observed in human SAH (albeit on a different time scale). Post-SAH reduction in CFTR protein expression in cerebral arteries was attenuated by C18 and lumacaftor treatment, as was ex vivo cerebral artery–augmented myogenic tone.

Post-SAH reductions in CBF also normalized after treatment with C18 and lumacaftor. C18 and lumacaftor reduced selective neuronal death (assessed by caspase-3 and Fluoro-Jade staining) in cortical regions and improved the modified Garcia neurological function scores comparable to those of sham-operated control mice.

Collectively, these studies show that CFTR is an important regulator of cerebral perfusion, acting by modulating cerebral myogenic tone. Importantly, its effects appear to be relatively selective for the cerebral vasculature, as CFTR-specific interventions did not alter myogenic tone in skeletal muscle or total peripheral resistance. This makes it an attractive target for a diverse array of disorders that disrupt cerebral autoregulation. Indeed, the authors show convincingly that CFTR corrector compounds C18 and lumacaftor normalize cerebrovascular reactivity, CBF, and neurobehavioral deficits in preclinical models of both HF and SAH (4). These are 2 very different diseases but with apparent overlap in vascular pathobiology. Lumacaftor is an especially attractive candidate drug because it is already FDA-approved and ripe for drug repurposing. But alas, cautious optimism is recommended, as the field of neurovascular protection is littered with numerous failed drugs and clinical trials. Thus, more rigorous preclinical testing is warranted using the STAIR (Stroke Therapy Academic Industry Roundtable Preclinical Recommendations) criteria (6) before engaging in clinical trials.

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