Cocoa, neurovascular coupling, and neurodegeneration

The good, the bad, and the ugly

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Though the human brain is only ~2% of body mass, it represents more than 20% of total body oxygen and energy consumption,[1,2] and the supply of blood to the active neurons must match their metabolic demand. Fortunately, the tight coupling between capillary endothelial cells, astrocytes, pericytes, and neurons—dubbed the neurovascular unit—ensures precise modulation of regional blood flow in response to local metabolic demand. This integration of supply and demand, termed neurovascular coupling (NVC), is critical to neurophysiologic health. Indeed, accumulating evidence shows an important role for cerebral vascular insufficiency in neurodegenerative diseases ranging from vascular cognitive impairment[3] to Alzheimer disease.[4] Therefore, targeting cerebral vascular pathology is a promising option for primary and secondary prevention of neurodegenerative diseases and subsequent cognitive impairments.

To this end, noninvasive assessment of NVC may have great utility for new innovations, and may provide a practical biomarker for proof-of-concept trials. NVC is already widely exploited as a biomarker, the best known example being functional MRI, in which the blood oxygenation signal represents increased blood flow to active brain regions, manifested as an increase in oxygenated hemoglobin. In this instance, the increased signal is a surrogate measure of the matching of supply to demand. However, the cost and methodologic complexity of task-based fMRI is impractical for clinical trials, and thus, innovative approaches to assessment of NVC are critical toward investigation of cerebral vascular pathology relative to specific cognitive functions.

In this issue of *Neurology*®, Sorond et al.[5] present a noninvasive method, demonstrating its utility as a biomarker in a pilot trial to explore the relationships among NVC, cerebral white matter (WM) integrity, cognitive function, and flavanol-rich cocoa consumption. Sorond et al. utilized middle cerebral artery (MCA) blood flow velocity measurements via transcranial Doppler (TCD) ultrasonography to assess NVC in cognitively intact older individuals. In particular, they measured MCA flow velocity during a control task with mostly motor and attentional demand (identify the letter "X" among a string of letters) and during a task with additional executive and working memory demands (2-Back task, identify a letter repeated every other letter). Subsequently, they used the ratio of change in flow velocity during the 2-Back task to that during the control task as the measure of NVC. Furthermore, the authors assessed integrity of WM tracts in a subset of volunteers via diffusion tensor imaging, and cognitive function in all participants. Consequently, they explored the relationships among NVC, cerebral WM integrity, and cognitive performance in a double-blind parallel-arm trial in response to flavanol-rich and flavanol-poor cocoa consumption for a month.

Intact NVC (defined as >5% increase in MCA blood flow during 2-Back task compared to that during control task) was associated with better executive function and with a more intact WM structure as evidenced by greater functional anisotropy and lower mean diffusivity. Perhaps more important, the latter association was most robust for WM hyperintensities, which may represent regions of small-vessel ischemia, and for frontal WM tracts, which may mediate important aspects of executive function. Thus, Sorond et al. demonstrate a convincing link among cerebral vascular function, structural integrity of the brain, and cognitive function, and showcase the remarkable potential for TCD ultrasonography as a biomarker for cerebral vascular pathology. While the authors did not find a difference in NVC or cognitive measures between the 2 treatment arms (flavanol-rich vs flavanol-poor cocoa), cocoa consumption improved NVC, as well as cognitive performance, in participants with impaired baseline neurovascular coupling (i.e., <5% blood flow responses to 2-Back task). Thus, regular cocoa consumption may be a strategy to minimize (perhaps even reverse) cerebral vascular pathology in neurodegenerative disorders, regardless of its flavanol content.

Though more work is needed to prove a definitive causative link among cocoa consumption, vascular pathology, and cognitive decline, the present study is a remarkable first step in several aspects. First, it demonstrates the practical utility of a simple, inexpensive, and noninvasive technique for measuring NVC in clinical research. While its spatial resolution is limited to

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large vessels, such as MCA or anterior cerebral artery, TCD affords considerable advantages over alternative methodologies for measuring brain blood flow during cognitive tasks, such as functional MRI. Second, the study shows a physiologic association of differences in cerebral blood flow responses during an executive function with frontal WM hyperintensities, which reflect small-vessel ischemia in brain regions associated with executive function. This association provides evidence for structural-functional correlation and represents an important validation for the link between vascular and cognitive function. In addition, the observation that a TCD measure of large-vessel brain blood flow is correlated with small-vessel brain ischemia is important because noninvasive methods for measuring the latter directly are valuable but may be difficult to develop. Third, this study demonstrates the utility of NVC as a biomarker of vascular function for clinical trials that target vascular interventions. For example, their observation that impaired NVC at baseline is associated with improved cognitive and neurovascular function after cocoa consumption is the type of biomarker that could guide proof-of-concept trials of cocoa or similar agents. Fourth, from a clinical aspect, this study suggests that vascular effects of cocoa may not be due to its flavanol content. There has been considerable interest in the development of polyphenols including flavanols as vascular interventions for neurodegenerative disease either as single chemical entities (such as epicatechin and resveratrol[6]) or as components of nutriceuticals such as cocoa,[7,8] but the results of this pilot trial argue against this hypothesis.

AUTHOR CONTRIBUTIONS

Paul B. Rosenberg: drafting/revising the manuscript, study concept or design. Can Ozan Tan: drafting/revising the manuscript.

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