Cocoa Flavanols, Cerebral Blood Flow, Cognition, and Health: Going Forward

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The articles in the issue provide important evidence for the acute effects of cocoa flavanols on the peripheral vascular response in humans. As Hollenberg and Luscher point out, "not only does flavanol-rich cocoa-induced nitric oxide production show a dramatic influence on blood vessels in healthy individuals, preliminary information available indicates that the influence on nitric oxide synthesis is evident in patients with advanced atherosclerosis, hypertension, or diabetes mellitus."[1]

Blood flow, of course, also has a fundamental role in brain function. Neuroimaging techniques designed to measure aspects of cerebral blood flow (CBF)—such as functional magnetic resonance imaging (fMRI), which is based on the increase in blood flow accompanying neural activity in the brain—have amply demonstrated the critical relationships of cerebrovascular responses and cerebrovascular health to human cognitive[2] and emotional[3] functions. The article by Francis et al[4] in this issue provides some of the first evidence that flavanol-rich cocoa can affect CBF in humans. Using blood oxygenation level-dependent (BOLD) fMRI they observed an increase in relative blood flow in brain areas subserving a cognitive switching task in 16 healthy young adults. Equally interesting are their findings from a pilot study on 4 healthy young adults in which arterial spin-labeling sequence (ASL) magnetic resonance imaging (MRI) was used to assess the time course of a single serving of flavanol-rich cocoa on brain blood flow. This study showed that flavanol-rich cocoa could acutely increase CBF in gray matter, suggesting it may have potential for the treatment of cerebrovascular deficits. The reason these data are important for documenting the effects of flavanol-rich cocoa on CBF is because unlike BOLD fMRI, arterial spin-labeling perfusion MRI technique provides a direct quantitative measure of CBF using arterial blood water as an endogenous contrast agent. With excellent reproducibility over long-term time periods[5,6] and minimal sensitivity to magnetic-field inhomogeneity effects,[7] perfusion fMRI is ideal for imaging the time course of flavanol-rich cocoa effects, and permitting comparisons of CBF before and after consumption of flavanol-rich cocoa. Perfusion fMRI also has reduced scanner noise level and reduced sensitivity to subject motion.[8] Figure 3 in Francis et al[4] illustrates the usefulness of arterial spin labeling MRI for tracking the temporal effects on CBF of an acute dose of high flavanols cocoa drink relative to the effects of a low flavanols cocoa drink. These data leave little doubt that quantitative neuroimaging methods (eg, arterial spin-labeling perfusion fMRI, positron-emission tomography, transcranial Doppler ultrasound) should be the techniques of choice for future studies of flavanol-rich cocoa effects on CBF.

Evidence that flavanols increase CBF is a key step in demonstrating their action in the cerebrovasculature, but ideally 1 would also hope to see changes in the functional status of brain, especially because increases in blood flow to neuronal vasculature accompany increases in neural activity in the brain.[2] This is the reason that functional MRI is such a popular and useful tool in the burgeoning area of cognitive neuroscience. Why then, were Francis et al[4] able to measure greater changes from the high flavanols cocoa drink (relative to the low flavanols cocoa

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Time and effort devoted to this paper were supported by Mars Inc. and the Institute for Experimental Psychiatry Research Foundation.
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drink) in the BOLD fMRI signal in areas of the brain that are known to subserve the switching task their healthy subjects performed in the scanner, without seeing changes in actual cognitive performance on the switching task? They discuss this issue and point out that in healthy adults performing near optimum on the switching task, the BOLD changes might have had neurobehavioral effects not evident in the task measures or not capable of being seen in high-performing healthy people. In other words, the selection of cognitive tasks used to assess flavanol-rich cocoa, the dependent metrics selected to index task performance, and the nature of the experimental design can have substantial consequences for detecting overt neurobehavioral performance changes. There is no doubt about these complications, and they warrant some discussion of the appropriate approach to finding neurobehavioral measures of the functional effects of flavanol-rich cocoa (whether or not they are mediated via CBF or cerebral flow velocities).

Rather than study the effects of flavanol-rich cocoa on difficult tasks with ceiling effects in healthy adults, future neurobehavioral studies of flavanol-rich cocoa might do better to use high-sensitivity measurements of basic cognitive functions (eg, attention, psychomotor vigilance, cognitive throughput, working memory), and tests of executive functions. This approach has proven useful in identifying the neurocognitive changes induced by ginseng,[9] caffeine[10] and some herbs.[11,12] It has considerable acceptance and face validity, and it can work well if healthy young adults are tested when somewhat impaired by fatigue, workload, or other factors—in these studies the intervention is evaluated for the extent to which it recovers function or protects against further deterioration in performance. A few more well-designed studies in healthy adults will be required to resolve whether or not the effects of flavanol-rich cocoa on CBF extend to functional changes in neuronal activity or whether they are confined to the vascular activity without affecting neurobehavioral capability.

The approach of using simpler more temporally accurate measures of nervous system speed (psychomotor and cognitive) to evaluate the neurobehavioral benefits of flavanol-rich cocoa is also appropriate when it comes to aging and CBF. Aging is marked by reductions in CBF[13] and speed of cognitive processing,[14,15] although few studies have assessed both domains simultaneously or their interrelationship in healthy elderly subjects.[16] Speed measures are more important than accuracy measures in assessing cognitive deficits and enhancements in the elderly, because the inherent bias of the human brain is to maintain accuracy at the expense of speed, and aging (at least healthy aging) is marked more by changes in speed than in accuracy. The digit symbol substitution task (DSST) has been consistently shown to reflect age-related changes in cognitive throughout.[14,15] It is also associated with status of diabetes.[17] Among the elderly, DSST performance has been found to be positively associated with motor performance (especially gait),[18] suggesting the DSST can serve as a general index of neurobehavioral capability in those in their seventh to ninth decades. The DSST should be considered as 1 of the tests to be targeted for evaluating the cognitive benefits of flavanol-rich cocoa in the elderly; vigilant attention (psychomotor vigilance)[19] is another test that is age-sensitive and could be of use in assessing effects of flavanol-rich cocoa on neurobehavioral functions.

Whether or not cognitive benefits from flavanol-rich cocoa are documented, I agree with Francis et al[4] when they conclude that "The fact that flavanol-rich cocoa has been shown to increase blood flow to key areas of the brain, suggests the potential for treatment of vascular impairment, including dementia and strokes, and thus for maintaining cardiovascular health." Improving blood flow in the body is considered clinically important because of the prevalence of diseases involving vascular health, and this is no less true of the brain, especially in the elderly, where peripheral vascular and cerebrovascular disease are responsible for significant loss of quality of life and an increase in mortality.

The report by Fisher et al[20] offers preliminary evidence on the basis of the transcranial Doppler ultrasound (TCD) that flavanol-rich cocoa could increase mean flow velocity in the middle cerebral artery in healthy subjects. Like Francis et al[4], they also provide pilot data using a more sophisticated quantitative measure—gadolinium perfusion MRI—that 1 week of flavanol-rich cocoa was associated with increased CBF. They report that decreased cerebral perfusion in the elderly has been associated with dementia, raising the prospect of studies aimed at determining whether flavanol-rich cocoa could retard the development of vascular dementia in the elderly. Prevention studies can be costly and would have to be predicated on a firm empirical base of evidence that flavanol-rich cocoa can have reliable clinical effects on CBF. More work on the effects of flavanol-rich cocoa in well-defined elderly groups is needed.

The intriguing evidence presented by Fisher et al[20] and Francis et al[4] suggests that the acute effects of flavanol-rich cocoa on cerebral vascular dynamics are definitely worth efforts to replicate and extend the empirical database on their reliability, magnitude and time course—just as the acute effects of flavanol-rich cocoa on peripheral circulation were firmly established via replication over the past few years. If the effects of flavanol-rich cocoa on CBF replicate, as hypothesized, dose-response studies will be needed (and ultimately perhaps clinical trials) to move forward to evaluate the extent of the health-related benefits derived from flavanol-rich cocoa. The challenges at this stage, however, are to determine if the effects of flavanol-rich cocoa on CBF replicate in larger numbers of subjects, to establish if they translate to functional benefits in the form of enhanced cognitive responses in healthy adults, and to enhance understanding of how they might improve the neurobehavioral or medical status of the aged population at risk for developing vascular dementia.

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