Cocoa, Even With Few Flavonoids, Boosts Cognition

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Drinking cocoa, whether rich in flavonoids or not, appears to boost the effect of blood flow on neuronal activity in the brain, known as neurovascular coupling (NVC).

A new study shows not only that drinking flavonoid-rich or flavonoid-poor cocoa improves NVC but also that higher NVC is associated with better cognitive performance and greater cerebral white matter structural integrity in elderly patients with vascular risk factors.

As researchers search for ways to detect dementia at the earliest possible stage, the study results could pave the way for using NVC as a biomarker for vascular function in those at high risk for dementia, said lead author Farzaneh A. Sorond, MD, PhD, Department of Neurology, Stroke Division, Brigham and Women's Hospital, Boston, Massachusetts.

"Our study shows that NVC is modifiable and can be enhanced with cocoa consumption," said Dr. Sorond.

The study is published online August 7 in *Neurology*.

Tight Correlation

The double-blind proof-of-concept study included 60 community-dwelling participants, mean age 72.9 years. About 90% of the participants were hypertensive, but with well-controlled blood pressure, and half had diabetes mellitus type 2 with reasonably good control. Three quarters were overweight or obese.

Dr. Farzaneh A. Sorond

Participants were randomly assigned to 2 cups a day of cocoa rich in flavonoids (609 mg per serving) or cocoa with little flavonoids (13 mg per serving). Diets were adjusted to incorporate the cocoa, each cup of which contained 100 calories. Participants were also asked to abstain from eating chocolate.

Researchers measured cerebral blood flow in these participants using transcranial Doppler ultrasonography. Among other things, they documented changes in the middle cerebral artery and blood flow velocity at rest and in response to cognitive tasks (NVC).

The study showed that NVC was tightly correlated with cognition; scores for Trail making Test B, a test of executive function, were significantly better in those with intact NVC (89 seconds vs 167 seconds; *P* = .002). Participants with intact NVC also had significantly better performance on the 2-Back Task, a test for both attention and memory (82% vs 75%; *P* = .02).

"The higher you increase your blood flow during a cognitive task, the better your cognitive performance," commented Dr. Sorond, adding that this is something that has never been shown before.

NVC was also correlated with cerebral white matter structural integrity. Higher NVC was associated with overall less white matter macro- and micro-structural damage. In general, those with intact NVC had a greater volume of normal white matter and smaller volume of white matter hyperintensities, higher fractional anisotropy, and lower mean diffusivity in the normal white matter and WMH.

Therapeutic Target

These results suggest that NVC could be an important therapeutic target. But before NVC can be considered a biomarker, it has to be shown to be changeable, and the clinical importance of the modification must be shown.

To that end, the study authors opted to use cocoa. They could have chosen many other potential modifiers but chose cocoa because the literature has shown the beneficial effects of cocoa on brain health and also because it's something that many people enjoy, said Dr. Sorond.

The study found that blood pressure, blood flow, and change in NVC were not significantly different between the 2 cocoa groups. In the combined cocoa groups, 30-day blood pressures were not significantly different from baseline (*P* > .5).

In contrast, response to cocoa differed significantly depending on NVC status. Cocoa had a significant effect on NVC in those with impaired (<5%) coupling at baseline. Of those with impaired NVC, 89% responded to 30 days of cocoa consumption and increased NVC compared with only 36% of those with intact NVC (*P* = .0002). In those with impaired baseline coupling, cocoa consumption was associated with an 8.3% (*P* < .0001) increase in NVC at 30 days.

The effect of cocoa consumption on Trail B scores was also significantly dependent on NVC status.

The authors were surprised at the lack of effect of flavonoids because previous research had indicated a dose-response with respect to cognitive performance. It could be something other than flavonoids in the cocoa, possibly caffeine, that improves NVC, or it could be that the 13 mg in the low-flavonoid cocoa group was enough to have an effect.

"I think there are effects of flavonol on brain blood flow no matter how low it is," said Dr. Sorond, adding that perhaps only a tiny amount is needed to activate an enzyme or some other trigger.

It's important to identify the component or mechanism, whatever it is, because just telling patients to drink cocoa could be risky, said Dr. Sorond. "Patients with diabetes or hypertension really don't need the extra sugar, extra calories, and extra fat that come with it."

Dr. Sorond thinks NVC could be measured in high-risk patients seen in the clinic. "I think this could be an easy, in-clinic quick test of vascular brain function that pertains to cognitive performance."

The ideal next step would be to carry out a larger study in patients with mild cognitive impairment that includes more detailed cognitive profiles and more control groups. "We need a cocoa arm; we need a caffeine arm; we need maybe other arms, to make sure that we understand this, and maybe look at some of the metabolites in the blood as a result of cocoa consumption that correlates with these things," said Dr. Sorond.

Remarkable First Step

In an accompanying editorial, Paul B. Rosenberg, MD, associate professor of psychiatry and behavioral sciences, Johns Hopkins School of Medicine, Baltimore, Maryland, and Can Ozan Tan, PhD, Harvard Medical School, Boston, write that in many ways, the study represents a "remarkable first step."

For one thing, it demonstrates the practical utility of a simple, inexpensive, and noninvasive technique for measuring NVC that has several advantages over functional MRI and other means of measuring blood brain flow during cognitive tasks.

In demonstrating a link between NVC and cerebral white matter structural integrity, the study provides an important validation for the association between vascular and cognitive function, according to Dr. Rosenberg.

The study demonstrates that NVC "hangs together" as a measure of vascular function, which could be used in studies targeting vascular interventions, said Dr. Rosenberg in an interview with *Medscape Medical News*. In this way, he added, the study is "promising for the development of new treatments for vascular dementia."

The study suggests that the vascular effects of cocoa are not due to its flavonol content, noted Dr. Rosenberg."It could be a placebo effect."

Dr. Rosenberg pointed out several strengths of the study, including its relatively large size for a pilot study and its "well-chosen" measures.

Among its weaknesses are that it's not a placebo-controlled study and the hypothesis that flavonoid-rich cocoa would work better than flavonoid-poor cocoa didn't pan out. The study may also not have been long enough, said Dr. Rosenberg. "It's nice to see a drug work for 30 days, but you really need a longer study."

The study didn't include patients with mild cognitive impairment who are at risk of developing dementia, which Dr. Rosenberg sees as another weakness. "It's one thing to show an effect in cognitively healthy older people; it's a very different thing to show an effect in people who have a brain disease," he said.

The Alzheimer's Association also sees weaknesses in the study. Not only is it a very small and very preliminary study, but it was also not well designed as a test of an intervention or therapy because it didn't include a control group for comparison with the group that drank cocoa, said Maria Carrillo, PhD, Alzheimer's Association vice president of medical and scientific relations.

Further, said Dr. Carrillo, it didn't appear that other factors that could possibly affect brain blood flow and/or cognition were controlled for, tracked, or accounted for in the study.

"There is no information on what else the 18 people with impaired cerebral blood flow did during the trial that might have improved their cerebral blood flow or cognitive performance: exercise, for example. A well-designed intervention trial anticipates, tracks, and accounts for these possible confounding factors to help ensure the credibility of the findings."

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