Editorial

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Cocoa flavanols and cognition: regaining chocolate in old age?[1–3]

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The relation between the human brain and food is a complex one that involves 2-way communications. On the one hand, the functional status of brain circuits determines how homeostatic, reward, and cognition-related information is processed and ultimately integrated to support adaptive eating behavior. On the other hand, nutrients that are present in foods also exert effects on the brain. A more detailed understanding of the latter pathway (i.e., the food-to-brain connection) and the identification of specific nutrients mediating such effects can pave the way for the design of nutritional interventions to promote brain and cognitive health.

Foods rich in flavonoids, an extensive family of plant-derived nutrients, have been under investigation over the past 2 decades for their antioxidant properties, cardiovascular benefits, and more recently, their potential capacity to support cognitive function (1). Among them is chocolate and, in particular, cocoa. In its natural, nonalkalized form, cocoa contains high amounts of a subtype of flavonoids called flavanols, mainly epicatechin, catechin, and their oligomers. Laboratory studies have shown that these compounds can benefit brain function via mechanisms that include activation of intracellular signaling pathways related to neuronal plasticity, changes in cerebrovascular function, and protection from neurotoxins and neuroinflammation (1, 2). Although experimental data are extensive, research in humans has been scarce to date, with only a few interventional studies [e.g., reference 3].

In this issue of the Journal, Mastroiacovo et al. (4) provide new evidence that daily consumption of cocoa flavanols can improve cognitive function in healthy, cognitively intact elderly individuals. The authors randomly assigned 90 subjects into 3 groups that received a daily drink containing either low (48 mg), intermediate (520 mg), or high (993 mg) amounts of cocoa flavanols. Importantly, the remaining composition of the drink, including caffeine and theobromine, was well matched across the 3 conditions. After 8 wk, participants assigned to the intermediate– and high–cocoa flavanol intake group showed a clear improvement in performance in neuropsychology tests that measure attentional/executive function and semantic memory and which are sensitive markers of cognitive decline and dementia. Participants also improved in a list of cardiometabolic variables, including blood pressure, insulin resistance, lipid profile, and a marker of oxidative stress. This study extends the results of a closely related trial in individuals with mild cognitive impairment (MCI) (5) to older adults with no evidence of cognitive impairment. When combined, this body of data supports the idea of including flavanol-rich cocoa products in the diet of this population, starting before cognitive decline occurs. However, replication of these results is warranted, and it has not yet been shown whether regular consumption of these nutrients could alter the onset or natural history of MCI and dementia. The durability of the effects beyond the intervention period also remains unknown, even though participants were tested ~24 h after the last drink. Future studies need to examine these relevant questions in longer-lasting clinical trials.

The study also offers some insights on potential mechanisms linking cocoa flavanols with cognition. As the authors noted, the largest contribution to cognitive improvements came from changes in insulin sensitivity, accounting for 17% of the effects in the current study and 40% in the previous study in subjects with MCI. Changes in blood pressure and oxidative stress accounted for only a small portion (~3–4% each). Because the study did not include acute or intermediate time points, it is difficult to determine whether the effects were driven by direct actions of cocoa flavanols or, rather, indirectly through improvements in cardiovascular function over time or by other changes in health. Cocoa flavanols affect both insulin sensitivity and endothelial vascular function through reciprocal mechanisms that involve nitric oxide (6, 7), and similar mechanisms may occur in the cerebrovascular system. Short-term interventions with flavanol-rich cocoa in elderly volunteers reported improvements in cerebral blood flow (8) and neurovascular coupling (9), a variable that reflects the coordination between neuronal activity, hemodynamic factors, and cellular interactions (10). As basic research continues to examine the specific action of cocoa flavanols in these pathways and the relation with the brain, there is a need to integrate more measures of cerebrovascular physiology and functional neuroimaging in future human studies.

Overall, this study is also of general interest as an example of a well-designed nutritional intervention with high potential. With the generation of baby boomers reaching advanced ages, and the rates of Alzheimer disease expected to triple by 2050, there is a need to identify nutrients that, in combination with other treatments, can

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help sustain brain and cognitive health and potentially reverse the impact of aging and dementia. The study by Mastroiacovo et al. (4) suggests that even at an intermediate intake of cocoa flavanols (~500 mg/d), there can be significant benefits in older individuals without cognitive impairment. Optimal intakes remain to be determined, and this may be difficult when other sources of these phytochemicals coexist (e.g., red wine, fruit, or tea). It is of note that this study was conducted in a Mediterranean country, Italy, and over a typical habitual intake of flavanols.

According to USDA databases, 100 g of dark chocolate contains ~100 mg of flavanols, an amount that doubles in the case of unsweetened baking chocolate and can reach up to 250 mg in 100 g of unsweetened cocoa powder that has not been processed with alkali (11). Finding new ways of preserving and enhancing flavanols in cocoa and chocolate while balancing energy content will contribute to optimize sources of these nutrients in the diet. Such improvements can lead to renovated uses of these ancient foods in the future.

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