The beneficial vascular effects of cacao flavanols: having your cake and eating it too

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A significant number of epidemiological studies report on the apparent beneficial effects of chocolate (i.e., cocoa) consumption on cardiovascular health, including reductions in morbidity and mortality (1, 2, 4). However, these reports are mostly of retrospective nature and do not demonstrate causality. Thus the need to implement well-designed prospective studies that unequivocally demonstrate a link between chocolate consumption and beneficial cardiovascular effects. These studies would need to take into account the variable and complex nature of cocoa product composition, since many of its constituents are known to have cardiovascular effects. Optimal trial design would test products with a defined composition that vary only the concentration of suspect bioactive molecules.

In this issue of the Journal of Applied Physiology, Monahan et al. (3) report on the results of a randomized, double-blind, placebo-controlled study indicating that acute cocoa ingestion dose dependently increases brachial artery flow-mediated dilation in healthy older adults. It is well known that in older individuals vascular reactivity is diminished partly due to endothelial dysfunction. Thus approaches that can restore normal endothelial reactivity if sustained over time, are likely to translate into improved cardiovascular health. The population studied (23 subjects) were of an average age of 63 yr and normotensive. The study utilized five different formulations of a low-calorie (~100 kcal) cocoa beverage, where most of the constituents (except total polyphenol, flavan-3-ols, and procyandins content) were held constant. As polyphenol content increased (from 330 to 1,470 mg), the concentration of suspect bioactive molecules (the flavanols catechin and epicatechin) also increased. Concentrations varied from 0 to 48 mg of catechin and 0 to 96 mg of epicatechin. In a random and blinded manner, all of the subjects were provided each of the five different formulations, thus generating responses that should be internally consistent. Beverages were only given once, thus the responses generated were of acute nature.

Results from this study demonstrate that cocoa beverages containing 420 mg of polyphenols or more led to dose-dependent increases in vascular reactivity that were evident by 1 or 2 h after ingestion. The study also reports on the relationship between serum epicatechin levels and vascular responses at 1 and 2 h showing modest but significant correlations. Results are interesting at several levels; first, the dose of cocoa required to trigger significant effects was actually quite low (5 g = ~1 tablespoon). As the dose increased, effects became more prominent (but not quite increasing in a linear fashion). As common chocolate products are high in calories, the observation that low doses of cocoa are sufficient to trigger vascular responses is encouraging. Interestingly, many of the reports on the protective cardiovascular effects of dark chocolate consumption (which typically has a high flavanol content) associate beneficial outcomes with the modest intake of such products (4). It should be noted that the most common types of chocolate products (i.e., milk chocolates), for all practical purposes, have an extremely low polyphenol content and have not been associated with beneficial cardiovascular effects (such as noted for the placebo beverage used in this study, which was formulated as a cocoa-free beverage). Second, by measuring the serum levels of epicatechin the authors were able to establish a correlation between the blood levels of this flavanol and flow-mediated dilation. Indeed, a specific epicatechin stereoisomer, (−)-epicatechin has been identified as the likely mediator of vascular effects (5). Third, this relatively simple study design can be readily adapted to study populations of patients suffering from endothelial dysfunction-related diseases to assess the effects that the consumption of epicatechin-rich cocoa products have on vascular function. This study also opens up the spectrum of pursuing long-term dosing studies to assess the effects that the sustained consumption of cocoa products have on vascular reactivity of normal (e.g., senile) and diseased populations. Well-designed studies of this type would also help to identify the mechanistic underpinnings of vascular actions, optimal dosification schemes, and the duration of effects.

It should be noted that the addition of (−)-epicatechin to cultured human coronary artery endothelial cells (HCAEC) leads to a time- and dose-dependent increase in endothelial nitric oxide synthase (eNOS) activation, leading to increases in nitric oxide (NO) levels (6). Thus NO is likely the main mediator of the vascular effects reported by Monahan et al. The effects noted in HCAEC were consistent with the apparent existence of an (−)-epicatechin receptor as evidenced by the reliance of responses on cell membrane associated G proteins. Effects were dependent on phospholipase C, calcium calmodulin-dependent kinase II, and induced increases in intracellular calcium resulting in changes in the phosphorylation status of key eNOS residues leading to its enhanced activation. Interestingly, (+)-catechin was only partially able to stimulate NO production. This result suggests that cocoa products enriched for the flavanol (−)-epicatechin may be seen as superior in their capacity to induce beneficial vascular effects.

The results from Monahan et al. (3) and previous studies make a strong case for the use of cocoa products rich in flavanols as a means to improve overall health. The associ-
ation of chocolate consumption with a 37% reduction in cardiovascular disease as reported by Buitrago-Lopez et al. (2) sets the stage for the reconsideration of cocoa products as potentially healthy like those recognized for red wine and olive and fish oils. However, the conveyance of this message needs to be clearly linked with the consumption of modest amounts of low-calorie (−)-epicatechin-rich cocoa products. Altogether, the cumulative evidence generated for the beneficial effects of the consumption of cocoa (i.e., flavanol)-rich products need to be validated in large, prospective, and well-designed trials and epidemiological studies. Studies such as the one by Monahan et al. (3) represent a step in the right direction.

DISCLOSURES
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AUTHOR CONTRIBUTIONS
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