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File: ■ Cocoa (*Theobroma cacao*)
■ Flavanols
■ Blood Pressure
■ Superoxide Anion

HC 031122-427

Date: June 30, 2011

RE: Review of Cocoa Flavanol Literature Shows that Blood Pressure-lowering Effects May Be Due to Modulation of Nitric Oxide and Superoxide Anion

Fraga CG, Litterio MC, Prince PD, Calabró V, Piotrkowski B, Galleano M. Cocoa flavanols: effects on vascular nitric oxide and blood pressure. *J Clin Biochem Nutr.* 2011;48(1):63-67.

The beneficial effects of fruits and vegetables on cardiovascular health have been ascribed to their content of flavonoids, according to epidemiological studies. Among many effects, flavonoids influence nitric oxide (NO), which regulates vascular homeostasis and thereby the blood pressure. By reviewing the literature on cocoa flavanols in particular, this paper presents evidence for the role of flavanols in regulating NO bioavailability and blood pressure through the modulation of superoxide anion production.

NO is formed from L-arginine through the action of the enzyme nitric oxide synthase (NOS). To fulfill its most important physiological effect, NO reacts with guanylyl cyclase to dephosphorylate guanosine triphosphate (GTP) to cyclic guanosine monophosphate (cGMP), which acts as a second messenger signaling smooth muscle relaxation in the vessels. Alternatively, NO can react with superoxide anion, which oxidizes it and thereby converts it to peroxynitrate, capable of cellular oxidative damage. This alternative removes NO from circulation and thereby can modulate its steady state concentrations. The main sources of superoxide anion in mammalian cells are the electron transport chain in the mitochondria and nicotinamide adenine dinucleotide phosphate-oxidase (NADPH oxidase, or NOX) in the endothelial cells. Superoxide anion from the latter source diffuses into the vessels, and this is where it reacts with NO.

Cocoa (*Theobroma cacao*) contains large amounts of flavan-3-ols, or flavanols, a complex subfamily of flavonoids that include monomers, oligomers, and polymers called procyanidins. In cocoa, the most physiologically important flavanols are (-)-epicatechin (EC), (+)-catechin, and procyanidins. When processed into chocolate, EC is the main flavanol present regardless of the process. Metabolic studies have shown that EC

passes through the stomach and is absorbed in the small intestine and can be measured in the blood following consumption of chocolate or cocoa products.

The effects of cocoa and chocolate on blood pressure have been shown in epidemiological studies of groups with lower blood pressure that could be attributed to their intake of cocoa[1] as well as intervention trials with various populations (normotensive – young, old, overweight, hypercholesterolemic; prehypertensive; hypertensive stage I; and hypertensive with impaired glucose tolerance) and several meta-analyses. Most of the intervention studies and meta-analyses showed a decrease in blood pressure due to cocoa or chocolate intake. The blood pressure-lowering effects were correlated with increases in NO in plasma and urine; improvements in flow-mediated dilation (FMD), indicating improved vascular function; and reduced oxidative stress. There is, however, a difficulty in comparing results of these studies as the cocoa and chocolate preparations used are not standardized.

The authors contend that animal studies in which purified compounds are used can circumvent this problem, and in fact, those using purified EC did show a correlation with improved blood pressure. However, most other animal studies either used flavanol-enriched cocoa, which presents the same standardization problems as when used in humans, or purified (+)-catechin, which is found in negligible levels in cocoa and chocolate.

Sufficient NO bioavailability is associated with normal vasodilation and blood pressure, while lowered NO concentrations lead to impaired vasodilation and elevated blood pressure. There are several ways in which cocoa flavanols could influence the steady state levels of NO in the vasculature positively: 1) decrease levels of superoxide anion in cells by direct antioxidant activity; 2) prevent production of superoxide anion by modulating NOX activity; 3) increase NO production via up-regulation of NOS; 4) decrease levels of other free radicals (reactive oxygen species [ROS]) via various metabolic pathways; 5) decrease levels of superoxide anion by preventing a NOS-related pathway that releases large amounts of superoxide anion; and 6) preservation of the arginine pool, the precursor of NO production, via down regulation of arginase, an enzyme which metabolizes arginine.

Since the concentrations of flavanols reached in the vasculature are not high enough to exert antioxidant effects (as purported in [1] above), the authors suggest that more specific interactions with proteins or lipids (as purported by [2-6] above) are more likely to be responsible for the beneficial effects. In vitro evidence supporting these mechanisms is presented to show that cocoa flavanols may exert their blood pressure-lowering effects via modulation of NO and superoxide anion.

—Risa Schulman, PhD

Reference

[1]Buijsse B, Feskens EJ, Kok FJ, Kromhout D. Cocoa intake, blood pressure, and cardiovascular mortality: the Zutphen Elderly Study. *Arch Intern Med.* 2006 Feb 27;166(4):411-417.

Referenced article can be found at
http://ukpmc.ac.uk/backend/ptpmcrender.cgi?accid=PMC3022066&blobtype=pdf.