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Review

Chocolate and the brain: Neurobiological impact of cocoa flavanols on cognition and behavior

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ABSTRACT

Cocoa products and chocolate have recently been recognized as a rich source of flavonoids, mainly flavanols, potent antioxidant and anti-inflammatory agents with established benefits for cardiovascular health but largely unproven effects on neurocognition and behavior. In this review, we focus on neuromodulatory and neuroprotective actions of cocoa flavanols in humans. The absorbed flavonoids penetrate and accumulate in the brain regions involved in learning and memory, especially the hippocampus. The neurobiological actions of flavanols are believed to occur in two major ways: (i) via direct interactions with cellular cascades yielding expression of neuroprotective and neuromodulatory proteins that promote neurogenesis, neuronal function and brain connectivity, and (ii) via blood-flow improvement and angiogenesis in the brain and sensory systems. Protective effects of long-term flavanol consumption on neurocognition and behavior, including age- and disease-related cognitive decline, were shown in animal models of normal aging, dementia, and stroke. A few human observational and intervention studies appear to corroborate these findings. Evidence on more immediate action of cocoa flavanols remains limited and inconclusive, but warrants further research. As an outline for future research on cocoa flavanol impact on human cognition, mood, and behavior, we underscore combination of functional neuroimaging with cognitive and behavioral measures of performance.

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1. Introduction

Cocoa products and especially, chocolate has taken a special place in our daily life and culture. This *food of the gods* as tells its Latin name *Theobroma cacao* given by the noted Swedish nosologist Carl Linnaeus in 1753, has been ennobled in many countries around the globe as a curative drug, a culinary delight, and even a currency for commodity trading, retaining its appeal over the centuries. No

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other natural product but chocolate has ever been viewed as having a positive effect on a wide variety of health conditions ranging from intestinal and female complaints, fever, and cardiovascular diseases to promotion of strength before military and sexual conquests (Wilson, 2010; Wolfe and Shazzie, 2005). Reports on chocolate's health benefits are dated back as far as Aztec and Maya medical practice (e.g., Hurst et al., 2002) and ever since, anecdotal evidence has been abundant on chocolate effects on health. Only by the end of the 20th century, however, claims on supposed health benefits of chocolate have increasingly drawn a scientific interest in cocoa products and chocolate, which eventually resulted in an approval by the European Food Safety Agency (EFSA, 2012) of a health claim for dark chocolate with high flavanol content as to its impact on "maintenance of normal endothelium-dependent vasodilation".

Most studies so far have been conducted on the effects of chocolate intake on the cardiovascular system, cholesterol concentrations, the release of neurotransmitters anandamide and serotonin, and on the health-related properties of high-quality dark chocolate, containing the stimulants theobromine and caffeine (Lamuela-Raventós et al., 2005; Katz et al., 2011). Dark chocolate also comprises high concentrations of flavanols (a flavonoid subgroup, mainly epicatechin; Whiting, 2001) known as potent antioxidative agents. While some work has been done on the influence of theobromine and caffeine on mood and cognition (e.g., Smit and Rogers, 2000; Smit et al., 2004; Smit and Blackburn, 2005; Nehlig, 2010), the impact of cocoa flavanols on human cognitive and affective function, executive control and behavior has yet to be determined. In accord with accumulating evidence for enhancing effects of chocolate consumption on cognitive function, Messerli (2012) reports, as an occasional note, a strong positive correlation between chocolate intake per capita and the number of Nobel laureates in various countries.

In contrast to potential effects on cognition and behavior, evidence-based benefits of cocoa and chocolate consumption for cardiovascular system are well established and include endothelium-dependent vasodilation recently found to contribute to normal blood flow (Engler et al., 2004; Hooper et al., 2012; Kay et al., 2006; Grassi et al., 2005, 2008). Cardiovascular health has been closely linked to cognitive performance (e.g., DeCarli, 2012). Animal studies have shown that the absorbed flavonoids directly interact with a number of cellular and molecular targets in the brain, exerting pronounced antioxidative effects and improving brain tissue and function in the regions mainly implicated in learning, memory, and cognition (Andrés-Lacueva et al., 2005; Passamonti et al., 2005; Vauzour et al., 2008). This suggests a potential neuromodulatory and neuroprotective role for cocoa flavanols and their significance for cognitive and affective function, executive control and behavior. However, only few human studies so far have specifically addressed neurobiological, cognitive, affective and behavioral effects of flavanol-rich cocoa products. The present review focuses on analysis of the existing evidence on potential neuromodulatory and neuroprotective actions of cocoa flavanols in humans. Our analysis highlights further ways in investigation of the impact of flavanol-rich cocoa products on neurocognition and behavior.

2. Cocoa flavanols in the brain signaling cascades

The flavanol monoisomers epicatechin and catechin are the predominant flavonoid compounds in cocoa, with the 2-phenyl-3,4-dihydro-2*H*-chromen-3-ol as underlying skeleton. These monomers represent the base molecules for concatenated oligomers, the proanthocyanidins. Antioxidant properties of flavanols are chemically mediated through oxidation of two aromatic hydroxyl groups to a quinone (Bors and Michel, 2002). In addition, flavanols foster antioxidant system through modulation of enzymatic activity (Stevenson and Hurst, 2007; Mann et al., 2009). Flavanols occur in high concentrations in beverages such as green tea and red wine, fruits and berries (e.g., apple skin, grapes, pears, blueberry), vegetables (tomatoes, soy, and olives), and, especially, cocoa (Manach et al., 2004; Neveu et al., 2010; Scalbert et al., 2011; Sies et al., 2012). The flavonoid contents in cocoa products and chocolate differ substantially depending on the cocoa variety (in some beans, amounting up to 20%), geographic origin, cultivating, agricultural and postharvest practices, and manufacturing (Wollgast and Anklam, 2000; Niemenak et al., 2006). In the Dutch population, chocolate contributes to about 20% of the total flavonoid intake in adults, with an even higher percentage in children (Arts et al., 1999). In American diet, chocolate represents the third top source of antioxidants after fruits and vegetables (255, 233, and 104 mg/day, respectively; Vinson et al., 2006). Also in the French adult population with the total daily dietary polyphenol intake of 1.2 g, including 99 mg catechins, cocoa products account for the third major source of epicatechin (17%) after green tea (28%) and apples (24%; Pérez-Jiménez et al., 2011). Yet human and animal studies on neuroprotective properties of flavonoids, especially in preventing cognitive decline, have mostly examined plant-derived substances other than cocoa flavanols (e.g., Macready et al., 2009). Flavonoid-rich pine extracts such as *Gingko biloba* are reported to delay the onset of memory loss, dementia, and Alzheimer's disease (Weinmann et al., 2010), but the evidence remains controversial (Birks and Grimley Evans, 2009).

Animal studies show that flavanols and their metabolites can cross the blood–brain barrier, inducing beneficial effects on the brain tissue and function (angio- and neurogenesis, changes in neuron morphology) and stimulating widespread blood circulation in the brain (Vauzour et al., 2008). The most common flavanol found in cocoa, epicatechin (Whiting, 2001), is rapidly absorbed in humans and is detectable in blood plasma already 30 min after intake. The epicatechin levels peak 2–3 h after intake, exhibiting a strong positive correlation with the dose of ingested chocolate (Richelle et al., 1999), and return to baseline by 6–8 h after consumption. The possibility of flavanols and metabolites to penetrate and accumulate in the brain regions mainly related to learning and memory, suggests they may exert a direct positive impact on the brain, including cognition and neuroprotection (Nehlig, 2013).

Neurobiological impact of flavanols on the brain, learning, memory, and cognition are believed to occur in two major ways (Fig. 1). First, flavonoids can specifically interact within a number of cellular signaling pathways, primarily with mitogen-activated protein (MAPK), extracellular-signal-regulated (ERK) and phosphoinositide 3-kinase (PI3-kinase/Akt) signaling cascades. These cascades trigger gene expression and protein synthesis for maintaining long-term potentiation (LTP) and establishing long-term memories (Kelleher et al., 2004). Flavonoids modulate the transcription factors engaged in signal transduction through protein-kinase inhibition (Goyarzu et al., 2004), and promote the expression of brain derived neurotrophic factor (BDNF) that is critical for neurogenesis, also in adult animals, synaptic growth and neuron survival, especially in the learning- and memory-related brain regions such as the hippocampus and subventricular zone (Kim et al., 2006; Valente et al., 2009). Second, flavonoids facilitate production of the signaling molecule nitric oxide, which inhibits the incidence of atheromatous plaque adhesion molecules causing inflammation (Gonzalez-Gallego et al., 2007), and importantly, improves vascular endothelial function by relaxing the smooth muscle tissue of blood vessels (e.g., Heiss et al., 2003; Schroeter et al., 2006). In this way, flavanol-rich cocoa can impose vasodilation in a nitric oxide-dependent way both at the cardiovascular and peripheral levels. This in turn results in enhanced cerebral blood flow and blood perfusion throughout the central and peripheral nervous system (Fisher et al., 2003, 2006; Hollenberg et al., 2009), affording better

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