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Review

The mechanisms of action of flavonoids in the brain: Direct *versus* indirect effects

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ABSTRACT

The projected increase in the incidence of dementia in the population highlights the urgent need for a more comprehensive understanding of how different aspects of lifestyle, in particular exercise and diet, may affect neural function and consequent cognitive performance throughout the life course. In this regard, flavonoids, found in a variety of fruits, vegetables and derived beverages, have been identified as a group of promising bioactive compounds capable of influencing different aspects of brain function, including cerebrovascular blood flow and synaptic plasticity, both resulting in improvements in learning and memory in mammalian species. However, the precise mechanisms by which flavonoids exert these actions are yet to be fully established, although accumulating data indicate an ability to interact with neuronal receptors and kinase signaling pathways which are key to neuronal activation and communication and synaptic strengthening. Alternatively or concurrently, there is also compelling evidence derived from human clinical studies suggesting that flavonoids can positively affect peripheral and cerebrovascular blood flow, which may be an indirect effective mechanism by which dietary flavonoids can impact on brain health and cognition. The current review examines the beneficial effects of flavonoids on both human and animal brain function and attempts to address and link direct and indirect actions of flavonoids and their derivatives within the central nervous system (CNS).

Contents

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1. Introduction

The increase in incidence and prevalence of neurodegenerative diseases, along with the absence of new and effective drug treatments to treat such diseases, highlights the need for a more comprehensive understanding of how different aspects of lifestyle, such as exercise and diet, may influence brain disorders in a preventative manner, affecting long-term neural function and consequent cognitive performance. In particular, flavonoids, found in a variety of fruits, vegetables and beverages, have been recognized as promising plant-based bioactives capable of influencing different aspects of synaptic plasticity, thus resulting in improvements in memory and learning in both animals and humans (Williams and Spencer, 2012; Spencer, 2008; Rodriguez-Mateos et al., 2014a). Indeed, evidence has emerged from human intervention trials that demonstrate consumption of flavonoid-rich foods is associated with cognitive benefits (for a review see Macready et al., 2009; Kennedy, 2014; Nehlig, 2013). The mechanisms by which flavonoids exert these actions on cognitive performance are currently being elaborated, with evidence from long-term supplementation in animal models suggesting that they can modulate synaptic plasticity through activation of neuronal receptors, signaling proteins and gene expression (Rendeiro et al., 2012; Rendeiro et al., 2013a; Spencer, 2007; Williams et al., 2008; van Praag et al., 2007) (Fig. 1). However, the ability of flavonoids to directly modulate brain plasticity may be dependent to some extent on their accessibility to the brain, which is likely to vary based on the structural characteristics of *in vivo* flavonoid metabolites (Youdim et al., 2004; Youdim et al., 2003). As such, whether flavonoid induced cognitive effects are mediated directly, within the brain or involve other mechanisms triggered from the periphery remains unclear.

With respect to the latter, there is substantial evidence in support of the beneficial effects of flavonoids on the peripheral vascular health (Wang et al., 2014; McCullough et al., 2012; Hooper et al., 2012; Mink et al., 2007). Notably, flavanols (Heiss et al., 2007; Heiss et al., 2010; Schroeter et al., 2006; Schroeter et al., 2010; Ried et al., 2012; Ellinger et al., 2012) and anthocyanins (Rodriguez-Mateos et al., 2014b; Rodriguez-Mateos et al., 2013; Cassidy et al., 2011) have shown capable of promoting clinically significant improvements in endothelial-dependent peripheral vascular function (measured using flow mediated dilatation of the brachial artery) and blood pressure. Such effects seem to be mediated by the actions of absorbed flavonoid metabolites on artery nitric oxide (NO) bioavailability, through their potential to either activate endothelial nitric oxide synthase (eNOS) (Schroeter et al., 2006; Heiss et al., 2005; Moreno-Ulloa et al., 2014) and/or inhibit nicotinamide adenine dinucleotide phosphate (NADPH) oxidase (Rodriguez-Mateos et al., 2013; Takumi et al., 2012) in the endothelium. The extent to which such benefits in vascular responses in peripheral

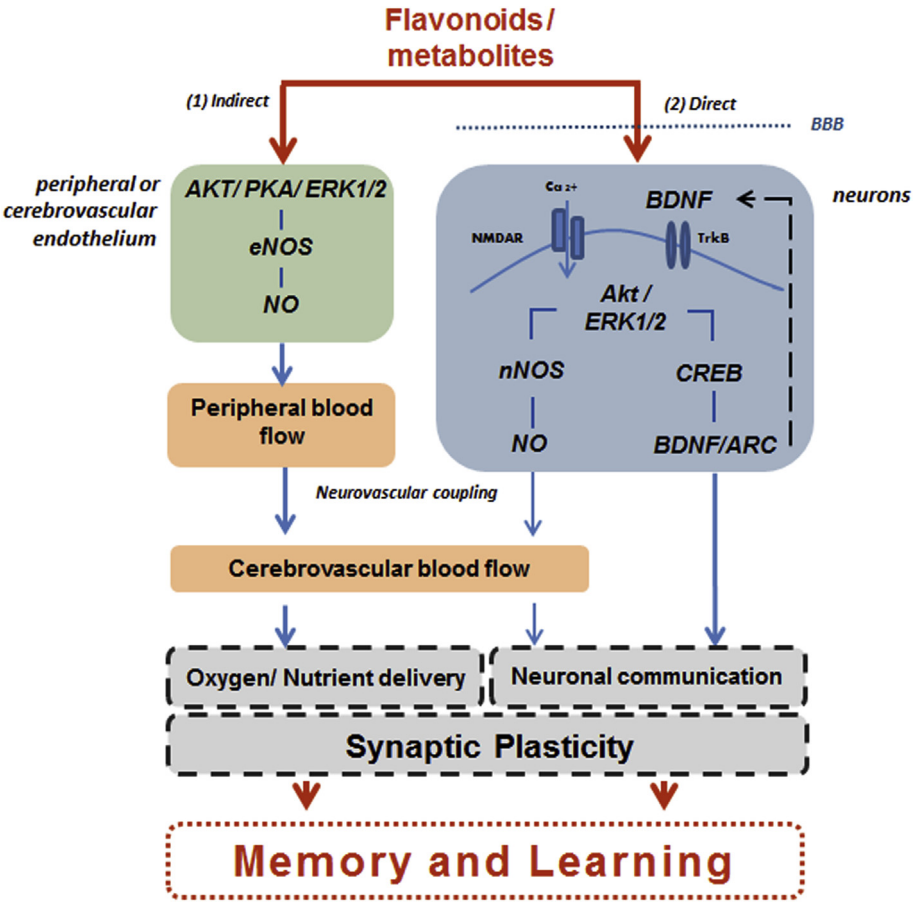

Fig. 1. Mechanisms underpinning the effects dietary flavonoids on memory and learning (Williams and Spencer, 2012). Circulating flavonoid metabolites might indirectly affect brain function and cognitive performance by modulating Nitric-Oxide (NO) dependent cerebrovascular function at the level of the cerebral endothelium or (Spencer, 2008) by crossing the Blood Brain Barrier (BBB), some flavonoid metabolites may act centrally by modulating neuronal receptors (e.g. TrkB, NMDA), signaling kinases (e.g. Akt, ERK1/2) and neurotrophins (e.g. BDNF) leading to changes in synaptic function.