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Mechanisms of dietary flavonoid action in neuronal function and neuroinflammation

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ABSTRACT

Flavonoids are a class of plant-derived dietary polyphenols that have attracted attention for their pro-cognitive and anti-inflammatory effects. The diversity of flavonoids and their extensive *in vivo* metabolism suggest that a variety of cellular targets in the brain are likely to be impacted by flavonoid consumption. Initially characterized as antioxidants, flavonoids are now believed to act directly on neurons and glia via the interaction with major signal transduction cascades, as well as indirectly via interaction with the blood-brain barrier and cerebral vasculature. This review discusses potential mechanisms of flavonoid action in the brain, with a focus on two critical transcription factors: cAMP response element-binding protein (CREB) and nuclear factor kappa-light-chain-enhancer of activated B cells (NF−κB). To advance beyond current understanding of cellular targets, critical bioavailability studies need to be performed to verify the identity and concentration of flavonoid metabolites reaching the brain after ingestion and to validate that these metabolites are produced not just in rodent models but also in humans. Recent advances in human induced pluripotent stem cell (iPSC) differentiation protocols to generate human neuronal and glial cell types could also provide a unique tool for clinically relevant *in vitro* investigation of the mechanisms of action of bioavailable flavonoid metabolites in humans.

1. Introduction

Flavonoids are a class of plant polyphenols that are consumed in the human diet via vegetables, fruits, cereals, spices, and other plant-based products. Epidemiological studies suggest that higher intake of flavonoid-rich foods and beverages is associated with better cognitive outcomes in individuals over 65 years old, including reduced cognitive decline (Letenneur et al., 2007), better cognitive performance (Nurk et al., 2009), and reduced risk of dementia (Commenges et al., 2000). Understanding the mechanisms by which flavonoids support cognitive function would be highly valuable for developing nutritional guidelines or for designing therapies to promote healthy aging.

2. Are flavonoids neuro-available?

A mechanistic understanding of flavonoid action is hindered by the paucity of data on the amount and chemical structures of flavonoids reaching the circulation and tissues after ingestion in humans (Clifford et al., 2013; Ottaviani et al., 2016). Although flavonoids share a basic 15-carbon structure consisting of two benzene rings linked by a heterocyclic pyrane ring, great structural diversity is present due to variations in hydroxylation pattern and substitutions along the pyrane ring, as well as binding to sugars as beta glycosides. Because of the complexity of flavonoid metabolism (Spencer, 2003), many metabolites can also be produced after the consumption of single compounds. For the original dietary flavonoid consumed, the bioavailability – the fraction of the compound reaching the systemic circulation in unchanged form – can be very low (Fig. 1). A recent study (Ottaviani et al., 2016) administered radiolabeled epicatechin (EC) to humans and observed high absorption (~90% of ingested radioactivity recovered) and extensive metabolism (>20 metabolites in urine and plasma) that led to undetectable levels of unmetabolized EC in plasma and urine. Over 80% of radioactivity was recovered in the urine following liver metabolism within 48 h, but only <2% was found in the circulation. Together, these data highlight i) the importance of using flavonoid metabolites identified in the circulation instead of native flavonoids

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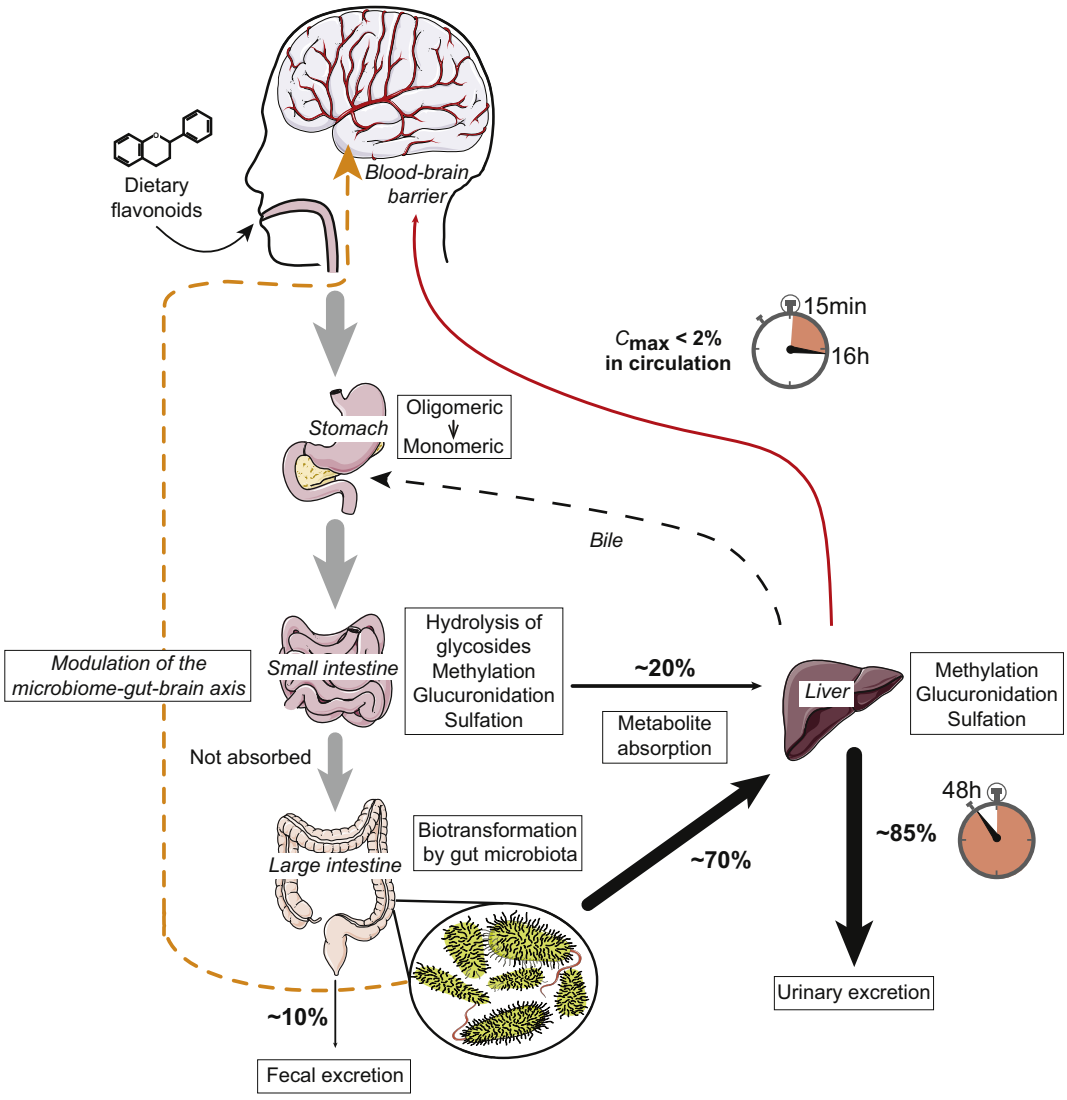

Fig. 1. Metabolism of ingested flavonoids. Flavonoids undergo extensive transformation *in vivo*, predominantly in the small and large intestines. Cleavage of glycosidic bonds releases aglycone forms of flavonoids, which can be absorbed unmodified or subject to glucuronidation, sulfation, or O-methylation in the small intestine and liver. Further transformation of unabsorbed flavonoids occurs via the intestinal microbiota. The relative production of metabolites can differ widely across species and based on the composition of the microbiome. Estimates shown are for ^{14}C-EC consumed orally by human subjects, as in Ottaviani et al. (Ottaviani et al., 2016). Although the majority of the radiolabeled flavonoid was absorbed and detectable in the urine, only a small fraction was detectable in the systemic circulation.

to investigate mechanisms of action *in vitro*, ii) the limited concentration of dietary flavonoid metabolites present in the circulation following ingestion, and iii) the key role played by the gut microbiota in the biotransformation of flavonoids in humans.

Once flavonoids or their metabolites reach the systemic circulation, they must still penetrate the blood-brain barrier (BBB) to have direct access to brain tissues and be 'neuro-available'. Multiple studies have demonstrated that some flavonoids or their metabolites can cross the BBB in rodents and pigs (Krasieva et al., 2015; Schaffer and Halliwell, 2012; Vauzour, 2012; Wang et al., 2012). Experimental evidence and mathematical correction methods (Friden et al., 2010) indicate that, when flavonoids do cross the BBB, they typically reach levels below 1 nmol/g of tissue (Schaffer and Halliwell, 2012; Vauzour, 2012). This finding suggests that *in vitro* studies using low micromolar concentrations or below are most likely to reflect reasonable physiological levels. Interestingly, some flavonoid classes were found to be retained in neural tissue longer than in plasma, which could increase their direct effect in the brain (Kalt et al., 2008; Milbury and Kalt, 2010).

Some studies have attempted to take the *in vivo* metabolism of flavonoids into account by performing follow-up analyses on metabolites identified after administration of a parent compound. For example, Wang and colleagues (Wang et al., 2012) orally administered a standardized grape extract enriched in either monomeric or polymeric forms of proanthocyanidins and then examined the metabolites present in brain. Crucially, only monomeric forms were effective in reaching the brain and improving cognitive function. One brain metabolite, 3′-*O*-methyl-epicatechin-5-*O*-β-glucuronide, was then studied further *in vitro* for effects on hippocampal physiology, and it was found to enhance both basal synaptic transmission and long-term potentiation (LTP). Other groups have taken flavonoid metabolites identified in urine and assessed their ability to cross the BBB and impact cognitive function. Al Rahim et al. (2009) observed that 4′-demethylnobiletin, a rodent metabolite of nobiletin, was detectable in the brain after a single acute injection and had *in vivo* effects on contextual fear memory. An