

Review

The mechanisms of action of flavonoids in the brain: Direct *versus* indirect effectsCatarina Rendeiro ^{a, b}, Justin S. Rhodes ^{a, b}, Jeremy P.E. Spencer ^{c, *}^a Beckman Institute for Advanced Science and Technology, 405 N. Mathews Ave., Urbana, IL 61801, USA^b Center for Nutrition, Learning and Memory, University of Illinois at Urbana-Champaign, USA^c Department of Food and Nutritional Sciences, School of Chemistry, Food and Pharmacy, University of Reading, PO Box 226, RG2 6AP, Reading, UK

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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).

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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

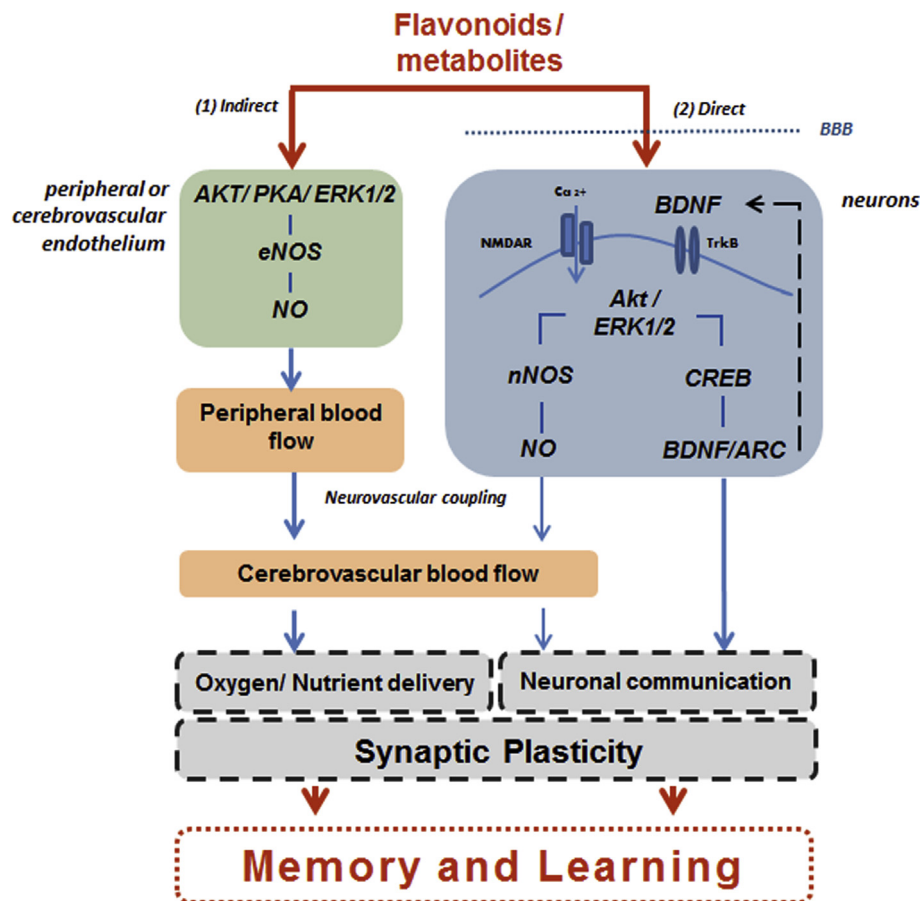


Fig. 1. Mechanisms underpinning the effects dietary flavonoids on memory and learning (Williams and Spencer, 2012). Circulating flavonoid metabolites might indirectly affect brain function and cognitive performance by modulating Nitric-Oxide (NO) dependent cerebrovascular function at the level of the 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.

arteries might be translatable to benefits in cerebral arteries and improved vascularization of the brain is currently being explored, with some encouraging clinical data showing increases in cerebral blood flow (CBF) matching closely the timing of peripheral responses following flavanols' intake (Francis et al., 2006; Fisher et al., 2006; Lampion et al., 2015). As such, it has been hypothesized that improvements in human cognitive function observed following flavonoid intake might be partly mediated by increases in CBF (Brickman et al., 2014) (Fig. 1). The ability of flavonoids to facilitate CBF is significant given that data indicate that accentuated declines in brain blood perfusion occur in parallel to aging and other neurological disorders closely implicated to the development of various dementias (Girouard and Iadecola, 2006; Iadecola, 2004; Ruitenberg et al., 2005; Nagahama et al., 2003).

Despite clear evidence regarding the acute vascular effects of flavonoids shown in humans (Schroeter et al., 2006; Schroeter et al., 2010; Rodriguez-Mateos et al., 2013; Heiss et al., 2005) and medium/long-term changes in synaptic plasticity markers demonstrated in animal studies (Rendeiro et al., 2012; Spencer, 2009a, 2010), the basic mechanisms of action of flavonoids in the brain remain to be established. In particular, the impact of flavonoids' on peripheral and cerebral blood flow reinforces the importance of understanding to what extent cognitive improvements are mediated by circulating metabolites in the periphery or/and directly by flavonoid metabolites within the brain. In the present review, we summarize human and rodent studies addressing mechanisms of action of flavonoids in brain function, and will specifically highlight how flavonoid modulation of peripheral and cerebral blood flow might affect synaptic plasticity processes and cognitive function.

2. Flavonoids and brain bioavailability

Once ingested, flavonoids undergo extensive metabolism in the small and large intestine, in the liver and in cells, resulting in a wide variety of metabolic derivatives, that are very different from the parent compounds found in foods (Manach et al., 2005; Williamson and Manach, 2005). The ability of flavonoids to influence the nervous system will depend to a certain extent to the ability of their *in vivo* metabolic derivatives to cross the blood brain barrier (BBB) and enter the brain (reviewed in Schaffer and Halliwell, 2012; Del Rio et al., 2013). The degree to which dietary flavonoids can enter the brain is still a matter of debate, despite a number of studies showing presence of flavonoids and their metabolites in brain tissue following oral administration of 1) flavanols, e.g. EGCG, (–) epicatechin (van Praag et al., 2007; Lin et al., 2007; Abd El Mohsen et al., 2002); 2) flavanones, both hesperetin and naringenin (Peng et al., 1998; Datla et al., 2001; El Mohsen et al., 2004); 3) flavonols, e.g. quercetin (de Boer et al., 2005; Ishisaka et al., 2011; Ho et al., 2013; Bieger et al., 2008; Huebbe et al., 2010) and 4) anthocyanins (El Mohsen et al., 2006; Talavera et al., 2005; Andres-Lacueva et al., 2005; Wang et al., 2014a; Kalt et al., 2008; Passamonti et al., 2005; Milbury and Kalt, 2010). Bioavailability feeding studies using polyphenols labeled with radioactive or stable isotopes further attempted more accurate measurements of all derivative metabolites that reach various tissues (Mullen et al., 2008; Janle et al., 2010; Abrahamse et al., 2005). However, whilst for example, Mullen et al. (2008) show small amounts of brain radioactivity after acute ingestion of [2-¹⁴C]- quercetin-4'-O-glucoside, Abrahamse et al. (2005) detected no radioactivity in the brain after 24 h of intake of ¹⁴C-labeled quercetin, reflecting some of the discrepancies in the literature. There is also some evidence suggesting that chronic intake of flavonoids (e.g. quercetin) do not result in higher accumulation of metabolites in tissues in comparison to one single dose, which indicates that brain levels are likely to reflect the

last meal and may not accumulate overtime (Bieger et al., 2008).

It has been suggested that the capacity of flavonoids and their metabolites to cross the BBB by trans-membrane diffusion is dependent on the degree of lipophilicity of each compound (Youdim et al., 2004). For example, flavonoids that are less polar, such as methylated derivatives, were shown to be capable of greater brain uptake than more polar metabolites *in vitro* (e.g. sulfated and glucuronides) (Youdim et al., 2003). Despite this, there is evidence from animal studies showing that glucuronide compounds can enter the brain (Bengtsson et al., 2009; Aasmundstad et al., 1995), including flavonoid glucuronides at doses (ranging from 500 to 900 pmol/g tissue) capable of exerting pharmacological actions (Wang et al., 2014a; Wang et al., 2012). A recent study by Ishisaka et al., examined the localization of quercetin-3-O-glucuronide (Q3GA), a major phase-II metabolite of quercetin, in human brain tissue by immunohistochemical staining using anti-Q3GA antibody and detected immunoreactivity in epithelial cells of the choroid plexus, which constitute the structural basis of the blood–cerebrospinal fluid (CSF) barrier, and also macrophages (Ishisaka et al., 2014). Altogether, this suggests that glucuronide metabolites can cross through the BBB, perhaps the CSF barrier and accumulate in specific cells (e.g. macrophages).

Other flavanols, such as (–) epicatechin and (+) catechin, and their methylated and glucuronidated metabolites have also been detected in the brain after both acute and short-term feeding with the pure compounds (van Praag et al., 2007; Abd El Mohsen et al., 2002) and with grape seed polyphenolic extracts (Wang et al., 2014a; Wang et al., 2012; Ferruzzi et al., 2009; Prasain et al., 2009). In particular, a recent study in a mouse model of AD (Tg2576) reported that only the monomeric fractions of grape derived polyphenols, specifically (–) epicatechin and (+) catechin, resulted in accumulation of metabolites in the brain (approx. 400 nM, mainly methylated and glucuronidated derivatives) in comparison to the remaining oligomeric fractions of the extract (Wang et al., 2012). This is in agreement with bioavailability studies in humans, showing that the procyanidin fractions of cocoa flavanols do not contribute to the pool of epi (catechin) metabolites following cocoa intake, but for example contribute significantly to the pool of colonic metabolites (e.g. valerolactones) (Ottaviani et al., 2012). With regards to gut-derived ring fission catabolites (e.g. valerolactones), there have been very few studies examining their presence in the brain and it is now becoming apparent that colonic metabolites comprise a considerable percentage of the overall metabolic profile after flavonoid intake (e.g. see Rodriguez-Mateos et al., 2013; Czank et al., 2013; Pereira-Caro et al., 2014). In that regard, Del Bo et al., detected small amounts of phenolic acids (e.g. Benzoic acid) in the range of the microg/g tissue after 4 and 8 weeks of blueberry intake in rats (Del Bo et al., 2010).

Importantly, flavonoid metabolites have been detected in areas of the brain such as hippocampus, cerebral cortex, cerebellum and striatum (Datla et al., 2001; Passamonti et al., 2005; Milbury and Kalt, 2010), which are important for learning and memory formation and are also adversely affected by aging and neurodegenerative diseases. However and despite emerging encouraging bioavailability in rodents, pigs and more recently in humans, further work is necessary before firm conclusions can be formulated with regards to the extent to which flavonoids can enter the brain and directly modulate brain function or whether such protective effects are mediated remotely through indirect mechanisms.

3. Impact of flavonoids on human cognition

The initial data concerning the impact of plant-derived flavonoids on cognitive function stemmed largely from observational studies and suggest that the regular, moderate intake of flavonoid-

rich foods results in cognitive benefits and/or a delay in the progression of age disease related cognitive impairments (Letenneur et al., 2007; Commenges et al., 2000; Nurk et al., 2009; Devore et al., 2012; Beking and Vieira, 2010). Despite a growing body of animal studies demonstrating long-term positive effects in learning memory after flavonoid intake (discussed in the next section), the human clinical trials are somewhat scarcer (for a review see Macready et al., 2009; Lampion et al., 2012). Historically, the human literature was dominated by human clinical trial data indicating the efficacy of isoflavones, a subgroup of flavonoids found predominantly in soy and soy-derived foods, on cognitive function in postmenopausal women (Casini et al., 2006; File et al., 2001; Duffy et al., 2003; Ho et al., 2007; Fournier et al., 2007; Krejčík-Kaspers et al., 2004; Cheng et al., 2015). More recently, studies addressing the effects of other flavonoid subgroups on human cognition have indicated that both blueberry anthocyanins and cocoa flavanols also promote positive effects on cognitive outcomes, especially in aged populations. For example, cocoa flavanols (520–994 mg of total cocoa flavanols) have been shown to enhance cognitive function and visual function in healthy young volunteers within 2 h of intake, specifically in highly effortful/demanding tasks (Scholey et al., 2010; Field et al., 2011). Similarly, acute studies in healthy older adults, result in improvements in human executive function (Saunders et al., 2011). The repeated daily intake of cocoa flavanols has been further shown to induce long-term changes in cognitive function in healthy elderly subjects (Brickman et al., 2014; Pase et al., 2013; Crews et al., 2008; Mastroiacovo et al., 2015) and aged volunteers displaying mild cognitive impairment (Desideri et al., 2012). Overall, these interventions suggest that short-term (4–8 weeks) intake of flavanols can impact on measures of mood (Pase et al., 2013), executive function, processing speed, working memory and verbal fluency (Mastroiacovo et al., 2015; Desideri et al., 2012). On the other hand, longer-term interventions (3 months) were shown to enhance hippocampal functioning within the dentate gyrus (DG) of the hippocampus (Brickman et al., 2014).

With respect to anthocyanins, acute studies have shown that blueberry flavonoids (579 mg; delivered and controlled as blueberry) induce cognitive improvements at 5 h post intake in both young and aged adults (Dodd, 2012). On the other hand, long-term supplementation (3 months) with blueberry juice in older adults with mild cognitive impairment resulted in working memory improvements and further reduced depressive symptoms (Krikorian et al., 2010). Similar results were found after a 3 month supplementation with Concord grape juice (Krikorian et al., 2010; Krikorian et al., 2012). Some recent and very novel data also addresses the cognitive impact of a single dose of a blueberry drink in children (8–10 yrs old). Remarkably, in comparison to the vehicle, the blueberry drink produced significant improvements in the delayed recall of a previously learned list of words, showing for the first time a cognitive benefit for acute flavonoid intervention in children (Whyte and Williams, 2015).

Finally, a recent intervention reports a positive modulation of global cognitive function following 8 weeks of citrus flavanone intake (as orange juice), in older healthy individuals (Kean et al., 2015). Overall and despite some encouraging cognitive outcomes emerging from human clinical trials, further studies are required to address these questions with adequate sample sizes and better characterization of the test materials in relation to their flavonoid content, as well as appropriate controls that are matched for all other micronutrients and macronutrients (Schroeter et al., 2010). On the other hand, the use of cognitive tests that are sensitive enough to detect effects of dietary interventions on human cognitive function is critical to fully assess the efficacy of flavonoid-rich foods in humans (Macready et al., 2010).

4. Direct mechanisms

4.1. Flavonoid modulation of synaptic plasticity: insights from animal models

In addition to human data, there is a large body of animal studies supporting the efficacy of flavonoid intake on cognitive function in both young and aged rodents, as well as in models of Alzheimer Disease (reviewed previously in Williams and Spencer, 2012; Rendeiro et al., 2012; Rendeiro et al., 2009). In particular, flavonoid enriched diets containing grape, pomegranate, strawberry, blueberry, cocoa as well as pure flavonoids, such as (+) catechin, (–) epicatechin, quercetin, have been shown capable of affecting several aspects of hippocampal dependent memory and learning (Williams et al., 2008; van Praag et al., 2007; Wang et al., 2014a; Hartman et al., 2006; Joseph et al., 1999; Wang et al., 2014b; Drouin et al., 2011; Bisson et al., 2008) (Table 1). The specific mechanisms by which flavonoids and their *in vivo* metabolites might affect the nervous system and improve cognitive outputs are being elaborated with evidence suggesting they can (Williams and Spencer, 2012) modulate receptor function; (Spencer, 2008) interact with neuronal signaling pathways crucial in modulating neuronal function and survival; (Rodríguez-Mateos et al., 2014a) promote the expression of genes and proteins involved in synaptic plasticity and neuronal repair; (Macready et al., 2009) modulate long-term potentiation (LTP) and further affect (Kennedy, 2014) morphological aspects important for neuronal communication such as spine density (for a review see Williams and Spencer, 2012; Spencer, 2008, 2007, 2010; Rendeiro et al., 2009; Spencer, 2009b) (Fig. 1).

Among flavonoids, anthocyanins, especially those derived from blueberries, have been one of the most studied in regards to their potential to modify different aspects of cognition, learning and memory in both young and aged animal models (Rendeiro et al., 2012; Rendeiro et al., 2013a; Williams et al., 2008; Joseph et al., 1999; Joseph et al., 1998; Shukitt-Hale et al., 2009; Galli et al., 2006; Carey et al., 2014; Willis et al., 2010; Casadesus et al., 2004; Goyarzu et al., 2004; Joseph et al., 2003; Rendeiro et al., 2013b). Studies by Joseph et al., were the first to show that both short and long-term supplementation with berries retards age-related decrements in cognitive and neuronal function (Joseph et al., 1999; Joseph et al., 1998). Initially, these effects were mainly attributed to an ability of anthocyanins to modulate antioxidant systems in the brain resulting in protective roles (Spencer, 2010; Joseph et al., 2000, 2009; Lau et al., 2007). However, more recently it has become apparent that other mechanisms are involved, particularly related to modulation of neuronal signaling pathways and gene expression, pivotal in controlling synaptic plasticity processes (Spencer, 2007, 2009a) (Table 1). For example, we have shown that blueberry-supplementation (2% w/w) can activate MAP kinases and PI3-kinase pathways, notably ERK-CREB-BDNF and Akt-mTOR-Arc pathways in the hippocampus of aged animals (Williams et al., 2008). In agreement with this, many other *in vivo* studies suggest that not only blueberry-flavonoids (Rendeiro et al., 2012; Rendeiro et al., 2013a; Williams et al., 2008; Casadesus et al., 2004; Joseph et al., 2003; Rendeiro et al., 2013b), but also pure anthocyanins (Rendeiro et al., 2013a), (–) epicatechin (Wang et al., 2012; Stringer et al., 2015), fisetin (Maher et al., 2006), fustin (Jin et al., 2009), EGCG (Li et al., 2009a; Li et al., 2009b) can modulate hippocampal ERK, Akt and CREB activation as well as protein and mRNA BDNF levels (Table 1). More detailed studies further indicate increases in BDNF mRNA expression in specific regions of the hippocampus, such as DG and CA1 following flavonoid-rich blueberry interventions (Rendeiro et al., 2012; Rendeiro et al., 2013a). Recent work in young rodents suggests modulation of hippocampal NMDA

Table 1
Summary of rodent supplementation studies investigating the effects of dietary flavonoids and flavonoid-rich foods on synaptic plasticity and memory and learning.

Intervention	Flavonoids' daily dose (per kg BW)	Duration of the intervention	Animal model	Cognitive measures	Mechanistic measures	Ref.
(–) epicatechin	200 mg/kg	14 wks	Young female mice	↓ Anxiety on Elevated plus maze and open field; No effect on Pattern separation	↑ BDNF, pro-BDNF, pAkt; ↑ TH, ↓ MAO-A; No effect on neurogenesis	Stringer et al. (2015)
(–) epicatechin and (+) catechin versus oligomers (grape derived)	80 mg/kg (both)	5 months	Tg2576 AD transgenic mice	↑ MWM just with monomers (–) epicatechin and (+) catechin	↑ pCREB and pCaMKII; ↓ senile plaques; <i>in vitro</i> : metabolite 3'-O-methyl (–) epicatechin glucuronide	Wang et al. (2012)
(–) epicatechin	125–1500 mg/kg	2–6 wks	Young female mice	↑ MWM	↑ LTP in hippocampal slices ↑ Spine density and angiogenesis in hippocampus; ↑ expression in genes related to synaptic plasticity, neurite outgrowth and angiogenesis; No effect on neurogenesis	van Praag et al. (2007)
Cocoa extract	8.4 mg/kg	1 year	Aged rats	↑ MWM just at 21 and 25 months	↑ urinary dopamine levels	Bisson et al. (2008)
blueberries (BB); anthocyanins (A); flavanols (F): (+) catechin and (–) epicatechin	BB: 17 mg/kg; A: 12 mg/kg; F: 5 mg/kg	6 wks	Aged rats	↑ working memory in X-Maze	↑ BDNF, pro-BDNF protein; ↑ BDNF mRNA (Only A) in hippocampus	Rendeiro et al. (2013a)
Blueberries	17 mg/kg	7 wks	Young rats	↑ working memory in RAM	↑ pERK, pCREB, BDNF, pro-BDNF hippocampus; ↑ mRNA BDNF in DG, CA1 in hippocampus	Rendeiro et al. (2012)
Blueberries	21 mg/kg and 42 mg/kg	3 wks	Young rats	↑ MWM	↑ PSA-NCAM in DG; ↑ NR2B; ↑ pERK, pCREB, BDNF; ↑ pAkt, mTOR; Arc in hippocampus	Rendeiro et al. (2013b)
Blueberries	17.5 mg/kg	12 wks	Aged rats	↑ working memory in X-Maze	↑ pERK, pCREB, BDNF; ↑ pAkt, mTOR; Arc in hippocampus	Williams et al. (2008)
Blueberries	NR	8 wks	Aged rats	↑ RAM	↑ IGF1, IGF1-R, pERK	Casadesus et al. (2004)
Blueberries	NR	6–8 wks	Aged rats	↑ LTP in CA1; ↑ NR2B	Coultrap et al. (2008)
Blueberries	NR	8 mo	APP + PS1 transgenic mice	↑ Y-maze	↑ carbachol-stimulated GTPase activity; ↑ pERK and PhPKCa	Joseph et al. (2003)
Fisetin	5, 10 and 15 mg/kg	single dose	Young rats	↑ Object recognition	↑ LTP; ↑ pERK and pCREB	Maher et al. (2006)
Fustin	50 and 100 mg/kg	11 days	AD model	↑ Passive Avoidance; ↑ Fear Conditioning	↑ muscarinic M1 receptor; ↑ pERK, pCREB, BDNF	Jin et al. (2009)
EGCG	40, 80 and 160 mg/kg	6 mo	Aged rats	↑ MWM	↑ pCREB and pCaMKII; ↑ BDNF, PSD95, Bcl-2	Li et al. (2009a)
EGCG	75 and 150 mg/kg	6 mo	Senescence-accelerated mouse prone-8 APPs we/PS1dE9 transgenic mice	↑ MWM	↑ pPKA, pCREB, pCaMKII; ↑ BDNF, PSD95	Li et al. (2009b)
Quercetin	20 or 40 mg/kg	16 wks	APPs we/PS1dE9 transgenic mice (AD model)	↑ MWM; ↑ Novel Recognition Object	↑ AMPK; ↑ mitochondrial membrane potential, ROS and ATP levels in hippocampus; ↓ senile plaques	Wang et al. (2014b)
Quercetin	5 mg/kg i.p.	2 wks	Cerebral ischemia (occlusion of the carotid arteries) in rats	↑ MWM	↑ LTP <i>in vivo</i> ; <i>in vitro</i> : 0.3, 3 and 30 mM quercetin ↓ amplitude of voltage dependent sodium currents in a dose- and voltage-dependent manner in CA1 neurons	Yao et al. (2010)
Quercetin	8.5 mg/kg and 17 mg/kg	13 wks	High fat diet model	↑ MWM (highest dose)	↑ pCREB, BDNF, PI3K, pAKT, Nrf2; ↓ Oxidative stress	Xia et al. (2015)
7,8-Dihydroxyflavone	5 mg/kg i.p.	5 wks	Aged rats	↑ MWM	↑ pTrkB, pCREB, pERK1/2, pCaMKII, pGluR1; ↑ Spine number and density; ↑ LTP in hippocampus	Zeng et al. (2012)

TH, Tyrosine hydroxylase; MAO-A, Monoamine oxidase-A levels; LTP, Long-term potentiation; MWM, Morris Water Maze; RAM, Radial Arm Maze; AD, Alzheimer's Disease; APP, Amyloid precursor protein; PS1, presenilin 1; NR, Not reported.

receptor composition in response to blueberry intake, specifically increases in the levels of the NR2B subunit (Rendeiro et al., 2013b), which is known to impact on the kinetics of activation of NMDA receptors increasing their capacity to exhibit LTP (Tang et al., 1999; Mony et al., 2009; Vasuta et al., 2007; Foster et al., 2010). In agreement with this, both *in vitro* and *in vivo* feeding studies suggest an ability of flavonoids to facilitate LTP. For example, chronic

interventions with blueberries (Coultrap et al., 2008) and pure quercetin (Yao et al., 2010) resulted in improvements in LTP in hippocampal slices of flavonoid-fed animals in comparison to control diet (Table 1). Supporting *in vitro* studies with human flavonoid metabolites also show that hippocampal LTP is enhanced after incubation with quercetin-3-O-glucuronide (Ho et al., 2013; Hu et al., 2008), 3'-O-methyl (–)-epicatechin 5-O-B-glucuronide

(Wang et al., 2012) and fisetin (Maher et al., 2006).

Despite the positive outcomes of flavonoid-rich foods supplementation on brain function, at present it is unclear whether specific flavonoids are driving these effects or whether the whole mixture of compounds is key to trigger such outcomes. In that regard, there is good evidence indicating that in addition to flavonoid-rich foods, also flavonoids in isolation, for example, (–) epicatechin, (+) catechin and quercetin are effective in protecting/reversing the course of neuronal and behavioral aging. In particular, recent studies show that both anthocyanin (malvidin, delphinidin, petunidin, peonidin and cyanidin) and flavanols ((–)-epicatechin, (+) -catechin) fractions of blueberry trigger similar effects on learning and memory and hippocampal BDNF levels as the whole blueberry diet (Rendeiro et al., 2013a). On the other hand, a study using a mice model of Alzheimer Disease (Tg2576) reported that the monomeric fractions of grape seed derived polyphenols, (composed mainly of (–) epicatechin and (+) catechin), but not the flavanol oligomers, resulted in improvements in spatial learning (as measured by Morris Water Maze, MWM) and also in accumulation of metabolites in the brain (approx. 400 nM) (Wang et al., 2012). Overall this supports the claim that flavonoids are the causal agents mediating the cognitive effects of flavonoid-rich foods but also highlights the fact that not all flavonoid derivatives (e.g. procyanidins) present will impact on neuronal and cognitive function. This is likely to be dependent on their structure and metabolism, absorption and potentially their ability to enter the nervous system.

Activation of neuronal signaling pathways and facilitation of LTP by flavonoids, suggests that these compounds might impact on synaptic plasticity by modulating receptor activity. In support of this, both *in vitro* and *in vivo* investigations have shown that flavonoid can modulate receptors such as GABA_A receptors (Goutman et al., 2003; Hanrahan et al., 2011; Fernandez et al., 2008; Adachi et al., 2006), TrkB (Jang et al., 2010), δ -opioid (Katavic et al., 2007; Panneerselvam et al., 2010; Panneerselvam et al., 2013), nicotinic (Lee et al., 2010; Lee et al., 2011), estrogen (Fernandez et al., 2010; Collins-Burrow et al., 2000; Huang et al., 2010), adenosine (Jacobson et al., 2002; Alexander, 2006; Moro et al., 1998) and testosterone (Xing et al., 2001). In particular, 7,8-dihydroxyflavone, a flavone derivative, was shown to be a high-affinity agonist of the BDNF receptor, TrkB, capable of inducing receptor dimerization and autophosphorylation in a similar manner to BDNF (Jang et al., 2010). Similarly to previous data with blueberry, *in vivo* administration of this flavone also resulted in activation of TrkB downstream signaling, such as ERK1/2, CaMKII and CREB (Yang et al., 2014) and improved learning and memory (Zeng et al., 2012; Castello et al., 2014; Zeng et al., 2012; Andero et al., 2012). 7,8-dihydroxyflavone was also shown to be able to cross the BBB and exert such effects directly at the TrkB receptor at the neuronal membranes, clearly demonstrating that at least some flavonoid metabolites can trigger pharmacological effects directly in the brain (Jang et al., 2010).

Fewer studies have indicated that morphological adaptations, such as increase in spine density and angiogenesis occur in response to flavonoid supplementation (van Praag et al., 2007) and also *in vitro* (Orban-Gyapai et al., 2014; Tangsaengvit et al., 2013). Effects on neurogenesis have proven scarce with, for example, (–) epicatechin supplementation showing consistently no effects on the number of newly formed neurons (van Praag et al., 2007; Stringer et al., 2015). However, an effect on survival of new neurons rather than increases in neurogenic rates, might be an alternative mechanism by which flavonoids can affect hippocampal function. For example, increased levels of polysialylated form of the neural adhesion molecule (PSA-NCAM) in the dentate gyrus, which is highly expressed in immature neurons, was also observed following intake of blueberry (Rendeiro et al., 2013b) and curcumin

(Conboy et al., 2009), potentially suggesting enhanced neuronal survival and integration in hippocampal circuitry (Gascon et al., 2007).

In summary, the ability of flavonoids to influence activity-dependent neuronal pathways and receptor activity suggest that these might underpin enhancements in spatial memory and learning through facilitation of changes in synaptic strength and induction of morphological changes, which are vital for learning and memory processes. Whether such effects translate to the human brain following comparable levels of intake remains to be established.

5. Indirect mechanisms

5.1. From the periphery to the brain: underlying mechanisms of flavonoid modulation of the neurovascular system

There is strong evidence to suggest that flavonoids are capable of promoting clinically significant improvements in cardiovascular health through their potential to lower blood pressure (Grassi et al., 2008; Grassi et al., 2005; Taubert et al., 2007a, 2007b; Cassidy et al., 2011; Fraga et al., 2011), improve endothelial function (Heiss et al., 2007; Schroeter et al., 2006; Heiss et al., 2005; Heiss et al., 2003), inhibit platelet aggregation (Murphy et al., 2003; Heptinstall et al., 2006; Peluso et al., 2015; Yang et al., 2012; Pearson et al., 2002) and reduce inflammation (Selmi et al., 2006; Sies et al., 2005). In particular, flavanols (Schroeter et al., 2006; Bondonno et al., 2012; Heiss et al., 2006; Balzer et al., 2006) and anthocyanins (Rodriguez-Mateos et al., 2014b; Rodriguez-Mateos et al., 2013) have been shown to modulate peripheral vascular function, as measured by flow-mediated dilatation (FMD) of the brachial artery. Peak plasma concentrations of flavonoid metabolites after intake of cocoa and/or blueberries coincide with improvements in FMD response in humans and also increased levels of circulating NO species (Schroeter et al., 2006; Rodriguez-Mateos et al., 2013; Bondonno et al., 2012). As such, such vascular effects have been linked to the actions of absorbed flavonoid metabolites on nitric NO bioavailability (Bayard et al., 2007), specifically through their potential to activate eNOS (Schroeter et al., 2006; Heiss et al., 2005; Heiss et al., 2003) and/or inhibit NADPH oxidase (Rodriguez-Mateos et al., 2013). Flavonoid ability to replenish NO reserves is of great significance since NO play a major role in the control of vascular tone, vasodilation and blood flow in the body (Tousoulis et al., 2012), and in particular in cerebral circulation and cerebral endothelium function (Toda et al., 2009; Atochin and Huang, 2011; Laranjinha et al., 2012) (Fig. 1). The control of cerebral blood flow is known to be temporally and spatially coupled with neuronal activity, a process called cerebrovascular coupling, which is of vital importance for the integrity of brain function and cognition (Fig. 2) (Iadecola, 2004; Attwell et al., 2010; Iadecola, 1993). Such coupling mechanism ultimately results in the enlargement of vessel diameter in response to the rising of metabolic demands imposed by neuronal activity, and is believed to be primarily mediated by NO (Toda et al., 2009), generated by both endothelial nitric oxide synthase (eNOS in the endothelium) (Faraci, 1993; Faraci and Heistad, 1998) and neuronal nitric oxide synthase (nNOS in neurons) (Lourenco et al., 2011; Ledo et al., 2005; Lourenco et al., 2014a; Lourenco et al., 2014b) (Fig. 2). Specifically, eNOS-derived NO is believed to have a less significant role as cerebral vessels become smaller and deeper, but to be critical to ensure efficient vasodilation of upstream arteries in response to blood-flow demands triggered locally upon neuronal activation (Dietrich et al., 2009; Dietrich et al., 1996; Busse and Fleming, 2003; Erinjeri and Woolsey, 2002). Since NO deficiency (and endothelium dysfunction) has been associated with cerebral hypoperfusion, vascular

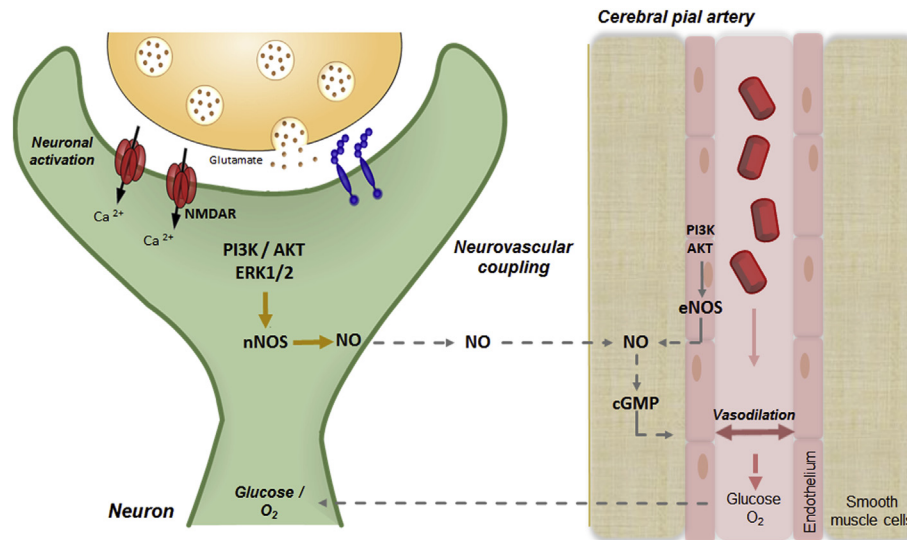


Fig. 2. Neurovascular coupling mediated by Nitric Oxide (NO) upon glutamatergic activation. Changes in localized blood flow and vasodilation in response to neuronal activation are mediated by NO, primarily generated in neurons by neuronal nitric oxide synthase (nNOS) but also in the endothelium by endothelial nitric oxide synthase (eNOS). NO is rapidly produced in response to neural activity in neurons, via activation of NMDA receptors and glutamate signaling, and diffuses to adjacent intracerebral arterioles and small capillaries, ensuring regional increases in blood flow. NO derived from eNOS activation (in the endothelium) also contributes to cerebral arterial dilatation, by migrating to vascular smooth cells and increasing blood flow at the blood–brain interface and it is particularly important in mediating vasodilation in larger vessels (such as pial arteries and intracerebral arterioles), having a less significant role as vessels become smaller and deeper. eNOS and nNOS activation are triggered by similar molecular mechanisms, involving Ca^{2+} -dependent cGMP/Akt/PKB signaling and resulting NO production is crucial to ensure local vasodilation and regional specific increases in blood flow to meet oxygen and nutrient demands.

dementia and even Alzheimer Disease (Girouard and Iadecola, 2006; Iadecola, 2004; Toda et al., 2014), the ability of flavonoids to increase bioavailability of NO might hold great potential to alleviate or prevent declines in vascularization of the brain, preserving synaptic function and cognitive abilities in aging and neurological disease.

5.2. Flavonoid-induced changes in cerebrovascular function: insights from human clinical trials

The time course of cognitive improvements following flavonoid intake, in particular those triggered by flavanols and anthocyanins, have been shown to match closely the increases in peripheral

vascular function (e.g. Schroeter et al., 2006; Scholey et al., 2010). Such observations motivated the exploration of a potential link between the vascular and cognitive effects of flavonoids (Table 2). This relationship has been mainly addressed in human clinical trials with cocoa flavanols, with studies suggesting improvements in CBF coinciding with peripheral vascular effects (reviewed in Fisher et al., 2006). Studies in young subjects show that a single acute dose (450 mg flavanols) of flavanol-rich cocoa can increase the CBF to gray matter within 2 h, whilst short-term intake of moderate doses (5 days of 172 mg) increases blood oxygenation level-dependent (BOLD) signal intensity in response to a cognitive task, as measured by functional magnetic resonance imaging (fMRI) (Francis et al., 2006) (Table 2). On the other hand, both acute

Table 2

Summary of randomized controlled trials investigating the effects of dietary flavonoids and flavonoid-rich foods on human cerebral blood flow.

Intervention	Flavonoids' daily dose	Intervention type/duration	Target population	Cerebral vascular measures	Cognitive function	Ref.
Cocoa flavanols	516 mg	Acute (2, 4 and 6 h)	Young healthy females	↑ CBF across gray matter (ASL MRI)	...	Francis et al. (2006)
Cocoa flavanols	172 mg	Short-term (5 days)	Young healthy females	↑ fMRI (BOLD) in dorsolateral prefrontal cortex, parietal and anterior cingulate cortex	↔ Letter digit task	Francis et al. (2006)
Cocoa flavanols	900 mg	Short-term (1 and 2 wks)	Aged healthy volunteers	↑ Mean blood flow velocity in MCA (TCD) at 1 and 2 wks	Sorond et al. (2008)
Cocoa flavanols	900 mg	Short-term (1–2 wks)	Aged healthy volunteers	↑ Mean blood flow velocity in MCA (TCD) correlated with MRI (ASL and gadolinium perfusion)	Sorond et al. (2010)
Cocoa flavanols	900 mg	Long-term (3 months)	Aged healthy volunteers	↑ CBF (fMRI) in DG	↑ Modified Benton task performance	Brickman et al. (2014)
Cocoa flavanols	494 mg	Acute (2 h)	Aged healthy volunteers	↑ CBF (ASL MRI) in anterior cingulate cortex and the central opercular cortex of the parietal lobe.	Lamport et al. (2015)
EGCG	135 and 270 mg	Acute (1–2 h)	Young healthy volunteers	↓ CBF in prefrontal cortex (Near-infrared spectroscopy)	↔ Cognitive performance and mood	Wightman et al. (2012)
Blueberries	579 mg	Acute (2 and 5 h)	Young and aged volunteers	↑ CBF in occipital cortex and precentral and middle frontal gyrus (fMRI)	↑ Immediate word recognition (young); ↓ susceptibility to priming (aged)	Dodd (2012)

CBF, Cerebral blood flow; ASL, Arterial Spin Labeling; (f)MRI, (functional) Magnetic resonance imaging; MCA, Middle cerebral artery; TCD, Transcranial Doppler ultrasound; BOLD, Blood-oxygen-level-dependent.

(Lampert et al., 2015) and short-term intake of cocoa (1–2 weeks) (Sorond et al., 2010, 2008) can increase regional blood flow (arterial spin labeling fMRI and gadolinium perfusion magnetic resonance imaging) and blood flow velocity in the middle cerebral artery (MCA) (transcranial Doppler ultrasound) in aged healthy volunteers. Most recently, longer-term interventions (3 months) with cocoa flavanols in also aged subjects revealed increases in cerebral blood volume (fMRI) in the DG of the hippocampus, which was highly correlated with improvements in performance in the DG-dependent Modified Benton task (Brickman et al., 2014). Altogether this suggests that cocoa flavanols can modulate CBF acutely but also indicates that continuous intake can improve baseline CBF, strongly suggesting long-lasting effects, particularly in aged populations (Table 2).

In addition to cocoa flavanols, there has been also interventions with the tea flavanol epigallocatechin gallate (EGCG) in young healthy volunteers reporting modulation in neuronal activity and cerebral blood flow (Scholey et al., 2012; Wightman et al., 2012; Borgwardt et al., 2012). Furthermore, reports of MRI studies with anthocyanin-rich blueberries in both young and aged adults, revealed acute increases in CBF in specific regions of the brain, such as the occipital cortex and in areas of the precentral and middle frontal gyrus (frontal lobe) as well as the angular gyrus (parietal lobe) (Dodd, 2012) (Table 2). No effect of the intervention was detected on whole brain or gray matter CBF. Furthermore, such changes were also paralleled by increased levels of circulating BDNF in comparison to the control drink (Dodd, 2012), which might be a mechanistic route by which blueberry flavonoids affect brain function (Karege et al., 2002; Zoladz et al., 2008).

Although the exact mechanisms by which flavonoids might be

interfering with CBF are still being elaborated, the ability of circulating flavonoid metabolites to increase bioavailability of NO at the cerebral endothelium, potentially *via* activation of Akt/eNOS, is likely to play a part (Fig. 1). Specifically, by facilitating endothelium-dependent cerebral vasodilation, similarly to what has been observed in peripheral arteries, flavonoid metabolites might actively affect the efficiency of neuronal activity-driven cerebrovascular coupling and ultimately result in improved local oxygen and nutrient delivery upon cognitive demand (Fig. 2). This might be particularly critical during aging and in conditions such as AD, that have been associated with decreases in NO production and reductions in CBF (Ledo et al., 2015; Kelleher and Soiza, 2013).

5.3. Flavonoid-induced changes in cerebrovascular function: insights from animal models

In addition to human clinical trials, supporting data from animal models seem to indicate that flavonoids are effective at reversing cognitive impairments and facilitating CBF in models of vascular dementia, cerebral ischemia and atherosclerosis (Table 3). For example, orally administered anthocyanins were protective against focal cerebral ischemic injury (Shin et al., 2006) and resulted in enhanced memory after occlusion of the right middle cerebral artery (Kaewkaen et al., 2012). In a similar model of vascular dementia, pure (–)-epicatechin, (5, 15 or 30 mg/kg), present in cocoa, exhibited significantly smaller lesion volumes and improved neurological scores compared to control animals (Shah et al., 2010).

Intracerebroventricular injection of streptozotocin (STZ) has been also used as a model of cerebrovascular impairment to test the functional effects of flavonoids in the brain. In particular, Tota et al.,

Table 3

Summary of rodent supplementation studies investigating the effects of dietary flavonoids and flavonoid-rich foods on cerebral vascular function, brain blood flow and cognitive function.

Intervention	Flavonoids' daily dose (per BW)	Duration of the intervention	Animal model	Cognitive measures	Vascular related measures	Ref.
(–) epicatechin	2.5, 5, 15 or 30 mg/kg	1 dose (before)	Brain ischemic mice: 1) middle cerebral artery occlusion (MCAO) or 2) NMDA excitotoxicity	↓ Neurologic deficit scores (NDS) for 5, 15 and 30 mg/kg doses	↓ Brain infarcts in MCAO and NMDA models; mechanism involves enzyme heme oxygenase 1 (HO1) and the transcriptional factor Nrf2	Shah et al. (2010)
(–) epicatechin	125–1500 mg/kg	2–6 wks	Young female mice	↑ MWM	↑ Angiogenesis	van Praag et al. (2007) Tota et al. (2010)
Quercetin	2.5, 5 and 10 mg/kg p.o.	3 wks	Intracerebral streptozotocin (STZ) reduction in CBF	↑ MWM; ↑ Passive Avoidance	↑ CBF (Laser Doppler Flowmetry); ↑ Nitrite, ATP, Acetylcholinesterase, Glutathione; ↓ Malondialdehyde	Drouin et al. (2011)
(+) catechin	30 mg/kg	3 mo	Atherosclerotic mice (C57B1/6LDLr–/–; hApoB+/+)	↑ MWM	↑ CBF upon stimulation (Laser Doppler Flowmetry); ↑ Ach- and FMD in cerebral artery; ↑ Sensitivity to eNOS inhibition; ↑ myogenic tone	Drouin et al. (2011)
(+) catechin	30 mg/kg	3 mo	Atherosclerotic mice (C57B1/6LDLr–/–; hApoB+/+)	–	↑ FMD in cerebral artery; ↑ Basal cerebral blood (Doppler optical coherence tomography); Remodeling cerebral wall and biochemical properties	Drouin et al. (2011)
Anthocyanins	2, 10 and 50 mg/kg	7 days before and 21 days after Rt.MCAO	Occlusion of the right middle cerebral artery (Rt.MCAO)	↑ MWM	↑ Neuron density in hippocampus; ↑ cholinergic neurons; ↑ Bcl-2	Kaewkaen et al. (2012)
Anthocyanins	300 mg/kg p.o.	1 single dose	Occlusion of the right middle cerebral artery (Rt.MCAO)	–	↓ JNK, p53; ↓ TUNEL positive cells; ↓ brain infarct volume	Shin et al. (2006)
Curcumin	10, 20 and 50 mg/kg	21 days before and 7 days after STZ	Intracerebral streptozotocin (STZ) reduction in CBF	↑ MWM; ↑ Passive Avoidance	↑ CBF (Laser Doppler Flowmetry)	Awasthi et al. (2010)

CBF, Cerebral blood flow; FMD, Flow-mediated dilatation; eNOS, endothelium Nitric Oxide synthase; TUNEL, Terminal deoxynucleotidyl transferase dUTP nick end labeling; MWM, Morris Water Maze.

showed that 3 weeks of quercetin intake restored ATP content and nitrite levels and improved CBF (as measured by Laser Doppler Flowmetry) in a dose-dependent manner (Tota et al., 2010). Such changes were also manifested in measures of cognitive function as assessed by MWM and Passive Avoidance, suggesting that quercetin's effects on cognitive function might be underpinned by actions on improved cerebral perfusion and increases in NO (Tota et al., 2010). Similarly, curcumin was shown to improve CBF in STZ treated mice in a dose dependent manner along with amelioration of memory deficits in the MWM. This was observed both when curcumin was administered before the STZ injection (preventive effect) and also when was administered after (therapeutic effect) (Awasthi et al., 2010).

More recently, a mice model of atherosclerosis (ATX: C57Bl/6-LDLR^{-/-} hApoB^{+/+}), which typically displays features of endothelial dysfunction (e.g. lower responses to Acetylcholine, Ach; decreased cerebral FMD and lower basal levels of CBF) has provided some important insights into the cerebrovascular effects of flavonoids (Drouin et al., 2011; Bolduc et al., 2012). In particular, a 3 month intervention with the cocoa flavanol, (+) catechin (30 mg/kg BW/day), restored endothelial function, reduced myogenic tone, improved ACh-responses in cerebral arteries and also prevented decline in learning abilities in ATX mice (Drouin et al., 2011). In support of the human literature on cocoa flavanols, (+) catechin also improved FMD measured in cerebral arteries, stimulated eNOS activity and restored the sensitivity to NOS inhibition, overall suggesting a NO-dependent mechanism underlying flavonoid-induced dilatation of vessels in the brain (Drouin et al., 2011). Interestingly, flavanol intake did not affect CBF basal levels or resting CBF, but only improved CBF upon neuronal stimulation, indicating that flavonoid modulation of CBF might be especially important in cerebrovascular coupling processes (Girouard and Iadecola, 2006; Iadecola, 1993). Furthermore, the same authors show that effects in vasodilation might be attributed to (+) catechin-induced changes in wall structure and biomechanics of cerebral arteries, resulting in improved arterial elasticity in ATX mice (Bolduc et al., 2012). Altogether this strongly indicates that in a mouse model of dyslipidemia, the cocoa flavanol monomer, (+) catechin, can prevent cerebrovascular dysfunctions, maintain cerebral blood flow and the associated learning abilities by preserving endothelial function and artery wall structure. To what extent this type of effect would also be apparent in a healthy mouse is not clear at the moment. However, such data highlights the potential of flavonoids in preserving cognitive abilities by interfering with the vascular system within the brain.

Long-term intake of flavonoids might also impact on vascularization of the brain by increasing number of new blood vessels. Angiogenesis itself is known to be accompanied by the production of endothelium-derived NO and vasodilation and NO to be a key regulator of vascular remodeling and angiogenesis (Ziche and Morbidelli, 2000; Cooke, 2003). For example, intake of pure (–) epicatechin (2.5 mg/day for 2 weeks) in healthy young mice was shown to increase angiogenesis in DG of the hippocampus and a trend towards an increase in the CA1 region (van Praag et al., 2007). Protocatechuic acid, an *in vivo* colonic catabolite of cyaniding-based anthocyanins (Rodriguez-Mateos et al., 2013; Vitaglione et al., 2007) (at physiological concentrations) promoted angiogenesis by activating PI3K/Akt signaling, eNOS and vascular endothelial growth factor (VEGF) in a human brain microvascular endothelial cell line (Kang et al., 2013). Therefore it may be possible that flavonoid-induced increases in NO levels (potentially through activation of Akt/eNOS) not only contribute to rapid acute increases in CBF upon neuronal activation but can further result in long-term adaptations in brain vasculature and angiogenesis, ultimately leading to better cerebrovascular communication (Fig. 1).

6. Discussion: future directions

The consumption of flavonoid-rich foods, such as berries and cocoa, throughout life may have the potential to limit or even reverse age-dependent declines in cognition and memory and potentially delay the onset and progression of dementia. The mechanisms by which flavonoids modulate cognitive function are yet to be fully established despite significant evidence suggesting they are can trigger beneficial effects in cognitive outcomes in both aging and healthy animal models and in humans. Both *direct* actions (i.e. through receptors' activation, neurotrophins and signaling pathways modulation) and *indirect* actions (i.e. enhancement of cerebrovascular blood flow) have been suggested as potential mechanisms (Fig. 1). However, to date, the associations between flavonoid intake and cognitive performance are mostly correlational. Before causal links can be established certain key questions need to be systematically addressed: 1) Firstly, the utilization of fully characterized and quantified intervention materials and appropriate placebo controls, matched for all macro and micronutrients, are crucial in order to validate outcome measures and to allow for direct comparison between studies (Schroeter et al., 2010). 2) Secondly, the cognitive outcome measures need to be sensitive enough to detect subtle, diet-induced changes in cognitive performance and should be combined with physiological measures clinically relevant for humans, notably measures of cerebrovascular blood flow using MRI and fMRI techniques, changes in gray matter density and biomarkers of neural stem and progenitor cells using proton nuclear magnetic resonance spectroscopy. 3) Thirdly, existing animal data needs to be translated into humans, in particular the translation of timeframes for intake and dosage needs to be addressed. Moreover, the translation of synaptic plasticity outcomes in animal studies to humans by using neuroimaging tools to measure brain activity and metabolism in a dynamic, quantitative and more mechanistic way (e.g. Brickman et al., 2014). 4) Finally, there is an urgent need to generate precise mechanistic data that causally link flavonoid intake to actions on cognitive function, such hard and rigorous evidence of effects in the brain is required for applications in the context of dietary recommendations and public health.

With respect to the latter, several pieces of evidence exist in the literature that can contribute to such causal relationships, specifically, *i*) the demonstration that the effects mediated by pure flavonoids constituents closely mimic the physiological effects of the whole foods (e.g. Rendeiro et al., 2013a; Wang et al., 2012); *ii*) dose–response studies allowing for identification of most effective doses (e.g. van Praag et al., 2007; Rodriguez-Mateos et al., 2013; Scholey et al., 2010; Tota et al., 2010); *iii*) demonstration that, at least some, flavonoid metabolites are transported to the brain (supporting a direct effect) (Williams et al., 2008; van Praag et al., 2007; Wang et al., 2012) or are present in the circulation (supporting an indirect effect), at the times of the beneficial effects on cognition (e.g. Saunders et al., 2011). However, the establishment of specific causal mechanisms of action will also require *i*) the inhibition of key molecular targets with concurrent observation of the abolishment of beneficial effects on cognition and other relevant physiological measures; *ii*) the withholding of the flavonoid compound or flavonoid-containing foods from the diet consistent with a reversal or an attenuation of the cognitive effects; *iii*) the identification of the specific *in vivo* flavonoid metabolites that are driving the beneficial effects following flavonoid intake. Overall, both human and animal studies should be designed taking such guidelines into consideration in order to maximize the relevance of the data generated.

Ultimately, the ability of flavonoids to modulate molecular players that are key to synaptic function, learning and memory, in

particular, CREB and TrkB/BDNF, is of great significance given the fact that these are typical targets in drug development aimed at improving brain health and cognitive function (Lu et al., 2013; Tully et al., 2003; Lynch, 2002). For example, TrkB/BDNF system has been of great therapeutic interest for their neurotrophic actions on several neurodegenerative diseases such as Parkinson's disease, Alzheimer disease and amyotrophic lateral sclerosis (ALS) (Siegel and Chauhan, 2000; Askanas, 1995). Despite major efforts, clinical trials using for example recombinant BDNF have presented major problems and limitations (Fletcher and Hughes, 2006; Ochs et al., 2000) and to date no exogenous agents have been identified that can trigger the *in vivo* activation of the TrkB/BDNF system in the CNS.

In addition to direct effects of flavonoids, there has been a growing interest on the potential indirect actions of circulating flavonoid metabolites in the brain through the vascular system. Such interest stemmed mainly from acute human studies showing effects on both endothelial vascular function and cerebral blood flow following intake of single doses of cocoa flavanols (e.g. Schroeter et al., 2006; Francis et al., 2006). Most importantly, supporting mechanistic studies indicate that, flavanols such as (–) epicatechin, can increase NO levels, by activating eNOS and upstream PI3K/Akt signaling in human artery endothelial cells (Moreno-Ulloa et al., 2014). As such, increases in eNOS-derived NO in the endothelium by flavonoids holds the potential to also affect vasodilation in cerebral arteries and modulate the efficacy of cerebrovascular coupling mechanisms during neuronal activation. For example, manipulation of NO bioavailability in the periphery, by intravenous administration of L-Arginine, a NO precursor, has been shown to result in transient increases in cerebral blood velocity in both young and aged human volunteers, with levels of cerebral blood flow returning to baseline levels after the completion of L-Arginine infusion (Okamoto et al., 2001; Pretnar-Oblak, 2014). Interestingly, this resembles closely the responses in both peripheral and cerebral blood flow observed following acute cocoa flavanols intake and further suggests that manipulation of NO in the periphery can effectively modulate blood flow in the brain. One way to address causally to what extent increases in circulating NO play a role in flavonoid-induced enhancement in cerebral blood flow is the use of NOS inhibitors, which block the conversion of L-arginine to L-citrulline and inhibit NO production (Iadecola and Xu, 1994). Future studies in animal models and even in humans (Heiss et al., 2005) should use L-arginine analogues such as nitro-L-arginine methyl ester (L-NAME), nitro-L-arginine (L-NIA) and L-N^G-mono-methyl-arginine (L-NMMA) to specifically and causally assess the contribution of NO production in mediating the effects of flavonoids in cerebral blood flow and cognitive performance.

The long-term effects of flavonoid intake on both vascular health and/or brain health (and indeed the link between the two) in humans have been less well studied. Existing data indicate that short/medium-term interventions (2–4 weeks) are effective at inducing an upward shift of baseline FMD response, suggesting potential long-lasting positive adaptations to flavonoid intake (Heiss et al., 2015). Recent studies in aged adults indicate that this might also be the case with regards to cerebral blood flow and cognitive performance (Brickman et al., 2014). This is particularly relevant given the fact that conditions such as atherosclerosis and obesity, which involve deregulation of endothelial function have been associated with cerebral hypoperfusion, indicating that factors that negatively affect peripheral vascular function also impact on brain health (Toda et al., 2014). Furthermore, the amelioration of cerebral blood flow by flavonoids holds the potential to directly affect different aspects of synaptic plasticity in the brain, such as overall better functioning of receptors, neuronal signaling pathways and more effective morphological modifications in neuronal

cells to accommodate synapse strengthening. This close relationship between plasticity and cerebral blood flow is illustrated in studies showing that declines in brain perfusion (e.g. aging, artificially induced models) affect LTP (Sekhon et al., 1997, 1998; Blau et al., 2012). As such, the beneficial effects of flavonoids might be particularly relevant to alleviate or prevent declines in vascularization of the brain and as such preserve synaptic function and cognitive abilities in aging and neurological disease.

Identification of which specific flavonoids or flavonoid combinations are most effective at inducing cognitive changes, as well as the timeframe and doses required to ensure maximal beneficial effects remain crucial aspects that need to be resolved in order to progress the field. Furthermore, a clearer mechanistic understanding of how flavonoid intake acutely mediates cognition and how such transient blood flow alterations may underpin longer-term and long-lasting physiological adaptations in humans is required. Indeed, such information is essential to support an effective translation of flavonoid research into effective interventions in the population and to establish specific dietary recommendations ('recommended daily intake'), in particular targeting individuals at most risk of dementia and age-related cognitive impairments. Finally, flavonoids might be also important precursor molecules for the development of a new generation of memory-enhancing drugs capable of counteracting or even reverse age or disease related impairments in cognitive performance.

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