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Postgraduate Symposium Flavonoids as modulators of memory and learning: molecular interactions resulting in behavioural effects

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There is considerable interest in the potential of a group of dietary-derived phytochemicals known as flavonoids in modulating neuronal function and thereby influencing memory, learning and cognitive function. The present review begins by detailing the molecular events that underlie the acquisition and consolidation of new memories in the brain in order to provide a critical background to understanding the impact of flavonoid-rich diets or pure flavonoids on memory. Data suggests that despite limited brain bioavailability, dietary supplementation with flavonoid-rich foods, such as blueberry, green tea and *Ginkgo biloba* lead to significant reversals of age-related deficits on spatial memory and learning. Furthermore, animal and cellular studies suggest that the mechanisms underpinning their ability to induce improvements in memory are linked to the potential of absorbed flavonoids and their metabolites to interact with and modulate critical signalling pathways, transcription factors and gene and/or protein expression which control memory and learning processes in the hippocampus; the brain structure where spatial learning occurs. Overall, current evidence suggests that human translation of these animal investigations are warranted, as are further studies, to better understand the precise cause-and-effect relationship between flavonoid intake and cognitive outputs.

Flavonoids: Memory: Learning: Hippocampus

Diet is an important lifestyle factor, which in recent times has been investigated for its influence on cognitive function and the incidence and onset of neurodegenerative disorders^(1,2). It has long been known that a diet high in saturated fats negatively impacts on cognitive processing and increases the risk of neurological dysfunction in both animals and human subjects^(3,4), while energy restriction (reduction in approximately 30% energy intake) protects the brain from injury^(5,6). Recently, significant evidence has emerged to indicate that phytochemical-rich foods, and in particular those rich in flavonoids, may reverse age-related deficits in cognitive function in both animals and human subjects^(7–9). For example, the PAQUID prospective study examined cognitive performance in 1640

subjects (aged at least 65 years and cognitively normal at baseline) on four occasions over a 10-year-period and found that flavonoid-intake was associated with a significantly better cognitive performance over time⁽⁷⁾ ($P = 0.046$). Furthermore, a cross-sectional study examining the relationship between the intake of three common flavonoid-containing foods (chocolate, wine and tea) and cognitive performance in elderly individuals revealed that there was a dose-dependent, positive relationship between the intake of these foods and performance on multiple cognitive outcomes (Kendrick Object Learning Test, Digit Symbol Test, Block Design, Mini-Mental State Examination and Controlled Oral Word Association Test)⁽¹⁰⁾. More recently, the consumption of dietary flavonoids, especially

Abbreviations: AD, Alzheimer's disease; Akt, protein kinase B; BDNF, brain-derived neurotrophic factor; CREB, cAMP response element binding protein; EC, epicatechin; EGC, epigallocatechin; ERK, extracellular-signal-regulated kinase; GB, *Ginkgo biloba*; LTP, long-term potentiation; MWM, Morris Water Maze; PKC, protein kinase C.

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flavonols (in twenty-three different developed countries) has been shown to be associated with lower rates of dementia⁽⁹⁾.

In agreement with this observational data, a large number of dietary intervention studies in both human subjects and animals, in particular those using flavonoid-rich foods or beverages derived from *Camellia sinensis* (tea)^(11–16) *Ginkgo biloba* (GB)^(17–20), *Theobroma cacao* (cocoa)^(21–23) and *Vaccinium* spp. (blueberry)^(24–28) have similarly demonstrated beneficial effects on memory and learning. Although there is evidence suggesting that these diets are capable of inducing improvements in cognitive function by protecting vulnerable neurons, enhancing existing neuronal function or by stimulating neuronal regeneration^(29–32), the precise mechanisms by which these compounds act in the brain are not fully established.

In order to effectively investigate the precise mechanisms by which flavonoids influence memory, learning and other cognitive processes, we must first consider how the memory works, including how such processes are controlled at the molecular level to facilitate acquisition and storage of sensory information as short- and long-term memory. Furthermore, how such information is processed in the hippocampus during specific cognitive events, such as the learning of spatial task information, will be illustrated. In particular, the roles that specific hippocampal regions play in the acquisition, consolidation and retrieval of information will help to elucidate how flavonoids are capable of exerting their specific cognitive improvements following supplementation. Lastly, the review will describe the various datasets from rodent studies that have investigated the impact of chronic supplementation with flavonoid-rich foods and/or beverages (green tea, blueberries and GB) and pure flavonoids on spatial memory and how that impacts on specific learning-related molecular events in the brain. Overall, a better understanding of the molecular basis underpinning the effects of flavonoid-rich foods on cognition will help us to determine how best to manipulate diet in order to increase the resistance of neurons to insults and promote mental fitness.

Flavonoids: dietary sources and bioavailability

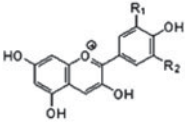
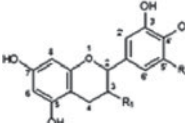
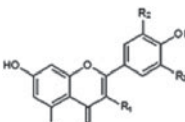
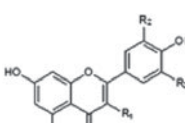
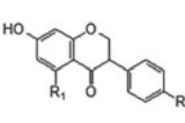
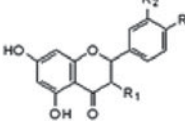
Flavonoids comprise the most common group of polyphenolic compounds in the human diet. Recent data show that the daily flavonoid intake per-capita is estimated to be about 182 mg in the UK and 177 mg in Ireland⁽³³⁾. The major sources of flavonoids include fruits, vegetables, tea, wine and cocoa⁽³⁴⁾. They may be divided into different subclasses according to the degree of oxidation of the heterocyclic ring, the hydroxylation pattern of the ring structure and the substitution in the three-position. Accordingly, the main dietary groups of flavonoids are: (1) anthocyanins whose main sources include red wine and berry fruits; (2) flavanols, found in green tea, red wine, cocoa; (3) flavonols found in onions, leeks and broccoli; (4) flavones which are abundant in parsley and celery; (5) isoflavones, typically found in soya and soya products and (6) flavanones which are mainly found in citrus fruits and tomatoes (Table 1). It has been reported that anthocyanins and flavanols may

account for approximately 65% of the total consumption of flavonoids in the UK⁽³³⁾. In general, flavonoids in foods exist as hydroxylated, methoxylated and/or glycosylated derivatives (except for catechins)^(35,36) and are linked to a sugar moiety that is often glucose or rhamnose.

Once ingested, flavonoids undergo extensive phase I and II metabolism in the small and large intestine, in the liver and in cells, resulting in very different forms in the body to those found in food itself^(37–40). Accordingly, all classes of flavonoids undergo extensive metabolism in the jejunum and ileum of the small intestine, with the resulting metabolites entering the portal vein where they will subsequently undergo further metabolism in the liver (Fig. 1). As mentioned, dietary flavonoids are substrates for phase I (hydrolysing and oxidising) and phase II (conjugating and detoxifying) enzymes, being de-glucosylated and metabolised into glucuronides, sulphates and *O*-methylated derivatives^(36,39,41,42). For instance, green tea catechins are typically metabolised in the liver to glucuronides, sulphates and *O*-methylated derivatives of these conjugates^(43–45). On the other hand, anthocyanins, unlike other flavonoids, do not appear to undergo extensive phase I and II metabolism of the parent anthocyanidin⁽⁴⁶⁾. Rather, only a relatively small percentage (<2%) of the parent compounds are detected in the blood or in the urine within 24 h of consumption^(47–50), suggesting a poor absorption of these compounds and/or their decomposition in the neutral or alkaline conditions of the small intestine⁽⁵¹⁾. However, experiments in ileostomy patients (lacking a colon) have suggested that up to 85% of anthocyanins from blueberry may traverse the small intestine intact, indicating that under normal physiological conditions a high amount of anthocyanins may reach the large intestine intact⁽⁵²⁾.

Although absorption is traditionally associated with the small intestine, the colon is also capable of absorbing many micronutrients. This process may involve their initial chemical or microbial transformation. Flavonoids are known to undergo extensive metabolism in the colon, in particular by gut microbiota which induce their breakdown to phenolic acids^(38,53) (Fig. 1). The microbiota catalyse this breakdown of the flavonoid structure in two steps, first by removing the conjugated moiety (formed in the small intestine) and second by cleaving the flavonoid backbone structure, usually across the A-ring. Many of these catabolites are efficiently absorbed in the colon, appear in the blood and are ultimately excreted in the urine. For example, *in vitro* studies have indicated that protocatechuic acid is one of the major bacterial degradation products of anthocyanins⁽⁵⁴⁾ and may be found in rat plasma after feeding cyanidin-3-*O*-glucoside⁽⁵⁵⁾. In a human intervention study involving orange-juice supplementation, protocatechuic acid was also the main product found in the blood and was estimated to account for up to 70% of total anthocyanin intake⁽⁵⁶⁾. Altogether, there is evidence to suggest that degradation products, such as protocatechuic acid, may be present in tissues at higher concentrations than the parent anthocyanidin. Therefore, it is clear that both the small intestinal conjugates of flavonoids and the bacterial-derived products formed in the colon are likely to contribute, at least in part, to the biological activities ascribed to anthocyanins and other flavonoids *in vivo*⁽⁵⁷⁾.

Table 1. Structure of the main flavonoids present in the human diet

Group	Functional groups	Structural formula	Examples	Food sources
Anthocyanins	R1 = H, OH, OCH3; R2 = H, OH, OCH3		Pelargonidin, cyanidin, delphinidin, petunidin, malvidin, paeonidin	Red wine, berries
Flavanols	R1 = gallate, OH R2 = H; OH		Catechin, epicatechin, epigallocatechin, epigallocatechin gallate	Green tea, cocoa
Flavonols	R1 = OH, R2 = H, OH, OCH3; R3 = H, OH		Quercetin, kaempferol, myricetin, isorhamnetin	Onion, Broccoli
Flavones	R1 = H; R2 = H, OH; R3 = H		Luteolin, apigenin	Parsley, Celery
Isoflavones	R1 = OH; R2 = H, OH		Genistein, daidzein	Soya
Flavanones	R1 = H; R2 = H, OCH3; R3 = H, OH		Naringenin, hesperetin	Citrus fruits, tomatoes

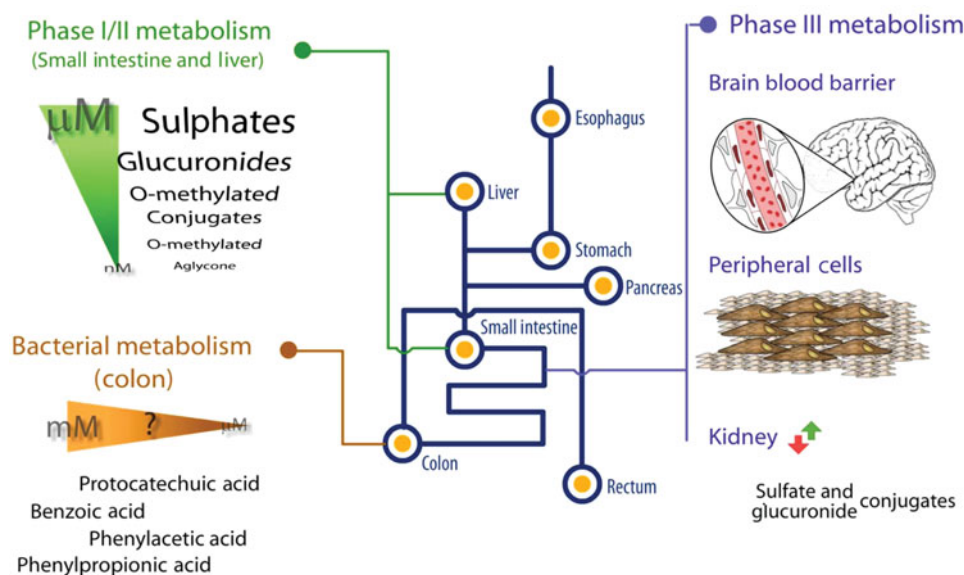


Fig. 1. Summary of the formation of metabolites and conjugates of flavonoids in human subjects. All classes of flavonoids undergo extensive phase II metabolism in the gastrointestinal tract and liver during which there is significant glucuronidation and sulfation of nearly all flavonoids by the action of uridine diphosphate-glucuronosyltransferase and sulfotransferase enzymes, respectively. There is also extensive *O*-methylation catalysed by the action of catechol-*O*-methyltransferase. Colonic microflora degrades flavonoids into smaller phenolic acids, such as phenylacetic acid, protocatechuic acid, phenylpropionic acid and benzoic acid, which may also be absorbed. Some of these metabolites are excreted through the kidneys. However, some may enter peripheral cells (e.g. endothelial cells) and cross the blood–brain barrier and enter the brain. Flavonoids may then undergo further intracellular metabolism (phase III), usually oxidative metabolism, P450-related metabolism and conjugation with thiols.

Bioavailability of flavonoids in the brain

In order for flavonoids to directly influence brain function, they must cross the blood–brain barrier⁽⁵⁸⁾ (Fig. 1). The extent of their blood–brain barrier penetration has been shown to be dependent on the lipophilicity of the compound⁽⁵⁹⁾. In theory, *O*-methylated flavonoid metabolites should be able to access the brain more easily than the more polar flavonoid glucuronides, although some drug glucuronides can cross the blood–brain barrier⁽⁶⁰⁾ and exert pharmacological effects⁽⁶¹⁾. The flavanol epigallocatechin (EGC) gallate, a relatively polar flavanol, has been reported to enter the brain after the gastric administration of (³H)-EGC gallate⁽⁶²⁾. Similarly, the flavanols EGC gallate and epicatechin (EC)^(62,63), as well as anthocyanins⁽⁶⁴⁾ such as pelargonidin⁽⁶⁵⁾, have all been found in the brain after oral administration. Furthermore, flavanones have also been found in rodent brain following intravenous administration⁽⁶⁶⁾.

With regard to specific brain localisation, several studies report anthocyanins in different regions of the brain of both rodents and pigs after supplementation with blueberry^(58,67,68) and grape extract⁽⁶⁹⁾ and (–)-EC and its *O*-methylated derivatives have been shown in the brains of mice supplemented with the pure compound for 2 weeks⁽⁷⁰⁾. Lastly, a 12-week blueberry supplementation was shown to result in accumulation of anthocyanins and flavanols in both the hippocampus and cortex⁽²⁴⁾, with the total amounts of flavanols (including flavanol metabolites) being much higher than that of anthocyanins despite

blueberry being higher in the latter. This confirms previous data suggesting that flavanols are more bioavailable than anthocyanins after oral administration (reviewed in⁽⁴⁵⁾).

Memory and learning

Spatial memory and its localisation in the brain

Learning and memory are two related processes by which information about the world (collected through sensory apparatus) is acquired, stored and later retrieved in the brain. There are two major types of memory: (1) declarative or explicit memory, which is designed to represent objects and events in the external world, as well as the relationships between them and (2) non-declarative or implicit memory, which is related with perceptual-motor skills and habits. The main difference between these is that while the retrieval of declarative memories requires conscious attention, non-declarative memories can be retrieved without conscious recollection⁽⁷¹⁾. These two parallel memory systems are dependent on different brain structures. Declarative memories are dependent on the integrity of the hippocampus, while non-declarative or implicit memories depend upon the integrity of structures such as amygdala and striatum^(71,72). Early discoveries in amnesic patients, such as the widely known ‘patient HM’, showed an important role for the hippocampus in the process of consolidating labile short-term explicit memories into a more stable form, the so-called long-term memory⁽⁷³⁾. It is also widely accepted that repeated exposure to

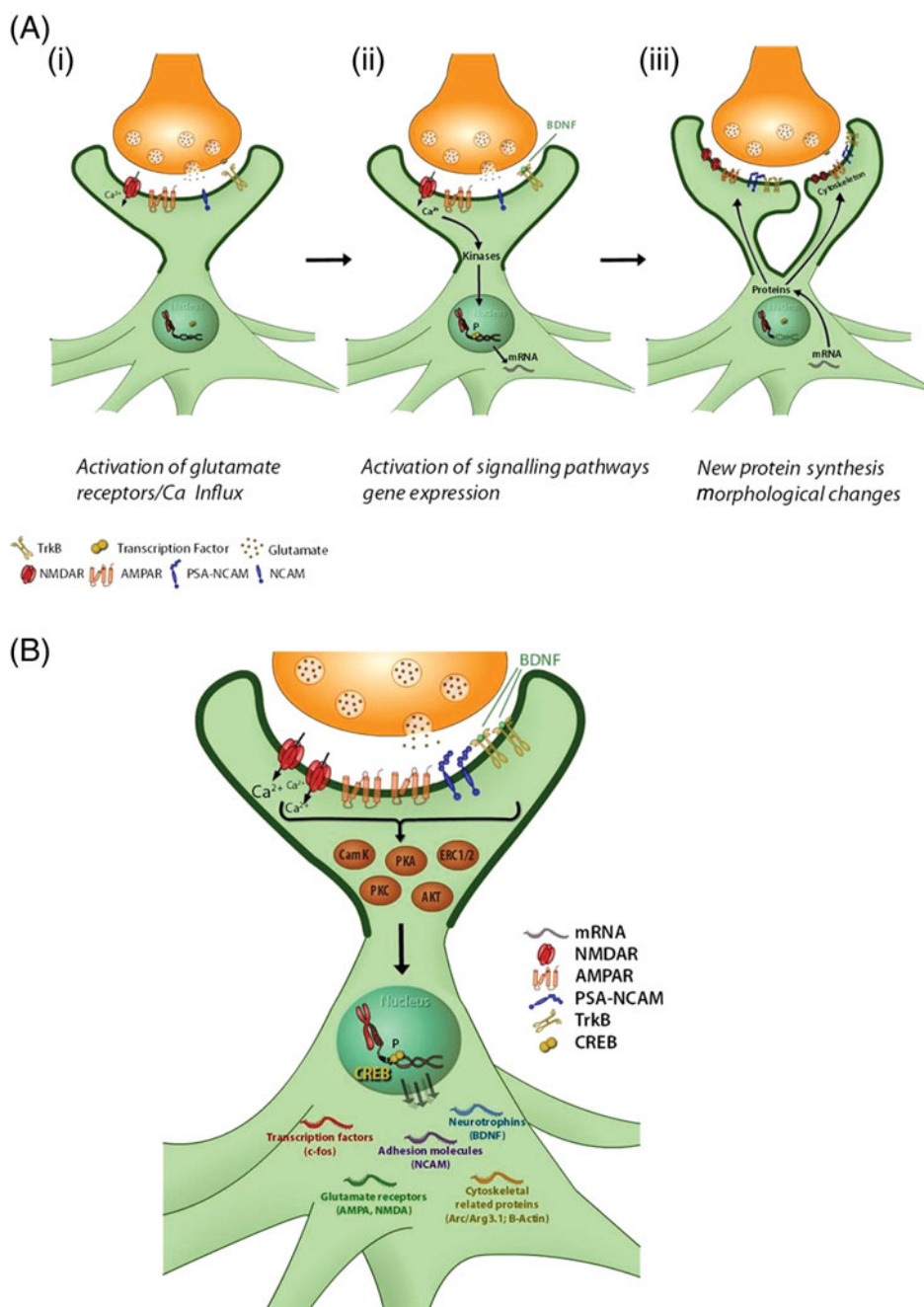


Fig. 2. (A) Molecular mechanisms underlying synaptic plasticity processes. (i) Activity-dependent release from presynaptic neurons lead to activation of α -amino-3-hydroxy-5-methylisoxazole-4-propionic acid receptors (AMPA) that causes depolarisation of the postsynaptic neuron, resulting in activation of N-methyl-D-aspartate receptors (NMDAR) and Ca^{2+} influx. (ii) Ca^{2+} influx causes activation of kinase signalling pathways, which induces activation of transcription factors and induces gene expression and new protein synthesis. (iii) This leads to stabilisation of synaptic changes and contributes to morphological changes at the synapse through regulation of the cytoskeleton which will ultimately impact on learning and retention of memories. (B) Signalling pathways involved in controlling memory and learning in the hippocampus. Activation of signalling pathways such as protein kinase A (PKA), protein kinase C (PKC), protein kinase B (also known as Akt); extracellular-signal-regulated kinase 1/2 (ERK1/2) and Ca-calmodulin kinase (CamK) converge to activate the transcription factor cAMP response element-binding protein (CREB) that regulates the transcription of many genes associated with synapse re-modelling, synaptic plasticity and memory. PSA-NCAM, polysialylated-neural cell adhesion molecule; TrkB, truncated tyrosin kinase B receptor; BDNF, brain-derived neurotrophic factor.

sensory information, i.e. via repetition or training, helps during the consolidation process of converting short-term memories into long-term ones^(74,75). Since these first observations, an extensive body of research has shown that disruption of the hippocampus primarily affects recently formed memories, but does not impair recollection of remote memories, believed to be stored in the neocortex. Thus, there is a general consensus that the hippocampus plays a time-limited role in learning processes, being particularly involved in the acquisition and the consolidation of memories^(76–78).

A particular aspect of declarative memory that has been used to access the effects of flavonoid-rich diets on behaviour is spatial memory. Spatial memory is well characterised in both rodents and human subjects and it is dependent on the hippocampus in both^(79–83). Rodents provide a good model in which to test spatial memory as they have an impressive ability to orientate themselves within a novel environment and can remember complex relationships between visuospatial cues in a way similar to human subjects^(84,85). As such, several maze environments, most notably the Radial Arm Maze⁽⁸⁶⁾ and Morris Water Maze (MWM)⁽⁸⁷⁾ have been developed to assess rodent spatial memory and learning. There is direct evidence that such spatial memory tasks are sensitive to hippocampal injury, suggesting that these are good models in which to access spatial memory in rodents^(88–90). In addition, it has been comprehensively reported that rats show distinct age-related deficits in spatial learning tasks, in a manner similar to those observed for human subjects in equivalent 'human' spatial memory tasks^(91–95). Thus, spatial memory constitutes an excellent model in which to evaluate the potential of flavonoids to reverse age-related cognitive deficits. To date, the majority of studies investigating the impact of flavonoid-rich diets on cognition have focused on spatial memory in either healthy, aged animals or senescence-accelerated animal models^(24,25,27,96).

Molecular basis of memory

It is widely accepted that the process of learning involves reversible changes in synaptic transmission within hippocampal neuronal circuitry which once stabilised, allow memory to be retained⁽⁹⁷⁾. The process by which these modifications occur is called synaptic plasticity and, although the mechanisms underlying this process during learning and memory are not completely understood, a growing body of research has provided important clues^(98,99). Long-term potentiation (LTP) is a form of synaptic plasticity widely accepted as the mechanism by which memories are laid down and subsequently stored^(100,101). LTP refers to a persistent increase in synaptic strength between neurons that typically occurs during learning⁽¹⁰²⁾. The initiation of LTP occurs when there is a simultaneous activation of both pre- and post-synaptic neuronal cells, which creates an associative link between the neurons involved.

During LTP, a release of glutamate from the presynaptic neuron leads to the activation of *N*-methyl-D-aspartate receptors in the postsynaptic cell, allowing an influx of Ca^{2+} ^(75,103) (Fig. 2(Ai)). When the intracellular levels

of Ca^{2+} are sufficiently elevated, it triggers the activation of signalling pathways, such as cAMP-dependent protein kinase A⁽¹⁰⁴⁾, protein kinase B (also known as Akt)^(105,106), protein kinase C (PKC)⁽¹⁰⁷⁾, Ca-calmodulin kinase^(108,109) and extracellular-signal-regulated kinase (ERK)^(110,111) (Fig. 2(B)). Phosphorylation of these kinases results in the modulation of synaptic efficacy, which typically involves activation of α -amino-3-hydroxy-5-methylisoxazole-4-propionic acid receptors^(112,113) and consequent modification of the biophysical properties of this receptor^(114,115). For example, the activation of ERK1/2 by phosphorylation results in its translocation to the nucleus which triggers *the novo* gene expression and protein synthesis, a process that is crucial to maintain LTP and convert short-term memories into a more stable long-term form^(116,117) (Fig. 2(Aii)).

The persistence of memory depends on structural and morphological changes in neuronal connections, a process primarily mediated by new protein synthesis (Fig. 2(Aiii)). In fact, there is extensive evidence from several different species that long-term memory requires the transcription and translation of new proteins in order to be retained^(118,119). In particular, the mammalian target of rapamycin, an Akt pathway target, plays a central role in translational control and has been shown to be critical for long-lasting plasticity^(120–122). Most importantly, extensive evidence derived from experimental systems ranging from molluscs to human subjects indicates that the cAMP response element binding protein (CREB) is a core component of the molecular switch that converts short- to long-term memory^(123–125). In mammals, CREB has been shown to regulate the expression of several genes during learning and memory, particularly gene products that are needed to stabilise the synaptic changes that are triggered during learning^(117,126,127) (Fig. 2(B)). The current list of target genes includes neurotrophins, proteins that influence cell signalling, cell structure and cell metabolism and other transcription factors, such as c-fos whose induction may trigger a second wave of changes in gene expression^(128–130) (Fig. 2(B)).

Neurotrophins are critical molecules that support the development, differentiation, maintenance and plasticity of brain function^(131,132). Among these molecules, brain-derived neurotrophic factor (BDNF) is involved in translating neuronal signals into structural changes in the synapse^(133–135). As such BDNF has been shown to be necessary to induce long-lasting structural changes at dendritic spines located at the terminals of excitatory synapses^(136,137). There is a considerable body of evidence suggesting that modulation of spine morphology correlates with synaptic plasticity and memory formation^(136,138). Specifically, the increase in α -amino-3-hydroxy-5-methylisoxazole-4-propionic acid receptors density at the synapse is thought to have a stabilising effect on spine morphology⁽¹³⁹⁾ (Fig. 2(Aiii)). For example, the activity-regulated cytoskeletal-associated protein (Arc/Arg3.1), whose expression is known to be dependent on Akt–mammalian target of rapamycin activation, was found to regulate α -amino-3-hydroxy-5-methylisoxazole-4-propionic acid receptor trafficking⁽¹⁰³⁾. In agreement with this, the expression of Arc/Arg3.1 was shown to facilitate changes in

synaptic strength and the induction of morphological changes, such as those dependent on actin-polymerisation^(140,141) (Fig. 2(B)).

In addition to this, cell adhesion molecules have been shown to play important roles in synaptic plasticity processes during memory formation⁽¹⁴²⁾. These molecules mediate the adhesion between cells, facilitating changes in synaptic connectivity. In particular, the neural cell adhesion molecule (NCAM) and its polysialated form, PSA NCAM, have been shown to regulate neurite outgrowth during memory formation, by mediating neuronal cell adhesion and signal transduction^(143–145). Overall, the stabilisation of connections between neuronal cells seems to be dependent on glutamate signalling that regulates and coordinates simultaneously both cytoskeletal and adhesion remodelling⁽⁹⁸⁾ (Fig. 2).

On the whole, the formation of a memory involves several phases, including acquisition, during which molecular changes are initiated in specific synapses, and consolidation, when those cellular modifications become stabilised allowing the memory to be retained. Typically the circuits linking dentate gyrus to *Cornu Ammonis* 3 (CA3) are more involved with the encoding of the spatial information, while CA3–CA1 are related to consolidation and recalling of the information. The resulting modified neuronal circuit underlies the neural representation of memory in the brain.

The impact of flavonoid-rich foods on memory and learning

Animal investigations have clearly indicated that flavonoid-rich foods such as spinach, strawberry, blueberry, GB and green tea are beneficial in retarding and/or counteracting functional age-related cognitive deficits^(19,24,25,27,146,147). Historically, these diets were thought to be protective due to their antioxidant activity^(35,148); however, it has become clear that antioxidant capacity alone is not responsible for the ability of flavonoid-rich diets to prevent or reverse age-related neuronal and cognitive changes^(27,30,149). Although the mechanisms by which flavonoids act in the brain remain a source of debate, a substantial number of flavonoid supplementation studies in animal models has provided important clues to their function. Investigations have pointed to many potential mechanisms, including the regulation of oxidative stress signals such as NF- κ B⁽¹⁵⁰⁾, enhancement of neuro-protective stress shock proteins⁽¹⁵¹⁾ and anti-inflammatory actions through the regulation of the expression of specific inflammatory genes (IL-1 β , TNF α)⁽¹⁵²⁾. In the following sections, we will focus on the potential of flavonoids to modulate and influence the molecular architecture responsible for learning and memory in the brain and how such activity may underpin behavioural changes induced by flavonoid-rich diets and pure compounds.

Green tea

There are an extensive number of studies regarding neuroprotection induced by green tea flavonoids in cellular and animal models, suggesting a potential therapeutic use

of these compounds in regenerating injured neuronal cells^(29,153,154). Green tea contains a high amount of flavanols (also referred to as catechins), which constitute 30–45% of the solid green tea extract^(155,156). The most abundant polyphenolic compound is (–)-EGC-3-gallate, followed by (–) EGC, EC and (–)-EC-3-gallate (Table 1)⁽¹⁵⁷⁾. Human epidemiological and animal data suggest that tea may decrease the incidence of dementia, Alzheimer's disease (AD) and Parkinson's disease^(14,158,159). In support of this, recent animal studies have shown that green tea intake helps to prevent age-related cognitive deficits (Table 2), particularly after long-term administration of green tea (approximately 6 months), which was shown to positively influence memory and learning in both normally aged and senescence-accelerated animals^(96,146,160).

Tea flavonoids have been reported to be potent Fe chelators, radical scavenging agents and to have anti-inflammatory activities^(161–166). In addition to these effects, recent studies have also indicated that they are capable of modulating signal transduction pathways and of regulating gene expression, and that these effects may also contribute to the neuroprotective effects of these compounds^(29,167). For example, *in vitro* and *in vivo* studies suggest an ability of green tea catechins to regulate apoptotic pathways^(168,169) as well as cell survival-related kinase signalling pathways, such as mitogen-activated protein kinase⁽¹⁷⁰⁾, PKC⁽¹⁷¹⁾ and phosphoinositide 3-kinase–Akt⁽¹⁷²⁾. A great deal of research has been devoted to the ability of green tea catechins, especially EGC-3-gallate, to activate the PKC pathway^(171,173,174). Notably, a 2-week pretreatment with a green tea catechin (EGC-3-gallate) was shown to be protective against A β -induced neurotoxicity by attenuating the depletion of PKC isoforms in the hippocampus and decreasing amyloid precursor protein⁽¹⁷³⁾. The PKC family has a fundamental role in the regulation of cell survival^(175,176), LTP and memory consolidation^(177–179).

In agreement with these molecular findings, the long-term administration of green tea flavanols has been shown to prevent spatial memory and learning impairments in a senescence-accelerated mouse model (senescence-accelerated mouse prone-8), which was paralleled by the activation of the protein kinase A–CREB pathway⁽⁹⁶⁾. Furthermore, green tea flavanol intake prevented reductions in the levels of key proteins involved in synaptic plasticity and structural plasticity, such as BDNF, post-synaptic density protein-95 and Ca²⁺/calmodulin-dependent protein kinase II⁽⁹⁶⁾ (Table 2). In support of this, another study using healthy, aged animals highlighted similar beneficial effects of green tea flavanols (6-month intervention) on spatial memory, along with increased levels of hippocampal CREB phosphorylation and increased levels of some of its target genes, such as BDNF and Bcl-2⁽¹⁴⁶⁾. These studies indicate that green tea flavanols may prevent memory decline by regulating crucial synaptic-related proteins in the hippocampus, potentially via the CREB pathway. The literature regarding the potential beneficial effects of green tea in young healthy subjects is limited, although there is some evidence of a significant ($P<0.0002$) improvement in working and reference memory of young rats (1-month-old) in Radial Arm Maze following a 6-month oral administration⁽¹²⁾ (Table 2).

Table 2. Effects of flavonoid-rich foods (*Ginkgo biloba*, green tea and blueberries) on memory and learning in rodents

Diet	Reference	Rodent models	Dose/feeding period	Learning paradigm	Learning output	Mechanistic output
<i>G. biloba</i>	Cohen-Salmon <i>et al.</i> ⁽¹⁹⁾	Young and aged	40 mg/kg BW – 1–3 weeks 50 mg/kg BW – 7 months	T-maze –	Acquisition/learning –	– Mossy fibres sprouting in the hippocampus
	Hoffman <i>et al.</i> ⁽²⁰⁸⁾	Young	10 mg/kg BW – 4 weeks	MWM	Short-term retention and reversal learning	–
	Williams <i>et al.</i> ⁽²¹⁴⁾	Young and aged	300 mg/ kg BW – 4 weeks	–	–	Enhanced LTP in hippocampus in aged animals
	Shif <i>et al.</i> ⁽¹⁸⁾	Young	10, 20 and 40 mg/kg BW – 2 weeks	MWM and RAM	Acquisition in RAM	–
	Wang <i>et al.</i> ⁽²¹⁷⁾	Aged	30; 60 mg/kg BW – 4 weeks	MWM	Acquisition and reversal learning	Enhanced LTP in CA1
	Oliveira <i>et al.</i> ⁽¹⁷⁾	Young	0.5 and 1.0 g/kg BW – 1–7 d	Fear conditioning	Acquisition of fear conditioning	Regulation of GAP-43 and CREB gene expression
	Blecharz-Klin <i>et al.</i> ⁽²¹⁰⁾	Aged	50, 100 and 150 mg/kg BW – 3 months	MWM	Short-term retention	Modulation of neurotransmitters (5-HT and 5-HT metabolite)
Green tea	Kim <i>et al.</i> ⁽¹⁵⁸⁾	Scopolamine-induced amnesic rat	0.2% (w/w) – 7 weeks	Y-maze	Short-term retention	Inhibition of AChE activity
	Haque <i>et al.</i> ⁽¹²⁾	Young	0.1; 0.5% (w/w) – 26 weeks	RAM	Reference and working memory	Lower plasma concentrations of lipid peroxides; increased plasma ferric-reducing antioxidation power; lower hippocampal ROS species
	Li <i>et al.</i> ⁽⁹⁶⁾	Aged	0.025, 0.05 and 0.1% (w/w) – 6 months	MWM	Acquisition and short-term retention	Activation of CREB and CaMKII; increased levels of BDNF, PSD95, Bcl-2
	Li <i>et al.</i> ⁽¹⁴⁶⁾	Senescence-accelerated mouse prone-8	0.025, 0.05 and 0.1% (w/w) – 6 months	MWM	Prevent decline in acquisition and short-term retention	Activation of PKA/CREB pathway, activation of CaMKII; increased levels of BDNF, PSD95
Blueberry	Joseph <i>et al.</i> ⁽²⁷⁾	Aged	2% (w/w) – 8 weeks	MWM	Acquisition	Increase in GTPase activity; Ca ²⁺ recovery and dopamina release
	Joseph <i>et al.</i> ⁽¹⁸⁰⁾	Alzheimer disease model (APP + PS1 transgenic mice)	2% (w/w) – 8 months	Y-maze	Prevention of working-memory deficits	Increases in carbachol-stimulated GTPase activity; hippocampal ERK and PhPKC α
	Casadesus <i>et al.</i> ⁽²⁵⁾	Aged	2% (w/w) – 8 weeks	RAM	Long-term reference memory	Increase in levels of IGF-1 and it's receptor (IGF-1R), ERK activation
	Andres-Lacueva <i>et al.</i> ⁽⁶⁷⁾	Aged	2% (w/w) – 10 weeks	MWM	No significant effect	Detection of anthocyanins in cerebellum, cortex and hippocampus. Performance correlated with anthocyanins in the brain
	Shukitt-Hale <i>et al.</i> ⁽¹⁸³⁾	Inflammation model (exposure to irradiation)	2% (w/w) – 8 weeks	MWM	Reversal learning	Increased dopamine release
	Coultrap <i>et al.</i> ⁽¹⁸⁸⁾	Young and aged	2% (w/w) – 6–8 weeks	–	–	Elevation of LTP in aged animals to levels seen in young; increased phosphorylation of NR2B subunit of glutamate receptor (NMDAR)
	Williams <i>et al.</i> ⁽²⁴⁾	Aged	2% (w/w) – 12 weeks	X-maze	Acquisition/working memory	Activation of ERK/CREB/BDNF pathway; activation of Akt/mTOR/Arc/Arg3.1 pathway

BW, body weight; MWM, Morris Water Maze; LTP, long-term potentiation; RAM, radial arm maze; CREB, cAMP response element binding protein; 5-HT, serotonin; AChE, acetylcholinesterase; ROS, reactive oxygen species; CaMKII, Ca²⁺/calmodulin-dependent protein kinase II; BDNF, brain-derived neurotrophic factor; PSD95, postsynaptic density protein-95; Bcl-2, B-cell lymphocytic-leukaemia proto-oncogene 2; PKA, protein kinase A; ERK, extracellular-signal-regulated kinase; IGF-1, insulin-like growth factor 1; IGF-1R, IGF-1 receptor; NMDAR, N-methyl-D-aspartate receptor; NR2B, N-methyl-D-aspartate receptor sub-type 2B; mTOR, mammalian target of rapamycin; GAP 43, growth associated protein 43; PhPKC, neutral sphingomyelin-specific phospholipase C.

Blueberry and other berries

There have been many studies reporting the potential effects of berry supplementation on spatial memory in aged animals^(27,180–183). Early studies indicated that long-term supplementation (from 6 to 15 months of age) with berries (blueberry or strawberry) retards age-related decrements in cognitive and neuronal function⁽¹⁸¹⁾. In subsequent experiments, supplementation with strawberry or blueberry reversed age-related deficits in spatial memory in aged rats⁽²⁷⁾ and a 2% blackberry-supplemented diet is effective in reversing age-related deficits in motor performance and spatial memory (MWM) when fed to aged rats (19-month-old) for 8 weeks⁽¹⁸²⁾. However, among berry fruits, blueberries have proved most effective at improving spatial learning and memory in old animals. Blueberries contain high levels of a variety of anthocyanins, such as malvidin, delphinidin, petunidin, peonidin and cyanidin⁽¹⁸⁴⁾, which could explain the particular beneficial effects of blueberries compared with other berries⁽¹⁸⁵⁾. However, blueberries also contain significant amounts of flavanols, flavonols and other phenolics, such as (–)-EC, (+)-catechin and quercetin (Table 1)⁽³⁴⁾, which may play a role in defining their beneficial effects. Furthermore, blueberry appears to have a more pronounced effect on short-term memory than on long-term memory, as demonstrated by an improved performance in several memory maze tasks, such as the MWM, eight-arm Radial Arm Maze and an X-maze^(24,27,186) (Table 2).

In addition to healthy, aged rodent models, blueberry supplementation has also been shown to have a positive impact on neuronal function and memory in rodent models of accelerated aging⁽¹⁸⁷⁾. These models are characterised by enhanced indices of oxidative stress and inflammation along with disruption of the dopaminergic system, similar to that observed in healthy, aged animals⁽¹⁸⁷⁾. Furthermore, a blueberry-rich diet was also shown to be protective in AD models (amyloid precursor protein/PS1 transgenic mice), preventing spatial memory deficits along with enhancement of memory-associated neuronal signalling⁽¹⁸⁰⁾. In particular, blueberry-supplemented amyloid precursor protein/PS1 mice exhibited greater levels of hippocampal ERK activation as well as hippocampal PKC α activation, both known to be involved in regulation of synaptic plasticity and consolidation of learning and memory⁽¹⁸⁰⁾. In agreement with this, blueberry-supplementation (2% w/w) in aged animals has been shown to regulate important markers of synaptic and structural plasticity, notably ERK–CREB–BDNF and Akt–mammalian target of rapamycin–Arc pathways along with improvement in spatial learning in the X-maze within 3 weeks of supplementation⁽²⁴⁾ (Table 2). These pathways are dependent on *N*-methyl-D-aspartate receptor activation and play a crucial role in gene expression and *de novo* protein synthesis⁽¹¹⁸⁾. In support of this, a 6–8-week supplementation with a blueberry extract resulted in improved *N*-methyl-D-aspartate receptor-dependent LTP in aged animals⁽¹⁸⁸⁾ (Table 2). Ultimately, these molecular mechanisms underlie the typical morphological changes that occur at the neuronal level during learning processes, although regulation at this structural level has not been investigated following blueberry supplementation.

On the other hand, increased ERK and insulin-like growth factor 1 activation has been observed in the dentate gyrus of blueberry-fed older animals and these cellular events were associated with increased neurogenesis (proliferation of precursor cells) and enhanced spatial memory⁽²⁵⁾ (Table 2). The link between dentate gyrus neurogenesis, cognitive performance and aging is well documented with increasing evidence showing that an increase in neurogenesis is associated with improved cognition^(189–195). Physical exercise, for instance, is described as one of the strongest neurogenic stimuli⁽¹⁹⁶⁾. Likewise, neurogenesis may represent one mechanism by which blueberry flavonoids improve memory by acting on the hippocampus. Overall, there is strong evidence suggesting that blueberry can improve memory and learning in aged animals and that these improvements are linked to the modulation of important structural and synaptic plasticity markers.

Ginkgo biloba

Standardised extracts of GB leaves have been extensively investigated for their potential to enhance memory and cognitive function. These extracts consist of numerous components, including flavonols (about 30%) and terpenelactones (7%), which are regarded as being responsible for the observed neuroprotective properties of GB⁽¹⁹⁷⁾. Several human interventions have reported beneficial effects of GB in the prevention and treatment of neurodegenerative disorders, such as AD, in particular, enhancement of cognitive function^(198–200), memory⁽²⁰¹⁾ and concentration^(202,203). Meta-analyses have also revealed significant beneficial effects of GB extract with regard to the treatment of dementia and cognitive functions associated with AD^(199,201,204). For instance, a significant effect was found (3% difference in the AD Assessment Scale-cognitive subtest) after a 3–6-month treatment with 120–240 mg GB extract on objective measures of cognitive function in AD^(204,205).

Early studies in rodents showed that chronic supplementation with GB extract resulted in substantial improvements in learning and memory in aged rodents^(19,147,206,207) (Table 2). Overall, chronic supplementation with GB seems to improve spatial learning in a number of different tasks, namely MWM, T-Maze and Radial Arm Maze. Although most studies seem to show a greater effect in aged and/or cognitively impaired animals, there are some studies showing positive effects on cognitive performance in young rodents^(17,18,208,209) (Table 2). While the mechanisms underlying the neuroprotective actions of GB are unclear, there is some evidence showing that GB extract can regulate the levels of neurotransmitters, such as serotonin⁽²¹⁰⁾, influence neurotransmitter receptors^(211–213), regulate structural changes in hippocampal circuitry⁽¹⁹⁾, affect neuronal excitability⁽²¹⁴⁾ and trigger neurogenesis in the hippocampus⁽²¹⁵⁾. In addition, GB-supplemented mice show an up-regulation of several neuromodulatory elements, such as α -amino-3-hydroxy-5-methylisoxazole-4-propionic acid-type glutamate receptors and microtubule-associated Tau⁽²¹⁶⁾. These data suggest a link between GB-induced improvements in memory and modulation of different aspects of synaptic plasticity. In support of this, 1 month of GB supplementation

Table 3. Effects of pure flavonoids on memory and learning in rodents

Pure compound	Reference	Rodent models	Dose/feeding period	Learning paradigm	Learning output	Mechanistic output
Fisetin	Maier <i>et al.</i> ⁽²¹⁸⁾	Young	5, 10 and 25 mg/kg BW – single dose	Object recognition	Improve long-term recognition	Activation of ERK and CREB; facilitation of LTP
Quercetin, rutin	Hu <i>et al.</i> ⁽¹⁵⁹⁾	Repeated cerebral ischaemia model	50 mg/kg BW – 2 doses after occlusions	RAM	Attenuation of spatial memory impairments	Reduction of ischaemia-induced neuronal death in CA1 in the hippocampus
(–) Epicatechin	van Praag <i>et al.</i> ⁽⁷⁰⁾	Young	2.5 mg per animal – 2 weeks	MWM	Short- and long-term retention	Increased angiogenesis and neuronal spine density in the DG of the hippocampus; upregulation of genes related to learning and angiogenesis, down-regulation of inflammation and cell death genes
Fustin	Jin <i>et al.</i> ⁽²¹⁹⁾	Alzheimer's model – Aβ (1–42)-centrally infused	50; 100 mg/kg BW – 11 d	Conditioned fear learning; Passive avoidance test	Attenuation of Aβ-induced impairments in fear learning and passive avoidance behaviour	Modulation of muscarinic M1 receptor; ERK and CREB activation and BDNF levels

ERK, extracellular-signal-regulated kinase; CREB, cAMP response element binding protein; LTP, long-term potentiation; RAM, radial arm maze; MWM, Morris water maze; DG, dentate gyrus; BDNF, brain-derived neurotrophic factor.

has been observed to increase the magnitude of LTP recorded in the hippocampal CA1 area of aged rats leading to an enhancement of spatial learning in MWM⁽²¹⁷⁾. More recently, 7 d intervention with GB in young animals has been observed to regulate hippocampal expression of the transcription factor CREB⁽¹⁷⁾.

Pure flavonoids

At present, the majority of the studies investigating the impact of flavonoids on memory, learning and cognition involve the supplementation of whole foods and beverages, rich in a complex array of macro- and micronutrients as well as a diverse range of different flavonoids. As such, causal relationships between individual flavonoids and function are difficult to establish. To address this, studies investigating the effects of individual flavonoids are beginning to emerge (Table 3). For example, the flavanol fisetin, typically found in strawberries, has been shown to enhance recognition memory in mice⁽²¹⁸⁾, through the activation of ERK and induction of CREB phosphorylation as well as a facilitation of LTP⁽²¹⁸⁾. Although the effect of fisetin on memory was assessed after oral supplementation *in vivo*, the approach used *ex vivo* to investigate the underlying mechanisms⁽²¹⁸⁾ limits the interpretation of the data since it excludes crucial factors that may affect the bioactivity of the compound, such as absorption and metabolism.

The flavanol (–)-EC (found in cocoa, blueberry and green tea) has been shown to improve the retention of spatial memory in the MWM when administered in its pure form. In the paradigms used in these studies, the effects of (–)-EC were enhanced when combined with exercise⁽⁷⁰⁾ and improvements in memory appeared to be associated with increased angiogenesis and neuronal spine density in the dentate gyrus of the hippocampus along with up-regulation of genes associated with learning⁽⁷⁰⁾. Oral administration of fustin, a flavonoid found in GB, has been shown to attenuate β-amyloid induced learning impairments⁽²¹⁹⁾, in a comparable way to that observed for EGb 761, a standard extract of GB. In agreement with data for other flavonoid-rich foods, the ERK–CREB–BDNF pathway was shown to be important for the M1 receptor-mediated cognition enhancing effects of fustin⁽²¹⁹⁾.

Although data are currently limited, pure flavonoids do appear to be able to induce learning and memory performance in a similar manner to flavonoid-rich foods and/or beverages. There is also evidence that pure flavonoids, such as (–)-EC and fisetin, are able to modulate molecular pathways necessary for memory and learning^(220,221). For example, pure (–)-EC induces both ERK1/2 and CREB activation in cortical neurons and subsequently increases CREB-regulated gene expression⁽²²¹⁾, while nanomolar concentrations of pure quercetin are effective at enhancing CREB activation⁽²²²⁾. Such evidence suggests that it is the flavonoids within these foods and beverages that mediate changes in memory formation *in vivo*.

Summary and future perspectives

Flavonoid-rich foods such as green tea and berries appear to be capable of influencing memory and learning through

an ability of the flavonoids they contain to modulate and enhance cellular events that underlie memory formation in the hippocampus. Most notably, flavonoids have been shown to affect different aspects of synaptic plasticity, from regulation of receptors activation⁽¹⁸⁸⁾, modulation of signalling pathways⁽²⁴⁾, activation of transcription factors^(96,146), regulation of gene expression and protein expression^(166,223), modulation of morphological and structural aspects of neurons⁽⁷⁰⁾ and promotion of LTP⁽²¹⁸⁾. Although many distinct signalling pathways are known to be involved in learning and memory formation, flavonoid interventions seem to interact primarily with ERK and Akt pathways, leading to modulation of the transcription factor CREB^(24,96,146) as well as up-regulation of CREB gene expression⁽¹⁷⁾.

The data to date suggest that CREB may be a crucial target for flavonoids. In this respect, there has been an interest in developing drugs that target CREB leading to enhancements in memory and learning⁽²²⁴⁾. Furthermore, the ability of these compounds to modulate neurotrophic factors such as BDNF makes them useful targets for the prevention of cognitive decline since these are crucial for neuronal survival and for the protection of neurons from injury⁽²²⁵⁾. BDNF levels are known to decline during aging and their levels have been shown to correlate with human learning and memory^(226–229), which has driven a considerable amount of research into design drugs that target BDNF and regulate its endogenous levels in the brain⁽²³⁰⁾. Indeed, drugs used to prevent AD such as memantine, as well as newly developed therapeutic interventions, both target BDNF and its levels in brain regions affected by the disease^(231–233). As such, further investigation into the impact of flavonoids and flavonoid-rich foods on levels of neurotrophins such as BDNF, is worthy of investigation. Allied to this, a more detailed examination of how flavonoids impact on BDNF levels in specific regions of the hippocampus when combined with highly specific behavioural tasks that engage preferentially specific areas of the hippocampus may help shed additional light on the underlying mechanisms of the action of flavonoids on different aspects of the learning process.

Future studies should also consider supplementation with pure flavonoids. A considerable level of complexity exists in interpreting this type of experimental data, stemming from the fact that the majority of dietary supplementation studies use complex mixtures of ingredients (foods or beverages). The identification of specific active molecules responsible for the claimed benefits or potentially synergetic effects of different compounds can help to shed light on the mechanisms by which flavonoids act in the brain and inform future human studies. The identification of the active components in foods and beverages is also a crucial step to establish a causal relationship between flavonoid intake and improvements in memory and learning measures. This should be paralleled with inhibitor studies to investigate whether pathway inhibition (e.g. ERK–CREB–BDNF) effectively blocks changes in spatial memory observed in flavonoid-supplemented animals. Furthermore, studies are required to establish the impact of flavonoids on structural aspects of synaptic plasticity such as synapse growth and dendritic spine density, events that are modulated by the

mentioned pathways. Recent data showing that flavonoids can impact on aspects of neuronal structure and morphology, such as spine density are highly promising⁽⁷⁰⁾. In particular, further investigation into whether these structural changes are specific to distinct regions of the hippocampus will be valuable given that it is well reported that aging leads to region- and circuit-specific losses of connectivity in the hippocampus^(95,234,235).

Since aging affects different aspects of synaptic plasticity, from activation of signalling pathways to structural changes neurons, it is not surprising that flavonoids, which also impact on these different levels of functioning, may help ameliorate age-related memory and learning impairments. However, there have been relatively few investigations into the potential of flavonoid-rich diets to improve memory and learning in young animals. Future investigations are warranted to fully explore the impact of flavonoids on young animal and to explore whether common mechanism of activity exist in both young and aged animals. Such studies will inform the design of future experiments required to address the temporal nature of these effects over the lifetime of an animal and clarify whether consumption of flavonoid-rich foods delays the onset of age-related cognitive impairments.

Overall, there is strong evidence that flavonoid-rich foods can impact on memory and learning and that this seems likely to involve, to some degree, regulation of signalling cascades, leading to changes in morphological aspects of neuronal cells, such as spine density, that ultimately impact on synaptic plasticity and more sustained LTP in the hippocampus. Future work should focus on investigating further these mechanisms in order to establish causal relationships between flavonoid intake, cognitive outputs and modulation of synaptic plasticity markers.

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