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REVIEW

Flavonoids and brain health: multiple effects underpinned by common mechanisms

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Abstract The neuroprotective actions of dietary flavonoids involve a number of effects within the brain, including a potential to protect neurons against injury induced by neurotoxins, an ability to suppress neuroinflammation, and the potential to promote memory, learning and cognitive function. This multiplicity of effects appears to be underpinned by two processes. Firstly, they interact with important neuronal signalling cascades leading to an inhibition of apoptosis triggered by neurotoxic species and to a promotion of neuronal survival and differentiation. These interactions include selective actions on a number of protein kinase and lipid kinase signalling cascades, most notably the PI3K/Akt and MAP kinase pathways which regulate pro-survival transcription factors and gene expression. Secondly, they induce peripheral and cerebral vascular blood flow in a manner which may lead to the induction of angiogenesis, and new nerve cell growth in the hippocampus. Therefore, the consumption of flavonoid-rich foods, such as berries and cocoa, throughout life holds a potential to limit the neurodegeneration associated with a variety of neurological disorders and to prevent or reverse normal or abnormal deteriorations in cognitive performance.

Keywords Flavonoid · Brain · Neurodegeneration · Neuroinflammation · Memory · Cognitive performance · Signalling

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Introduction

Macronutrients, such as lipids are vital components of both neurons and glial cells and their profile (saturated or unsaturated) has been proposed to play a huge role in brain function [3]. Furthermore, the brain has a very high energy demand and as such utilises a large proportion of the dietary intake of carbohydrates in order to function effectively. However, it is less obvious how other dietary-derived nutrients or non-nutrient components may impact on the functioning of the brain. Despite this, a large number of dietary intervention studies in humans and animals, in particular those using foods and beverages derived from *Vitis vinifera* (grape), *Camellia sinensis* (tea), *Theobroma cacao* (cocoa) and *Vaccinium* spp. (blueberry) have demonstrated beneficial effects on human vascular function and on improving memory and learning [15, 16, 32, 60, 69, 76, 80]. While such foods and beverages differ greatly in chemical composition, macro- and micronutrient content and caloric load per serving, they have in common that they are amongst the major dietary sources of a group of phytochemicals called flavonoids.

Historically, the biological actions of flavonoids, including those on the brain, have been attributed to their ability to exert antioxidant actions [51], through their ability to scavenge reactive species, or through their possible influences on intracellular redox status [50]. However, it has been speculated that this classical hydrogen-donating antioxidant activity cannot account for the bioactivity of flavonoids in vivo, particularly in the brain, where they are found at only very low concentrations [59]. Instead, it has been postulated that their effects in the brain are mediated by an ability to protect vulnerable neurons, enhance existing neuronal function, stimulate neuronal regeneration and induce neurogenesis [60]. Indeed, it has become

evident that flavonoids are able to exert neuroprotective actions (at low concentration) via their interactions with critical neuronal intracellular signalling pathways pivotal in controlling neuronal survival and differentiation, long-term potentiation (LTP) and memory [61, 74, 78]. This review will examine the potential for flavonoids to influence brain function and will attempt to clarify the mechanisms which underpin such actions in the brain.

Inhibition of neuroinflammation

Neuroinflammatory processes in the brain are believed to play a crucial role in the development of Alzheimer's and Parkinson's disease [19, 47] as well as injury associated with stroke [81]. Activated microglia and/or astrocytes release cytokines and other mediators which have been linked to the apoptotic death of neurons. In particular, increases in cytokine production (interleukin-1β, IL-1β; tumour necrosis factor-alpha, TNF-α), inducible nitric oxide synthase (iNOS) and nitric oxide ($NO^{\bullet}$), and increased NADPH oxidase activation [31] all contribute to glial-induced neuronal death (Fig. 1). The majority of these events are controlled by upstream mitogen-activated protein kinase (MAPK) signalling which mediates both the transcriptional and post-transcriptional regulation of iNOS and cytokines in activated microglia and astrocytes [6, 45]. Evidence suggests that the non-steroidal anti-inflammatory drug, ibuprofen, may be effective in delaying the onset of neurodegenerative disorders, particularly as Parkinson disease, by reducing inflammatory injury in specific brain regions [8]. As such, there is a desire to develop new drugs capable of preventing progressive neuronal loss linked to neuroinflammation. Recently, the flavanone naringenin found at high concentrations in citrus fruits has been found to be highly effective in reducing LPS/IFN-γ-induced glial

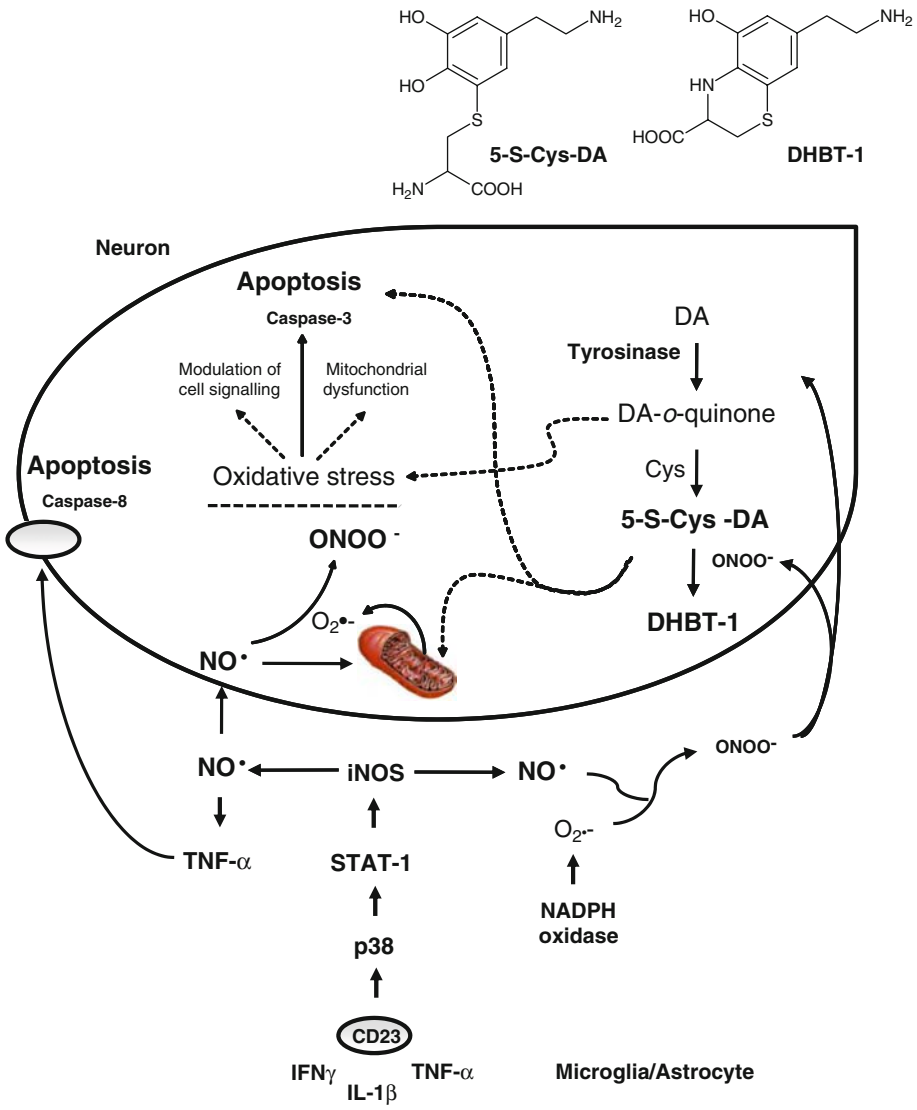

Fig. 1 Involvement of neuroinflammation, endogenous neurotoxins and oxidative stress in neurodegeneration. The structures of the 5-*S*-cysteinyl-dopamine (5-*S*-Cys-DA) and dihydrobenzothiazine-1 (DHBT-1) are shown

cell activation and resulting neuronal injury [70], via an inhibition of p38 and STAT-1, and a reduction in iNOS expression (Fig. 2). The structurally related flavanone hesperetin and other flavonoids appeared incapable of inhibiting pathways leading to $NO^{\bullet}$ production, although they were found to partially alleviate neuroinflammation through the inhibition of TNF-α production [70].

Flavonoids present in blueberry have also been shown to inhibit $NO^{\bullet}$, IL-1β and TNF-α production in activated microglia cells [33], while the flavonol quercetin [9], the flavones wogonin and bacalein [35], the flavanols catechin and epigallocatechin gallate (EGCG) [38] and the isoflavone genistein [4] have all been shown to attenuate microglia and/or astrocyte mediated neuroinflammation via mechanisms that include inhibition of: (1) iNOS and cyclooxygenase (COX-2) expression, (2) $NO^{\bullet}$ production, (3) cytokine release, and (4) NADPH oxidase activation and subsequent reactive oxygen species (ROS) generation, in astrocytes and microglia. All of these effects appear to rely via on an ability to directly modulate the protein and lipid kinase signalling pathways [58, 61, 78], for example, via the inhibition of MAPK signalling cascades, such as p38 or ERK1/2 which regulate both iNOS and TNF-α expression in activated glial cells [6] (Fig. 2). In this respect, fisetin inhibits p38 MAP kinase phosphorylation in LPS-stimulated BV-2 microglial cells [82] and the flavone luteolin inhibits IL-6 production in activated microglia via the inhibition of the JNK signalling pathway [21]. The effects of flavonoids on these kinases may influence downstream pro-inflammatory transcription factors important in iNOS transcription. One of these, nuclear factor-Kappa B (NF-κB), responds to p38 signalling and is involved in iNOS induction [7], suggesting that there is interplay between signalling pathways, transcription factors and cytokine production in determining the neuroinflammatory response in the CNS. In support of this, some flavonoids have been shown to prevent transcription factor activation, with the flavonol quercetin and the flavanone naringenin able to suppress NF-κB, signal transducer and activator of transcription-1 (STAT-1) and activating protein-1 (AP-1) activation in LPS- and IFN-γ-activated microglial cells [9, 70].

Inhibition of neurodegeneration

The underlying neurodegeneration observed in Parkinson's, Alzheimer's, and other neurodegenerative diseases is believed to be triggered by multi-factorial processes, including neuroinflammation, glutamatergic excitotoxicity, increases in iron and/or depletion of endogenous antioxidants [5, 22, 67]. There is a growing body of evidence to suggest that flavonoids and other polyphenols may be able to counteract this neuronal injury, thereby delaying the progression of these brain pathology [41, 58, 59]. For example, a Ginkgo biloba extract has been shown to protect hippocampal neurons against nitric oxide- and beta-amyloid-induced neurotoxicity [39]; and studies have demonstrated that the consumption of green tea may have beneficial effect in reducing the risk of Parkinson's disease [28, 42–44]. In agreement with the latter study, tea extracts and pure (−)-epigallocatechin-3-gallate (EGCG) have been shown to attenuate 6-hydroxydopamine-induced toxicity

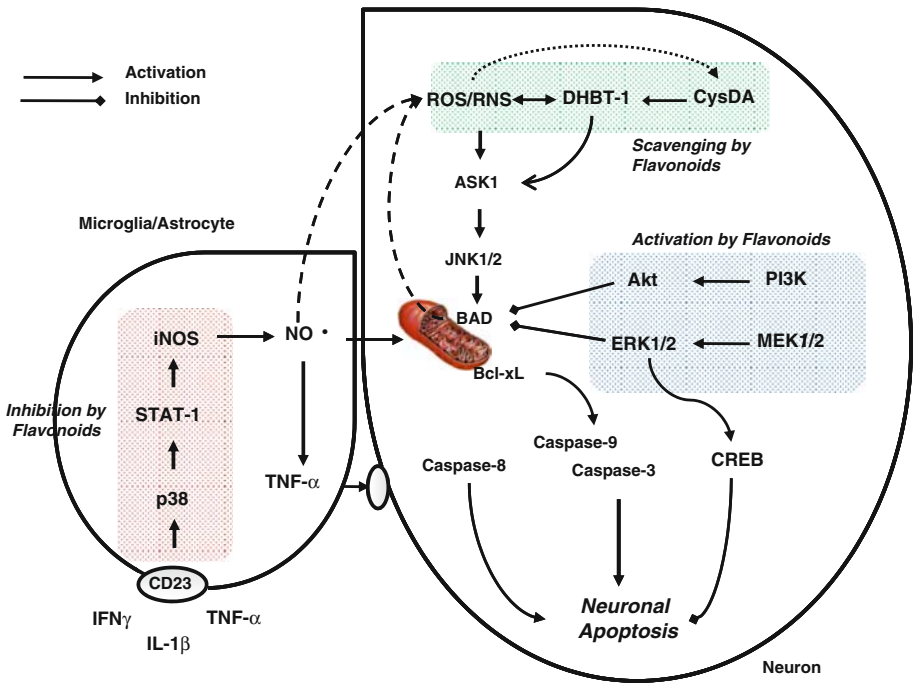

Fig. 2 The cellular mechanisms by which flavonoids and their metabolites protect against neuroinflammation and neuronal injury induced by 5-*S*-Cys-DA, DHBT-1 and related ROS. Flavonoids inhibit the p38 pathway glia cells leading to a reduction in iNOS expression and $NO^{\bullet}$ release. In neurons, they scavenge neurotoxic species and induce pro-survival signalling pathways, such as ERK1/2 and PI3-kinase/Akt, leading to an inhibition of neuronal apoptosis

[37], to protect against hippocampal injury during transient global ischemia [34] and to prevent nigral damage induced by 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) [36].

The death of nigral neurons in Parkinson's disease is thought to involve the formation of the endogenous neurotoxin, 5-*S*-cysteinyl-dopamine (5-*S*-cys-DA) and its oxidation product, dihydrobenzothiazine (DHBT-1) [18, 65] (Fig. 1). 5-*S*-cysteinyl-catecholamine conjugates possess strong neurotoxicity and initiate a sustained increase in intracellular ROS in neurons leading to DNA oxidation, caspase-3 activation and delayed neuronal death [65] (Fig. 1). Such adducts may be generated by reactive species [73] and have been observed to be elevated in the human substantia nigra of patients who died of Parkinson's disease [62], suggesting that such species may be potential endogenous nigral toxins. However, 5-*S*-cysteinyl-dopamine-induced neuronal injury is effectively counteracted by nanomolar concentrations of various flavonoids, including pelargonidin, quercetin, hesperetin, caffeic acid, the 4′-O-Me derivatives of catechin and epicatechin [73] (Fig. 2). Furthermore, in the presence of the flavanol, (+)-catechin, tyrosinase-induced formation of 5-*S*-cysteinyl-dopamine was inhibited by a mechanism linked to the capacity of catechin to undergo tyrosinase-induced oxidation to yield cysteinyl-catechin adducts [72]. In contrast, the inhibition afforded by flavanones, such as hesperetin, was not accompanied with the formation of cysteinyl-hesperetin adducts, indicating that it may inhibit via direct interaction with tyrosinase [72].

Reactive oxygen and nitrogen species have also been proposed to play a role in the pathology of many neurodegenerative diseases [22] (Fig. 1). There is abundant evidence that flavonoids are effective in blocking this oxidant-induced neuronal injury, although their potential to do so is thought not to rely on direct radical or oxidant scavenging activity [63, 64]. Instead, they are believed to act by modulating a number of protein kinase and lipid kinase signalling cascades, such as the PI3 kinase (PI3K)/Akt, tyrosine kinase, protein kinase C (PKC) and MAPK signalling pathways [58, 78]. Inhibitory or stimulatory actions at these pathways are likely to profoundly affect neuronal function by altering the phosphorylation state of target molecules, leading to changes in caspase activity and/or by gene expression [78]. For example, flavonoids have been observed to block oxidative-induced neuronal damage by preventing the activation of caspase-3, providing evidence in support of their potent anti-apoptotic action [63, 64]. The flavanols epicatechin and 3′-O-methyl-epicatechin also protect neurons against oxidative damage via a mechanism involving the suppression of JNK and downstream partners, c-jun and pro-caspase-3 [53]. Flavanones, such as hesperetin and its metabolite, 5-nitro-hesperetin, have been observed to inhibit oxidant-induced neuronal apoptosis via a mechanism involving the activation/phosphorylation of signalling proteins important in the pro-survival pathways [71]. Similarly, the flavone, bacalein, has been shown to significantly inhibit 6-hydroxydopamine-induced JNK activation and neuronal cell death and quercetin may suppress JNK activity and apoptosis induced by hydrogen peroxide [20, 75], 4-hydroxy-2-nonenal [68] and tumour necrosis factor-alpha (TNF-alpha) [30].

Modulation of memory and learning

There is now much evidence to suggest that fruit and vegetable derived phytochemicals, in particular flavonoids, are capable of promoting beneficial effects on memory and learning [23–27, 56, 57, 79]. It appears that these low molecular weight, non-nutrient components are able to impact upon memory through their ability to exert effects directly on the brains innate architecture for memory [60]. This innate cellular and anatomical architecture of the brain, and its role in the acquisition, storage and retrieval of memories, was originally postulated by Immanuel Kant in 1781 in his revolutionary "Critique of pure reason" [29]. Kant suggested that there must be such 'architecture' in the brain, in order that we may interpret sensory information (Kant's so called 'a priori' or 'innate knowledge'). This may now be interpreted not only psychologically but also physiologically [40, 46], in that one does not come to sensory data as a 'blank tablet', but rather brings a sort of relational structure within the nervous system to interpret sense data [1, 2, 46]. Consequently, the nature of our sensory impressions is determined a priori by the physiological apparatus of our senses or by the sensory nerve centres and the memory acquisition, storage and recall centres of the brain [2]. It is now understood that this underlying structure has a molecular basis and thus interaction with this physiological apparatus may yield changes in the way we acquire, store and retrieve memory. Furthermore, this innate cellular architecture is well known to deteriorate with aging, with neuronal populations or synaptic connections lost over time, leaving the system less efficient in the processing and storage of sensory information.

The ability of flavonoids to impact upon this memory system appears to be, in part, underpinned by an ability to interact with this molecular and physiological apparatus. The concentrations of flavonoids and their metabolites which reach the brain are thought to be sufficiently high to exert pharmacological activity at receptors, kinases and transcription factors. Although the precise site of their interaction with signalling pathways remains unresolved, evidence indicates that they are capable of acting in a

number of ways: (1) by binding to ATP sites on enzymes and receptors, (2) by modulating the activity of kinases directly, i.e. MAPKKK, MAPKK or MAPK, (3) by affecting the function of important phosphatases which act in opposition to kinases, (4) by preserving Ca^{2+} homeostasis, thereby preventing Ca^{2+}-dependent activation of kinases in neurons, and (5) by modulating signalling cascades lying downstream of kinases, i.e. transcription factor activation and binding to promoter sequences. By affecting such pathways they have the potential to induce new protein synthesis in neurons and thus an ability to induce morphological changes which have a direct influence on memory acquisition, consolidation and storage.

Various individual cascades have been linked with this control of de novo protein synthesis in the context of LTP, synaptic plasticity and memory (Fig. 3): (i) cAMP-dependent protein kinase (protein kinase A), (ii) protein kinase B (PKB/Akt) 78, (iii) protein kinase C (PKC), (iv) calcium-calmodulin kinase (CaMK) 80 and (v) extracellular signal-regulated kinase (ERK) [61]. All five pathways converge to signal to the cAMP-response element-binding protein (CREB), a transcription factor which binds to the promoter regions of many genes associated with synapse re-modelling, synaptic plasticity and memory (Fig. 3). Flavonoids are now well known to modulate neuronal signalling pathways crucial in inducing synaptic plasticity [61], and although each of these pathways are known to be involved

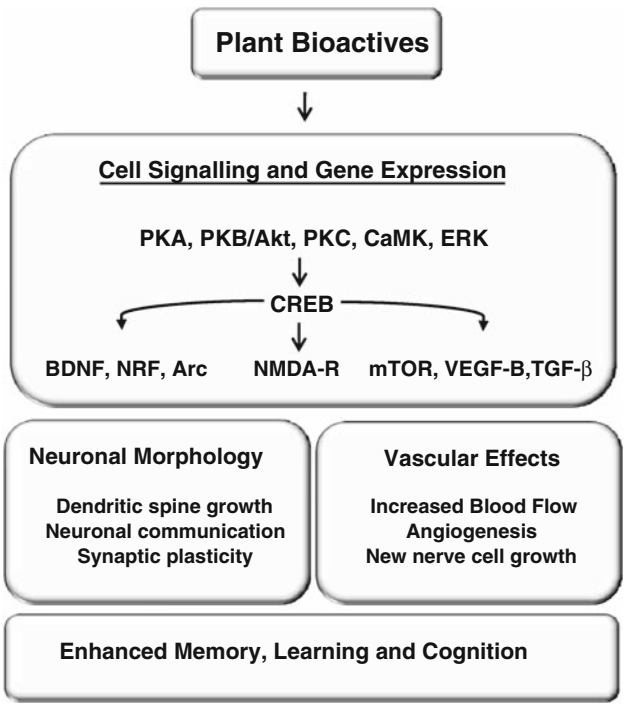

Fig. 3 Flavonoid-induced activation of neuronal signalling and gene expression in the brain. Such processes may lead to changes in synaptic plasticity and neurogenesis in the brain which ultimately influence memory, learning and cognition

in increasing the number of, and strength of, connections between neurons, flavonoids appear to interact primarily with the ERK and PKB/Akt pathways [55, 58, 66]. The activation of these pathways by blueberry flavonoids, along with the activation of the transcription factor CREB and production of neurotrophins such as brain-derived neurotrophic factor brain-derived neurotrophic factor (BDNF) is known to be required during memory acquisition and consolidation and agents capable of inducing pathways leading to CREB activation will have the potential to enhance both short-term and long-term memory [79], by providing a more efficient structure for interpreting afferent nerve or sensory information. One mechanism by which this may come about is through flavonoid-induced increases in neuronal spine density and morphology, two factors considered vital for learning and memory [17]. Changes in spine density, morphology and motility have been shown to occur with paradigms that induce synaptic, as well as altered sensory experience, and lead to alterations in synaptic connectivity and strength between neuronal partners, affecting the efficacy of synaptic communication (Fig. 3). In support of this, high flavanol and anthocyanin supplementation has been shown to cause activation of mTOR and an increased expression of hippocampal Arc/Arg3.1 [79], events which are likely to facilitate changes in synaptic strength through the stimulation of the growth of small dendritic spines into large mushroom-shaped spines.

There is also evidence to suggest that flavonoids may be capable of preventing many forms of cerebrovascular disease, including those associated with stroke and dementia [10, 11]. Flavonoids may exert effects on endothelial function and peripheral blood flow [54], and these vascular effects are potentially significant as increased cerebrovascular function is known to facilitate adult neurogenesis in the hippocampus [14] (Fig. 3). Indeed, new hippocampal cells are clustered near blood vessels, proliferate in response to vascular growth factors and may influence memory [49]. Efficient cerebral blood flow (CBF) is vital for optimal brain function, with several studies indicating that there is a decrease in CBF in patients with dementia [48, 52]. Brain imaging techniques, such as ‘functional magnetic resonance imaging’ (fMRI) and ‘trans-cranial Doppler ultrasound’ (TCD) has shown that there is a correlation between CBF and cognitive function in humans [52]. For example, CBF velocity is significantly lower in patients with Alzheimer disease and low CBF is also associated with incipient markers of dementia. In contrast, non-demented subjects with higher CBF were less likely to develop dementia. In this context, flavonoids have been shown to cause significantly increased CBF in humans, 1–2 h post intervention [12, 13]. After consumption of a flavanol-rich cocoa drink, the ‘flow oxygenation level dependent’ (BOLD)-fMRI showed an increase in blood flow in certain regions of the brain, along

with a modification of the BOLD response to task switching. Furthermore, 'arterial spin-labelling sequence magnetic resonance imaging' (ASL-MRI) [77] also indicated that cocoa flavanols increase CBF up to a maximum of 2 h after ingestion of the flavanol-rich drink. In support of these findings, an increase in CBF through the middle cerebral artery has been reported after the consumption of flavanol-rich cocoa using TCD [12].

Summary

The neuroprotective actions of dietary flavonoids involve a number of effects within the brain, including a potential to protect neurons against injury induced by neurotoxins, an ability to suppress neuroinflammation, and the potential to promote memory, learning and cognitive function. This multiplicity of effects appears to be underpinned by two processes. Firstly, they interact with important neuronal signalling cascades in the brain leading to an inhibition of apoptosis triggered by neurotoxic species and to a promotion of neuronal survival and differentiation. These include selective actions on a number of protein kinase and lipid kinase signalling cascades, most notably the PI3K/Akt and MAP kinase pathways which regulate pro-survival transcription factors and gene expression. It appears that the concentrations of flavonoids encountered in the brain may be sufficiently high to exert such pharmacological activity on receptors, kinases and transcription factors. Second, they are known to induce beneficial effects on the peripheral and cerebral vascular system, which lead to changes in cerebrovascular blood flow. Such changes are likely to induce angiogenesis, new nerve cell growth in the hippocampus and changes in neuronal morphology, all processes known to important in maintaining optimal neuronal function and neuro-cognitive performance.

The consumption of flavonoid-rich foods, such as berries and cocoa, throughout life holds a potential to limit neurodegeneration and prevent or reverse age-dependent deteriorations cognitive performance. However, at present, the precise temporal nature of the effects of flavonoids on these events is unclear. For example, it is presently unclear as to when one needs to begin consuming flavonoids in order to obtain maximum benefits. It is also unclear which flavonoids are most effective in inducing these changes. However, due to the intense interest in the development of drugs capable of enhancing brain function, flavonoids may represent important precursor molecules in the quest to develop of a new generation of brain enhancing drugs.

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