Potential Neuroprotective Actions of Dietary Flavonoids

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David Vauzour, Marcus Rattray, Robert J. Williams and Jeremy P. E. Spencer

Contents

Abstract

Flavonoids exert a multiplicity of neuroprotective actions 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,

D. Vauzour (✉)
Department of Nutrition, Norwich Medical School, Faculty of Medicine and Health Sciences, University of East Anglia, Norwich, UK
e-mail: d.vauzour@uea.ac.uk

M. Rattray
Reading School of Pharmacy, University of Reading, Reading, UK
e-mail: m.a.n.rattray@reading.ac.uk

R.J. Williams
Department of Biology and Biochemistry, University of Bath, Bath, UK
e-mail: r.j.williams@bath.ac.uk

J.P.E. Spencer
Molecular Nutrition Group, Centre for Integrative Neuroscience and Neurodynamics, School of Chemistry, Food and Pharmacy, University of Reading, Reading, UK
e-mail: j.p.e.spencer@reading.ac.uk

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learning, and cognitive function. These effects appear to be underpinned by their interaction with critical protein and lipid kinase signaling cascades in the brain leading to an inhibition of apoptosis triggered by neurotoxic species and to a promotion of neuronal survival and synaptic plasticity. Through these mechanisms, the consumption of flavonoid-rich foods throughout life holds the potential to limit neurodegeneration, decrease neuroinflammation, and prevent or reverse age-dependent loses in cognitive performance. The intense interest in the development of drugs capable of enhancing brain function means that flavonoids may represent important precursor molecules in the quest to develop a new generation of brain-enhancing drugs.

Keywords

Flavonoids • memory • neurodegeneration • neuroinflammation • signaling pathways

Abbreviations

AD	Alzheimer's disease
Arc/Arg3.1	Activity-regulated cytoskeletal-associated protein
ASK1	Apoptosis signal-regulating kinase 1
BBB	Blood-brain barrier
BDNF	Brain-derived neurotrophic factor
CaMKIV	Calcium/calmodulin kinase IV
CREB	Cyclic AMP regulatory-binding protein
EGCG	Epigallocatechin-3-gallate
ERK1/2	Extracellular signal-regulated kinase 1 and 2
GSPE	Grape seed polyphenolic extract
JNK	c-jun N-terminal kinase
LTP	Long-term potentiation
MAPK	Mitogen-activated protein kinase
MPTP	1-Methyl-4-phenyl-1,2,3,6-tetrahydropyridine
mTOR	The mammalian target of rapamycin
NGF	Nerve growth factor
PD	Parkinson's disease
PI-3K	Phosphoinositide 3-kinase
PKB	Protein kinase B
PKC	Protein kinase C
ROS	Reactive oxygen species

1 Introduction

Due to significant advances in medical science over the past century, there has been a gradual increase in human life span, with people over the age of 60 expected to

double between 2000 and 2050 [1]. Although this is a great achievement, an increase in age-related diseases including neurodegenerative disorders has been observed to parallel the extended life span. This will soon have profound economical and social implications, and it is already becoming a burden for health-care systems. Aging is an important risk factor for neurodegenerative diseases, of which Alzheimer's disease and Parkinson's disease are the most common. Neuronal loss underlies the clinical impairment in these conditions, and this cell death is associated with numerous pathogenic cellular and molecular events [2]. The majority of existing drug treatments for neurodegenerative disorders can afford symptomatic relief but are not disease-modifying, that is, cannot prevent the underlying degeneration of neurons. Therefore, there is an urgent need to develop therapeutic interventions capable of preventing the progressive loss of neurons. Because many of these neurodegenerative diseases have been linked to increases in oxidative stress, strong efforts have been aimed at exploring dietary and therapeutic antioxidant strategies to combat the neuronal damage. Recent attention has focused on the neuroprotective effects of major dietary polyphenols called flavonoids, which have been effective in protecting against both age-related cognitive and motor decline in vivo. While historically research focused on their antioxidant properties [3], recent data support the view that flavonoids, and their in vivo metabolites, do not act as conventional hydrogen-donating antioxidants but may exert modulatory actions in cells through actions at protein kinase and lipid kinase signaling pathways [4]. This chapter will highlight the neuroprotective mechanisms of flavonoids through their ability to interact with neuronal signaling pathways and their potential to modulate neuroinflammation, to counteract neurotoxin-induced neurodegenerative disorders, and to enhance memory, learning, and cognitive performances.

2 Flavonoid Bioavailability and Accessibility to the Brain

Many studies have reported the bioavailability of flavonoids in the systemic circulation [5–8], however, little is known about their uptake within the central nervous system (CNS; brain and spinal cord). In order to understand whether these phenolic compounds affect neurons and glial cells, it is crucial to ascertain their presence within the cerebral tissue. In order for flavonoids to access the brain, they must first cross a tightly regulated, selectively permeable endothelial cell layer which isolates the CNS tissue from the vasculature, the blood-brain barrier (BBB). The BBB is permeable to nutrients and actively excludes many substances from the central nervous system [9]. Using in vitro models, researchers have provided the first information on the capacity of flavonoids to traverse the BBB [10] and demonstrated that less polar *O*-methylated metabolites appear to be capable to greater brain uptake than the more polar flavonoid glucuronides [11]. The degree of entry of flavonoids or their metabolites into the CNS was also observed to depend on their interactions with transporters, such as P-glycoprotein, expressed in the BBB whose function is to export xenobiotics and unwanted metabolites [12].

For example, P-glycoprotein is considered to be responsible for the differences between naringenin and quercetin flux into the brain in situ [10]. Further to in vitro models, animal investigations have also substantiated these findings and indicated that flavanones were able to enter the brain following their intravenous administration [13], while epigallocatechin gallate [14], epicatechin [15], and anthocyanins [16, 17] were found in the brain after their oral administration. Furthermore, several anthocyanins have been identified in different regions of the rat [18, 19] and pig brains [20, 21] of blueberry-fed animals. Altogether, these results indicate that many flavonoids are able to traverse the BBB and localize in the brain, suggesting that they can directly exert neuroprotective and neuromodulatory actions.

3 Flavonoids and Memory, Learning, and Neurocognitive Performance

There is a growing interest in the potential of phytochemicals to improve memory, learning, and general cognitive ability [22, 23]. A recent prospective study aimed at examining flavonoid intake in relation to cognitive function and decline has provided strong evidence that dietary flavonoid intake is associated with better cognitive evolution, that is, the preservation of cognitive performance with aging [24]. In particular, subjects included in the two highest quartiles of flavonoid intake had better cognitive evolution than subjects in the lowest quartile and after 10 years follow-up. Subjects with the lowest flavonoid intake had lost on average 2.1 points on the Mini-Mental State Examination, whereas subjects with the highest quartile had lost 1.2 points. Such data provides a strong indication that regular flavonoid consumption may have a positive effect on neurocognitive performance as we age.

There has been much interest in the neurocognitive effects of soy isoflavones, primarily in postmenopausal women [25, 26]. Isoflavone supplementation has been observed to have a favorable effect on cognitive function [27], particularly verbal memory, in postmenopausal women [28], and a 6- and 12-week supplementation was observed to have a positive effect on frontal lobe function [29]. Furthermore, animal studies have also indicated that isoflavones are capable of improving cognitive function [30, 31]. However, there is still uncertainty regarding their effects as some large intervention trials have reported that isoflavone supplementation does not lead to cognitive improvements [32]. The rationale behind the potential of isoflavones to exert positive effects on cognitive function is believed to lie primarily in their potential to mimic the actions and functions of estrogens in the brain [33]. For example, postmenopausal women who undertake estrogen replacement therapy have a significantly lower risk for the onset of Alzheimer's disease than women who do not [34]. They may also be effective by affecting the synthesis of acetylcholine and neurotrophic factors such as brain-derived neurotrophic factor (BDNF) and nerve growth factor (NGF) in hippocampus and frontal cortex [35, 36].

There is also extensive evidence that berries, in particular blueberries, are effective at reversing age-related deficits in motor function and spatial working memory [37–39]. In addition to spatial memory, blueberry supplementation has

been shown to improve "object recognition memory" [40] and "inhibitory fear conditioning learning" [41, 42]. Blueberry appears to have a pronounced effect on short-term memory [42] and has also been shown to improve long-term reference memory following 8 weeks of supplementation [38]. Tests using a radial arm maze have supported these findings and have provided further evidence for the efficacy of blueberries [39]. Indeed, these have shown that improvements in spatial memory may emerge within 3 weeks, the equivalent of about 3 years in humans. The beneficial effects of flavonoid-rich foods and beverages on psychomotor activity in older animals have also been reported [37, 43]. In addition to those with berries, animal studies with tea [44] and pomegranate juice [45] or pure flavonols such as quercetin, rutin [46], or fisetin [47] have provided further evidence that dietary flavonoids are beneficial in reversing the course of neuronal and behavioral aging.

The flavonoid-rich plant extract, *Ginkgo biloba*, has also been shown to induce positive effects on memory, learning, and concentration [48, 49]. *Ginkgo biloba* has a prominent effect on brain activity and short-term memory in animals and humans suffering from cognitive impairment [50, 51] and promotes spatial learning in aged rodents [52, 53]. Furthermore, *Ginkgo biloba* promotes inhibitory avoidance conditioning in rats with high-dose intake leading to short-term, but not long-term, passive avoidance learning in senescent mice [54, 55]. However, the pharmacological mechanisms by which *Ginkgo biloba* promotes cognitive effects are unclear, with its ability to elicit a reduction in levels of reactive oxygen species (ROS) [56], to increase cerebral blood flow [57], to modulate membrane fluidity [54], to interact with muscarinic cholinergic receptors [58], and to protect the striatal dopaminergic system [59] all being suggested as possible mechanisms underlying its actions in the CNS.

4 Flavonoids and Neurodegeneration

There are a number of epidemiological studies which suggest that plant-derived flavonoid-rich foods or supplements might delay the initiation and progression of Alzheimer's disease (AD) and related neurodegenerative disorders. With regard to AD, independent prospective cohort studies have associated the consumption of polyphenolic-rich vegetables, fruit juices, and red wine with delayed onset of the disease [60, 61]. This is in accordance with previous studies linking high consumption of flavonoids to improvements in dementia [24, 62], and collectively, these reports lend some support to the underlying hypothesis that dietary intervention with plant-derived flavonoid-rich foods or supplements could impact on the development of AD. Not all prospective studies have reached the same positive conclusions however, and in the Honolulu-Asia aging study, midlife flavonoid intake, as estimated using mean intake of green and black tea, was not associated with altered risk of late-life incident dementia [5]. Despite this, much of the subsequent work in the field has focused on the potential bioactivity of catechins which are abundant in tea. Indeed, the green tea flavanol epigallocatechin-3-gallate (EGCG) is regarded as a lead candidate molecule for use in AD and is part of an ongoing clinical trial

where it is being given in combination with donepezil to 50 patients with AD (NCT00951834).

Many of the preclinical studies of the effects of flavonoids in AD have focused on models where there is increased production of beta-amyloid (Aβ). Aβ is a small protein produced by the enzymatic cleavage of amyloid precursor protein (APP). Aβ is aggregation prone and forms oligomeric species which are directly toxic to synapses and can aggregate further to form amyloid plaques, extracellular protein deposits which are a hallmark of Alzheimer's disease pathology [63]. Studies using transgenic mouse models of AD pathology have begun to address the possible mechanisms involved in the apparently beneficial effects of catechin-rich diets. Oral administration of EGCG for 6 months to Tg2576 mice, a strain which overexpresses the Swedish mutation of APP, reduced Aβ pathology and improved cognition [64]. Similarly, long-term green tea catechin administration improved spatial learning and memory in senescence-prone mice [65]. The mechanisms underlying these changes are not clear but might be linked to increased non-amyloidogenic processing of APP, through stimulating the activity of α-secretase, which cleaves APP at a site which prevents the formation Aβ species [66–68], or could be due to disruption of the interaction of amyloid with cAbl/Fe65 which might alter its ability to be processed into toxic species [69]. Alternatively, it is conceivable that EGCG reduces Aβ plaque pathology by inhibiting amyloid aggregation and fibrillization either as a result of metal chelation activity [70–72] or by favoring the formation of nontoxic (off-target) oligomers [73]. Interestingly, in addition to possessing the ability to inhibit the formation of β-sheet rich amyloid fibrils, EGCG also converts large mature Aβ fibrils into smaller nontoxic aggregates [74]. These are significant observations although very serious consideration must be given as to whether dietary EGCG could drive Aβ disaggregation in AD brain as the micromolar concentrations required to exert these effects in vitro will not be easily achievable in vivo. Anti-amyloidogenic activity is not unique to EGCG, and a number of other flavonoids, most notably myricetin, bind to Aβ fibrils and prevent further fibrillization [75–77]. Gallic acid and catechin-rich grape seed polyphenolic extract (GSPE) administered for 5 months to Tg2576 mice also inhibited cognitive deterioration coincident with reduced levels of soluble high molecular weight oligomers of Aβ [78]. Repeated intraperitoneal injection of the polymethoxylated citrus flavone, nobiletin, has similar effects [79]. However, it is worth noting that beneficial effects have been observed with flavonoids in some AD mouse models without obvious alterations in pathology. For example, feeding blueberry to APP + PS1 double transgenic mice prevented deficits in cognitive performance at 12 months but without altering the Aβ burden [80].

Although these are clearly important studies in that they show in principle that chronic exposure to polyphenolics can influence AD pathology and behavior in vivo, it is likely that the optimal flavonoid structures possessing the necessary bioactivity and bioavailability have not yet been identified. Other mechanisms of action are also possible. Interestingly in this regard, certain flavonols and flavones have been reported to inhibit and suppress expression of an enzyme BACE-1, which is required for the production of Aβ from APP [81, 82]. This observation is

consistent with some of the observed Aβ lowering effects reported for flavonoid-rich extracts in vivo and in vitro. The identification of those flavonoid structures possessing the greatest potential inhibitory activity at BACE-1 and defining their precise mechanisms of action are needed.

Despite the well-established and compelling link between Aβ and AD, Aβ pathology and cognitive deficits are not well correlated. Consequently, beneficial effects of flavonoids on cognition may be unrelated to changes in Aβ per se but to key downstream changes, for example, in phosphorylation and fibrillization of tau, a protein which, when abnormally phosphorylated, is found in neurofibrillary tangles: another pathological hallmark of AD. Indeed, a number of flavonoids including myricetin and epicatechin 5-gallate have been shown to potently inhibit heparin-induced tau aggregation [83]. Moreover, grape seed polyphenolic extract (GSPE) also inhibits tau fibrillization, promotes the loss of preformed tau aggregates, and disrupts paired helical filaments [84–87]. (−)-Epigallocatechin-3-gallate (EGCG) appears to have broadly similar effects. (−)-Epicatechin and hesperetin hold the potential to inhibit the development of tau pathology through an alternative mechanism relating to their ability to enhance phosphorylation of a key regulatory enzyme, Akt, to inhibit GSK3β-induced hyperphosphorylation of tau [88, 89]. Whatever the mechanisms involved, collectively, this suggests that orally active flavonoids could have utility in AD beyond anti-Aβ actions.

The potential utility of flavonoids in neurodegeneration extends beyond dementia, and there is also considerable interest in their therapeutic potential in Parkinson's disease (PD). The neurodegeneration observed in PD appears to be triggered by multifactorial events including neuroinflammation, glutamatergic excitotoxicity, increases in iron, and/or depletion of endogenous antioxidants. There is a growing body of evidence to suggest that flavonoids may be able to counteract the neuronal injury underlying these disorders and thus slow the progression of the disease [23, 90]. There is good evidence to suggest that the consumption of green tea may have a beneficial effect in reducing the risk of PD [91], as has been extensively reviewed elsewhere [92, 93]. The efficacy of green tea is likely to be mediated by the effects of EGCG, which has been shown to attenuate the selective degeneration of dopamine neurons in animal models of PD induced by toxins including 6-hydroxydopamine [94] and MPTP [95]. The mechanism of protection is not known, but EGCG has been noted to interact with and modulate signaling pathways involved in neuroprotection, notably protein kinase C (PKC) and PI3 kinase, and has been implicated in reducing dopamine neuron damage in the substantia nigra by the chelation of iron: a mechanism which is also relevant to AD pathology. In vitro studies have also indicated that flavonoids might act to prevent PD pathology via their ability to prevent the formation of the endogenous neurotoxin, 5-*S*-cysteinyl-dopamine [96, 97].

EGCG can also reduce hippocampal neuronal injury induced by transient global ischemia [98]. Neuroprotective effects of flavonoids have also been observed in animal models of Huntington's disease, where the flavonol fisetin has been reported to be effective in reducing pathophysiology through its actions on the extracellular

signal-regulated kinase (ERK) pathway [99, 100]. Collectively, these studies suggest that flavonoids have the potential to confer benefit in diverse neurodegenerative disorders. Some of the major neuroprotective mechanisms are discussed in more detail below.

On a note of caution, however, there is still insufficient data to support the clinical use of flavonoids in the treatment of neurodegeneration, and there have been a number of disappointing results from human intervention studies for dementia with various dietary polyphenolics and antioxidants such as curcumin and Gingko biloba. The challenge ahead, therefore, is to proceed cautiously until rigorous randomized controlled clinical trials have been undertaken to determine empirically if flavonoids have efficacy in individuals affected by dementia and other neurodegenerative conditions.

5 Flavonoids and Neuroinflammation

Neuroinflammation is an important defense mechanism in the CNS which typically results from cellular damage but may also arise from other stimuli including infection. While it is a beneficial process, sustained neuroinflammatory processes are known to participate in CNS disease states [101]. For example, neuroinflammation contributes to the progressive neuron death observed in Alzheimer's disease [102], Parkinson's disease [103], and also with neuronal cell death and damage associated with cerebral ischemia [104].

Neuroinflammation is a complex process which involves several CNS cell types and is characterized by a strong reaction of glial cells, namely, microglia: cells within the CNS with an immune function, similar to macrophages; and astrocytes: cells which support neuronal function and maintain BBB integrity. During neuroinflammation, proinflammatory chemical mediators can be released from cells resident in the CNS, including neurons themselves, endothelial cells of the vasculature, and glial cells [101]. If the BBB is impaired, the neuroinflammatory stimulus may involve infiltrating T and B lymphocytes and macrophages which interact with cells resident in the CNS (neurons, microglia, astrocytes) through a complex series of interactions which are not completely understood [105]. In either case, the neuroinflammatory state is characterized by a marked activation of microglia and astrocytes. This response is typically associated with a coordinated cellular response which includes activation of intracellular pathways dependent on the proinflammatory transcription factor NF-κB (nuclear factor kappa-light-chain-enhancer of activated B cells). During neuroinflammation, activated microglia and astrocytes can release a number of factors which are toxic to neurons; these include inflammatory cytokines such as interleukin-1 beta (IL1β), tumor necrosis factor alpha (TNFα), nitric oxide (NO), and glutamate [101, 106, 107].

The best example of a CNS disease state with a major neuroinflammatory component is multiple sclerosis (MS), a chronic debilitating disease which is characterized by demyelination, progressive irreversible axonal damage, and inflammation [105]. The most effective therapies to date act by reducing inflammation and activation of the

immune system [108], showing that suppression of neuroinflammation has a positive effect in the disease. Dietary modification to improve multiple sclerosis symptoms and progression is an attractive proposition. Many patients with MS already use special diets, for example, gluten-free and milk-free or dietary supplementation with polyunsaturated fatty acids, vitamins, antioxidants, and/or herbal supplements (e.g., *Gingko biloba*). However, so far, a truly beneficial supplement or protective factor with a sound scientific base has not been elucidated. In part, this is attributed to poor design of the clinical trials [109] but also reflects the fact that the most potent interventions have not been found or, indeed, searched for systematically. Although to date there is no correlation between dietary intake of fruit and vegetables and incidence of MS [110, 111], flavonoids have the potential to be clinically useful in abrogating MS pathology. The studies to date have not excluded links between fruit and vegetable consumption and lowered MS incidence [112]. Dietary supplementation with flavonoid compounds has not been tested in man.

There is data which show encouraging positive effects of flavonoids in animal and in vitro models relevant to MS. A flavanol, (−)-epigallocatechin-3-*O*-gallate (EGCG), delivered orally reduces symptom severity in the autoimmune encephalomyelitis model of relapsing-remitting MS by reducing inflammation and increasing neuroprotection [113]. The flavonol quercetin has also been reported to be effective in the Experimental Autoimmune Encephalomyelitis (EAE) mouse model and reduces T cell proliferation in vitro at concentrations exceeding 10 μM [114]. Two Dutch groups independently identified a number of promising flavonoids using in vitro assays. Hendriks et al. [115] tested six flavonoids and found that one, luteolin, was the most effective at suppressing myelin phagocytosis by the macrophage cell line RAW 264.7 (IC_{50} of 20 μM). Several other flavonoids (quercetin, fisetin, and apigenin) were also effective in this assay but with potencies an order of magnitude lower. In the rat EAE model, luteolin (but not quercetin) showed clinical protection [116]. A separate group tested six flavonoids for their ability to alter T cell proliferation [117]. They showed that micromolar concentrations of luteolin, apigenin, fisetin, and quercetin (but not morin or hesperetin) suppress the production of the cytokine interferon-gamma (IFNγ) from lymph node-derived T cells but, paradoxically, worsen clinical severity in the EAE model. There is strong evidence that the flavone wogonin and a related compound baicalein can inhibit inflammatory responses in macrophages in vitro and in vivo [118, 119]. Thus, the studies to date show promising proof of concept of beneficial effects of flavonoids in suppressing immune and inflammatory responses in models of MS.

During activation of glial cells in neuroinflammatory states, various transcription factors including NF-κB, activator protein-1 (AP-1), and the signal transducer and activator of transcription-1 (STAT-1) have been shown to be involved in proinflammatory responses in astrocytes and microglia [120–124] which can contribute to neuronal death. Of these transcription factors, the NF-κB system is the most studied system in the context of neuroinflammation. Suppression of this pathway can be neuroprotective [125]. Its activation is seen in a number of neurodegenerative states, for example, in postmortem Alzheimer's disease patients, cells

in the vicinity of β-amyloid plaques show increased NF-κB immunoreactivity. Numerous flavonoids have been shown to have the ability to inhibit NF-κB in different cell types. The flavonol quercetin (50 μM) reduces phosphorylation of NF-κB subunits in human peripheral blood mononuclear cells [126] and suppresses NF-κB in a microglial cell line [127]. The flavanone oroxylin A (80 μM) reduces LPS-induced NO production and NF-κB activity in RAW 246.7 macrophages [128]. The flavone apigenin (5–15 μM) blocks LPS stimulation of the NF-κB pathway in RAW 246.7 macrophages and reduces κB-transcriptional activity [129]. The flavanol EGCG (5–15 μM) reduces LPS-induced NFκB-activity in peritoneal macrophages [130] and reduces T cell proliferation accompanied by inhibition of NF-κB [113]. Catechin (0.13–2 mM) has been reported to increase mouse microglial cell survival following exposure to the oxidative agent *tert*-butyl hydroperoxide (tBHP) by suppressing NF-κB activation [131]. The flavone luteolin (20 μM) reduced LPS-induced NF-κB transcriptional activity in fibroblasts [132]. The flavone wogonin (50 μM) was shown to reduce NF-κB activation in C6 glioma cells and prevent microglial activation [133], and baicalein is reported to inhibit $NO^{\bullet}$ production and NF-κB activity in microglia [134, 135]. The isoflavone genistein has been shown to reduce expression of iNOS in astrocytes, through inhibition of NF-κB activation [136]. While the data gives proof of principle that NF-κB is a potential target of flavonoids, the concentrations required for positive effects of those particular compounds in vitro are high, in the micromolar range, that is, at concentrations which cannot be obtained through the diet. It is likely that, for most of those studies, the antioxidant effects of the flavonoids used account for the positive effects on suppressing NF-κB activation. We have tested dietary-relevant concentrations of flavonoids and shown them to be bioactive in suppressing certain responses in primary astrocytes mediated by transcription via the antioxidant response element [137]. However, at this concentration range (0.1–1 μM), we find flavonoids of different classes are unable to suppress NF-κB signaling pathways in primary astrocytes [169]. Therefore, while flavonoids may be effective agents at suppressing neuroinflammation in vivo, at this time, we do not regard the NF-κB signaling system as the primary signaling system responsible for the effects of flavonoids in vivo.

6 Mechanisms Underpinning the Beneficial Effects of Flavonoids

Historically, the biological actions of flavonoids have been attributed to their antioxidant properties, either through their reducing capacities per se or through their possible influences on intracellular redox status. However, their classical hydrogen-donating antioxidant activity is unlikely to be the sole explanation for the bioactivity of flavonoids in vivo, as during absorption they are extensively metabolized to glucuronides, sulfates, and *O*-methylated forms which are reduced in their antioxidant potential [4]. Rather, it has become evident that flavonoids are more likely to exert their neuroprotective actions by the modulation of intracellular

signaling cascades, of particular interest in this context are those protein kinases which are central to pro-survival or pro-death pathways in neurons.

After ingestion, flavonoids are thought to reach sufficiently high concentrations in the CNS, that is, in the high nanomolar range, to exert pharmacological activity by binding to specific protein targets. Numerous studies now show important effects of flavonoids at sub-micromolar concentrations where antioxidant effects are unlikely to be relevant. The effects of flavonoids on neuronal signaling pathways are highly concentration dependent and are likely to be related to their ability to exert high-affinity receptor agonist-like actions at low concentrations (low to mid nanomolar) and direct enzyme inhibition at higher concentrations (high nanomolar to micromolar) [138, 139].

The precise site for the first point of interaction of flavonoids with neurons is still unclear in most cases. Potential flavonoid-binding sites on neurons include adenosine [140], $GABA_A$ [141, 142], and testosterone receptors [143], and a specific plasma membrane binding site for polyphenols in CNS tissue has been proposed [144]. Evidence indicates that they are capable of regulating signaling pathways, particularly protein kinases, in a number of ways which include: (1) binding to enzymes or receptors which control kinase activation, (2) by modulating the activity of kinases directly, (3) by affecting the function of important phosphatases, which act in opposition to kinases, and (4) by modulating signaling cascades lying downstream of kinases, that is, transcription factor activation to selectively control gene expression [23, 145]. It is beyond the scope of this chapter to list all the pathways which have been shown to be regulated by flavonoids, so we focus on a few key signaling pathways which are intimately associated with neuron survival and plasticity.

There is much evidence to support the actions of nanomolar concentrations of flavonoids, in particular flavanols and flavanones, on the ERK pathway [89, 146], which are, in general, calcium dependent and mediated by interactions with upstream kinases MEK1 and MEK2 and potentially membrane receptors [147]. ERK activation often leads to the activation of the cAMP response element-binding protein (CREB), a transcription factor. CREB is considered to be critical in the induction of long-lasting changes in synaptic plasticity and memory [148, 149]. CREB activation regulates the expression of a number of important genes, including brain-derived neurotrophic factor (BDNF), thus has a pivotal role in controlling neuronal survival and synaptic function in the adult central nervous system [150, 151]. Regulation of BDNF is of particular interest as it is linked with the control of synaptic plasticity and long-term memory [152]. Decreases in BDNF and pro-BDNF have been reported in Alzheimer's disease [153], and a polymorphism that replaces valine for methionine at position 66 of the pro-domain of BDNF is associated with memory defects and abnormal hippocampal function in humans [154].

Recent studies have shown that spatial memory performance in rats supplemented with blueberry correlates well with the activation of (CREB) and with increases of BDNF in the hippocampus [42]. Blueberry flavonoid-induced activation of CREB and BDNF expression has also been shown to lead to the activation of the PI3 kinase/Akt signaling pathway [42], via the binding of BDNF to

pre- or postsynaptic TrkB receptors. Fisetin, a flavonoid found in strawberries, has been shown to improve long-term potentiation and to enhance object recognition in mice by a mechanism dependent on the activation of ERK and CREB [155].

In general, in vitro studies show that many flavonoids, at submicromar concentrations, activate ERK, as determined by measuring increased phosphorylation of this enzyme. In cortical neurons, the flavanol (−)-epicatechin (0.1 and 0.3 μM) induces both ERK1/2 and CREB activation [47], while nanomolar concentrations of quercetin are effective at enhancing CREB activation [156]. Other flavonoids have also been found to influence the ERK pathway, with the citrus flavanone, hesperetin, capable to activating ERK1/2 signaling in cortical neurons at nanomolar concentrations [157], and flavanols such as EGCC restoring ERK1/2 activities in 6-hydroxydopamine-treated or serum-deprived neurons [94]. This ability to activate the ERK pathway is not restricted to neurons and has also been observed in fibroblasts exposed to nanomolar concentrations of epicatechin [158].

As well as effecting the ERK/CREB/BDNF axis, flavonoids are known to modulate the activity of an enzyme system associated with neuroprotection, Akt (also known as PKB). One of the major enzymes which controls Akt/PKB activity is the lipid kinase, PI3K. In cortical neurons, flavonoids such as the citrus flavanone hesperetin (0.1 and 0.3 μM) cause the activation of Akt/PKB and the consequent inhibition of proteins associated with cell death such as apoptosis signal-regulating kinase 1 (ASK1), Bad, caspase-9, and caspase-3 [89]. The activation of Akt by flavonoids in hippocampal neurons has been shown to trigger the increased translation of specific mRNA subpopulations [159], including the activity-regulated cytoskeletal-associated protein (Arc/Arg3.1) [42]. Arc is also under the regulatory control of both BDNF [160] and ERK signaling [161]. Increased Arc expression may facilitate changes in synaptic strength and the induction of morphological changes in dendritic spines [162]. In support of this, studies have indicated that changes in neuronal morphology occur in response to flavonoid supplementation [163] and that certain flavonoids can influence neuronal dendrite outgrowth in vitro [164] (Fig. 84.1).

As well as pro-survival effects, some flavonoids may inhibit important protective enzymes. Flavonoids can inhibit PI3K via direct interactions with its ATP binding site [165]. The structure of flavonoids determines whether or not they act as potent inhibitors of PI3K [166]. One of the most selective PI3K inhibitors available, LY294002, was modeled on the structure of quercetin [167, 168]. Quercetin and some of its in vivo metabolites have been shown to be neurotoxic in vitro, by inhibiting pro-survival Akt/PKB signaling pathways by a mechanism of action consistent with quercetin and its metabolites acting at and inhibiting PI3K activity [156]. In addition, some flavonoids may be capable of interacting directly with ERK kinases, such as MEK-1 to cause ERK inhibition: the flavone backbone (2-phenyl-1,4-benzopyrone) has close structural homology to a specific MEK-1 inhibitor, PD98059 (2′-amino-3′-methoxyflavone). This data suggests that flavonoid supplementation must be treated with caution; while many compounds are likely to enhance neuroprotective signaling, others may produce unwanted inhibition of key enzymes important for cell survival.

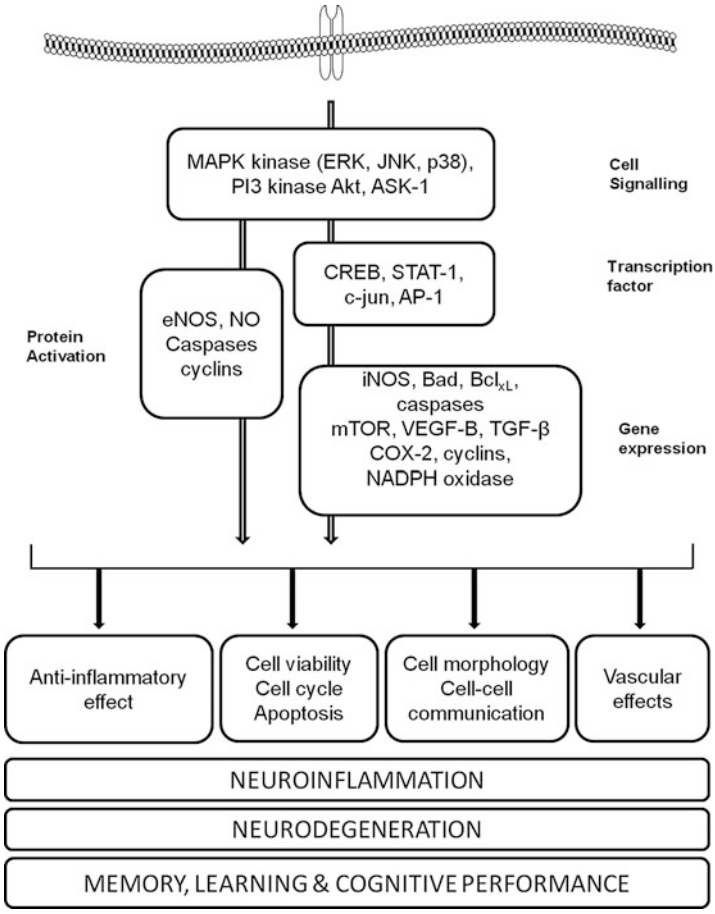

Fig. 84.1 *The interaction of flavonoids with cellular signaling pathways involved in neurodegeneration, neuroinflammation, and learning and memory*. Flavonoid-induced activation and/or inhibition of MAP kinase and PI3 kinase signaling leads to the activation of transcription factors which drive gene expression. For example, activation of ERK/Akt and the downstream transcription factor CREB by flavonoids may promote changes in neuronal viability and synaptic plasticity, which ultimately influence neurodegenerative processes. Flavonoid-induced inhibition of the JNK, ASK1, and p38 pathways leads to an inhibition of both apoptosis in neurons and a reduction of neuroinflammatory reactions in microglia (reduction in iNOS expression and $NO^{\bullet}$ release). Alternatively, their interaction with signaling may lead to direct activation of proteins such as eNOS, which controls nitric oxide release in the vasculature and thus may influence cerebral blood flow

7 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 their capacity to interact with important neuronal signaling cascades in the brain leading to an inhibition of apoptosis triggered by neurotoxic species and to a promotion of neuronal survival and differentiation. Although the consumption of flavonoid-rich foods throughout life may hold a potential to limit neurodegeneration and prevent or reverse age-dependent deteriorations in cognitive performance, at present, the precise temporal nature of the effects of flavonoids on these events is unclear. For example, when one needs to begin consuming flavonoids in order to obtain maximum benefits is not yet known. There are a vast number of flavonoids available, and while many have similar beneficial effects on neuroprotection in animal models, those flavonoids which are the most effective are not yet known. 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 a new generation of brain-enhancing drugs.

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