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Neurohormetic phytochemicals: low-dose toxins that induce adaptive neuronal stress responses

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Diets rich in vegetables and fruits are associated with reduced risk of several major diseases, including neurodegenerative disorders. Although some beneficial phytochemicals might function solely as antioxidants, it is becoming clear that many of the beneficial chemicals in vegetables and fruits evolved as toxins (to dissuade insects and other predators) that, at subtoxic doses, activate adaptive cellular stress-response pathways in a variety of cells including neurons. Examples of such 'preconditioning' or 'neurohormesis' pathways include those involving cell-survival signaling kinases, the transcription factors NRF2 and CREB, and histone deacetylases of the sirtuin family. In these ways, neurohormetic phytochemicals such as resveratrol, sulforaphanes and curcumin might protect neurons against injury and disease by stimulating the production of antioxidant enzymes, neurotrophic factors, protein chaperones and other proteins that help cells to withstand stress. Thus, as we discuss in this review, highly conserved longevity and survival pathways in neurons are the targets of many phytochemicals.

Neurohormesis: what it is and how it works

Hormesis refers to a process in which exposure to a low dose of an agent that is toxic at higher doses induces a beneficial effect on the cell or organism. The term hormesis has been widely used in the toxicology field, where it is defined as 'an adaptive response characterized by biphasic dose responses of generally similar quantitative features with respect to amplitude and range of the stimulatory response that are either directly induced or the result of compensatory biological processes following an initial disruption in homeostasis' [1]. This article focuses on 'neurohormesis', which we define as the adaptive process by which neurons (and hence nervous systems and organisms) respond to a moderate level of stress by enhancing their ability to resist a more severe stress that might otherwise be lethal or cause dysfunction or disease (Figure 1). Examples of neurohormesis include ischemic preconditioning [2] and adaptive responses of neurons to moderate-intensity excitatory neurotransmission [3], exercise [4] and dietary restriction [5]. Several endogenous neurotoxic molecules can induce neurohormesis, including nitric oxide [6], carbon monoxide [7], glutamate [8] and Ca^{2+} [9].

In most of the cases where neurohormesis has been documented and the mechanism investigated, exposure of neurons to the hormetic stressor results in changes in gene expression that appear to mediate stress resistance (Figure 1). For example, ischemic preconditioning induces the expression of genes encoding neuroprotective proteins including protein chaperones such as heat-shock proteins (HSP) [10], neurotrophic factors such as brain-derived neurotrophic factor (BDNF) [11], anti-apoptotic proteins such as Bcl-2 family members [12] and mitochondrial uncoupling proteins [13]. Similarly, dietary restriction upregulates the expression of HSP-70, BDNF and mitochondrial uncoupling proteins [14–16]. Transcription factors that mediate neurohormesis responses to various stressors include NF-κB, cAMP-response-element-binding protein (CREB), nuclear factor E2-related factor (NFE2L2, or NRF2) and hypoxia-inducible factor 1 (HIF1) [17–20]. Additional neurohormetic mechanisms might include modulation of the expression of proteins involved in the regulation of oxidative stress and cellular Ca^{2+} homeostasis [21].

Health-promoting phytochemicals: an evolutionary perspective

Why do plant cells contain so many different chemicals that exert biological effects on organisms that ingest them? Evolutionary considerations suggest that many of the phytochemicals with biological activities that are beneficial for mammals evolved as toxins that protect the plants against insects and other damaging organisms [22]. In contrast to motile organisms. which can escape predators, immobile plants discourage predators by concentrating noxious chemicals in their leaves, flowers and roots. Plants have been evolving and improving their natural chemical defenses against predators for hundreds of millions of years, during which time they developed metabolic pathways to produce chemicals that target specific molecules in the cells of insects and other organisms [23]. There are thousands of such 'biopesticides', which include numerous classes of molecular structures [22]. Examples include: flavonoids such as rotenone and myricetin; terpenoids such as frarnesol and camphor; alkaloids such as strychnine, nicotine and caffeine; indoles such as indole-3-acetonitrile; glucosinolates such as 2-pentylethyl isothiocyanate; coumarins such as xanthotoxin and coumarin; phenylpropanols such as myristicin and eugenol; and cardenolides such

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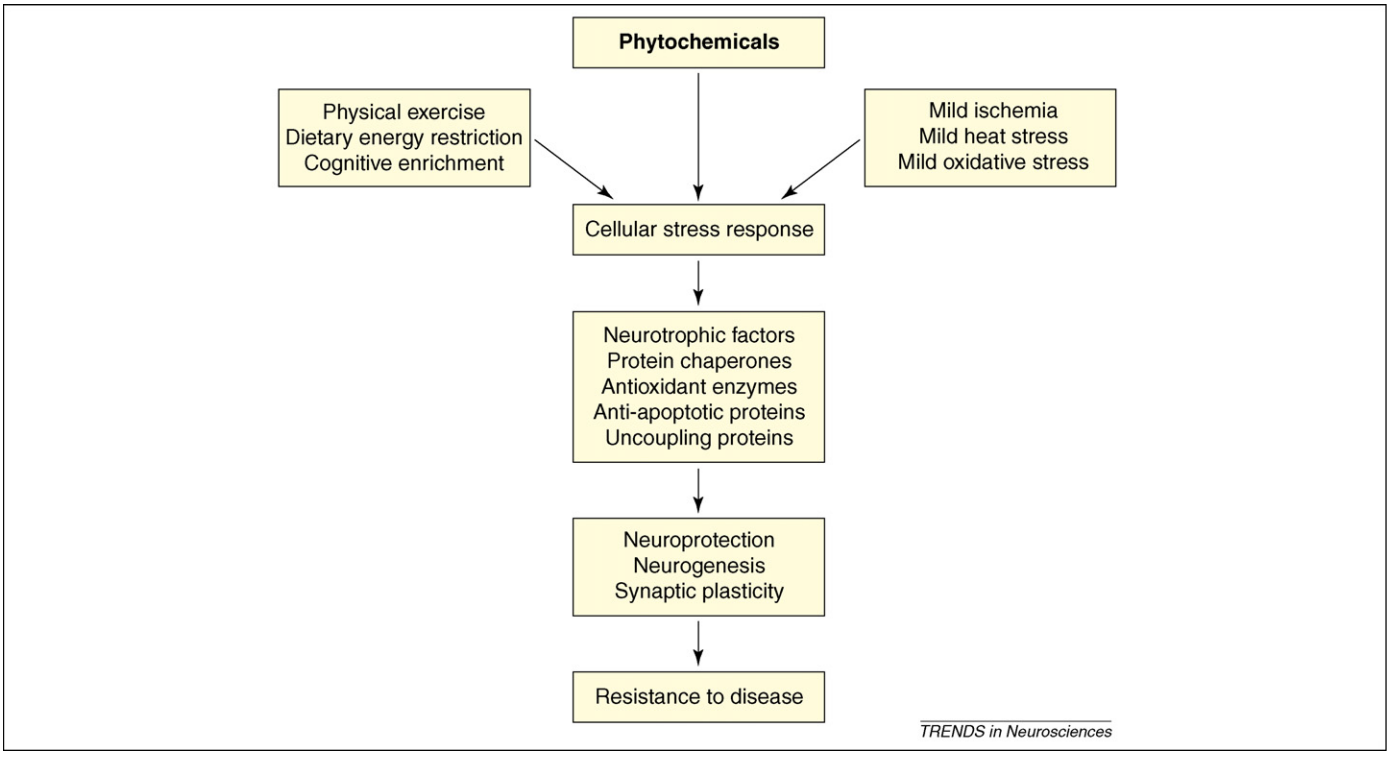

Figure 1. Disparate environmental and dietary factors activate common hormetic cellular stress-response pathways. Exercise, dietary energy restriction and cognitive stimulation are all known to enhance neurogenesis and synaptic plasticity, and can protect neurons against injury and neurodegenerative disorders. Exposure to one or more of these environmental factors induces the expression of neuroprotective proteins such as neurotrophic factors, protein chaperones, antioxidant enzymes, anti-apoptotic proteins and mitochondrial uncoupling proteins. More direct exposure of neurons to sublethal levels of oxidative stress, heat stress or metabolic stress (e.g. mild ischemia) also induces the expression of multiple stress-resistance proteins. Phytochemicals might exert many of their beneficial actions by inducing a mild stress in neurons.

as digitoxin. However, whereas at high doses many different phytochemicals are carcinogens and/or neurotoxins, at lower doses they can be beneficial for health. This is perhaps best established in the cancer literature, where many different 'carcinogens' can actually prevent the development of cancers when cells or animals are exposed to low doses of the same chemical [24].

Before focusing on the effects of phytochemicals on the nervous system, it is of value to describe briefly a few examples of evidence supporting the health-promoting effects of phytochemical toxins. Garlic and onions contain high amounts of allium phytochemicals, which are responsible for the strong smell and taste of these foods. The allium chemicals exhibit potent anticancer activities in animals by a mechanism involving induction of phase 2 enzymes, a cellular stress response designed to protect organisms against toxins [25]. Some cardiac conditions are treated using phytochemical toxins. Examples include digitalis, produced in high amounts by the purple foxglove (*Digitalis purpurea*), and atropine, produced by *Atropa belladonna* [26]. It has often been said that medicines are toxins taken at low doses. In this view, one of the goals of pharmaceutical companies is to identify toxins that at low doses exert beneficial effects on health, for example by killing cancer cells or altering synaptic signaling in neurons.

To be effective, it is not necessary for toxic phytochemicals to kill insects and other organisms that feed on them. Instead, the plants need only dissuade organisms from eating them. It is therefore not surprising that many of biopesticides produced by plants target the nervous systems of insects and other predators; chemosensory receptors (for olfaction and taste) are primary targets of many such chemicals. For example, alkaloids produced by various plants activate GABA and glycine receptors on olfactory neurons in insects [27]. Biopesticides that act on chemosensory receptors need be present in the plant only at relatively low concentrations because of the immediate proximity and easy accessibility of chemosensory receptors. As we will describe in the rest of this article, numerous phytochemicals modify neuronal excitability by activating or inhibiting specific receptors or ion channels. A well-characterized example is capsaicin, the phytochemical responsible for the striking noxious physiological effects of hot peppers; capsaicin activates specific Ca^{2+} channels called vanilloid receptors [28].

Phytochemical mechanisms of action on the nervous system: antioxidants and/or low-dose toxins?

Epidemiological studies of human populations, and experiments in animal models of neurodegenerative disorders, have provided evidence that phytochemicals in fruits and vegetables can protect the nervous system against disease [29,30]. The vast majority of studies of health benefits of phytochemicals have focused on the fact that many of the active chemicals possess antioxidant activity. Hundreds of articles have been published reporting neuroprotective effects of compounds in natural products, including α-tocopherol, lycopene, resveratrol, ginkgo biloba and

ginsenosides [31]. Neuroprotective effects of various phytochemicals are associated with reduced levels of oxidative stress. For example, resveratrol, quercetin and catechins reduced oxidative stress and protected cultured hippocampal neurons against nitric-oxide-mediated cell death [32]. Despite the fact that many phytochemicals possess antioxidant properties, evidence is emerging that in many cases other biological activities of the phytochemicals account for their health benefits. The biphasic dose–response relationship for many phytochemicals (low-dose beneficial effects and high-dose toxic effects) argues against an exclusive antioxidant mechanism of action; instead, it suggests that such hormetic chemicals act as mild stressors to induce adaptive expression of stress-resistance genes such as those encoding antioxidant enzymes. Indeed, most antioxidants are effective only when present at the micromolar concentrations required for them to scavenge free radicals effectively, whereas in many cases, including those described in this article, much lower concentrations exhibit neuroprotective activity.

There are several examples of neurotoxic phytochemicals that have little or no antioxidant activity but can exert beneficial hormesis-like effects at low doses. Kainic acid and domoic acid are excitotoxins produced by algae; they kill neurons by over-activating the kainate and AMPA subtypes of ionotropic glutamate receptor [33]. Both domoic acid and kainic acid can induce epileptic seizures and can damage and kill hippocampal neurons, resulting in learning and memory impairment when administered systemically. However, sub-neurotoxic doses of kainic and domoic acids can protect neurons against ischemic and excitotoxic death [34,35], probably by inducing a mild stress response that results in upregulation of the expression of neurotrophic factors and protein chaperones [15]. Moreover, kainate and AMPA receptors have fundamental roles in long-term potentiation of synaptic transmission (LTP), a process associated with learning and memory, and subtoxic levels of activation of these receptors can enhance LTP [36]. Indeed, drugs that are agonists of kainate and/or AMPA receptors are being developed for the treatment of memory disorders in humans [37]. 3-Nitropropionic acid (3-NPA) is an inhibitor of mitochondrial succinate dehydrogenase that is produced by fungi and certain plants, and is believed responsible for the neurodegenerative process in a group of children who ingested mildewed sugar cane in China [38]. In rodents, high doses of 3-NPA cause degeneration of striatal neurons and motor dysfunction similar to Huntington's disease. However, treatment of rats with lower doses of 3-NPA protects neurons against subsequent cerebral ischemia-induced death [39]. Low doses of 3-NPA might protect neurons against ischemia by inducing the activation of mitochondrial K^+ channels [40], a mechanism previously suggested to have a role in ischemic preconditioning [41].

Figure 2. Neurohormetic phytochemicals include compounds from a range of botanical sources and chemical classes. Resveratrol is a polyphenolic compound present in high amounts in red grapes and wine, and in peanuts and soy. Broccoli and other cruciferous vegetables contain high amounts of the isothiocyanate sulforaphanes. Curcumin is the yellow pigment in the roots of turmeric. Green tea contains high amounts of catechins. Garlic is rich in allicin, allium and other organosulfur compounds. St John's wort contains the phenanthroperylene quinone hypericin.

Evidence that phytochemicals activate neurohormesis pathways

Although the number of phytochemicals reported to have beneficial effects on neurons in cell culture and *in vivo* is large, knowledge of the underlying cellular and molecular mechanisms is meager. In this section, we have chosen to focus on only a few phytochemicals for which there is accumulating evidence supporting a hormetic mechanism of action. They include resveratrol, sulforaphane, curcumins, catechins, allium and related organosulfur compounds, and hypericin (Figure 2).

Resveratrol, a phytophenol present in high amounts in red grapes and wine, has received considerable attention as the chemical probably responsible for the health benefits of red wine [42]. Resveratrol exhibits antioxidant activity and it was originally believed that it was this action that is responsible for the protective effects of resveratrol against atherosclerosis and cancer. However, more recent findings suggest an alternative, hormesis-based mechanism of action of resveratrol. Thus, resveratrol might extend lifespan in worms by activating the histone deacetylase Sir2 and inducing the expression of proteins involved in adaptive responses to endoplasmic reticulum stress [43]. *In vivo* studies have shown that resveratrol enters the CNS rapidly following peripheral administration, and can protect neurons in the brain and spinal cord against ischemic injury [44,45]. Expression of mutant polyglutamine-repeat proteins in neurons of *Caenorhabditis elegans* and knockin mice results in cell dysfunction and death that can be attenuated by resveratrol administration [46]. Data in that study also provided evidence that resveratrol exerts its beneficial effects by activating stress-resistance pathways involving Sir2 and forkhead transcription factors [46] (Figure 3). Indeed, axon

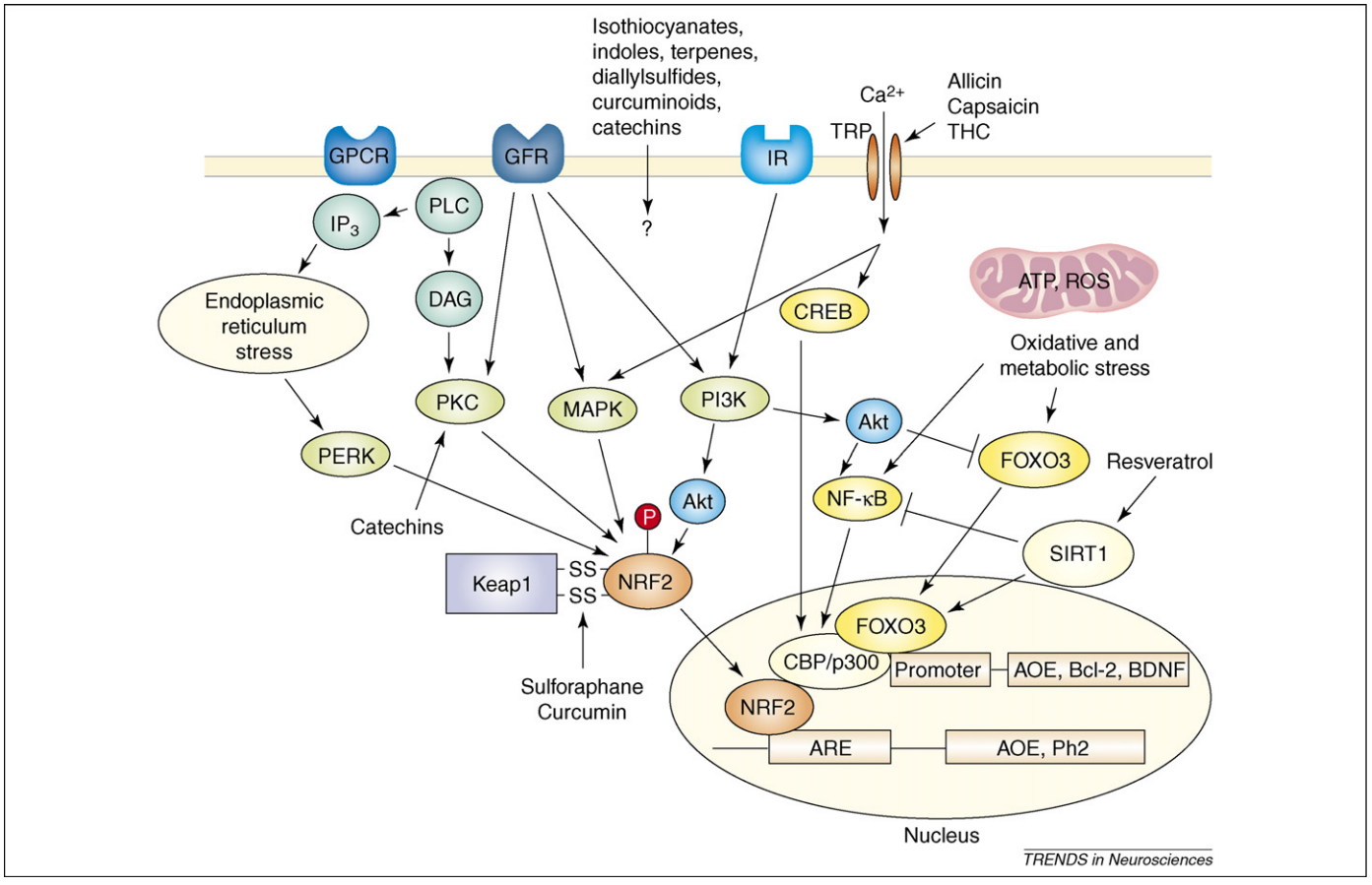

Figure 3. Phytochemicals activate cellular stress-response pathways resulting in the upregulation of neuroprotective gene products. Multiple signaling pathways are normally activated by ligands that bind (for example) to G-protein-coupled receptors (GPCR), growth factor receptors (GFR) and insulin receptors (IR). These three receptors activate kinase cascades including those that involve protein kinase C (PKC), mitogen-activated protein kinases (MAPK) and phosphatidylinositol-3-kinase (PI3K). Endoplasmic reticulum stress results in the activation of the PKR-like endoplasmic reticulum kinase (PERK). PKC, MAPK, PI3K and PERK can each activate the nuclear factor erythroid 2-related factor 2 (NFE2L2 or NRF2). NRF2 then translocates to the nucleus and binds to the antioxidant response element (ARE) in genes that encode cytoprotective proteins such as antioxidant enzymes (AOE) and phase 2 (Ph2) proteins. Phytochemicals including isothiocynates, indoles, terpenes, diallyl sulfides, curcuminoids and catechins have been shown to activate one or more pathways upstream of NRF2. The precise mechanisms by which the pathways are activated are largely unknown, although catechins have been shown to increase the activity of PKC. Sulforaphane and curcumin might interact with cysteine residues that are crucial for the sulfhydryl-mediated interaction of the protein Keap1 with NRF2, thus freeing NRF2 so that it can translocate to the nucleus. Other phytochemicals such as allicin, capsaicin and tetrahydrocannabinol (THC) might directly activate specific ionotropic transient receptor potential (TRP) receptors in the plasma membrane resulting in Ca^{2+} influx; Ca^{2+}, in turn, activates neuroprotective kinase cascades via MAPK, and also activates the transcription factor cAMP-response-element-binding protein (CREB); CREB induces the expression of brain-derived neurotrophic factor (BDNF), a mediator of neurohormesis. In addition, phytochemicals can activate the transcription factor NF-κB, which can mediate adaptive cellular stress responses, for example by inducing the expression of Mn-superoxide dismutase and Bcl-2. Another important hormetic pathway activated by metabolic and oxidative stress involves transcription factors of the forkhead (FOXO) family, which activate genes that encode antioxidant enzymes and other stress-response proteins. Phytochemicals such as resveratrol can tap into the FOXO pathway by activating sirtuins such as SIRT1. Activated SIRT1 deacetylates, and thereby activates, FOXO3; however, it also inhibits NF-κB and so can reduce the cellular stress response. Such pathways might also mediate hormetic responses to extrinsic stress (e.g. dietary energy restriction and physical exercise) and intrinsic stress [e.g. endoplasmic reticulum stress and mitochondrial stress, involving increased levels of ATP and reactive oxygen species (ROS)]. Additional abbreviations: CBP, CREB-binding protein; DAG, diacylglycerol; IP_3, inositol (1,4,5)-trisphosphate; PLC, phospholipase C.

degeneration can be prevented by increasing NAD levels and activating SIRT1 (the mammalian homologue of Sir2) in mice [47]. Another hormetic pathway activated by resveratrol involves induction of the expression of phase 2 enzymes and the antioxidant enzymes catalase and glutathione *S*-transferase [48]. Resveratrol has been shown to protect the heart against ischemia–reperfusion injury by activating a hormesis pathway involving mitogen-activated protein (MAP) kinases [extracellular-signal-regulated kinase (ERK)1/2 and p38] and CREB [49]. Resveratrol has been shown to activate NRF2 and the antioxidant-response element (ARE), resulting in upregulation of the antioxidant enzyme heme oxygenase 1 (HO-1) in PC12 cells [50]. However, SIRT1 has been shown to deacetylate the RelA/p65 subunit of NF-κB, which inhibits the activity of NF-κB in cancer cells [51]; if this occurs in neurons it could adversely affect their survival. Collectively, the available data suggest that resveratrol activates multiple hormetic pathways, but might also promote cell death in certain cell types. It will therefore be of considerable interest to identify the molecular target(s) of resveratrol that transduce its beneficial effects on neurons.

Sulforaphane is an isothiocyanate present in high amounts in broccoli sprouts. It exhibits antioxidant properties, but is also known to stimulate NRF2-dependent antioxidant enzyme expression, thereby protecting cells from oxidative injury [52]. Interestingly, in astrocytes sulforaphane can activate NRF2, which binds to the ARE and results in the production of substances that protect neurons against oxidative stress [53] (Figure 3) – an example of trans-cellular hormesis. Ultraviolet light can damage retinal pigment epithelial cells resulting in macular degeneration. Pretreatment with sulforaphane protected cultured retinal pigment cells against photo-oxidative damage by a mechanism involving activation of NRF2 and production of glutathione and NAD(P)H:quinone oxidoreductase [54]. Activation of this hormetic pathway by sulforaphane has been shown to upregulate thioredoxin and protect retinal cells against light-induced damage [55].

Curcumin (diferuloyl methane) is a chemical in the curcuminoid family of phenolic compounds isolated from the roots of *Curcuma longa* and is the key component of curry spice [56]. Dietary curcumin treatment for two months before transient global forebrain ischemia in gerbils reduced damage to CA1 hippocampal neurons and ameliorated motor deficits by a mechanism involving suppression of apoptosis [57]. Rats that were maintained on a diet supplemented with curcumin exhibited reduced brain damage and improved functional outcome following traumatic brain injury [58]. Dietary supplementation with curcumin (160–5000 ppm) in a transgenic mouse model of Alzheimer's disease (APPSw Tg2576 mice) resulted in decreased accumulation of amyloid-β peptide (Aβ), and reduced expression of markers of oxidative stress and inflammation in the cerebral cortex [59]. It has been reported that chronic dietary curcumin intake (1–10 mg kg^{-1} body weight d^{-1} for 14 d) reduces depression-like and anxiety-like behaviors and increases levels of 5-hydroxytryptamine (5-HT or serotonin) and noradrenalin in the hippocampus in rats [60]. Curcumin can activate the hormetic NRF2 pathway, resulting in the production of HO-1, a redox stress-inducible protein known to protect cells against various types of stress [61]. Induction of HO-1 by curcumin involves p38 MAP kinase, consistent with a hormesis mechanism.

Catechins are polyphenols suggested to be responsible for the anticancer effects of consumption of green tea [62]. Catechins exhibit neuroprotective activities that are mediated, in part, by activation of protein kinase C (PKC) and transcription factors that induce the expression of cell-survival genes [63]. Catechins have been suggested to suppress processes involved in the pathogenesis of Alzheimer's disease, including production of Aβ [64], and to protect neurons against the toxicity of Aβ [65]. Studies have shown that catechins and their metabolites activate multiple signaling pathways that can exert cell-survival and anti-inflammatory actions, including altering the expression of pro-apoptotic and anti-apoptotic proteins, and upregulating antioxidant defenses [66].

Organosulfur compounds, such as the allium and allicin present in high amounts in garlic and onions, have been shown to be neuroprotective. For example, *S*-allyl-L-cysteine protected cultured hippocampal neurons against death induced by Aβ and tunicamycin [67]. In addition to their antioxidant activities, allyl-containing sulfides might activate stress-response pathways, resulting in the upregulation of neuroprotective proteins such as mitochondrial uncoupling proteins [68]. Another stress-resistance mechanism activated by garlic organosulfur compounds is the NRF2–ARE pathway [69]. Moreover, allicin activates transient receptor potential (TRP) ion channels in the plasma membrane of neurons [70]. Numerous other phytochemicals also activate TRP channels in neurons, including isothiocyanates, garlic alliums and cannabinoids, resulting in adaptive cellular stress responses [70,71].

Hypericin is a naphthodianthrone in the extracts of *Hypericum perforatum* L. (St John's wort). Beneficial effects of hypericin and St John's wort have been reported in models of neurodegenerative and psychiatric disorders, and in human clinical trials in depression and anxiety disorders [72]. Hypericum extract administered orally increased levels of 5-HT in the brains of wild-type mice, but not in interleukin-6 knockout mice, suggesting that it induces a mild cellular stress response [73]. Evidence that hypericin can activate cellular stress-resistance pathways comes from studies in which cells treated with hypericin exhibit increased resistance to apoptosis by a mechanism involving increased Bcl-2 phosphorylation [74]. Collectively, the available data suggest that hypericin can promote neuronal plasticity and stress resistance by a hormesis-based mechanism.

Evidence suggests that other phytochemicals might also exert beneficial effects on cells and organisms by activating adaptive stress-response pathways. For example, celastrol, a quinone methide triterpene and an active component of a Chinese herbal medicine, has been shown to activate heat-shock transcription factor 1 (HSF1), a mechanism responsible for its cytoprotective hormetic actions [75]. Uwhangchungsimwon is a traditional Korean medicine used for the treatment of stroke that might protect neurons by inducing a stress response that

increases the expression of the anti-apoptotic proteins Bcl-2 and Bcl-xL, and bone morphogenetic protein 7 (BMP7) [76]. Ondamtanggagambang is a herbal medicine prescribed to treat anxiety disorders and depression in Korea that seems to act via a hormetic mechanism: it can protect cardiomyocytes against oxidative injury by a mechanism that involves the induction of HO-1 [77]. Although numerous other phytochemicals have been shown to have beneficial effects on neurons, in most cases their mechanism of action is unknown. Hormesis should therefore be considered as a possible mechanism in each case.

Concluding remarks

Many dietary and lifestyle factors that promote health of the nervous system might act by imposing a mild stress on neural cells, which respond to the stress by enhancing their ability to cope with more severe stress and resist disease. Physical exercise [78], dietary energy restriction [5] and cognitive stimulation [79] all induce adaptive cellular stress responses in neurons resulting in enhanced neurogenesis and synaptic plasticity, and resistance to injury and disease. Dietary energy restriction and cognitive stimulation seem to result in moderate levels of metabolic and oxidative stress in neurons, similar to those seen in animal models of ischemic preconditioning (Figure 1). Hormetic phytochemicals might tap into the same adaptive stress-response pathways, resulting in the activation of stress-responsive transcription factors and upregulation of the expression of a range of cellular stress-resistance proteins. Examples of transcription factors activated by neuroprotective phytochemicals include NRF2, CREB, FOXO-3 and NF-κB (Figure 3). These four transcription factors regulate expression of a range of neuroprotective proteins, including antioxidant enzymes, protein chaperones, Bcl-2 family members and neurotrophic factors. Such highly conserved pathways are important in neuronal survival and plasticity, and resistance to disease. However, how beneficial phytochemicals might activate such neuroprotective pathways is largely unknown. The phytochemical might interact directly with a transcription factor or upstream kinase, or perhaps activate a cell surface receptor coupled to a hormetic stress-response pathway.

The development of cellular and *in vitro* assays to assess the activity of specific hormetic pathways will be valuable for the identification and characterization of neurohormetic phytochemicals. For example, neural cells expressing reporter constructs responsive to NRF2, CREB or NF-κB could be used to screen candidate phytochemicals. Once a neurohormetic phytochemical is identified, preclinical and clinical studies can be performed to establish its efficacy in animal models of, and humans with, neurological disorders. In addition, the structure of a neurohormetic phytochemical could be modified using medicinal chemistry approaches to develop novel therapeutic agents for neurological disorders. The implications of phytochemical hormesis as a major mechanism responsible for the health benefits of chemicals in fruits and vegetables are far-reaching. For example, much of the current basic and translational research on phytochemicals assumes that their biological activities are a direct consequence of their antioxidant properties. If, instead, they act as toxins that stimulate cell stress-response signaling pathways, then issues such as how much and how often the phytochemical is ingested becomes very important. We already know that it is possible to 'overdose' on many different types of plants; for example, apple seeds (which contain cyanide) and certain types of mushrooms (that contain phalloidins). As is the case with preclinical drug development, dose–response studies with phytochemicals will be crucial to establish the dose range in which hormesis pathways are activated without the adverse effects that are likely at high doses.

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