Published in final edited form as:

Neurochem Int. 2015 October ; 89: 271–280. doi:10.1016/j.neuint.2015.03.009.

Neurohormetic Phytochemicals: An Evolutionary - Bioenergetic Perspective

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Abstract

The impact of dietary factors on brain health and vulnerability to disease is increasingly appreciated. The results of epidemiological studies, and intervention trials in animal models suggest that diets rich in phytochemicals can enhance neuroplasticity and resistance to neurodegeneration. Here we describe how interactions of plants and animals during their co-evolution, and resulting reciprocal adaptations, have shaped the remarkable characteristics of phytochemicals and their effects on the physiology of animal cells in general, and neurons in particular. Survival advantages were conferred upon plants capable of producing noxious bitter-tasting chemicals, and on animals able to tolerate the phytochemicals and consume the plants as an energy source. The remarkably diverse array of phytochemicals present in modern fruits, vegetables spices, tea and coffee may have arisen, in part, from the acquisition of adaptive cellular stress responses and detoxification enzymes in animals that enabled them to consume plants containing potentially toxic chemicals. Interestingly, some of the same adaptive stress response mechanisms that protect neurons against noxious phytochemicals are also activated by dietary energy restriction and vigorous physical exertion, two environmental challenges that shaped brain evolution. In this perspective article, we describe some of the signaling pathways relevant to cellular energy metabolism that are modulated by ‘neurohormetic phytochemicals’ (potentially toxic chemicals produced by plants that have beneficial effects on animals when consumed in moderate amounts). We highlight the cellular bioenergetics-related sirtuin, adenosine monophosphate activated protein kinase (AMPK), mammalian target of rapamycin (mTOR) and insulin-like growth factor 1 (IGF-1) pathways. The inclusion of dietary neurohormetic phytochemicals in an overall program for brain health that also includes exercise and energy restriction may find applications in the prevention and treatment of a range of neurological disorders.

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Keywords

adaptive stress response; Alzheimer's disease; AMPK; hormesis; mTOR; sirtuin

1. Introduction

Plants play important roles in human life, not only as food sources, but also as sources of medicines used in traditional healing practices and Western medicine as well. Consumption of diets rich in vegetables and fruits is often associated with health benefits for the body and brain (Lee et al., 2014; Nair et al., 2007). Epidemiological studies suggest that diets rich in phytochemicals can reduce the risk of cardiovascular disease, stroke, diabetes, some cancers, rheumatoid arthritis and neurodegenerative diseases (Carter et al., 2010; Mattson et al., 2007; Slavin and Lloyd, 2012). For example, intake of flavonoids in more than 1300 subjects over 65 years old was inversely associated with the risk of dementia (Commenges et al., 2000). Often the beneficial effects of phytochemicals are thought to be due to their intrinsic antioxidant properties, owing to the fact that oxidative stress plays a key role in most chronic age-related diseases. However to achieve such antioxidant capacity in the blood requires micromolar concentrations of the phytochemicals, which in most cases would require consumption of amounts of fruits and vegetables orders of magnitude greater than what are actually consumed. Alternatively, lower amounts of some phytochemicals may exert disease preventive and therapeutic effects by activation of adaptive cellular stress responses (Lee et al., 2014). By activating stress resistance pathways, phytochemicals can induce the expression of endogenous antioxidant enzymes (e.g. heme oxygenase 1 and glutathione peroxidase) and/or redox enzymes (e.g. nicotinamide adenine dinucleotide phosphate quinone oxidoreductase 1) (Calabrese et al., 2010a).

Understanding the evolutionary events taking place during hundreds of millions of years of co-evolution of plants and animals could provide answers to the question of how and why plants produce a bewildering arsenal of phytochemicals, as well as the complex counter-defense mechanisms developed by the animals that consume the plants (Figure 1). Plants constantly face numerous biotic and abiotic environmental stressors including heat, cold, drought, and attack by herbivores and pathogens (Grassmann et al., 2002; Krasensky and Jonak, 2012). In the case of attack by animals, plants have evolved two major strategies, namely, physical defenses and chemical defenses (Grassmann et al., 2002). Plants synthesize secondary metabolites, broadly termed 'phytochemicals' as defenses to dissuade insects and other herbivores from eating them. Most of these phytochemicals, which are usually bitter in taste, are present at a relatively low level in the plant materials. The co-evolution of plants and animals enabled adaptation of animals to these otherwise potentially toxic substances. At low doses, phytochemicals have beneficial or stimulatory effects on animal cells, whereas when consumed in high amounts the phytochemicals can be toxic. This is an example of "hormesis" – when cells and organisms are challenged with mild stress by some of the noxious phytochemicals present in the plants, they respond adaptively in ways that help them withstand more severe stress (Lee et al., 2014; Mattson, 2008a). Hormetic phytochemicals such as resveratrol, sulforaphane, curcumin, catechins, allicin and hypericin

are reported to activate adaptive stress response signaling pathways that increase cellular resistance to injury and disease (Mattson and Cheng, 2006).

The present article provides a mini-review of hormetic properties of health-promoting phytochemicals in fruits, vegetables, spices and other plant products from an evolutionary perspective. We focus on the nervous system as a target for action of the hormetic phytochemicals because it is neurons that detect and respond to these potentially noxious phytochemicals, thereby determining if and how much of a particular plant or plant product is consumed. We describe several cellular energy metabolism pathways that are affected by multiple beneficial neurohormetic stressors including exercise, energy restriction and phytochemicals. We will describe how these pathways highlight the robust evolutionarily fundamental interactions of food acquisition with energy intake and expenditure.

The strongest evidence for phytochemicals having beneficial effects on the nervous system via hormesis-based mechanisms comes from studies of phenolic chemicals and we therefore focus on this class of phytochemicals. Less is known regarding if, and to what extent, alkaloids and terpenes activate adaptive stress response signaling pathways in neurons. However, compared to the widely studied phenolics, the possibility that alkaloids and terpenes affect neuronal plasticity and vulnerability to stress is largely unexplored. Nevertheless, there are a few well-known neuroactive alkaloids that appear to influence neuronal plasticity and brain function, at least in part, via hormesis. Three examples are galantamine, psilocybin and caffeine. Galantamine is an alkaloid produced by *Galanthus caucasicus* (Caucasian snowdrop). By inhibiting cholinesterases, galantamine increases the amount of acetylcholine at synapses in the brain. This results in increased activation of muscarinic acetylcholine receptors which are coupled to Ca^{2+} release from the endoplasmic reticulum and activation of Ca^{2+} -responsive kinases and transcription factors, thereby bolstering synaptic plasticity. Galantamine is used to treat patients with Alzheimer's disease (Houghton and Howes, 2005). The psychoactive effects of caffeine are well known, and recent findings further suggest that caffeine consumption can enhance synaptic plasticity/learning and memory, and may help forestall neurodegeneration in Alzheimer's and Parkinson's diseases (Sonsalla et al., 2012; Sallaberry et al., 2013; Laurent et al., 2014). Psilocybin is an alkaloid present in numerous species of mushroom in the genus *Psilocybe*, and is widely known as a potent hallucinogen that acts as a partial agonist of serotonin receptors. Functional magnetic resonance imaging studies in human subjects has shown that psilocybin has dramatic effects on neuronal network activity (Muthukumaraswamy et al., 2013). Interestingly, emerging findings suggest that psilocybin can alleviate depression (Baumeister et al., 2014) perhaps, we suggest, by enhancing neuronal stress resistance.

2. The properties of neurohormetic phytochemicals: Bitter is better

Plants are the major food source for a wide range of animals including humans. Owing to their static nature and direct exposure to pathogens and herbivores, plants have evolved biosynthetic pathways that produce toxic and/or antifeedant secondary metabolites (Berenbaum, 1995; Kennedy, 2014; Lee et al., 2014; Wöll et al., 2013). Co-evolutionary interactions of plants with animals and pathogens has been a driving force to augment the diversity of phytochemicals synthesized by the plants (Kubitzki and Gottlieb, 1984).

Synthesized not only for immediate survival, but also to increase their reproductive fitness in challenging environments, phytochemicals play many roles which can be broadly classified as 1) defenses against consumption by animals, infection by pathogens and competition from other plants for limited energy resources; and 2) signals for attraction of pollinator species or seed dispersion (Kennedy and Wightman, 2011; Wink, 2003). The metabolic pathways for the production of these phytochemicals have been subjected to natural selection during evolution (Wink, 2003). It is therefore not surprising that the deterrent phytochemicals are usually bitter tasting to dissuade insects and mammalian and avian herbivores from eating them. These antifeedant phytochemicals usually are concentrated selectively in the vulnerable parts of the plants that are directly accessible to animals such as flowers, fruit skins, leaves and roots. Other parts that are important for reproduction such as buds and seeds also contain higher amounts of these phytochemicals. In addition to their bitter taste, the noxious phytochemicals possess several other properties including anti-proliferative, anti-microbial and allelopathic (Kennedy, 2014).

Most phytochemicals produced by plants to cope with environmental stressors fall within three chemical groups, namely, alkaloids, phenolics and terpenoids. Across these three groups, there is a range of functions and ecological roles (Kennedy and Wightman, 2011). Alkaloids occupy the toxic extreme with a main role as substances that deter insects and herbivores. On the other hand, phenolics have multiple adaptive roles contributing to the overall fitness of plants. Their primary roles include nontoxic interactions with herbivores and symbiotic organisms. For example, anthocyanins are phenolics responsible for the vibrant colors that attract pollinators. Terpenoids have a broad range of functions including as attractants and repellents, and airborne volatile scents (volatile oils) (Grassmann et al., 2002; Kennedy, 2014; Kennedy and Wightman, 2011; Lee et al., 2014; Nair et al., 2007). Besides the three main phytochemical groups, plants also synthesize numerous other substances such as cyanogenic glycosides and glucosinolates that are present in pungent plants such as mustard and horseradish. Another 'strategy' by which plants reduce consumption by insects is by producing phenolic phytoestrogens that disrupt endocrine functions. One or more of these different groups of phytochemicals may be present in a single plant, however one chemical group tends to predominate in the defensive capability of a given plant (Kennedy, 2014). The expression of genes that encode proteins involved in the biosynthesis of phytochemicals, as well as the concentration of the phytochemicals produced, are influenced directly by the environmental conditions (Valladares et al., 2002; Wöll et al., 2013).

Most, if not all, readers of this article have experienced the potent and robust actions of phytochemicals on sensory neurons that innervate their skin and mucous membranes of the mouth, nose and eyes. Encounters with poison ivy, stinging nettles, and hot peppers are common examples. However, when ingested (or inhaled) other phytochemicals readily enter the brain where they can alter brain function, as illustrated dramatically by psychoactive phytochemicals such as cannabinoids, psilocybin and mescaline (Halpern, 2004). Such behavior-altering phytochemicals are very potent, being active in picomolar concentrations, and exert their actions by binding directly to specific neurotransmitter receptors. On the other hand, neuroactive phytochemicals present in commonly consumed fruits, vegetables and nuts have a bitter or sour taste, but are generally well tolerated (Lee et al., 2014; Wöll et

al. 2013). Bitter phytochemicals do not usually harm insects or other animals, but are sufficiently noxious to deter feeding. These phytochemicals are hormetic in that they can be toxic if ingested in high amounts, but are beneficial to the animals in the lower amounts usually consumed (Mattson, 2015). Their effects are represented as a biphasic dose – response curve, with the first phase being a positive/beneficial effect and the second phase being a progressively negative/toxic effect (Calabrese et al., 2007; Mattson et al., 2007). In the amount normally consumed, hormetic phytochemicals are present in the body at concentration much lower than their toxic level, thus explaining their beneficial effects (Mattson et al., 2007). Commonly ingested plants containing neurohormetic phytochemicals include broccoli, brussel sprouts, green leafy vegetables, citrus fruits, berries, grapes, turmeric root, tea, coffee and dark chocolate (Mattson and Cheng, 2006).

3. Co-evolution of nervous systems and neurohormetic phytochemicals

Co-evolution can be defined as the process whereby two or more different species genetic (and resultant phenotypic) compositions affect each other's evolution reciprocally (Tuller et al., 2010). Plants and insects have a long history of co-existence of over 400 million years (Grimaldi and Engel, 2005). Much of the phytochemical diversity of plants is attributed to their function as natural anti-feedants/pesticides (Kennedy, 2014; Koul, 2005). During their co-evolution, plants and animals have engaged in defense and counter-defense strategies, characterized by alternating adaptive radiations of the plant and insect species (Kennedy, 2014). Over time, this “chemical arms race” or “animal – plant warfare” process has resulted in diversification of phytochemical synthesis by plants, and the acquisition by animals of mechanisms to detoxify or tolerate the phytochemicals (Kennedy, 2014; Nair et al., 2007; Wöhl et al., 2013).

The early period of animal – plant co-evolution likely involved changes in physical structure, whereby plants developed mechanical defenses such as thorns, spines and hard shells as adaptive responses to herbivory (Figure 1). In turn, animals developed physical adaptations to overcome the physical defenses of plants including grinding teeth and thick skin (Wöhl et al., 2013). In a second phase, plants evolved a chemical defense system by producing noxious chemicals that exert toxic effects on the animals upon ingestion. In response to this, animals developed sensory and behavioral neuronal response systems to counter the negative effects of the noxious phytochemicals. The latter adaptations included sophisticated olfactory and gustatory sensory systems to aid in dietary selection (Wöhl et al., 2013). Because plants contain valuable nutrients, animals benefited from not completely avoiding ingestion of plants with noxious chemicals, and instead limited their intake to a range that was nutritionally helpful, but physiologically and toxicologically tolerable (Iason and Villalba, 2006). Plants then diversified and refined their chemical arsenals to counter the eating patterns of herbivores (Valladare et al., 2002). The levels of noxious phytochemicals were controlled by regulated expression of their biosynthetic enzymes in response to environmental stressors, and the phytochemicals were selectively concentrated in highly vulnerable parts of the plants such as the skin of fruits and the buds of vegetables (Kubitzki and Gottlieb, 1984).

As a further counter-measure to noxious phytochemicals, animals evolved novel detoxification mechanisms involving the cytochrome P450 (CYP450) enzyme superfamily (Gonzalez and Nebert, 1990). Thus, arose the so-called phase 1 and phase 2 detoxification enzymes of animals that act to degrade the phytochemicals and promote their excretion in the urine (Wöll et al., 2013) (Figure 1). During the co-evolution of plants and animals, these phytochemicals have driven the evolution CYP450-linked detoxification mechanisms in the animals (Nair et al., 2007). Interestingly, the biosynthesis of many phytochemicals in plants also involves (different) CYP450 enzymes (Hallahan and West, 1995). Such adaptation, counter-adaptation strategies led to the establishment of the huge family of phytochemical metabolizing enzymes. In humans as in other mammalian herbivores, the phytochemical-metabolizing enzymes are concentrated in the liver, an organ into which phytochemicals (and nutrients) pass directly upon absorption/transport into the blood from the intestines.

In a third phase of evolutionary competition between plants and animals, plants diversified the structure of their chemicals so that they became toxic upon degradation by CYP450 enzymes in the cells of animals. In turn, animals developed so-called phase 3 or transporter proteins such as the efflux protein (P-glycoprotein) or multidrug resistance (MDR) pumps and organic ion transporters (Wöll et al., 2013). The transporter protein mechanisms are often responsible for the commonly encountered poor bioavailability and pharmacokinetics issues of many phytochemicals used for drug development. In what may be a new phase of plant – animal co-evolution, Stermitz et al. (2000) reported that berberine alkaloid-producing plants can synthesize an inhibitor of the MDR pump, resulting in enhanced accumulation of berberine in cells of animals that consume those plants.

In many cases the effects of neurohormetic phytochemicals on the human nervous system reflects their ecological roles in plants (Kennedy and Wightman, 2011). During the fascinating events of evolution described here and in more detail by Wöll et al., (2013), animals not only evolved mechanisms to tolerate or rapidly eliminate potentially toxic phytochemicals, they also benefited directly from these noxious phytochemicals. Nerve cell networks of animals are the “first line responders” to environmental challenges (Mattson, 2008b). Neurons sense noxious phytochemicals via the olfactory, gustatory or pain receptors, which trigger a ‘stop eating’ response (Lee et al., 2014). A classic example in humans involves the response to capsaicin, the chemical responsible for the ‘hotness’ of hot peppers of the genus *Capsicum*, which elicit a rapid robust stress response in sensory neurons (Mattson et al., 2007). Other herbs and spices (e.g., turmeric, garlic, oregano etc.) also trigger a rapid sensory response when ingested; however, when consumed in moderate amounts these phytochemicals are perceived as pleasant/stimulatory. Other phytochemicals may exhibit no overt sensory responses upon ingestion, and instead have delayed effects on nervous system function; examples include: stimulants such as caffeine and ephedrine; psychoactive substances such as cannabinoids, mescaline and psilocybin; and analgesics such as morphine and other opioids (Lee et al., 2014).

It should be noted that phytochemicals may activate some of the same signaling pathways in mammalian cells that they evolved to activate in the plants. While, to our knowledge, there is little empirical evidence for this, it certainly merits investigation. One potential example of such a cross-kingdom signaling via conserved pathways involves abscisic acid, which

activates mitogen-activated signaling pathways in plants in response to stress (Danquah et al., 2014). While its potential neurohormetic actions have not been investigated, it has been shown that dietary abscisic acid can reverse glucose resistance and inflammation in a mouse model of obesity and diabetes (Guri et al., 2007).

Why might phytochemicals have beneficial effects on the human nervous system if they are produced to protect plants? Herbivores, and omnivorous animals including humans, have been ingesting plants as part of their diet throughout their evolutionary history (Nair et al., 2007). Human neurons have conserved many of the same signaling pathways that first evolved in insects and other herbivores that preceded humans in evolution. Examples include pathways that signal via Nrf2, SIRT1 and AMPK (Menendez et al., 2013; Misra et al., 2013; Trinh et al., 2010). Activation of one or more of these signaling pathways that evolved to defend cells against potentially toxic phytochemicals appears to be a major reason why ingestion of the phytochemicals can protect neurons against injury and disease (Calabrese et al., 2008; Lee et al., 2014).

Learning and memory is essential for the survival of all animals and, in this regard, remembering encounters with and locations of specific food sources is of fundamental importance. Different plants have distinct tastes and odors that are readily distinguished and remembered by the nervous systems of animals. Decisions of whether or not a particular animal consumes a particular plant or part of a plant (fruit, leaves or roots) are undoubtedly based on several factors including energy density (e.g., low calorie grasses and leaves versus high calorie fruits and nuts) and palatability. Recent findings suggest that chimpanzees develop a 'botanical encyclopedia' which they use to reliably locate different types of fruit based on the animals knowledge of the location of the plants species and the time of year that species bears ripe fruit (Janmaat et al., 2013). Because most plants produce bitter- or sour-tasting chemicals and concentrate them in exposed vulnerable structures (e.g., the skins/peels of fruits), these chemicals may or may not be ingested depending upon the intensity of the bitterness or sourness. Thus, humans typically remove the skins of citrus fruits and bananas, but consume the skins of apples, cherries, blueberries and many other fruits.

Emerging findings suggest that some of the chemicals concentrated in the skins of fruits can improve learning and memory and can protect against cognitive impairment in animal models of aging and Alzheimer's disease (AD). Examples include improvement of object recognition memory in old rats fed a blueberry supplemented diet (Malin et al., 2011) and ameliorated age-related spatial learning and memory impairment by administration of green tea catechins to mice (Li et al., 2009). Both blueberry and green tea phytochemicals may improve learning and memory by enhancing activation of the transcription factor cyclic AMP response element-binding protein (CREB) (Li et al., 2009; Schroeter et al., 2007; Williams et al., 2008). Interestingly, caffeine, which is the most widely consumed psychoactive phytochemical, is known to enhance cognitive function by increasing levels of intracellular Ca^{2+} and cyclic AMP, which in turn activate kinases that phosphorylate and thereby activate CREB.

4. Signaling pathways shared by hormetic phytochemicals and bioenergetic challenges

Regular vigorous exercise and dietary energy restriction can reduce the risk of cardiovascular disease, diabetes and stroke. Increasing evidence also suggests that exercise and energy restriction can protect the brain against AD and Parkinson's disease (PD) (Barnard et al., 2014; Mattson, 2012). Hormesis appears to be the general mechanism responsible for all of these beneficial effects of exercise and energy restriction. For example, by causing a mild transient stress on cardiac and vascular cells, exercise up-regulates the expression of genes encoding proteins involved in cellular stress resistance such as heat-shock proteins and growth factors. Both exercise and energy restriction impose bioenergetic stress on cells tissues and organs, resulting in major shifts in energy metabolism (from utilization of glucose to 'burning' of fats) production of ketone bodies, and enhanced insulin sensitivity of muscle, liver and brain cells (Marosi and Mattson, 2014; Mattson et al., 2014; Mercken et al., 2012). Multiple cellular stress resistance systems are enhanced by energy restriction and exercise including increased production of: neurotrophic factors such as brain-derived neurotrophic factor (BDNF) and fibroblast growth factor 2; the protein chaperones GRP-78 and HSP-70; the DNA repair enzymes such as APE-1; the antioxidant enzyme heme oxygenase 1; and PGC-1, a transcription factor critical for mitochondrial biogenesis (Arumugam et al., 2010; Cheng et al., 2012; Longo and Mattson, 2014; Mattson, 2012; Yang et al., 2014).

Recent findings suggest that adaptive cellular stress responses to phytochemicals are mediated via some of the same pathways that mediate responses to energy restriction and exercise (Mattson, 2012; Milisav et al., 2012). As described below, commonly consumed phytochemicals are capable of inducing mild stress in neural cells that can enhance the ability of nervous system to cope with stress and promote optimal function and longevity of the nervous system. As with exercise and energy restriction, intake of neurohormetic phytochemicals typically occurs on intermittent basis which provides a 'recovery period' that allows cells to shift back-and-forth from a "stress resistance mode" to a "growth/plasticity mode" for cell repair and growth (Mattson, 2015). The activation by phytochemicals of adaptive cellular stress pathways related to oxidative stress, such as those involving nuclear factor erythroid 2-related factor 2-antioxidant response element (Nrf2-ARE) and nuclear factor κ B (NF- κ B), by neurohormetic phytochemicals was previously reviewed (Lee et al., 2014; Mattson et al., 2007; Mattson and Cheng, 2006; Son et al., 2008). Here, we describe several other phytochemical responsive pathways that are known to play key roles in adaptive response to metabolic stress; they include pathways involving sirtuins, adenosine monophosphate activated protein kinase (AMPK), mammalian target of rapamycin (mTOR) and insulin-like growth factor 1 (IGF-1). These signaling pathways are key energy sensors that enable cells to adapt to variability in food availability and accessibility (Cantó and Auwerx, 2011; Hardie, 2011); collectively, they comprise an interacting signaling network that coordinates responses to energetic challenges (Testa et al. 2014).

4.1 Sirt 1

An important cellular defense mechanism activated by calorie restriction, exercise and some phytochemicals involves a family of proteins called sirtuins which are nicotinamide adenine dinucleotide (NAD⁺)-dependent deacetylases and mono-adenosine diphosphate (ADP)-ribosyl transferases (Baur et al., 2012; Donmez, 2012; Testa et al., 2014). The first identified and most intensively studied sirtuin is SIRT1; it functions as an intracellular energy sensor to detect the concentration of NAD⁺ and regulate metabolic status via its deacetylase activity which can remove an acetyl group from lysine residues of specific target proteins including histones, nuclear transcriptional factors and cytosolic enzymes (Kume et al., 2013). The substrates of SIRT1 include the tumor suppressor protein p53, Ku70 and forkhead box proteins (FOXO), which upon deacetylation confer resistance to cellular stress by mediating DNA repair, autophagy and apoptosis (Bauer and Helfand, 2009; Brunet et al., 2004; Duan, 2013; Finkel, 2009; Freca et al., 2005; Zhang et al., 2011). Other protein substrates targeted by SIRT1 are involved in cellular metabolism including peroxisome proliferator-activated receptor gamma (PPAR γ) and peroxisome proliferator-activated receptor gamma coactivator 1-alpha (PGC-1 α) (Rodgers et al., 2005). SIRT1 also regulates glucose and lipid metabolism by deacetylating proteins involved in insulin signaling (Liang et al., 2009). While SIRT1 has been intensively researched, emerging research suggests that SIRT3, a mitochondrial sirtuin, can enhance antioxidant defenses and bolster cellular energy metabolism (Bell and Guarente, 2011). Sirtuins mediate stress tolerance, and may counteract the aging process and the development of aging-related diseases such as diabetes, obesity, cardiovascular disease and neurodegenerative disorders (Calabrese et al., 2008; Donmez, 2012; Guedes-Dias Pedro and Oliveira Jorge, 2013; Kume et al., 2013).

SIRT1 function as an anti-aging protein in yeast, *Caenorhabditis elegans* and *Drosophila*, and may, in part, mediate the extension of lifespan by caloric restriction (Guarente, 2007). The role of SIRT1 in regulating mitochondrial biogenesis via PGC-1 α pathway may be central to the effect of calorie restriction, though SIRT1 also acts on other metabolic and stress-resistance pathways (Guarente, 2007). Some phytochemicals can improve energy metabolism via the activation of sirtuins, albeit to a much lesser extent than dietary energy restriction or exercise (Lee et al., 2014; Mattson, 2012). Sinclair first showed that resveratrol can mimic calorie restriction by activating Sir2 (the yeast homolog of mammalian SIRT1) and extending lifespan in a yeast model (Howitz et al., 2003). Data suggest that resveratrol can activate yeast Sir2/SIRT1, although whether this action of resveratrol results from a direct interaction with SIRT1 or is secondary to a less specific cellular stress response is unclear (Calabrese et al., 2010b; Kaeberlein et al., 2005a). Resveratrol was also reported to extend the lifespan of mice fed a high fat/calorie diet, which was associated with increased SIRT1 activity and mitochondrial biogenesis in muscle cells (Baur and Sinclair, 2008; Lagouge et al., 2006). Furthermore, resveratrol induces gene expression patterns in multiple tissues similar to those induced by intermittent fasting (Pearson et al., 2008). Growing evidence suggests that resveratrol can have beneficial effects on the health of aging animals including non-human primates and human (Dal-Pan et al., 2011a; Novelle et al., 2015). During one year of intervention in mouse lemurs (*Microcebus murinus*), both calorie restriction and resveratrol were well tolerated and caused metabolic responses consistent with improved health (Dal-Pan et al., 2011b). In another study using SAMP8 mice, a model

of accelerated aging, a resveratrol-supplemented diet increased mean life expectancy and maximal life span (Porquet et al., 2013). In addition, resveratrol counteracted AD-like changes by decreasing the amyloid burden and tau hyperphosphorylation in the SAMP8 mice (Porquet et al., 2013). In a randomized, double-blind crossover trial over a 30 day period, resveratrol at 150 mg/day (given in the form of the nutraceutical product resVida®) significantly reduced sleeping and resting metabolic rate of healthy obese men. During resveratrol treatment the muscles of the subjects exhibited increased levels of activated AMPK, SIRT1 and PGC-1 α as well as decreased inflammation markers (Timmers et al., 2011).

In addition to resveratrol, other phytochemicals that have been reported to increase SIRT1 activity in neuronal cells or animal models include epigallocatechin-3-gallate (Ye et al., 2012), quercetin (Davis et al., 2009), icariin (Wang et al., 2009; Zhang et al., 2010; Zhu et al., 2010), baicalin (Chen et al., 2011), caffeic acid and rosmarinic acid (Pietsch et al., 2011), persimmon oligomeric proanthocyanidins (Yokozawa et al. 2009), butein, fisetin and piceatannol (Howitz et al., 2003).

4.2 Adenosine monophosphate activated protein kinase (AMPK)

AMPK is involved in the regulation of energy metabolic homeostasis, serving as a detector of cellular fuel deficiency that is activated when the cellular (AMP+ADP)/ATP ratio rises (Hardie, 2011; McCarty, 2014). There is a positive feedback loop interaction between AMPK and SIRT1, whereby the activation of AMPK increases the intracellular level of NAD⁺, thus stimulating the activity of SIRT1. In turn, SIRT1 deacetylates liver kinase B1 (LKB1), an upstream activator of AMPK leading to activation of AMPK and AMPK-activated pathways (Duan, 2013). In addition, AMPK directly regulates mammalian FOXO3, a transcription factor known to promote resistance to oxidative stress, inhibit tumor cell survival, and promote longevity (Greer et al., 2007). AMPK is also emerging as a key nutrient-sensitive signaling protein that contributes to lifespan extension by energy restriction (Lee and Min, 2013).

Evidence suggests that AMPK activators can improve health (McCarty, 2014). Park et al. (2012) reported that metabolic effects of resveratrol arise from inhibition of cAMP-degrading phosphodiesterases. This in turn activates the exchange protein directly activated by cAMP 1 (Epac1), which increases intracellular calcium and activates calcium/calmodulin-dependent protein kinase 2 beta (CamKK β) which in turn activates AMPK leading to increased NAD⁺ and SIRT1 activity (Park et al, 2012). Likewise, a protective effect of resveratrol against rotenone induced-induced neurodegeneration (an animal model of PD) is mediated by AMPK, SIRT1 and increased autophagy (Wu et al., 2011). In skeletal muscle of rats, curcumin improves insulin resistance by increasing levels of phosphorylated (activated) AMPK (Na et al., 2011). Anthocyanin-rich bilberry extract ameliorates hyperglycemia and insulin resistance in diabetic mice via activation of AMPK in white adipose tissue, skeletal muscle and liver (Takikawa et al., 2010). Thus, enhancement of cellular and systemic energy metabolism by triggering AMPK activation appears to be one mechanism by which some hermetic phytochemicals improve health.

4.3 Mammalian target of rapamycin (mTOR)

Target of rapamycin (mTOR) is a serine/threonine kinase that plays important roles in cell growth and metabolism (Hall, 2008). mTOR activity is affected by nutrient (particularly amino acid) availability (Lee and Min, 2013), and mTOR activation stimulates protein synthesis, whereas its inhibition promotes degradation of damaged protein and intracellular organelles via autophagy (Lee and Min, 2013; Wullschleger et al., 2006). Inhibition of the mTOR pathway may counteract aging processes in various organisms by decreasing downstream effector molecules of mTOR, the ribosomal protein S6 kinase 1 (S6K1) and eukaryotic initiation factor 4E binding protein 1 (4E-BP1) (Ghosh et al., 2010; Selman et al., 2009). SIRT1 negatively regulates mTOR signaling possibly by deacetylation of a protein(s) in the tuberous sclerosis protein 1 or 2 (TSC1/2) complex (Ghosh et al., 2010). On the other hand, AMPK inhibits the activity of mTOR complex either by phosphorylating the regulatory-associated protein of mTOR (raptor), a regulator of mTORC1, or phosphorylation of TSC 2 (Jung et al., 2010; Mihaylova and Shaw, 2011).

Calorie restriction is thought to increase lifespan of yeast, worms and flies, in part, by suppressing TOR (Kaeberlein et al., 2005b; Wullschleger et al., 2006). Resveratrol decreases both the expression and phosphorylation of Akt in glioma cells (Jiang et al., 2009, Leo and Sivamani, 2014) and attenuates phosphorylation (reduces activity) of mTOR and S6K1 (Jiang et al., 2009; Zhu et al., 2011). Likewise, curcumin at physiological concentrations (i.e., concentrations reached in vivo after ingestion of turmeric/curcumin) inhibits phosphorylation of mTOR, S6K1 and 4E-BP1; however, its inhibitory action on Akt phosphorylation was only seen at a much higher concentration (Beevers et al., 2006). (–)-Epigallocatechin-3-gallate (EGCG) found in green tea is a dual inhibitor that inhibits both PI3K and mTOR at physiological concentrations (Van Aller et al., 2011), while gartanin, a compound found in mangosteen caused reduced expression of S6K1 and 4E-BP1 in bladder cancer cell lines (Liu et al., 2013). Pomegranate extract (Adhami et al., 2012) and wogonin, an O-methylated flavone from *Scutellaria baicalensis* (Chow et al., 2012) have also been shown to inhibit the mTOR pathway and stimulate autophagy.

4.4 Insulin-like growth factor 1 (IGF-1)

Insulin/IGF-1 signaling responds adaptively to metabolic states, including calorie restriction, intermittent fasting, exercise and stress (Lee et al., 2014). The insulin/IGF-1 signaling pathway is evolutionarily conserved and plays a regulating role in the rate of aging across the organisms from yeast to humans (Barbieri et al., 2003; Dupont and Holzenberger, 2003; Kenyon, 2011; Shimokawa et al., 2003). Calorie restriction and exercise reduce circulating IGF-1 levels (Anisimov et al., 2005), but may increase cellular sensitivity to IGF-1. Indeed, it is well-established that insulin and IGF-1 levels are reduced when insulin sensitivity is increased as occurs during dietary energy restriction and with regular exercise, consistent with a beneficial effect of insulin/IGF-1 signaling in neurons (Stranahan and Mattson, 2008). In the nervous system, IGF-1 plays important roles in neurogenesis, synaptic plasticity and neuronal survival (Lee et al., 2014). Phytochemicals also have been shown to affect the insulin/IGF-1 signaling pathway resulting in improvement of brain function and insulin related metabolic deficits. Genistein modulates the IGF-1/Akt signaling and may have beneficial effects on neurons (Gao et al., 2012). Curcumin also enhances IGF-1

signaling and can reduce cognitive impairment caused by streptozotocin in rats (Isik et al., 2009). A flavonoid, troxerutin attenuates cognitive impairment and oxidative stress induced by D-galactose in mouse brain by reducing reactive oxygen species and advanced glycation end products, and enhancing PI3K/Akt activation (Lu et al., 2011). In another model cognitive deficits caused by a high fat diet and associated insulin resistance were reversed by troxerutin (Lu et al., 2011). Resveratrol increases the survival and shifts the physiology of middle-aged mice on a high-calorie diet to that of standard diet by increasing insulin sensitivity, which is associated with reduced IGF-1 levels and increased AMPK and PGC-1 α activities and mitochondrial biogenesis (Baur et al., 2006).

The insulin/IGF-1 signaling pathway controls the downstream PI3K/Akt/phosphoinositide-dependent kinase-1 (PDK-1) cascade, resulting in inhibition of FOXO transcriptional activity (Lee et al. 2014; Testa et al. 2014). FOXO is suggested to be involved in age-related neurodegenerative diseases including AD (Manolopoulos et al., 2010). In rat and human cell lines, three black tea theaflavins, namely theaflavin 3-*O*-gallate, theaflavin 3'-*O*-gallate and theaflavin 3,3'-di-*O*-gallate, and thearubigins were identified as insulin/IGF-1 action mimetics on mammalian FOXO1a (Cameron et al., 2008). Administration of the carotenoid lycopene to rats ameliorated insulin signaling deficits and improved cognitive function in rats (Yin et al., 2014). The latter findings, and additional findings reviewed previously (Kapogiannis and Mattson, 2011; Russell et al., 2013) suggest that some neurohormetic phytochemicals can enhance activation of insulin/IGF-1 signaling to bolster cellular bioenergetics and improve neuronal resistance to dysfunction and degeneration. Collectively, the available data suggest that phytochemicals that modulate the insulin/IGF-1/FOXO signaling pathway merit investigation as potential therapeutic agents for insulin resistance-related metabolic and neurodegenerative disorders.

4.5 Mitogen-activated protein kinases

Receptors for numerous neurotransmitters, neurotrophic factors and neuropeptides are coupled to enzymes that activate one or more mitogen-activated protein kinases (MAPK), among which the extracellular signal-regulated kinases (ERKs) and p38 MAP kinases have been most intensively studied (Wiegert and Bading, 2011). Depending upon the type of neuron and its metabolic state, activation of ERKs can either be neuroprotective (Franceschini et al., 2006; Dagda et al., 2008) or can promote cell death (He and Aizenman, 2010; Kurokawa et al., 2011). Studies of hippocampal neurons have shown that ERK activation mediates mitochondrial biogenesis in response to BDNF which, in turn, promotes synapse formation and maintenance (Cheng et al., 2012). Activation of p38 has been shown to trigger neuronal death in various experimental models (Harper and LoGrasso, 2001). Several neuroprotective phytochemicals have been shown to activate ERK in neurons. For example, gastrodin (present in the orchid *Gastrodia elata*) protected cultured rat hippocampal neurons against amyloid toxicity via an ERK-mediated mechanism (Zhao et al., 2012), and hesperetin (present in citrus fruits) protected cultured cortical neurons against oxidative stress by increasing ERK activation (Vauzour et al., 2007). However, the mechanism by which such phytochemicals activate ERKs is unclear and could either be by a direct interaction with the enzymes or by activating upstream pathways such as Ca²⁺ influx.

3. Conclusions and Future Directions

The available evidence suggests that the ability to tolerate at least moderate amounts of noxious bitter-tasting phytochemicals benefited animals by enabling them to glean the carbohydrates, proteins and fats in the plants without adverse consequences of consuming the noxious phytochemicals. We suggest that the molecular genetic variation that underlies the diversity of enzymes involved in the production of plant secondary metabolites was prominently influenced by the co-evolution of the animals that consumed them. This process of evolutionary reciprocal adaptation of plants and animals that consume them resulted in an 'armamentarium' of bioactive phytochemicals, and the development of novel detoxifying mechanisms and adaptive stress signaling pathways in animal cells.

Studies of animal models and humans subjects have shown that regular exercise and dietary energy restriction can protect various organ systems against many major diseases including cardiovascular disease, diabetes, cancers and neurodegenerative disorders. These bioenergetic challenges activate evolutionarily conserved signaling pathways that protect cells against oxidative and metabolic stress. Emerging findings, some of which are described in the present article, suggest that neurohormetic phytochemicals also activate some of the same adaptive stress responses that are activated by energetic challenges. By activating AMPK, SIRT1 and insulin/IGF-1, and/or inhibiting mTOR, phytochemicals mimic the neuroprotective actions of exercise and energy restriction. In addition to enhancing neuronal bioenergetics, neurohormetic phytochemicals can up-regulate intrinsic antioxidant defenses via the Nrf2 – ARE pathway, and/or can stimulate the production of neurotrophic factors such as BDNF (Lee et al., 2014). It is important to recognize that such hormesis-based mechanisms of phytochemical action are in contradistinction to the notion the phytochemicals reduce oxidative stress by directly scavenging free radicals. Indeed, when administered phytochemicals with intrinsic free radical-scavenging actions at the high doses required to significantly neutralize free radicals in cells (micromolar concentrations), health outcomes are not improved and are in some cases worsened (Pham and Plakogiannis, 2005; Robinson et al., 2006). Perhaps the reason that 'swamping' cells with free radical-scavenging antioxidants can be detrimental is that the antioxidants prevent activation of intrinsic adaptive stress response pathways in the cells, thereby rendering them more vulnerable to stress (Mattson and Cheng, 2006; Lee et al., 2014).

The ability of certain phytochemicals to activate the same adaptive stress response pathways activated by exercise and energy restriction implies that those phytochemicals may improve brain health and reduce the risk of neurodegenerative disorders. The dysfunction and death of neurons that occurs in neurodegenerative disorders such as AD and PD involves oxidative stress, impaired cellular bioenergetics and mitochondrial function, and the accumulation of protein aggregates (Mattson and Magnus, 2006). As described above and elsewhere (Lee et al., 2014) there is emerging evidence that neurohormetic phytochemicals can activate pathways that prevent or reverse oxidative damage, bolster bioenergetics and enhance removal of proteopathic proteins such as amyloid β -peptide and α -synuclein. However, much further research will be required to answer several major outstanding questions regarding the neurobiological mechanisms of action of specific phytochemicals, their clinical efficacy in animal models and human subjects.

Acknowledgments

This work was supported by the Intramural Research Program of the National Institute on Aging, NIH.

Abbreviations

Aβ	amyloid beta-peptide
Akt	protein kinase B
AMPK	adenosine monophosphate-activated protein kinase
BDNF	brain-derived neurotrophic factor
CamKKβ	calcium/calmodulin-dependent protein kinase 2 beta
CNS	central nervous system
CYP450	cytochromeP450
EGCG	(-)-Epigallocatechin-3-gallate
Epac1	exchange protein directly activated by cAMP 1
FOXO	forkhead box proteins
IGF-1	insulin-like growth factor 1
LKB1	liver kinase B1
MDR	multidrug resistance
mTOR	mammalian target of rapamycin
NAD⁺	nicotinamide adenine dinucleotide
NF-κB	nuclear factor κ B
Nrf2-ARE	nuclear factor erythroid 2-related factor 2-antioxidant response element
PDK-1	phosphoinositide-dependent kinase-1
PGC-1α	peroxisome proliferator-activated receptor gamma coactivator 1-alpha
PI3K	phosphatidylinositol 3-kinase
PPARγ	peroxisome proliferator-activated receptor gamma
Raptor	regulatory-associated protein of mTOR
SIRT	sirtuin
TOR	target of rapamycin
TSC1/2	tuberous sclerosis protein 1 or 2

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Figure 1. Model for reciprocal evolutionary biochemical changes that occurred during the co-evolution of plants and animals

One type of evolutionary adaptation of plants is physical ‘armor’ such as hard exposed surfaces and thorns that prevent consumption by animals. A second defense mechanism of plants is the production of noxious phytochemicals that are toxic to animal cells. Animals, in turn, developed novel mechanisms to protect cells against damage by phytochemicals and mechanisms to detoxify the phytochemicals. Diversification of phytochemical synthesis by plants has driven the evolution of the CYP450 super family of phytochemical-metabolizing enzymes in animals which, in mammals, are concentrated in the liver. More recently evolved plants produce phytochemicals that when metabolized by CYP450 enzymes generate toxic metabolites. To counteract these phytochemicals, animals developed the so called “phase 3 transporter proteins” such as the P-glycoprotein or multidrug resistant (MDR) pumps and organic ion transporters.

Figure 2. Cellular energy metabolism signaling pathways affected by exercise and energy restriction that are also targets of some hormetic phytochemicals

SIRT1 functions as an intracellular energy sensor to detect the concentration of NAD⁺, and regulates metabolic status by deacetylating various target proteins including transcription factors such as FOXO3 and PGC-1α. Dietary energy restriction, exercise and phytochemicals such as resveratrol, EGCG, icariin, butein and fisetin activate SIRT1. AMPK serves as a detector of cellular energy states that is activated when the cellular AMP +ADP)/ATP ratio rises. AMPK and SIRT1 influence each other; activation of AMPK increases the intracellular level of NAD⁺, thus stimulating the activity of SIRT1 and, in turn, SIRT1 deacetylates liver kinase B1 (LKB1) which can increase the activity of AMPK. AMPK also directly regulates FOXO3. Energy restriction, exercise and resveratrol activate the AMPK pathway, leading to increased NAD⁺ and SIRT1 activity. The mTOR pathway up-regulates protein synthesis while inhibiting autophagy. IGF-1 activates receptors coupled to the PI3K – Akt pathway which can activate mTOR. SIRT1 negatively regulates mTOR signaling pathway. AMPK inhibits the activity of mTOR complex either by phosphorylating the regulatory-associated protein of mTORC1 or phosphorylation of TSC1/TSC2. Resveratrol, EGCG and curcumin decrease both the expression and phosphorylation of Akt/PKB and PI3K. Likewise, curcumin, resveratrol and gartanin inhibit phosphorylation of mTOR, S6K1 and 4E-BP1. **Abbreviations:** ADP, adenosine diphosphate; AMP, adenosine monophosphate; ATP, adenosine triphosphate; Akt/PKB, protein kinase B; AMPK, adenosine monophosphate activated protein kinase; EGCG, (–)-Epigallocatechin-3-gallate; FOXO3, forkhead box protein 3; IGF-1, insulin-like growth factor 1; LKB1, liver kinase B1; mTOR, mammalian target of rapamycin complex 1; NAD⁺, nicotinamide adenine dinucleotide; PGC-1α, peroxisome proliferator-activated receptor gamma coactivator 1-α; PI3K, phosphatidylinositol 3-kinase; Rheb, Ras homolog enriched in brain; SIRT1, sirtuin 1; S6K1, S6 kinase 1; TSC1/TSC2, tuberous sclerosis protein 1 or 2; 4E-BP1, eukaryotic translation initiation factor 4E (eIF4E)-binding protein 1.