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Review Article

Natural plant products and extracts that reduce immunoexcitotoxicity-associated neurodegeneration and promote repair within the central nervous system

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Abstract

Our understanding of the pathophysiological and biochemical basis of a number of neurological disorders has increased enormously over the last three decades. Parallel with this growth of knowledge has been a clearer understanding of the mechanism by which a number of naturally occurring plant extracts, as well as whole plants, can affect these mechanisms so as to offer protection against injury and promote healing of neurological tissues. Curcumin, quercetin, green tea catechins, balcalein, and luteolin have been extensively studied, and they demonstrate important effects on cell signaling that go far beyond their antioxidant effects. Of particular interest is the effect of these compounds on immunoexcitotoxicity, which, the authors suggest, is a common mechanism in a number of neurological disorders. By suppressing or affecting microglial activation states as well as the excitotoxic cascade and inflammatory mediators, these compounds dramatically affect the pathophysiology of central nervous system disorders and promote the release and generation of neurotrophic factors essential for central nervous system healing. We discuss the various aspects of these processes and suggest future directions for study.

Key Words: Cell signaling, flavonoids, immunoexcitotoxicity, nutraceuticals, polyphenols

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INTRODUCTION

Over the last 50 years we have learned a lot about the molecular mechanisms involved in neurological damage occurring during central nervous system (CNS) insults, such as strokes, traumatic brain injuries (TBIs), exposure to neurotoxic substances, autoimmune disorders, infections, and the major neurodegenerative disorders. We are also beginning to understand the dynamic changes that occur in the CNS during these pathological events. Pharmacological treatments directed toward reducing this damage, and especially those capable of promoting brain healing and repair, are quite few in number. Furthermore, some of the mainstay treatments, such as the use of synthetic glucocorticoids, have been shown to be quite neurotoxic, especially to the aging brain.[205,209,261]

In parallel with our expanding knowledge concerning the molecular mechanisms of CNS neurodegenerative

pathophysiology has been our understanding of the molecular mechanisms of action of a growing number of natural substances and extracts of particular plants and herbs shown to prevent much of this damage and to promote CNS repair. In fact, this information has undergone a virtual explosion in the last two decades.[18,44,69,78,230] Unfortunately, this knowledge is far less well known and appreciated, especially by the practicing neurosurgeon and neurologist. Yet many of these natural substances can be used to attain goals desired by those treating these disorders and are presently available as highly purified extracts.

We have increased our understanding not only of some of the better known nutraceuticals, such as the basic vitamins and minerals, for example, ascorbate, tocopherol, the carotenoids, magnesium, zinc, selenium, and the B vitamins, but also of a unique group of substances called polyphenols, which include extracts from plants such as anthocyanidins, resveratrol, chalcones, flavonols, flavans, and flavones (collectively called flavonoids). Unlike pharmaceuticals, in physiological systems these naturally occurring compounds interact both synergistically and additively in a way that can affect their ultimate beneficial function – that is, they do not act as drugs.[4,84,176] This is primarily due to the fact that they operate through different receptors and cell signaling mechanisms and affect individual parts of the cell in very complex ways.

Over 4000 flavonoid compounds have been isolated from plants, with more being discovered every year.[191] It has also been shown that many of these compounds undergo extensive metabolism in the gut, liver, and regional tissues, producing a wide array of physiologically active metabolic products – many of which have beneficial effects equal to or beyond those of the parent compound.[230] Many of these compounds have been shown to have a number of useful properties, including anticarcinogenic, antiviral, anti-inflammatory, antibacterial, antifungal, immune modulating, antioxidant, and anti-excitotoxic effects.[41,186,208,223,259]

Flavonoids have three very useful properties in CNS protection: First, they are very powerful and versatile antioxidants that neutralize reactive oxygen and nitrogen species, several of which are not neutralized by the usual antioxidant vitamins, such as the peroxynitrite radical.[31,36] Peroxinitrite plays an especially destructive role in the neurodegenerative disorders. They are also powerful inhibitors of destructive lipid peroxidation products, such as acrolein and 4-hydroxynonenal (4-HNE), which are also significantly elevated in Alzheimer's disease (AD), Parkinson's disease (PD), and amyotrophic lateral sclerosis (ASL).[278] Third, many are potent chelators of iron and/or copper as well as other neurotoxic metals.[167]

Our understanding of ways to enhance substance bioavailability has also improved substantially. Such knowledge is of practical importance; low bioavailability has been one of the stumbling blocks facing the clinical use of medicinal plant extracts. Some plant extracts have remarkable beneficial effects when used in cell cultures. However, if the product is not efficiently absorbed from the gut and distributed to the tissues targeted, it will be of little clinical use. Nonetheless, there are now a number of ways to improve bioavailability that were not known a decade ago, such as phospholipid microencapsulation and nanoscaling.

PATHOPHYSIOLOGY OF NEURODEGENERATION

There is compelling evidence that a combination of proinflammatory immune overactivation and excitotoxicity is central to the progressive neurodegenerative process.[28] The lead author coined the term 'immunoexcitotoxicity' to describe this destructive interaction.[27] Central to this pathological process is chronic activation of the brain's innate immune system, primarily involving microglial cells and less so astrocytes. Both these glial cells, when activated, can release neurodestructive levels of proinflammatory cytokines, chemokines, interferons, and several excitotoxins, including glutamate, aspartate, and quinolinic acid (QUIN).

A growing number of studies confirm proinflammatory cytokines and glutamate-type receptors cross talk in a manner that greatly enhances the sensitivity of the glutamate receptor system.[44,71] This has changed our thinking concerning excitotoxicity, since we now know that excitotoxicity can occur even with low levels of extracellular glutamate when the receptors are hyperactive, as in the presence of CNS inflammation.[128] As the pathology develops, the CNS becomes more vulnerable because of a loss of antioxidant systems, such as antioxidant enzymes (superoxide dismutase, catalase, glutathione reductase, and glutathione peroxidase) and cellular glutathione. The high levels of extracellular glutamate, as occurs during neurodegeneration, reduce astrocytic glutathione, the major source of neuronal glutathione, by suppressing the glutamate/cystine antiporter.[48,234] The cystine/glutamate antiporter is increasingly recognized as an important alternative excitotoxic pathway in multiple sclerosis by increasing the release of glutamate from macrophages and microglia.[185] The lower levels of glutathione have been described in AD, PD, and ASL.[8,212,216]

Inflammation enhances sensitivity to excitotoxicity by a number of mechanisms, including upregulation of glutaminase (the astrocytic enzyme-producing glutamate from glutamine), recruitment of microglia, stimulation of microglial migration, inhibition of glutamate reuptake mechanism (excitatory aminoacid transporters [EAATs]), inhibition of glutamate removal enzymes (glutamate

dehydrogenase, glutamine synthetase, and glutamic acid decarboxylase), and increased trafficking of glutamate receptors, especially AMPA receptors.[37,134,272] Both inflammation and excitotoxicity dramatically enhance free radical formation and lipid peroxidation of cell membrane structures. It appears that CNS inflammation primarily produces neurodestruction by enhancing excitotoxicity since studies in which glutamate receptors are blocked greatly attenuate proinflammatory cytokine injury to neurons.[172] Likewise, excitotoxicity triggers CNS inflammation by activation of microglia.

Recent studies have shown that trafficking of glutamate receptors plays a major role in progressive neurodegeneration associated with both spontaneously occurring diseases as well as acute and chronic traumatic encephalopathy (CTE).[28] Glutamate receptors are the most abundant and most complex receptor types in the CNS, making up 90% of neurotransmission in the cortex. Sensitivity to glutamate signaling is modulated by changing the sensitivity of the functional glutamate receptor type inserted in the synaptic membrane via receptor trafficking.[243]

Of great interest in neurotrauma and neurodegenerative disorders are the α-amino-3-hydroxy-5-methyl-4-isoxazoleproprionic acid (AMPA)-type glutamate receptors, which are composed of a number of subunits. Normally, AMPA receptors contain a GluR2 subunit, which makes them impermeable to calcium.[9] Under certain physiological conditions and a growing number of pathological conditions, the endoplasmic reticulum rapidly manufactures special GluR2-lacking AMPA receptors that are calcium permeable, as is the case with N-methyl-D-aspartate (NMDA) receptors.[163] These are transported to the synaptic membrane and inserted in the active receptor site, rendering the synapse significantly more sensitive to excitatory activation. In certain circumstances, these special AMPA receptors can lead to progressive neurodegeneration over long periods of time. For example, one of the powerful triggers for GluR2-lacking AMPA receptor trafficking to the synaptic membrane is the presence of elevated levels of tumor necrosis factor-α (TNF-α), which is an indicator of CNS inflammation.[135] Furthermore, recent studies have demonstrated higher concentrations of GluR2-lacking, calcium permeable AMPA receptors in CNS injury, strokes, seizures, and neurodegenerative disorders, such as ALS, PD, and AD.[154,226]

Immunoexcitotoxicity is driven by the chronic activation of microglia, resulting from interference with the normal switching mechanisms, which normally shut off microglial activation, thus eliciting the pathological release of proinflammatory cytokines and excitotoxins. A number of stimuli may interfere with microglial switching including TBI, occult infections, exposure to neurotoxic metals and pesticides/herbicides, autoimmune disorders, some addictive drugs, brain aging, and special neurotoxins such as 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) and 6-hydroxydopamine (6-OHDA).[151,189,213,231]

Because immunoexcitotoxic cascades generate high levels of free radicals and lipid peroxidation products, they can cause widespread damage to a number of tissues and cellular components, including microvessels, the blood–brain barrier (BBB), mitochondria, proteosomes, cell membranes, nuclear and mitochondrial DNA, and the endoplasmic reticulum. It should also be appreciated that the suppression of neuronal energy production, primarily by mitochondrial injury, greatly increases sensitivity to glutamate excitotoxicity. There is growing evidence that mitochondrial energy loss is an early event in many neurodegenerative disorders.[11,115,228] Both glutamate and proinflammatory cytokines suppress mitochondrial energy production and mitochondrial migration along dendrites, essential to synaptic function.[177,220] The ongoing process of positive feedback interactions between free radicals, lipid peroxidation products, inflammatory cytokines, and glutamate can further activate and recruit microglia, leading to a state of chronic progressive neurodegeneration.

New evidence indicates that a large number of natural products can reduce the pathological cell signaling and metabolic disruptions associated with a number of neurological disorders.

HUMAN STUDIES: EVIDENCE OF BENEFIT IN HUMAN COGNITION

Nutraceutical treatment of human neurological disorders has remained the redheaded stepchild of medicine. This is unfortunate since compelling scientific evidence suggests that natural extracts are powerful neuroprotectants and promoters of CNS healing.[7,10,18,33,47] Few practicing physicians appreciate the extensive research that has been conducted on these plant extracts. Many of the mechanisms by which nutraceuticals promote healing are quite complex, and contrary to pharmaceutical drugs, they do not address single-cell enzymes or processes. Rather many interact with cell membrane components, receptors, cell signaling systems, mitochondrial enzymes, DNA physiology, and the cell's internal structure. A number of commercial companies now manufacture plant extracts that are of extremely high quality and purity and are carefully standardized, most of which qualify as pharmaceutical grade.

There is a relative scarcity of clinical trials examining the therapeutic benefits of natural compounds. These trials are widely accepted as 'gold standards' and as such greatly influence clinical practice. However, unlike animal studies in which the diet, living conditions, and exposures to

other confounding factors are carefully controlled, many population studies are poorly controlled and depend on accurate reporting and compliance by thousands of participants in the studies.

If one were conducting a study of vegetable intake and risk of PD, a negative study would have a large impact on physician recommendations. Yet, many of these studies do not control for a number of conditions that would completely alter the results. For example, most such studies do not even name the vegetable type, with many low-nutrient or even harmful nutrient "vegetables" being included in the study (i.e., French fries).[55,196,239] In contrast, there is a dramatic difference in outcomes when the studies are limited to assessing the intake of high-nutrient-density cruciferous vegetables.[126]

It should also be noted that the vast majority of vegetables are heavily contaminated with pesticides/herbicides and fungicides, many of which are known to have significant neurotoxic effects. For example, studies have shown a strong association between intake of the pesticide rotenone, the herbicide paraquat, and the fungicide maneb and the PD risk.[252] Many pesticides/herbicides stimulate microglial activation with a triggering of immunoexcitotoxicity and many suppress mitochondrial function.[66] Thus, pesticide residue can greatly reduce the beneficial effects of the plant polypenols, vitamins, and minerals. In spite of this, many studies do not control for washing of vegetables.

In spite of the above limitations, there is strong evidence from human clinical trials for flavonoid protection of cognition, as exemplified by the prospective Personnes Agees QUID (PAQUID study), which involved a total of 1640 subjects (aged 65 years or older) who were free from dementia at baseline.[136] These individuals were followed for a 10-year period and underwent a battery of cognitive tests (Mini Mental Sate Exam, Benton's Visual Retention Test, and "Isaacs" set test) four times during their follow-up. The study was adjusted for age, sex, and educational level, and a careful assessment was done for flavonoid intake. Those in the two highest quartiles of flavonoid intake had significantly better cognitive function and significantly better evolution of performance over time.

A number of studies using vitamin E in cases of PD or AD have reported little or modest benefit with vitamin E supplementation.[29,79] However, the reason for such outcome may simply be an inadequate choice of the specific form of nutrient used. For example, a majority of studies have used α-tocopherol, either as DL-α-tocopherol or a D-α-tocopherol, as the chosen supplement. The doses vary widely, but in most studies the doses are quite small. Vitamin E is composed of eight classes of compounds: α-, β-, γ-, and Δ-tocopherol and α-, β-, γ-, and Δ-tocotrienol. Until recently, only α-tocopherol was considered of any interest. Newer studies have shown that γ-tocopherol and its metabolite, γ-CEHC (2,7,8-trimethyl-2-(beta-carboxyethyl)-6-hydroxychroman), have far greater anti-inflammatory effects than does the alpha component.[109] Indeed, γ-tocopherol, but not α-tocopherol, significantly reduced both proinflammatory prostaglandin E2 (PGE2) synthesis and lipid peroxidation and inhibited formation of leukotriene B4 in rats.[109] It also reduced TNF-α and nitric oxide release. γ-Tocopherol also reduced protein nitration and ascorbate oxidation in rats with inflammation.[110]

Studies also show that γ-tocopherol is taken up by cells much more efficiently than α-tocopherol, which is vital in protecting internal cellular membranes, such as mitochondrial and endoplasmic membranes.[35,140] γ-Tocopherol also appears to be a superior modulator of PPAR, an important anti-inflammatory compound, compared to α-tocopherol.[35] Of great importance is the finding that supplementation with γ-tocopherol in humans significantly lowers serum γ-tocopherol levels (mean of 58%).[102]

Overlooked in human trials are the tocotrienols. By using rat striatal cultures exposed to hydrogen peroxide, Osakada *et al*. found that unlike -tocopherol, which offered no protection, the tocotrienols (especially α-tocotrienol), were highly protective in this oxidative stress model.[173] One recent animal study, using a stroke model, showed that α-tocotrienol and γ-tocopherol significantly reduced the size of the infarct.[164] Not only tocotrienols affect inflammation, but they seem to profoundly protect against excitotoxicity as well. By using primary cortical neurons, Khanna *et al*. found that α-tocotrienol robustly protected the neurons from excitotoxic death even in nanomolar concentrations.[120] The mechanism of protection appeared to be inhibition of 12-lipoxygenase by α-tocotrienol, suggesting that vitamin E neuroprotection extends beyond its antioxidant effects.

In light of these animal studies, previous human trials using α-tocopherol should be reconsidered and repeated using higher doses of mixed tocopherols or known neuroprotective vitamin E classes.

CURCUMIN, QUERCETIN, AND RELATED FLAVONOIDS: EFFECTS ON CELL SIGNALING AND INFLAMMATION

There is growing evidence that neuroinflammation, especially if prolonged, plays a major role in a number of human CNS disorders, including strokes, TBIs (including concussions), autoimmune CNS disorders, infections, environmental neurotoxic exposures, and hypoxia and ischemia.[5,119,211] As stated, a number of natural substances have been shown to alter glial function in beneficial ways and to affect downstream

cell signaling that reduces the neurodestructive cascades of immunoexcitotoxicity. Besides vitamin C, the carotenoids, vitamin E, zinc, selenium, and magnesium, a number of plant flavonoids have shown superior ability not only to reduce inflammation but also to inhibit free radical and lipid peroxidation product generation, lower nitric oxide levels, attenuate inflammatory prostaglandin production, reduce excitotoxicity, and suppress microglial activation.[24,58,129,227,239,245,268] *In vivo*, flavonoids are less potent as antioxidants than those *in vitro*. Their antioxidant effects appear to act through cell signaling rather than through direct scavenging.[216]

A recent review of the literature identified more than 1500 papers examining the effects of curcumin alone. The authors reviewed all these abstracts and 300 full papers and concluded that compelling evidence confirms curcumin is a powerful anti-inflammatory, anticarcinogenic, antioxidant, and an overall neuroprotectant.[23] According to the reviewed sources, in animals models, for example, curcumin showed either a curative or a preventive effect on a number of human diseases, such as atherosclerosis, cancer, diabetes, respiratory, hepatic, pancreatic, intestinal, eye, and neurological disorders. It was also concluded that curcumin had a very high margin of safety even in very large oral concentrations.[23]

Curcumin is a flavonoid extracted from the spice turmeric, a native plant of Asia. It is in the family of plants called Zingiberaceae, a relative of ginger. This bright-yellow extract gained attention based on the observation that populations in India, who eat a diet high in turmeric, experienced a 4.4-fold lower incidence of AD and dramatically lower rates of colon cancer than those eating a typical Western diet.[73] The most obvious link was its ability to dramatically reduce inflammation. It does this by inhibiting NF-κB, COX, and lipooxygenase (LOX) enzymes and by stimulating nuclear factor erythroid-2 (NrF2), all linked to inflammation.[277]

Like many complex plant extracts, curcumin contains a number of metabolically related compounds, the main ones being the curcuminoids—curcumin, demethyoxycurcumin, and bisdemethyoxycurcumin. It is a highly lipophilic compound that is virtually insoluble in water, making it difficult to absorb as a dry powder from the gut, but readily enters the brain from the plasma.[16] One of its main beneficial effects on the CNS is its ability to downregulate NF-κB, which is a regulator of a number of gene products controlling inflammation (COX-2, IκB, TNF-α, cyclin D1, intercellular adhesion molecule-1 (ICAM-1), c-myc, B-cell lymphoma-2 (bcl-2), matrix metalloproteinase-9 (MMP-9), iNOS, interleukin-6 (IL-6), and interleukin-8) IL-8).[1,15,192]

Inflammation is also driven by the metabolism of arachidonic acid released from the cell membrane by phospholipase A2, which is then metabolized by the COX and LOX enzymes into inflammatory prostaglandins (PGE2). Excitotoxicity enhances COX-2 activation and inflammatory prostaglandin generation in strokes, TBIs, and neurodegenerative disorders.[89,104] Curcumin and quercetin (found in teas, capers, onions, and berries) have been shown to decrease the breakdown of arachidonic acid into leukotrienes, prostaglandins, and prostacyclins by inhibiting COX and LOX enzymes and to suppress inducible nitric oxide synthase (iNOS) activation and the generation of nitric oxide.[10,144,276] Unlike many products that inhibit only COX enzymes, curcumin also directly inhibits the enzyme that synthesizes PGE2 (PGE2 synthase-1 enzyme), the highly inflammatory prostaglandin.[178] (−)-Epigallocatechin gallate (EGCG) from green tea and curcumin both have anti-inflammatory effects, and curcumin can induce cellular glutathione generation, which is a major antioxidant system within all cells and is significantly lowered in neurodegenerative disorders and CNS inflammatory disorders.[158,195] Another way curcumin suppresses inflammation is by stimulating NrF2, a nuclear transcription molecule that enhances cell antioxidant defences and reduces inflammation.

In physiological concentrations, curcumin has been shown to inhibit mammalian target of rapamycin (mTOR), a cell signaling factor that, when activated, suppresses autophagy, an essential cleaning mechanism for cells, which removes damaged organelles and misfolded proteins.[21] Autophagy is severely suppressed in neurodegenerative diseases and can lead to an accumulation of damaging misfolded proteins.[51] This may be the first supplement having the ability to restore this vital process. Unlike the drug rapamycin, which also suppresses mTOR, curcumin does not dangerously suppress immunity.

New evidence demonstrates that resveratrol (found in red wine, grapes, and berries) has a number of major neuroprotective effects as well, including suppression of inflammatory prostaglandin generation, inhibition of nicotinamide adenine dinucleotide phosphate oxidase (NADPH oxidase) and other microglial neurotoxic factors, activation of peroxisome proliferator activated receptor-gamme (PPAR-γ), stimulation of mitochondrial biogenesis, activation of SIRT1 deacetylase, inhibition of NF-κB, stimulation of protective NrF2, stimulation of AMP-activated protein kinase (AMPK)-related energy modulation, and elevation of levels of antioxidant enzymes.[25,60,130,184,202,207,231]

Another important property of polyphenols is their ability to chelate metals, especially neurotoxic metals such as iron, aluminum, and copper. Iron and copper both appear to play a major role in neurodegeneration, especially in AD and PD, with both ions triggering oxidative stress when found in excess.[112] Baum and Ng showed that a

submicromolar concentration of curcumin can bind iron and copper, thus preventing a major mechanism for ROS production in neurodegenerative diseases, such as AD and PD.[17] It is known that iron levels increase with aging associated with neurodegenerative disorders.[156]

Further studies show that curcumin, another iron-chelating flavonoids, can chelate toxic levels of iron without interfering with its physiological functions.[59,156] Curcumin and quercetin do not prevent iron absorption at the gut level, but rather prevent pathological accumulation in tissues. Catechins will bind iron in the gut and prevent absorption, as will a number of other flavonoids within plant vegetables.[59,121] Quercetin, apigenin, naringenin, kaempferol, myricetin, bacalein, luteolin, and rutin also have iron chelation properties.[30,50,155,169,188]

Studies also show that curcumin reduces CNS iNOS, inflammatory cytokines, and lipid peroxidation, all of which are central to neurodegenerative pathology triggered by immunoexcitotoxicity.[28,56] For example, Bala *et al.* found that chronically administered curcumin greatly reduced age-associated elevations in brain lipid peroxidation and lipofuscin deposits while raising levels of protective antioxidant systems and membrane Na^+/K^+ ATPase, a major cell energy system, in the cerebral cortex, hippocampus, cerebellum, and medulla.[10]

CURCUMIN AND OTHER POLYPHENOLS: EFFECT ON AD AND PD

Compelling evidence suggest that most neurodegenerative diseases are strongly linked to prolonged, smouldering inflammation within selected areas of the CNS and that this inflammation is also linked to excitotoxicity, a process referred to as immunoexcitotoxicity. Immunoexcitotoxicity appears to play an important role in the abnormal processing of amyloid β-protein precursor (AβPP) as well as the development of neurofibrillary tangles (NFTs). For a more in-depth review of immunoexcitotoxicity.[28]

Several studies have shown that curcumin, both by its anti-inflammatory and anti-oxidant properties as well as by effects on pathological cell signaling, strongly suppresses abnormal AβPP processing and the formation of the hyperphosphorylated protein tau, which is the main constituent of NFTs. For example, in an *in vivo* study using a genetic model of AD (Tg2576 mice), Yang *et al.* clearly demonstrated that very low concentrations of curcumin can inhibit Aβ aggregation and at increasingly higher concentrations it can promote disassembly of preformed amyloid aggregates.[270] Importantly, they also demonstrated that ingested curcumin efficiently crosses the BBB. Compared with naproxen and ibuprofen, curcumin inhibited Aβ aggregation at a significantly lower dose. In a study by Ansari *et al.*, pretreatment of primary hippocampal cells with quercetin significantly attenuated $A\beta_{1-42}$-induced cytotoxicity, protein oxidation, lipid peroxidation, and subsequent apoptosis.[7]

The new thinking in AD research is that the most toxic element is the soluble Aβ oligomers rather than the mature fibrils.[131] While curcumin at very low concentrations can efficiently prevent neurotoxic Aβ oligomer formation, the goal in most clinical settings is a reversal of already existing amyloid plaque. Experiments using mouse models of AD, where animals exhibit higher amyloid accumulation than that typically observed in human cases of AD, showed that animals fed with curcumin demonstrated a significant reduction in plaque burden in their hippocampus and cortex.[270]

Similarly, Garcia-Alloza *et al.* demonstrated that feeding curcumin to a transgenic AD mice (APPswe/PS1de9 mice) for 7 days clears or reduces existing plaque, as monitored by longitudinal imaging.[74] Consistent with Begum *et al.*'s study, they found curcumin to have powerful disaggregating effects on amyloid plaques.[22] Importantly, curcumin treatment also demonstrated a significant reversal of structural changes in dystrophic dendrites. In addition, Garcia-Alloza *et al.* showed that curcumin from the systemic blood circulation efficiently crossed the BBB and bound avidly to amyloid deposits.

As with AD, curcumin plays a number of beneficial roles in prevention as well as treatment of PD. Similar to other neurodegenerative disorders, PD is largely a chronic inflammatory disorder with a major contribution from excitotoxicity.[237] The source of both inflammatory mediators and excitotoxins is the glial cells – microglia and astrocytes, with microglia being the main mediator of brain immunoexcitotoxicity.

One of the early events in PD is a suppression of mitochondrial function within neurons of the substantia nigra, with inhibition of complex I of the electron transport chain being central to the process.[70,211] Immunoexcitotoxicity suppresses mitochondrial function, in part by triggering high levels of nitric oxide production, which by combining with superoxide leads to an accumulation of the powerful radical peroxynitrite. Mythri *et al.* have shown that curcumin prevents peroxynitrite damage to mitochondria, thus preventing complex I inhibition.[175] Curcumin has also been shown to significantly protect against 6-OHDA damage to the substantia nigra, a frequently used PD model in animals.[273] In addition, curcumin inhibits monoamine oxidase-B (MAO-B) in astrocytes cell cultures.[165] MAO-B inhibitors protect against oxidative neurodegeneration. Rajeswari demonstrated curcumin-induced neuroprotection in another PD animal model.[195] By using the neurotoxin MPTP, which causes a rapid-onset parkinsonism in humans, he found a dramatic reduction in glutathione (GSH) depletion and lipid peroxidation in both the

substantia nigra and the striatum in animals given curcumin at the time of MPTP exposure. An increase in activity of the antioxidant enzymes, superoxide dismutase, and catalase in these brain regions was also observed in response to curcumin treatment.

Curcumin appears to stimulate brain repair as well. Some of its protective effects on excitotoxicity may be secondary to an increased release of neurotrophins such as brain-derived neurotrophic factor (BDNF).[255] Furthermore, administration of curcumin to adult mice resulted in a significant increase in the number of newly generated cells in the dentate gyrus of the hippocampus.[124] The latter observations suggest that curcumin is able to stimulate neurogenesis in the adult hippocampus. Studies using a mild TBI model showed that curcumin dramatically reduced the oxidative damage and normalized levels of brain repair factors (brain derived neurotrophic factor [BDNF] and cAMP response element binding (CREB) that were altered by the trauma.[265] Curcumin was also protective against the cognitive impairment caused by the TBI.[265]

In one interesting study, researchers used male Sprague-Dawley rats approximately 2 years old, which were fed one of four diets for 4 weeks, after which half of the animals were exposed to a mild fluid percussion injury.[215] The diets contained either curcumin plus chow or regular animal chow alone. Animals in each group were assigned to be exposed to a TBI or no-TBI. The study showed that both the sham controls and injured animals demonstrated a significant elevation in hippocampal energy production when fed curcumin with their chow (158 and 130% in the sham and TBI animals' hippocampus, respectively). These results suggest that curcumin activates mechanisms that act to conserve ATP levels in the hippocampus in both the uninjured hippocampus and the injured brain.

Because of their strong effects at very low concentrations and easy accessibility to the brain, curcumin, as well as several other neuroprotective flavonoids, hold much promise as agents to reduce one's risk of neurodegenerative diseases, including CTE. Unlike many of the drugs being used for AD treatment, curcumin has a very impressive safety record. Oral doses as high as 8000 mg/day have been used in human cases without toxic effects.[49] In addition, curcumin lowers both serum and tissue cholesterol levels and can stimulate neuronal protective mechanism (heat shock protein [HSP] elevation), suppress microglial activation, reduce IL-1β release from microglia, inhibit subarachnoid hemorrhage-induced vasospasm, reduce stroke damage, stimulate neurogenesis in the hippocampus, and act as an antidepressant.[227,238,250,268,269]

Because of inefficient absorption of the dry powder, a number of new technologies are being utilized to improve gut absorption of curcumin, including mixing it with specific oils, phospholipid microencapsulation, and nanoscaling techniques. Curcumin can also be given intravenously.[22]

GREEN AND WHITE TEA EXTRACTS AND BRAIN PROTECTION

Green and white tea contain a number of compounds, called catechins, that have significant beneficial effects on the CNS. Like curcumin and many of the other flavonoids, green tea extract is a potent anti-inflammatory and antioxidant; it suppresses immune overreactivity; it chelates metals and has anticarcinogenic properties.[156,159] White tea is a younger harvested tea and has a higher level of catechins than green tea has.

The main components of green tea are EGCG, epicatechin gallate (ECG), and epicatechin (EC). The vast majority of the research has focused on EGCG and has been directed at its anticarcinogenic effects and neuroprotective properties. One of the common pathological reactions observed in a number of neurological disorders is intermittent hypoxia/ischemia. Recent studies suggest that vascular dementias are rapidly catching up in prevalence with sporadic-type dementias and that AD has a considerable vascular component.[204]

Green tea polyphenols (GTPs), in particular EGCG, markedly reduces hypoxic/ischemic tissue loss in models of ischemic stroke and may do so in part by the inhibition of caspase-3.[100,262] Severe hypoxia leads to marked upregulation of inflammation and associated free radical generation and membrane lipid peroxidation.[29,267] Ischemia/hypoxia triggers inflammation in the brain by the upregulation of COX-2 metabolism of arachidonic acid into the highly proinflammatory prostaglandin PGE2, which increases vascular permeability and vasodilatation.[141] In addition, ischemia/hypoxia activates a number of genes in the brain associated with inflammation, leading to microglial activation in a neurodestructive mode.[79,206] The hippocampus and prefrontal cortex are particularly sensitive to hypoxic and ischemic events, and this can lead to significant cognitive deficits.[79] Biacalein, quercetin, curcumin, luteolin, silymarin, hesperidin, resveratrol, and a number of other polyphenols can reduce ischemia/hypoxia-mediated damage by regulating a number of cell signaling processes and controlling gene activation.[39,76,77,101,143]

Burchhardt *et al.* demonstrated the protective effect of green tea extract by using Sprague-Dawley rats exposed to either intermittent hypoxia or normal room air.[33] The animals exposed to the intermittent hypoxia demonstrated high levels of lipid peroxidation in their cerebral cortex. Those fed GTPs showed a 33% reduction in lipid peroxidation levels. The level of PGE2 in the hippocampal CA1 area was significantly elevated in

animals exposed to intermittent hypoxia, but this was dramatically attenuated in animals fed GTP during the intermittent hypoxia. Other studies showed that GTP significantly reduced glial activation associated with intermittent hypoxia.[79]

GREEN TEA EXTRACTS AND AD

Because AD, like TBI, is now considered to be a chronic inflammatory disease, researchers have examined the anti-inflammatory effect of green tea extracts on AD pathophysiology. Several studies have shown that EGCG can alter soluble amyloid β-protein precursor (sAPP) processing by modulating protein kinase C activity.[138,139] In addition, EGCG can inhibit the activities of the proinflammatory cytokines, probably by inhibiting inflammatory cell signaling cascades mediated by activating protein-1 (AP-1) and nuclear factor kappa B (NF-κB).[2,85] EGCG also reduces expression of TNF-α, a cytokine that plays a significant role in a number of neurodegenerative disorders and brain trauma.[185]

By using a 94% pure extract of EGCG, Rezai-Zedheh *et al.* found that neurons from an AD mouse model (TgAPPsw) exposed to the extract switched from the amyloidogenic metabolite pathway during AβPP processing to the nonamyloidogenic α-secretase processing, which significantly reduced Aβ production and markedly increased brain protective levels of sAPP-α.[1,200] The treated mice showed decreased $Aβ_{1-40,42}$ and β-amyloid plaques in their brains. The study also showed that the beneficial effects of EGCG on APP processing were not peripheral, but rather a central CNS effect was. The effects were both time and dose dependent. The EGCG reduced both soluble $Aβ_{1-40,42}$ (by 54 and 44%, respectively) and insoluble $Aβ_{1-40,42}$ (by 47 and 38%, respectively). Furthermore, a 40% increased cleavage by α-secretase in the EGCG-treated neurons was observed and was inversely associated with total Aβ levels. At 14 months of age, the Aβ deposits in mice brains were significantly reduced (by 47 to 54% and 35% and 46%, respectively), in the hippocampal and cortical brain regions. The EGCG did not suppress β-secretase, but rather the effect was mostly secondary to α-secretase stimulation. Interestingly, they found that gallocatechin and catechins, either alone or in combination, markedly reduced the ability of EGCG to inhibit Aβ buildup in the brain. They concluded that the ability of purified EGCG alone to reduce pathological APP processing was much greater than that of the whole green tea extract.

It should be emphasized that sAPP produced by α-secretase is neuroprotective, having both neurotrophic and synaptotrophic effects.[61] In the case of neurotrauma, as well as spontaneous neurodegenerative disease, APP processing is diverted so as to reduce protective brain sAPP.[196]

Like curcumin, green tea extract and EGCG are potent chelating agents for iron and copper.[111] Both green tea catechins and curcumin bind and neutralize a number of neurotoxic metals, some strongly associated with both AD and PD.[113,125] In fact, EGCG has a greater iron binding ability than does dexferrioxamine.[200] This makes EGCG of great value in modulating excess iron accumulation, which occurs in a number of neurological disorders, such as stroke, TBI, AD, PD, and ALS. Reduced iron accumulation triggers the generation of destructive free radicals and lipid peroxidation products. Green tea catechins reduce free radical and lipid peroxidation damage both directly and indirectly by binding free iron in brain tissues.

In PD, there is abnormal iron accumulation in the substantia nigra pars compacta in surrounding activated microglia and in association with neuromelanin.[114] Lewy bodies, the pathological hallmark of PD, are composed of oxidized lipids, redox-active iron, and aggregated α-synuclein. Iron also converts inert α-synuclein into toxic aggregates. It is also interesting to note that MPTP and 6-OHDA induced PD in rodents and primates is iron dependent.[139] EGCG has been shown to prevent MPTP induction of PD in animal models. EGCG also increased brain antioxidant enzymes – catalase and superoxide dismutase.[202] In essence, iron appears to be playing a major role in the pathogenesis of PD and other neurodegenerative disorders, and naturally occurring iron chelators, such as tea catechins and curcumin, as well as many other polyphenols may play a major role in preventing these diseases. Both curcumin and EGCG readily enter the brain from the blood stream.[22]

Other studies have shown that both green tea and EGCG can attenuate MPTP-induced PD and it appears that this occurs via suppression of neuronal nitric oxide synthetase (nNOS) within the substantia nigra.[52] There is a link between iron and neuronal nitric oxide synthetase upregulation.[114] These beneficial effects of green tea and EGCG are attainable by tea drinking and oral extracts. Population studies show that green tea drinkers have lower rates of PD.[112] Because green and white tea can be consumed several times a day over a lifetime, they offer an excellent way to reduce neurodegeneration in the long-term.

The various components of green tea vary in their protective ability against specific targets. Guo *et al.* defined the ability of the various components to protect these specific targets.[82] They tested EGCG, ECG, and EC and compared their effectiveness. The greatest overall protection in terms of stability of the compound and its strength was in the order of EGCG>ECG>EC.

OMEGA-3 FATTY ACIDS AND CNS PROTECTION

A considerable number of studies have shown that the omega-3 fatty acids (N-3 oils by the new nomenclature) possess a number of neuroprotective properties.[64,122,124] There is strong evidence that docosahexaenoic acid (DHA) is the most neuroprotective component of the N-3 oils and makes up the most abundant fatty acid in neural membranes, especially synapses. In addition, a number of population studies show at least some positive effects by adhering to the Mediterranean diet high in omega-3 oils, in terms of reducing the risk of AD, age-related memory loss, and other cognitive difficulties.[67]

Of particular interest is the impact of DHA oils on cognitive function. Lower levels of DHA have been found in the brains of AD patients and in those with lesser degrees of cognitive impairment.[57] In a prospective Framingham Heart Study, 899 men and women of a median age of 76 years and free of dementia at baseline were followed for a mean of 9.1 years and evaluated for the development of dementia.[210] Plasma phosphotidylcholine–DHA (PC-DHA) content were measured and it was found that subjects in the upper quartile of plasma PC-DHA levels had a 47% reduction in the risk of developing AD. In a study of 815 nondemented subjects (aged 65–94 years) who were followed for 2.3 years, Morris *et al.* found that those who consumed fish at least once a week or more had a 60% less risk of developing AD.[173] Interestingly, reductions in risk correlated with total N-3 intake and DHA intake but not with eicosapentaenoic acid (EPA) intake.

DHA supplementation is also supported by a number of studies in AD animal models and in cell culture. For example, Menard *et al.* showed that the treatment of brain slices with DHA (but not EPA) markedly reduced excitotoxicity triggered by AMPA-type glutamate receptors in the CA1 region of the hippocampus.[166] Newer research suggest that abnormal trafficking of calcium-permeable AMPA receptors is strongly linked to brain inflammation.[9,226] Also of critical importance is the finding that omega-3 fatty acid deficiency in rats increases the release of proinflammatory cytokines IL-6 and TNF-α and raises C-reactive protein.[151] In this study they also found significantly greater serotonin metabolism in the frontal cortex, hypothalamus, and ventral striatum, which, in the presence of brain inflammation, shifts tryptophan metabolism toward QUIN generation. QUIN, an excitotoxin, is a potent inducer of the hyperphosphorylation of tau, a critical process in NFT.[193]

Deficiencies in DHA increase abnormal APP processing, leading to amyloid deposits in the brain. Conversely, supplementation with DHA increases the sAPP secretion, which inhibits apoptosis and protects the synapse, as discussed above.[63] DHA when given prior to injury also reduces axonal damage in rats subjected to TBI.[167] This would have applications in preventing CTE and possibly ameliorating the postconcussion syndrome. Dietary administration of DHA protects against and reduces impairment in learning resulting from infusion of $A\beta_{1-40}$ in an AD rat model.[85] Oksman *et al.* demonstrated a significant reduction in Aβ levels as well as activated microglia in the hippocampus of transgenic APPswe/PS1dE9 mouse model of AD when DHA was given for 3–4 months.[177] Similarly, DHA has also been shown to suppress microglial activation in ischemic injury and increase levels of the antiapoptotic factor Bcl-2.[131]

A recent study by Quinn *et al.* failed to find a benefit from DHA supplementation in mild and moderate AD, or at least that is how it was reported in the lay press. This was a randomized, double-blind, placebo-controlled trial involving 51 centers, in which 295 participants were given either 2 g/day of DHA ($N = 171$) or a placebo ($N = 124$).[192] The study participants were followed for 18 months. Outcome measures included two standardized rating scales and MRI measures of progressive atrophy. There was no statistical difference in the rate of decline in cognitive or functional measure with DHA versus placebo supplementation.

One of the main flaws in this study was in using DHA as one would test a drug, that is, used alone. Under conditions of intense reactive oxygen/reactive nitrogen species (ROS/RNS) and lipid peroxidation, as seen in AD, one would expect severe degrees of preexisting DHA depletion and oxidation. Under less severe conditions, DHA, when oxidized, is converted into several powerful antioxidant/anti-inflammatory metabolites, such as neuroprotection D1.[18,149] Yet, this system can be overwhelmed without the presence of elevated levels of other components of the antioxidant network. It is also known that neural membrane insertion of DHA is a very slow process, requiring many months or possibly even years to accomplish.[239] With levels of DHA being severely depressed in the synaptic membranes of AD patients, it may take much longer to reach adequate levels for synaptic functional repair than were allowed in this study. Another possibility is that there may be abnormalities in incorporation of the DHA into synaptic membranes in AD. There are also problems in the analysis of multicenter studies that could account for their failure to find benefit. Using a mixture of antioxidants and allowing a longer time frame may yield different results than were seen in this study.

RESVERATROL AND Aβ CLEARANCE IN AD MODELS

Besides curcumin, quercetin, and DHA, another polyphenol – resveratrol – is associated with Aβ clearance from the AD brain and neurons from AD model systems.

Interest in this compound was based on the observations that moderate wine consumption significantly reduced the risk of AD.[146,148,237] Marambaud *et al*. used several AD animal cell lines (HEK293 cells transplanted with human APP695 and N2a cells transfected with Swedish mutant human APP695 cDNAs) and measured the effect of three powerful polyphenols from grapes – quercetin, catechins, and resveratrol – on AβPP processing.[152] The results showed that resveratrol, but not quercetin or catechins, markedly reduced total secreted Aβ (including $Aβ_{1-40}$ and $Aβ_{1-}$). Resveratrol treatment also reduced the total levels of intracellular Aβ. Interestingly, the effect was not immediate but appeared after 24 hours of incubation and gradually increased after 48–72 hours of incubation. The mechanism of action was not via inhibition of APP processing, that is, lowering of Aβ production, but rather via selective modulation of proteosome degradation of pathological Aβ. Interestingly, proteosomal activity is greatly reduced in AD brains.[115,147] Aβ itself may inhibit proteosomal activity.[81] Finally, resveratrol reduced 6-OHDA-induced lipid peroxidation, protein carbonyl, and inflammatory prostaglandin production in a rat model of PD.[117] Resveratrol also upregulated antioxidant status (glutathione reductase, glutathione peroxidase, catalase, and superoxide dismutase) in the animals' brain.

SUPPRESSION OF MICROGLIAL ACTIVATION BY NUTRACEUTICALS

Central to the immunoexcitotoxic process is activation of microglia. When pathologically activated, microglia secrete large amounts of proinflammatory cytokines, interferons, chemokines, and three excitotoxins – glutamate, aspartate, and QUIN.[27] There is strong evidence that chronic neurodegeneration may occur when activated or primed microglia are unable to undergo normal switching to the quiescent (ramified) phenotype, which normally occurs following pathological activation. Switching of microglia is controlled by a number of molecules such as fractalkines and CD200.[180,231] Abnormalities in these switching molecules have been seen in neurodegenerative disorders. While some of the tetracycline antibiotics, such as minocycline and doxycycline, can suppress microglial activation, they may have significant side effects with long-term usage.[98,106]

Many nutraceuticals can alter microglial activation states and reduce the release of neurotoxic molecules. For example, curcumin can reduce neurodestructive microglial activation, lower the generation of ROS/RNS and lipid peroxidation products, and prevent inflammation-triggered increases in brain glutamate.[67,102] Curcumin can also inhibit the release of inflammatory cytokines from microglia, a major process in neurodegenerative pathology.[110] Importantly, curcumin can affect the switching of microglia from a neurodestructive phenotype to a neuroprotective phenotype. Lin *et al*. found general suppression of microglial activation by curcumin in an AD mouse model, except those near plaque.[143] These results suggest curcumin-stimulated phagocytosis by the microglia, which would aid in plaque clearance. Consistent with this, Zhang *et al*. showed that macrophages from AD patients demonstrated defective phagocytosis in the presence of Aβ and that this defect was significantly improved by treatment with curcumin.[270]

The green tea catachin EGCG potently inhibits lipopolysaccharide (LPS)-induced microglial activation, reduces TNF-α, and downregulates iNOS, all of which play a critical role in immunoexcitotoxicity.[27] In doing so, the EGCG protects dopaminergic neurons from injury in PD animal models.[140]

A number of compounds suppress nitric oxide generation and release by activated microglia, including naringenin, silymarin, chyrsin, apigenin, blueberry extract, butyrate, and baicalein.[101,124,198,251,258] In general, the dose needed to attain these beneficial effects is within attainable dietary goals or by using available commercial extracts. Silymarin was shown to suppress microglia activation at low concentrations.[100] Of great interest is the finding that luteolin, a flavonoid found in high levels in celery and parsley, promotes the conversion of activated microglia to the resting (ramified) state.[61] This is important when considering that microglial switching defects may underlie the pathology of a number of neurodegenerative disorders. Luteolin also inhibits IL-6 production in LPS-activated microglia and significantly reduces microglial activation, neuronal death, and inflammation in a mouse model of hippocampal inflammation and PD model.[46,104,105]

By using aged mice stressed with the immune activator LPS, Jang *et al*. found that animals given luteolin had enhanced spatial working memory whereas control animals exhibited deficits in their working memory.[104] The beneficial effect was attributed to microglial suppression and concomitant suppression of hippocampal inflammation. Both apigenin and luteolin suppress, dose dependently, interferon-γ (IFN-γ)-induced microglial activation – a commonly seen pathological mechanism in neurodegeneration, especially with pesticide exposure.[199] Unlike many other flavonoids, these effects were not related to suppression of NF-κB, but rather AP-1, JNK, and STAT1 suppression, which are also involved in microglial activation of neurodegeneration.[105,198] The short-chain fatty acid butyrate also selectively suppresses INF-γ activation of microglia.[186] Similarly, ferulic acid reduces IFN-γ activation of microglia in a mouse model of Aβ hippocampal microglial stimulation.[172] IFN-γ is thought to be involved in microglial priming associated with aging.[139]

Wogonin, a component in the plant *Scutellaria baicalensis*

Georgi, potently inhibited microglial migration toward the chemokine monocytes chemoattractant protein-1 in nanomolar concentrations, which were insufficient to significantly suppress cytokine or chemokine production.[189] This finding is of significant clinical importance as monocyte (macrophage) migration into the CNS is thought to be a major source of destructive microglial phenotype during neurodegeneration. *N*-Acetyl-L-cysteine had a similar effect.[182] Biacalein, also from *S. baicalensis* Georgi, inhibited microglial NO generation by iNOS.[45]

Amentoflavone, a component in *Ginkgo biloba*, not only inhibits microglial activation but also suppresses caspase-3 activation, excitotoxicity, and microglial activation of iNOS and cyclooxygenase-2 (COX-2), both inflammatory mediators.[213] Blueberry extract suppresses microglial activation and associated activation of COX-2 and iNOS.[132]

MITOCHONDRIAL ENERGY RESTORATION

There is compelling evidence that one of the earliest changes in a number of neurodegenerative diseases is a progressive attenuation of mitochondrial function.[69] This is not only seen in the brain but also in peripheral tissues. The etiology of mitochondrial dysfunction is currently unknown even though, as in the case of PD, exposure to known mitochondrial toxins, such as MPTP and rotenone, appears plausible. Abnormalities in mitochondrial fission and fusion are seen throughout the course of these diseases.[42] Immunoexcitotocity is associated with both mitochondrial dysfunction secondary to free radical damage and interference with mitochondrial migration along dendrites and axons.

Apart from direct generation of free radicals associated with mitochondrial dysfunction, there is a dramatic increase in sensitivity to excitotoxins. Thus even physiologic levels of extraneuronal glutamate can become neurotoxic under low-energy conditions.[19] Many earlier studies dismissed excitotoxicity as a major mechanism based on the absence of extreme elevations in extracellular glutamate levels. However, one must keep in mind that glutamate receptors can change sensitivity under a number of conditions, such as impaired energy production, so that excitotoxicity can occur at much lower concentrations of glutamate and other excitotoxins. Consistent with this interpretation, a number of studies have shown that stimulating mitochondrial function reduces brain sensitivity to excitotoxicity, not only by reducing free radical production and lipid peroxidation but also by improving mitochondrial regulation of cytoplasmic calcium levels.

There are several ways to stimulate mitochondrial function. Much has been learned utilizing metabolic vitamin/mineral coenzymes and energy substrates in treating mitochondrial disorders. In animal and some human studies, ascorbate, vitamin K, thiamine, riboflavin-5 phosphate, pyridoxal-5 phosphate, magnesium, acetyl L-carnitine, *R*-α-lipoic acid, niacinamide (nicotinamide), curcumin, pyruvate, and quercetin have improved mitochondrial function and reduced excitotoxicity.[243,244]

Nicotinamide, in particular, is a major source of nicotinamide adenine dinucleotide (NAD), and elevations in NAD have been attributed to its ability to protect the brain against ischemia, traumatic injury, and excitotoxicity.[144] Nicotinamide plays a major role in glycolysis and oxidative phosphorylation by conversion of glyceraldehydes-3-phosphate into pyruvate, which is the entry point into the Krebs cycle. By using a concussion brain injury model in Sprague-Dawley rats, Hoane *et al.* tested 50 mg/kg of nicotinamide given intraperitoneally at 15 min, 4 h, or 8 h, followed by five boosters at 50 mg/kg every 24 h after the impact injury and found that the treatment significantly reduced behavioral impairments and led to a more rapid improvement and functional recovery.[93] Notably, Hoane *et al.* showed that the beneficial effects on sensorimotor tasks occurred even if the treatment started as late as 4 or 8 h after the injury. In contrast, improvements in working memory and reference memory tasks were seen only if the treatment started at 15 min and 4 h after the injury. Analysis of the lesions demonstrated that treatment with nicotinamide at 15 min and 4 h dramatically prevented brain tissue loss. Protection, however, was not observed in treatments started 8 h after the injury.

It is known that severe brain injury is associated with a dramatic and rapid increase in the activity of poly(ADP-ribose) polymerase (PARP), which leads to severe depletion of neuronal NAD.[33] Nicotinamide restores neuronal energy levels by elevating NAD levels.[39] Animal studies show that nicotinamide supplementation reduces neuronal death and brain edema and attenuates BBB disruption in TBI.[90,91] Also of importance is the finding that nicotinamide reduces glial proliferation in brain injuries.[94-96]

It is known that axonal injury precedes neuronal loss in most neurodegenerative diseases, such as AD as well as peripheral neuropathies.[219,249] A recent study by Wang *et al.* found that in Wallerian degeneration slow mice, there is a dramatic fall in NAD levels and that nicotinamide can delay the onset of axonal degeneration associated with NAD depletion.[249] Interestingly, the protection was not related to nicotinamide's effects on SIRT1, but rather energy generation. This was confirmed by the finding that pyruvate also protected the axons from degeneration.[249]

The question of SIRT1's contribution to neuroprotection is complex, given that SIRT1 stimulation by resveratrol

and SIRT1 inhibition by nicotinamide both protect the brain from ischemic damage in a stroke model. Liu *et al.* examined this question and found that with ischemia-induced excitotoxicity, SIRT1 deacetylase activity fell significantly and PARP levels rose at the same time in response to DNA damage by free radicals.[144] Both SIRT1 and PARP require large amounts of energy and therefore consume neuronal NAD, thus leading to neuronal death. Nicotinamide supplementation did not change SIRT1 protein levels, but protected neurons from energy depletion induced by excitotoxicity by reducing SIRT1 deacetylase activity and by the maintenance of NAD^+ levels. The SIRT1 activator resveratrol at a low concentration (25 mM) protected neurons from excitotoxic glutamate-induced NAD^+ depletion and death, whereas at high concentrations, resveratrol had either no effect or exacerbated excitotoxic neuronal death.[144] Nicotinamide also protect against MPTP-induced striatal damage to dopaminergic neurons in mouse models of PD.[6]

Also of interest is the finding that damage to the brain in cases of thiamine deficiency and Wernicke's encephalopathy may be secondary to microglial activation induced by energy disruption.[236,248] Energy deficiencies can significantly enhance excitotoxicity and this may involve microglial activation.

Riboflavin supplementation inhibits astrocyte activation, reduces brain edema, and improves behavioral outcomes in TBI models.[95] Riboflavin can also inhibit glutamate release from cortical nerve terminals, thus reducing excitotoxicity.[252] A number of interesting studies have demonstrated the presence of B-vitamin–type fibers in selected areas of the monkey brain, including those for thiamine, riboflavin, folic acid, and pyridoxal.[159-162] In addition, vitamin C immunoreactive neuronal cell bodies were found in the hypothalamic nuclei and anterior commissure, suggesting a unique function for these vitamins in the mammalian brain.[159]

MAGNESIUM AND NEUROPROTECTION

Magnesium is one of the most abundant ions in the brain and plays a major role in a plethora of biochemical and physiological CNS tissue functions. In both humans and animals, low magnesium levels alone can trigger inflammation in a number of tissues, including the brain, as well as lower seizure thresholds. Experimentally, during progression of magnesium deficiency in a rodent model there is a significant increase in inflammatory cytokines, such as IL-1β, IL-6, and TNF-α, as well as substance P, within 5 days. The latter is known to stimulate the release of the proinflammatory cytokines.[253] A number of human studies have also shown elevations in inflammation with hypomagnesemia as measured by C-reactive protein.[3,181]

TBI is associated with a rapid and sustained fall in blood and brain magnesium levels. The prognoses is significantly worse in patients when magnesium levels fall, even if they are corrected within 24 h following the injury.[220] In a series of animal studies, Vink *et al.* measured the dynamics of this effect and its impact on neurodegeneration and neurological function. In the case of focal and diffuse brain injury, there is a decline in both free and total tissue magnesium concentrations.[241] In a diffuse axonal injury model, Heath and Vink observed a highly significant and sustained decline in intracellular-free magnesium 4 days after the trauma with full recovery by day 6.[86] All animals showed a significant neurological deficit. In a similar study using rats, there was a 60% decline in preinjury magnesium levels that lasted 5 days and recovered by day 8.[242]

Cernak *et al.* examined plasma magnesium, calcium, and oxidative status in 31 males with TBI and found a significant fall in plasma magnesium levels in patients with mild to severe brain injury.[37] Interestingly, magnesium levels remained low the longest in patients with mild to moderate brain injury. Oxidative stress is correlated with magnesium deficiency and is particularly high in the aged brain.[196] Low magnesium is also associated with a significant fall in cellular glutathione and a dramatic increase in free radical generation.[44,163]

Two patterns of decline in magnesium levels occur in animal models in which the animals either have a diffuse brain injury alone or in combination with subdural hematoma.[87] The latter demonstrated an immediate fall in brain magnesium followed by recovery to preinjury levels and then a second decline. This secondary decline occurred despite administration of a bolus of magnesium 30 min after the injury.

Several studies demonstrated significant neuroprotection by magnesium sulfate infusions following TBI in experimental animals. Browne *et al.* using parasagittal fluid percussion brain injury in young rats found that giving a bolus of magnesium sulfate significantly reduced progressive tissue loss in the hippocampus, demonstrating long-term protection following an injury.[31] Improvements in neurological function not only are limited to sensory or motor function but also involve behavior and cognition.[89,92] Barbre and Hoane found that riboflavin and magnesium infusions improved functional recovery to a greater extent than either alone following a frontal cortical contusion injury in rats.[13] Ghabriel *et al.* showed that magnesium replacement reduced brain edema following a diffuse TBI in male Sprague-Dawley rats.[76]

Magnesium infusions also significantly reduce posttraumatic depression and anxiety following a diffuse TBI in animals.[71] The incidence of depression was 61% in the animals after the injury, which is similar to that

seen clinically. Animals receiving the magnesium bolus 30 min following the injury demonstrated an incidence of depression of 30%, which persisted for the entire 6-week observation period.

One of the vital functions for CNS magnesium is modulation of the NMDA glutamate receptor. Low levels of magnesium significantly enhance excitotoxic sensitivity and may be one of the mechanisms by which magnesium depletion precipitates seizures in otherwise healthy individuals.[216] Furthermore, magnesium deficiency has been demonstrated in neurodegenerative disorders, such as AD, where it was correlated with cognitive scores. Patients with lowest magnesium levels had the lowest Global Deterioration Scale scores and Clinical Dementia Ratings.[52] A review of studies found that magnesium may be useful in improving cognitive function and other symptoms in AD patients.[179]

Recent population assessments reveal magnesium deficiency in the majority of the population. While total plasma magnesium remains rather stable in healthy individuals throughout life, total body and intracellular stores tend to decrease with age.[12] There are a multitude of reasons for this loss, including poor absorption from the gut, reduced bone uptake and mobilization, reduced adaptability to stress, progressive insulin resistance, and increased urinary loss. Thus, magnesium deficiency is commonly found in chronic stress, illness, diabetes, autoimmune disorders, acute and chronic infections, and poor diets. Moreover, a number of drugs commonly used in neurological patients are known to deplete magnesium, including steroids, diuretics, and cardiac drugs.[97]

Ironically, few neurosurgeons add magnesium to their patient's intravenous fluids, even though they will routinely add potassium. Over 45 million Americans suffer from metabolic syndrome and a larger number from insulin resistance, both of which are associated with magnesium deficiency.[170] In addition, many neurosurgical patients are either elderly or young athletes and are subjects of this deficiency. With abundant evidence for the vital role of magnesium in a multitude of metabolic reactions, synaptic function, antioxidant protection, anti-inflammatory effects, and protection against excitotoxicity, it makes little sense to ignore this mineral in neurosurgical treatments.

Measuring magnesium sufficiency is challenging since 99% is intracellular and only 1% resides in the plasma. Moreover, studies show that a person can have normal plasma magnesium levels but severe depletion in the tissues.[53] The best clinical measures for magnesium are taken from the red blood cells. It should also be appreciated that magnesium enters the brain slowly, and oral supplementation may take months for repletion within deep brain structures.[209] Intravenous infusions can enter the cortex and circumventricular organs of the brain within hours but can take much longer to enter the deeper brain structures.

CONCLUSION

In this review, I have presented the evidence supporting a profound effect of selected neutraceuticals on a number of pathological conditions pertinent to human neurological disorders, including AD, PD, strokes, TBIs, concussions, posttraumatic stress syndrome, ischemia/hypoxia, and brain edema.

In a previous paper, we demonstrated that growing evidence strongly suggest that a central mechanism in many of these disorders is a process called immunoexcitotoxicity. Essential to this process is prolonged, intense microglial activation. Because a number of natural products have been shown to affect cell signaling mechanisms, which also impact immunoexcitotoxicity, we suggest that more research be directed toward their clinical use. Most have shown a high degree of safety, even when used in rather large doses, as well as remarkable efficacy at very low concentrations, which can be easily reached with an oral intake of existing supplements. With newer methods of delivery and encapsulation, bioavailability can be further increased, making these extracts more clinically relevant.

It should be noted that natural products act additively and synergistically in their positive effects on pathophysiological processes and thus work best when a healthy diet is also followed. While animal and *in vitro* studies strongly support the use of nutraceuticals in promoting CNS repair from a variety of insults, better conducted, long-term human studies are required in order to aid in developing more efficient and specific therapies.

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