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Natural Support for Neurologic Health: A Multiple Pathway Approach

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ABSTRACT: *As more people than ever before reach their "golden years," there is growing concern about maintaining neurologic health and brain function. Diseases and disorders that affect neurologic function, including the dementias, cerebrovascular disease, and progressive disorders like Alzheimer's or peripheral neuropathies, are significant health concerns for aging patients. While some decline in neurologic function during the aging process is normal, progression to actual neurologic disease is not inevitable. Some of these disorders may result from the cumulative effect of imbalanced biochemical pathways that propagate premature neurologic senescence. Four major biochemical pathways that may underlie neurologic decline are identified and the appropriate nutritional support discussed. By addressing optimal function in these pathways, the healthcare professional may be able to help their patients live out their lives with optimal neurologic health and brain function.*

With advances in hygiene, science, and medicine, modern man has become the longest-lived in human history and life expectancy continues to lengthen. Diseases and disorders that affect the nervous system more often in aging persons are being diagnosed in record numbers in the United States: up to 6.8 million suffer from dementia; approximately 4 million have Alzheimer's disease (AD), a number expected to jump to 14 million by the year 2050; and up to 1.5 million may suffer from Parkinson's disease (PD), with 50,000 newly diagnosed each year. Dysfunction in older patients should not be assumed to be secondary to normal aging; disease processes should be considered.[1,2]

As there are a wide variety of neurologic disorders that can affect patients in their older years, it is important to screen for early warning signs of neurologic deterioration (Table 1). Interventions begun in the initial stages of the disease process may prevent or delay the course of deterioration. Early intervention may also result in improvement, rather than simply treating the symptoms once a diagnosis is made.[3-6]

Table 1. Early Warning Signs of Neurologic Degeneration[2,3]

- Impaired expression or comprehension of written or spoken language.
- Difficulty in decision making and problem-solving.
- Agitation—a state of hyperarousal, increased tension, and irritability.
- Disturbances in or loss of memory, especially for recent events.
- Difficulty in carrying out tasks with multiple steps.
- Impaired judgement.
- Intellectual decline.
- Confusion or disorientation, hyperactivity, and overt hostility.
- Depression.
- Anxiety.
- Poor hygiene and appearance.
- Loss of balance and coordination.
- Impaired motor function.
- Rhythmic tremors in a hand or foot, particularly when at rest.

THE GENETIC COMPONENT OF AGE-RELATED DISEASES

It is tempting to assume that the loss of certain physiological functions in humans is related to genetic factors alone. However, research indicates that nutrition and other environmental factors can modify the *phenotype*—the way our genes are expressed.[7] By nutritionally supporting the balance and function of biochemical pathways underlying neurologic health, it may be possible to prevent the expression of "aging" phenotypes, including neurologic diseases.[3-7]

THE FOUR BIOCHEMICAL PATHWAYS

Four major biochemical pathways recognized as possible pathophysiological mediators of both aging and neurodegenerative processes are outlined below. These include I.) chronic inflammation, II.) mitochondrial dysfunction, III.) endocrine imbalance, and IV.) hypomethylation.

It should be noted that although the concept of oxidative stress does not comprise a fifth pathway in this discussion, its impact on the propagation of other pathways is indeed important. A large body of evidence suggests that oxidative injury either causes or exacerbates neuronal injury and leads to primary or secondary pathophysiological mechanisms underlying many neurologic disorders.[6,8-10] The brain may be particularly vulnerable to oxidative damage due to the fact that it has a high energy requirement and a high oxygen consumption rate, is rich in peroxidizable fatty acids, contains high levels of metals (e.g., iron), and has a relative deficit of antioxidant defenses compared to other organs.[6,8-10] Antioxidant support should, therefore, accompany therapies that address the four pathways discussed herein.

I. CHRONIC INFLAMMATION

Though inflammation as a mechanism is usually protective, downstream effects of this process when it is maintained beyond its usefulness in defense can be harmful to all tissues. Chronic inflammation is intimately linked to oxidative stress and has long been recognized as a possible pathophysiological mechanism in age-associated neurodegeneration.[5,11-15] Interestingly, epidemiological evidence indicates that populations taking anti-inflammatory drugs for other conditions have a sharply reduced risk of neurodegenerative disease.[5]

Poly(ADP-ribose) polymerase (PARP) is a nuclear enzyme that is activated by DNA strand breaks and involved in the repair of DNA. Chronic cellular insults resulting from such things as oxidative stress (especially peroxynitrite) or inflammation may lead to increased genetic damage and PARP activation. PARP activity appears to increase with age and is prominent in vascular stroke and other neurodegenerative processes, including AD.[16-19]

Chronic inflammation is capable of propagating premature brain aging and neuronal cell death by:

- activating transcription factors such as nuclear factor kappaB (NF-KB), which give rise to both aging and inflammation phenotypes.[15]
- encouraging the expression of genetic characteristics associated with neurologic disease (e.g., apolipoprotein E4, amyloid precursor protein).[20]
- increasing coagulation and altering vasomotor tone in cerebral vasculature, thereby increasing the risk of ischemic brain damage.[15,16]
- compromising blood brain barrier (BBB) integrity.[21]
- releasing pro-inflammatory mediators (e.g., cytokines, prostaglandins, interleukins) that promote neurotoxicity, thereby exacerbating neuronal damage.[12,15,21,22]
- generating reactive nitrogen species (RNS) and reactive oxygen species (ROS) that damage neuronal receptors (e.g., acetylcholine), proteins, lipids, membrane thiols (e.g., glutathione), and DNA.[23,24]
- stimulating PARP.[19]

II. MITOCHONDRIAL DYSFUNCTION

Tissues that have a high energy (ATP) requirement, such as the brain and heart, have a higher density of mitochondria—the cell's energy-producing powerhouses. Since the brain depends so highly on mitochondrial energy supply, dysfunction of mitochondria may affect the central nervous system (CNS) more severely than other tissues.[25-27]

The probability that age-associated diseases, including neurologic disease, may be precipitated, propagated, or caused by impaired mitochondrial function is a prevailing theory. Changes in mitochondria that occur with age and cause dysfunction include loss of membrane potential and function, reduced enzyme activity, increased mutations in mitochondrial DNA (mtDNA), reduced ATP synthesis, increased oxidant production and leakage, a fall in the apoptotic threshold of neurons, and decreased antioxidant defenses.[25,27,28]

As a result of the high metabolic demands on mitochondria, mtDNA experiences about 10 times as much oxidative damage and has about 17 times the mutation rate of nuclear DNA.[29] Accumulation of these mutations over time causes bioenergetic deficits leading to neurodegeneration, and can be accelerated by individual genotype.[25,30,31]

The research suggests two methods of supporting mitochondrial health and function: 1.) supporting healthy mitochondrial energy production, and 2.) combating ROS/RNS production and damage by increasing mitochondrial antioxidants.[25-31]

III. ENDOCRINE IMBALANCE

Endocrine function directly and indirectly influences neurologic aging through its complex effects on inflammatory balance, cerebral and overall glucose metabolism, neurotransmitter and neurotrophic factor production, circulatory function, and the stress response.[32]

Hypothalamic-Pituitary-Adrenal Influences in Neurologic Aging
The hypothalamic-pituitary-adrenal (HPA) axis is an endocrine closed-loop system that controls the secretion of stress hormones (glucocorticoids). Aging is associated with a reduced ability to adapt to stress, increased HPA activation, and chronic elevations of glucocorticoids (e.g., cortisol).[33,34] Animal and human data suggest that cumulative exposure to high levels of glucocorticoids can be particularly detrimental to the aged hippocampus (the brain structure involved in learning and memory).[33]

Under sustained immune, traumatic, metabolic, or emotional stress, chronically elevated glucocorticoid levels can propagate neurologic decline in many ways. They can contribute to inflammatory 5-lipoxygenase (5-LOX) gene expression; increase neuronal sensitivity to toxins and ischemia; inhibit sex steroid and growth hormone secretion; affect mood and behavior; permanently downregulate hippocampal cell receptors; alter neurotransmitter function; disrupt memory, recall, and cognition; and eventually result in neuronal atrophy and death.[34-37]

Lifestyle changes and natural interventions that help reduce glucocorticoid levels and enhance the body's ability to cope with stress are two ways to intervene in the neurologic decline associated with hyperglucocorticoidemia.

Dysglycemia
During aging, changes in glucose and insulin metabolism may result in dysglycemia, which can lead to neuronal degeneration. Peripheral neuropathic changes can be seen early in dysglycemic states, even before the formal diagnosis of diabetes. Though the mechanism is unclear, reduced glucose metabolism and transport have been observed in AD. In addition, hypoglycemia is known to contribute to neuronal damage in stroke. On the other hand, hyperglycemia upregulates glycation (the reaction of blood glucose with proteins) of structural and functional proteins in the nervous system resulting in the formation of damaging advanced glycation endproducts (AGEs).[38] Structural and functional damage to proteins in membranes and inner structures of neurons may be associated with declining cognitive function in aging.[38,39]

In individuals with dysglycemia, proper diet, exercise, and modulation of their condition with nutritional factors such as fiber, chromium, vanadium, magnesium, antioxidants, and conjugated linoleic acid (CLA) may help reduce the associated neurologic decline.

IV. HYPOMETHYLATION

Methylation, the transfer of a methyl group (CH_3) from one molecule to another, is required for numerous biochemical reactions vital to good health. In fact, methylation of DNA influences binding of transcription factors and is an integral means by which gene expression is regulated. Hypomethylation is considered by some researchers to be a biological marker of aging.[40] In addition, many important second messenger and information-carrying molecules, such as catechol neurotransmitters, require methylation.[40-42]

Homocysteine (Hcy)
Hcy is an amino acid product of protein digestion that can accumulate to harmful levels in the blood if there is an insufficiency of one or more of the vitamin cofactors of methylation; these include folate and vitamins B_6 and B_{12}.[43] In addition, genetic polymorphisms that lead to less efficient Hcy methylation are not uncommon.[44]

An increase in blood Hcy levels is strongly linked to cognitive decline.[64,65] In fact, hyperhomocysteinemia is a very strong and graded independent risk factor for cerebrovascular disease (CD), which is the second most common cause of irreversible dementia.[45,46] In one study, 42% of CD patients had hyperhomocysteinemia.[46] In addition, those with AD have significantly higher blood Hcy levels and lower folate and vitamin B_{12} levels compared to controls.[47] In another study, up to 27% of psychogeriatric patients had hyperhomocysteinemia despite normal levels of blood folate and vitamin B_{12}.[48]

NUTRITIONAL MODULATION OF THE FOUR PATHWAYS OF NEUROLOGIC DECLINE

Multimodal nutritional intervention creates the opportunity for healthcare professionals to simultaneously intervene in the multiple and overlapping pathways leading to neurologic decline. By combining nutrients that have high CNS activity and address chronic inflammation, mitochondrial dysfunction, endocrine imbalance, and hypomethylation, as well as the free radical load that propagates these pathways, there is a better chance of interrupting the damaging cascade (Table 2, Figure 1).

Niacinamide

Niacinamide is a potent inhibitor of PARP, and thereby reduces the cyclic inflammatory cascade.[49,50] In animal models of ischemia, administration of niacinamide inhibited PARP, resulting in reduced brain damage and neurologic functional losses.[17,51]

As a co-factor for the production of mitochondrial NAD, niacinamide dose-dependently reduces neuronal necrosis, presumably through preserving neuronal NAD and ATP.[51] In rats, administration of niacinamide has also been shown to inhibit oxidant-induced activation of signaling molecules that are potentially neurotoxic.[52,53]

Niacinamide, unlike niacin, does not cause flushing and pruritis. Mild side effects, mostly limited to gastrointestinal disturbances, can be managed by taking niacinamide with food or fluids.

Essential Fatty Acids: EPA and DHA

The brain is particularly rich in polyunsaturated fatty acids (PUFAs), such as arachidonic acid (AA), eicosapentaenoic acid (EPA), and docosahexaenoic acid (DHA). Changes in the tissue membrane composition of these essential fatty acids are reflective of intake.[54] Fish oils, which contain EPA and DHA, are precursors of anti-inflammatory eicosanoids and are well known for their anti-inflammatory activity. Research indicates that substitution of EPA and DHA for AA in brain phospholipids may result in less cyclooxygenase (COX)-dependent cerebrovascular reactivity.[55] Furthermore, DHA is required for normal brain function in adults and is utilized up in preference to other fatty acids. Decreases in brain DHA content are associated with age-related cognitive decline, dementias, and AD.[56] The amount of EPA and DHA estimated to prevent deficiency in the elderly is 300 to 400 mg per day combined.[57] Anti-inflammatory activity in conditions of chronic inflammation is observed at doses of 6 g/day.

Resveratrol

Resveratrol is a polyphenol found in the skins of red grapes and various other plants. In vitro, animal, and epidemiologic research suggests that resveratrol may be protective against CNS disorders.[58] In one study, chronic administration of resveratrol in young-adult rats protected the olfactory cortex and hippocampus from an injected toxin.[59] It has also been shown to inhibit the COX-1, COX-2, and 5-LOX inflammatory pathways and prevent the activation of NF-κB.[60,61] (It is important to note that therapies which solely inhibit the COX-2 pathway may increase the production of leukotriene B4 (one of the most potent endogenous inflammatory factors) via the 5-LOX pathway.[5]) Resveratrol also has potent antioxidant activity, inhibits the oxidation of lipids, inhibits platelet aggregation, and induces hepatic Phase II detoxification activity.[58,62]

N-Acetylcysteine (NAC)

The protective effect of NAC is believed to be related to its restoration of brain glutathione (GSH) levels.[63] However, GSH does not cross the BBB, so oral supplementation with precursors such as NAC and alpha-lipoic acid are the best way to increase brain levels. GSH is central to antioxidant defenses in the brain, is an important component of the cellular detoxification of ROS, and is involved in the disposal of exogenous peroxides by astrocytes and neurons.[64] In preclinical stages of PD, a decrease in total GSH concentrations in the substantia nigra has been observed.[65]

NAC has been shown to increase mitochondrial complex I activity and markedly improve mitochondrial electron transport chain activity. In animal models of traumatic brain injury, NAC significantly restored mitochondrial energy producing mechanisms (electron transfer, energy coupling capacity, calcium uptake activity).[63]

Table 2. Nutritional Modulation of the Pathways That Impact Neurologic Health

Pathway	Nutrient	Mechanism
Chronic Inflammation	Niacinamide	PARP inhibitor, NOS inhibitor
	EPA and DHA	Replaces AA in brain cells, downregulates inflammatory COX activity
	Ginkgo	Antioxidant, vasodilator, inhibits platelet-activating factor (PAF)
	Resveratrol	Antioxidant, inhibits inflammatory COX and LOX activity and products, reduces platelet aggregation
	CoQ10, alpha-lipoic acid, vitamin E, mixed carotenoids	Antioxidant
Mitochondrial Dysfunction	Niacinamide	Cofactor for NAD production
	Magnesium	Membrane integrity, ATP transfer
	Thiamin	Enzyme activity
	CoQ10	Antioxidant, respiratory chain activity, enzyme activity
	Ginkgo, mixed carotenoids	Antioxidant
	Acetyl-L-carnitine	Transport and clearance of fatty acids, increases cardiolipin
	N-acetylcysteine	Antioxidant, increases GSH, improves mitochondrial electron transport chain
	Alpha-lipoic acid	Cofactor in ATP synthesis, antioxidant
Endocrine Imbalance	Ginkgo	Adaptogenic properties, decreases glucocorticoids
	Adaptogenic herbs	Improves the body's ability to cope with stress
	Magnesium	Deficiency can increase physiologic susceptibility to stress
	Dysglycemia program (including alpha-lipoic acid)	Nutrients that improve glycemic control help prevent neuronal damage mediated by hypoglycemia and nerve protein glycation mediated by hyperglycemia
Hypomethylation	Folate, Vitamin B_6, Vitamin B_{12}	Methylation of DNA, DNA stability, neurotransmitter synthesis, reduce homocysteine levels

Alpha-Lipoic Acid (ALA)
ALA is a cofactor in the synthesis of ATP and improves overall mitochondrial function.[66] It may also enhance mitochondrial function by protecting mtDNA and preventing oxidative changes in the mitochondrial membrane, which would impact its functional, energy-producing capacity.[67,67]

ALA is an excellent antioxidant agent for neurodegenerative diseases due to the fact that it can interrupt the free radical cascade at several points. It also extends the functional capacities of other critical antioxidants in neurologic health, namely vitamins C and E and coenzyme Q10. Animal research has shown that ALA supplementation reduces lipid peroxidation, elevates antioxidants in various brain regions, and improves memory in aged mice.[66,68] In addition, ALA supports the removal of glucose from the bloodstream via the insulin signaling pathway. The vast majority of human research on ALA has been done in patients with diabetic neuropathy, showing clinical benefit at doses of 800 to 1200 mg/day.

Acetyl-L-Carnitine (ALC)
Carnitine is a vitamin-like substance that is responsible for the transport of fatty acids into and out of the mitochondria. It also increases cardiolipin—an important phospholipid that serves as a cofactor for a number of critical mitochondrial transport proteins.[29,69,70] Supplementation with ALC may improve energy production within brain cells. Carnitine in the form of ALC is thought to be substantially more active in the CNS and is the form found naturally in brain tissue.[70]

An analysis of controlled studies reports that persons with subclinical or clinical dementia given 1.5 to 3 g ALC daily have shown improvement in numerous clinical measures of cognitive function. In two large multicenter, crossover trials, geriatric patients given 1500 mg ALC daily for 90 days experienced improvements in clinical tests of cognition, memory, and depression over controls.[71,72] In other double-blind, placebo-controlled trials, ALC-treated subjects showed less mental deterioration as rated by cognitive and AD assessment test scores.[73,74]

In addition to its beneficial impact on mitochondrial function, ALC supports the synthesis of the neurotransmitter acetylcholine, which is responsible for memory and brain function. Research suggests that ALC may be very beneficial in the early stages of neurodegeneration.[29,70]

Magnesium
Magnesium plays an important role in maintaining the integrity and permeability of the mitochondrial membrane. Also, magnesium binds phosphate groups in ATP, forming a complex that assists in the transfer of ATP, which is critical for energy production.[43,75]

Magnesium deficiency increases susceptibility to physiologic damage produced by stress and hyperglucocorticoidemia.[76] Furthermore, magnesium deficiency, or dietary imbalances that intensify magnesium inadequacy, may increase risk of cerebrovascular constriction and occlusion.

Thiamin
Thiamin is a cofactor in mitochondrial metabolism. Deficiency results in depressed activity of enzyme complexes, resulting in a decrease in citric acid cycle activity and activities of the respiratory chain. Thiamin deficiency also decreases erythrocyte transketolase activity—an enzyme that catalyzes phosphate reactions.[43,77] Abnormal transketolase activity is associated with several metabolic disturbances including impairment of ATP synthesis, acetylcholine disturbances, and abnormalities in the serotonergic system.[43,77]

Coenzyme Q10 (CoQ10)
CoQ10 is a lipid-soluble mitochondrial antioxidant cofactor that has been shown to be neuroprotective.[6] In addition to being a potent free radical scavenger in lipid and mitochondrial membranes, CoQ10 is critical for the function of the mitochondrial respiratory chain. Physiological levels are known to decrease with age and supplementation has proven efficacious in a variety of age-related illnesses.[78]

Low levels of CoQ10 are associated with reduced mitochondrial enzyme activity (complexes I and II/III).[79] In Parkinsonian patients, administration of CoQ10 showed a trend toward an increase in complex I activity.[79] Treatment of patients having various mitochondrial cytopathies with 150 mg/day CoQ10 improved all brain variables. A dose of 200 mg/kg in 12- and 24-month-old rats produced significant increases in CoQ10 levels of the cerebral cortex mitochondria.[78] CoQ10 administration was also shown to protect against striatel lesions and dopamine depletion produced by toxins.[78] Vitamin E and CoQ10 taken together are believed to have an interactive effect, wherein CoQ10 has a sparing effect on vitamin E and vitamin E plays a key role in determining tissue retention of exogenous CoQ10.[80]

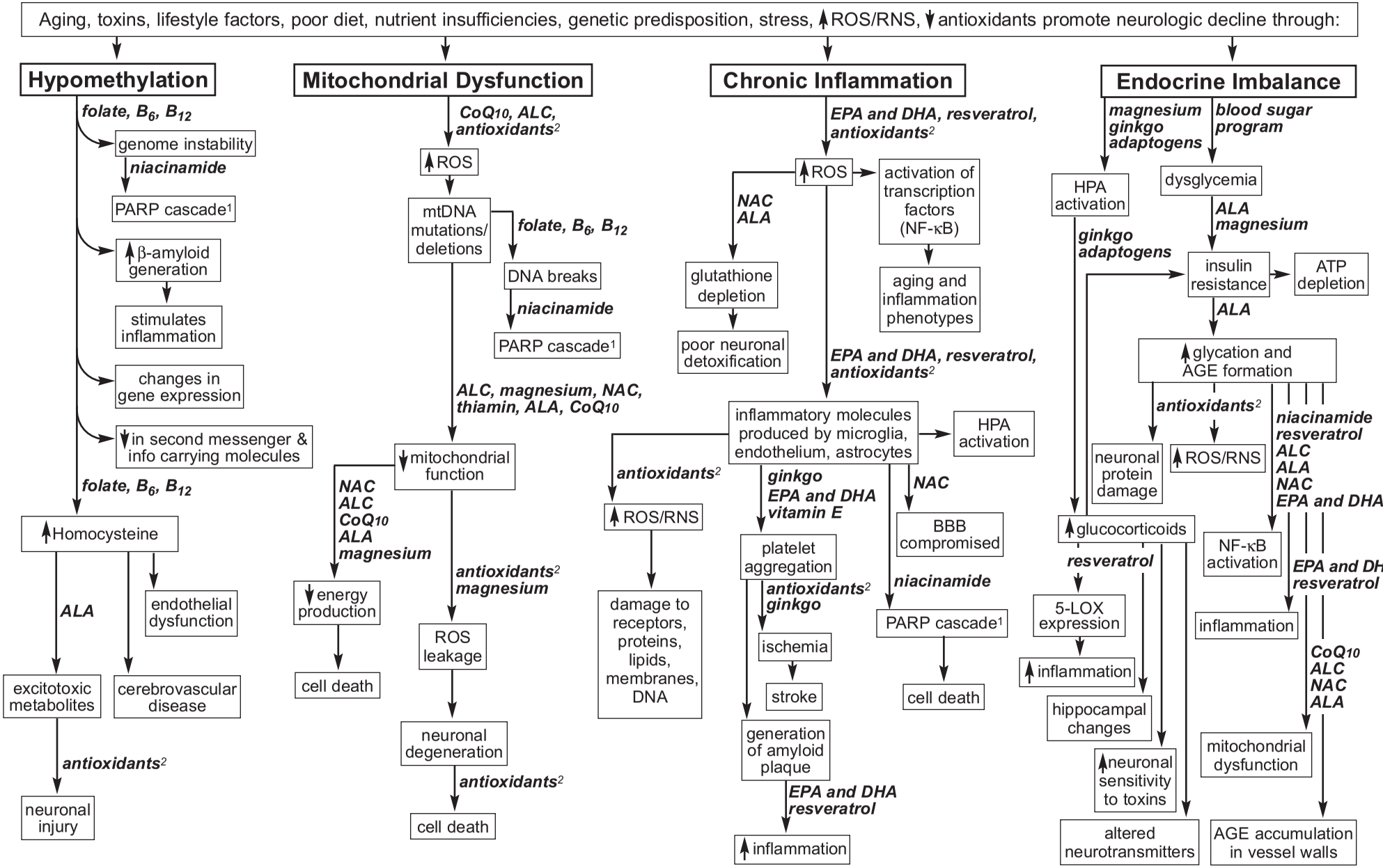
Vitamin E
Vitamin E is the primary lipid soluble antioxidant found in all tissues. Low vitamin E levels are consistently associated with an increased risk and occurrence of neurologic disease, including AD and PD.[81,82] Patients with prolonged deficiency may develop decreased reflexes, failure of muscular coordination (ataxia), dementia, and blindness.[83] In a double-blind, placebo-controlled, randomized, multicenter trial in patients with AD, treatment with 2000 IU/day of vitamin E for 2 years was beneficial in delaying the primary outcome (time to the occurrence of death, institutionalization, loss of ability to perform activities of daily living, severe dementia) of disease progression.[84] In fact, the estimated increase in median survival with vitamin E supplementation was 7.5 months. The results of other studies of neurodegeneration have been mixed and further clinical trials in the early stages of neurodegeneration are needed.

Peroxynitrite is a potent RNS formed by the reaction of nitric oxide and superoxide. It is implicated in multiple phases of neurologic damage. The gamma-tocopherol form of vitamin E is a potent trapper of peroxynitrite and should be taken in conjunction with alpha-tocopherol.[85]

Ginkgo (*Ginkgo biloba*)
Ginkgo biloba extract (GBE) is an approved treatment for dementia in Germany, and it is the only nonprescription substance considered a treatment for dementia in Canada.[86] Many European clinical studies have demonstrated the effectiveness of GBE in the treatment of patients with age-associated memory and cognitive impairment as well as dementia and AD.[87-90] The first clinical trial conducted in the U.S. to assess the efficacy and safety of GBE was published in the *Journal of the American Medical Association*.[91] In this randomized, double-blind, placebo-controlled study, patients with dementia and AD received 120 mg/day GBE or placebo for 1 year. The results of the study indicated that GBE was safe and improved the cognitive performance and social functioning of the patients in a substantial number of cases, in contrast to worsening of these functions in controls.

GBE has been shown to have several mechanisms of action: it scavenges oxidative radicals, inhibits platelet aggregation, improves circulation to the brain, and may help normalize cerebral metabolism under hypoxic conditions.[90,92] In addition, GBE may also prevent changes in mitochondrial morphology and function associated with aging of the brain.[93] High quality GBE is typically standardized to 24% ginkgo flavone glycosides (quercetin, kaempferol, and isorhamnetin) and 6% terpene lactones (primarily ginkgolides and bilobalide), and most clinical trials have used a dose of 120 mg/day. GBE also shows anti-stress and adaptogenic properties in animals: it decreases blood glucocorticoid levels and increases adrenocorti-

Figure 1. Natural Support for Neurologic Health: A Multiple Pathway Approach



1. **PARP cascade:** DNA strand breaks → excessive PARP activation → NAD depletion → ↓ATP synthesis → ↓energy production → neuron cell death via necrosis or apoptosis → excessive apoptosis or necrosis damages neighboring tissues & stimulates inflammation

2. **Antioxidants include:** NAC, ginkgo, resveratrol, mixed carotenoids, CoQ10, ALA, vitamin E, etc.

Acronym Key: AGE: advanced glycation end products, ALA: alpha-lipoic acid, ALC: acetyl-L-carnitine, ATP: adenosine triphosphate, BBB: blood brain barrier, DHA: docosahexaenoic acid, EPA: eicosapentaenoic acid, HPA: hypothalamic-pituitary-adrenal axis, 5-LOX: 5-lipoxygenase, mtDNA: mitochondrial DNA, NAC: N-acetylcysteine, NAD: nicotinamide adenine dinucleotide, NF-κB: nuclear factor kappaB, PARP: poly(ADP-ribose) polymerase, ROS: reactive oxygen species, RNS: reactive nitrogen species.

cotrophic hormone levels, showing positive potential for stress-related cognitive impairment; prevents stress-induced learning impairment and elevations in stress hormones; and increases acetylcholine synthesis and the turnover of norepinephrine.[94-96]

Adaptogenic Herbs

Due to the decreased ability to handle stress and increased activation of the HPA axis associated with aging and neurodegeneration, additional herbs with adaptogenic properties may be beneficial. Ayurvedic herbs such as ashwagandha (*Withania somnifera*), holy basil (*Ocimum sanctum*), and brahmi (*Bacopa monniera*) have a positive influence on stress response, mental function, and cognition.

Mixed Carotenoids

Carotenoids are a class of naturally occurring plant pigments that provide the bright red, orange, and yellow colors of fruits and vegetables. A balanced intake of mixed carotenoids, as found in a healthy diet, provides the best protection against oxidative damage and maintains their spectrum of activities. A variety of biological activities may account for the association of carotenoids with lower risk of age-associated chronic diseases. For example, beta-carotene is more effective at protecting membranes from damage by free radicals than other carotenoids and lutein is more efficient in scavenging ROS.[43] As potent quenchers of singlet oxygen—a highly reactive and destructive free radical that also forms peroxynitrite—carotenoids may support neurologic tissue health.

Folate, Vitamin B_6, and Vitamin B_{12}

Folate and vitamins B_6 and B_{12} are needed for proper methylation, genome stability, and Hcy metabolism. Cognitive health conditions associated with insufficiencies of these nutrients include forgetfulness, memory loss, confusion, depression, dementia, and mood and sensory changes.[43,97,98] Rosenberg and Miller of the USDA Human Nutrition Research Center on Aging state that age-related impairment of cognitive function is likely related to mild or subclinical vitamin deficiencies, and is "preventable or reversible with improved vitamin nutriture, especially vitamin B_{12}, vitamin B_6, and folate."[97]

Methods of reducing Hcy have been a target of investigation due to its extremely harmful effects on body systems—including the nervous system. Studies have repeatedly shown that supplementation with the B vitamins required for Hcy metabolism are effective in lowering blood Hcy levels.[99,100]

In a placebo-controlled study, 100 men with hyperhomocysteinemia were randomly assigned to 5 groups and treated with a daily dose of either a placebo, 650 mcg of folic acid, 400 mcg of vitamin B_{12}, 10 mg of vitamin B_6, or a combination of the three vitamins for 6 weeks.[101] Compared to the control group, plasma Hcy concentrations were reduced by 41.7% in the folic acid group, 14.8% in the vitamin B_{12} group, and 49.8% in the group supplemented with all three vitamins. Vitamin B_6 alone did not significantly reduce plasma Hcy concentrations.

CONCLUSION

Healthcare professionals and their patients must take a preventative stance against neurologic decline. By looking for early warning signs and providing nutritional guidance that addresses chronic inflammation, mitochondrial dysfunction, endocrine imbalance, and hypomethylation, perhaps more patients can live out their most rewarding years with mind and body intact.

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Natural Support for Neurologic Health: A Multiple Pathway Approach
A Summary

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Conditions that affect the nervous system, such as Alzheimer's and Parkinson's disease, are being diagnosed in record numbers in the United States.[1,2] Research suggests that certain biochemical pathways can greatly impact neurologic decline. By maintaining healthy function of these pathways, it may be possible to achieve optimal neurologic and brain function.

FOUR BIOCHEMICAL PATHWAYS IMPLICATED IN NERVOUS SYSTEM DECLINE

I. Chronic Inflammation—Excessive inflammation over time is capable of propagating premature brain aging and nerve cell death.[5,15]

II. Mitochondrial Dysfunction—Mitochondria are energy-producing powerhouses that are highly concentrated in the brain. Dysfunction of mitochondria may affect the central nervous system (CNS) more severely than other tissues.[25-30]

III. Endocrine Imbalance—Aging is associated with a reduced ability to adapt to stress and chronic elevations of stress hormones called glucocorticoids (e.g., cortisol).[33,34] Animal and human data suggest that high levels of glucocorticoids can be particularly detrimental to the hippocampus (the brain structure involved in learning and memory).[33] In addition, changes in glucose and insulin handling during the aging process can lead to neuronal degeneration due to negative effects on nerve cell structure and function.

IV. Hypomethylation—Methylation, the transfer of a methyl group (CH3) from one molecule to another, is required for numerous biochemical reactions vital to good health. However, insufficient levels of folate and vitamins B_6 and B_{12} can cause reduced methylation, or hypomethylation, which in turn can produce elevated levels of the amino acid homocysteine (Hcy).[43] Elevated Hcy levels are strongly linked to cognitive decline and irreversible dementia.[45,46]

NUTRITIONAL MODULATION OF THE FOUR PATHWAYS

Interventions begun in the initial stages of the disease process may prevent or delay the course of neurologic deterioration.[3-6] The following nutrients may help prevent and interrupt the damaging cascade that contributes to neurologic decline.

Niacinamide—Niacinamide, a form of the B vitamin niacin, is a potent inhibitor of inflammation.[49-50] In animal models, administration of niacinamide resulted in reduced brain damage and reduced neurologic functional losses.[51,53]

Essential Fatty Acids—Fish oils, which contain eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), are well known for their anti-inflammatory activity. Furthermore, DHA is required for normal brain function in adults. Decreases in brain DHA content are associated with age-related cognitive decline, dementia, and AD.[56]

Resveratrol—Resveratrol is a polyphenol found in the skins of red grapes and various other plants. In vitro, animal, and epidemiologic research suggests that resveratrol may protect against inflammation and CNS disorders.[58-61]

N-Acetylcysteine (NAC)—The protective effect of NAC is believed to be related to its restoration of brain glutathione (GSH) levels.[63] GSH is central to antioxidant defenses in the brain and cellular detoxification of free radicals. In addition, NAC has been shown to support proper mitochondrial function.

Alpha-Lipoic Acid (ALA)—ALA is a cofactor in the synthesis of ATP (energy required for tissue function) and improves overall mitochondrial function.[66] ALA is also an excellent antioxidant agent in neurodegenerative diseases due to the fact that it can interrupt free radical damage at several points. Animal research has shown that ALA supplementation elevates antioxidants in various brain regions and improves memory in aged mice.[68] In addition, ALA supports healthy blood glucose levels and insulin activity.

Acetyl-L-Carnitine (ALC)—ALC is a vitamin-like substance that may improve energy production within brain cells via its effect on mitochondria.[29,69,70] An analysis of studies reports that persons with dementia given 1.5 to 3 grams of ALC daily have shown improvement in numerous clinical measures of cognitive function such as memory, depression, and mental deterioration.

Magnesium & Thiamin—These nutrients play important roles in maintaining the energy-producing machinery of the mitochondria.[43,75,76]

Coenzyme Q10 (CoQ10)—CoQ10 is a mitochondrial antioxidant cofactor that has been shown to be neuroprotective.[6] In addition to being a potent free radical scavenger, CoQ10 is also critical for healthy mitochondria.[78,79]

Vitamin E—Vitamin E is the primary antioxidant found in all tissues. Low vitamin E levels are consistently associated with an increased risk and occurrence of neurologic disease, including AD and PD.[81-83]

Ginkgo (*Ginkgo biloba*)—*Ginkgo biloba* extract is an approved treatment for dementia in Germany, and it is the only nonprescription substance considered a treatment for dementia in Canada.[86] Many clinical studies have demonstrated the effectiveness of ginkgo in the treatment of patients with dementia, AD, and age-associated memory and cognitive impairment.[87-90]

Adaptogenic Herbs—Ayurvedic herbs such as ashwagandha (*Withania somnifera*), holy basil (*Ocimum sanctum*), and brahmi (*Bacopa monniera*) have a positive influence on stress response, glucocorticoid levels, mental function, and cognition.

Mixed Carotenoids—Carotenoids are a class of naturally occurring plant pigments that provide the bright red, orange, and yellow colors of fruits and vegetables. A balanced intake of mixed carotenoids, as found in a healthy diet, provides the best protection against oxidative damage.[43]

Folate, Vitamin B6, and Vitamin B_{12}—These vitamins are needed for proper methylation and to keep Hcy within a normal range.[101] Insufficiencies of these nutrients may result in forgetfulness, memory loss, confusion, depression, dementia, and mood and sensory changes.[97,98,100]

CONCLUSION

Healthcare professionals and their patients must take a preventative stance against neurologic decline. By looking for early warning signs and providing nutritional guidance that simultaneously addresses chronic inflammation, mitochondrial dysfunction, endocrine imbalance, and hypomethylation, perhaps more people can live out their most rewarding years with mind and body intact.