

Retarding Cognitive Decline with Science-based Nutraceuticals

Joshua Reynolds*, Laguna Beach, California
 Richard D. Hamill, PhD, Laguna Hills, California
 Rita Ellithorpe, MD, Tustin Longevity Center, Tustin, California
 Robert Settineri, MS, Sierra Research, Irvine, California

ABSTRACT

A review of five natural ingredients that combine with potential synergy to address key multiple factors common to normal and accelerated cognitive decline. A combination of well-studied pleotropic ingredients has been shown to provide broad spectrum antioxidant, anti-plaque, anti-excitotoxicity and anti-inflammatory neuroprotective effects, while enhancing neurotransmitter function, cerebral energy metabolism, calcium homeostasis and mitochondrial function.

INTRODUCTION

“Cognitive vitality is essential to quality of life and survival in old age. With normal aging, cognitive changes such as slowed speed of processing are common, but cognitive decline is clearly not inevitable. Various therapeutics, including cognitive enhancers and protective agents such as antioxidants and anti-inflammatories, may eventually prove useful as adjuncts for the prevention and treatment of cognitive decline with aging.” *Mayo Clinic, 2002*

Cognitive decline is a relative term. Decline rate can be age-associated, i.e., normal, or accelerated, i.e., abnormal. There are *states* of cognitive function, aka *cognitive status*, ranging from normal and low normal, e.g., AAMI, or age-

associated memory impairment,¹ to the borderline transitional state of MCI, or mild cognitive impairment,² to Alzheimer’s disease (AD). Each state has standardized memory and cognitive test score metrics allowing for clinical assessment based on percentile, or standard deviations (SD) from the general population and/or age-matched norms.

AAMI is indicated by a memory score at or below 1SD (i.e., 17th percentile) of a young, high functioning group or population, e.g., a 20-30 year old. AAMI may apply to 50% or more of the general population over age 50-60. Statistically, AAMI is three times more likely to progress to dementia. MCI is indicated by a memory score at or below 1.5SD below age-matched norms, and progresses to AD at the rate of 10-15% per year.² Incidence of full blown AD approaches 50% by age 80-90. Alzheimer’s is now assumed to be a 20-40 year process until its obvious manifestation and clinical diagnosis. AD has been identified via PET scans in late 20 and early 30 year old brains.

The author’s patented, (US Pat 5,911,581; 6,435,878) computerized and web-enabled cognitive tests of brain processing speed, clinically validated by Stanford and used by medical schools such as Scripps and UC Irvine, were administered to nearly 100,000 individuals and revealed a “normal” decline in processing speed (aka brain power) by up to 50% by age 50. A score between the 17th percentile and 33rd percentile is typically considered normal, albeit “low normal.”

The bottom line is that the brain appears to be declining faster than the body. This is a gradual process and it may be important if not mandatory, in today’s stressful and neurotoxic environment, to intervene and address this

* Correspondence:

Joshua Reynolds
 445 St. Ann’s Dr.
 Laguna Beach, CA 92651
 Phone: 949-306-6189 Fax: 949-715-2258
 E-mail: brainman001@gmail.com

decline before it accelerates and converts from a normal to an impaired status.

One purpose of this review is to put forth a comprehensive theory, including common mechanisms of action, of the multiple causes and contributory factors to normal age associated cognitive decline, accelerated decline including low normal states, and transitional and abnormal states of impairment. A second purpose is to put forth an ideal formulation of the fewest number of natural ingredients that can optimally address the multiple mechanisms and factors underlying normal age-associated states of cognitive decline, accelerated rates and stages of decline, and abnormal states of cognitive impairment, e.g., AD.

Multifactorial Nature of Cognitive Decline

Many (if not most) states of cognitive decline from healthy normal to diseased (e.g., AD) share common underlying causative or contributory factors, principally: decreased brain blood flow (CBF), cerebral circulation (blood volume, or CBV), cerebral metabolism (CMR) and oxygen utilization (CMRO₂);^{3,4,5,6,7} increased oxidative stress, especially within the mitochondria;⁸ deficits in calcium [Ca²⁺] regulation,⁹ cholinergic,¹⁰ and mitochondrial function;^{8,11} inflammation (immunity dysfunction); and glutamate-induced NMDA receptor over-activation (excitotoxicity) and subsequent calcium [Ca²⁺] mobilization and ultimate cellular overload.⁹

Many of these factors are often locked into self-reinforcing feedback loops such as amyloid-beta or Abeta=>oxidative stress=>Abeta, etc.,¹² Abeta=> decreased blood flow=> increased Abeta=> reduced blood flow=>increased oxidative stress,¹⁰ and others.

Micro array gene chip analysis of age-related genes in cognitive function has revealed downregulation of transcriptional regulators expressed by mid-life in the absence of observable cognitive deficits.¹³ These transcriptional events were found to predict later cognitive impairment, therefore, changes in gene expression at the transcriptional level may significantly precede and predict later cognitive impairment. This suggests the necessity to address a number of the above referenced causal or contributory factors, especially reduced CBF, CBV, CMR, cholinergic and increased oxidative stress factors that are believed to begin relatively early in the process of accelerated brain aging, cognitive decline and ultimate impairment.

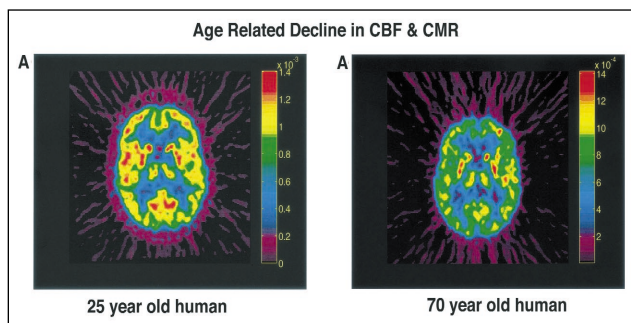
Reduced Brain Metabolism, Blood Flow and Volume, or Cerebral Circulation

General brain aging and cognitive decline, as well as states of impairment, are accompanied by reduction in cerebral vascular blood flow (CBF) and metabolism (CMR).^{3,4} Regional cerebral blood flow (CBF) and cerebral blood volume (CBV, aka cerebral circulation), and cerebral oxygen utilization (CMRO₂) decline approximately 5% per decade,⁷ possibly exceeding that rate in accelerated brain

aging. In addition, reduced brain blood flow and cerebral circulation directly impact brain metabolism and energy dynamics. Impaired brain energy production may drive AD pathogenesis leading to Abeta overproduction,¹⁴ a process representing one of the earliest pathogenic events in AD and possibly akin to the plaque accumulation process in atherosclerosis.

Cerebral blood flow and volume (circulation), or CBF&V, can be compromised by a number of factors, including age, reduced capillary elasticity and vasodilatory capacity, cholinergic deficits, vascular lesions and plaques, oxidative stress, inflammation, stress (cortisol) and others, thereby reducing oxygen and glucose supply to the brain, as well as impairing glucose and oxygen uptake and utilization.⁵ This leads to further oxidative stress-induced energy deficits, vascular insults and blood flow decline resulting in an eventual neurodegenerative cascade effect.¹⁴ Reduced blood flow can also promote the vascular and neuronal deposition of Abeta plaques, which increase oxidative stress and in turn, render neurons significantly more susceptible to the damaging effects of reduced blood flow.¹⁰ Reduced brain blood flow can also compromise cholinergic function, a leading theory of AD, and cholinergic dysfunction can further compromise blood flow.¹⁰

The following PET scans show the dramatic age-related difference in cerebral blood flow and metabolism.



Reference: Bentourkia M., et al., (2000) Comparison of regional cerebral blood flow and glucose metabolism in the normal brain: effect of aging. *Journal of the Neurological Sciences*. 181;19-28

CHOLINERGIC DYSFUNCTION

The prevailing conventional wisdom regarding the cause of AD is the “cholinergic dysfunction” theory. (10) In recognition of the key role of impaired cholinergic function in cognitive impairment, the first four FDA approved drugs for Alzheimer’s, i.e., tacrine, donepezil, rivastigmine and galantamine, were based on improving levels of acetylcholine (ACh) by inhibiting the enzyme acetylcholinesterase (AChE). AChE breaks down and thus reduces the synaptic levels of acetylcholine. These pharmaceutical agents along with a most promising herbal agent,

huperzine A, are collectively known as acetylcholinesterase inhibitors (AChEIs) and are used to slow down the rate of cognitive decline.

Cholinergic deficits may be one of the earliest contributors to mild forms of cognitive decline, such as AAMI. In fact, the acetylcholinesterase inhibitor, donepezil (Aricept), was successfully used to retard memory decline in airline pilots with AAMI.¹⁵ Cholinergic enhancement may also help normal individuals as evidenced by use of the plant based cholinesterase inhibitor, huperzine A, to improve learning and memory in university students.¹⁶

Cholinergic deficits may promote the vascular and neuronal deposition of amyloid beta (Abeta) plaques, which in turn contribute to further chronic hypoperfusion.¹⁰ Lower ACh levels have been linked to decreased cerebral vascular blood flow as well as an increase in inflammation, including microglial activation of pro-inflammatory cytokines, now believed to contribute to both the formation and/or support of Abeta plaques, a hallmark of AD pathology. ACh levels and cholinergic deficits also coincide with the level of impairment or cognitive status (e.g., MCI, AD).

CEREBRAL ENERGY METABOLISM

Cerebral glucose metabolism (CMR) is reduced in pre-clinical AD, suggesting that impaired energy production may be an early pathologic event in AD, as well as in the earlier stages of accelerated and even normal age-associated cognitive decline. CMR may be one of the earliest indicators, if not causative trigger factors, in the initial stages of accelerated decline. The question is, does decreased CBF&V reduce CMR, or vice versa?

Research has shown that experimentally induced impairment of energy production in the brain increases Beta-secretase [beta-site amyloid precursor protein-cleaving enzyme 1 (BACE1)], a key rate-limiting enzyme for the production of beta-amyloid (Abeta) peptide, which is directly involved in the pathogenesis of Alzheimer's disease. Therefore, a reduction in cerebral glucose metabolism may drive AD pathogenesis by elevating BACE1 levels and activity, which in turn leads to Abeta overproduction and neuro-degeneration.¹⁴ Cerebral energy deficits have also been shown to lead to an increase in both reactive oxygen and nitrite radicals, such as the highly neuro-toxic peroxynitrites, and have been widely implicated in oxidative neuronal apoptosis. Lipid peroxidation and peroxynitrites inflict significant damage to cellular proteins, lipids and nucleic acids. Thus, cerebral energy enhancers such as vinpocetine and acetyl-l-carnitine combined with antioxidants specific to hydroxyl radicals, peroxynitrites and lipid peroxidation (e.g., vinpocetine, acetyl-l-carnitine, alpha-lipoic acid, Rhodiola, ginkgo and huperzine A) might contribute significantly to prevent and retard the accelerated rate of cognitive decline.

OXIDATIVE STRESS

Oxidative stress may represent one of the earliest and yet most pervasive and ubiquitous contributing factors to neuro-cognitive decline and impairment. One reason is because a multitude of factors contribute to oxidative stress, including reduced brain blood flow, reduced oxygen and glucose metabolism, mitochondrial dysfunction, hypercortisolemia ("stress"), brain plaques (e.g., Abeta, AGEs, calcium, cholesterol, et al.) and inflammation.^{10,12}

Natural agents that address oxidative stress by conferring neuroprotective antioxidant and anti-inflammatory effects within the cellular cytoplasm and mitochondria have a positive effect in reversing or at least retarding brain aging and consequent decline in cognitive function. Antioxidants such as acetyl-l-carnitine, alpha-lipoic acid, Rhodiola, vinpocetine and huperzine A, and especially the combination of the five, scavenge extra-and intra-cellular reactive oxygen and nitrogen species, including super oxide, hydroxyl and peroxy radicals, hydrogen peroxide, nitric oxide and peroxynitrite, and may offer ideal synergy for the prevention or amelioration of cognitive decline.

MITOCHONDRIAL DYSFUNCTION

Mitochondria produce 80-90% of the brain and body's primary energy source, ATP (adenosine triphosphate). Mitochondrial function also decays with cellular aging and is a leading theory of aging.^{8,11,17} Aging mitochondria membranes lose their membrane potential resulting in depolarization, loss in ATP and increase in ROS generation and cell death. One primary cause is the significant (>50%) reduction in membrane cardiolipin levels, a key lipid that is essential in maintaining adequate (electric) membrane potentials.

Acetyl-l-carnitine has been shown to significantly improve age-associated decline in cardiolipin.

Age-associated accumulation of oxidative damage to mitochondria protein, lipid and nucleic acid leads to eventual neuronal and cognitive dysfunction. Oxidative damage to nucleic acids occurs predominantly in RNA. Dietary administration of nutraceutical ingredients, acetyl-l-carnitine and alpha-lipoic acid has been shown to significantly reduce oxidized mitochondrial RNA, as well as reverse age-associated mitochondrial structural decay.^{8,17} Acetyl-l-carnitine and vinpocetine have also been shown to improve lipid, oxygen and glucose delivery for enhanced energy metabolism and generation of ATP.^{17,18}

GLUTAMATE-CALCIUM NEUROTOXIC EXCITOTOXICITY

Glutamate is the major excitatory neurotransmitter in the brain. Glutamate receptors, including sub-type NMDA (N-methyl-D-aspartic acid) and AMPA receptors, are prone to excessive excitability, especially within an environment

of reduced blood flow, increased energy deficits and oxidative stress. Glutamate-induced NMDA and possibly AMPA receptor over stimulation drive cellular calcium destabilization, mobilization and subsequent excessive cellular influx and overload. This can especially impair NMDA function within the hippocampus, critical to long-term memory storage. Most seriously, cellular calcium overload can depolarize the mitochondrial membrane, causing impaired ATP synthesis, reduced energy metabolism and increased transmembrane leakage of harmful metabolites of respiration, including over-oxidized enzymes and other reactive oxygen species, ultimately leading to cell death. Perhaps uniquely, acetyl-L-carnitine, huperzine A, vinpocetine, and especially the synergy of the three, downregulate glutamate-induced excitotoxicity by acting as NMDA and AMPA receptor antagonists, thus exerting a major neuroprotective effect and re-normalizing cerebral vascular, cellular and intracellular calcium regulation.^{4,19,20,21,22} Additionally, vinpocetine supports calcium efflux from cellular cytoplasm and mitochondrial compartments, protecting the mitochondria membrane from calcium uptake and consequent depolarization and death.²³

COGNITIVE SUPPORT WITH NUTRACEUTICALS

Enhancement of cognitive function in normal and abnormal states has been achieved via pharmaceutical and natural agents addressing: CBF&V enhancement (vinpocetine ginkgo, acetyl-L-carnitine); CMR and CMR02 enhancement (vinpocetine, acetyl-L-carnitine); cholinergic system enhancement via acetylcholinesterase inhibitors (donepezil, galantamine, rivastigmine, huperzine A); cholinergic agonists (galantamine, huperzine A); choline donors and ACh precursors (Alpha-GPC, CDP-choline, phosphatidyl choline, choline chloride, citrate and bitartrate); and acetylcholine synthesis enhancers (acetyl-L-carnitine); catecholaminergic system, dopamine and norepinephrine enhancers (methylphenidate, selegiline, Rhodiola, huperzine A, acetyl-L-carnitine and vinpocetine); glutaminergic system, NMDA receptor antagonists (memantine, huperzine A); and antioxidants, anti-inflammatory agents and enzymes (alpha-lipoic acid, acetyl-L-carnitine, ginkgo, Rhodiola, vinpocetine, huperzine A, curcumin, ibuprofen, vitamin E, N-acetyl-cysteine, glutathione, SOD and quercetin).

Following is a review of five natural ingredients that offer promising synergistic potential to address the multiple factors common to most stages of cognitive decline, especially the progressive states of low normally non-medical impairment, e.g., AAMI to possibly MCI and even early AD.

ACETYL-L-CARNITINE

Acetyl-L-carnitine (ALC) is a quaternary amine found in all animal tissue, especially skeletal muscle and liver. ALC functions as a cofactor involved in the transport of

long chain fatty acids for oxidation in the mitochondria, thereby generating ATP (adenosine triphosphate).^{8,17} ALC also reverse-transport oxidized long, intermediate and short chain lipids out of mitochondria, thus helping to clear away metabolic debris before it accumulates to overload and downregulate mitochondrial function. ALC increases intracellular levels and binding affinity of choline acetyltransferase (ChAT), the enzyme involved in acetylcholine synthesis.^{8,17} Levels of ChAT are considered biomarkers of cognitive health, with lower levels typically found in cognitive impairment and correlated to the degree of impairment.

ALC enhances cerebral vascular blood flow,²⁵ and the functional synthesis and release of acetylcholine via donation of its acetyl moiety. Therefore, ALC helps normalize cholinergic deficits and improve cholinergic function.²⁶ ALC has also been shown to downregulate the formation of Abeta plaques, a hallmark of cognitive impairment, including AD.²⁷ ALC is a potent antioxidant²⁸ and scavenges some of the most neurotoxic oxyradicals, including protection against amyloid-beta peptide 1-42-mediated oxidative stress and neurotoxicity.²⁹ ALC confers a neuroprotective effect via antagonism of the NMDA receptor.¹⁹ ALC is perhaps most highly acknowledged for its antioxidant and neuroprotective effects within the mitochondria.^{8,11} ALC also buffers the brain, especially the hippocampus, against the deleterious effects of the stress hormone, cortisol, apparently by normalizing the HPA (hypothalamus-pituitary axis).³⁰

ALC has been repeatedly shown to enhance memory and other cognitive functions in normal and impaired (MCI and AD) individuals.^{8,26,31,32} ALC has also been shown to significantly enhance the effect of acetylcholinesterase inhibitors, including in non-responders to AChE inhibitors.³³ ALC has been shown to act as an anti-depressant.³¹

ALPHA-LIPOIC ACID

Alpha-lipoic acid (ALA), also known as alpha-lipoate and thioctic acid, is a disulfide compound and a cofactor in vital energy-producing reactions in the body. ALA is found widely in plant and animal sources. ALA is a broad spectrum antioxidant against reactive oxygen species, such as superoxide radicals, hydroxyl radicals, hypochlorous acid, peroxy radicals and singlet oxygen.³⁴

ALA is a potent, broad spectrum neuroprotective and antioxidant agent that most uniquely expresses its effects within the mitochondria. ALA revitalizes glutathione, one of the mitochondria's most important antioxidant enzymes.³⁵ ALA also recycles other neuroprotective and antioxidant agents, such as vitamins E and C, and CoQ10.³⁴

ALA improves glucose tolerance, lowers insulin resistance, and reduces the glycation of proteins and production of advanced glycation end-product (AGE) plaques.³⁶ AGEs cause deleterious effects, including the generation of free

radicals and the partial blockage of micro-vessels feeding important neuro-cognitive areas and networks within the brain. ALA has been shown to reverse neuropathy and alcohol liver damage.

ALA's other mechanisms of action include: enhancing ALC's effects at mitochondrial levels;⁸ re-enforcement of intra cellular and mitochondrial antioxidant and metabolic enzymes, e.g., carnitine acetyltransferase;^{8,11,17} isocitrate dehydrogenase, alpha-ketoglutarate dehydrogenase, succinate dehydrogenase, NADH-dehydrogenase and cytochrome-c-oxidase;³⁵ reducing neurotoxic by-products of Abeta plaque³⁷ inhibition of formation of β -amyloid fibrils from amyloid β -protein³⁸; and activation and support of phase II detoxification enzymes.³⁹

ALA has been shown to improve memory.⁸ ALA alone and especially when combined with acetyl-l-carnitine has demonstrated efficacy in slowing down brain aging at the mitochondrial level, and restoring old brain cells to more youthful levels of health and function.^{8,17}

RHODIOLA

Rhodiola (RHO) is an herbal supplement derived from the root of the *Rhodiola rosea* plant, also known as goldenroot, or roseroot. RHO appears to buffer the brain against the negative effects of stress (cortisol) and other environmental, physical and biochemical stressors such as mental overload and work fatigue.⁴⁰⁻⁴² RHO is shown to enhance function of the entire catecholamine class of neurotransmitters, bringing about neuro-endocrine balance and downregulation of cortisol. RHO is also a brain monoamine modulator within the limbic as well as the frontal and prefrontal cortex.⁴³ RHO improves serotonin, dopamine and norepinephrine function. It has also been shown to improve alertness, enhance mood and reduce depression via direct action on neuro-endocrine limbic centers, including amygdala and hypothalamus. RHO reduces hyper excitability of the emotional system by helping to buffer the hypothalamic-pituitary-adrenal (HPA) axis against stress-induced perturbations. Hyperexcitability undermines cognitive function and accelerates oxidative stress and other neurotoxic factors.⁴⁴

Studies have shown RHO to improve mental performance in medical students and pilots under mental, physical and emotional stress.⁴⁰⁻⁴² RHO was recently shown to have an anti-depressant effect.⁴⁵

VINPOCETINE

Vinpocetine (VIN; ethyl apovincaminat) is a synthetic analog of a major component of vincamine, an extract of the Periwinkle flower, *vinca minor*. VIN is best known as a potent vasodilator,^{46,47} regional cerebral vascular and global cerebrovasculature blood flow enhancer.^{48,49} VIN is a potent enhancer of cerebral metabolism via upregulation

of glucose and oxygen utilization.⁴⁹ VIN is a broad-spectrum antioxidant and neuroprotective agent,²³ especially protecting against calcium [Ca²⁺] overload and neurotoxicity,⁴ including the hippocampal CA1 pyramidal and NMDA receptor cells.²² VIN works at fundamental metabolic levels within the mitochondria's electron transfer chain, specifically upregulating function at ETC complexes II, III and IV, principal sources of electron loss and generation of reactive oxygen species.⁵⁰ In addition, vinpocetine has been found to suppress cytokine production by microglia.⁵¹

Perhaps most unique of vinpocetine's many mechanisms of action is its ability to alter the rheological properties of red blood cells by increasing the erythrocyte's deformability.⁴⁸ VIN also decreases platelet aggregation.⁵² These two actions combine to enable the blood cells to better penetrate the small, often obstructed vessels of the cerebrovasculature, thus delivering adequate supplies of glucose, oxygen and other energy substrates and cell nutrients for improved neuro-cognitive health and function. VIN has also been shown to facilitate the release of oxygen from hemoglobin and increase blood oxygenation.^{44,53}

Vinpocetine's neuroprotective action is partially based on its inhibition of voltage-dependent sodium channels, effectively blocking intra-cellular accumulation of sodium, thus decreasing potential damage from ischemia and reperfusion, and the toxic effects of oxidative stress resulting from hypoxia and ischemia.^{4,18} VIN has demonstrated an ability to attenuate the oxidative stress and metabolic dysfunction induced by amyloid-beta peptides in PC12 cells.⁵⁰

Like Vitamin E, VIN is an effective scavenger of hydroxyl radicals. It is also able to inhibit lipid peroxidation,⁵⁴ a particularly important function since the brain is almost 70% fat, by dry weight, and lipid membranes are highly susceptible to peroxide radicals. Recently it has been shown that (E)-4-hydroxy-2-nonenal (HNE), a metabolite of lipid peroxidation, is extremely neuro-pathologic and may be a primary contributor to accelerated brain aging and neuro-cognitive dysfunction, disease and death.⁵⁵ VIN has also been shown to act as a chelating agent for calcium and aluminum in the central nervous system.⁵⁶ Vinpocetine is a cerebral vascular, cellular and mitochondrial calcium normalizing agent.^{22,53}

VIN has been shown to enhance cortical levels of norepinephrine, a key neurotransmitter for alertness and long-term potentiation for enhanced memory storage. Vinpocetine has been clinically shown to improve memory in both cognitively normal and compromised or impaired groups.^{57-9,60}

HUPERZINE A

Huperzine A (HUP) is a potent, reversible, selective inhibitor of AChE with similar or higher potency than donepezil.^{20,61} HUP is a weak nicotinic agonist and cerebral

blood flow enhancer.⁶² HUP downregulates APP processing and thus reduces generation of Abeta plaques. It also attenuates Abeta induced oxidative damage and neuronal degeneration.^{20,63,64} HUP is a potent antioxidant and enhancer of NGF (nerve growth factor),^{20,65} a dopamine and norepinephrine modulator,⁶⁶ and a NMDA receptor antagonist.^{20,21,67} HUP also reduces deleterious lipid peroxidation and hydrogen peroxide formation.²⁰

HUP has demonstrated memory enhancing effects in cognitive states ranging from normal to impaired, including AD.^{16,20,21,65}

SUMMARY

In light of the aging brain suffering from one or more, and likely many of the above causal and contributory factors to accelerated cognitive decline, it eventually reaches a

threshold level of compromise, injury and toxicity.²⁴ Consequently, the seemingly slightest stressor, such as a head injury, sickness or infection, acute anxiety, Transient Ischemic Attack (TIA), chronic or acute alcohol intake, a traumatic stress event, a disease condition or physical injury, can trigger a breakdown cascade with consequent acceleration of cognitive decline and progression to and through states of cognitive impairment culminating in dementias such as AD.

It would therefore seem prudent to address (intervene) and support the underlying multiple mechanisms of the aging brain as early as possible, before cumulative factors combine to overload the system and trigger breakdowns culminating in the acceleration of normal cognitive decline, impairment and eventual dementia. The combination of nutraceuticals covered herein offer a comprehensive, broad spectrum and synergistic approach to retard cognitive decline.

Mechanisms of Action of Proposed Ingredients & Commonly Used Drugs

	ALC	ALA	VIN	HUP	RHO	GIN	DON	MEM
INCREASED	Cerebral Blood Flow	*		**	*		*	
	Cerebral Blood Volume (circulation)	*		**			*	
	Oxygen Utilization			**				
	rCMR	*		**				
	Acetylcholine	**			**	*	*	**
	Dopamine	*			*	**		
	Norepinephrine			*	*	**		
	Serotonin					*	*	
	Mitochondria Fnx	**	**	*	*	*		
	Antioxidant Defense	**	**	*	*	*	**	
	Ca Balance			**				
DECREASED	Glutamate Excitotoxicity			*	*			**
	Inflammation		*	*	*	*	*	
	Abeta Neurotoxicity	*	*	*			*	

ALC = Acetyl-l-carnitine

ALA = Alpha-lipoic Acid

RHO = Rhodiola

GIN = Ginkgo Biloba

VIN = Vinpocetine

HUP = Huperzine A

DON = Donepezil HCL (Aricept™)

MEM = Memantine HCL (Nemanda™)

REFERENCES

1. Crook TH, Ferris SH. Age associated memory impairment. *BMJ*. 1992;304:714.
2. Petersen RC, Smith GE, Waring SC, Ivnik RJ, Tangalos EG, Kokmen E. Mild cognitive impairment: clinical characterization and outcome. *Arch Neurol*. 1999;56(6):760.
3. Martin AJ, Friston KJ, Colebatch JG, Frackowiak RS. Decreases in regional cerebral blood flow with normal aging. *J Cereb Blood Flow Metab*. 1991;(4):684-689.
4. Hadjiev D. Asymptomatic ischemic cerebrovascular disorders and neuroprotection with vinpocetine. The asymptomatic ischemic cerebrovascular disorder (AICVD) is an early manifestation of cerebrovascular disease. *Ideggyogy Sz*. 2003;56(5-6):166-172.
5. Hoyer S, Oesterreich K, Wagner O. Glucose metabolism as the site of the primary abnormality in early-onset dementia of Alzheimer type? *J Neurol*. 1998;235:143-148.
6. Pettegrew JW, Panchalingam K, Klunk WE, McClure RJ, Muenz LR. Alterations of cerebral metabolism in probable Alzheimer's disease: a preliminary study. *Neurobiol Aging*. 1994;15,117:132.
7. Leenders KL, Perani, D, Lammertsma AA, Heather JD, Buckingham P, Jones TR, Healy MJ, Gibbs JM, Wise RJS, Hatazawa J, Herold S, Beaney RP, Brooks, DJ, Spinks T, Rhodes C, Frackowiak RSJ. Cerebral Blood Flow, Blood Volume and Oxygen Utilization. *Brain*. 1990;1131:27-47.
8. Liu J, Killilea DW, Ames B. Age-associated mitochondrial oxidative decay: Improvement of carnitine acetyltransferase substrate-binding affinity and activity in brain by feeding old rats acetyl-L- carnitine and/or R-lipoic acid. *PNAS*. 2002;99(4):1876-1881.
9. Khachaturian ZS. Calcium hypothesis of Alzheimer's disease and brain aging. *Ann NY Acad Sci*. 1994;747:1-11.
10. Claassen J, Janson R. Cholinergically Mediated Augmentation of Cerebral Perfusion in Alzheimer's Disease and Related Cognitive Disorders: The Cholinergic-Vascular Hypothesis. *J Gerontol A Biol Sci Med Sci*. 2006;61:267-271.
11. Shigenaga MK, Hagen TM, Ames BN. Oxidative damage and mitochondrial decay in aging. *Proc Natl Acad Sci U S A*. 1994;91(23):10771-10778.
12. Reddy PH. Amyloid precursor protein-mediated free radicals and oxidative damage: Implications for the development and progression of Alzheimer's disease. *Jnl Neurochemistry*. 2006;96:1-13.
13. Blalock EM, Chen KC, Sharrow K, Herman JP, Porter NM, Foster TC, Landfield PW. Gene microarrays in hippocampal aging: statistical profiling identifies novel processes correlated with cognitive impairment. *J Neurosci*. 2003 May 1;23(9):3807-19.
14. Velliquette RA, O'Connor T, Vassar R. Energy inhibition elevates beta-secretase levels and activity and is potentially amyloidogenic in APP transgenic mice: possible early events in Alzheimer's disease pathogenesis. *J Neurosci*. 2005;23;25(47):10874-83.
15. Yesavage JA, Mumenthaler MS, Taylor JL, Friedman L, O'Hara R, Sheikh J, Tinklenberg J and Whitehouse. Donepezil and flight simulator performance: Effects on retention of complex skills. *Neurology*. 2002;59:123-125.
16. Sun QQ, Xu SS, Pan JL, Guo HM, Cao WQ. Huperzine-A capsules enhance memory and learning performance in 34 pairs of matched adolescent students. *Acta Pharmacol Sin*. 1999;20(7):601-603.
17. Hagen TM, Ingersoll RTM, Wehr C, Lykkesfeldt J, Vinarsky V, Bartholomew JC, Song M-H and Ames BN. Acetyl-L-carnitine fed to old rats partially restores mitochondrial function and ambulatory activity. *Proc Natl Acad Sci* 1998;95:62-66.
18. Gabryel B, Adamek M, Pudelko A, Malecki A, Trzeciak HI. Piracetam and vinpocetine exert cytoprotective activity and prevent apoptosis of astrocytes in vitro in hypoxia and reoxygenation. *Neurotoxicology*. 2002;23(1):19-31.
19. Forloni G, Angeretti N, Smiroldo S. Neuroprotective activity of acetyl-L-carnitine: studies in vitro. *J Neurosci Res (USA)*. 1994;37(1):92-96.
20. Wang R, Yan H, Tang XC. Progress in studies of Huperzine A, a natural cholinesterase inhibitor from Chinese herbal medicine. *Acta Pharmacol Sin*. 2006;27(1):1-26
21. Ved HS, Koenig ML, Dave JR, Doctor BP. Huperzine-A, a potential therapeutic agent for dementia, reduces neuronal cell death caused by glutamine. *Neuroreport*. 1997;8(4):963-968.
22. Zelles T, Franklin L, Koncz I, Lendvai B, Zsilla G. The nootropic drug vinpocetine inhibits veratridine-induced [Ca²⁺]_i increase in rat hippocampal CA1 pyramidal cells. *Neurochem-Res*. 2001;26(8-9):1095-1100.
23. Pereira C, Agostinho P, Moreira PI, Duarte AI, Santos MS, Oliveira CR. Neuroprotection strategies: effect of vinpocetine in vitro oxidative stress models. *Acta Med Port*. 2003;16(6):401-406.
24. Brewer GJ. Neuronal plasticity and stressor toxicity during aging. *Experimental Gerontology*. 2000;35:1165-1183.
25. Postiglione A, Soricelli A, Cicerano U. Effect of acute administration of L-actyl-carnitine on cerebral blood

- flow in patients with chronic cerebral infarct. *Pharmacol Res.* 1991;23:241-246.
26. Ando S, Tadenuma T, Tanaka Y, Fukui F, Kobayashi S. Enhancement of learning capacity and cholinergic synaptic function by carnitine in aging rats. *J Neurosci Res.* 2001;66(2):266-271.
 27. Virmani MA, Caso V, Spadoni A, Rossi S, Russo F, Gaetani F. The action of acetyl-L-carnitine on the neurotoxicity evoked by amyloid fragments and peroxide on primary rat cortical neurones. *Ann NY Acad Sci.* 2001;939:162-178.
 28. Rani PJA and Panneerselvam C. Carnitine as a free radical scavenger in aging. *Exp Gerontol.* 2001;36(10):1713-1726.
 29. Abdul HM, Calabrese V, Calvani M, Butterfield DA. Acetyl-L-carnitine-induced up-regulation of heat shock proteins protects cortical neurons against amyloid-beta peptide 1-42-mediated oxidative stress and neurotoxicity: Implications for Alzheimer's disease. *Journal of Neuroscience Research.* 2006;84;(2):398-408.
 30. Bruno G, Scaccianoce S, Bonamini M, Patacchioli FR, Cesarino F, Grassini P, Sorrentino E, Angelucci L, Lenzi GL. Acetyl-L-carnitine in Alzheimer disease: a short-term study on CSF neurotransmitters and neuropeptides. *Alzheimer Dis Assoc Disord (USA).* 1995;9(3):128-131.
 31. Pettegrew JW, Levine J and McClure RJ. Acetyl-L-carnitine physical-chemical, metabolic, and therapeutic properties: relevance for its mode of action in Alzheimer's disease and geriatric depression. *Molecular Psychiatry.* 2000;5;(6):616-632.
 32. Montgomery SA, Thal LJ, Amrein R. Meta-analysis of double blind randomized controlled clinical trials of acetyl-L-carnitine versus placebo in the treatment of mild cognitive impairment and mild Alzheimer's disease. *Int Clin Psychopharmacol.* 2003;18(2):61-71.
 33. Bianchetti A, Rozzini R, Trabucchi M. Effects of acetyl-L-carnitine in Alzheimer's disease patients unresponsive to acetylcholinesterase inhibitors. *Curr Med Res Opin.* 2003;19(4):350-3.
 34. Packer L, Witta E, Tritschler HJ. Alpha-lipoic acid as a biological antioxidant. *Free Radical Biology and Medicine.* 1995;19(2):227-250.
 35. Arivazhagan P, Ramanathan K, Panneerselvam C. Effect of DL-alpha-lipoic acid on glutathione metabolic enzymes in aged rats. *Exp-Gerontol.* 2001;37(1):81-7.
 36. Thirunavukkarasu V, Anitha Nandhini AT, Anuradha CV. Lipoic acid improves glucose utilisation and prevents protein glycation and AGE formation. *Pharmazie.* 2005;60(10):772-775.
 37. Zhang JM, Hu GY. Huperzine A, a nootropic alkaloid, inhibits N-methyl-D-aspartate-induced current in rat dissociated hippocampal neurons. *Neuroscience.* 2001;105 (3):663-9.
 38. Ono K, Mie Yamada H, Yamada M. α -Lipoic acid exhibits anti-amyloidogenicity for β -amyloid fibrils in vitro. *Biochemical and Biophysical Research Communications.* 2006; 341(4):1046-1052.
 39. Flier J, Van Muiswinkel F L, Jongenelen CA, Drukarch B. The neuroprotective antioxidant alpha-lipoic acid induces detoxication enzymes in cultured astroglial cells. *Free-Radic-Res.* 2002; 36(6):695-9.
 40. Shevtsov VA, Zhulus BI, Shervarly VI, Vol'skij VB; Korovin YP, Khristich MP, Roslyakova NA, Wikman GK. A randomized trial of two different doses of a SHR-5 Rhodiola rosea extract versus placebo and control of capacity for mental work. *G. Phytomedicine.* 2003;10(2-3):95-105.
 41. Spasov AA, Wikman GK, Mandrikov VB, Mironova IA, Neumoin VV. A double-blind, placebo-controlled pilot study of the stimulating and adaptogenic effect of Rhodiola rosea SHR-5 extract on the fatigue of students caused by stress during an examination period with a repeated low-dose regimen. *Phytomedicine.* 2000 Apr; 7(2):85-9.
 42. Darbinyan V, Kteyan A, Panossian A, Gabrielian E, Wikman G, Wagner H. Rhodiola rosea in stress induced fatigue-a double blind cross-over study of a standardized extract SHR-5 with a repeated low-dose regimen on the mental performance of healthy physicians during night duty. *Phytomedicine,* 2000;7(5):365-71.
 43. Stancheva SL, Mosharrof A. Effect of the extract of Rhodiola rosea L. on the content of the brain biogenic monamines. *Med Physiol* 1987;40:85-87.
 44. Saratikov A, Mar'ina TF, Fisanova LL. Effect of golden root extract on processes of serotonin synthesis in CNS. *Jnl Biological Sciences* 1978:6.
 45. Darbinyan V, Aslanyan G, Amroyan E, Gabrielyan E, Malmström C, Panossian A. Clinical trial of Rhodiola rosea L. extract SHR-5 in the treatment of mild to moderate depression. *Nordic Journal of Psychiatry.* 2007;61(5)3:43-348.
 46. Bonocz P, Panczel G, Nagy Z. Vinpocetine increases cerebral blood flow and oxygenation in stroke patients: a near infrared spectroscopy and transcranial Doppler study. *Eur-J-Ultrasound.* 2002;15(1-2):85-91.
 47. Gulyás B, Halldin C, Sandell J, Karlsson P, Sóvágó J, Kárpáti E, Kiss B, Vas A, Cselényi Z, Farde L PET studies on the brain uptake and regional distribution of [11 C]vinpocetine in human subjects. *Acta Neurologica Scandinavica,* 2002;106(6):325-332.
 48. Hayakawa M. Effect of vinpocetine on red blood cell

- deformability in stroke patients. *Arzneimittelforschung*. 1992;42(4):425-427.
49. Szilágyi G, Nagy Z, Balkay L, Boros I, Emri M, Lehel, Márián T, Molnár T, Szakáll S, Trón L, Bereczki D, Csiba L, Fekete I, Kerényi L, Galuska L, Varga J, Bönöczk P, Vas A, and Gulyás B. Effects of vinpocetine on cerebral blood flow and metabolism in chronic ischaemic stroke patients after a two-week long administration: A PET study. *J. Neur. Sci.* 2005;229-230:275-284.
 50. Pereira C, Agostinho P, Oliveira CR. Vinpocetine attenuates the metabolic dysfunction induced by amyloid beta-peptides in PC12 cells. *Free-Radic-Res*. 2000;33(5):497-506.
 51. Yoshikawa M, Suzumura A, Tamaru T, Takayanagi T, Sawada M. Effects of phosphodiesterase inhibitors on cytokine production by microglia. *Multiple Sclerosis*. 1999;5(2):126-133.
 52. Akopov SE, Gabrielian ES. Effects of aspirin, dipyridamole, nifedipine and cavinton [Vinpocetine] which act on platelet aggregation induced by different aggregating agents alone and in combination. *Eur J Clin Pharmacol*. 1992;42:257-259.
 53. Tohgi H, Sasaki K, Chiba K, Nozaki Y. Effect of vinpocetine on oxygen release of hemoglobin and erythrocyte organic polyphosphate concentrations in patients with vascular dementia of the Binswanger type. *Arzneimittelforschung*. 1990;40(6):640-643.
 54. Santos MS, Duarte AI, Moreira PI, Oliveira CR. Synaptosomal response to oxidative stress: effect of vinpocetine. *Free-Radic-Res*. 2000;32(1):57-66.
 55. Lovell MA, Xie C, Markesbery WR. Acrolein, a product of lipid peroxidation, inhibits glucose and glutamate uptake in primary neuronal cultures. *Free Radic Biol Med*. 2000;29(8):714-720.
 56. Yasui M, Yano I, Ota K, Oshima A. Calcium, phosphorus and aluminium concentrations in the central nervous system, liver and kidney of rabbits with experimental atherosclerosis: preventive effects of vinpocetine on the deposition of these elements. *J Int Med Res*. 1990;18(2):142-152.
 57. Polich J, Gloria R. Cognitive effects of a ginkgo biloba/vinpocetine compound in normal adults: systematic assessment of perception, attention and memory. *Hum Psychopharmacol*. 2001;16(5):409-416.
 58. Nicholson CD. Pharmacology of nootropics and metabolically active compounds in relation to their use in dementia. *Psychopharmacology*. 1990;101:147-159.
 59. Subhan Z, Hindmarch I. Psychopharmacological effects of vinpocetine in normal healthy volunteers. *Eur J Clin Pharmacol*. 1985;28:567-571.
 60. Wollschlaeger B. Efficacy of vinpocetine in the management of cognitive impairment and memory loss. *JANA*. 2001;4:25-30.
 61. Liang YQ, Tang XC. Comparative effects of huperzine A, donepezil and rivastigmine on cortical acetylcholine level and acetylcholinesterase activity in rats. *Neuroscience Letters*. 2004;361;(1-3):56-59.
 62. Wang LM, Han YF, Tang XC. Huperzine A improves cognitive deficits caused by chronic cerebral hypoperfusion in rats. *Eur J Pharmacol*. 2000;9;398(1):65-72.
 63. Xiao XQ, Wang R, Tang XC. Huperzine A and tacrine attenuate-amyloid peptide-induced oxidative injury. *J Neurosci Res*. 2000;61:564-569.
 64. Xiao XQ, Zhang HY, Tang XC. Huperzine A attenuates amyloid beta-peptide fragment 25-35-induced apoptosis in rat cortical neurons via inhibiting reactive oxygen species formation and caspase-3 activation. *J Neurosci Res*. 2002;67(1):30-6.
 65. Zhang HY, Tang XC. Neuroprotective effects of huperzine A: new therapeutic targets for neurodegenerative disease. *Trends Pharmacol Sci*. 2006;27(12):619-25.
 66. Zhu X-D, Giacobini E. Second generation cholinesterase inhibitors: Affect of (L)-huperzine-A on cortical biogenic amines. *Journal of Neuroscience Research*. 2004;41(6):828-835.
 67. Gordon RK, Nigam SV, Weitz JA, Dave JR, Doctor BP, Ved HS. The NMDA receptor ion channel: a site for binding of Huperzine A. *J Appl Toxicol*. 2001;21:47-51.