The MOSS NUTRITION REPORT

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Product Review

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BRAIN SELECT™ – A NEW COGNITIVE SUPPORT PRODUCT FROM MOSS NUTRITION

Interestingly, there is a fascinating and sad irony that accompanies the impressive results of the American health care system, which includes both allopathic and alternative approaches, in increasing lifespan of the population during the last 30-40 years. Now, in contrast to our parents' and grandparents' generations whose greatest fears revolved around premature death, the baby-boomer generation and those that arrived subsequently have, to a great extent, replaced fear of premature death with fear of loss of quality of life during those increased years gained due to the health care advances of the last several decades. Of course, "quality of life" means different things to different people. However, there seems to be a general consensus among many of the most recent generations that the quality of life issue feared the most that often accompanies aging is loss of cognitive function.

Can nutritional supplementation make a difference in terms of preventing age-related loss of cognitive function? Given that loss of cognitive function during aging is a complex issue that involves many factors including genetics plus various environmental stressors which may include but not be limited to diet, this is a difficult question to answer. Nevertheless, there exists promising research on several natural substances, many of which can be found in our new cognitive support product, **Brain Select™**. As you will see from the enclosed technical support bulletin, many of the most popular and well-documented cognitive support constituents such as acetyl-L-carnitine, phosphatidylserine, and vinpocetine are found in **Brain Select™.** However, there is one that, while its name is familiar to many, is less well known in terms of its impact on cognitive function. Therefore, in this newsletter I will be focusing on one of the key constituents of **Brain Select™**, huperzine A.

Huperzine A and Alzheimer's disease

Certainly, when most of us consider the issue of age-related loss of cognitive function, the sound-bite that comes to mind most often is Alzheimer's disease. Therefore, I would now like to discuss two literature review papers that highlight the large volume of research on the relationship between huperzine A and Alzheimer's disease. However, to truly understand the impact of huperzine A on loss of cognitive function, it is important to first review the leading theories about the underlying metabolic imbalances that are suggested to predispose to Alzheimer's disease. First and foremost are findings relating to the buildup of senile plaques and neurofibrillary tangles (NFTs) in the brain. In "Huperzine A: is it an effective disease-modifying drug for Alzheimer's disease?" by Qian and Ke (Qian ZM & Ke Y. *Frontiers Aging Neurosci,* Vol. 6, published online August 19, 2014) the following is stated:

"The senile plaques and neurofibrillary tangles (NFTs), which are composed of self-polymerized amyloid-β peptide (Aβ) and hyperphosphorylated tau proteins, respectively, are the two major pathological hallmarks in Alzheimer's disease (AD) brains."

These plaques and NFTs, in turn, lead to death of cholinergic neurons:

"Accumulated data showed that senile plaques and NTFs are associated with the death of cholinergic neurons in AD."

With the above in mind, one of the most successful therapies in reducing AD symptoms and slowing progression has been agents that delay breakdown of what is produced by cholinergic neurons, acetylcholine. In "Potential therapeutic targets of huperzine A for Alzheimer's disease and vascular dementia by Zhang et al (Zhang HY et al. *Chemico-Biological Interactions*, Vol. 175, pp. 396-402, 2008) the following is stated:

"Among the effective therapeutic agents for AD patients, acetylcholinesterase inhibitors (AChEIs) are generally regarded as the main palliative treatments that slow the progression of dementia symptoms. Similar to those in AD, studies on pathogenic mechanisms have revealed that patients with vascular dementia (VaD) exhibit cholinergic abnormalities and disturbance of cognitive function."

As noted by Qian and Ke, huperzine A has been found to have properties similar to the acetylcholinesterase inhibitors:

"Huperzine A (HupA) is a natural inhibitor of acetylcholinesterase (AChE) derived from the Chinese folk medicine *Huperzia serrata* (Qian Ceng Ta). There is a long history of using *H. serrata* as a medicine in China to treat different kinds of disorders, including bruises, strains, swelling, rheumatism, schizophrenia, myasthenia gravis, and fever. HupA is a licensed anti-Alzheimer's disease drug in China and is available as a nutraceutical in the US. A growing body of evidence has demonstrated that HupA could effectively reverse or attenuate cognitive deficits in rodents, primates, and humans. A recent systematic review and meta-analysis of randomized clinical trials concluded that HupA could improve cognitive function, daily living activity, and global clinical assessment in patients with Alzheimer's disease (AD), with relatively few and mild adverse effects mainly related to its effect on the cholinergic system."

With the above stated, though, as many of you are probably aware, the idea that AD is a simple issue of loss acetylcholine related to the buildup of senile plaques and NFTs) is far from universally accepted. Qian and Ke state:

"…these two major pathological hallmarks might be just a consequence of the disease process rather than an initial event that causes AD. The failed result of several major clinical trials targeting Aβ is one of the strongest supports for this viewpoint."

What other metabolic imbalances have been suggested to be involved in the development and progression of AD? As you will see, research suggests that the ones involved are those we have been learning about for years as underlying factors in virtually every chronic illness, i.e., inflammation, excessive free radical activity, etc. Fortunately, huperzine A also has an impact on these non-cholinergic factors that contribute to AD. Qian and Ke note:

"A number of recent studies have reported that HupA has neuroprotective properties, possessing both 'cholinergic' and 'non-cholinergic' effects on AD."

What follows is a summary of some of the non-cholinergic factors impacted upon by huperzine A as discussed by Qian and Ke.

Oxidative injury – **"Studies have demonstrated that HupA could enhance the cell viability and the activities of antioxidant enzymes including glutathione peroxidase (GSH-Px), superoxide dismutase (SOD), and catalase (CAT); decrease the level of malondialdehyde (MDA) in PC12 (neuron-like rat pheochromocytoma) cells and cultured rat primary cortical neurons; and markedly reduced the MDA level in chronic cerebral hypo-perfusion rats and aged rats."**

With the above in mind, the authors state:

"These results indicate that HupA can function as an antioxidant in Aβ-induced oxidative stress model by increasing the activities of antioxidant enzymes."

Mitochondrial malfunction – **"Perturbations in mitochondrial function have long been observed in samples derived from clinically confirmed patients with AD, including altered mitochondrial morphology, compromised enzyme complexes in the tricarboxylic acid cycle, and reduced cytochrome c oxidase activity. In addition, accumulated evidence showed that mitochondria are direct targets of Aβ."**

Furthermore:

"The neurotoxicity induced by Aβ will trigger a vicious cycle in which excessive Aβ accumulation and sustained mitochondrial dysfunction synergize to activate a cascade of neurodegenerative pathways."

What is the impact of huperzine A on mitochondrial malfunction? Qian and Ke state:

"Studies have provided evidence that HupA has the ability to effectively ameliorate the mitochondrial malfunction."

Excessive excitatory activity related to glutamate activity on N-methyl-D-aspartate (NMDA) receptors – According to Qian and Ke:

"Glutamatergic synapses mediate virtually all excitatory neurotransmission in mammalian brains. Glutamate released from presynaptic terminals activates several types of glutamate-gated ion channels on postsynaptic membranes, including *N*-methyl-D-aspartate (NMDA) receptors."

With the above in mind:

"Excitotoxicity caused by disturbances of glutamatergic neurotransmission in the brain has been shown to be involved in the pathogenesis of AD."

Qian and Ke then point out:

"Huperzine A could inhibit NMDA-induced toxicity in a dose-dependent way in cultured primary neuronal cells."

Furthermore:

"HupA reversibly inhibited NMDA-induced current in acutely dissociated rat hippocampal pyramidal neurons…"

Dysregulation of nerve growth factor – Qian and Ke state:

"Nerve growth factor (NGF), a neurotrophin, plays a trophic role both during development and in adulthood, and exerts its biological action by interacting with the specific receptor tropomyosin kinase receptor A (TrkA)."

Huperzine A may, according to Qian and Ke, have a positive impact on nerve growth factor:

"…HupA has a direct or indirect neurotrophic activity, which might be beneficial in treatment of neurodegenerative disorders such as AD."

Excessive iron in the brain – Qian and Ke note the following:

"Misregulation in brain iron has been considered to be one of the primary causes of neuronal death in neurodegenerative disorders. Evidence has also been gathered to imply that Aβ production, precipitation, and toxicity in AD are caused by abnormal interactions with neocortical iron."

The authors then point out the positive impact of huperzine A on brain iron:

"Our findings provided direct evidence for the inhibitory effect of HupA on brain iron, and implied that the beneficial effects of HupA on AD is caused by the reduction in brain iron in…mice."

What follows next are two non-cholinergic effects of huperzine A that were pointed out by Zhang et al.

Excessive inflammation – Zhang et al point out the following about the relationship between inflammation and AD:

"Inflammatory mechanisms have been strongly linked to the pathogenesis of both AD and VaD. It is reported that inflammatory cytokines, such as interleukin 1β (IL-1β), tumor necrosis factor α (TNF-α), and interleukin 6 (IL-6), located close to amyloid plaques, might be cytotoxic when chronically produced and might stimulate the production of Aβ peptides. High levels of TNF-α and IL-6 have been reported in the cerebrospinal fluid of patients with VaD, which suggested a possible involvement of inflammatory mechanisms in the pathogenesis of cognitive impairment in patients with cerebrovascular disease."

The authors then point out the positive impact of huperzine A on inflammation:

"In our recent study, we proved the protective effects of HupA against focal cerebral ischemia injury, and suggested that this anti-ischemia effect might associate with an anti-inflammation effect."

Other neuroprotective effects of huperzine A – According to Zhang et al:

"HupA not only affects the level of acetylcholine in the brain, it could also target on the noradrenergic (NE) and dopaminergic (DA) system. NE, DA and acetylcholine levels were significantly increased after administration of HupA in the medial prefrontal cortex (mPFC) of rats with Aβ injection…"

Huperzine A: A clinical study

As you probably noticed, much of the research I have discussed above was animal research. Therefore, I wanted to discuss a clinical paper on huperzine A and cognitive function. This paper, which is a review of several studies employing huperzine A with schizophrenic patients, is entitled "Adjunctive huperzine A for cognitive deficits in schizophrenia: a systematic review and meta-analysis" by Zheng et al (Zheng W et al. *Human Psychopharmacol*, Vol. 31, pp. 286-295, 2016). The findings of the paper are the following:

"In this first meta-analysis of 12 randomized controlled studies with a total of 1117 patients suffering from schizophrenia, we found that HupA augmentation was significantly superior regarding memory quotient, verbal intelligence quotient, performance intelligence quotient, full intelligence quotient, response administer errors, non-perseverative errors, and total and positive psychopathology symptoms. Additionally, all-cause discontinuation and adverse drug reactions were similar to controls."

What mechanism did the authors propose to explain the positive findings? As you will see, it is what was mentioned above:

"The mechanisms behind cognition-improving effect of HupA may be explained by the hypothesis that acetylcholinesterase inhibition increases the synaptic concentration of acetylcholine acting in many cognitive functions (e.g., cortical modulation of sensory information processing, attention, memory and learning."

In their concluding comments, Zheng et al suggest that optimal dosing is 200 mcg per day (Each serving of **Brain Select™** contains 250 mcg).

SOME FINAL THOUGHTS

As I mentioned above, one of the most feared and mysterious concerns about aging in the US today is loss of cognitive function. While there is still much to learn, I continue to be excited about the large volume of research that addresses the relationship between lifestyle, natural substances, and cognitive function. We at Moss Nutrition have done our best to take the best of this research and create a supportive product, **Brain Select™** that can provide some level of assistance.

Brain Select™ – Moss Nutrition

Contents: 60 VC and 120 VC