2021

A Review of Huperzine A Effects on Concussive Brain Injuries

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B.S., Southern Illinois University, 2018

A Research Paper
Submitted in Partial Fulfillment of the Requirements for the
Master of Science

Department of Human Sciences
in the Graduate School
Southern Illinois University Carbondale
December 2021

RESEARCH PAPER APPROVAL

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for the Degree of

Master of Science

in the fields of Food & Nutrition and Kinesiology

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November 9, 2021

ACKNOWLEDGMENTS

To my classmates, coaches, and professors that I have had the pleasure to learn from and work with, thank you. Thank you for riding along with me during my journey these past few years at Southern Illinois.

DEDICATION

I dedicate the work done to this paper towards my girlfriend, who suffered from a series of concussions throughout her sports playing career and is still suffering from the potential long-term side effects a concussion can do. May the work of this paper bring those who suffer like her more hope as well for a better recovery.

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CHAPTER 1

INTRODUCTION

Since the start of the 21st century, sports concussions have become a major health concern. On average approximately up to 4 million new cases of sports-related concussions happen each year in the US (Theriault et al. 2011). Depending on the severity of the concussion, some can have short- or long-term effects that can impact a person's well-being on performing daily life skills, cognitive thinking, and memory. Common symptoms of a concussion include are headaches, nausea, fatigue, anxiety, confusion or memory impairment, sleep disturbances, or mood swings (Team**,** 2019) (Kelly and Erdal, 2017). In fact, a majority of athletes that have sustained a concussion will experience post-traumatic pain including headaches or migraines. Athletes who have had one concussion are four to six times more likely to sustain another one, and depending on the age or severity, they may have longer recovery times (Team, 2019). The effects of concussions cumulate overtime, meaning that if an athlete sustains a second or third concussion, the recovery time may extend into weeks, months, or even years (Team, 2019). Further support for this was provided by Theriault and colleagues (2011) stating what they found that "previous concussions induce lasting damage that accumulate to render concussed athletes more at risk of sustaining subsequent concussions together with suffering from more severe post-concussion symptoms" (Theriault et al. 2011, p. 31). There is little research on procedures to follow post-concussion, besides the most recent recommendation which is the athlete should rest and not return to play until there are no post-concussion symptoms (Merritt, Rabinowitz, and Arnett, 2014). There are no protocols to follow post-concussion that have been proven to help with recovery, downgrade the severity, or eliminate prolonged symptoms. Many of these individuals with prolonged symptoms may develop post-concussion syndrome, meaning that

their symptoms may extend beyond the initial recovery period disrupting normal daily activities caused by headaches, dizziness, concentration, and memory loss.

The application use of Huperzine A in the form as a supplement during recovery after sustaining a concussion may be the breakthrough needed in order to find a new way of reducing the severity of a concussions and symptoms into possibly returning the athlete to normal functioning state at a more successful rate. In recent years, Huperzine A has been used in many studies to help individuals who are suffering from Alzheimer's disease and dementia by stimulating the brain to help improve memory and other mental functions (Wu, Chen, and Jinn, 2011) (Yang et al. 2013) (Zhang, 2012) (Zhang and Tang, 2006). One meta-analysis study Yang et al. (2013) stated in their report that supplementing Huperzine A established beneficial effects for Alzheimer's disease by improving cognitive functions. The improved cognitive functions included memory, focusing, and motor skills. Thus, providing significance towards concussed athletes because of some symptoms can be related to those who suffer from Alzheimer's disease and dementia. The purpose of this research is to review research on the effects of Huperzine A on concussive brain injuries. One study, Merritt, V.C., et al. (2014) suggests that identifying athletes that are at greatest risk of increased symptom reporting will help develop better interventions to aid recovery for the targeted individuals who most likely benefit.

Research Question:

Can Huperzine A have any effects on concussive brain injuries?

CHAPTER 2

CONCUSSIONS AND HUPERZINE A

Brain Disorders and Brain Injuries

Our brain is the main control center hub that controls what our bodies do and is connected to our central nervous system through a large network of nerves and neurons. There are three main parts that make up our brain: the cerebrum that controls our senses and the way we think, the cerebellum that controls our coordination and fine motor skills, and the brain stem that controls our fundamental body functions such as breathing and heartbeat (Johns Hopkins Medicine (n.d.)). Each part of the brain plays a significant role and have significant traits that make up the way we live. Damage to any of the three areas can be detrimental to our well-being. Some of the damage done to different regions of our brains caused by either illness, genetics, or traumatic injury can affect our memory, sensations, and our personality. Disorders and disabilities can be developed depending on the severity of this damage (Johns Hopkins Medicine (n.d.)).

Brain injuries are commonly caused by blunt trauma that disturbs normal brain functions. The damage can affect how the brain can respond to the rest of the body. These injuries include hematomas, blood clots, contusions, cerebral edema, concussions, and strokes. Many physical complications may develop after sustaining a brain injury such as seizures, hydrocephalus (built-up fluid in the brain), infections in the protective tissues lining the brain, blood vessel damage, headaches, and even vertigo. Not only physical complications may occur but intellectual complications as well. Such as cognitive, executive functioning, communication skills, behavior, and emotions (Mayo Foundation for Medical Education and Research, 2021). Most of these injuries are mild and treatment may include medication, observation, and rehabilitation.

However, more serious, or repeated injuries can cause prolonged recovery and even reoccurring symptoms that can last for months or even years (Centers for Disease Control and Prevention, 2021).

Concussions and Mild Traumatic Brain Injuries

A concussion is a mild traumatic brain injury (MTBI). It can occur after sustaining an impact or violent whiplash-type injury that causes the brain to shake back and forth violently inside the skull (Centers for Disease Control and Prevention, 2021). The brain is made up of soft tissue, which is very delicate, and the skull protects this delicate matter (Johns Hopkins Medicine (n.d.)). However, a strong enough impact can create enough force that can cause the brain itself to smash against the skull, damaging itself in return, can cause serious trauma to the brain. TBI is categorized into three distinct groups: mild, moderate, and severe. For the purpose of this paper, the focus is on mild TBI. In Gardner and Yaffe (2015) study, cited the World Health Organization (WHO) Collaborating Center Task Force and the Centers for Disease Control (CDC) on what a MTBI is by stating,

> MTBI is an acute brain injury resulting from mechanical energy to the head from external physical forces. Operational criteria for clinical identification include: (1) one or more of the following: confusion or disorientation, loss of consciousness for 30 min or less, post-traumatic amnesia for less than 24 h, and/or other transient neurological abnormalities such as focal signs, seizure, and intracranial lesion not requiring surgery; and (2) Glasgow Coma Scale score of 13–15 after 30 min post-injury or later upon presentation for healthcare. (3) These manifestations of MTBI must not be due to drugs, alcohol, medications, caused by other injuries or treatment for other injuries (e.g., systemic injuries, facial injuries or intubation), caused by other problems (e.g., psychological

> trauma, language barrier or coexisting medical conditions) or caused by penetrating craniocerebral injury. (Gardner and Yaffe, 2015, p. 2)

Not all MTBIs are treated the same, even though the WHO and CDC provides a very descriptive definition on MTBIs, there are still over 50 different definitions used globally pertaining to what MTBIs are and how to treat them (Gardner and Yaffe, 2015). This in return may alter the way MTBIs are reported, and therefore are most likely underreported.

Gardner and Yaffe (2015) and Blennow et al. (2016), reported that because many individuals sustaining MTBI may not report or seek medical attention, incidences more than likely exceed 600 for every 100,000 people annually (i.e., about forty-two million worldwide each year). Majority of known MTBI incidences making up anywhere between 70-90% of all cases reported with rates higher among males and females (Gardner and Yaffe, 2015) (Blennow et al. 2016). Surveillance data indicates sports related MTBI reported incidences in the US is 152/100,000, majority happening among individuals under 19 years of age (Blennow et al., 2016). In addition to their findings, increasing TBI severity correlates with increasing risks of dementia, Alzheimer's disease, and other cognitive functions such as memory loss (Blennow et al. 2016).

Correlations With Neurodegenerative Diseases and Mild Traumatic Brain Injuries

Today, more studies out there are showing individuals who have suffered from multiple MTBIs are correlated to greater risks of developing neurodegenerative diseases later in life such as dementia, Alzheimer's, and chronic traumatic encephalopathy (CTE). Gardner and Yaffe (2015) reported previous meta-analyses shown compelling evidence in risks relevant to development of these neurodegenerative diseases, specifically dementia. However, it is not clear if some of these individuals already are predisposed to neurodegenerative diseases because of

genetics. After sustaining repetitive concussive injuries has been extensively recorded increases in the development of neurodegenerative diseases (Gardner and Yaffe, 2015). Thought to be believed that CTE, once known as *dementia pugilistica* from the late 1920s until the 1940s, was only predominant in boxers. Recent research suggests that neuropathological evidence shows a wider range of athletes, who are in contact sports involving multiple impacts to the head, initiating neurodegeneration, and triggering CTE (Blennow et al., 2016) (Gavett et al., 2010). Cruz-Haces et al. (2017) study stated in their findings have shown pathologically that after sustaining a TBI disruption in the brain causes protein neuropathy, creating oxidative stress alternating ion balance in the mitochondria similarly to the development of Alzheimer's disease (AD), Parkinson's disease (PD), and CTE. Also, stated similarities in behavioral changes between post-TBI dementia and AD and PD via brain tissue damage in the hippocampus and basal ganglia, respectively. After reviewing MRI cases examining TBI damaged brain tissue after, Cruz-Haces and his colleagues concluded correlations in neuropathological functional changes that may play a significant role to the pathogenesis of neurodegenerative diseases (Cruz-Haces et al, 2017). In a study from Graham and Sharp (2019), they compiled evidence that associates neurodegeneration that are precursors to specific neurodegenerative diseases from TBIs. In multiple studies with animal models and postmortem humans identify abnormalities in the brain effected by TBI that are similar to brains impacted by neurodegenerative diseases. Graham and Sharp (2019) also stated post-traumatic proteinopathies (abnormal accumulation of aggregated proteins) triggers apoptosis (the death of cells), damages the mitochondria in cells, and weakens nerve impulses similar to progressing AD and dementias.

Huperzine A (Hup A)

Huperzine A is one of 5 biologically active *Lycopodium* alkaloids extracted from

Huperzia serrata, a Chinese club moss, which is used in Chinese medicine today to alleviate the progression of AD and dementia with fewer side effects than conventional drugs and medicine. For over two thousand years, *Huperzia serrata* has been traditionally used throughout China to relieve pain, inflammation, and function as an antidote for poison. Along with treatment for neurodegenerative diseases, Hup A has also been used in treatment for memory and learning enhancement, treatment for a muscle disease called myasthenia gravis, and protection against nerve gasses (Wu, Chen, and Jinn, 2011) (Wang, Yan, and Tang, 2006). First extracted in 1986, Hup A contains potent and well tolerated acetylcholinesterase (AChE) inhibitor in the brain improving neurotransmitters and neuroprotective activities. Compared to other drugs in the market, Hup A has been the most effective in penetrating brain to blood barrier, higher bioavailability, and has a longer duration of effectiveness. AChE raises acetylcholine levels in the brain that uses this to help communicate, muscles, and possibly prevent death of cells. Hup A also helps regulate antioxidative enzyme activity to lessen dysfunctional mitochondria's and destroy reactive oxygen species (ROS) that may cause apoptosis and damage to proteins (Wu, Chen, and Jinn, 2011) (Wang, Yan, and Tang, 2006). Through multiple clinical studies on Hup A, results continue to show promising effects on uses as treatment for neurodegenerative diseases.

Huperzine A Effects on Neurodegenerative Diseases

Unlike memantine and donepezil, drugs used in combination to treat neurodegenerative diseases such as AD and dementia as a tolerated AChe inhibitor, several studies including Wang, Yan, and Tang (2011) and Zhang and Tang (2006) have suggested a drug, Huperzine A, which has multifunctional compounds, well-tolerated for the patient, and effective neuroprotective functions may provide better treatment. Hup A potency exceeds that of galanthamine, donepezil,

rivastigmine, and tacrine without any severe side effects (Esopenko and Levine, 2015) (Zhang and Tang, 2006). Inhibition of AChe enhances the release of synaptic ACh and cholinergic neurotransmission. Hup A neuroprotective effects entails muscarinic and nicotinic acetylcholine receptors activation, enhancing the production of neurotrophic factors, and seizing overstimulated NMDA receptors which are important to memory function (Wu, Chen, and Jinn, 2011). Muscarinic and nicotinic ACh receptors play a crucial role in communication between neurons and regulation of cognition, while a disturbance to the brain can cause abnormal processing of APP, creating Aβ plaques which can affect cognitive responses and impair brain functions. ACh not only acts a neurotransmitter, but also acts as a cytokine used in neuroprotective pathways like neurotophins nerve growth factor (NGF), stimulating the non-amyloidogenic APP pathway (Zhang and Tang, 2006). Hup A also has shown to have antioxidant effects by activating antioxidant enzymes glutathione peroxidase (GPX) and catalase (CAT) and diminishing malondialdehyde (MDA) that plays a role in mitochondrial dysfunction and development of AD (Esopenko and Levine, 2015).

Amyloid precursor protein (APP) are large proteins that play essential roles in neural growth and repair. When functioning normally, these proteins are broken down into smaller fragments to function as proteases or secretases, known as α, β, and γ. In Zhang and Tang's (2006) study, they state that secretory amyloid precursor protein α (sAPPα) has neuroprotective properties against excitotoxic and oxidative stresses. Also, regulates synaptogenesis (formation of synapses) and employs trophic effects (growth and function) on cerebral neurons. Administration of Hup A has shown to improve APP processing and increase levels of sAPPα, which reduces the levels of Aβ plaques. β-amyloid (Aβ) plaques build up in the brain by abnormal processing of APP causing detrimental damage to the cells in the brain which is

believed as a main cursor that causes neurodegenerative diseases (Esopenko and Levine, 2015). Hup A possesses properties to protect apoptosis caused by the accumulation of Aβ by binding to proteins that regulates the mitochondria to release cytochrome-c that activates apoptotic protease activating factor 1. Hup A protected against mitochondrial abnormality and regulate ATP output which transitions to maintain functioning enzymes for the TCA cycle, protein levels for the electron transport chain, the pyruvate dehydrogenase complex and α-ketoglutarate dehydrogenase complex, and increasing sodium (Na+) and potassium (K+) ATPase for ion homeostasis (Esopenko and Levine, 2015). Hup A with its multiple neuroprotective functions has proven to be a more susceptible drug used as treatment for individuals suffering from neurodegenerative diseases.

Summary

The brain plays an incredibly significant role for how our body's function. How our organs function, how our muscles and bones move, and how we think and feel. Damage done to the brain may be detrimental for an extensive period of time. More clinical studies are being performed on neurodegenerative diseases on how they may be developed earlier in life from impacts to the brain from either sports, accidents, or explosive blasts. There are more research studies recording that there are correlations between MTBIs and progressions on developing neurodegenerative diseases at a faster rate (Gardner and Yaffe, 2015) (Cruz-Haces et al, 2017) (Graham and Sharp, 2019). As clinical trials are being conducting on the use of Huperzine A and how effective it is on neurodegenerative diseases, researchers may be able to delve into the use of Huperzine A on patients long suffering from PCE or affected by multiple MTBIs. Huperzine A shows promising results on how effective it is in the brain as a well-tolerated AChe inhibitor, improving neurotransmitters, and neuroprotective compounds with higher

bioavailability and a longer duration of effectiveness than other drugs used for neurodegenerative diseases (Wu, Chen, and Jinn, 2011) (Wang, Yan, and Tang, 2006).

CHAPTER 3

CONCLUSION

As evidence may show promising results, science is still in the infantile stage about how our brain functions and recovers after sustaining a TBI. There are evidence linking neurodegenerative diseases and TBI, but we still do not fully understand whether TBI does contribute to progressing early stages neurodegenerative diseases earlier in life or not. However, a crucial factor that needs to be shifted on to minimize progression or prevent degenerative effects after a single or multiple TBI by understanding the damage done to the different areas of the brain through neuroimaging and study fluid biomarkers. Certain biomarkers play significant roles on how much damage can be attributed from a TBI and Hup A may be a breakthrough needed as treatment in monitoring biomarkers in the brain to diminish short- and long-term damage done to the affected areas of the brain. Right after sustaining a TBI, the blood brain barrier is compromised by microglia and astrocytes producing an inflammatory response for hours and days. With microglia remaining active, it attributes to long-term effects of diffuse axonal damage (Graham and Sharp, 2019). Hup A may play a significant role used as treatment here at diminishing these long-term effects with its potent and well tolerated anti-inflammatory response, inhibition of AChE, and ameliorate proteinopathies. In Cruz-Haces et al. (2017) and Graham and Sharp's (2019) studies, they created a better understanding on what to look for connecting TBI and degenerative disease post-TBI and how to examine neurodegeneration after TBI (Cruz-Haces, et al. 2017) (Graham and Sharp, 2019). Utilizing neuroimaging and electroencephalography (EEG) recordings in clinical trials while supplementing Hup A as treatment would be a start for future studies.

There are some limitations to the extent of this research review. There has not been a research study done exclusively on the use of Huperzine A as treatment for concussions. There have not been any clinical studies conducted on the safety and effectiveness for its use. As well as long term effects on the use of Huperzine A as medicine with neurodegenerative patients. The China club moss *Huperzia serrata,* where Huperzine A is extracted from, mainly grows in China and parts of Australia of about a total of 500 species. Extensive harvesting has put this club moss into danger of being extinct in recent years. Without finding better ways to cultivate this plant with high turnover rates extracting Hup A or synthetically produce Hup A efficiently, Hup A could be on the brink of extinction without ever finding out its full potential in the medical field.

Future studies should conduct clinical trials on the use of Huperzine A as medication for MTBI or those suffering from post-concussive syndrome (PCS) through EEG recordings to document brain activity and what areas of the brain are affected by the concussion and how Hup A helps treat the affected area. Along with performing a series of Automated Neuropsychological Assessment Metrics (ANAM) exams to study cognitive functions and how quickly the patients respond. The more we understand the affected areas of the brain and how certain biomarkers play a role in damaging neurons and prolonging symptoms, the better we can attack on how Hup A works as treatment. There may be potential in the use of Huperzine A outside of herbal use and clinical trials on neurodegenerative diseases.

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Research Paper Title:
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