Neuroprotective Agents for Traumatic Brain Injury
THEORETICAL THERAPY OR THE FUTURE OF TREATMENT?
INTRODUCTION

Athletes and injuries have always gone hand in hand, and an estimated 300,000 sport-related concussions occur in the United States each year.¹ In the last decade, however, there has been a growing concern for diagnosis and prevention of further injury. For example, recent concussion management practices recommend 24-48 hours of rest.² While this prevents the athlete from sustaining another concussion during that time, it does not stop the underlying cellular mechanisms that occur in the brain after injury. Many athletes will return to play within two weeks after their symptoms seemingly vanish, unaware that neurophysiological deficits in cognitive performance and memory exist for at least six months post-concussion.³,⁴ As a result, concussions should be monitored for detrimental changes in behaviour and mental status, and should be considered a serious medical concern.

Concussion management and treatment in athletes is one of the most critical challenges in sports medicine. Concussion is the most frequent form of mild traumatic brain injury (mTBI) that affects not only athletes, but also people who are involved in motor vehicle accidents, recreational activities, and falls.⁵ Traumatic brain injury (TBI) is a significant global health concern and a major cause of mortality; in the United States alone, it is estimated that 1.7 million people experience TBIs annually, resulting in 52,000 deaths.⁵,⁶

In general, mild traumatic brain injury is often difficult to diagnose due to limitations in available technology and our understanding of cellular mechanisms. The current applications of CT and magnetic resonance imaging (MRI) scans

behaviourally, and emotionally.⁷ Even small concussions can result in difficulties performing everyday tasks and returning to jobs.⁸,⁹

These long-term disabilities and difficulties in memory, learning, and cognitive performance often result from delayed subcellular processes that occur days, and sometimes weeks, after the initial injury. Such cellular mechanisms include excitotoxicity and white matter injury, which can lead to neuronal death and axotomy, respectively. Although there is no current clinical treatment available to reduce their progression, the future promises a greater understanding of the biological processes that occur in the brain following TBI. This understanding could allow for the development of neuroprotective agents that can be administered to patients with TBI in order to disrupt damaging cellular mechanisms.

DIAGNOSIS

In order to effectively treat TBI, there needs to be an accurate and efficient method of diagnosing the injury and assessing the level of severity. Currently, physicians use the Glasgow Coma Scale (GCS), neurological examinations, and computed tomography (CT) imaging to diagnose TBI.¹⁰ The GCS rating is used to assess a patient’s neurological state and therefore determine the level of severity; a GCS score of 3-8 classifies severe TBI, 9-12 indicates moderate TBI, and 13-15 describes mild TBI.¹¹ While this makes the GCS useful in measuring a patient’s neurological state and providing information on possible outcomes, it does not show the physiological source of the symptoms, and can be complicated by drug use and multiple traumas.¹²

TRAUMATIC BRAIN INJURY (TBI) IS A SIGNIFICANT GLOBAL HEALTH CONCERN AND A MAJOR CAUSE OF MORTALITY; IN THE UNITED STATES ALONE, IT IS ESTIMATED THAT 1.7 MILLION PEOPLE EXPERIENCE TBIs ANNUALLY, RESULTING IN 52,000 DEATHS.⁵,⁶

An increasing awareness of concussions in sports has led researchers to uncover that brain tissue damage is not instantaneous, but rather a delayed process following the initial injury. Recently, neuroprotective agents have been developed that will be administered after injury to reduce the effects of Traumatic Brain Injury (TBI). These agents include NMDA receptor antagonists that aim to interfere with excitotoxicity and reduce neuronal death. While these agents have improved learning and cognitive performance in animal models, their effects have not been as positive in clinical trials. Calpain inhibitors have also shown neuroprotective effects, and protect against axonal damage in the white matter of the brain. In the future, a better understanding of the cellular mechanisms of TBI will allow better development of neuroprotective agents for clinical use.

ABSTRACT

An increasing awareness of concussions in sports has led researchers to uncover that brain tissue damage is not instantaneous, but rather a delayed process following the initial injury. Recently, neuroprotective agents have been developed that will be administered after injury to reduce the effects of Traumatic Brain Injury (TBI). These agents include NMDA receptor antagonists that aim to interfere with excitotoxicity and reduce neuronal death. While these agents have improved learning and cognitive performance in animal models, their effects have not been as positive in clinical trials. Calpain inhibitors have also shown neuroprotective effects, and protect against axonal damage in the white matter of the brain. In the future, a better understanding of the cellular mechanisms of TBI will allow better development of neuroprotective agents for clinical use.

HELEN GENIS
Bachelor of Health Sciences (Honours) Program, Class of 2017
Correspondence should be addressed to olena.genis@learnlink.mcmaster.ca
are limited in the case of mTBIs. Scans often appear normal, either because there is no structural damage to the patient’s brain or the scans do not have the resolution to visualize the microscopic damage that occurs in mTBI cases. This leads to incomplete medical treatment for many patients since their MRI and CT scans show no detectable pathologies. Instead, the patients are released once they stop exhibiting clinical symptoms. Ultimately, understanding the full cellular mechanism behind TBI will lead to better diagnosis and treatment.

**CELLULAR MECHANISMS: EXCITOTOXICITY**

Until recently, it was thought that the initial physical impact to the brain was the ultimate cause of brain tissue damage. However, in the past two decades, experiments have shown that secondary injury – the delayed cellular mechanisms that occur hours and even days after the initial injury – is actually responsible. Since this process evolves over time, there may be an opportunity to introduce neuroprotective therapies that will reduce brain damage.

Research has uncovered that one of the major processes responsible for neuron damage in TBI is excitotoxicity, which involves a large release of the excitatory neurotransmitter glutamate which subsequently leads to neuronal death. Under normal conditions in the brain, glutamate is released into the synaptic cleft where it increases in concentration, but quickly decreases within milliseconds. This is a result of the glutamate-glutamine shuttle in which astrocytes convert glutamate into glutamine, and the resulting glutamine diffuses readily back into the neuronal membrane. However, following TBI, cell membranes are compromised and release K⁺ as well as Na⁺ and Ca²⁺. This results in the depolarization of the membrane. The injury also causes mitochondrial dysfunction, which leads to reduced rates of ATP synthesis and a decreased activity of the enzyme Na⁺-K⁺-ATPase. Therefore, membrane depolarization increases, causing an influx of Ca²⁺ through voltage-dependent channels and a release of glutamate. However, the glutamate-glutamine shuttle does not uptake the majority of the glutamate because of a down-regulation of glutamate transporters, and an altered Na⁺/K⁺ gradient that decreases glutamate transport capacity. As a result, increased levels of extracellular glutamate activate glutamate receptors (NMDA and AMPA) cause a neuronal influx of Ca²⁺. This results in cell death by necrotic or apoptotic mechanisms.

Since glutamate receptors mediate neuronal death, glutamate receptor antagonists have been studied in rat models as a possible neuroprotective treatment. Recently, it has been shown that multiple post-injury administrations of an NMDA antagonist increase the number of surviving neurons in the hippocampus and improve learning and cognitive performance. However, clinical trials using glutamate receptor antagonists have not been as successful. One study focused on treating severe TBIs using Selfotel, a competitive NMDA receptor blocker, but was terminated during the third phase of the clinical trial after preliminary reports showed no positive outcomes. Other studies reported no adverse effects, but also have insufficient data to conclude that NMDA antagonists display neuroprotective effects in patients with TBI. This may be because a majority of NMDA antagonists cannot readily cross the blood-brain barrier. As such, physicians would have to administer larger doses than given in the animal models to achieve the same neuroprotective effects. Unfortunately, this could also result in systemic toxicity in the patient. In addition, NMDA receptor antagonists can result in further damage if administered outside its limited therapeutic window. This is because glutamate receptor antagonists interfere with “upstream” signals, which subsequently affect various “downstream” signaling pathways. Furthermore, since there are many pathways that may result in neuronal death, using glutamate receptor antagonists to limit the calcium influx will not guarantee neuronal survival. In the future, researchers should focus on TBI treatments that may block multiple pathways involved in neuronal death.

**WHITE MATTER INJURY**

Another possible neuroprotective treatment for TBI targets white matter injury. White matter is the area of the brain that consists of glial cells and myelinated axons that transmit signals between different areas of grey matter in the brain. Diffuse axonal injury (DAI) has shown a strong association with TBI and appears in about 50% of TBI patients who require hospitalization. Until recently, it was believed that the initial impact to the brain caused mechanical tearing in the majority of the axons, or axotomy. Research conducted in the last decade, however, suggests that the main mechanism is secondary or delayed axotomy.

**RECENTLY, RAT MODELS HAVE SHOWN THAT MULTIPLE POST-INJURY ADMINISTRATIONS OF AN NMDA ANTAGONIST INCREASE THE NUMBER OF SURVIVING NEURONS IN THE HIPPOCAMPUS AND IMPROVE LEARNING AND COGNITIVE PERFORMANCE.**
that evolves following the initial impact.\textsuperscript{27} This has been largely attributed to high levels of intracellular calcium that activates a group of enzymes known as calpains. These enzymes degrade intracellular proteins such as αII-spectrin, a protein responsible for the structure and shape of the axon. Over time, the breakdown of spectrin causes damage to their relatively low solubility and metabolic instability. Thus, the pharmacodynamics of calpain inhibitors must be optimized prior to their use in clinical trials.\textsuperscript{32}

\textbf{CONCLUSION}

Traumatic brain injury is a significant health concern that can result in life-long disability, or even death. Current diagnosis is largely based on the Glasgow Coma Scale, neurological assessment, and CT imaging; however, both GCS scores and neuroimaging lack the ability to detecting the physiological consequences of having sustained a concussion. Although TBI is initiated by blunt force trauma or by rapid acceleration-deceleration movements, damage to the brain largely as a result of secondary injury. During this time, cellular processes such as excitotoxicity and abnormal calcium homeostasis results in neuronal death and axonal damage in white matter. Glutamate receptor antagonists and calpain inhibitors are being examined as possible neuroprotective agents, and have shown better functional outcomes by protecting axonal structure in animal models. Further research into the cellular mechanisms that occur during secondary injury is warranted, and will allow for the development of novel neuroprotective agents. \textsuperscript{21}

Although no clinical treatment for TBI has been proven effective, calpain inhibitors have already shown neuroprotective capabilities in animal models.\textsuperscript{30,31} Unlike glutamate receptor antagonists, calpains remain largely inactivated under normal conditions.\textsuperscript{32} As a result, inhibiting calpains would not have been proven effective, calpain inhibitors have been examined as possible neuroprotective agents, with the ultimate goal of developing novel therapies to treat concussions.

\textbf{REFERENCES}


3. Baillargeon A, Lassonde M, Leclerc M. The functional anatomy of the frontal eye field in the left hemisphere in the brain, is one of the primary locations of injury in DAI. While administering the treatment post-injury in animals was successful in protecting the axonal structure, the surviving axons were not as functional as the normal axons.\textsuperscript{30} Other drawbacks of calpain inhibitors include their delayed process.\textsuperscript{28,29}


