Using neuroplasticity to induce self-healing in the brain of patients with stroke...

Science, Biology

Neuroplasticity is defined as the ability of the brain to generate physiological changes within itself. The capability to “ rewire” itself allows the brain to respond, learn, and adapt to changes in the environment. Furthermore, it is the mechanism through which repair of damaged connections can be made upon injury. Stroke is a common brain injury that can result in large regions of tissue damage causing severe neurological dysfunction and lasting disability. Promoting neuroplastic repair around the damaged area has the potential to reduce many post stroke dysfunctions. Neuroplastic response can stimulated by a variety of mechanisms such as: physical therapy, stem cell treatment, or electrical induction. Thesis Overview Introduction Brain injury from stroke can result in a variety of symptoms, ranging from physical to cognitive disabilities. The medical field is continuously improving treatment for these patients, however serious long-term defects still remain. Through the process of neuroplasticity, however, it is possible that the brain can reorganize around the damaged lesion and restore function. (Khan et al, 2017). Synaptic connections are reinforced through activity, the more it fires the stronger the connection. Therefore, by stimulating two neurons to fire together, a new connection can be made. (Moritz, 2018).

This mechanism has the possibility to aid brain-injured patients utilize additional areas of the brain to perform tasks that have been lost. (Caeyenberghs et al, 2018) Research Problem Post stroke behavior and therapeutic choices can have a profound effect on the functional outcome of the patient. The therapies often chosen typically require multiple sessions in order to generate transient improvement. However, harnessing the process of neuroplasticity, it is possible to stimulate the brain’s ability to self-heal,

producing long lasting changes. Research Questions After stroke, many patients are left with significant neurological dysfunctions that require extensive treatment. How can the process of neuroplasticity be utilized to provide patients with maximal and long lasting functional restoration? Can neuroplasticity be induced through physical therapy? Can neuroplastic changes be stimulated through stem cell transplant? How can a neuroplastic response be initiated through electrical stimulation? Hypothesis The hypothesis is that by utilizing specific neuroplastic inducing therapies, long lasting plastic changes can alleviate post stroke dysfunctions. By stimulating the brain to heal itself can significantly improve the quality of life for many post stroke patients. Purpose of Research The purpose of this research is to determine how self-repair of the brain can be induced in order to restore function to patients with stroke induced disabilities. Many patients are unable to restore lost function, even with extensive therapy. By utilizing the process of neuroplasticity this can give these patients back their quality of life. Methodology Peer reviewed articles was extensively used, through the Nova Southeastern University Alvin Sherman Library, Research and Information Technology Center. Many of the sources were found from the National Center for Biotechnology Information (NCBI). Stroke Treatment Through Neuroplastic Response Introduction Neuroplasticity, or “ rewiring” of the brain, is a complex series of events to generate new connections between neurons. These connections are in a delicate balance between generation of new synapses and destruction of old ones. In order to generate long lasting plasticity, signaling cascades activate and modify neuronal gene

expression. These genes then translate into various synaptic protein receptors promoting synaptic plasticity (Gulyaeva, 2017).

Neuroplasticity in Stroke Treatment: Physical Therapy Neurorobotic Devices

Gait dysfunctions are a common detrimental effect due to stroke. Most stroke damage occurs in one hemisphere of the brain. Therefore, restoration of interhemispheric communication between the corticospinal tract and somatosensory tract of both the damaged and undamaged hemispheres is necessary. Post injury neuroplastic adaptation results in changes in frontoparietal effective connectivity (FPEC) located within the prefrontal, supplementary motor, and centroparietal regions. These regions control: motor initiation, movement coordination, and motor execution respectively (Calabrò et al, 2018). In the study by Calabró et al, it was observed that neurorobotic devices, such as robotic- assisted gait training with body weight support known as Ekso, combined with overground gait training (OGT) resulted in an improvement in gait abnormalities post stroke. This study compared the effects of Ekso gait training (EGT) combined with overground gait therapy verses OGT alone. The terminal stance phase within the gait cycle was primary affected by Ekso, which lead to improvements in gait velocity and quality, balance, reduced limb asymmetries, and overall performance. Increases in neuroplastic activity was determined by measuring FPEC via EEG, and corticospinal excitability and sensory motor integration via transcranial magnetic stimulation. It was observed that the patients that received EGT had increased communication restoration throughout both hemispheres as opposed to OGT that had restoration

isolated to the damaged hemisphere. In addition, EGT demonstrated increased neuroplastic effects especially in the supplementary motor region, suggesting enhanced motor coordination, compared to OGT. These improvements require high intensity and frequency of therapeutic sessions to strengthen the neuroplastic mechanisms (Calabrò et al, 2018).

High-intensity Interval Training Aerobic activity is beneficial for many systems of the human body and can even help drive neuroplastic recovery after cerebral ischemia. According to Pin-Barre et al, this is achieved by “ upregulating the neurotrophin levels, enhancing synaptogenesis, and limiting microglia-mediated proinflammatory cytokine release in the perilesional zone.” In this study it was observed that high-intensity interval training (HIT), started within the first five days post stroke, was more effective in promoting cerebral plasticity and functional recovery than moderate-intensity aerobic training (MOD). After stroke, serum cortisol levels increase which increases lactate levels. A resting hyperlactatemia is associated with decreased cerebral recovery. Aerobic exercise, however, increases lactate transporter expression thereby reducing lactate levels and promoting an environment for recovery (Pin-Barre et al, 2017).

Brain derived neurotrophin factor (BDNF) expression is correlated with synaptic plasticity, specifically by increasing P75NTR levels. Although BDNF levels were elevated with aerobic activity in general, it was observed that P75NTR levels were higher in the ipsilesional level in the HIT trained subjects than the MOD trained subjects. HIT is more effective than MOD in reducing neuroinflammation, which can be detrimental to neuroplastic processes.

After MOD exercises, microglial Iba-1 cells, ionizing calcium binding adaptor molecule 1, remained elevated. These cells produce free radicals and proinflammatory signals, indicating increased microglial activity, therefore increased neuroinflammation. Furthermore, alterations in these microglial cells were affected by aerobic exercise. In MOD training the microglia remained in the amoeboid state, proinflammatory state, and were in the more branched form after HIT (Pin-Barre et al, 2017).

Neuroplasticity in Stroke Treatment: Stem Cells Another therapeutic option for post stroke recovery is through the transplantation of stem cells. Mesenchymal stem cells (MSCs) posses the ability to differentiate into a multitude of various cells types necessary for the repair of damaged brain tissue, and protection of the synaptic microenvironment. Damaged brain tissue becomes inflamed and excitotoxic due to neuronal cell death. As a result, astrocytes are activated and initiate the formation of a glial scar around the affected area to protect the surrounding tissue. However, this scar can interfere with synaptic reformation. MSCs reduce this glial scar thickness, therefore allowing synaptic reconnection. Further modification of the microenvironment is accomplished via the secretion of cytokines that initiate neurogenesis and angiogenesis. These cells can then replenish glial cells and neurons by differentiating into neural stem cells (NSC) (Sophie et al, 2016). NSCs possess the ability to differentiate into “ functional nerves, astrocytes, and oligodendrocytes, and integrate into existing neuronal circuitry.” Furthermore, they have the ability to move towards inflamed areas of the brain via chemokine receptors. Once in position NSCs secrete

neurotrophic factors, BDNF, nerve growth factor (NGF), and fibroblast growth factor (FGF), to increase cell growth, differentiation, and survival. Chemokines are also secreted to alter the inflammatory response, which further aids in new cell survivability (Sophie et al, 2016). There are two main sources for MSCs, bone marrow derived (BM-MSCs) and umbilical cord derived (UCB-MSCs). The cells obtained from both sources are effective, however it has been observed that UCB-MSCs have a higher survivability and increased proliferative activity. This method is also preferred due to the less invasive acquisition of samples, in comparison to a lumbar puncture with BM-MSCs (Sophie et al, 2016) In the study by Xiong et al, recovery of function from brain injury was improved in rats that received NSC transplants. These cells have the capability to differentiate to replace the damaged neurons and supportive glial cells and can release signaling molecules for synaptic rewiring. The degree of synaptic rewiring is determined by measuring the synaptophysin levels. Synaptophysin is a prevalent presynaptic membrane protein signifying high synaptic density. When brain tissue is damaged these synaptophysin levels drop. Once NSC is engrafted into damaged cortical tissue, however, these levels rise suggesting regenerated synaptic function (Xiong et al, 2016).

NSCs release an important neurotrophic factor, BDNF, an essential growth factor for neuron growth and synaptic plasticity during both development and adulthood. Increases in BDNF levels influence synaptophysin levels due to BDNF mediated gene expression. Some of the major genes activated are the Wnt and Bcl- 2 genes, which are involved in determination of cell fate

and growth. Therefore, transplantation of NSCs after cortical injury can stimulate a whole series of signaling pathways resulting in increased synaptic reconnections and healing. (Xiong et al, 2016). Neuroplasticity in Stroke Treatment: Electrical Therapy Vagus Nerve Stimulation Vagus nerve stimulation (VNS) paired with rehabilitative motor training can stimulate long term neuroplastic processes after stroke damage. Not only does this therapy increase functional recovery for the specific trained movement, but the benefit can generalize to improvements in similar untrained functions. The corticospinal tract (CST) is a common motor pathway that is damaged during a stroke. Since the CST is one of the major motor pathways in the CNS, injury to this can result in significant motor dysfunction. Therefore, it is necessary that reconnections in this pathway is necessary for lost motor recovery. Although the exact mechanism is still unknown, VNS has been observed to increase synaptic connections along the descending CST (Meyers et al, 2018). According to the study by Meyers et al, rats were subjected to ischemic cortical lesions, resulting in decreased forelimb function.

These rats then received VNS combined with rehabilitative motor therapy targeted for recovery of forelimb supination function. This resulted in improvement in forelimb movement and strength during the supination task in comparison to the rats that only received rehabilitative therapy. This increase in functional recovery further extended to tasks that were not specifically trained for. Furthermore, the rats that received VNS therapy also demonstrated an increased ability to perform a forelimb pull task. The ability of VNS therapy to stimulate rapid neuroplasticity in the CST can be very

useful in the clinical setting. This would have the potential to reduce the number of therapy sessions required for a patient to recover a particular function, and free up sessions for other therapies (Meyers et al, 2018). Transcranial Alternating Current Induction of cortical neuroplasticity can be enhanced through non-invasive brain stimulation (NIBS) utilizing continuous theta burst stimulation (cTBS). The amount of cortical inhibition, primarily through the actions of GABA, determines how responsive the brain is to neuroplastic changes. Neuroplastic activity is inversely related to GABA activity, the more GABA the less neuroplasticity. This increased GABA inhibition is influenced by alpha rhythm activity. Therefore, the timing of cTBS within the different phases of the alpha rhythm is critical to the enhancement of neuroplasticity. For maximal neuroplastic induction, stimulus needs to be applied during the periods of reduced alpha wave inhibition. Transcranial alternating current (tACS) is utilized to trigger alpha rhythms within the brain, then cTBS is applied during the trough of the alpha wave inducing a neuroplastic response (Goldsworthy et al, 2016).

Transcranial alternating current can enhance a neuroplastic response in a specific manner. This is determined by the frequency of the peaks of the alpha rhythm. Increased neuroplastic activity in task related cortical processing is associated with higher alpha frequencies when induced by tACS (Goldsworthy et al, 2016). Discussion Implications for the PA profession The ability to guide the process of neuroplastic changes within the brain would allow Physician Assistants to recommend better treatments for patients. This is especially true for those patients whom traditional therapies

have failed to produce significant changes. By understanding that there are multiple methods to induce neuroplasticity, a PA would be able to tailor treatment according to patient needs. Strength of the Research Analysis of the articles used for this research exhibited many strengths. For each of the articles discussing the various methods for inducing neuroplasticity, that specific mechanism was described in detail. In this way an overview of neuroplastic processes was able to be revealed. In addition, many of the articles utilized was among the more recent research. This way, the most up to date theories were utilized. Weaknesses of the Research Throughout the articles that were reviewed some weaknesses in the research stood out. It was noticed that in the majority of these studies, pre-stroke risk factors and comorbid were not taken into account. This is important because different disease states can alter physiological processes within the body.

These alterations could have an effect on the outcomes of the various research. In addition, long term follow up of the results of the various studies should be obtained. This is critical to determining if the induced neuroplastic changes are indeed long lasting. Recommendations for Future Research Future research in the field of neuroplasticity for stroke treatment should determine which type of inducing modality produces which type of neuroplastic change. Different induction methods produce different changes in the brain. It would be interesting to determine which therapies would be ideal to produce a specific result. In this way, a particular therapy can be chosen specifically according to the needs of the patient. Conclusion The ability of the brain to repair damage can be utilized in the recovery of

function after a stroke. Various methods have been observed to produce neuroplastic changes such as: physical therapy, stem cell transplantation, and electrical therapy. Utilizing these various methods has the potential to dramatically improve the recovery of stroke victims, by stimulating the brain’s natural repair process.