Vegetative and Minimally Conscious State: A Review of Neurological Processes

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The vegetative and minimally conscious states are disorders of consciousness that are a consequence of a coma that persists for an extended period of time. The vegetative state is characterized by a lack of awareness of self and environment and sleep and wake cycles, in which patient's may keep their eyes open or closed for hours at a time. Brain stem autonomic and hypothalamic functions, such as breathing, heart rate, and regulation of body temperature, are also maintained. The minimally conscious state is characterized by sleep and wake cycles and purposeful movements, such as reaching for an object and following commands. Patients may be able to visually fixate by maintaining eye contact on an object and following the object if it moved. They may also be able respond to sensory information, such as pain, via verbalization. These states can be caused by traumatic and non-traumatic brain injuries that negatively impact and suppress neurological functions. Studies have implicated genetic factors and neurological underpinnings in the susceptibility of entering the vegetative and minimally conscious states. Additionally, researchers have investigated the use of drugs to arouse patients from these states. This review seeks to explore the neurological processes that characterize the vegetative and minimally conscious states.

The definition of consciousness varies depending on the theoretical and biological framework that is being considered. Psychoanalysts describe consciousness as the interaction between the external perception of the environment via sensory organs and internal perception of self (Solms, 1997). Thus, perceiving the world using vision, sight, sound, touch, and taste - and integrating that information into psychological or emotional states, such as anger, fear, happiness, pain, etc., - that is unique to the individual constitutes consciousness. Biologically, consciousness is a result of the neurological processes that occur in the brain (Miller, 2005). By incorporating both perspectives of consciousness, alterations and disorders in consciousness can be better understood. Impaired consciousness is associated with brain damage or injury due to trauma, degenerative diseases, infections of the central nervous system, or metabolic disorders (Giacino et al., 2013). Notable impaired states of consciousness are the vegetative state (VS) and the minimally conscious state (MCS). The vegetative state is characterized by brainstem autonomic and hypothalamic function, the appearance of sleep-wake cycles, and the absence of the awareness of self or the environment (Giacino et al., 2013). Patients in a vegetative state are also unable to respond purposefully to noxious stimuli, express or understand language. However, they may have cranial nerve and spinal reflexes, such as swallowing, blinking, and knee-jerk reflexes (Shea et al., 2013; Laureys et al., 2002). The vegetative state is usually the consequence of a coma that lasts for longer than a month and can be categorized into either a persistent vegetative state, or permanent vegetative state. A coma due to a traumatic brain injury that persists for over 12 months or a coma due to a non-traumatic brain injury that persists for over 3 months is considered a permanent vegetative state. A coma that lasts more than a month is considered a persistent vegetative state (Georgiopoulos et al., 2010). Patients in a permanent vegetative state are less likely to recover compared to those in a persistent vegetative state. During wake cycles, the eyes open and move but do not fixate on a particular target and the limbs may move meaninglessly. Painful and noxious stimuli can elicit reflexes and physiological progresses such as eye opening, increase in respiratory rate, heart rate, and blood pressure (Laureys et al., 2002). The preservation of pupillary, corneal, oculocephalic, and gag reflexes also allow vegetative patients to display spontaneous movements such as chewing, teeth-grinding, swallowing, moaning, and smiling (Laureys et al., 2002). Compared to healthy individuals, the resting brain metabolism of patients in a vegetative state is 50-60% lower (Laureys et al., 2002). PET studies and mapping analysis have revealed that the brain regions associated with metabolic impairment are the prefrontal, premotor, and parietal-temporal cortices, and the posterior cingulate region (Laureys et al., 2002). These cortices are involved in attention, working memory, episodic memory, language, and conscious perception while the posterior cingulate region is in-

volved in conscious waking (Laureys et al., 2002). Conversely, the metabolism of the brain stem, basal forebrain, and posterior hypothalamus are relatively preserved (Laureys et al., 2002). These regions play a crucial role in sleep-wake cycles, autonomic control, and cranial nerve reflexes that are observed in patients in a vegetative state (Laureys et al., 2002).

The minimally conscious state is distinguished from the vegetative state by the presence of inconsistent behavioral evidence of consciousness and partial awareness (Giacino et al., 2013). Patients in minimally conscious states are characterized by sleep/wake cycles and purposeful movements. They are able to maintain visual fixations, localize auditory stimuli, verbalize and gesture, follow commands, and may give emotional responses (Davis, 2007). However, a patient's health and cognitive abilities can influence their motor, visual, and auditory abilities, as these abilities may deteriorate in patients with poor health or reduced cognition. Although few brain imaging studies have been done on patients in the minimally conscious state, it has been revealed that the cingulate cortex and parietal cortex remain functional (Davis, 2007). This suggests that the neurological networks that are involved in consciousness retain their functionality. Despite current knowledge concerning these states of consciousness, questions still arise about how these states of consciousness emerge and are maintained biologically. This review will investigate both the vegetative and minimally conscious states by considering biological and neurological pathways that can result in either states of consciousness and current advancements that aim to treat these conditions.

Genetic Implications

Although there are neurological underpinnings that determine the progression and emergence of the vegetative and minimally conscious states, genetic factors can increase the susceptibility to the vegetative and minimally conscious states and influence the neural networks associated with these states of consciousness. The most common cause of disorders of consciousness is traumatic brain injury. The severity and brain regions affected in the event can determine a patient's outcome, while post-injury neuronal repair can determine the recovery of their outcome (Bennett et al., 2016). Genes that influence the severity of the injury and the repair post-injury are pro- and anti-inflammatory cytokines and neurotrophic genes (Bennett et al., 2016). During the initial phases of a brain injury, cytokines may act to prematurely exacerbate the injury or may offer neuroprotective properties (Bennett et al., 2016). Tumor necrosis factor α (TNFα) is a pro-inflammatory cytokine that plays a role in the development and regulation of the immune system and generation of T-cells (Stubgen, 2007). It has been implicated in neurological disorders, such as Guillain-Barre syndrome. TNFα has been shown to damage peripheral nerve, Schwann cells and myelin sheaths, and prevent action potential transmission (Stubgen, 2007). TNFα is up-regulated in the first hours following a traumatic brain injury but returns to normal gene expression levels within 24 hours (Bennett et al., 2016). Knockout studies have suggested that this up-regulation may have neuroprotective properties (Scherbel et al., 1999). Short-term, mice that lacked TNFα were found to have less cognitive impairments compared to mice with the gene. However, long-term, the mice without TNFα had more motor deficits and cortical tissue loss compared to mice with TNFα (Scherbel et al., 1999). This suggests that while TNF has initial adverse neuronal effects, it can positively influence future repair after brain injury. Interleukin-1 (IL-1) is another pro-inflammatory cytokine associated with brain injuries. By working with TNFα, cytokines in this family can increase inflammation and body temperature after a brain injury (Bennett et al., 2016). Studies have demonstrated that not only do IL-1 increase following brain injury but that it is also associated with severity, with high IL-1 levels being associated with more severe brain injuries (Bennett et al., 2016). However, other studies have also reported that IL-6 may lend neuronal benefits as higher levels of IL-6 resulted in better outcomes and recovery in patients with brain injuries (Bennett et al., 2016). Apolipoprotein E (APOE) is a gene that is associated with neuronal growth and repair, synaptodendritic connection maintenance, and inflammation (Bennett et al., 2016). Following stress and injury, APOE is produced by astrocytes and microglia and may have negative effects on cognition (Bennett et al., 2016). Lastly, human brain-derived growth factor (BDNF) is a gene that is involved in synaptic connectivity, plasticity, neuronal growth and survival, memory, and executive function (Bennett et al., 2016). Studies have demonstrated BDNF's importance in cognition following brain injury as it has been shown to increase in the hippocampus following brain injury and influence repair (McAllister et al., 2012). These genes play a critical role in the emergence of vegeta-

tive and minimally conscious states following brain trauma. By modulating the repair processes and inflammation following brain injuries, these genes can have a significant effect on the outcomes of these injuries by offering neuroprotective benefits that reduce the chances of entering a vegetative or minimally conscious state. Thus, polymorphisms or mutations in these genes can negatively impact the repair process following a brain injury and increase the chance of entering a vegetative or minimally conscious state.

Mutations

Polymorphisms in TNFα, specifically -238 A/G and -308 A/G, have been implicated in the outcome of inflammatory conditions. Studies have demonstrated that unfavorable outcomes following traumatic brain injury such as death and vegetative state were more likely in individuals with the -308 A allele. It is suggested that this may be due to the effect this allele has on the expression of TNFα, as those with the -308 A allele have increased expression of TNFα after injury. Studies investigating polymorphisms in IL-1 suggest that they are associated with unfavorable outcomes following brain injuries. The APOE4 allele has been linked to the development of Alzheimer's Disease due to its influence in the development of amyloid beta in the brain. Additionally, individuals with this allele have an increased risk of developing Alzheimer's Disease if they have a history of brain injury. It has also been suggested that this allele can result in poorer outcomes following brain injury and a higher chance of experiencing loss of consciousness (Bennett et al., 2016). However, due to the differences between individuals in the severity of brain, age, and health, there are conflicting studies that imply that there is little to no association between APOE polymorphisms and unfavorable outcomes following brain injury (Liberman et al., 2002).

Polymorphisms in BDNF has been associated with cognitive function following brain injuries. Studies have demonstrated that in healthy patients, stroke patients, and psychiatric patients with the Val66Met polymorphism had impaired cognitive abilities (Bennett et al., 2016). This polymorphism has been linked to a decrease in hippocampus volume and prefrontal cortex gray matter (Bagnato et al., 2012). Similar results have been revealed in patients following brain injury. This suggests that patients with this polymorphism would be more susceptible to poor outcomes and disorders of consciousness. However, Bagnato et al revealed that the Val66Met polymorphism may not affect the improvement of cognitive abilities in patients in a vegetative state following traumatic brain injuries. The percentage of patients with and without the Val66Met polymorphism who emerged from the vegetative state did not statistically differ. Additionally, the cognitive functions were similar between these patients (Bagnato et al., 2012). Therefore, although polymorphisms in BDNF impact brain structures and are implicated in impaired cognition, it does not seem to have a prominent effect on the recovery or cognition of patients in a vegetative state.

The effect of these polymorphisms on the outcomes following brain injuries imply that there is a genetic susceptibility factor that can make an individual more at risk of entering a vegetative and minimally conscious state.

Subcellular Organelles

There are few studies that have elucidated the role of subcellular organelles in vegetative and minimally conscious states. However, diseases, such as Alzheimer's disease, that have organelle dysfunction sometimes progress into vegetative and minimally conscious states. Alzheimer's disease is a common type of cortical dementia that is characterized by severe memory impairments and mostly affects people over the age of 65. Mitochondrial dysfunction plays a key role in the onset of this disease (Moreira et al., 2010). In healthy individuals, mitochondria are involved in proper neuron function by generating adenosine triphosphate (ATP) for energy needs and monitoring cellular health. Dysfunctions in mitochondria result in a decreased production of ATP and a released of pro-apoptotic factors (Moreira et al., 2010). Additionally, impaired mitochondria are unable to serve as an intracellular calcium buffer, which is required for calcium homeostasis and neuron function. As a result, cell death and neurodegeneration can occur, which contributes to the loss of cognitive abilities seen in Alzheimer's patients (Moreira et al., 2010). Due to neurodegeneration, 4-12 years after a patient has been diagnosed with Alzheimer's, they can progress into a vegetative state (Heston et al., 1977). A study conducted by Jaul et al. revealed that 30.5% of elderly patients with dementia had persistent vegetative state (Jaul et al., 2007). However, a study done by Volicer et al demonstrated that it is unlikely for Alzheimer's disease to progress into a vegetative state (Volicer et al., 1997). Both studies noted the difficulty in diag-

nosing patients with Alzheimer's disease, since the cognitive abilities are not stable and can differ from patient to patient. Additionally, it was suggested that there was a low level of awareness among hospital staff about persistent vegetative state and minimally conscious state in patients with Alzheimer's disease. These limitations could affect the extent to which the results of the studies can be applied to populations of patients with Alzheimer's disease.

Action Potentials

Event-related potentials (ERPs) are voltages generated by the brain due to sensory, motor, or cognitive stimuli. During ERPs, cortical pyramidal neurons fire action potentials as the brain is processing the stimuli. The summation of these postsynaptic potentials reflects the type of the ERP (Sur et al., 2009). For example, N1 waves is elicited when an auditory stimulus is presented (Sur et al., 2009). A P2 wave may be elicited in response to sensation seeking behavior (Sur et al., 2009). P3 waves may be elicited in response to unexpected target words (Sur et al., 2009). Studies have been conducted on patients in vegetative and minimally conscious states to investigate cortical functions by evaluating ERP responses to auditory cues. In a study done by Kotchoubey et al, all patients exhibited a ERP response, however the types of responses varied. Most patients displayed N1 and P2 waves while a third displayed P3 waves. Patients in the vegetative state were also found to have slightly lower ERP results compared to those of patients in the minimally conscious state (Kotchoubey et al., 2005). A study conducted by Perrin et al investigated semantic processing in patients in vegetative and minimally conscious states, by attempting to evoke ERPs using the auditory recordings of the patient's name, revealed similar results. P3 waves were elicited in all minimally conscious patients and 60% of patients in a vegetative state (Perrin et al., 2006). Collectively, these studies imply that patients in vegetative and minimally conscious states have retained their auditory and language comprehension abilities. However, these results do not reflect consciousness, as ERPs can be generated in healthy unconscious patients as well.

Neurotransmitters

GABA (gamma-Aminobutyric acid) is an inhibitory neurotransmitter and glutamate is a excitatory neurotransmitter. Both modulate activity and communication between neurons (Pontes et al., 2013). After brain injuries, a surge of GABA and glutamate enter the brain. The presence of glutamate results in the ischemic microenvironment becoming stabilized as apoptotic brain cells absorb toxic metabolites (Clauss, 2010). However, the inhibition caused by GABA begins to dominate, causing a suppression of cell metabolism to protect the cells. Brain functions are gradually suppressed as well, which results in a loss of consciousness. Subsequently, GABA starts to flow from the brain to the blood and the brain becomes depleted of GABA (Clauss, 2010). GABA receptors may then become over sensitive to the presence of GABA if GABA levels remain low in the brain. This will cause the brain to remain suppressed, resulting in a vegetative or minimally conscious state (Clauss, 2010). Suzuki et al investigated the presence of GABA, glutamate, and 39 other neurotransmitters commonly found in the body in order to characterize the role of neurotransmitters following a traumatic brain injury. They demonstrated that glutamate levels were lower in the jugular vein compared to that in the artery while GABA levels was higher in the jugular vein compared to the that in the artery. It was suggested that the secretion of GABA may prevent glutamate neurotoxicity, while glutamate's ability to circulate may increase during trauma, resulting in more glutamate in the arteries (Suzuki et al., 2002).

Neurotransmitter release

Due to GABA's role in inducing vegetative states, researchers have sought to alter GABA levels and transmission to stimulate arousal in patients in the vegetative state. Zolpidem, a non-benzodiazepine sedative drug, has been used to treat insomnia. By binding to GABA receptors, it mimics the effects of GABA and induces sleep (Clauss, 2010). However, Zolpidem has been shown to have opposite effects in patients in vegetative and minimally conscious states. It has been suggested that when Zolpidem binds to GABAA receptors, the receptors' structure is distorted. This results in an increased GABA receptor activity, which turns off neurodormancy and prevents abnormal cell metabolism. Previously dormant cells would then become active. Depending on how large the dormant areas are, Zolpidem may stimulate arousal in a patient in a vegetative or minimally conscious state (Kim et al., 2016). Clauss et al demonstrated efficacy of Zolpidem in three patients in a permanent vegetative state. After being administered the drug, there were significant changes in

the patients' behavior. Each patient transitioned from unresponsive, before treatment, to displaying meaningful responses, such as maintaining visual fixations, following commands, responding to auditory, visual, and physical stimuli, and speaking. However, the changes observed in the patients were not permanent as the patient would return to vegetative state once the drug's effect wore off (Clauss et al., 2006).

Ion channels

The complex formed by GABAA receptors and chloride channels are implicated in sedative drugs and the disorders of consciousness (Clauss, 2006). GABAA mediates the chloride's permeability to the cell membrane by increasing chloride ion conductance and opening chloride ion channels. Chloride flows into the cell membrane, making the intracellular side negative relative to the extracellular side. Action potentials are less likely to occur as depolarization and neuronal firing is prevented. This produces inhibition in the neurons (Stephenson., 1988). The key receptor that Zolpidem affects is the benzodiazepine receptor in the GABAA receptor-chloride channel complex. By binding to GABAA, the drug increases GABAergic transmission, which results in the opening of chloride channels in neuronal membranes. Zolpidem shows specificity for omega 1 subunits on these receptors, which is suggested to play a critical role in its ability to elicit arousal in vegetative and minimally conscious patients. This is supported by studies that have demonstrated that non-selective benzodiazepine receptor agonists are unable to evoke the same response as Zolpidem (Pistoia et al., 2010). Drugs, such as baclofen, that activate GABAB receptors, have also been used to treat patients in vegetative and minimally conscious states. Similar to the GABAA receptors, GABAB receptors form a complex with potassium and calcium channels. GABAB inhibits neuronal firing by decreasing calcium conductance and inwardly rectifying potassium (Olsen et al., 1999). It has been suggested that baclofen activation of GABAB receptors result in further activation of glutamate receptors, which can lead to arousal in vegetative and minimally conscious patients (Sara, 2009).

Current Advancements

As previously mentioned, there are several drug treatments that are currently used to try to induce arousal in vegetative and minimally conscious patients. Lamotrigine, a drug used to treat epilepsy and mood disorders, has also been suggested as a treatment. This drug is involved in blocking sodium ion channels, which prevents multiple action potentials from firing and results in a reduction in seizure frequency (Pistoia et al., 2010). Studies have demonstrated that by blocking sodium channels, Lamotrigine also has anti-glutamatergic by preventing the release of glutamate in excitatory synapses. Additionally, it increases GABA in the temporal lobe and hippocampus (Cunningham et al., 2000). Additionally, researchers have revealed that lamotrigine encourages cognitive function in patients with severe brain injuries (Showalter et al., 2000). These drugs have been demonstrated to be very effective as multiple patients have been awoken from vegetative and minimally conscious states. However, the disadvantages to the use of these drugs are that the effects are dependent on the duration of the drug in the body. Thus, a patient may only be awake for 1-2 hours before re-entering the vegetative or minimally conscious state. It has been suggested that continual use of these drugs could constitute a therapy program (Clauss et al., 2006). However, further studies must be conducted to determine the long term neurological effects.

Conclusions

Vegetative and minimally conscious states are disorders of consciousness that are commonly caused by traumatic brain injuries. Polymorphisms in cytokines, neurotrophic genes, and GABAergic transmission have been implicated as factors that may make brain injury patients more susceptible to entering vegetative or minimally conscious states (Bennett et al., 2016; Pistoia et al., 2010). Despite the current scientific knowledge surrounding the vegetative and minimally conscious state, there are still gaps in the neurological and biological processes that characterize these disorders. Difficulty in accurately diagnosing vegetative and minimally conscious patients can prevent studies from producing generalizable results. Additionally, differences in the type of trauma, the severity of injury, brain regions affected, and age can prevent a complete assessment of a drug's neurological effects or cognitive abilities. Future studies exploring the role of the external environment, such as the clinical setting, interaction between individuals and patients, on recovery from vegetative and minimally conscious states could elucidate non-biological factors that influence cognition in these patients. It has been revealed that the brains of patients in vege-

tative and minimally conscious states produce event related potentials when exposed to auditory cues of their names (Kotchoubey et al., 2005). Additionally, researchers have suggested via functional magnetic resonance imaging (FMRI) and auditory cues that some vegetative and minimally conscious patients are capable using auditory attention to respond and communicate with other individuals (Naci and Owen, 2013). These findings suggest that there may be methods to stimulate consciousness. The vegetative and minimally conscious states are debilitating conditions that require further investigation of underlying mechanisms to provide treatment options to patients.♦

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