THE BRAIN AND MOTOR CONTROL:

PATHWAYS, PATHOPHYSIOLOGY AND A HISTORY OF EXPERIMENTATION

By

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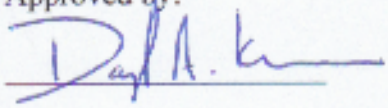

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The Brain and Motor Control:

Pathways, Pathophysiology and a History of Experimentation

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Abstract

The control of movement is complex. A motor plan is formed with the involvement of the primary motor cortex, the supplementary motor areas and other brain structures such as the basal ganglia and cerebellum. This plan is encoded into electrical signals which are propagated along many neurons in the form of action potentials. These signals travel from layer V of the primary motor cortex through the pyramidal tract to the upper motor neuron and interneurons of the spinal cord. Motoneurons carry the signals out through the ventral horn of the spinal cord through the periphery to the neuromuscular junction at the muscle cell. A series of events here ultimately result in contraction. Injuries to the brain and spinal cord can cause a myriad of motor symptoms. Disorders such as Multiple Sclerosis, Amyotrophic Lateral Sclerosis, Parkinson's Disease and Huntington's Disease also have motor symptoms caused by various pathophysiologies occurring at the cellular level. These symptoms can usually be alleviated with pharmacological intervention. A brief history of central nervous system experimentation from 1870 to present is also discussed.

Brain Areas associated with Motor Control

The brain is a complex organ, containing many nuclei with multiple roles involved in the control of movement. One of those roles has to do with planning and generating motor movements. The cascade necessary for movement to occur often begins with sensory stimuli travelling from the periphery to the brain via afferent sensory neurons (Soechting & Flanders, 1995). The brain also receives visual stimuli that are important for initiating movement and generating a motor plan to move one or more body parts in space (DeWolf & Eliasmith, 2011). It has been suggested that single neurons in the brain are responsible for a frame of reference, that is, firing due to a learned stimulus. The firing of these particular sensory neurons in the brain may lead to activation of the premotor area, where the brain reconciles all the information it has received and begins to develop a motor plan (Soechting & Flanders, 1995).

Premotor Areas

The motor cortex consists of the primary motor cortex (M1) and six premotor areas. All six premotor areas have direct connections with M1. The premotor areas are organized somatotopically – that is, certain regions of each area correspond to specific body parts. These regions can overlap and are different from one another in how they contribute to movement (Dum & Strick, 2005).

One premotor area that is particularly important is the Supplementary Motor Area (SMA). This region is located in Brodmann's area 6 on the medial wall of the cerebral hemisphere. One special feature of the SMA that is not shared by all premotor areas is that it not only projects directly to M1, but also has projections to the cervical spinal cord. As a result, the SMA can directly influence a movement without passing through the rest of the motor pathway (Dum & Strick, 2005). The SMA is also different in that it has an extra connection that the other

premotor areas do not to the pre-SMA. The pre-SMA, located between the prefrontal cortex and the premotor areas in the frontal lobe, is responsible for motor learning (Jeannerod, 2005).

Premotor areas located within the cingulate sulcus of the frontal lobe near the SMA include the rostral cingulate motor area (CMAr), the dorsal cingulate motor area (CMAd) and the ventral cingulate motor area (CMAv) (Dum & Strick, 2005). The ventral premotor area (PMv) and the dorsal premotor area (PMd) are located just anterior to the motor cortex in the frontal lobe and may play a role in force generation and lifting (Chouinard & Paus, 2006). Like the SMA, these areas receive input from other areas of the brain, particularly from the prefrontal cortex and other pre-premotor cortical areas. The PMv, the CMAr and the CMAv receive input directly from the dorsolateral prefrontal cortex. These connections are limited and have been shown to be active when motor movement is part of some other cognitive or executive function being carried out by an individual. The CMA areas also receive input from the limbic cortex and subcortical areas such as the basal ganglia, the cerebellum, the thalamus and the globus pallidus. The premotor areas and M1, however, also provide input to the basal ganglia and other subcortical areas, creating neuronal loops within the brain. The motor cortex also receives input from the somatosensory corticies that are receiving information from the periphery, helping to plan a movement (Dum & Strick, 2005).

Primary Motor Cortex

The primary motor cortex (M1) is where information from other parts of the brain (relayed through the premotor areas) is consolidated and the electrical signals that will ultimately travel down the spinal cord via upper motor neurons of the pyramidal tract are generated. The threshold for electrical stimulation in this area of the brain is much lower than that of other motor areas. M1 is located within cortical layers I-VI and the assembly of information that occurs here

allows for complex motor movement to occur and may also play a role in stabilizing that movement (Dum & Strick, 2005).

A special aspect of the motor cortex is in how it is organized. The areas of the motor cortex are organized somatotopically; that is, each area codes for a specific area of the body or limb (Penfield & Boldrey, 1937). It has been found, however, that this organization is relatively plastic and can change if a limb is amputated and the area responsible for that missing limb is no longer needed. Interestingly, if a myoelectric prosthetic is used in place of the limb, then the somatotopic area is conserved and can be reorganized to include that limb again (Jeannerod, 2005). This organization has been termed the homunculus, and was generated by Penfield in 1928 in a series of surgeries. These experiments led to the conclusion that the generation of movement for a certain body area is localized to a specific brain area and that the generation of movement as a whole, while influenced by many brain areas, is primarily located in the motor cortex (Penfield & Boldrey, 1937).

Control Theories

Theories regarding the motor control cascade in the brain differ in exactly what occurs in each area involved, but all theories generally point to the same parts of the brain being involved in the generation of the action potential in the efferent motor neuron that will eventually trigger movement in the body. One such theory is the Neural Optimal Control Hierarchy, or NOCH theory. This theory describes how control is integrated in M1 as a product of inputs from other brain areas. It identifies the brain areas involved in a certain movement and suggests that these inputs come in parallel as opposed to in a linear fashion, through one brain area and then the next. The function of the brain in this particular theory was illustrated using patients with lesions in different brain areas and observations of what aspect of their motor control was affected. One

group of people studied had Huntington's disease, a disorder in which the individual can no longer control their bodily movement. Another group had cerebellar dysfunction and were not able to correct motor errors in the way most people can. These observations are consolidated into the NOCH theory (DeWolf & Eliasmith, 2011).

According to this theory, movement is initiated in the premotor cortex and the supplementary motor area, both located in the frontal lobe of the brain. It is here that sensory and visual stimuli are received and reconciled into a clear picture of the target or stimulus. Motor learning and the psychological perception of motor control are also housed in the frontal lobe (DeWolf & Eliasmith, 2011). People with anosognosia believe they are aware of their motor movements when in fact they are not. They suffer from spatial neglect as well, and are not able to successfully execute motor movements due to lesions in the primary motor area. This leads to the conclusion that this area is also responsible for monitoring motor movement (Berti, 2005). The premotor cortex and supplementary motor area are at the top of the motor control hierarchy and have a great deal of influence as to what kind of motor movement occurs in response to the sensory stimuli received.

The basal ganglia is another area of the brain that is highly involved in motor movement (DeWolf & Eliasmith, 2011). The basal ganglia interacts with the primary motor cortex as a result of the basal ganglia's association to dopamine-producing cells in the substantia nigra. Neurons involved in this circuitry can be dopaminergic or GABAergic with the neurotransmitter release involved determining the effect that particular neuron has on the primary motor cortex, either excitiaory or inhibitory (Luft, 2009). The basal ganglia has been describes as a "winner take all" part of the motor circuit, as it receives both excitatory and inhibitory input and has an important influence on whether or not a movement occurs (DeWolf & Eliasmith, 2011).

At the same level as the basal ganglia on the hierarchy, the cerebellum helps to generate rhythmic movement as well as correct errors in movements that are in progress. It receives input from the premotor area and receives a copy of the motor plan. "Awareness" of the movement that is supposed to occur helps the cerebellum to correct motor errors. It also receives input from the body and can send information out to the body via medial spinal tracts (DeWolf & Eliasmith, 2011).

The primary motor cortex receives information from the premotor cortex and supplementary motor area about the movement that is to occur. Neurons in this area of the brain project out to the brain stem and spinal cord (DeWolf & Eliasmith, 2011). The purpose of having many different inputs into M1 may have to do with how quickly movements have to occur. It is thought that multiple areas contributing to the movement may decrease the response time and increase the flexibility of the response, as the plan may have to change as the movement is occurring (Dum & Strick, 2005). M1 is primarily responsible for coding all the signals it receives from peripheral parts of the brain. In Brodmann area 4 of the motor cortex, the neurons are "directionally tuned," meaning that neurons oriented at an angle closer to the direction of the movement fire and have a larger influence over the movement than neurons less associated with that direction. Neurons in this area do not only code for direction, as there are many other factors that influence movement. Certain neurons are associated with certain muscles and the generation of force in those muscles, as any motor movement requires a cooperative effort from any number of muscles and muscle groups. The amount of force needed to be produced is also coded for in this region, along with the ultimate position, velocity and acceleration of the limb. It has been found that the motor cortex is mostly responsible for the spatial aspects of movement that are most important to its overall execution (Ashe, 2005). The motor cortex ultimately codes

for what needs to happen in a requested movement and when that movement needs to occur. All the aforementioned brain areas (primary motor cortex, somatosensory areas, and premotor areas) play a role in preparation for a movement. An individual can also draw on memory to help decide how to execute a given task. This input to the different brain areas allows the reaction time to that stimulus and the timing of the movement to occur more quickly than if the task was new and the individual had no specific memory to draw from (Riehle, 2005).

Descending Pathways

The Pyramidal Tract

The M1 gives rise to the pyramidal tract neurons that carry the electrical signals generated down the spinal cord and will synapse with spinal neurons. Pyramidal tract dendrites spread out in cortical layers V and VI and receive input from many cortical neurons. A pyramidal tract neuron can be classified as such if it is activated by cerebral peduncles, medullary pyramids or both. Pyramidal tract neurons (PTNs) can also be further classified as fast or slow, with fast PTNs eliciting excitatory responses and slow PTNs eliciting inhibitory responses (Ghosh et al, 1988). These pyramidal neurons synapse with spinal neurons that will ultimately carry nerve impulses out to the peripheral motor neuron.

The pyramidal tract plays an important role in the conduction of signals from the motor cortex in the brain to the spinal neurons. It has been suggested that this pathway would not exist if it was not advantageous and that this connection plays an important role in motor coordination. If the pyramidal tract is sectioned in an animal, the animal presents with severe motor deficit. While there are other extrapyramidal pathways involved in the control of movement, these pathways have less of an influence over the movement produced. Data shows that monosynaptic connections between the pyramidal neurons and spinal neurons are important for dexterous

movement (Shapovalov, 1973). There are many advantages associated with this monosynaptic connection, with the first being that this connection is direct, and this direct connection allows for fine motor control to occur. This allows information processing that occurred at the cerebral level to remain intact whilst travelling through the spinal cord (Shapovalov, 1973).

The Spinal Cord

Spinal neurons travel from the brain stem down the spinal cord to a central synapse in the grey matter of the spinal cord. The central synpase allows the descending spinal neurons to communicate with the peripheral (alpha) motoneurons that will actually travel through the ventral horn of the spinal cord out to the muscle (Fyffe, 2001; Bailey, 2013). The white matter of the spinal cord contains both the ascending (sensory) and descending (motor) axons. The grey matter contains the cell bodies of spinal interneurons and motoneurons (Bailey, 2013).

The neurotransmitters released at this junction can either be excitatory or inhibitory. There are several types of neurotransmitters released into the synapse between spinal and alpha motoneurons. Two types of inhibitory neurotransmitters, GABA and glycine, are released from F-type terminal boutons (Fyffe, 2001). The purpose of releasing an inhibitory neurotransmitter at this synapse is to create an inhibitory post-synaptic potential, and make it less likely that the peripheral motor neuron is going to fire its own action potential. Excitatory neurotransmitters are released by upper motor neurons at this synapse in order to allow propagation of the action potential down the peripheral motoneurons to the muscle. The primary neurotransmitter involved at this level is glutamate, although recent studies suggest that acetylcholine can be coreleased at this site (Fyffe, 2001; Nishimaru, Restrepo, Ryge, Yanagawa & Klein, 2005).

Excitation of spinal neurons at the cervicomedullary junction ultimately leads to movement of primarily the arms, but can also produce movement in the leg. Leg movements can

also be elicited via stimulation of the cervical or thoracic spine. Large electrical stimulation of the cervicomedullary junction often produces leg movements (Taylor & Gandevia, 2004).

It has been suggested that the spinal cord itself does not play a large role in the shaping of the final motor movement, and is more of a conduction pathway. However, the spinal cord can generate its own movements via reflex loops. For example, postural issues such as stance and gait are thought to be largely controlled more by spinal reflexes than by descending input (Pierrot-Deseilligny & Burke, 2012).

Peripheral Pathways

Interneurons and Reflex Loops

A reflex loop consists of an alpha motoneuron, a gamma motoneuron and sometimes interneurons located in the spinal cord grey matter. The muscle contains sensors, such as muscle spindles, that are associated with their own afferents that travel back to the spinal cord. The IA afferent that originates in the muscle spindle is termed a gamma motoneuron. This particular neuron fires when the muscle is stretched. The impulse from this neuron never reaches the brain, as it synapses in the spinal cord directly with the alpha motoneuron. This causes the muscle to contract, reducing stretch and "resetting" the muscle spindle as the muscle is no longer overstretched. A similar mechanism is in use with the IB afferent travelling from the Golgi tendon organ to the spinal cord. This sensor detects the amount of force produced, and this signal is transmitted by the stretch of the tendon connecting the muscle to the bone. An impulse from this organ travels along its afferent then through an interneuron, where it ultimately inhibits the alpha motoneuron reducing muscle contraction. This is protective because it helps to regulate force production in the muscle (Bailey, 2013).

The Action Potential

Action potentials are electrical impulses that are carried by excitable cells. Neurons are specialized cells that are intrinsically charged – an ion gradient established by sodium and potassium causes the cell to be more negative on the intracellular side relative to the extracellular side (Hodgkin, Huxley & Katz, 1952). When depolarization occurs an action potential travels down the axon of the neuron in the form of an electrical signal, carried by sodium and potassium ions (Hodgkin & Huxley, 1952).

The established ion gradient is dependent on both sodium and potassium ions. Due to the high permeability and intracellular concentration of potassium ions, the resting membrane potential of the nerve cell is about -70 mV relative to the outside of the cell. This is close to the equilibrium potential for potassium ions. When the axon potential begins at the axon hillock, the nerve cell suddenly becomes more permeable to sodium ions, allowing the initial depolarization to occur (Hodgkin et al., 1952). If the neuron becomes permeable enough to sodium to depolarize the cell about 15 mV above its resting potential, voltage-gated sodium channels at the axon hillock open and more sodium is allowed into the cell, depolarizing the cell to a voltage of about +40 mV. At this point, the sodium channels inactivate. The cell becomes more permeable to potassium ions as a result of the depolarization (Stanescu, 2011). The outflow of these potassium ions allows the cell to repolarize back towards the resting membrane potential (Hodgkin et al., 1952). This actually causes the nerve cell to overshoot the resting membrane potential by about 20 mV, essentially hyperpolarizing the cell. Closure of outwardly-rectifying potassium channels in the membrane eventually brings the cell back to resting potential. This hyperpolarization is useful to keep the action potential travelling in one direction down the axon and also sets a maximum rate of discharge for that neuron (Stanescu, 2011).

The Muscle

The Neuromuscular Junction

The alpha motoneuron travels from the grey matter, through the ventral horn of the spinal cord, through the periphery. It then synapses with multiple muscle cells. A motoneuron and all the muscle fibers it innervates is termed a motor unit. Impulses along this particular neuron only affect those innervated muscle fibers (Powers & Howley, 2004).

The synapse of the motoneuron with the muscle cell is called the neuromusclular junction. Here, the electrical signal generated by the brain for movement is converted to a chemical signal with the release of acetylcholine from vesicles in the terminal bouton of the pre-synaptic neuron. Impulses travelling to the neuromuscular junction (NMJ) along this motor neuron are always excitatory, unlike other body systems. When the action potential arrives at the terminal bouton, voltage-gated calcium channels open, allowing an influx of calcium ions. This influx of calcium is ultimately what allows the acetylcholine-filled vesicles to bind to the terminal membrane and empty out into the synapse. Acetylcholine then diffuses across the synapse and binds to an acetylcholine receptor on the muscle cell membrane (Arrowsmith, 2007). The post-synaptic acetylcholine receptor, once occupied, opens a non-specific cation channel and allows ions to flow across the membrane. This causes a depolarization of the muscle cell that triggers the opening of voltage-gated sodium channels (Arrowsmith, 2007).

Muscle Anatomy

Skeletal muscle is innverated and controlled by lower (alpha) motoneurons. The muscle itself is covered by a layer called the epimysium. This connective tissue membrane covers bundles of muscle fasicles. The fasicles are covered by their own protective layer called the perimysium. Each muscle fascile is made up of several muscle fibers. Each muscle cell is

covered by a layer of connective tissue termed the endomysium. An individual muscle fiber is considered to be a muscle cell, and each cell is innervated by exactly one motoneuron. Each cell also has multiple nuclei, and are comprised of many sarcomeres (Tortora & Derrickson, 2011). The filaments of the sarcomere are what perform the actual contraction of the muscle.

Fiber Types

In humans, there are three different types of muscle fibers – Type I, Type IIa and Type IIx. These fibers can be classified either due to their oxidative capacity or their twitch speed. Type I fibers are classified as slow oxidative fibers. These fibers are capable of performing sustained contraction due to their high aerobic capacity. Type IIa and IIx fibers are both classified as fast twitch fibers. Due to their innate energy production pathways, however, type IIa fibers are less fatigueable than type IIx fibers because they have more oxidative enzymes and are capable of performing both glycolysis and oxidative phosphorylation as a means to produce ATP. Type IIx fibers primarily perform glycolysis as a means of ATP production, and thus fatigue much faster than the other two types of fibers (Powers & Howley, 2004).

Spread of an Action Potential

As mentioned before, acetylcholine released from the terminal boutons of a lower motor neuron at the neuromusclular junction binds to acetylcholine receptors on the muscle cell membrane. This opens a non-specific cation channel. As positively charged ions begin to flow into the muscle cell, an end-plate potential is generated. If this potential sufficiently depolarizes the muscle cell membrane, also called the sarcolemma, then voltage-gated sodium channels adjacent to the neuromuscular junction are activated and open. The opening of these channels allows the membrane to be more permeable to sodium ions. As with the neuron, the concentration of sodium ions is much higher outside the muscle cell than on the intracellular side

when the muscle cell is electrically "at rest." The membrane change in permeability to sodium ions allows the muscle cell to depolarize. This depolarization spreads rapidly along the sarcolemma. The design of the muscle cell includes invaginations of the sarcolemma deep into the muscle cell called transverse tubules (t-tubules). Those allow the electrical signal to travel directly to structures in the muscle cell that help to convert this electrical signal to a chemical signal inside the cell (Hopkins, 2006).

The arrival of the action potential at the t-tubule causes a change in the conformation of a membrane protein connected to the sarcoplasmic reticulum (SR) inside the muscle cell. The SR is the major intracellular store of calcium ions; the ions are bound to calsequestrin in the SR lumen. The change in the shape of this membrane protein allows the calcium channel in the sarcoplasmic reticulum to open and calcium to flow out of the SR, down its concentration gradient into the cytoplasm of the cell. Calcium can then bind to the troponin-C molecule on the actin filament and exposes a binding site that allows contraction to occur (Hopkins, 2006).

Mechanism of Contraction

The sarcomere is the contractile unit in the muscle cell. The sarcomere consists of overlapping thick (myosin) and thin (actin) filaments bounded by a Z-disk on both sides and the M-line in the middle. A sarcomere is not one-dimensional in space as it is often drawn; the thick filament is surrounded by many thin filaments, all of which can bind the myosin head when contraction is occurring. This arrangement is hexagonal in shape (Zachar, 1971).

The model used to describe the mechanism of muscle contraction is called the sliding filament model. This model proposes that the sarcomere shortens and lengthens via interactions between actin and myosin filaments. It is known that this occurs via a process termed cross-bridge cycling. First described in 1955 by Hodgkin and Huxley, the cycle beings with the

myosin head cocked back. The myosin head is then able to bind with the myosin binding site on the actin filament, which was previously covered by a protein called tropomyosin. The calcium released from the sarcoplasmic reticulum during the spread of the muscle action potential binds to the tropomyosin and changes its conformation, allowing this binding site on the actin to be exposed. The power stroke phase then occurs. During this phase, the cocked-back myosin head moves, pulling the actin filament towards the M-line. The ADP bound to the myosin head during this stage then needs to be re-phosphorylated in order for the myosin head to disengage from the actin and re-cock, ready for the next cycle. As it is described, energy is necessary for each cross-bridge cycle to occur (Zachar, 1971).

Pathophysiology

Traumatic Brain Injury

Traumatic brain injury occurs when a person suffers a blow to the head or any sort of movement that would cause the brain to hit the skull. This type of injury is complex – any number of primary and secondary insults can occur and no two cases are the same. Primary injuries include contusion of the brain, diffuse axonal injury due to sudden acceleration, deceleration or rotation of the head, and any number of hemorrhages (Dombovy 2011; Caeyenberghs, Leemans, Geurts, Vander Linden, Smits-Engelsman, Sunaert & Swinnen, 2011). Injuries that can occur secondarily during the recovery phase include but are not limited to cerebral infarction (stroke), hydrocephalus, hypoxia-ischemia and infection. The part of the brain where the injury occurs most often determines the deficits a person will suffer (Dombovy, 2011). In the case of motor control, these injuries produce the largest deficits in movement when they involve area 4 of the brain where M1 is located and consequently where some of the descending projections to the spinal cord begin (Lotze, Grod, Rodden, Gut, Schonle, Kardatzki

& Cohen, 2006). If the injury includes damage to the motor cortex, akineasia may occur. The person is unable to plan or initiate a movement. If the injury is ischemic in nature, it can affect other structures in the brain associated with motor control, such as the basal ganglia. These injuries usually lead to Parkinsonian symptoms and ataxia, or trouble coordinating movements (Dombovy, 2011). It has been suggested that the overall metabolic processes occurring in the brain change with TBI. Sometimes some recovery of function is possible due to the plasticity of the brain, however injuries that occur to the descending motor pathways and corticospinal tract have shown to be the hardest to recover from (Lotze et al., 2006).

Caeyenberghs et al. (2011) found that diffuse axonal injury is the primary mechanism of injury in TBI leading to motor impairment. This occurs due to the shearing forces the brain experiences as a result of a sudden movement or impact. It is hard to see exactly what has been damaged with an MRI scan. It has been proposed that white matter damage is correlated with motor impairment after TBI. A new imaging technique, called diffusion tensor imaging, can be used to look at water molecule diffusion in white matter bundles, with the rates and direction of diffusion being characteristically different in healthy and damaged white matter. Caeyenberghs et al. (2011) also found that diffusion is increased in damaged white matter and that when imaged, much of the diffuse axonal injury was actually to the corpus callosum. This is important because the corpus callosum plays a role in interhemispheric communication and how fast a signal is processed by the rest of the brain. As has been shown, many parts of the brain are responsible for motor control so injury to any part of the brain may affect it. Also, diffuse axonal injury to the corticospinal tract is correlated with poor balance. This particular study was only correlational but provides a new way to think about TBI and how to treat individuals suffering from various insults.

Spinal Cord Injury

Spinal cord injuries (SCIs) are most often caused by motor vehicle accidents, falls, and penetrating wounds. Most of the symptoms associated with spinal cord injury occur due to the loss of vasculature to the spinal cord, which can result in neuronal death or cord compression due to injury and inflammation. In most cases, symptoms include muscle paralysis. The degree of paralysis depends on where in the spinal cord the insult occurred. When an injury to the spinal cord occurs, accessory neuronal cells such as microglia become phagocytotic in nature, removing dead and damaged tissue. In the case of SCI, this can actually cause the spinal cord neurons to further degenerate and worsen the injury. In some cases, however, some functionality can be regained, depending on the extent and location of the injury (LiVecchi, 2011). Some reflexes are maintained due to the nature of the reflex loop and can be regained below the level of the injury (Yezierski & Vierck, 2010).

Previously discussed GABA release in the spinal cord has been shown to be associated with central neuropathic pain in the spinal cord following SCI. This could be due to the changes that occur in the spinal cord secondarily to an injury, such as the upregulation of glutamate receptors and proinflammatory cytokine release. This ultimately causes neuronal hyperexcitability and a greater pain response with a lower threshold for the onset of that response. GABA release should inhibit the transmission of pain signals back to the brain, but these neurons may become hypofunctional as a result of the remodeling that takes place after SCI. This could also contribute to the increased amount of central neuropathic pain experienced by people who have suffered an SCI (Gwak & Hulsebosch, 2011).

Movement Disorders

Multiple Sclerosis

Multiple Sclerosis (MS) is a disease characterized by progressive demyelination of the nervous system. Symptoms of this disease include recurrent pain, facial drooping, paralysis, as well as bladder, bowel and vision problems. This ultimately leads to decreased conduction of the action potential along the axon as well as slower speed of action potential propagation. The age of onset for this disease is between 20 and 40, and more often affects women. People of European descent have a higher risk of developing the disease. It has been suggested that living in a temperate climate is a risk factor for developing MS, and exposure to a virus similar in shape to the myelin protein may induce the onset of the disease. It is not a genetic disease but may cluster in families due to risk factor exposure. It has also been suggested that the primary pathology of this disease involves first the destruction of myelin producing cells, and then progressive stripping of myelin and plaque formation in the CNS (Blumenthal, 2006).

Motor symptoms of this disease include disrupted gait and spasms in body parts such as the legs and face. One of the most commonly described motor symptoms of this disease is tremor. Tremor occurs due to demyelination occurring in the cerebellum, whereas facial spasm may have to do with lesions in the ipsilateral facial nucleus. Interestingly, if and when the disease is in remission, these symptoms disappear despite demyelination and lesions being permanent. However, some motor symptoms, such as restless leg syndrome, occur due to the inflammation that occurs as a result of demyelination (Mehanna & Jankovic, 2013). Treatments for MS include drugs that suppress the immune system, such as interferon (Blumenthal, 2006). People with MS do not usually die from the disease but become progressively more physically and neurologically disabled as it progresses (Sandroff, Sosnoff & Moti, 2013).

Amyotrophic Lateral Sclerosis

Amyotrophic lateral sclerosis (ALS), also called Lou Gehrig's disease, is a degenerative disease that destroys upper and lower motor neurons as well as cells located in the ventral horn of the spinal cord. This results in muscle degeneration whilst the person's cognition remains intact. This disease affects more men than women and usually onsets between the ages of 55 and 75. This disease is fatal – death often occurs within five years of the onset. The leading cause of death in ALS patients is usually asphyxiation due to diaphragm dysfunction and degeneration. Early symptoms include an inability to swallow and disturbed speech. As the disease progresses, a process called gliosis occurs where the motor neurons are replaced by fibrous astrocytes. This causes the spinal cord to harden, giving the disease its name of "lateral sclerosis." The cause of this disease is unknown but familial and geographic clusters do occur, suggesting that neurotoxic agents may play a role in the acquisition of the disease (Walling, 1999).

There is no cure for ALS, but a lot of research is being done to find pharmacologic agents that can slow the progression of the disease. One promising drug is called Riluzole and affects glutamate release in neurons. The drug does this by blocking sodium channels in the axon of the neuron. Glutamate is thought to accumulate in the synapses of motor neurons in people with ALS and cause those cells to die – this is due to the inability of the neurons to re-uptake glutamate, resulting in glutamate toxicity. If the neurons are not releasing glutamate, perhaps the destruction of the neurons can be attenuated (Bensimon, Lacomblez & Meninger, 1994).

Parkinson's Disease

Parkinson's disease (PD) is a disorder characterized by tremors, slowness of movement, muscle rigidity and a loss of balance due to the death of dopamine-producing cells in the substantia nigra in the brain. This disease most commonly affects person over the age of 60,

with a few cases onsetting before the age of 40. It is not known why the cells in the substantia nigra die, only that that genetic factors and environmental exposure may play a role (Standaert, 2002).

Dopamine produced in the substantia nigra usually excites the striatum. This upregulation of activity in the striatum allows excitation of the motor cortex, allowing movement. In Parkinson's disease, the dopamine that usually excites the striatum is no longer present. This ultimately downregulates activity of the striatum and, in turn, downregulates activity in the motor cortex. Without excitatory input to the cortex, movement cannot occur. This explains some of the symptoms like slowness, rigidity and loss of balance (Gilbert, 2010). A recent fMRI study showed that people with Parkinson's disease may have trouble formulating and carrying out a motor plan due to hypoactivation of the motor cortex. This occurs due to the malfunction of the cascade of actions that should take place in the deeper brain structures (Cameron, Pari, Alahyane, Brien, Coe, Stroman & Munoz, 2012).

Parkinson's disease is treated in a number of ways. The most common treatment is Levadopa, a precursor to dopamine that can cross the blood-brain barrier and can be converted to dopamine in the brain. This can relieve the tremor associated with PD in the early stages of the disease. This drug does have side effects though, such as dyskineasias (spasms and other involuntary movements). Another increasingly common treatment is the implantation of electrodes in the subthalamic nucleus. These electrodes are connected to a battery pack and switch implanted in the chest area. This stimulation has been shown to reduce rigidity and slowness of gait when the device is turned on. However, when the device is turned off, the person's disability returns. The stimulation of the subthalamic nucleus in turn inhibits the globus pallidus that then inhibits the thalamus and allows for excitation of the motor cortex, "righting"

the circuit and allowing an increase in activity in the motor cortex (Limousin, Krack, Pollack, Benazzouz, Ardouin, Hoffman & Benabid, 1998; Gilbert, 2010).

Huntington's Disease

Huntington's disease (HD; also called Huntington's Chorea) is a disorder characterized by hyperkineasia. These movements are complicated, aimless and cannot be controlled by the affected person. This is an autosomnal dominant disorder, meaning that if a person has above 40 CAG repeats in the huntingtin protein-coding gene on the short arm of one copy of chromosome 4, then they will have the disease (Gilbert 2010). This occurs even if the gene on other chromosome is completely normal (Coneally, 1984; Macdonald & Halliday, 2002). The age of onset is usually between 30 and 45, but can onset earlier or later (Coneally, 1984). This has been shown to correlate with the number of repeats a person has – the more repeats there are, the more likely the onset will begin earlier in life (Gilbert, 2010).

These symptoms are a result of degeneration of the subcortical basal ganglia circuitry due to the abnormal huntingtin protein accumulating in the area (Macdonald & Halliday, 2002). The destruction of the striatum and the globus pallidus of the basal ganglia ultimately removes inhibition to the cortex that usually occurs, regulating movement (Gilbert, 2010). Without this inhibition to the cortex, jerking and spastic movements occur without the person being able to control them. Another consequence of Huntington's disease is the loss of pyramidal cells in the corticospinal tract. The destruction of the involved brain structures affects the pyramidal cells, which degenerate as a result. It has also been shown that over time the primary motor cortex begins to degenerate as well. This process seems counterintuitive because M1 is being used, but perhaps the brain no longer uses areas specifically for fine motor control since that is lost with the onset of Huntington's disease (Macdonald & Halliday, 2002).

Huntington's disease is not fatal. Death most commonly occurs in HD patients as a result of pneumonia brought on by the chorea (Conneally, 1984). There is no cure for the disease but certain medications, such as benzodiazepines, SSRIs and other antipsychotics, have been shown to reduce the motor symptoms (Gilbert, 2010). Antipsychotic drugs block dopamine receptors, and dopamine is one of the neurotransmitters involved in this disease. It has also been suggested that certain neuroprotective agents can slow the progression of the disease. One of these is the supplement creatine. It is thought that this supplement will slow cell death in the striatum, although no clinical trials have been conducted. Other drugs used to treat the symptoms, such as SSRIs, are thought to be neuroprotective in that they stimulate production of a brain-derived neurotrophic factor and downregulate ion channels, decreasing conductance (Frank & Jankovic, 2010).

History

Throughout human history, humans have always been curious as to how the brain functions. Ancient Egyptians removed the human brain before mummifying a person because they did not think it was necessary for the person to have it in the afterlife. This was because they did not know the purpose of the brain. Hippocrates purported that the brain had something to do with movement as far back as the 5th century B.C.E. (Gross, 2007). The conception of the brain's purpose and the ways in which it has been studied have changed over time. The more that was known, the more the experimental methods that were used changed, resulting in the wealth of knowledge that exists today about the brain and its role in motor control.

One of the first people to stimulate the brain with electricity was a man called Hitzig. In 1870, he used an electrode to stimulate the occipital region of the brain of a man, which in known now to be important for visual processing. He noted that, upon receiving stimulation to

the brain, the man's eyes moved. This caused him to perform a series of animal experiments on dogs in which he stimulated their cortex and recorded that these stimulations produced muscle spasms (Gross, 2007).

Roberts Bartholow was a surgeon in 1890 who had figured out that electricity had an effect on the brain. He had the opportunity to test the effect of electrical stimulation on a human subject when a female patient called Mary Rafferty came to him with an infection in an open sore caused by the whale bone in her wig (Penfield & Boldrey, 1937). Once he had cleared the infection from the area, he could see that the brain was exposed (this woman had "fallen into the fire, burning her scalp so badly that 'hair was never reproduced… When she presented herself for relief, this had eroded the skull over a space 2 in. in diameter" (Bartholow, 1874). One of his first observations was that the brain, when touched, did not elicit any response from the patient, that is, it did not have the capability to convey any sensation. Dr. Bartholow used needles connected to an electrode on an induction machine, which was a primitive electricity-producing machine. He observed that when he touched the needles to the dura mater on the left side of the head, a small amount of current elicited movements of the arm and the leg on the right side. Interested by this observation, Dr. Bartholow turned up the current and noted that Mary was in a great deal of pain and exhibited signs of distress. She became unconscious and experienced pain in her extremities when conscious. Mary died as a result of these experiments three days later (Harris & Almerigi, 2009).

After Dr. Bartholow, a number of other people replicated his results in humans. Another important discovery to be made was the location of the motor and somatosensory areas. This was accomplished by Dr. Wilder Penfield in a series of 163 operations starting in 1928. These operations were carried out under anesthesia, unlike those that came before. Dr. Penfield noted

the exact response he got from stimulating a certain brain area on a series of charts. Dr. Penfield mapped out the exact body representation areas in the primary motor cortex using these charts. This "map" is known as the homunculus – it shows gross overrepresentation of the hands, face and tongue (Penfield & Boldrey, 1937). The mapping of the homunculus was important as this model of motor representation is still used today.

In the 1950's, experiments were conducted to determine the function of the neuron. The first people to do this were Hodgkin, Huxley and Katz in 1952. They used the giant axon of a squid, primarily for its large size. Using electrodes and a voltmeter, they measured the voltage across the cell membrane. This led to later experiments to determine that current was carried by sodium and potassium ions and the voltage maintained by a number of established ion gradients (Hodgkin et al., 1952). This model of experimentation was new in that it was done ex-vivo. This is a more popular way of performing experiments now as individual cells are much easier to work with than whole animals and can tell us what is going on at the cellular level and how that affects the system as a whole.

Recently it has been determined that both the brain and spinal cord can be stimulated by magnets without having to insert electrodes into either organ. In 1980, Merton and Morton came up with a way to stimulate the cortex by passing high-voltage electricity through the skull. They were able to stimulate the cortex and produce descending volleys with this technique. Another technique, developed in 1985 by the same team, used "rapidly-changing magnetic fields" that also stimulated the cortex through the skull (Taylor & Gandevia, 2004). Magnetic stimulation at the cervicomedullary junction can also be used to stimulate only the spinal cord, and can be used to study whether a certain response is cortical or spinal in origin. This technique was developed

and tested in 2004 and was only mildy painful to the patient receiving the stimulation (Taylor & Gandevia, 2004).

Over the last two centuries, the way scientists think about and study the brain, spinal cord and peripheral motor control pathways has changed drastically. From animal studies and experiments without anesthesia to non-invasive stimulation methods used in the present day, progress has been made in designing and implementing experimental technique in ethical ways since the mid 1800's. Scientists discovered much of what is known from the older experiments, which would not have been carried out now due to ethical concerns. As time has passed, new methods to study the brain have been developed. Ex-vivo experiments can now be done to model just about anything. That is not to say everything there is to know has already been discovered – much is left to learn. With the development of modern technology, more creative ways to study motor control systems in an ethical and humane fashion can be developed.

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