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The Physiology of Restless Legs Syndrome

Restless Legs Syndrome (RLS) is a common sleep disorder wherein the symptoms range from annoying to insufferable. I was diagnosed with RLS at the age of 19 after spending most of my second semester at American University completely sleep deprived. My mother was diagnosed with disorder over 14 years ago and her father had it, as well. My maternal grandfather also had narcolepsy but a connection was never definitively established as to whether being sleep-deprived due to RLS caused his extreme daytime sleepiness. As I progressed in my major, I became increasingly interested in abnormal physiology, especially neurophysiology. I was astounded at the millions of tiny processes the human body completes every minute and how the smallest of changes can cause complete dysfunction of a system. When it came time to choose a topic for my Capstone, I knew I wanted to work on something relevant to my life and almost immediately came to the decision to research the physiology of RLS.

Clinical Background

RLS is defined as a sensorimotor disorder in which the primary symptom is a severe, compelling, almost uncontrollable urge to move the legs. The sensations can occur in either leg or both and varies greatly in severity. It is also possible for these sensations to move to other body parts, most commonly the arms and hands (Benes et al., 2007).

The “urge” most patients describe is an increase in the compulsion to move, and not moving or not being able to move the legs results in feelings that range from unpleasant to absolutely unbearable. However, for these urges to be characterized as those common to RLS, they must be engendered or worsened by rest, relieved if movement occurs, and worsen at night or with the individual’s circadian rhythm of night. Suppression of these urges can cause jerking in the limbs of many of those with RLS. This can cause many individuals to avoid social situations where their RLS would be obvious such as going to the movies or sitting through a long car ride. Many patients describe having issues falling asleep which leads to a decrease in the total amount of sleep, deep sleep, and REM sleep patients experience. This lack of sleep is most likely what contributes to the cognitive issues some RLS patients report (Benes et al., 2007).

Most patients experience sleep issues (as described above) as well as daytime fatigue, depression, and/or anxiety and cognitive issues. Patients with RLS have an unusually high occurrence of depression or anxiety. Most people with RLS also have Period Leg Movements of Sleep (PLMS). PLMS is the jerking of the legs while sleeping and can cause the person to awaken (Benes et al., 2007).

RLS is usually self-reported but the patient must experience provocation by rest and worsening of their symptoms at night for a definitive diagnosis. Many patients have a family history of the disorder, which helps in diagnosis. A positive response to dopaminergic drug treatment for their symptoms also aids doctors in defining a patient’s condition as RLS. Onset of symptoms usually occurs in mid- to late-life but it can begin at any age (Benes et al., 2007).

Causes and Relations to Other Diseases

RLS is a chronic condition and comes in both a genetic and idiopathic form (Benes et al., 2005). It has been reported that, in 60% of all cases, there is family history of RLS. Twin studies have found that it is highly likely if one twin has RLS, the other twin does as well. Upon studying pedigrees, some researchers suggest that it is an autosomal-dominant condition (Ondo, 2005).

ADHD (attention deficit hyperactivity disorder) and ADD (attention deficit disorder) have commonly been linked with RLS, especially in children. Forty-four percent of patients with ADHD have RLS and 20% of RLS patients have some ADHD/ADD symptoms. This could be a clue that these disorders share common biological etiology (Benes et al., 2007). The exact link between these two disorders is uncertain and further research is required in order to discover this link (Cortese et al., 2005). Children presenting to their physicians with symptoms of RLS are often misdiagnosed with ADHD and ADD as the syndrome is not seen as frequently in children as are ADD or ADHD. Secondary RLS is the presentation of the disease due to another condition or illness a patient has, meaning that if the previous condition did not exist, the patient would not have the disorder. It is seen in those who are anemic, have end-stage renal disease, or are pregnant. There is preliminary research linking the female sex hormones to RLS but nothing specific has been found (Benes et al., 2007). As an aside, my mother's neurologist felt that, in addition to the genetic component, there had been findings that aging, particularly a drop in estrogen levels as women approach menopause, could have been the reason that her symptoms appeared in her mid-forties.

Mimics of RLS, or other conditions or disorders commonly misdiagnosed as RLS, include neuroleptic-induced akathisia, neuropathy, arthritis, and many more. Neuroleptic-induced akathisia most closely resembles RLS and is characterized by similar sensations to that of RLS but is caused by antipsychotics. However, it has no circadian pattern, insomnia does not occur, and movement does not relieve the sensations in the legs. Arthritis has symptoms similar to RLS in that there is cramping in the lower limbs but it is mostly confined to the joints. Also, there is no real circadian pattern, movement actually worsens the pain, and there is no response to dopaminergic drugs. (Benes et al., 2007).

Neurobiology/Overview of the CNS

As RLS is a sensorimotor disorder, the central nervous system (CNS) is incredibly important for understanding its physiology. The CNS is comprised of two major parts, the brain and spinal cord. The areas of the brain involved in the CNS are the cerebral hemispheres, diencephalon, and brainstem. The brainstem is, in turn, made up of the medulla, pons, cerebellum, and midbrain. The CNS is responsible for the analysis and integration of sensory and motor information. Basically, it interprets information received from the internal and external environments. It then sends signals to the rest of the body as to how to respond to that incoming information (Neuroscience, 2007).

The CNS is constantly receiving sensory information and initiating motor responses. The signals from both the external and internal environment are received by the sensory components of the peripheral nervous system. The information enters the body through sensory receptors, which are at the surface and within the body. These

signals are then sent to the sensory ganglia and nerves that transmit the signal to the CNS. The incoming signals are analyzed, at the level of either the spinal cord or the brain, and converted into outgoing signals, which are then sent to the motor components in the visceral and somatic motor systems. These motor outputs then result in muscle movement. Neuronal cell bodies and dendrites in the spinal cord are located in two regions; the dorsal horn (input) and the ventral horn (output) of the gray matter. Ascending sensory tracts (axons) located in the dorsal side of the spinal cord relay sensory signals to the brain. The ventral side of the spinal cord, in general, contains axons of descending fibers that synapse with motor neurons located in the ventral horn. Motor neurons provide output signals that travel to smooth, cardiac, and skeletal muscles (Neuroscience, 2007).

The signals in the CNS are mostly transmitted by neurotransmitter release across synaptic clefts. The neurotransmitter likely responsible for the aberrant signals that occur in RLS is dopamine (Civelli et al., 1993). Dopamine receptors are found in all areas of the brain but D3 receptors, which are believed to be involved in RLS, are located in the tubercule-Islands of Calleja, hypothalamus, striatum, and substantia nigra (Civelli et al., 1993).

Role of Dopamine

Dopamine is a precursor to epinephrine and norepinephrine. It is involved in cognition, sleep, motivation and reward, learning, attention, and, most importantly, motor activity. However, dopamine cannot cross the blood-brain barrier and, therefore, cannot be used clinically. As a result, precursors or dopamine-like drugs are used to

treat conditions where dopamine does not work correctly. Most of these drugs operate in one of two manners, either as agonists that activate dopamine receptors that are not being stimulated correctly in vivo due to degeneration of the cells that secrete dopamine or as antagonists, preventing dopamine from binding to its receptor (Civelli et al., 1993).

Dopamine receptors have similar overall structures despite their type and function. They contain membrane-spanning α-helices with the amino ends on the outside of the cell and the carboxyl ends inside the cell. These helices form a narrow hydrophobic cleft surrounded by three inner and three outer loops. The amino end is where the consensus sequence for glycosylation and dopamine binding is located. Dopamine receptors are divided into two main types, D1-like and D2-like. D1-like receptors include D1 and D5 receptors while D2-like include D2, D3, and D4 receptors. D1-like receptors interact with G_s proteins to activate adenyl cyclase and increase intracellular cAMP, while D2-like receptors couple to and activate various G_i protein complexes to inhibit cAMP production. It is the D2-like receptors that are important in RLS with D3 receptors specifically implicated in the physiology of this condition (Civelli et al., 1993).

There are three major dopaminergic pathways in the body. The nigrostriatal pathway is comprised of the neurons from the substantia nigra, which is located in the mesencephalon in the midbrain and is part of the basal ganglia. This pathway releases dopamine and sends it to the neurons of the striatum. The degeneration of this pathway is what is thought to cause Parkinson's disease. The mesocorticolimbic

pathway, which can also be broken down into two individual pathways, the mesolimbic and mesocortical pathways, is composed of neurons of the ventral tegmentum that connect with the limbic forebrain on the floor of the midbrain. This pathway is responsible for emotional stability and its dysfunction can cause schizophrenia. The tuberoinfundibular pathway includes neurons of the hypothalamus. Dopamine secreted by hypothalamic neurosecretory cells into the portal blood system travels to the pituitary where it regulates prolactin secretion. This pathway influences lactation and fertility (Civelli et al., 1993).

Proposed Physiology

However, none of these pathways are consistent with what occurs in RLS. Clemens et al. (1993) describe another dopaminergic pathway consistent with the RLS phenotype and is illustrated by their research with mice. In 1685, Thomas Willis suggested, when describing RLS, that the spinal cord was involved in the physiology. The physiology of RLS is still not completely understood but the pathway described by Clemens et al. may be the starting point (Clemens et al., 2006).

Clemens et al. describe the diencephalic dopamine cluster in the A11 nucleus of the dorsal-posterior hypothalamus and how the hypofunctioning of this cluster could be the cause of RLS. The A11 nucleus is involved in local hypothalamic connections, including projections to the neocortex and dorsal raphe, and is the sole source of dopamine to the spine. However, it contributes a very small amount of the total dopamine in the brain, which is most likely why no one has investigated it previously. These neurons are not involved in other pathways because their axons extend into the

spinal cord and not the pituitary, as the dopaminergic tuberoinfundibular pathway does. Descending inputs from the A11 nucleus are responsible for inhibition at serotonergic synapses in the dorsal horn of the spinal cord. These inputs are also the main source of spinal dopamine through the dorsolateral funiculus, or the white matter along the dorsal horn in the spinal cord. In normal conditions, the dopamine from the A11 nucleus inhibits the intermediolateral nucleus, regulating sympathetic drive. In RLS, dopamineric inputs from A11 are reduced. Without these presynaptic dopamine inputs, the dorsal horn now experiences a loss of inhibition, which may be the source of the aberrant signals to the muscles in RLS. This disinhibition of sensory inputs will cause an increase in the number of signals sent to the muscle efferents and to the muscles themselves. It also alters autonomic output and increases sympathetic drive, which increases heart rate, and, therefore, increases blood pressure (Clemens et al., 2006).

Because neurons in the A11 nucleus have very long and extensive axons, they are susceptible to damage. If these neurons are damaged, dopaminergic synapses in the spinal cord are at risk for dysfunction. RLS has resulted from spinal cord injury and spinal anesthesia, which could have damaged the A11 axons (idiopathic form). The damage can also be due to age or other pathological processes. There have also been numerous genes implicated in RLS so the exact cause of the damage or compromised cell function of the A11 axons is not yet known for those with the genetic form. It can create a chain reaction that causes the abnormal muscle sensations. Regardless of the specific cause, the compromised cell function may be degenerative which is why RLS symptoms are usually seen in the lower limbs first and then gradually in the upper

limbs. To better determine the role of A11 processes, Clemens et al. studied A11-lesioned rats and rats lacking a functional D3 receptor (D3KO) to determine the specific role of these dopaminergic inputs in RLS (Clemens et al., 2006).

Clemens et al. found that both A11-lesioned rats and D3KO mice were hyperactive and experienced increased wakefulness across the circadian cycle. The A11-lesioned rats also had a longer-lasting reduction in their sensory thresholds, all of which is similar to the RLS phenotype. Also, the D3KO mice experienced disinhibition of spinal reflexes and a decrease in the levels of the dopamine-synthesizing enzyme tyrosine-hydroxylase at night. These findings suggest that removal of the A11 nucleus or blocking D3 dopamine receptors impairs dopaminergic activity in the spinal cord which, in turn, causes abnormal signaling to the muscles (Clemens et al., 2006).

Clemens et al. (2006) also describe a positive feedback loop with four main steps as the circuit underlying RLS. Normally, the A11 nucleus releases dopamine which inhibits sympathetic preganglionic fibers in the intermediolateral nucleus (IML) in the dorsal horn of the spine. These are the dominant inputs to the IML. This dopamine input is in contrast to a serotonin input to the IML, which is very excitatory. If the A11 nucleus is compromised as it is in RLS, the dopamine is not released in the IML and the signals to the IML shift from inhibitory to excitatory. This creates an increase in sympathetic drive and explains why selective-serotonin reuptake inhibitors (SSRIs) exacerbate RLS symptoms as they cause even more serotonin to bind to receptors in the IML and continue transmitting excitatory signals (Clemens et al., 2006).

The increase in sympathetic drive leads to an increase in release of epinephrine and norepinephrine from the adrenal gland which then stimulates the irregular activation of higher threshold muscle afferents, causing the abnormal muscle sensations characteristic of RLS (Clemens et al., 2006).

In addition, there is disinhibition of lamina I in the cerebral cortex, which is a region that relays high-threshold deep afferent inputs to the brain. This disinhibition, resulting from the loss of dopaminergic control, causes increased outputs from lamina to the muscles . In order to block this transmission, non-pain-encoding muscle propioceptors are activated, inhibiting the high-threshold muscle afferent pathways by "gate-control" mechanisms. This activation, however, leads to muscle movement, hence, the restless legs (Clemens et al., 2006).

This entire circuitry is exacerbated by compromised modulation of higher order sensory processing in the prefrontal and frontal cortex due a compromised A11 nucleus. It is important to remember that there has been minimal research regarding this and this circuitry is only proposed. Clemens et al. have yet to test all four parts of the cycle in vitro but this is what they have proposed based on the results of the studies completed on the lesioned and knockout rats (Clemens et al., 2006).

In summary, a damaged A11 nucleus has multiple effects that can be separated into four interconnected steps (1) a loss of dopaminergic inhibition in the IML, causing (2) an increase in sympathetic drive, which leads to (3) increased aberrant signals in the muscles that can be blocked by (4) movement-activated propioceptors (Clemens et al., 2006).

Case Study/Personal Observation

My mother was diagnosed with RLS in the 1990s. She was given numerous prescriptions before her physician settled on Klonopin, a medicine used in higher doses to treat epilepsy or anxiety. She has been taking the same dose for almost 15 years, only finding it necessary to double the dosage when she has traveled to the West Coast and experienced an exacerbation of symptoms due to the time change. I am currently on Requip XL to treat my RLS. I was previously on regular Requip but the newer drug has an extended release factor so it works all day. When I was on the regular Requip, my dosage was increased almost every six months and I was experiencing the sensations in my legs during the day due to the medication. Requip binds to D3 receptors to act as dopamine would, theoretically reinhibiting the IML. My doctor was not sure as to why I needed higher dosage other than just building a tolerance to the drug. Therefore, he suggested trying Requip XL. This prescription is much more expensive and needs a special order each time I need a refill. However, it does seem to work better. The unfortunate side of it is that I do experience one pretty strong side effect, nausea. I can be nauseous for a week at a time, only being able to swallow liquids. At one point in time, I lived on milkshakes and smoothies just because the idea of eating made me sick to my stomach.

With the medication, I am not finding my RLS interfering with my daily activity. I do try to avoid going to movies because I am constantly moving about and annoying the people around me. I am also dreading the 16-hour flight to Israel that I will be going on in May. The two-hour flight from DC to Miami over winter break was bad enough. I

plan to try to sleep for the entire flight so as not to drive myself, and everyone sitting near me, crazy.

Before I was being treated, however, the disorder was severely impacting my life. I literally did not sleep more than one hour over the course of a night during the second semester of my freshman year. However, because RLS follows a circadian pattern, I could sleep during the day. This meant a twenty-minute nap before class turned into a four- or five-hour nap, causing me to miss class and exacerbating my inability to sleep at night. My grades suffered somewhat and it made it hard to go out with my friends because I would be absolutely exhausted all the time. I would lie in bed at night feeling like I had bugs crawling under my skin or that I had to run a marathon before I could sleep. It was a horrible experience. My mother did not even believe me at first when I complained about it because she thought I was too young. I was seeing a neurologist for migraines that had plagued me during high school so when I went for my yearly appointment, I told him about my symptoms. He immediately diagnosed me with RLS and prescribed Requip.

I do think I will eventually need to go on Klonopin like my mom since I need my dosage increased for my Requip too often. She has never had to change her dosage, except on the rare occasions mentioned above, and the drug itself is less costly and actually aids her in falling asleep. Requip does not help me to fall asleep and it is not supposed to; it is only supposed to stop the restless leg feelings. The one thing I am really not looking forward to is the fact that I cannot use either drug during pregnancy. In addition, pregnancy can exacerbate the sensations. Therefore, if and when I become

pregnant, I will likely be sleep-deprived for nine months unless researchers can find a less toxic drug or treatment before then.

Future Studies

The research of Clemens at al. could be a major breakthrough in RLS physiology and therefore, a major breakthrough in RLS treatment. If they can discern exactly what causes the abnormal signaling, they will be able to make drugs that better target the affected area(s). If a compromised A11 nucleus is the cause of RLS, drugs can target the IML and shift its inputs back to inhibitory by restoring dopamine inputs to that region of the spine. Also, perhaps steps could be taken to reduce any further damage to the A11 axons or nucleus. It is unknown how many cells need to be damaged or compromised for the phenotype to actually present but if this pathway is the physiological cause of RLS, research could examine how much damage can be sustained before symptoms appear and how quickly the symptoms progress. My thoughts here are about how the legs are affected initially, eventually progressing to the arms. Hopefully, with an increase in stem cell technology, scientific research may lead to a repair of the A11 nucleus itself.

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