DOPAMINE

From Parkinson's Disease To Fibromyalgia

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Until recently, the neurotransmitter dopamine has been of interest only to researchers and clinicians studying Parkinson's disease. Before James Parkinson described this disease in 1817, patients with Parkinsonian tremors and severe motor neuron dysfunction were considered histrionic and sent to mental institutions. There was no apparent cause of their inability to control their limbs, shuffling gait, speech impediments, and other symptoms. So, in its infinite (and short-sighted) wisdom, medical authority deemed it psychiatric and delivered many of these patients to sanitariums to live out their lives abandoned and mislabeled. Sound familiar?

Many different neurotransmitters have been discovered over the past century, such as serotonin, norepinephrine, substance P, etc., and some are still in search of a disease. But, not dopamine.

Dopamine is primarily synthesized in the central brain from an amino acid precursor, tyrosine. In the adrenal gland, dopamine is the precursor of norepinephrine and epinephrine (adrenaline). Traditionally, dopamine has been considered an important signal between neurons which coordinates smooth movement and muscle control. More recent research has described the discovery of at least five different dopamine receptors ($D_{1\text{-}5}$)[1]. Secreted dopamine from one neuron must cross a space called a synapse and attach to a dopamine receptor to transmit a signal. Interestingly, each of these five related receptors appears to fulfill different roles and exist in different locations in the central nervous system. Consequently, additional research now must elucidate the specific role and location of these receptors to reveal the ultimate and intricately complex nature of dopamine as a neuroregulatory molecule.

The modern history of Parkinson's disease began with the discovery that individuals with this condition had lost the ability to manufacture adequate amounts of dopamine in an area of the central brain called the basal ganglia. The most densely rich region for dopamine producing cells is the substantia nigra.

Muscles function smoothly due to a balance between stimulatory and inhibitory signals. Normal production of dopamine leads to a balanced inhibition of motor control. Excessive inhibition produces a flaccid, useless muscle while inadequate inhibitory tone causes chaotic spasm and tremor.

Muscles are designed to be able to fire rapidly when needed and therefore maintain a positive tone. A resting arm on a table has active muscle tone. Properly balanced with an inhibitory signal from the substantia nigra, the muscle can be poised to fire, but not fire indiscriminately. For the patient with Parkinson's disease, these muscles are poorly controlled leading to the hallmark diagnostic finding in Parkinson's disease: tremors at rest. Picture the sprinter, ready at the block, constantly false starting because he cannot make himself wait for the gun to fire. Inhibitory control is invaluable for normal, precise muscle function.

Dopamine & Fibromyalgia

After centuries of disrespect and scorn, no one questions the validity of Parkinson's disease today. It is ironic that the same neurotransmitter, dopamine, appears to play a control role in another enigma: fibromyalgia. The historic similarities are striking as evidence of dopaminergic control mechanisms begin to emerge with respect to pain,

sleep, arousal and the autonomic nervous system. Each of these central nervous system functions are relevant to fibromyalgia, but hopefully FM will be sorted out and effectively treated more quickly compared to Parkinson's disease patients.

Mainstream research in fibromyalgia has followed a logical and respectable pathway to establish the veracity of abnormal central brain pain processing abnormalities in fibromyalgia.[2] Almost anything measurable has been measured in patients in fibromyalgia. But, dopamine is not measurable, except in samples of cerebrospinal fluid requiring a lumbar puncture. In addition, the five newly discovered dopamine receptors and their independent functions are not yet measurable. Brain biopsies remain an unattractive option for patients and researchers.

Since it cannot be easily measured, dopamine has not attracted much attention. Dopamine is not measured in Parkinson's disease patients, either. So, how did study of dopamine become the backbone of Parkinson's disease research and emerge as an important issue for patients with FM?

Serendipity. A drug, Levo-dopa, the precursor for dopamine, miraculously reversed Parkinson's disease symptoms for the first time over a half a century ago. The unexpected clinical response shook the world. There are many examples of serendipity in medicine. It fueled another medical field when a fungal contaminant in a laboratory experiment left overnight appeared to unexpectedly kill a bacterial culture. Serendipity revealed that this particular mold naturally produced penicillin to protect itself from bacteria: as a result, a new world of antibiotics was born. Sometimes years of selfless labor at the bench top leads to discovery and cure, and sometimes serendipity plays an equally important role.

Such an analysis of the clinical response to a specific treatment can prove very useful, especially when the medical intervention is specific. If we know enough about how a drug works, and see a dramatic clinical response to it, then we may be able to work back to understand the original disease. So far, patients with fibromyalgia and researchers dedicated to finding an effective treatment have been deserted by serendipity. The hard work has been admirable, but there has not been much good luck or many breaks.

We have studies that demonstrate a 'statistically significant' benefit, but it is usually mathematical significance more than clinical significance. Our best placebo-controlled trials, such as those for tramadol[3], fluoxetine, and amitriptyline[4], only produced an average improvement of 35% in a few parameters like pain, fatigue, or function. While some patients may respond dramatically to a variety of therapeutic options, many more are left behind.

There is no cure for fibromyalgia, but some serendipity may have surfaced somewhat analogous to that seen years ago for patients with Parkinson's disease. In October 2004, at the American College of Rheumatology Annual Meeting, the first randomized, placebo-controlled trial of pramipexole was reported as a late breaking abstract.[5] Comparing trials by the benchmark of how many patients achieve a >50% reduction in pain, those taking pramipexole for 14 weeks achieved possibly the highest level of response to any single medication yet tested for fibromyalgia. To be fair, not all patients responded. However, the clinical response to pramipexole and the implications for further study of dopamine were equally important.

Pramipexole is a medication with very limited human effects. Unlike many other centrally acting medications, pramipexole stimulates only one receptor family (D2) and primarily one receptor, the dopamine 3 receptor (D_3).[6] Consequently, we need to know much more about the role of dopamine and specifically, the role of D_3 in the cause and perpetuation of fibromyalgia. Pramipexole is FDA approved for treatment of Parkinson's disease and is typically dosed 0.25-1.5 mg up to three times per day. The recent fibromyalgia study dosed pramipexole in increasing doses each week up to a target dose of 4.5 mg at bedtime after 14 weeks. Both the unique nighttime dosing and the gradual escalation to the target dose were important. While the nighttime dosing scheme was also explored in earlier reports dating back to 2002[7] and 2000,[8,9] this study in 60 patients was the first placebo-controlled trial.

Patients with restless legs syndrome (RLS) also take pramipexole, as well as the only other available D_3 receptor agonist, ropinirole, at bedtime. Neither medication has been FDA approved for this indication although ropinirole may be indicated for RLS within the year. Similar to fibromyalgia, the cause of RLS is not known, but all medications approved to treat Parkinson's disease are generally helpful for patients with RLS. The utility of other Parkinson's medications for fibromyalgia is unclear,[10] but a large ropinirole trial for fibromyalgia is currently underway in Europe.

We need to discover the role of dopamine, and more specifically the D_3 receptor, in fibromyalgia. While some may argue that no medication has only one biochemical effect, a preponderance of the basic science evidence would argue against another unforeseen effect. Still, it would be foolish to ignore the past and make assumptions without further evidence.

Unlike the penicillin story, my patients with fibromyalgia were not left in a petri dish overnight and 'contaminated' with pramipexole. The logic of considering pramipexole at heretofore inconceivably high doses at bedtime was grounded in a logical approach spanning about ten years. While traditionalists with significant grant resources assayed and measured neurotransmitters, hormones, muscle function, and exercise parameters and tested muscle relaxants, sedative hypnotics, antidepressants, analgesics, and neutraceuticals, I was interested in an extension of what Harvey Moldofsky described in 1975.

The Autonomic Nervous System

Moldofsky essentially reproduced symptoms of fibromyalgia 15 years before the American College of Rheumatology established specific criteria.[11] Patients developed global pain and tenderness after a few nights of sleep interrupted by a loud, auditory arousal during their deepest sleep stages (III/IV).[12] A similar disruption of REM sleep did not cause fibromyalgia.[13] Consequently, clinicians attempted to restore deep sleep with amitriptyline, cyclobenzaprine, and other antidepressants and muscle relaxants with modest success. However, many patients did not respond to this approach, and so research turned elsewhere abandoning the pivotal role of sleep deprivation. Increasingly, it seems that our usual pharmacologic attempts to restore deep sleep fail, since these medications do not address the underlying excessive autonomic arousal.

At about the same time, in the late 1990's, Martínez-Lavín described a fundamental abnormality of the autonomic nervous system inherent in fibromyalgia.[14] Yunus also reviewed this concept[15] and confirmed a much higher incidence of RLS in patients with fibromyalgia (30%) compared to controls (2%).[16] I believed that Moldofsky was right, but there were two unforeseen problems. First, his study preceded the establishment of criteria so readers were unsure if he had actually reproduced fibromyalgia. Secondly, we did not yet understand the role of his auditory arousal fragmenting deep sleep or the autonomic nature of arousal inherent in us all. To make matters worse, Russell was unable to reproduce Moldofsky's result in 1998.[17] These events, and our ineffective attempts to induce 'normal' sleep encouraged most of my peers to believe that pain led to poor sleep and that we should focus more research on central pain processing errors, spinal cord neurotransmission, NMDA receptor dynamics affecting pain, and anything but sleep physiology.

I believe that they are all correct: Bennett, Martínez-Lavín, Russell, Moldofsky, Crofford, Clauw, and Yunus. They *can* all be correct if dopamine plays a pivotal role. The results of the Russell study can be rationalized by the fact that he did not completely duplicate Moldofsky's experimental protocol. While Moldofsky employed a startling, computer generated arousal, Russell allowed subjects to choose music. Both studies achieved fragmentation of deep sleep stages, but the arousal was important. Music would not generally be considered startling, barring my children's music. Interestingly, Lentz did reproduce Moldofsky's findings and cause fibromyalgia in middle-aged women deprived of stage III-IV sleep in 1999.[18]

The startling nature of the arousal matters if one envisions that Martínez-Lavín and Yunus

are right. Patients with fibromyalgia describe so much more than just sleep disturbance, fatigue, muscle spasm, and pain. Many other organ systems under the control of the autonomic nervous system are misbehaving. Temperature regulation, sweat glands, gastric acidity, bowel motility, heart rate, blood pressure, and stress responses are often problematic. The role of the autonomic nervous system in fibromyalgia was already reviewed by Martínez-Lavín in a past issue of *Fibromyalgia Frontiers* (2002, Volume 10, #1).

When Moldofsky administered his auditory arousal, he activated a startle reflex, which arises from the autonomic nervous system. Consequently, we can either *make* patients sleep (overwhelm the arousal with sedating medications) or *let* them sleep (reduce the arousal). Discovering a medication capable of turning down the autonomic arousal that fragments sleep to 'let patients sleep' is an intuitive but uncommon approach to fibromyalgia. We have failed in our past attempts to induce proper, restorative sleep, but this theoretical approach to address unwanted nighttime arousal may be reasonable. Restore normal sleep, and we will all see if Moldofsky was indeed correct.

This theory of arousal fragmenting sleep led to another therapeutic pathway for patients with FM. Initially, I started to add medications capable of treating RLS to the medications of those fibromyalgia patients who had both FM and RLS. Both benzodiazepines, lorazepam, and clonazepam effectively treat RLS. When added to a second medication able to deepen sleep, like a muscle relaxant or sedating antidepressant, fibromyalgia tender point scores decrease significantly.[19,20] As a caveat, I initially met Harvey Moldofsky at my first poster presentation of this very data in 1998. He encouraged me to consider this approach in patients with fibromyalgia who did not exhibit RLS symptoms. He intimated that some have EEG arousal similar to RLS and periodic limb movement, yet they do not move at night. He was correct.

Apparently, one can have RLS EEG activity and have no clinical features of RLS to report when interviewed. While colleague neurologists have no clear understanding of the actual pathogenesis of RLS, an excessive autonomic arousal state seems possible. Other arousals that may reflect abnormal autonomic activity at night may include bruxism (grinding teeth), racing thoughts, and disruptive dreams. The sleep disturbance responsible for pain, fatigue, cognitive problems, and muscular spasm may simply be another consequence of excessive autonomic activity, a consequence attributable to its abnormal activity at night blocking the restorative benefits of deep sleep stages.

Therefore, controlling autonomic arousal becomes critical, and if RLS is one of many potential expressions of excessive autonomic arousal, then new RLS options should be considered for treatment of fibromyalgia. The best clinical response demonstrated in a RLS trial was attributable to the dopamine agonists, pramipexole[21] and ropinirole.[22] The doses used to treat RLS are generally lower, about 15% of those studied in fibromyalgia. The higher doses of pramipexole appear to address fibromyalgia more effectively. The European study may provide additional insight regarding a therapeutic role for ropinirole.

The autonomic nervous system deals with housekeeping functions in the body, including survival. Crofford[23] is correct to point out the many influences of the endocrine system on fibromyalgia, but each system, endocrine and autonomic, cannot work in isolation. Both systems, the autonomic and the endocrine, coordinate their effects to work in concert to address endogenous and exogenous stressors. Eventually, we will be able to measure the autonomic nervous system at a biochemical level to see which system plays the primary role and which system follows the lead of the other. Thyroid and adrenal aberrations certainly affect sleep quality, but an autonomic survival arousal intuitively seems a more potent inhibitor of normal sleep.

The Influence Of The Limbic System

Finally, Patrick Wood, M.D., may be the closest to explaining a role for dopamine in fibromyalgia.[24] While most of the researchers mentioned do not necessarily agree with each other, I find validity in each of their messages. Wood contends that dopamine and dopamine subreceptors inherently control a variety of important limbic functions with respect to the stress response. The limbic system is in the central brain, near the pituitary and above the brainstem structures containing the stimulatory portion of the autonomic nervous system. Fibers leaving the locus ceruleus, which generates autonomic arousal, must pass through the limbic system to have a physiologic effect. As gatekeeper of the autonomic nervous system, the limbic system may be very important.

Clearly, pramipexole has a positive effect for fibromyalgia based on the recent study to be published later this year. Its manufacturer believes that it is dopamine receptor specific. The clinical response suggests that arousal is decreasing, and sleep and fibromyalgia symptoms are improving with an increasing pramipexole dose. But, there are no D_3 receptors in the brainstem where the autonomic arousal is generated. How does pramipexole work if there are no receptors for it in the brainstem?

Wood explains that the limbic system is rich with dopamine receptors, including D_3. In rats, low doses of pramipexole feed back on the neurons to decrease their firing and physiologic effects.[6] In the limbic system, this would mean that limbic neurons would become less functional at low pramipexole doses. As a gate for brainstem arousal, the gate would be left wide open. Arousal would go unchecked, and excessive autonomic stimulation could wreak havoc on sleep and other autonomically controlled functions in the skin, blood vessels, bowels, bladder, etc.

Higher pramipexole doses in rats do the opposite. As the concentration at the neuron increases with increasing dose, postsynaptic neurotransmission is favored over presynaptic transmission. In other words, higher pramipexole concentration increases limbic function to block the brainstem arousals and let one sleep. This central limbic control might also be expected to reverse the other autonomic problems faced by patients with fibromyalgia, such as irritable bowel, irritable bladder, abnormal sweating, and temperature regulation and palpitations.

Dopamine And The Symptoms of Depression

The theories emerging from the consideration of dopamine may also turn the table on psychiatric disease. In contrast to believing fibromyalgia to be a psychiatric disease, unraveling fibromyalgia, autonomic regulation and dopamine regulation may begin to explain psychiatry. Anxiety is a fight-or-flight reaction, and a panic attack is a poorly regulated survival instinct. Regulation of autonomic arousal is fundamental to the symptomtology of fibromyalgia, the nature of stage III/IV sleep deprivation and an avenue to better options for and understanding of stimulatory psychiatric disorders. It is not surprising that panic disorder, anxiety disorder, and post-traumatic stress disorder are very common in patients with fibromyalgia. Is there an underlying thread of autonomic dysregulation among them? Certainly, controlling excessive autonomic arousal or the fight-or-flight response would be expected to decrease the intensity of anxiety and panic symptoms.

Also, in a blinded clinical trial comparing pramipexole to fluoxetine to placebo in patients with depression, pramipexole was superior.[25] The 20 mg fluoxetine dose and the 1.0 mg pramipexole dose were equally effective and superior to placebo, but the 5.0 mg pramipexole dose was superior to fluoxetine in controlling depressive symptoms. Interestingly, this is nearly the dose tested for treatment of fibromyalgia (4.5 mg). How dopamine affects depression is beyond the scope of this article, but the autonomic effects of pramipexole may also have relevance to depression. Only additional rigorous research will explore these questions adequately, but it will not be surprising if dopamine ultimately surpasses serotonin in press coverage and clinical interest.

Parkinson's disease teaches an important lesson for those with 'mysterious and unproven' diseases. If we keep our eyes open, we may find answers in unexpected places.

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