Editorial

An Elephant Among Us: The Role of Dopamine in the Pathophysiology of Fibromyalgia

Exploration of the pathophysiology underlying fibromyalgia (FM) has become an exciting field of inquiry as we strive to improve our understanding of this enigmatic disorder. While evidence of a neuro-dysregulatory state mounts and insights are gained as to potential contribution of specific neurotransmitters, a review of recent literature demonstrates that not all relevant neurotransmitters are being considered equally or with disinterest. Specifically, the potential contribution of serotonin and norepinephrine has been emphasized, ostensibly due in part to the qualified success of trials of serotonin-norepinephrine reuptake inhibitors, while a general awareness of the potential contribution of dopamine-related dysfunction lags.

Indeed, the text of recent reviews, and even peer-reviewed continuing medical education test articles, have contained either scant reference or, in a majority of cases, conspicuous neglect regarding the question of dopamine's role in FM. Despite the recent European League Against Rheumatism consensus recommendation to consider a dopamine agonist for treatment of FM[1], most clinicians and even medical authorities in the field routinely fail to acknowledge the mounting evidence for a role for dopamine in the pathogenesis of FM.

The proposition that a disruption of normal dopaminergic neurotransmission may make a substantial contribution to the pathophysiology of FM was initially based on 3 key observations: (1) FM has been characterized as a "stress-related" disorder due to its frequent onset and apparent exacerbation of symptoms in the context of stressful events[2]; (2) the experience of chronic stress results in disruption of dopaminergic activity in otherwise healthy organisms[3]; and (3) dopamine plays a dominant role in natural analgesia within multiple brain centers[4].

The first hint in the medical literature of a connection between FM and dopamine was provided by Russell, *et al*, who in 1992 reported lower concentrations of metabolites of dopamine, norepinephrine, and serotonin in the cerebrospinal fluid of patients with FM in comparison to matched controls[5]. An increased prevalence of restless legs syndrome (RLS) among FM patients has also been described[6]. While the exact etiology of RLS remains poorly understood, there is mounting evidence from both neuroimaging studies[7] and from patient response to pharmacological intervention[8] to indicate a role for central dopamine in the pathogenesis of RLS.

Indirect pharmacological evidence of dopaminergic dysfunction in FM was first provided by Malt, *et al*, who reported that FM patients had an augmented prolactin release in response to a single challenge dose of buspirone in comparison with controls[9]. Given that the release of prolactin in response to buspirone has been related to the medication's putative activity as a partial dopamine antagonist, the authors concluded that FM may be characterized by increased sensitivity or density of dopamine D2 receptors, which would be in keeping with functional denervation hypersensitivity.

A series of studies performed in Scandinavia have demonstrated that a large subset of FM patients respond to systemic administration of sub-dissociative levels of ketamine with reductions in experimental pain, referred pain, and muscle tenderness[10-12]. While ketamine has traditionally been conceived of primarily as an n-methyl-d-aspartate (NMDA) receptor antagonist, recent reevaluation of its pharmacological activity has demonstrated that at the low doses typically used in analgesic (versus anesthetic) applications, ketamine acts largely as a dopamine D2 receptor agonist[13].

Additional indirect insights regarding the nature of dopaminergic disruption are provided by Harris, *et al*, who used positron emission tomography (PET) and reported a significant reduction in mu-opioid receptor availability in the nucleus accumbens in FM patients with a significant negative correlation between mu-opioid receptor-binding potential and affective pain, as reflected by scores on the McGill Pain Questionnaire[14]. In light of this evidence demonstrating a disruption of opioidergic neurotransmission in FM, it is intriguing to note that data from animal models indicate that the analgesic capacity of mu-opioids within the nucleus accumbens is predicated in part on intact dopaminergic neurotransmission[15]. Similarly, dopamine release is stimulated by mu-opioid receptors within cortical regions in which dopamine plays a role in antinociception as well[16].

Finally, 2 recent studies that utilized PET have provided direct evidence of a disruption in dopaminergic neurotransmission in patients with FM. The first of these utilized 6-[^{18}F]fluoro-L-DOPA to determine the presynaptic activity of dopaminergic neurons in female patients with FM in comparison with matched controls[17]. While a small sample size represented a potential limiting factor, a significant reduction in uptake was nonetheless demonstrated in the dopaminergic centers of the mid-brain (i.e., ventral tegmental area and substantia nigra) and in multiple regions of the pain neuromatrix wherein dopamine plays a role in natural analgesia, including the thalamus, insula, and cingulate cortex. Moreover, a negative correlation was noted between an index of clinical pain and dopamine metabolism specifically within bilateral insula ($r = –0.89$, $p = 0.04$).

A subsequent PET study demonstrated dramatic disruption in dopaminergic reactivity to a tonic painful stimulus within the basal ganglia as demonstrated by ^{11}C-raclopride, a radio-ligand with specificity for dopamine D2/D3 receptors[18]. In control subjects, the amount of dopamine released in response to tonic pain correlated with subjective ratings of pain intensity, while no such relationship was demonstrated in patients with FM. Notably, dopamine receptor availability specifically in the right putamen of FM patients demonstrated significant positive correlation with the defining characteristic of the disorder, i.e., tenderness to manual palpation as reflected by tender point index ($r = 0.73$, $p = 0.01$). Taken together, these neuroimaging studies provide the most compelling evidence to date of the involvement of dopamine in the pathophysiology of FM and strongly suggest that maneuvers to enhance dopaminergic activity are physiologically relevant to the disorder.

Accordingly, direct pharmacological evidence of a role for dopamine in FM has been provided by Holman and Myers, who reported the results of a randomized controlled trial (RCT) of pramipexole, a dopamine D2/D3 agonist, for the treatment of FM[19]. The primary outcome in this 14-week study was improvement of pain as indicated on a 10-cm visual analog scale (VAS); secondary measures of efficacy included subjective tenderness and quality of life. Compared with the placebo group, patients receiving pramipexole experienced significant improvement in measures of pain as reflected by an average 36% decrease in VAS pain across the active treatment group, with 42% of these achieving ≥ 50% decrease in pain (vs 14% of those on placebo). A number of other measures, such as fatigue and global well-being, similarly showed significant symptom improvement. A notable aspect of this trial was that participants were not required to discontinue their current medical regimen in order to enroll, and, indeed, as many as 44% in the active treatment group were taking narcotic analgesic as compared to 67% in the placebo arm. While inclusion of those taking concomitant medications might complicate interpretation of results, one would counter that by so doing it was possible to enroll individuals with more severe disease, thereby highlighting the effectiveness of the agent under evaluation. Moreover, the relevance of the medications that participants were taking at the time of enrollment to the pathophysiology of the disorder would appear to be limited, given that participants continued to experience significant clinical effect, including mean VAS pain > 7 and a mean Fibromyalgia Impact Questionnaire score > 50 (range 0–80).

Three pharmaceutical companies have since either sponsored or conducted randomized placebo-controlled trials using dopamine agonists: GlaxoSmithKline with ropinirole (2004-5), Schwarz/UBC Pharma with rotigotine (2006-current), and Boehringer-Ingelheim with pramipexole (2008). While the pramipexole trial suggested superior benefits for pain, fatigue, and function in comparison with other tested medications[20], including pregabalin, duloxetine, milnacipran, and sodium oxybate, 2 clinical trials with ropinirole, another dopamine agonist, have provided mixed results. For example, the 2004 ropinirole trial reduced VAS pain by ≥ 50% for 45% taking ropinirole (n = 20) compared to 30% on placebo (n = 10) without achieving a difference of statistical significance[21]. While the failure of this trial may be related to inadequate size, another larger European RCT that evaluated the efficacy of a novel extended-release formulation also failed to demonstrate a treatment benefit[22]. As of this writing, sponsored trials of rotigotine and pramipexole are under way.

The relative success of the pramipexole RCT could also be related to target dose (4.5 mg qhs), which favors postsynaptic limbic neurotransmission[23]. Lower doses, as used in both the ropinirole RCT (5–8 mg or 33% dose equivalence to 4.5 mg pramipexole), favor presynaptic neurotransmission and might, accordingly, be predicted to result in limited efficacy or even a paradoxical increase in pain and autonomic dysregulation. Moreover, there were specific exclusion criteria employed in the original pramipexole RCT that were not used in the RCT of extended-release ropinirole, including the presence of obstructive sleep apnea and evidence of positional cervical cord compression (PC3). The rationale for these exclusion criteria pertains to their representing potent sources of autonomic arousal that might ostensibly interfere with the beneficial effects of a dopamine agonist. Indeed, consideration of independent sources of autonomic arousal in the context of clinical trials in FM appears especially salient given the observation that dysautonomia features as an essential component of the disorder[24].

It is noted that medications currently approved for the treatment of FM by the US Food and Drug Administration (FDA) are not directly related to dopaminergic neurotransmission. Indeed, the variability in patient responses to these and other medications does not appear to support a primary role of any neurotransmitter, including dopamine. The potential existence of biological subgroups within the

greater patient population may be in part responsible for this. For example, recent studies have demonstrated the existence of subgroups of patients distinguishable both by physiologic and psychometric variables[25,26]. These findings may be interpreted to suggest that the "fibromyalgia phenotype" (i.e., chronic widespread pain with a diffuse tenderness to palpation) may represent the end result of different central processes to which various neurotransmitters (e.g., dopamine, norepinephrine, serotonin) make differential contribution.

Alternatively, the beneficial effects of both duloxetine and pregabalin in patients with FM might be related to their influence on a source of pain other than the essential pathophysiology of the disorder. For example, recent data suggest that as many as 65% of FM patients may have comorbid, intermittent PC3[27]. It is then plausible that duloxetine reduces some of the pain associated with FM in the context of comorbid PC3 by enhancing that component of spinal cord descending inhibition specifically related to serotonin or norepinephrine, while pregabalin might hypothetically reduce spinal hyperexcitability that develops secondary to PC3 through its effects as an alpha-2-delta ligand, which is thought to attenuate excitatory neurotransmission by reducing neuronal calcium influx.

Because dynamic cervical magnetic resonance imaging was not assessed in the context of these pivotal studies, these considerations must necessarily remain a matter of speculation. As noted, however, the original pramipexole study did exclude subjects with cervical pain with prolonged extension because this was interpreted by the investigators to represent an inexpensive surrogate for MRI to detect PC3, which might have contributed to the robust outcomes of that trial. Investigations are under way to determine whether individuals with PC3 represent an independent FM subtype. In the interim, we would offer that future clinical trials in FM might ultimately benefit from consideration of comorbid PC3 should it be demonstrated that this condition has a substantial impact on clinical outcomes.

Finally, if dopamine indeed plays a critical role in the pathophysiology of FM, then one would expect the disorder to be associated with other phenomena related to central dopamine. A review of research findings suggests this may indeed be the case. As noted, FM is associated with increased prolactin release in response to dopamine antagonism, which is indicative of a denervation hypersensitivity as would be expected in the context of reduced dopaminergic activity[9]. Other neuroendocrine abnormalities among subsets of FM patients include attenuated growth hormone response to physiological challenge[28] and mild hypocortisolemia[29]. While dopamine stimulates growth hormone release, the reactivity of striatal dopamine in response to challenge corresponds with cortisol levels such that conditions characterized by low cortisol would be expected to be similarly associated with attenuated dopamine release[30]. Given that FM is associated with dysautonomia, it is noteworthy that cortical dopamine plays a role in modulating autonomic function[31].

Intriguingly, many aspects of the greater "fibromyalgia syndrome" share considerable overlap with prodromal Parkinson's disease[32]. A variety of clinical symptoms associated with the disorder may therefore be linked to abnormal dopaminergic neurotransmission, including RLS, muscle stiffness ("gel phenomena"), and non-dermatomal paresthesias. Preliminary data also indicate that FM may be associated with an increased prevalence of attention-deficit disorder, which is also linked to deficits in dopaminergic neurotransmission[33]. Thus, an attenuation of dopamine synthesis and release might contribute to the cognitive dysfunction that is increasingly recognized as a critical aspect of the disorder.

In conclusion, we would suggest that dopaminergic hypofunction and its potential contribution to human clinical pathology is no longer a topic solely for neurologists interested in Parkinson's disease. Rather, it is the elephant waiting to be noticed as it occupies an increasing amount of floor space in the vault of our knowledge regarding FM. Given the mounting evidence of a dopamine-related pathology in at least a substantial subset of patients, further progress in our understanding and management of this disorder requires a better understanding of dopaminergic neurotransmission. Incorporation of dopamine-related research findings into the development of novel FM treatment paradigms appears increasingly rational.

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