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Stress and dopamine: implications for the pathophysiology of chronic widespread pain

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Summary Fibromyalgia has been called a "stress-related disorder" due to the onset and exacerbation of symptoms in the context of stressful events. Evidence suggests that inhibition of tonic pain is mediated by activation of mesolimbic dopamine neurons, arising from the cell bodies of the ventral tegmental area and projecting to the nucleus accumbens. This pain-suppression system is activated by acute stress, via the release of endogenous opioids and substance P within the ventral tegmental area. However, prolonged exposure to unavoidable stress produces both reduction of dopamine output in the nucleus accumbens and development of persistent hyperalgesia. It is proposed that a stress-related reduction of dopaminergic tone within the nucleus accumbens contributes to the development of hyperalgesia in the context of chronic stress and thus plays a role in the pathogenesis of fibromyalgia. A stress-related dysfunction of mesolimbic dopaminergic activity might serve as the basis for other fibromyalgia-associated phenomena as well.

Background

The cardinal feature of fibromyalgia (FM) is pain, the experience of which involves both afferent and efferent processes. The experience of chronic pain may result from dysfunction of either of these factors, or a combination thereof. In fact, a growing body of evidence suggests that elements of each exist in the context of FM [1]; however, the exact mechanism of FM pain remains to be determined. FM has been characterized as a 'stress-related' disorder due to its onset and exacerbation of symptoms in the context of stressful events [2]. While exposure to acute stress is known to produce stress-induced analgesia, the induction of which depends on activation of dopamine (DA) containing neurons within the nucleus accumbens (NAc) [3], rat studies have demonstrated that prolonged exposure to stress eliminates this response, resulting instead in a state of stress-induced hyperalgesia [4]. Chronic stress has been shown to result in the attenuation of DAergic activity within the NAc, and is therefore proposed to contribute to the development of stress-related hyperalgesia.

Insofar as FM is concerned, a number of clinical and investigational phenomena suggest a disruption of DAergic function, including but not limited to decreased DA metabolites in cerebrospinal fluid (CSF) [5,6] and high rates of co-morbid restless legs syndrome (RLS) [7]. The objective of this paper, then, is to review literature concerning the impact of stress on DAergic activity within the mesolimbic pathway and discuss its potential relevance to FM.

Findings

Exposure to acute stress causes activation of DAergic neurons within the ventral tegmental area

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(VTA) [8,9] via the release of substance P (SP) and endogenous opioids. This activation results in the release of DA in a number of centers to which VTA neurons project [10,11], including the NAc, which is anatomically part of the ventral striatum and functionally included in the limbic system. A variety of stressors result in the release of DA within the NAc, including acute psychological stress [12–15].

Whereas exposure to acute stressors increases DA activity within the NAc, Gambarana and associates at the University of Sienna have demonstrated that rats exposed to chronic unavoidable stress experience decreased DA output in the NAc shell, which is associated with a reduced activity of DAergic neurons under both the basal and cocaine-stimulated conditions [16]. The stress-related decrease in DAergic tone is also associated with an increased sensitization to DAergic stimulation. Concomitant treatment with imipramine during stress exposure maintains basal and stimulated DAergic at control level. Rats exposed to 7 days of unavoidable stress have a decrease in DAergic tone in the NAc shell, and reduced DA and serotonin (5-HT) accumulation after cocaine administration in both the medial pre-frontal cortex (mPFC) and NAc shell [17]. This reduction in DAergic tone within the NAc shell remains significant up to 14 days after the stress exposure. A significant decrease in 5-HT accumulation following cocaine administration is observed at day 3, but not at day 14. Thus, the experience of chronic stress induces long-term modifications to DAergic activity within the NAc, which apparently outlasts the impact on 5-HT. Expression of the pre-synaptic neuronal DA transporter (DAT) is an index of DA receptor activation. Exposure to a chronic stress reduces the number and affinity of DAT binding sites within the NAc shell, as would be predicted by the foregoing, while increasing the number and affinity of post-synaptic DA binding sites, in keeping with the principle of dennervation hypersensitivity [18].

Altier and Stewart's efforts have shown that activation of the VTA-NAc DA circuit also plays an important role in mediating the stress-induced suppression of tonic pain [3]. Rats receiving bilateral intra-VTA infusions of the SP analogue, DiMe-C7, either immediately prior to or 25 min following an injection of formalin into one hind paw evince an attenuated pain response for approximately 30 min, the analgesia being more potent when DiMe-C7 is infused following, rather than prior to, the early pain phase [19]. Conversely, stress-induced analgesia is prevented by blockade of tachykinin NK-1 receptors in the VTA by means of intra-VTA infusions of a tachykinin NK-1 receptor antagonist [20]. Rats tested in the formalin test following infusions of amphetamine into the NAc, which acts to induce the release of DA while simultaneously inhibiting its reuptake, demonstrate significant attenuation of pain response. Similar infusion into the medial prefrontal cortex fails to alter pain response. These findings are interpreted to mean that activation of mesolimbic DA neurons contributes to suppression of tonic (versus phasic) pain. The infusion of DA D2 receptor antagonists into the NAc under conditions of stress-induced analgesia obliterates this response [21]. Similarly, the infusion of both mixed DA receptor antagonism and DA D1/D5 receptor antagonism attenuates stress-induced analgesia. Blockade of opioid receptors within the VTA by bilateral infusions of naltrexone also reduces stress-induced analgesia, thereby confirming a role for endogenous opioids in stress-induced analgesia [22]. The direct application of these various agents within the VTA and NAc appears to contradict earlier work which suggests that increasing DAergic tone via systemic administration of apomorphine actually *attenuates* stress-induced analgesia (and that DA receptor antagonists *increase* stress-induced analgesia (SIA)) [23,24]. However, the apparent contradiction is resolved when one takes into account the regulatory mechanisms exerted by mesocortical circuits over mesolimbic function [25,26], the influence of which is likely invoked by the systemic administration of these agents.

Thus, the VTA-NAc DA circuit acts in part as a pain-suppression mechanism that is triggered by exposure to acute stress, through the release of SP and endogenous opioids. Yet, whereas this system plays a fundamental role in the phenomenon of stress-induced analgesia in acute circumstances, a very different phenomenon occurs in the context of chronic stress. To wit: da Silva et al. have shown that rats submitted to chronic restraint evince hyperalgesia in the tail-flick test [4]. This hyperalgesic response remains in effect for up to 28 days following the cessation of chronic restraint. Rats undergoing repeat stress also display decreased morphine sensitivity, suggesting that chronic stress modifies the activity of opioidergic systems. Although not explicit, this fact may imply an effect on DAergic function vis-à-vis the VTA as well.

In addition, Quintero et al. have shown that rats subjected to an inescapable subchronic stress evince thermal hyperalgesia and enhanced nociceptive behavior in the formalin test [27]. Hyperalgesia to both thermal and chemical stimulants persists up to 9 days after the stress exposure. The selective 5-HT reuptake inhibitors clomipramine and fluoxetine, as well as the 5-HT precursor

tryptophan, blocks development of both types of hyperalgesia, suggesting that repeated stress produces a long-lasting increase in pain sensitivity to both phasic or tonic noxious stimuli related, in part, to diminished central 5-HT activity. Rats exposed to the same type of inescapable subchronic stress also demonstrate increased c-Fos-immunoreactive nuclei in the lumbar spinal cord following both pain stimulation and at rest, suggesting that repeated inescapable and uncontrollable stress induces both sensitization and activation of sensory neurons at the spinal level [28].

Discussion

A review of the current literature fails to demonstrate direct evidence implicating the phenomenon of chronic stress-induced decrease in DAergic tone within the NAc contributing to the development of hyperalgesia induced by similar circumstances. It is proposed herein that the two are intimately related. Whereas the supplementation of serotonergic tone during subchronic stress exposure appears to provide prophylaxis of stress-induced hyperalgesia, this does not obviate a role for DA. In fact, whereas there is a disruption of *both* serotonergic and DAergic function that occurs within the NAc following chronic stress, the impact on DA outlasts that on 5-HT. One would therefore postulate that: (1) there is a regulatory interaction between 5-HT and DA during stress-induced analgesia; (2) a disruption of this interaction contributes to the inception of stress-induced hyperalgesia; and (3) DAergic dysfunction, which outlasts that of 5-HT, may be responsible for the persistent expression of stress-induced hyperalgesia after serotonergic function has normalized. Indeed, this may explain why strategies aimed at boosting serotonergic function in patients with chronic widespread pain have met with limited success insofar as analgesia is concerned. Given that FM is a stress-related disorder, one would predict that strategies aimed at boosting DAergic function within the mesolimbic pathway would have superior efficacy.

There exists both clinical and experimental evidence that FM embodies a hypo-DAergic state. Yunus and Aldag [29] report that RLS is significantly more prevalent in patients with FM than in normal controls. While the exact pathology underlying the phenomena of RLS remains to be determined, both pharmacological evidence and central imaging studies suggest it is related to a disruption of central DAergic function [30]. It is likewise noted that DAergic agents are the best studied and most successful agents for treatment of RLS [31]. Other options include the use of opioids, benzodiazepines, anticonvulsants, and adrenergic medications — all of which may therefore have therapeutic bearing on patients with FM. Investigations by both Russell et al. [5] and Legangneux et al. [6] have also demonstrated a decrease in the concentration of DA metabolites (along with those of 5-HT and norepinephrine) in patients with FM relative to controls. Fibromyalgia is frequently associated with a number of subjective symptoms including fatigue, dysphoria and difficulty concentrating. Normal human subjects undergoing experimental catecholamine depletion experience decreased happiness, energy, vigor and attentiveness, and increased sleepiness, fatigue and sedation as a result of decreased DAergic activity, which also results in an increased DA D2 receptor binding potential [32]. Pharmacological evidence for a disruption in central DAergic activity in FM (via an augmented prolactin response to buspirone) has recently been provided by Malt et al. [33]. These last findings are taken as preliminary corroboration of the current hypothesis, which awaits further confirmation by means of analysis utilizing positron emission tomography (i.e. PET/SPECT) of DAT expression, 3,4-dihydroxy-6-[(18)F]fluorophenylalanine (FDOPA) uptake, and DA D2 receptor profiling. This author's predictions are that central imaging of DAergic activity in patients with FM will demonstrate: (1) an increase in postsynaptic DA D2 receptor expression and affinity; (2) a slight decrease in FDOPA uptake in the striatum; and (3) a decrease in DAT expression in patients with FM.

Conclusion

This paper proposes that FM represents a stress-induced, hypo-DAergic state. The reduction in DAergic tone is further proposed to result in a number of phenomena associated with the disorder, including but not limited to hyperalgesia. However, given the complexity of nociceptive systems, there may ultimately be no single mechanism that results in the development of chronic widespread pain. Rather, the breakdown of any number of regulatory mechanisms might result in what is broadly termed 'fibromyalgia'. Whereas much energy has been expended in an effort to sub-classify FM patients according to psychosocial factors [34—36], clinically effective therapies will likely be guided by the recognition of a multiplicity of organic abnormalities currently embodied within the greater FM construct.

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