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Chronic Pain, Dopamine and Depression: Insights from Research on Fibromyalgia

Katharina Ledermann and Chantal Martin-Sölch

Abstract

There have been several indications that pain and reward are partly mediated by similar neural pathways in the central nervous system, and that these common pathways are related to both the dopamine (DA) and the opioid systems. Several studies have demonstrated the analgesic effects of rewarding stimuli or activities on positive affective states. On the other hand, chronic pain was shown to impair several aspects of reward processing by possibly altering pain-reward interactions. However, the precise mechanisms of the mutual pain-reward interaction are unclear and few studies have investigated the influence of pain on rewards and vice versa in humans. Therefore, we aim to summarize recent findings on the neuroanatomical and molecular changes associated with chronic pain conditions, particularly fibromyalgia syndrome (FMS) with a focus on the dopamine system. Recent findings on the mechanisms involved in the alterations of the brain reward circuit in chronic pain and FMS as well as the role of DA in the pathophysiology of FMS and other chronic pain conditions will be discussed. Furthermore, we aim to discuss the interplay between the dopaminergic reward system and depression in chronic pain, as the prevalence of co-morbid depression in chronic pain is quite high.

Keywords: chronic pain, dopamine, fibromyalgia, depression

1. Chronic pain and fibromyalgia

1.1 The burden associated with chronic pain

Chronic pain is defined as “a pain that persists past the normal time of healing” ([1], p. 4). In practice, chronic pain is defined as a pain that lasts for more than 3–6 months [1, 2]. With an estimated prevalence up to 40%, chronic pain is regarded as a major health problem with approximated direct and indirect costs reaching to 5% of the gross national product in western European countries [3]. Also in terms of prevalence, chronic pain represents an important public health issue. A recent epidemiological survey indicated that almost one in five Europeans report having experienced moderate to severe pain in the last month and at least twice a week [3]. Chronic pain significantly decreases individuals’ health status and quality of life [4] and is linked with a wide range of physical and mental problems such as sleep disorders, depression, anxiety disorders, and alcohol or substance abuse, either as antecedent conditions or as consequences of the development of pain [5]. The fact

that the number of people suffering from a chronic pain condition is steadily rising [6], in spite of the overall improving standards of health care, emphasizes the urgent need for novel insights informing better diagnosis, prevention and treatment of patients with chronic pain.

1.2 The specific case of Fibromyalgia

Fibromyalgia syndrome (FMS) is a chronic, painful musculoskeletal disorder characterized by widespread pain, accompanied by a broad spectrum of associated somatic and psychological manifestations, including fatigue, sleep disturbances, stiffness, anxiety and cognitive dysfunction [7, 8]. The current diagnostic criteria of FMS emphasize the behavioral and psychological aspects of the disease and are based on self-reported evaluation of symptoms [9]. This is an important change compared to the previous diagnostic criteria that required tender point examination [8], while the new criteria are essentially based on self-reported symptoms. The development of new diagnostic criteria for FMS is related to the evolution of the understanding of the underlying pathophysiology of this disorder [10]. While the old criteria conceptualized FMS as peripheral musculoskeletal condition, the new criteria account better for the role of the central nervous system (CNS) in the etiology of FMS. In addition, they simplify the diagnosis in primary care and integrate the diversity of symptoms (somatic and behavioral) associated with FMS [10] better.

The population prevalence of FMS in industrialized countries has been reported to range from 0.5 to 4% [11], with a ratio of 3.5% in women to 0.5% in men [12]. FMS is one of the most prevalent chronic pain conditions [12]. Like other chronic pain conditions, FMS often leads to disability, affective disturbance and poor quality of life and is also associated with high direct and indirect disease related costs [13]. The etiology of FMS is widely unknown; and this disorder remains very difficult to treat. However, accumulated evidence over the past years suggests that a wide range of factors that could potentially underlie the disorder, including dysfunctions of the central CNS and autonomic nervous systems, neurotransmitters, hormones, immune system, external stressors, psychiatric aspects and others [14]. Although there is increasing evidence for changes in the CNS, FMS is differentiated from neuropathic pain as there is no evidence for a primary lesion or disease of the somatosensory system in FMS [15]. It has been hypothesized however that FMS and neuropathic pain phenomena may be variations of the same condition [16, 17] with many common features such as precipitation or aggravation by stress, as well as complaining about similar symptoms such as tingling, numbness, cutaneous hyperalgesia or pain attacks [18]. Finally, the recent evidence for impaired small fiber function in FMS patients also points towards a neuropathic nature of pain in FMS [19].

1.3 Challenges for the treatment of FMS

Despite this high clinical significance, the neural correlates and the interaction between psychological and neurobiological processes in the pathophysiology of FMS are still poorly understood, which in turn makes the development of treatment strategies difficult. At pharmacological level, three medications have been approved by the FDA for the treatment of fibromyalgia [20]: one anti-epileptic drug (pregabalin) and two antidepressive drugs (duloxetine and milnacipran). Interestingly, all of them directly act on the CNS. However, recent research indicates that current pharmacological treatments are not really effective in the reduction of pain or improvement in function in patients with FMS, and there is still a lack of effective drugs for the treatment of FMS over time [21]. Furthermore, the current

evidence-based guidelines for the treatment of patients with FMS are inconsistent [22]. Finally, recent meta-analyses conclude that optimal treatment interventions should include components aimed at enhancing adaptive cognitive and behavioral responses [23, 24], and large improvements have been observed with treatment plans that include non-pharmacologic interventions [25]. This is in line with the current international guidelines that recommend aerobic exercise, cognitive-behavioral therapy (CBT), and multicomponent treatment as first choice for the care of FMS patients [22]. These conclusions are also in agreement with the current state of research concerning the treatment of chronic pain in general. For chronic pain also, most of the available medications show poor efficacy, are accompanied by severe side effects with chronic use, or, in the case of opioids, may lead to dependence or addiction [26]. In addition, chronic pain is commonly associated with comorbid affective disorders (e.g. anxiety, depression) and cognitive deficits (e.g. memory impairment), suggesting on one hand critical involvement of higher order neural brain processing [27], and on the other hand the necessity to develop specific interventions targeting the comorbid mental disorder the mood and cognitive dysfunctions as well (see for instance [28]).

This chapter will therefore focus on specific neural changes associated with chronic pain in general, and with FMS in particular, that could bring new advances in the development of efficient treatment strategies for these conditions. These neural factors concern the changes in the dopamine function observed in chronic pain and their implication for responses to rewarding stimuli.

2. The dopamine function in chronic pain and in fibromyalgia

2.1 Changes in dopamine function in chronic pain disorders and in FMS

Among the neural changes observed in chronic pain, there is increasing evidence for alterations in the dopamine (DA) system. These changes seem to be related with a reduction of the DA function in chronic pain conditions. Evidence supporting a hypodopaminergic state in chronic pain comes from both preclinical [29] and clinical data [30, 31]. For instance, alterations in the DA function were described in burning mouth syndrome and atypical facial pain [32, 33]. The high incidence of central pain (including neuropathic pain) in patients suffering from Parkinson's disease suggests that pain is a common symptom in patients with hypofunctional nigrostriatal dopaminergic pathways [34], and that low DA may contribute to increased pain [35]. Similar changes were observed in FMS. For instance, two PET-studies showed that self-reported pain induced by hypertonic saline injection in healthy volunteers correlated with the amount of DA released in the basal ganglia [32, 33]. These findings suggest an involvement of DA activity in endogenous analgesia [36, 37]. In contrast to healthy subjects, FMS patients did not show DA release in response to noxious stimulation [36]. Furthermore, activity of the ventral tegmental area was decreased during both pain perception and expectation of pain relief in FMS patients in an fMRI (functional Magnetic Resonance Imaging) study [30] suggesting a dysregulation of DA signaling in these patients. A previous study by our group added evidence of a reduced DA function in FMS patients, and indicated a role of depression in the relation between pain perception and DA changes [38]. Our main results yielded that investigation of the DA function allows differentiating between FMS patients with and without depression, as well as between FMS patients and healthy subjects and that the neurobiological mechanisms underlying depressive symptoms in FMS patients with depression are different from the ones reported in depressed patients without pain.

Even among healthy individuals, low DA receptor availability has been associated with enhanced pain responses [39]; and DA depletion has been shown to influence pain affect and not the sensory aspects of acute painful stimuli [40]. This could suggest that in chronic pain, a low DA function could lead to changes in affective states [41]. Additionally, recent studies using animal models of neuropathic pain link changes in DA receptor signal transduction, the amount of released DA and other neurochemical adaptations in the midbrain DA circuit with depression-like behaviors and reduced motivation [42–44]. This is in line with findings showing that aberrant dopaminergic transmission in the mesolimbic DA network underlay several mood disorders [45]. On the other hand, accumulating evidence suggests that the mesolimbic DA system modulates the perception of nociceptive information, and the affective symptoms of chronic pain [46]. Notably, several diseases associated with dysfunctional DA transmission are comorbid with chronic pain, including Parkinson's disease, drug addiction and major depression [41].

Taken together, there are now multiple lines of evidence showing that chronic pain, including FMS, leads to a hypodopaminergic state that results in enhanced pain sensitivity and might impair motivated behavior [47]. In addition, DA is involved in descending inhibitory modulation of pain transmission, which is an additional link between hypodopaminergia and chronic pain [48]. Strategies to restore dopamine signaling may therefore represent a novel approach to manage pain symptoms in FMS.

2.2 Alterations of the brain reward circuit in chronic pain and FMS

It is well documented that the mesocorticolimbic and mesostriatal DA systems play a role in the processing of reward information [49–51], even if other neurotransmitter systems, such as the opiate system, are also important in the mediation of reward [52]. Recent studies indicating that alterations of the mesolimbic reward pathway contribute to the pathology of chronic pain [53, 54] suggest a neurobiological overlap between pain processing and the reward circuitry. Pain and reward can be regarded as opponent processes that interact and influence each other [55]. Several studies demonstrated that rewards, including pleasurable stimuli and activities and positive affective states have an analgesic effect and decrease pain sensitivity [55–58]. Finally, some findings suggest that pain and reward are mediated by similar neural pathways in the central nervous system and that these pathways are related to both the DA and the opioid systems [55, 58]. At a neurochemical level, several preclinical and clinical findings suggest that chronic pain leads to a hypodopaminergic condition in the reward circuitry, resulting in the diminution of the hedonic tone (see Section 2.1). This suggests that the brain reward center might play a key role in the modulation of nociception, and that adaptations in dopaminergic circuitry may affect several sensory and affective components of chronic pain syndromes. These adaptations involve changes in the levels of released DA, as well as postsynaptic changes in the levels of receptors and signal transduction molecules [59].

After having established that pain and reward might influence each other through the implication of the DA system, the next subsections will provide an overview of the findings reporting changes in the responses to reward in chronic pain first, and then secondly specifically in FMS.

2.2.1 Changes in the brain reward circuitry in chronic pain

Findings from functional neuroimaging studies indicate that a network of brain regions, including the orbitofrontal cortex, the ventral (specifically the nucleus

accumbens, Nacc) and dorsal striatum, the amygdala and the anterior cingulate gyrus, specifically interact to process reward information [60] and form the so-called cerebral reward system. In chronic pain, alterations in brain structural features, functional connectivity, or activity of these regions have been reported [37, 46, 61]. Additional evidence from clinical studies links chronic pain conditions to aberrant functioning of circuits involved in mood and motivation, including the dopamine brain reward center [62, 63]. The neural changes observed in regions associated with the cerebral reward system could provide a possible explanation for the high incidence of comorbid affective disorders in chronic pain patients [59]. In summary, the reported empirical evidence suggests that pain, in particular chronic pain, impairs several aspects of reward processing: (1) chronic pain is associated with anhedonia, that is, the inability to enjoy pleasurable activities [44, 64]; (2) decreased reward sensitivity and/or decreased motivation was observed in rats with neuropathic pain [65]; (3) impaired operant learning of pain sensitization and habituation was found in FMS patients [66]; and (4) impaired decision making based on reward and punishment was reported in patients with chronic back pain and complex regional pain syndrome (CPRS) [67]. Decreased reward responsiveness may therefore underlie a key system mediating anhedonia and depression common with chronic pain [41, 68, 69]. This is highly relevant since the prevalence of depression in chronic pain exceeds 20% [70] and often includes anhedonia [44, 64]. Anhedonia is also one of the cardinal symptoms of depression, and has been hypothesized to be associated with an hypofunction of the DA system, what in turn could affect the neural processing of rewarding information [51]. As a matter of fact, a large body of research has evidenced reduced neural activation as well as reduced DA transmission in response to reward information in patients with major depressive disorder (MDD) (see for instance [71–73]). Recent evidence from animal studies suggest that suppression of dopaminergic neurotransmission in the meso-limbic reward circuit may be a common neuroplastic change underlying chronic pain and depression that develops in a time-dependent manner [74].

2.2.2 Changes in the brain reward circuitry in FMS

To our knowledge, there is so far only one study that has directly investigated the DA responses to reward in vivo in FMS patients [59]. In this research of our group, we used the [¹¹C]Raclopride positron emission tomography (PET), a radiotracer that is sensitive to changes in intrasynaptic DA concentrations while participants were performing a slot machine compared FMS participants with and without depression with healthy controls (all women). We expected the patients' groups to have reduced DA responses to reward, expressed as a larger Raclopride binding in the FMS groups of participants than in the group of healthy controls. In addition, we expected this alteration to be stronger in FMS patients with than in FMS patients without depression. However, our results showed, at the contrary of our hypothesis, the greatest [¹¹C]Raclopride displacement in response to rewards in the group of FMS participants with depression [59], which is thought to reflect the largest increase in DA transmission. This can be explained by a greater increase of synaptic DA transmission or by adaptative receptor changes in this group, but necessitate further investigation to be more clearly understood. Our results also indicated that the depression associated with FMS has different neurochemical correlates as primary major depressive disorder. More specifically, a previous study by our group [71] using the same methodology found no [¹¹C]Raclopride displacement in response to rewards in a group of MDD patients without pain symptoms, suggesting reduced DA responses in the brain of depressive patients at the contrary of our group of FMS patients with depression. In conclusion, there is first evidence for a

hypodopaminergic state in FMS and an alteration of the neural reactions to reward mediated by the DA system. Even if the exact mechanisms by which the brain reward center modulates chronic pain resp. FMS are not completely established yet, this opens new treatment avenues. Certainly, pharmacological interventions targeting the DA system could be an option. However, we will focus here on psychological interventions that might directly work on the behavioral responses to reward and in turn might be able to restore the DA function.

3. Implications for the treatment of FMS

The current international guidelines for the treatment of FMS all recommend psychological interventions, more specifically cognitive behavioral therapy (CBT), as one of the treatments of choice for the care of FMS patients [22]. According to a recent meta-analysis, CBT is significantly better than the other psychological interventions for which randomized controlled trials exist [75]. The effects of CBT are relatively small but robust and similar to those reported for other pain and drug treatments [75], but have limited success in ameliorating affective and social complaints in FMS patients [25, 75, 76]. There is therefore a need for the development of new CBT methods targeting specific behavioral, emotional or cognitive processes in the treatment of chronic pain. Recently, the so-called “third wave” cognitive-behavior therapies [77] have integrated mindfulness-based cognitive therapy as additional intervention. Mindfulness is defined as “a process of bringing a certain quality of attention to moment-by-moment experience” [78]. Mindfulness capacity can be developed using various meditation techniques that originate from Buddhist spiritual practices [78]. A growing body of research has demonstrated that mindfulness-based interventions are clinically effective for a wide range of problematic conditions (for a review see Grossmann et al. [78]) and have gained increasingly wide use for the treatment of chronic pain conditions including FMS, showing promising results [79, 80]. A recent systematic review indicates a moderate significant effect for mindfulness on the amelioration of mood-related outcomes in FMS [81]. Among these new interventions, Mindfulness-Oriented Recovery Enhancement (MORE) is a mental training program that unites complementary aspects of mindfulness training, CBT and positive psychological principles into an integrative treatment strategy [82]. MORE was originally designed as a behavioral medical intervention for addictive behaviors [83, 84], but was more recently adapted to address chronic pain among individuals receiving long-term opioid analgesic therapy [82]. A randomized clinical trial showed that MORE significantly reduces pain symptoms [82] in chronic pain patients. First empirical evidence suggests that MORE is also associated with behavioral and neurophysiological changes in reward processing [85, 86], suggesting that interventions working on the reward system might be efficient for pain reduction.

4. Conclusion

In conclusion, CBT-based treatments specifically working on the awareness of pleasant experiences, such as MORE, seem to be effective in restoring the behavioral and neural responses to reward and also to diminish pain symptoms in chronic pain patients. Although not yet tested in FMS patients, this could be a promising new treatment alternative for this group of patients, in which changes in the DA function and in the responses to reward have been evidenced, but for whom no efficient treatment is available so far.

Conflicts of interest

There are no conflicts of interests.

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Author details

Katharina Ledermann^{1,2*} and Chantal Martin-Sölch¹

1 Unit of Clinical and Health Psychology, IReach Lab, University Fribourg, Fribourg, Switzerland

2 Department of Liaison Psychiatry and Psychosomatics, University Hospital Zurich, University Zurich, Switzerland

*Address all correspondence to: katharina.ledermann@unifr.ch

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