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Relation of dopamine receptor 2 binding to pain perception in female fibromyalgia patients with and without depression – A [^{11}C] raclopride PET-study

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Abstract
Dopamine D2/D3 receptor availability at rest and its association with individual pain perception was investigated using the [^{11}C] raclopride PET-method in 24 female Fibromyalgia (FMS) participants with (FMS+, N=11) and without (FMS−, N=13) comorbid depression and in 17 healthy women. Thermal pain thresholds (TPT) and pain responses were assessed outside the scanner. We compared the discriminative capacity, i.e. the individual's capacity to discriminate between lower and higher pain intensities and the response criterion, i.e. the subject's tendency to report pain during noxious stimulation due to psychological factors. [^{11}C] raclopride binding potential (BP), defined as the ratio of specifically bound non-displaceable radioligand at equilibrium (BP_{ND}) was used as measure of D2/D3 receptor availability. We found significant group effects of BP_{ND} in striatal regions (left ventral striatum, left caudate nucleus and left nucleus accumbens) between FMS+ and FMS− compared to healthy subjects. Correlational analysis showed negative associations between TPT and D2/D3 receptor availability in the left caudate nucleus in FMS-, between TPT and D2/D3 receptor availability in the right caudate nucleus in FMS + and positive associations between TPT and D2/D3 receptor

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availability in the left putamen and right caudate nucleus in healthy controls. The response criterion was positively associated with D2/D3 receptor availability in the right nucleus accumbens in FMS − and negatively with D2/D3 receptor availability in the left caudate nucleus in healthy controls. Finally, no significant associations between D2/D3 receptor availability and discriminative capacity in any of the groups or regions were determined. These findings provide further support for a disruption of dopaminergic neurotransmission in FMS and implicate DA as important neurochemical moderator of differences in pain perception in FMS patients with and without co-morbid depression.

1. Introduction

Fibromyalgia syndrome (FMS) is an idiopathic, diffuse soft-tissue pain syndrome with unclear pathophysiology (Wolfe, 1990). Major depressive disorder (MDD) is the most frequent psychiatric comorbidity in FMS (Fietta et al., 2007). A growing awareness of the role of mesolimbic dopamine (DA) in pain perception, specifically in anti-nociception, has emerged in recent years (Hagelberg et al., 2004; Jarcho et al., 2012; Wood, 2008). Although its precise function in nociceptive processes is only partially understood, DA regulation has been shown to be disrupted in MDD and chronic pain (Epstein et al., 2006; Wood, 2008). Several Positron Emission Tomography (PET)- studies demonstrated altered post-synaptic striatal DA neurotransmission in chronic neuropathic pain syndromes including burning mouth, and atypical facial pain, (Hagelberg et al., 2003a, 2003b; Wood et al., 2007b) while an alteration of pre-synaptic DA transmission was evidenced in FMS (Wood et al., 2007a). Results of *in vivo* DA studies in MDD brought contradictory results (recently reviewed by Savitz and Drevets (2013)). When differences were found they indicated a reduced DA function in MDD that was however influenced by medication. However, postsynpatic DA function has not been investigated so far in FMS and the role of depression in the DA changes observed in chronic pain is not clear.

Moreover a positive correlation between individual pain sensitivity and striatal baseline raclopride binding was observed in healthy volunteers (Hagelberg et al., 2002; Pertovaara et al., 2004; Scott et al., 2006). Pain sensitivity can be determined using the Signal Detection Theory (SDT) that distinguishes two measures: the discriminative capacity, a measure of neurosensory sensitivity, reflecting the subject's ability to discriminate between two stimuli of similar, yet distinct, intensities. A low discriminative capacity is associated with relative insensitivity to noxious stimulation and indicates an attenuation of neural activity in the sensory system (Clark and Mehl, 1971). The response criterion is independent from discriminability and locates the person's overall tendency to report pain; a high value indicates a stoical attitude (Clark and Mehl, 1971). The response criterion and thermal pain threshold (TPT) were shown to be inversely correlated with the D2/D3 Binding Potential (BP) in the right putamen in healthy volunteers, whereas the sensory discriminative capacity was not significantly correlated with the D2/D3 BP in any striatal region (Pertovaara et al., 2004). The association between measures of pain sensitivity with D2/D3 binding has not been yet examined in chronic pain conditions.

Here, we investigated the D2/D3 receptor availability at rest between FMS participants with (FMS+) and without (FMS-) comorbid depression compared to healthy controls using the [^{11}C] raclopride PET method to measure post-synaptic striatal D2/D3 receptor availability. We expected FMS patients to show reduced [^{11}C] raclopride binding (measures as the ratio of specifically bound to non-displaceable radioligand at equilibrium BP_{ND}) in striatal regions compared to healthy controls, reflecting a decreased postsynaptic availability of D2/D3 receptors in these patients as already described at the presynaptic levels (Wood et al., 2007a) and in agreement with findings for neuropathic pain conditions (Hagelberg et al., 2003a, 2003b). We expected the reduction to be more pronounced in FMS+ patients than FMS− patients. Additionally, we aimed to test the association between pain sensitivity and striatal D2/D3 receptor availability with regard to the role of comorbid MDD. We expected FMS patients to have decreased thermal pain thresholds (TPT) and thermal pain tolerance (TOL), correlated to altered D2/D3 receptor availability, but for pain responses to show no correlation with BP_{ND} in striatal regions. Together, we believe that such evidence would indicate that the dopaminergic influence on pain sensitivity is impaired in FMS.

2. Experimental procedures

2.1. Subjects

Given the predominance of women in FMS (Wolfe et al., 1995) and to reduce the heterogeneity of study samples, we decided to only include women in this study. A total of 24 female FMS patients were compared to 17 age- and gender-matched healthy control subjects. Among the FMS patients 11 subjects were diagnosed with comorbid MDD. All FMS+ patients had the onset of MDD subsequent to the FMS diagnosis. A description of clinical and demographic data parameters for the FMS patients is provided in Table 1. FMS patients fulfilling the American College of Rheumatology (ACR) classification criteria for Fibromyalgia (Wolfe et al., 1990) with decreased pressure pain thresholds at a minimum of 11 of 18 specific tender points, located in 9 paired regions of the body, were recruited from the Division of Rheumatology at the University Hospital Zurich. They were recruited through flyers in medical practices, advertisements in newspapers, and advertisements on websites associated with FMS. Controls were recruited through flyers on bulletin boards in