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Review

Striatal dopamine D2 receptors in modulation of pain in humans: a review

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Abstract

We review evidence indicating that the striatum and striatal dopamine D2 receptors are involved in the regulation of pain in humans. Painful stimulation produces an increase in regional cerebral blood flow in the human striatum. Pain is a common symptom in patients with nigrostriatal dopaminergic hypofunction. Positron emission tomography findings show that a low dopamine D2 receptor availability in the striatum of healthy subjects (indicating either a low density of dopamine D2 receptors or a high synaptic concentration of dopamine) is associated with a high cold pain threshold and a low capacity to recruit central pain inhibition by conditioning stimulation. Patients with chronic orofacial pain have higher dopamine D2 receptor availability than their age-matched controls. We propose that the striatal dopamine D2 receptor may be an important target for the diagnosis and treatment of chronic pain.

Keywords: Dopamine D2 receptor; Positron emission tomography; Pain; Striatum

Contents

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1. Introduction

The basal ganglia consist of four main nuclei (the striatum, the globus pallidus, the subthalamic nucleus and the substantia nigra), which provide a major link between the thalamus and the cerebral cortex. These nuclei receive multimodal input from all sensory systems providing a gating station for continuous sensory information, including pain. Dysfunctions of the basal ganglia result in movement disorders indicating an important role in motor control. Depletion of dopamine in the nigrostriatal dopaminergic neurons leads to impaired movement as occurs in Parkinson's disease. The dopaminergic system in the basal ganglia has also been implicated in attention, cognition, and stress (Kaasinen and Rinne, 2002; Kandel et al., 2000; Nieoullon, 2002; Pani et al., 2000). Although less intensively studied, the basal ganglia also appear to have a role in pain (for a comprehensive review, see the work of Chudler and Dong, 1995). In this review, we present evidence suggesting that particularly the striatum, consisting of the putamen and the caudate nucleus, and the striatal dopamine D2 receptor may have a significant role in the modulation of pain sensation both in experimental and clinical conditions.

2. Experimental animal studies

Animal studies suggest that the basal ganglia play a major role in the processing of somatosensory information including noxious stimuli (Chudler and Dong, 1995). Neurons in the substantia nigra and striatum respond to noxious thermal (Chudler, 1998; Barasi, 1979; Pay and Barasi, 1982), mechanical (Chudler, 1998; Chudler et al., 1993; Schultz and Romo, 1987) and electrical stimulation (Bernard et al., 1992; Gao et al., 1990). Electrical and chemical lesions of nigrostriatal neurons have been shown to enhance nociception (Lin et al., 1981, 1984). Chemical lesions of nigrostriatal dopaminergic cell bodies or nerve terminals with 6-hydroxydopamine augment nociceptive responses (Lin et al., 1981; Saade et al., 1997) indicating that nigrostriatal dopaminergic cells are involved in pain regulation. This regulation may be mediated by dopamine D2 receptors as striatal administration of dopamine D2 receptor agonists (such as quinpirole) suppresses and dopamine D2 receptor antagonists (such as eticlopride) enhances pain-related responses in animal experiments (Ben-Sreti et al., 1983; Lin et al., 1981; Magnusson and Fisher, 2000). In contrast, striatal administration of dopamine D1 receptor agonists or antagonists does not influence pain-related responses (Ben-Sreti et al., 1983; Lin et al., 1981; Magnusson and Fisher, 2000). In addition, spinal (reviewed in Millan, 2002) and systemic (Michael-Titus et al., 1990; Morgan and Franklin, 1991) administration of dopamine D2 receptor agonists have been reported to induce antinociception indicating an antinociceptive action for dopamine D2 receptors in general. Interestingly, systemic administration of dopamine D2 receptor antagonists may also produce antinociception, probably due to opioidergic mechanisms (Weizman et al., 2003).

3. Human studies

3.1. Striatal dopamine is involved in pain regulation

Striatal dopamine may have an important role in pain regulation also in humans. This is suggested by the clinical observation that pain is a frequent symptom in degenerative diseases of the nigrostriatal dopaminergic system such as Parkinson's disease (Ford, 1998; Goetz et al., 1986; Witjas et al., 2002). Burning sensations characteristic of central pain have been reported in patients with Parkinson's disease (Ford et al., 1996; Koller, 1984; Schott, 1985; Snider et al., 1976; Witjas et al., 2002). Apomorphine, a mixed dopamine D1/D2 receptor agonist, has been reported to relieve pain in Parkinson's disease (reviewed in Factor, 2004). Although systemically administered levodopa has also been reported to relieve pain symptoms in patients with Parkinson's disease, the effects have been inconsistent. However, there are studies suggesting that levodopa may be useful in treating some other neuropathic pain conditions (Ertas et al., 1998; Kernbaum and Hauchecorne, 1981), and in relieving mechanical hyperalgesia in patients with restless leg syndrome (Stiasny-Kolster et al., 2004). The dopamine reuptake inhibitor bupropion has also been effective in the treatment of neuropathic pain (Semenchuk et al., 2001). Although these reports suggest that dopaminergic agents may have a clinical analgesic effect, they do not give direct evidence for a spinal or supraspinal mechanism of action or the involvement of dopamine D2 receptors.

Brain imaging studies frequently show increased regional cerebral blood flow in the striatum during various types of painful stimulation (Casey et al., 1996; Coghill et al., 1999; 2002; Derbyshire et al., 1997; Iadarola et al., 1998; Jones et al., 1991; Svensson et al., 1997). Although basal ganglia activation is often attributed to the inhibition or preparation of motor activity, it has also been proposed to represent an engagement of cerebral attentional systems during sustained neuralgic pain (Downar et al., 2003). Activation studies, however, do not allow determining whether the increased regional cerebral blood flow in the striatum is associated with the activity of dopaminergic neurons. A recent positron emission tomography study indicates that polymorphism for the catechol-*O*-methyltransferase (COMT) $met^{158}val$ allele influences pain-evoked μ-opioid responses in the striatopallidal pathway in healthy subjects (Zubieta et al., 2003). Individuals with low COMT activity associated with the met^{158} allele of

the COMT enzyme-coding gene show diminished striatopallidal opioid system responses and high pain ratings during acute sustained pain. As low COMT activity indicates high synaptic dopamine levels in the basal ganglia, these findings imply that striatal dopamine may be involved in the opioid-mediated modulation of human pain responses.

3.2. Dopaminergic pain modulation is mediated by the dopamine D2 receptor

Recent positron emission tomography studies show that striatal dopamine D2 receptors may be involved in the regulation of cold pressor pain in healthy subjects. Individuals with a low dopamine D2 receptor availability in the right putamen exhibit a high cold pain threshold, and a low heat pain modulatory capacity by conditioning cold pressor pain is associated with a low dopamine D2 receptor availability in the left putamen (Fig. 1A and B; Hagelberg et al., 2002b). However, the pain modulatory effect of striatal dopamine D2 receptors may depend on the submodality of the pain stimulus, since the magnitude of mechanical hyperalgesia following a freeze lesion of the skin is not associated with striatal dopamine D2 receptor binding potential (Fig. 1C; Hagelberg et al., 2002a).

Dopamine D2 receptors may also play a role in chronic pain. Dopamine D2 receptor hypersensitivity has been proposed to underlie the enhanced prolactin response to buspirone in patients with fibromyalgia (Malt et al., 2003) and the augmented response to apomorphine in individuals suffering from migraine (Blin et al., 1991). Recent positron emission tomography studies show that dopamine D2 receptors in the striatum may be involved in chronic orofacial pain. Patients with burning mouth syndrome (Hagelberg et al., 2003b) and atypical facial pain (Hagelberg et al., 2003a) exhibit higher dopamine D2 receptor availability in the putamen when compared to healthy age- and sex-matched controls. In burning mouth syndrome, 6-[^{18}F]fluorodopa uptake in the putamen is diminished indicating hypofunction of the nigrostriatal dopaminergic system (Jääskeläinen et al., 2001). However, these results have to be cautiously interpreted, as the number of patients in the studies is relatively small.

3.3. Potential mechanisms underlying the association of pain with striatal dopamine D2 receptor availability

Striatal dopamine D2 receptor availability assessed as the binding potential of [^{11}C]raclopride with positron emission tomography represents the number of free receptors and tracer affinity. It is influenced by age (Antonini and Leenders, 1993; Rinne et al., 1993), gender (Pohjalainen et al., 1998b), and genetic factors (Duan et al., 2003; Pohjalainen et al., 1998a). [^{11}C]Raclopride binding potential has also been shown to be sensitive to alterations in the synaptic concentration of endogenous dopamine (Laruelle, 2000). Thus, the underlying neurobiological mechanism for the variability in striatal dopamine D2 receptor binding potential and its association with pain could be a difference in dopamine D2 receptor density, tracer affinity, or in the synaptic concentration of endogenous dopamine. Variability in tracer affinity is unlikely, as it has been shown to be relatively constant between subjects (Farde et al., 1995). A low dopamine D2 receptor density as an underlying cause for a high cold pain threshold and a low capacity to recruit more pain inhibition by conditioning stimulation would imply that dopamine D2 receptors have opposite roles in tonic and dynamic control of pain. Accordingly, a high dopamine D2 receptor density in patients with chronic orofacial pain

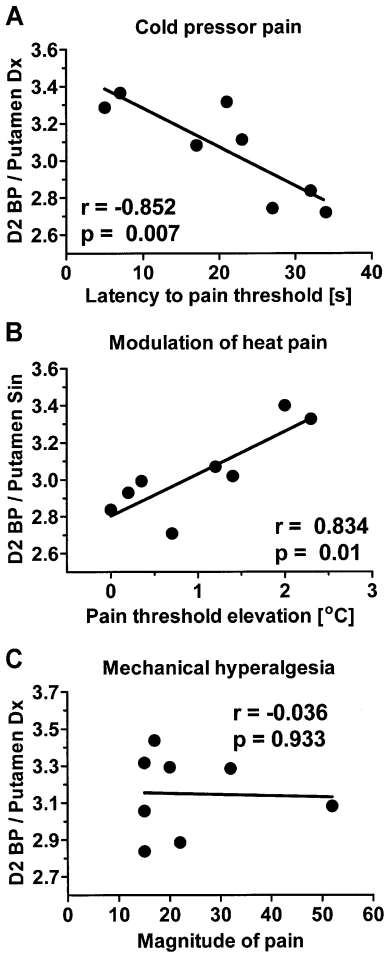

Fig. 1. Association of striatal dopamine D2 receptor binding potential (D2 BP) with the pain response in healthy human subjects. (A) Latency to cold pressor pain threshold was inversely correlated with D2 BP in the right putamen. (B) Increase of heat pain threshold by conditioning cold pressor pain was directly correlated with D2 BP in the left putamen. (C) The magnitude of mechanical hyperalgesia following a freeze lesion of the skin was not associated with D2 BP in the right putamen (shown in the graph) or elsewhere in the striatum. In each graph, *r* indicates the Pearson coefficient of correlation and *p* its significance level. The linear regression curves are also shown in the graphs. Graphs A and B were adopted and modified from Hagelberg et al. (2002b) and graph C calculated from data reported by Hagelberg et al. (2002a).

would indicate that dopamine D2 receptors tonically enhance pain. This explanation, however, contrasts with the results of earlier animal studies, which reported that striatal administration of a dopamine D2 receptor agonist suppresses pain-related responses (Ben-Sreti et al., 1983; Lin et al., 1981; Magnusson and Fisher, 2000). It is also possible that patients with a high striatal dopamine D2 receptor availability have an increased dopamine D2 receptor density representing a plastic change secondary to a chronically active dopamine system in a similar way as has been suggested to be the underlying mechanism for the increased opioid receptor binding potential in patients with chronic pain (Jones et al., 1994, 1999).

Alternatively, variability in the basal synaptic concentration of endogenous dopamine could underlie the observed associations between dopamine D2 receptor availability and pain. According to this explanation, a high basal level of synaptic dopamine would cause a low availability of dopamine D2 receptors and a high cold pain threshold. Moreover, the association between a low availability of dopamine D2 receptors and a low pain modulation capacity could be explained by a reduced capacity to increase dopamine release in response to conditioning stimulation. This is supported by the diminished striatopallidal opioid system response and high pain ratings during acute sustained pain in individuals with low COMT activity (Zubieta et al., 2003). A high availability of striatal dopamine D2 receptors in patients with chronic orofacial pain would thus indicate diminished synaptic dopamine levels and a subsequently deficient control of pain (Hagelberg et al., 2003a,b). In burning mouth syndrome, this is in line with the diminished striatal [^{18}F]fluorodopa uptake (Jääskeläinen et al., 2001), which is considered a good estimate of tissue dopamine levels (Yee et al., 2001). Striatal dopaminergic hypofunction in these pain conditions is further supported by the deficient habituation of the R2 component of the blink reflex (Forssell et al., 2002; Jääskeläinen et al., 1997, 1999), a brainstem reflex controlled by dopamine (Basso and Evinger, 1996; Basso et al., 1996; Evinger et al., 1993), diminished levels of dopamine metabolites in the cerebrospinal fluid of the trigeminal cistern in chronic facial pain patients (Bouckoms et al., 1992), and the high prevalence of burning mouth symptoms reported in patients with Parkinson's disease (Clifford et al., 1998).

3.4. Efferent pathways for the pain modulatory action induced by striatal dopamine D2 receptors

The sensory signal mediating pain sensation may be modulated at various levels of the neuraxis from the spinal dorsal horn to the cerebral cortex. In addition to the modulation of the pain-mediating sensory signal, also modulation of various nonsensory factors, such as response bias or the subject's attitude towards pain, may significantly influence the subject's pain response (Clark, 1974). The association of striatal dopamine D2 receptor binding potential with pain sensitivity in healthy humans and the occurrence of chronic pain in patients with a dysfunction of striatal dopaminergic system do not indicate whether striatal dopamine D2 receptors modulate pain due to a supraspinal action, brainstem-spinal action, or both. The current evidence does not even allow determining whether the influence of striatal dopamine D2 receptors on reported pain is due to action on sensory factors (modulation of pain signals) or nonsensory factors (e.g., dopaminergic modulation of the subject's response criterion). Nevertheless, striatal dopamine D2 receptors appear to influence the subject's response to pain, one way or the other. In animal studies, the pain suppressive effect induced by striatal administration of dopamine D2 receptor agonists has been described for pain-related responses involving supraspinally organized behavior (Lin et al., 1981; Magnusson and Fisher, 2000). This supports the hypothesis that striatal dopamine D2 receptors might predominantly modulate pain responses via supraspinal mechanisms. However, the striatum has direct and indirect efferent connections also to various brainstem structures known to be involved in descending modulation of pain (Chudler and Dong, 1995). Thus, further studies are needed to assess a possible contribution of brainstem-spinal pathways to pain modulation induced by striatal dopamine D2 receptors.

4. Potential implications

Positron emission tomography studies in healthy subjects and in patients with chronic orofacial pain indicate that the nigrostriatal dopaminergic system and striatal dopamine D2 receptors may have an important role in the regulation of experimental and pathophysiological pain. According to these findings, the analgesic effect of dopaminergic compounds may, at least partly, be explained by their action on striatal dopamine D2 receptors. Imaging of striatal dopamine D2 receptors might not only help in determining a potentially underlying dopaminergic dysfunction for chronic pain but also in choosing a mechanism-based selective treatment. Interestingly, motor cortex stimulation, which has proved effective in treating some painful conditions in humans (Brown and Barbaro, 2003), increases release of striatal dopamine (Strafella et al., 2003). This finding suggests that in addition to selective pharmacotherapy with centrally acting dopamine D2 receptor agonists, transcranial magnetic stimulation of the motor cortex may provide an alternative method for suppressing pain due to action on striatal dopamine D2 receptors.

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