REVIEW

The hypothalamic-spinal dopaminergic system: a target for pain modulation

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Abstract

Nociceptive signals conveyed to the dorsal horn of the spinal cord by primary nociceptors are subject to extensive modulation by local neurons and by supraspinal descending pathways to the spinal cord before being relayed to higher brain centers. Descending modulatory pathways to the spinal cord comprise, among others, noradrenergic, serotonergic, γ-aminobutyric acid (GABA)ergic, and dopaminergic fibers. The contributions of noradrenaline, serotonin, and GABA to pain modulation have been extensively investigated. In contrast, the contributions of dopamine to pain modulation remain poorly understood. The focus of this review is to summarize the current knowledge of the contributions of dopamine to pain modulation. Hypothalamic A11 dopaminergic neurons project to all levels of the spinal cord and provide the main source of spinal dopamine. Dopamine receptors are expressed in primary nociceptors as well as in spinal neurons located in different laminae in the dorsal horn of the spinal cord, suggesting that dopamine can modulate pain signals by acting at both presynaptic and postsynaptic targets. Here, I will review the literature on the effects of dopamine and dopamine receptor agonists/antagonists on the excitability of primary nociceptors, the effects of dopamine on the synaptic transmission between primary nociceptors and dorsal horn neurons, and the effects of dopamine on pain in rodents. Published data support both anti-nociceptive effects of dopamine mediated by D2-like receptors and pro-nociceptive effects mediated by D1-like receptors.

Key Words: *A11 nucleus; descending modulation; dopamine; dorsal horn; dorsal root ganglia; D2 receptors; D1 receptors; nociceptors; pain; spinal cord*

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Introduction

Noxious stimuli are detected and transduced into electrical signals by the peripheral terminals of primary nociceptors (pain-sensing neurons) whose cell body is located in the dorsal root ganglia (DRG) (Caterina and Julius, 1999; Julius and Basbaum, 2001; Woolf and Ma, 2007; Basbaum et al., 2009). This initial pain signal is then conveyed by primary nociceptors to the dorsal horn of the spinal cord (DHSC), the first relay station in the pain pathway where pain signals are modulated and integrated by local neurons and by descending pathways from supraspinal nuclei before being relayed to higher brain centers by dorsal horn projection neurons (Basbaum and Fields, 1984; Millan, 2002; Todd, 2010). There is strong consensus that after the initial activation of nociceptors, the final experience of pain is the result of complex interactions between the dorsal horn neuronal circuits engaged to transduce and transmit the pain signals and the modulatory actions from higher brain centers whose activity can be influenced by emotion, motivation, anxiety, and other cognitive states that can ultimately exacerbate or mitigate the overall pain experience associated with specific noxious stimuli.

Neuronal pathways involved in the descending modulation of pain originate mainly from the hypothalamus, the amygdala, and the anterior cingulate cortex with projections to the midbrain periaqueductal gray and to brainstem nuclei such as the locus coeruleus and the rostral ventral medulla. Descending pathways projecting to the spinal cord include, among others, noradrenergic, serotonergic, γ-aminobutyric acid (GABA)ergic, and dopaminergic fibers. For the contributions of descending noradrenergic, serotonergic, and GABAergic pathways to pain modulation I refer to some excellent and extensive papers and reviews (Basbaum and Fields, 1984; Fields et al., 1991; Porreca et al., 2001; Millan, 2002; Benarroch, 2008; Ossipov et al., 2010, 2014; Bannister and Dickenson, 2016; Chen et al., 2017; Francois et al., 2017). Here I will focus on the contribution of the descending dopaminergic pathway to pain modulation in the DHSC. The A11 nucleus located in the periventricular, posterior region of the hypothalamus contains at least three neurochemical-distinct types of neurons: neurons expressing tyrosine hydroxylase (TH), the rate limiting enzyme in the synthesis of catecholamines, necessary to synthetize L-3,4-dihydroxyphenylalanine; neurons expressing calbindin; and neurons expressing both TH and calbindin (Ozawa et al., 2017). TH-expressing neurons in the A11 nucleus also express the aromatic L-amino acid decarboxylase, the enzyme that converts L-3,4-dihydroxyphenylalanine to dopamine, and the vesicular monoamine transporter 2 which is necessary for packaging dopamine into vesicles, strongly supporting the dopaminergic phenotype of the TH-expressing neurons in the A11 nucleus. In contrast, TH-expressing neurons in the A11 nucleus lack the dopamine transporter and D2 receptors (Pappas et al., 2008; Barraud et al., 2010; Koblinger et al., 2014). Hypothalamic A11 dopaminergic neurons project to all levels of the spinal cord and provide the main source

of spinal dopamine (Bjorklund and Skagerberg, 1979; Swanson and Kuypers, 1980; Skagerberg et al., 1982; Skagerberg and Lindvall, 1985; Holstege and Kuypers, 1987; Mouchet et al., 1992; Ridet et al., 1992; Holstege et al., 1996; Qu et al., 2006; Benarroch, 2008; Koblinger et al., 2014). Descending fibers from the A11 nucleus terminate both in the dorsal and ventral horn of the spinal cord and establish axodendritic synapses or terminate sparsely, suggesting, in addition to the classical synaptic transmission, also the possibility of volume transmission (Ridet et al., 1992). In turn, the hypothalamic A11 nucleus receives innervation from midbrain and brainstem nuclei involved in pain modulation, such as the periaqueductal gray and the parabrachial nucleus, and from cortical areas, including the cingulate cortex, infralimbic cortex, and striata terminalis (Abrahamson and Moore, 2001; Qu et al., 2006), involved in the affective and emotional aspects of pain and the behavioral responses to aversive or threatening stimuli (Rainville et al., 1997; Johansen et al., 2001; Oertel et al., 2008; King et al., 2009; Qu et al., 2011; Hayes and Northoff, 2012; Thibault et al., 2014). Although beyond the focus of this review, it should be noted that different populations of DRG neurons, including the C low threshold mechanoreceptors specialized in detecting low-threshold mechanosensory stimuli (Seal et al., 2009; Olausson et al., 2010; Li et al., 2011) and those innervating pelvic organs (Price and Mudge, 1983; Philippe et al., 1993; Brumovsky et al., 2006, 2012), as well as some spinal interneurons (Hou et al., 2016), express TH and thus might provide an additional source of spinal dopamine. Nonetheless, it remains to be determined which catecholamine(s) are synthetized and released from these TH-expressing neurons (Lackovic and Neff, 1980; Philippe et al., 1993; Weil-Fugazza et al., 1993). The author has performed a PubMed literature search of articles published in the period 1970–2018 with the key words: descending pain modulation; neuropathic pain; inflammatory pain; chronic pain; dopamine; hypothalamus; A11 nucleus; spinal cord; dorsal horn; dorsal root ganglia; D1 receptors; D2 receptors; D3 receptors; D4 receptors; nociceptors.

Dopamine Receptors

Two families of dopamine receptors mediate the function of dopamine: D1-like receptors (comprising D1 and D5 receptors) and D2-like receptors (comprising D2, D3, and D4 receptors). D1 and D5 receptors are coupled to $G\alpha_s$ proteins which stimulate the activity of adenylyl cyclase and the production of 3′,5′-cyclic adenosine monophosphate; D2, D3, and D4 receptors are coupled to $G\alpha_{i/o}$ proteins which inhibit the activity of adenylyl cyclase and the production of 3′,5′-cyclic adenosine monophosphate (Missale et al., 1998; Vallone et al., 2000; Beaulieu et al., 2015). All dopamine receptors are expressed in the spinal cord and in the mesencephalic trigeminal nucleus (a structure functionally equivalent to the DHSC), with the density and the level of expression that may change in different laminae (Dubois et al., 1986; Bhargava and Gulati, 1990; Yokoyama et al., 1994; Matsumoto et al., 1996; van Dijken et al., 1996; Lazarov and Pilgrim, 1997; Ciliax et al., 2000; Levant and McCarson, 2001; Bergerot et al., 2007; Zhu et al., 2007; Charbit et al., 2009). In addition to the spinal cord and the mesencephalic trigeminal nucleus, it has been shown that dopamine receptors are expressed also in DRG neurons (Xie et al., 1998; Galbavy et al., 2013) and in the trigeminal ganglion neurons (functionally equivalent to DRG neurons) (Peterfreund et al., 1995), suggesting the possibility that they are also expressed on primary afferent fibers making synaptic contacts in the dorsal horn of the spinal cord. The expression of dopamine receptors on primary afferent fibers is of particular significance because it suggests that dopamine exerts its effects not only at postsynaptic sites, but also at presynaptic sites.

Effects of Dopamine on Dorsal Root Ganglia Neurons and Spinal Neurons

In vitro studies have provided compelling evidence that dopamine can modulate the intrinsic excitability and the synaptic transmission of DRG neurons and spinal neurons involved in pain signaling. In the dorsal root ganglia, dopamine regulates the intrinsic excitability of DRG neurons (Gallagher et al., 1980; Abramets and Samoilovich, 1991; Molokanova and Tamarova, 1995; Galbavy et al., 2013), the activity of calcium channels (Marchetti et al., 1986; Formenti et al., 1993, 1998), tetrodotoxin-sensitive sodium channels (Galbavy et al., 2013), and transient receptor potential vanilloid type 1 receptors (Lee et al., 2015; Chakraborty et al., 2016). In the DHSC, dopamine inhibits the excitatory postsynaptic potential (Garraway and Hochman, 2001) and the extracellular field potential (Garcia-Ramirez et al., 2014) recorded from deep dorsal horn neurons, as well as the action potentials evoked in substantia gelatinosa neurons upon stimulation of the dorsal root (Tamae et al., 2005). Inhibitory effects of dopamine have been also reported on spinal reflexes using the intact spinal cord preparation *in vitro*. Electrical stimulation of the dorsal root elicits a monosynaptic stretch reflex potential (MSR) followed by a slow ventral root potential at the corresponding ventral root. The MSR is an A fiber-(group I muscle spindle afferents) evoked response. On the other hand, the slow ventral root potential is a C fiber-evoked polysynaptic response believed to reflect nociceptive transmission in the spinal cord. In one study, low doses of dopamine (1 μM) decreased the MSR amplitude in wild-type mice and increased it in D3 knockout mice (Clemens and Hochman, 2004). The D3 receptor agonists pergolide and PD 128907 reduced the MSR amplitude in wild-type but not D3 knockout mice, while the D3 receptor antagonists GR 103691 and nafadotride increased the MSR in wild-type but not in D3 knockout mice. In comparison, the D2 agonists bromocriptine and quinpirole depressed the MSR in both groups (Clemens and Hochman, 2004). In another study, low doses of dopamine (1 μM or less) were found to depress the slow ventral root potential, while no effects were reported on the MSR. The inhibitory effects of dopamine on the slow ventral root potential were attenuated in the presence of D1-like receptor antagonists (SCH23390 and LE300) and mimicked by D1-like receptor agonists

(SKF83959 and SKF81297) (Kawamoto et al., 2012), suggesting an anti-nociceptive effect upon activation of D1-like receptors in the ventral root. These observations raise the intriguing possibility that activation of D1-like receptors may have opposite effects according to their localization, with pro-nociceptive effects in the DHSC *versus* anti-nociceptive effects in the ventral horn. In a recent study carried out in horizontal spinal cord slices *in vitro* (Lu et al., 2018), dopamine was found to inhibit the excitatory postsynaptic currents recorded from lamina I projection neurons upon stimulation of the L4–5 dorsal root. This study provided three additional pieces of evidence to support a role for dopamine in the modulation of pain signaling in the DHSC. First, dopamine was found to inhibit the excitatory postsynaptic currents elicited by stimulation of high threshold Aδ- and C-fiber nociceptors, both at baseline and after peripheral inflammation induced by injection of complete Freund's adjuvant in the ipsilateral hindpaw. Second, it was shown that dopamine can inhibit the synaptic transmission from primary nociceptors to lamina I projection neurons ascending to the parabrachial nucleus, a well-established spinal cord circuit for pain transmission from the spinal cord to supraspinal nuclei (Marshall et al., 1996; Todd et al., 2000; Spike et al., 2003; Li et al., 2015). Third, this study provided the first clear demonstration that dopamine can modulate pain signals by acting on presynaptic targets (D3 and D4 receptors) in addition to postsynaptic targets. The findings of the above *in vitro* studies are well complemented by electrophysiological recordings *in vivo*. Electrical or pharmacological stimulation of the A11 nucleus were found to inhibit the nociceptive responses recorded from spinal dorsal neurons or trigeminocervical complex neurons (Fleetwood-Walker et al., 1988; Bergerot et al., 2007; Charbit et al., 2009; Taniguchi et al., 2011). Similarly, C-fiber-evoked action potential firing of trigeminal wide dynamic range neurons was inhibited or enhanced by D2-like receptor agonists or antagonists, respectively (Lapirot et al., 2011). In addition, the levels of dopamine in the lumbar spinal cord are decreased following lesion of A11 nuclei with 6-hydroxydopamine (Zhao et al., 2007). Taken together, these studies well support a role for the A11 nucleus and the descending dopaminergic pathway to modulation of pain signaling in the DHSC.

Functional Studies *In Vivo*

Several behavioral studies *in vivo* support the anti-nociceptive effects of dopamine in the DHSC, and there is consensus that these effects are mediated by activation of postsynaptic D2-like receptors, in line with their coupling to inhibition of adenylyl cyclase and subsequent reduction in 3′,5′-cyclic adenosine monophosphate levels. These studies include: 1) electrical stimulation of the A11 nucleus selectively inhibited the nociceptive response of spinothalamic and spinomesencephalic neurons located in laminae III-V of the dorsal horn, and this effect could be mimicked by D2 agonists and blocked by D2 antagonists (Fleetwood-Walker et al., 1988). 2) Intrathecal administration of apomorphine increased the hot plate response latency and the tail flick latency, an effect that was reversed by prior intrathecal administration of cis-flupenthixol (D2 antagonist) (Jensen and Smith, 1982; Jensen and Yaksh, 1984). 3) Intrathecal administration of apomorphine increased the tail flick latency, an effect that was mimicked by LY171555 (D2 agonist), but not by SKF38393 (D1/D5 agonist), and blocked by D2 antagonists (Barasi and Duggal, 1985; Barasi et al., 1987). 4) A similar increase in the tail flick latency was observed upon intrathecal administration of dopamine, an effect that was reversed by sulpiride (D2 antagonist), but not SCH23390 (D1/D5 antagonist) (Liu et al., 1992). 5) Intrathecal administration of dopamine or quinpirole (D2 agonist), but not SKF38393 (D1/D5 agonist), increased the mechanical threshold measured with the von Frey anesthesiometer (Tamae et al., 2005). 6) Intrathecal administration of LY171555 (D2 agonist), but not SKF38393 (D1/D5 agonist), rescued the thermal withdrawal latency measured with the Hargreaves apparatus in a model of carrageenan-induced peripheral inflammation (Gao et al., 2001). 7) Intrathecal administration of quinpirole (D2 agonist) increased the mechanical threshold measured with the von Frey anesthesiometer, while no effects were observed on the thermal withdraw latency measured with the Hargreaves apparatus, and the effect was reversed by a mix of D2, D3, and D4 antagonists (Almanza et al., 2015). These findings point to a contribution of D3 and D4 receptors, in addition to D2 receptors, in mediating the effects of dopamine in the DHSC, and are consistent with recent findings in spinal cord slices *in vitro* (Lu et al., 2018). 8) A decreased thermal withdraw latency was reported in two studies carried out in D3 knockout mice, suggesting a contribution of D3 receptors to thermal stimuli as well (Keeler et al., 2012; Meneely et al., 2018), in addition to mechanical stimuli reported by Alamnza et al. (2015). Nonetheless, these results in the global D3 knockout mice need to be confirmed in conditional D3 knockout mice to exclude possible developmental changes of dopamine receptors. 9) Activation of D2-like receptors with quinpirole inhibited, whereas blocking D2-like receptors with sulpiride enhanced both facial formalin- and capsaicin-evoked pain behavior and C-fiber-evoked action potential firing of trigeminal wide dynamic range neurons (Lapirot et al., 2011).

Behavioral studies *in vivo* also support a role for dopamine and D2-like receptors in the modulation of neuropathic pain. These studies include: 1) intrathecal administration of levodopa produced a decrease in tactile and cold allodynia measured with the von Frey anesthesiometer and acetone drop, respectively, in the chronic constriction injury model of the sciatic nerve, an effect that was blocked by sulpiride (D2 antagonist) (Cobacho et al., 2010). 2) In a follow up study from the same group, quinpirole (D2 agonist) decreased both tactile and cold allodynia in the chronic constriction injury model of the sciatic nerve (Cobacho et al., 2014). 3) In a recent paper, using a trigeminal neuropathic pain model in mice, it was shown that stimulation of A11 dopaminergic neurons with designer receptor exclusively activated by designer drug was able to attenuate trigeminal neuropathic pain *via* activation of D2 receptors (Liu et al.,

2018). Nonetheless, the authors used a dopamine transporter-Cre mouse to express designer receptor exclusively activated by designer drugs in A11 dopaminergic neurons and did not provide any data to support the selectivity of this approach. This may raise some concerns considering that other groups have provided evidence for the lack of dopamine transporter expression in TH-expressing neurons in the A11 nucleus (Barraud et al., 2010; Koblinger et al., 2014).

There are also studies that have reported pro-nociceptive effects of dopamine mediated by postsynaptic D1/D5 receptors, consistent with their coupling to activation of adenylyl cyclase and subsequent increase in 3′,5′-cyclic adenosine monophosphate levels. These studies include: 1) intrathecal administration of SCH23390 (D1/D5 antagonist) was shown to reduce the thermal hyperalgesia induced by intra plantar injection of carrageenan (Gao et al., 2001), consistent with the interpretation that activation of D1/D5 receptor by dopamine promotes a pro-nociceptive effect. 2) Activation of D1/D5 receptors with SKF38393 was shown to induce long term potentiation of C-fibers evoked field potentials in the DHSC *in vivo*, and the effect was abolished by pretreatment with SCH23390 (D1/D5 antagonist) (Yang et al., 2005). 3) In two recent publications from the same group, it was suggested that activation of postsynaptic D1/D5 receptors may promote the transition to chronic pain in a model of hyperalgesic priming (Kim et al., 2015; Megat et al., 2018).

Conclusions

A11 dopaminergic neurons project to all levels of the spinal cord and provide the main source of spinal dopamine. A11 dopaminergic neurons are predominantly sensory driven, responding to tactile and visual sensory modalities (Reinig et al., 2017). Like other midbrain and brainstem nuclei involved in the descending modulation of pain, the A11 nucleus is interconnected with higher cortical areas devoted to encoding the affective and emotional aspects of pain, providing a mechanistic basis to explain how exogenous factors can act on the dopaminergic, noradrenergic, and serotonergic systems to influence the overall experience of pain.

Based on the data reported in the literature, there is a consensus that dopamine can exert both anti-nociceptive and pro-nociceptive effects, with activation of D2-like receptors mediating the anti-nociceptive effects, and activation of D1-like receptors mediating the pro-nociceptive effects. Although some recent studies have suggested that activation of D3 and D4 receptors, in addition to D2 receptors, may mediate the anti-nociceptive effects of dopamine in the DHSC (Almanza et al., 2015; Lu et al., 2018), additional pharmacological studies, possibly combined with genetic tools, are needed to determine the contributions of specific dopamine receptors to pain modulation. For future translational aspects, it will be beneficial to fully characterize the expression of dopamine receptors in specific cell types in the DHSC and DRG neurons, and establish how different dopamine receptors will modulate the activity of specific neurons and dorsal horn neuronal circuits involved in pain signaling.

Dysregulation or disengagement of the descending inhibitory pain modulatory systems may be responsible for promoting and/or maintaining chronic pain. A better understanding of the mechanisms by which dopamine modulates pain can provide novel therapeutic targets to treat or ameliorate chronic pain.

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