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

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Abstract

Noxious 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

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 Dickinson, 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 neurochemically-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 spuriously, 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 striatal terminals (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; Bruunovsky 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 Gαs, proteins which stimulate the activity of adenyl cyclase and the production of 3′,5′-cyclic adenosine monophosphate; D2, D3, and D4 receptors are coupled to Gαi, proteins which inhibit the activity of adenyl 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 amplitude in wild-type mice and increased it in D3 knockout mice. In comparison, the D2 agonists bromocriptine and quinpirole decreased the MSR amplitude in wild-type but not in 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.
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 withdrawal 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 (Liu et al., 2018). 8) A decreased thermal withdrawal 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 Almanza 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., 2014).
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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References

Abrahamson EE, Moore RY (2001) The posterior hypothalamic area: chemoarchitecture and afferent connections. Brain Res 889:1-22.

Abramets, II, Samoilovich IM (1991) Analysis of two types of dopaminergic responses of neurons of the spinal ganglia of rats. Neurosci Behav Physiol 21:435-440.

Almanza A, Simon-Arceo K, Coffeen U, Fuentes-Garcia R, Contreras B, Pellicer F, Mercado F (2015) A D2-like receptor family agonist produces analgesia in mechanonociception but not in thermoneociception at the spinal cord level in rats. Pharmacol Biochem Behav 137:119-125.

Bannister K, Dickenson AH (2016) What do monoamines do in pain modulation? Curr Opin Support Palliat Care 10:143-148.

Barasi S, Duggal KN (1985) The effect of local and systemic application of dopaminergic agents on tail flick latency in the rat. Eur J Pharmacol 117:287-294.

Barasi S, Ben-Sreti MM, Clatworthy AL, Duggal KN, Gonzalez JP, Robertson J, Rooney KE, Sewell RD (1987) Dopamine receptor-mediated spinal antinociception in the normal and haloperidol pretreated rat: effects of sulpiride and SCH 23390. Br J Pharmacol 90:15-22.

Barraud Q, Obeid I, Aubert I, Barriere G, Contamin H, McGuire S, Ravenscroft P, Porras G, Tison F, Bezard E, Ghoseiray I (2010) Neu-ronanatomical study of the A11 diencephalospinal pathway in the non-human primate. PLoS One 5:e13306.

Basbaum AI, Fields HL (1984) Endogenous pain control systems: brainstem spinal pathways and endorphin circuitry. Annu Rev Neurosci 7:309-338.

Basbaum AI, Bautista DM, Scherrer G, Julius D (2009) Cellular and molecular mechanisms of pain. Cell 139:267-284.

Beaulieu JM, Espinoza S, Gainetdinov RR (2015) Dopamine receptors - IUPHAR Review 13. Br J Pharmacol 172:1-23.

Benarroch EE (2008) Descending monoaminergic pain modulation: bidirectional control and clinical relevance. Neurology 71:217-221.

Bergerot A, Storer RJ, Goadby PJ (2007) Dopamine inhibits trigemi-novascular transmission in the rat. Ann Neurol 61:251-262.

Bhargava HN, Gulati A (1990) Modification of brain and spinal cord dopamine D1 receptors labeled with [3H]SCH 23390 after morphine withdrawal from tolerant and physically dependent rats. J Pharma col Exp Ther 252:901-907.

Bjorklund A, Skagerberg G (1979) Evidence for a major spinal cord projection from the diencephalic A11 dopamine cell group in the rat. Brain Res 177:170-175.

Brumovsky P, Villar MJ, Hokfelt T (2006) Tyrosine hydroxylase is expressed in a population of small dorsal root ganglion neurons in the adult mouse. Exp Neurol 200:153-165.
Brunovsky PR, La JH, McCarthy CJ, Hokfelt T, Gebhart GF (2012) Dorsal root ganglion neurons innervating pelvic organs in the mouse express tryptase hydroxylase. Neuroscience 223:77-91.

Caterina MJ, Julius D (1999) Sense and specificity: a molecular identity for nociceptors. Curr Opin Neurobiol 9:525-530.

Chakraborty S, Rebicchi M, Kaczocha M, Puopolo M (2016) Dopamine modulation of transient receptor potential vanilloid type 1 (TRPV1) receptor in dorsal root ganglia neurons. J Physiol 594:1627-1642.

Charbit AR, Akerman S, Holland PR, Goadsby PJ (2009) Neurons of the dopaminergic/calcitonin gene-related peptide A11 cell group modulate neuronal firing in the trigeminocephalic complex: an electrophysiological and immunohistochemical study. J Neurosci 29:12532-12541.

Chen Q, Roeder Z, Li MH, Zhang Y, Ingram SL, Heinricher MM (2017) Optogenetic evidence for a direct circuit linking nociceptive transmission through the parabrachial complex with pain-modulating neurons of the rostral ventromedial medulla (RVM). eNeuro 4:ENEURO.0022-17.2017.

Cilius BJ, Nash N, Helman C, Sunahara R, Hartney A, Tiberi M, Rye DB, Caron MG, Niznik HB, Levey AI (2000) Dopamine D(5) receptor immunolocalization in rat and monkey brain. Synapse 37:125-145.

Clements S, Hochman S (2004) Conversion of the modulatory actions of dopamine on spinal reflexes from depression to facilitation in D3 receptor knock-out mice. J Neurosci 24:11337-11345.

Cobacho N, de la Calle JL, Paine CL (2014) Dopaminergic modulation of neuropathic pain: analgesia in rats by a D2-type receptor agonist. Brain Res Bull 106:62-71.

Cobacho N, de la Calle JL, Gonzalez-Escalada JR, Paine CL (2010) Levodopa analgesia in experimental neuropathic pain. Brain Res Bull 83:304-309.

Dubois A, Savasta M, Curet O, Scotton B (1986) Autoradiographic distribution of the D1 agonist [3H]SKF 38393, in the rat brain and spinal cord. Comparison with the distribution of D2 dopamine receptors. Neuroscience 19:125-137.

Fields HL, Heinricher MM, Mason P (1991) Neurontinized in nociceptive modulatory circuits. Annu Rev Neurosci 14:219-245.

Fleetwood-Walker SM, Hope PJ, Mitchell R (1988) Antinociceptive actions of descending dopaminergic tracts on cat and rat dorsal horn somatosensory neurons. J Physiol 399:335-348.

Formenti A, Arrignoni E, Mancia M (1993) Two distinct modulatory effects on calcium channels in adult rat sensory neurons. Biophys J 64:1029-1037.

Formenti A, Martina M, Plebani A, Mancia M (1998) Multiple modulatory effects of dopamine on calcium channel kinetics in adult sensory neurons. J Physiol 509:395-409.

Francois A, Low SA, Sypek EI, Christensen AJ, Sotoudeh C, Beier KT, Formenti A, Martina M, Plebani A, Mancia M (1998) Multiple modulatory effects of dopamine on calcium channel kinetics in adult sensory neurons. J Physiol 509:395-409.

Levodopa analgesia in experimental neuropathic pain. Brain Res 145.

Kim JY, Tillu DV, Quinn TL, Mejia GL, Shy A, Asiedu MN, Murad E, Schumann AP, Totsch SK, Sorge RE, Marth M, Suss T, Dussor G, Price TJ (2015) Spinal dopaminergic projections control the transition to pathological pain plasticity via a D1/D5-mediated mechanism. J Neurosci 35:6307-6317.

King T, Vera-Portacarrero L, Gutierrez T, Vanderah TW, Dussor G, Lai J, Fields HL, Porreca F (2009) Unmasking the tonic-aversive state in neuropathic pain. Nat Neurosci 12:1364-1366.

Koblinger K, Fuzesi T, Ejdrygiewicz J, Krajacic A, Bains JS, Whelan PJ (2014) Characterization of A11 neurons projecting to the spinal cord of mice. PLoS One 9:e109636.

Lackovic Z, Neff NH (1980) Evidence for the existence of peripheral dopaminergic neurons. Brain Res 193:289-292.

Lapiort O, Melin C, Modolo A, Nicolas C, Messaudy Y, Moncondurt L, Artola A, Laccarin P, Dallal R (2011) Tonic and phasic descending dopaminergic controls of nociceptive transmission in the medullary dorsal horn. Pain 152:1821-1831.

Lazarov N, Pilgrim C (1997) Localization of D1 and D2 dopamine receptors in the rat mesencephalic trigeminal nucleus by immunocytochemistry and in situ hybridization. Neurosci Lett 236:83-87.

Lee DW, Cho PS, Lee HK, Lee SH, Jung SJ, Oh SB (2015) Trans-activation of TRPV1 by D1R in mouse dorsal root ganglion neurons. Biochem Biophys Res Commun 465:832-837.

Levant B, McCarrison KE (2001) D3 dopamine receptors in rat spinal cord: implications for sensory and motor function. Neurosci Lett 303:9-12.

Li J, Kritzer E, Craig PE, Baccei ML (2015) Aberrant synaptic integration in adult lamina I projection neurons following neonatal tissue damage. J Neurosci 35:2438-2451.

Li L, Rutlin M, Aabraira YE, Cassidy C, Kus L, Gong S, Jankowski MP, Luo W, Heintz N, Koerber HR, Woodbury CJ, Ginty DD (2011) The functional organization of cutaneous low-threshold mechanosensory neurons. Cell 147:1615-1627.

Liu QS, Qiao JT, Dafny N (1992) D2 dopamine receptor involvement in spinal dopamine-produced antinociception. Life Sci 51:1485-1493.

Liu S, Tang Y, Shu H, Tatum D, Bai Q, Crawford J, Xing Y, Lobo MK, Bellinger L, Kramer P, Tao F (2018) Dopamine receptor D2, but not D1, mediates descending dopaminergic pathway-generated analgesic effect in a trigeminal neuropathic pain mouse model. Pain doi: 10.1097/J.Pain.0000000000001414.

Lu Y, Doroshenko M, Lauzadis J, Kaniyip MP, Rebecchi MJ, Kaczocha M, Puopolo M (2018) Presynaptic inhibition of primary nociceptive signals to dorsal horn lamina I neurons by dopamine. J Neurosci 38:8809-8821.

Marchetti C, Carbone E, Lux HD (1986) Effects of dopamine and noradrenaline on Ca channels of cultured sensory and sympathetic neurons of chick. Pfluegers Arch 406:104-111.
Puopolo M (2019) The hypothalamic-spinal dopaminergic system: a target for pain modulation. Neuro Regen Res 14(6):925-930. doi:10.4103/1673-5374.250567

Marshall GE, Shehab SA, Spike RC, Todd AJ (1996) Neurokinin-1 receptors on lumbar spinohalamic neurons in the rat. Neuroscience 72:255-263.

Matsumoto M, Hidaka K, Tada S, Tasaki Y, Yamaguchi T (1996) Low levels of mRNA for dopamine D4 receptor in human cerebral cortex and striatum. J Neurochem 66:915-919.

Megat S, Shiers S, Moy JK, Barragan-Iglesias P, Pradhan G, Seal RP, Dussor G, Price TJ (2016) A critical role for dopamine D5 receptors in pain chronicity in male mice. J Neurosci 36:379-397.

Meneely S, Dinkins ML, Kassai M, Luy S, Liu Y, Lin CT, Brewer K, Li Y, Clemens S (2018) Differential dopamine D1 and D3 receptor modulation and expression in the spinal cord of two mouse models of restless legs syndrome. Front Behav Neurosci 12:199.

Millan MJ (2002) Descending control of pain. Prog Neurobiol 66:355-474.

Missale C, Nash SR, Robinson SW, Jaber M, Caron MG (1998) Dopamine receptors: from structure to function. Physiol Rev 78:189-225.

Morokonova EA, Tamarova ZA (1995) The effects of dopamine and serotonin on rat dorsal root ganglion neurons: an intracellular study. Neurosci Lett 185:89-92.

Mouchet P, Manier M, Feuerstein C (1992) Immunohistochemical study of the catecholaminergic innervation of the spinal cord of the rat using specific antibodies against dopamine and noradrenaline. J Chem Neuroanat 5:427-440.

Oertel BG, Freibisch C, Wallenhorst T, Hummel T, Geisslinger G, Lantehrmann H, Lortsch J (2008) Differential opioid action on sensory and affective cerebral pain processing. Clin Pharmacol Ther 83:577-588.

Olausson H, Wessberg J, Morrison I, McGlone F, Vallbo A (2010) The neurophysiology of unmethylated tactile afferents. Neurosci Biobehav Rev 34:185-191.

Ossipov MH, Dussor GO, Porreca F (2010) Central modulation of pain. J Clin Invest 120:3779-3787.

Ossipov MH, Morimura K, Porreca F (2014) Descending pain modulation and chronification of pain. Curr Opin Support Palliat Care 8:143-151.

Ozawa H, Yamaguchi T, Hamaguchi S, Yamaguchi S, Ueda S (2017) Three types of A11 neurons project to the rat spinal cord. Neurochem Res 42:2142-2153.

Pappas SS, Behrouz B, Janis KL, Goudreau JL, Lookingland KJ (2008) Lack of D2 receptor mediated regulation of dopamine synthesis in A11 diencephalospinal neurons in male and female mice. Brain Res 1214:1-10.

Peterfreund RA, Kosofsky BE, Fink JS (1995) Cellular localization of dopamine D2 receptor messenger RNA in the rat trigeminal ganglia. Anesth Analg 81:1181-1185.

Philippe E, Zhou C, Audet G, Geffard M, Gaulin F (1993) Expression of dopamine by chick primary sensory neurons and their related targets. Brain Res Bull 30:227-230.

Porreca F, Burgess SE, Gardell LR, Vanderah TW, Malan TP, Jr., Osipov MH, Lappi DA, Lai J (2001) Inhibition of neuropathic pain by selective ablation of brainstem medullary cells expressing the mu-opioid receptor. J Neurosci 21:5281-5288.

Price J, Mudge AW (1983) A subpopulation of rat dorsal root ganglion neurons is catecholaminergic. Nature 301:241-243.

Qu C, King T, Okun A, Lai J, Fields HL, Porreca F (2011) Lesion of the rostral anterior cingulate cortex eliminates the aversiveness of spontaneous neuropathic pain following partial or complete axotomy. Pain 152:1641-1648.

Qu S, Ondo WG, Zhang X, Xie WJ, Pan TH, Le WD (2006) Projections of diencephalic dopamine neurons into the spinal cord in mice. Exp Brain Res 168:152-156.

Rainville P, Duncan GH, Price DD, Carrier B, Bushnell MC (1997) Pain affect encoded in human anterior cingulate but not somatosensory cortex. Science 277:968-971.

Reinig S, Drierewer A, Arenenberg AB (2017) The descending diencephalicic dopamine system is tuned to sensory stimuli. Curr Biol 27:318-333.

Riedt JL, Sandillon F, Rajaofetra N, Geffard M, Privat A (1992) Spinal dopaminergic system of the rat: light and electron microscopic study using an antiseraum against dopamine, with particular emphasis on synaptic incidence. Brain Res 598:233-241.

Seal RP, Wang X, Guan Y, Raja SN, Woodbury CJ, Basbaum AI, Edwards RH (2009) Injury-induced mechanical hypersensitivity requires C-few threshold mechanoreceptors. Nature 462:651-655.

Skagerberg G, Lindvall O (1985) Organization of diencephalic dopamine neurones projecting to the spinal cord in the rat. Brain Res 342:340-351.

Skagerberg G, Bjorklund A, Lindvall O, Schmidt RH (1982) Origin and termination of the diencephalo-spinal dopamine system in the rat. Brain Res Bull 9:237-244.

Spike RC, Puskas Z, Andrew D, Todd AJ (2003) A quantitative and morphological study of projection neurons in lamina I of the rat lumbar spinal cord. Eur J Neurosci 18:2433-2448.

Swanson LW, Kuyper HS (1980) The paraventricular nucleus of the hypothalamus: cytoarchitectonic subdivisions and organization of projections to the pituitary, dorsal vagal complex, and spinal cord as demonstrated by retrograde fluorescence double-labeling methods. J Comp Neurol 194:555-570.

Tamae A, Nakatsuka T, Koga K, Kato G, Furue H, Katafuchi T, Yoshimura M (2005) Direct inhibition of substantia gelatinosa neurones in the rat spinal cord by activation of dopamine D2-like receptors. J Physiol 568:243-253.

Tanimaguchi W, Nakatsuka T, Miyazaki N, Yamada H, Takeda D, Fujita T, Kumamoto E, Yoshida M (2011) In vivo patch-clamp analysis of dopaminergic antinociceptive actions on substantia gelatinosa neurones in the spinal cord. Pain 152:95-105.

Thibault K, Lin WK, Rancillac A, Fan M, Snollaerts T, Sordoilet V, Hamon M, Smith GM, Lenkei Z, Pezet S (2014) BDNF-dependent plasticity induced by peripheral inflammation in the primary sensory and the cingulate cortex triggers cold allodynia and reveals a major role for endogenous BDNF as a tun of the affective aspect of pain. J Neurosci 34:14739-14751.

Todd AJ (2010) Neuronal circuitry for pain processing in the dorsal horn. Nat Rev Neurosci 11:823-836.

Todd AJ, McGill MM, Shehab SA (2000) Neurokinin 1 receptor expression by neurons in laminae I, III and IV of the rat spinal dorsal horn that project to the brainstem. Eur J Neurosci 12:689-700.

Vallone D, Picetti R, Borrelli E (2000) Structure and function of dopamine receptors. Neurosci Biobehav Rev 24:125-132.

van Dijken H, Dijk J, Voorn P, Holstege JC (1996) Localization of dopamine D2 receptor in rat spinal cord identified with immunocytochemistry and in situ hybridization. Eur J Neurosci 8:621-628.

Weil-Fugazza J, Onteniente B, Audet G, Philippe E (1993) Dopamine as trace amine in the dorsal root ganglia. Neurochem Res 18:965-969.

Woolf CJ, Ma Q (2007) Nociceptors—noxious stimuli detectors. Neuron 55:353-364.

Xie GX, Jones K, Peroutka SJ, Palmer PP (1998) Detection of mRNAs and alternatively spliced transcripts of dopamine receptors in peripheral sensory and sympathetic ganglia. Brain Res 785:129-135.

Yang HW, Zhou LJ, Hu NW, Xin WJ, Liu XG (2005) Activation of spinal d1/d5 receptors induces late-phase LTP of C-fiber-evoked field potentials in rat spinal dorsal horn. J Neurophysiol 94:961-967.

Yokoyama C, Okamura H, Nakajima T, Taguchi J, Ibata Y (1994) Autoradiographic distribution of [3H](YM-09151-2, a high-affinity and selective antagonist ligand for the dopamine D2 receptor, in the rat spinal cord. Neuroscience 55:353-364.

Xie WX, Jones K, Peroutka SJ, Palmer PP (1998) Detection of mRNAs and alternatively spliced transcripts of dopamine receptors in peripheral sensory and sympathetic ganglia. Brain Res 785:129-135.

Yoshida M (2011) In vivo patch-clamp analysis of dopaminergic antinociceptive actions on substantia gelatinosa neurones in the spinal cord. Pain 152:95-105.

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