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REVIEW ARTICLE

Role of Descending Dopaminergic Pathways in Pain Modulation

Changsheng Li[1,†], Sufang Liu[2,†], Xihua Lu[1,*] and Feng Tao[2,*]

[1]*Department of Anesthesiology, Henan Cancer Hospital & The Affiliated Cancer Hospital of Zhengzhou University, Zhengzhou, China;* [2]*Department of Biomedical Sciences, Texas A & M University College of Dentistry, Dallas, Texas, USA*

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Abstract: Pain, especially when chronic, is a common reason patients seek medical care and it affects the quality of life and well-being of the patients. Unfortunately, currently available therapies for chronic pain are often inadequate because the neurobiological basis of such pain is still not fully understood. Although dopamine has been known as a neurotransmitter to mediate reward and motivation, accumulating evidence has shown that dopamine systems in the brain are also involved in the central regulation of chronic pain. Most importantly, descending dopaminergic pathways play an important role in pain modulation. In this review, we discuss dopamine receptors, dopaminergic systems in the brain, and the role of descending dopaminergic pathways in the modulation of different types of pain.

Keywords: Chronic pain, dopamine, dopamine receptors, descending dopaminergic pathways, neuromodulation, descending pain control.

1. INTRODUCTION

Dopamine, discovered in 1958, is a monoamine neurotransmitter in the brain [1]. It is well known for its role in cognition, pleasure, and reward-motivated memory [2, 3]. In recent years, an increasing number of studies have shown that dopamine homeostasis in the central nervous system (such as spinal cord, hypothalamus, and anterior cingulate cortex) is disrupted by nociceptive stimuli and that dopaminergic pathways contribute to the transition from acute to chronic pain or pain chronicity [4-6]. Dopamine is released from the terminals of dopaminergic neurons and activates two types of receptors named D1-like and D2-like receptors. However, the two types of dopamine receptors are expressed differentially in different neurons, leading to different roles in pain modulation. In this review, we will discuss the different functions of dopamine receptors and the related pathways in terms of pain perception, development, and chronicity.

2. MATERIALS AND METHODS

We searched PubMed using the following keywords in the title or abstract: *dopaminergic neuron* and *pain*, in combination with the keyword *descending pathways*. Additional studies examining the role of descending dopaminergic pathways in pain modulation were identified using the following keywords: *descending dopaminergic pathways* and *chronic pain*. Searches were limited to the papers that were published in English in peer-reviewed journals. We summarize 79 papers in this review. The papers regarding other descending pain modulation pathways (serotonin- and norepinephrine-mediated) have been excluded in the current review.

3. DOPAMINE RECEPTORS

Dopamine is derived from its precursor named L-3, 4-dihydroxyphenylalanine (L-DOPA), which is converted into dopamine by aromatic amino acid decarboxylase. As a monoamine neurotransmitter, synthesis of dopamine is limited by tyrosine hydroxylase [7]. Dopamine is stored in the vesicles that are released into the synaptic cleft, which is controlled by phasic and tonic transmission. The dopaminergic neuron firing patterns correlate with different behaviors. Low frequency tonic firing in dopaminergic neurons is mainly related to the selection of habitual motor programs independent of reward, while high frequency phasic bursts of action potential in dopaminergic neurons are related to a reward seeking movement [8].

Dopaminergic neurons mainly originate from the midbrain, including the ventral tegmental area (VTA), substantia nigra (SN), and hypothalamus [5]. Most dopaminergic neuron cell groups are derived from a single embryological cell group that originates at the mesencephalic–diencephalic junction. The ventral side of the mesencephalon contributes

*Address correspondence to these authors at the Feng Tao, 3302 Gaston Ave., Dallas, TX 75246, USA; Tel: 1-214-828-8272; E-mail: tao@tamhsc.edu and Xihua Lu, 127 Dongming Road, Zhengzhou, Henan 450008, China; Tel: 86-371-6558-7320; E-mail: hnlxh66@163.com

†C.L. and S.L. contributed equally to this work.

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to 90% of the dopaminergic neurons. There are several dopaminergic cell groups from A8 to A16 that distribute in different areas of the brain. Most of them are involved in the ascending pathways, and a few of them are related to descending pathways [9]. Dopamine receptors include D1-like and D2-like receptors. These dopamine receptors have differing pharmacological, biochemical, and physiological functions. The D1-like receptor family includes D1 and D5 receptors, while the D2-like receptor family includes D2, D3, and D4 receptors. In addition, D1 and D5 receptors share very high homology in their transmembrane domains, while D2, D3, and D4 receptors are closely related with highly conversed transmembrane sequences [10].

The dopamine receptors distribute differentially in the brain. The D1 receptor mainly distributes in the striatum, nucleus accumbens (NAc), olfactory tubercle, hypothalamus, and thalamus. In contrast, the D5 receptor is mainly expressed in the hippocampus, the lateral mammillary nucleus, and parafascicular nucleus of the thalamus. Both D1 and D5 receptors are expressed in pyramidal neurons of the cortex, including the prefrontal cortex and anterior cingulate cortex. As far as the D2-like receptor family is concerned, the D2 receptor is mainly located in the core of NAc, striatum, and olfactory tubercle. The expression of D3 receptor in the brain is much less than that of D2 receptor [11]. In particular, the D3 receptor can form a heteromer with the D1 or D2 receptor and express in areas associated with psychiatric disorders, such as NAc, thalamus, hippocampus [12-14]. It has been shown that D4 receptors mainly locate in the prefrontal cortex, hippocampus, hypothalamus, and mesencephalon [10, 15].

Dopamine receptors differ in structure and pharmacology, and they are classified into different metabotropic G protein-coupled receptors (GPCRs) subfamilies with seven transmembrane-spanning domains [16]. The GPCR receptors participate in synaptic transmission in brain neural circuits by activating the G protein to induce intracellular signaling. The D1-like dopamine receptors are coupled to the $G\alpha_s$, which activates adenylate cyclase to produce a higher level of cyclic adenosine monophosphate (cAMP) and then enhances the activity of protein kinase A (PKA). In contrast, D2-like dopamine receptors are coupled to the $G\alpha_{i/o}$, which inhibits adenylate cyclase and reduces intracellular cAMP concentration and then inhibits the activity of PKA [17]. In addition, D1/D2 heteromers and D5 receptor can activate $G\alpha_q$ and trigger phospholipase C (PLC) downstream signaling pathways besides enhancing the PKA activity [18, 19]. Moreover, the D2 receptor can also activate the PLC pathway by binding $G\beta\gamma$ to increase calcium concentration and enhance the activity of calcium/calmodulin-dependent protein kinase II [20].

Dopamine receptors and *N*-methyl-D-aspartate (NMDA) receptors can interact in the neostriatum. Previous studies have shown that the striatum D1 receptor facilitates and enhances the activity of NMDA receptors, which is mediated by dopamine and cAMP-regulated phosphoprotein (32 kDa) [21-23]. The C-terminal tail of D1 receptor can cross-talk with NMDA receptor subunits NR1, NR2A, and NR2B in the synaptosomal membrane fraction [21-23]. However, the interaction between the D2 receptor and NMDA receptors remains unclear. Several studies showed that a D2 receptor agonist inhibits NMDA receptor excitability [24-26], while another study reported that the D2 receptor is not associated with NMDA receptors [27]. In addition, the interaction between the dopamine receptors and alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptors has also been demonstrated [28, 29]. In rodent studies, the expression of D1 and D2 receptors in the contralateral NAc is down-regulated on day 28 of chronic neuropathic pain [30]. We recently reported that the D2 receptor plays a critical role in the descending inhibition of trigeminal neuropathic pain [31]. Therefore, the dopamine receptors could be indispensable in regulating neuronal excitability.

4. DOPAMINE PATHWAYS AND THEIR FUNCTIONS

There are eight dopamine pathways in the brain. The four major pathways are: 1) The mesolimbic pathway from VTA to NAc; 2) The mesocortical pathway from VTA to prefrontal cortex; 3) The nigrostriatal pathway from the SN pars compacta (SNc) to the caudate nucleus; and 4) The tuberoinfundibular pathway from tuberal hypothalamus to pituitary gland [32]. The four minor pathways are from VTA to amygdala, hippocampus, cingulate cortex, and olfactory bulb, respectively [16].

Among these dopamine pathways, three pathways are involved differentially in ascending projections, including mesolimbic, mesocortical, and nigrostriatal pathways [9]. These ascending dopaminergic pathways are related to reward-cognition and motor function regulation [33, 34]. Besides these ascending projections, there are some dopamine cell groups that are involved in descending pathways. The A11 nucleus in the posterior hypothalamus is an important dopamine cell group that can project to both brainstem and spinal cord [4, 6]. This descending dopaminergic pathway plays a critical role in locomotor function regulation and pain modulation [6, 35-37]. For instance, the pathway from A11 nucleus to the spinal cord contributes to motor recovery after spinal cord injury [4, 35]. The descending dopaminergic projections from A11 nucleus to the spinal dorsal horn or spinal trigeminal nucleus caudalis (Sp5C) are involved in descending pain modulation [4, 6]. It has been reported that the descending dopaminergic pathway can send direct inhibitory projections to the target areas [38]. For instance, the dopaminergic neurons in the hypothalamic A11 nucleus directly project to the Sp5C and excitation of the descending dopaminergic neurons inhibits orofacial neuropathic pain [31]. The A11 dopaminergic neurons also send direct inhibitory projections to the spinal dorsal horn, which may be the sole source of spinal dopamine [38].

5. ROLE OF DESCENDING DOPAMINERGIC PATHWAYS IN PAIN MODULATION

In the descending dopaminergic pathways from A11 nucleus to Sp5C or spinal dorsal horn for pain modulation, D1-like receptors contribute to pain development and maintenance, whereas D2-like receptors exert an anti-nociception effect [39]. It has been reported that dopamine receptors D1/D5 engage the mechanism of spinal hyperalgesic priming and maintenance of pathological pain plasticity and that

D1/D5 agonists induce mechanical hypersensitivity [4]. Our recently published work demonstrates that activation of dopaminergic neurons in the hypothalamic A11 nucleus attenuates peripheral nerve injury-induced neuropathic pain, which is mediated by D2-like dopamine receptors [31]. Taylor and colleagues found that microinjection of selective D2-like dopamine receptor agonist quinpirole in the NAc inhibits formalin-induced persistent nociception in the hind paw [40]. Taken together, these studies indicate that D1-like and D2-like dopamine receptors play opposite roles in pain modulation. In addition, another study reported that D2-like dopamine receptors are not involved in the decreased postoperative nociceptive threshold induced by plantar incision [41]. Therefore, the role of descending dopaminergic pathways in pain modulation is not only dependent on dopamine receptor types, but also related to pain models. In the clinic, patients with burning mouth syndrome showed a much higher number of unoccupied D2 receptors in the left putamen and a lower D1/D2 ratio in the bilateral putamen [5, 42]. The decrease in the D1/D2 ratio suggests the decline of endogenous dopamine in the putamen of patients with burning mouth syndrome.

Emotional pain is related to attention, anxiety, memory and expectations [43]. Previous studies have shown that dopamine homeostasis determines pleasure-seeking or pain-avoidance, which are closely associated to the emotional component of pain [44, 45]. Phasic and tonic dopamine release works together to maintain homeostasis of dopamine levels that regulates emotional component of pain [44, 45]. Phasic or transient dopamine release represents the depolarization of dopamine neurons and the dopamine release is obtained by opening the classic voltage-dependent calcium channel, which is due to behavioral stimuli, such as feeding [46]. The tonic mechanism is mediated by the activation of NMDA receptors at the terminals of dopaminergic neurons, which results in calcium influx and triggers dopamine release. Tonic dopamine release is to maintain extracellular dopamine levels for dopamine receptor stimulation [45]. However, a recent study reported that although dopamine appears to affect expectations and desires, dopamine changes in the brain do not affect emotional pain in patients with chronic neuropathic pain after placebo intervention [47]. Using von Frey and conditioned place preference tests, we observed that activation of the descending dopaminergic pathway from hypothalamic A11 nucleus to Sp5C inhibits both sensory and emotional components of pain induced by peripheral nerve injury [31].

Here, we summarize the role of descending dopaminergic pathways from hypothalamus, hippocampus, or NAc in pain modulation.

5.1. Hypothalamus

By using retrograde tracing, five hypothalamic areas are shown to project to the Sp5C, including the paraventricular nucleus, the lateral hypothalamic area, the perifornical hypothalamic area, the A11 nucleus, and the retrochiasmatic area [48]. This suggests that the hypothalamus A11 nucleus, a key dopaminergic cell group, may contribute to trigeminal pain modulation. Dopamine denervation of the A11 nucleus mediates formalin-induced trigeminal pain in rats [6]. Moreover, serotoninergic and dopaminergic descending pathways that project to the trigeminocervical complex (TCC) can interact with each other through dopamine D2-like receptors and serotonin 5-HT1B/1D receptors. By using electrophysiological recordings, it has been shown that selective D2-like receptor agonist (quinpirole) and 5-HT1B/1D receptor agonist (naratriptan) induce a reversal of the facilitation of nociceptive cell firing in the TCC. And after A11 lesion, the nociceptive cell firing in the TCC is inhibited by quinpirole and quinpirole plus naratriptan application [49], which suggests that both dopaminergic and serotonergic pathways can produce antinociceptive effects simultaneously through the activation of D2-like receptor and 5-HT1B/1D receptor, respectively.

Abdallah and colleagues published two papers to demonstrate that the descending dopaminergic pathway from the hypothalamus A11 nucleus to Sp5C contributes to formalin-induced orofacial pain in rats [6, 48]. The dopaminergic neurons in the A11 are also involved in the maintenance of mechanical hypersensitivity in mice [4]. And the lesion of A11 dopaminergic neurons reverses the mechanical pain maintenance [4]. In spared nerve injury (SNI)-induced neuropathic pain, activation of dopamine D2 receptors in the A11 nucleus inhibits neuropathic hypersensitivity. Using D1-Cre and D2-Cre transgenic mice, we observed that both D1 and D2 receptors are expressed in the Sp5C and the two types of dopamine receptors mostly distribute in different neurons, suggesting that dopamine may exert different pain regulation by binding to different receptors. In a trigeminal neuropathic pain animal model, induced by chronic constriction injury of the infraorbital nerve, we observed that optogenetic excitation or chemogenetic activation of the descending dopaminergic pathway from the hypothalamic A11 to Sp5C alleviates the neuropathic pain *via* activation of D2 receptors in the Sp5C [31]. Moreover, 6-OHDA-produced A11 lesion of dopaminergic neurons exacerbates such pain, suggesting that the descending A11-Sp5C dopaminergic pathway is pain-inhibitory [31].

Migraine is the most common form of headache. In clinic, D5 dopamine receptor upregulation is observed in some patients suffering from migraine, suggesting an involvement of dopamine in the headache pathogenesis [50]. In addition, dopamine receptor antagonists have been used to treat migraine, and all neuroleptics used to block dopaminergic pathways are antagonists of dopamine D2 receptors [51, 52]. In animal experiments, Haarmann and colleagues found that dopamine D2 receptors can modulate the initiation of spreading depression related to migraine, suggesting that the D2 receptor antagonist sulpiride may be used as a potential therapy for migraine pain [53]. In addition, a recent clinical study reported that migraine sufferers are showing a close association with dopamine beta hydroxylase gene polymorphisms [54]. The dopamine modulation of migraine has been summarized in a review article published in 2013 [55]. Moreover, the simultaneous influence of dopamine receptors and 5-HT1B/D receptors can produce migraine pain relief by inhibiting neuronal activities [49].

A clinical study indicates that patients with migraines show enhanced hypothalamic activation by positron emission tomography (PET) scans during and after migraine at-

tacks. However, the exact location of the involved hypothalamus is unclear due to resolution issues [56]. A high-resolution 3T functional magnetic resonance imaging (fMRI) scan confirms the role of the hypothalamus in migraine attacks [57]. And this study shows that the acute pain phase is closely associated with the posterior part, while the episodes and development of migraine involve the anterior part of the hypothalamus [57]. Analysis and summarization of fMRI image processing demonstrate that different stages of migraine attacks involve different brain-oxygen-level-dependent changes in brain regions [58].

5.2. Hippocampus

Shamsizadeh and colleagues found that dopamine receptors in the dorsal hippocampus (CA1) region are involved in orofacial pain induced by subcutaneous injection of formalin [59]. Using microinjection of D1-like and D2-like dopamine receptor antagonists or agonists into hippocampus CA1 area, they observed that D1-like receptor agonist SKF-38392 produces analgesic effect on first (early) and second (late) phases of formalin-induced orofacial pain and that D2-like receptor agonist quinpirole also inhibits the orofacial pain in both phases [59]. Moreover, the antagonists of D1-like and D2-like dopamine receptors reversed such analgesic effects produced by respective dopamine receptor agonist [59]. These results suggest that dopamine receptors in the dorsal hippocampal CA1 region play an important role in formalin-induced orofacial pain.

In a recently published review article [60], the authors discussed the important role of hippocampus in migraine. And the relationship between hippocampus and migraine, including hippocampal structure and volume, migraine onset, frequency, prognosis, and associated allodynia, has been demonstrated by studies using fMRI [60]. Moreover, a clinical study examined the 3T scanned images from 61 migraine patients and 57 healthy people and showed that the severity of migraine is significantly correlated with the decrease of hippocampal volume on the left side [61]. The connectivity between the hippocampus and the limbic system is related to the severity of allodynia symptoms, but not the frequency of headache in migraine patients [61]. However, another study showed the right hippocampal volume, but not the left part, is related to migraine attacks by conducting MRI scans of 31 healthy people and 122 migraine patients [62]. And this study also showed that migraine frequency is dependent on hippocampal volume changes [62]. Additionally, a research team from the Headache and MRI center in Italy, analyzed fMRI images, and their data indicate that the hippocampus plays a key role only in the first phase of a migraine attack [58]. Although clinical studies have shown a link between hippocampus and migraine, it is unknown how dopamine or dopamine receptors in the hippocampus are involved in migraine.

5.3. NAc

In a clinical study, altered grey matter in NAc was found in patients with idiopathic trigeminal neuralgia and these patients have larger NAc volumes, suggesting NAc structure changes may contribute to ongoing trigeminal pain [63]. Another study showed that NAc activity correlates with different cortical circuitry in patients with chronic back pain and thus the regulation of NAc activity may have analgesic effect [64]. The dopaminergic pathway in the NAc have been shown to contribute to inflammatory pain [40]. Microinjection of quinpirole, a dopamine D2 receptor agonist, into the NAc inhibits formalin-induced pain in the hind paw and pretreatment with raclopride, a dopamine D2 receptor antagonist, blocks this anti-nociceptive effect [40], suggesting that the dopaminergic activity in the NAc can be regulated to treat pain. A recent study reported that the shell of NAc is involved in peripheral nerve injury-induced neuropathic pain [65]. And inhibition or activation of spiny projection neurons in the NAc can alter tactile allodynia status and this study suggests that the NAc may contribute to central pain processing and ascending nociceptive transmission [65].

Dopamine in the NAc is critical for reward and motivation, including the reward from pain relief, thus targeting reward/motivation circuits could be used for pain modulation [66, 67]. Dopaminergic neurons coding motivational valence are more common in the VTA that projects to the NAc shell; however, dopaminergic neurons coding motivational salience are more common in dorsolateral SN that projects to the NAc core [68]. Therefore, the dopaminergic pathways in different NAc areas may play different roles in reward/motivation-related pain processing. In a spinal nerve ligation-induced neuropathic pain rat model, microdialysis analysis showed that pain relief caused by intrathecal injection of pregabalin increases intra-NAc dopamine release during the early phase of the neuropathic pain (17-20 days after ligation), but not in the late phase of the neuropathic pain (31-34 days after ligation) [69]. In addition, the dopaminergic neurons projecting from VTA to NAc participate in exercise-produced pain relief in a spinal nerve ligation-induced neuropathic pain model [70].

Painful stimulation can regulate dopamine signaling in different parts of NAc [71]. In anesthetized rats, induction and termination of tail pinch-induced pain trigger dopamine release in the core and shell of NAc, respectively, which probably depends on the distribution of dopamine receptors in different parts of NAc [71]. In the direct pathway of NAc, dopamine enhances GABAergic direct spiny projection neurons by acting on the D1 receptor, which is associated with reward and positive emotions; in the indirect pathway, dopamine acts on the D2 receptor and inhibits GABAergic indirect spiny projection neurons [65, 72]. After spared nerve injury, increased excitability of NAc GABAergic indirect spiny projection neurons worsens tactile allodynia [65]. Moreover, during 7 to 12 days after chronic pain induction, the amplitude of miniature excitatory postsynaptic currents (EPSCs) is decreased in D2-expressing neurons of the NAc, most likely attributing to the declined ratio of AMPA receptor-mediated EPSCs to NMDA receptor-mediated EPSCs [73].

An animal study has shown that cortical spreading depression increases dopamine release in the NAc, but reduces dopamine release in the nucleus caudate [74], which is related to the redistribution of oxygen supply in the subcortical regions [74]. In a clinical study using MRI and PET scans, changes in endogenous μ-opioid receptors were observed in the NAc of migraine patients [75]. Compared with healthy

controls, migraineurs showed a decrease in the volume of left nucleus caudate and right NAc, which is significantly associated with the duration of migraine attack [76]. And the lasting time of migraine burden depends on the connection of the right NAc and bilateral anterior cingulate cortex [76]. In a migraine-like pain animal model by injection of inflammatory mediators into the rat dura mater, migraine induction elicits dopamine release in the NAc, and relief of migraine pain activates the dopaminergic reward pathway to cause negative reinforcement of behavior [77].

CONCLUSION

The descending pain modulation is mainly mediated by monoaminergic pathways, including descending projections mediated by dopamine, norepinephrine, and serotonin [78, 79]. We focus on discussing descending dopaminergic pathways in this review. By activating different types of receptors, the descending dopaminergic pathways can exert either facilitatory or inhibitory pain-modulating effects [4, 31]. The overall balance between pain facilitation and pain inhibition mediated by these dopaminergic pathways contributes to top-down pain modulation.

CONSENT FOR PUBLICATION

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CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

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