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Review Article

The Distinct Functions of Dopaminergic Receptors on Pain Modulation: A Narrative Review

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Chronic pain is considered an economic burden on society as it often results in disability, job loss, and early retirement. Opioids are the most common analgesics prescribed for the management of moderate to severe pain. However, chronic exposure to these drugs can result in opioid tolerance and opioid-induced hyperalgesia. On pain modulation strategies, exploiting the multitarget drugs with the ability of the superadditive or synergistic interactions attracts more attention. In the present report, we have reviewed the analgesic effects of different dopamine receptors, particularly D1 and D2 receptors, in different regions of the central nervous system, including the spinal cord, striatum, nucleus accumbens (NAc), and periaqueductal gray (PAG). According to the evidence, these regions are not only involved in pain modulation but also express a high density of DA receptors. The findings can be categorized as follows: (1) D2-like receptors may exert a higher analgesic potency, but D1-like receptors act in different manners across several mechanisms in the mentioned regions; (2) in the spinal cord and striatum, antinociception of DA is mainly mediated by D2-like receptors, while in the NAc and PAG, both D1- and D2-like receptors are involved as analgesic targets; and (3) D2-like receptor agonists can act as adjuvants of μ-opioid receptor agonists to potentiate analgesic effects and provide a better approach to pain relief.

1. Introduction

Recently, the definition of pain has been revised by the International Association for the Study of Pain as "an unpleasant sensory and emotional experience associated with, or resembling that associated with, actual or potential tissue damage" [1, 2]. Vital to survival, pain functions as a protective alarm for an organism to identify and avoid possible life-threatening situations [3]. When pain lasts beyond normal tissue healing time (i.e., more than three months), it is known as chronic pain: a pathological condition with dramatic costs and suffering [4–6]. Pain is the integration of nociception with consciousness, feeling, and emotion and differs from nociception. It relies on the peripheral signaling pathway and involves several regions of the brain, including the thalamus, medial prefrontal cortex (mPFC), nucleus accumbens (NAc), periaqueductal gray (PAG), insula, somatosensory cortex, amygdala, and striatum [7–9].

The most widely prescribed analgesic drugs for pain relief, such as nonsteroidal anti-inflammatory drugs (NSAIDs), cyclooxygenase-2 (COX-2) inhibitors, and opioids, may have some adverse effects [10, 11]. For instance, a number of reports have proven that NSAIDs increase the risk of severe bleeding (especially gastrointestinal bleeding) and cardiovascular diseases (such as myocardial infarction and strokes), resulting in a higher rate of mortality [12, 13]. COX-2 selective inhibitors like celecoxib and rofecoxib show equivalent or superior analgesic and anti-inflammatory effects compared to conventional NSAIDs and carry a lower risk of gastrointestinal bleeding [14]. However, it has been demonstrated in animal models that inhibition of COX-2 activity might suppress bone healing [15, 16]. Although among analgesic agents, opioids are the most potent drugs for treating severe pain (e.g., cancer and perioperative pain), the efficiency of their long-term use for chronic pain is controversial [17, 18]. The critical problem is that long-term

administration of opioids can cause addictive behaviors in patients (22.6%), further contributing to the opioid crisis [19, 20]. This evidence indicates that it is essential and urgent to investigate the analgesic efficacy of other known drugs or to develop new analgesic drugs with reduced side effects and abuse liability that target novel pathways.

A growing body of evidence from preclinical and clinical studies suggests that the dopamine (DA) system contributes to the pathology of the most chronic pain conditions [21, 22]. For instance, the studies with functional magnetic resonance imaging (fMRI) technique provided solid evidence suggesting that the mesolimbic dopamine circuit and pain modulation system are largely overlapped, including the ventral tegmental area (VTA), prefrontal cortex (PFC), amygdala, and nucleus accumbens (NAc) [23–25]. The functional connectivity between the aforementioned brain regions and their gray matter volumes was significantly different between chronic pain patients and healthy controls [26, 27]. And positron emission tomography (PET) used in the evaluation of patients with fibromyalgia syndrome demonstrated that synthesis and release of DA reduced in the presynaptic neurons [28]. Similar results were found in patients with back pain, indicating that altered brain DA function was associated with pain sensitivity and the affective state [29]. Besides this, several clinical studies have shown that the administration of levodopa, the precursor of DA, alleviates pain associated with Parkinson's disease in humans [30–32]. In animal models, injection of levodopa into the intrathecal (IT) space or some regions of the central nervous system (such as the NAc, dorsolateral striatum, and prefrontal cortex) had adequate analgesic effects [33, 34]. In general, these results indicate that the regulation of the dopaminergic system may be a novel strategy to manage pain effectively.

DA mainly acts on two subfamilies of DA receptors: D1-like (D1 and D5) and D2-like (D2, D3, and D4) receptors [35]. This classification is based on the biochemical and pharmacological properties of the receptors [36]. D1 subfamily receptors are coupled to G-protein alpha subunits ($G_{\alpha s}$ and $G_{\alpha olf}$), induce $3',5'$-cyclic adenosine monophosphate (cAMP) production, and activate protein kinase A (PKA) [37]. Members of the D2 subfamily are generally coupled to $G_{\alpha i}$ and $G_{\alpha o}$ subunits, inhibit the activity of adenylate cyclase, reduce the production of cAMP, and, subsequently, reduce PKA activity [38]. Although DA receptors are widely distributed in the brain, the densities of the receptor subtypes vary between different areas [39]. The D1 receptor is the most widespread protein in rat brains, whereas the D2 receptor is mainly distributed in specific regions such as the striatum, NAc, and some limbic regions [36, 40].

Previous reports have proven the role of the hypothalamic-spinal DAergic system on pain modulation, suggesting that the antinociceptive effects of DA are mediated by D2-like receptors, while the pronociceptive effects are mediated by D1-like receptors [41]. However, the available data fail to definitively elucidate the role of D1-like receptors on pain modulation and the effect of the central DAergic system on pain processing [41]. In the present review, we more comprehensively investigated the roles of DA receptor subtypes on pain modulation, especially D1 and D2 receptors in the central nervous system (CNS), to illustrate their potential analgesic features.

2. Spinal Cord

The spinal cord is the first relay station in the transmission of nociceptive information from the periphery to the brain. It has been proven that all types of DA receptors are present in the primary nociceptors and different laminars of the dorsal horns of the spinal cord and that D2 receptors are the most abundantly expressed [41, 42]. This indicates that DA functions in the modulation of pain signals by affecting presynaptic and postsynaptic neurons [41]. Numerous studies illuminated the contributions of D1- and D2-like receptors in the spinal cord during pain modulation. In cases of acute pain, intrathecal (IT) administration of DA or quinpirole (a D2/3 receptor agonist) was reported to increase the mechanical pain threshold, measured using a von Frey anesthesiometer. This analgesic effect was reversed by IT coadministration of D2, D3, and D4 antagonists [43, 44]. It was also demonstrated that IT administration of apomorphine or DA could enhance the thermal threshold, which was estimated by the tail-flick test [45–47] and the hot plate test [47]. These features were mimicked by administration of LY171555 (a D2-like receptor agonist), but not SKF-38393 (a D1/D5 receptor agonist), and inversed by D2 antagonists (e.g., *cis*-flupenthixol and sulpiride) [47]. For inflammatory pain induced by carrageenan, IT administration of LY171555, but not SKF-38393, rescued the thermal withdrawal latency (measured with Hargreaves apparatus) [48]. Similar findings were obtained from a neuropathic pain model of chronic constriction injury (CCI) of the sciatic nerve in which IT administration of levodopa decreased tactile and cold allodynia. This effect was blocked by sulpiride [34]. Furthermore, in a follow-up study, the same group found that lumbar IT injection of quinpirole produced short-term inhibition of responses to cold and tactile stimuli, which coincided with pain relief by levodopa administration in neuropathic pain [49].

Because DA can affect both exploratory and goal-oriented movements, the findings of these studies on the analgesic effects of DAergic drugs should be carefully interpreted [50]. These effects could potentially interfere with the results of pain-related behavioral tests, since the majority of measurements of the pain threshold utilize a withdrawal movement to a nociceptive stimulus [51]. For example, an effective analgesic dose of quinpirole administered systemically was proven to affect locomotion and exploratory activities of rats in an open-field maze [33]. While the intracisternal injection of quinpirole could successfully relieve formalin- and capsaicin-evoked trigeminal pain, a higher dose of quinpirole (20 nmol) had no effect on motor performance in the rotarod test (commonly used to evaluate motor coordination) [52]. Briefly, systematic administration of a high dosage of quinpirole may have affected the locomotor and exploratory activities of rats, while IT infusion of low doses had no significant effect on locomotion. Besides, the effects of D2 receptor agonists on locomotion might be strain-dependent, as shown in spontaneously hypertensive

rat (SHR) and SLA16 isogenic (SHR.Lewis-*Anxrr16*; anxiety-related response #16) rat strains [53]. In summary, the dosage of drugs, route of administration, and strain of animals should be considered when investigating the possible analgesic effects of DAergic drugs.

In vitro studies have provided compelling evidence that DA is involved in pain signaling by modulation of intrinsic excitability and synaptic transmission of dorsal root ganglion neurons and spinal neurons [54]. For the first time, Tamae et al. used the whole-cell patch-clamp technique to record the excitability of spinal dorsal horn neurons and study the effects of DA receptor agonists. They found that bath application of DA hyperpolarized the membrane potential of substantia gelatinosa neurons and suppressed electrical stimulation action potential in the dorsal root. Quinpirole simulated a DA-induced outward current, which was not produced by SKF-38393 [43]. Moreover, activated D2 receptors in neurons of the superficial medullary dorsal horn inhibited the C-fiber-evoked action potentials of wide dynamic range neurons in the trigeminal spinal nucleus [52]. Consistent results were revealed in neuropathic pain, which reported that C-fiber-evoked action potentials in the spinal dorsal horn were dose-dependently ameliorated by spinal superfusion of quinpirole in both nerve-injured and sham-operated rats [55]. Collectively, D2 receptors may play an analgesic role in the spinal cord by reducing the amount of sensory inputs from nociceptors to the CNS (Table 1).

Interestingly, D1-like receptor agonists (SKF-83959 and SKF-81297) mimic the inhibitory effects of DA on slow ventral root potentials, which is attributed to responses evoked by C-fibers that reflect nociceptive transmission in the spinal cord. In addition, the inhibitory effects were attenuated by D1-like receptor antagonists (SCH-23390 and LE300) [56]. Taken together, there is widespread disagreement among *in vitro* studies about the role of D1-like receptors. However, *in vivo* investigations found that the D1 receptor had no significant analgesic effect in the spinal cord. These findings could be related to the lower affinity of DA for D1 receptors. Thus, only a few reports found that the activation of D1 receptors in the spinal cord could mimic the role of dopamine, while, in *in vivo* studies, not even a faint effect could be observed in behavioral testing.

3. Brain

The brain contains a high density of DA receptors in regions that functionally contribute to integrating the consciousness and emotion of pain, such as the ventral tegmental area (VTA), mPFC, NAc, PAG, and striatum [57, 58].

3.1. Ventral Tegmental Area (VTA). The VTA, a part of the DAergic system, is composed of mesolimbic DA neurons that project to the NAc and mPFC [59, 60]. It is involved in various physiological functions such as pain processing and motivation [59]. For instance, the excitability of VTA DA neurons decreased significantly in CCI mice models. Optogenetic stimulation of VTA DA neurons produced analgesic effects [61]. In another study, voluntary wheel running was shown to produce hypoalgesia by reversing the inactivation of VTA DA neurons in a rat model with neuropathic pain [62]. Noxious footshocks are believed to inhibit the activities of DA neurons in the dorsal VTA, but physically excite the activities of DA neurons in the ventral VTA, suggesting that VTA DA neurons are heterogeneous in the processing of rewarding and aversive events [63]. Furthermore, a few reports have focused on the roles of different DA receptors in pain modulation. Pretreatment of VTA with both sulpiride [64] and SCH-23390 [65] could inhibit antinociception induced by intralateral hypothalamus (LH) microinjection of carbachol, obtained by the tail-flick test. The precise function of VTA DA neurons in the pain process is still unclear.

3.2. Nucleus Accumbens (NAc). Functionally, NAc contributes to a wide range of reward-related behaviors [66]. As one of the two main projection target regions of VTA DAergic neurons (the other being the mPFC) [67], the NAc is a rostral telencephalic gray mass with a heterogeneous structure. Anatomically, it can be divided into the shell and core regions [68]. The shell is the outer region innervated by DAergic neurons and is closely related to the mesolimbic system. It has been identified as playing a profound role in motivation and pain modulation pathways [60, 69]. In contrast, the NAc core region, which connects to the caudate-putamen and striatum, is involved in goal-directed behaviors [70, 71]. Both D1 and D2 receptors were reported to be expressed in the whole NAc, while D3 receptors are selectively expressed in the shell region [69]. The past few decades have witnessed a drastic rise in the number of studies attempting to identify the analgesic effects of DA receptors in the NAc region. For example, stimulation of D2 receptors in the NAc was revealed to inhibit the persistent phase of formalin-induced nociception. The recommended dose of quinpirole did not produce overt behavioral changes, as shown in the rotarod treadmill test. However, the D1-selective agonist SKF-38393 had no significant effect on the nociceptive behavior induced by formalin [70]. Even so, a number of reports have demonstrated that blocking both D1- and D2-like receptors of the NAc attenuated analgesia induced by forced swim stress [72] and carbachol injection into the LH [73] in the formalin test, particularly in the late phase. And intra-accumbal administration of SCH-23390 and sulpiride dose-dependently prevented intra-VTA orexin-induced antinociception measured by the tail-flick test [74]. In addition, mRNA levels of D2 and D1 receptors both decreased in the NAc of animals with neuropathic injury, including spared nerve injury [75] and CCI [76].

Although the analgesic effects of D2 receptors in the NAc are more profound, blocking both D1- and D2-like DA receptors showed similar pharmacological effects [71, 72, 74]. The similarity of D1 and D2 receptors in the NAc may be attributed to their distinct DAergic innervations. The first relates to rewarding and pleasurable effects that act on primary D1 receptors of spiny neurons via direct pathways, and the second relates to aversive and negative effects that indirectly operate on spiny neurons, which is diminished by the activation of D2 receptors [77]. In other words, the activation of D1 receptors in the NAc probably weakens pain by enhancing the reward and pleasure effects, while D2

Table 1: The role of DA receptors on pain modulation in the spinal cord.

Authors	Drugs	Models	Measurements	Main results
Almanza et al. [44]	Quinpirole (D2/3 agonist)	Acute pain	Von Frey Hargreaves apparatus	(i) The activation of dopamine D2 receptors increased mechanical threshold
Barasi and Duggal [45] Jensen and Smith [46] Liu et al. [47]	LY171555 (D2 agonist) SKF38393 (D1/D5 agonist)	Acute pain	Tail-flick test Hot plate test	(i) The D2 agonist mimicked the analgesic effect of DA, but the D1 agonist did not
Gao et al. [48]	LY171555 SKF38393	Inflammatory pain induced by carrageenan	Hargreaves apparatus	(i) The D2 agonist rescued the thermal withdrawal latency, but the D1 agonist did not
Cobacho et al. [49]	Levodopa Sulpiride (D2 antagonist)	Neuropathic pain induced by chronic constriction injury	Tactile and cold allodynia test	(i) Levodopa decreased the tactile and cold allodynia, which was blocked by the D2 antagonist
Tamae et al. [43]	Quinpirole SKF 38393	Acute pain	Von Frey filament whole-cell patch-clamp technique	(i) The D2 agonist simulated the analgesic effect of DA at both behavioral and electrophysiological levels, but the D1 agonist did not
Lapirot et al. [52]	Quinpirole Sulpiride	Acute pain	Unitary extracellular recordings Facial capsaicin and formalin test	(i) The activation of D2 receptors inhibited both formalin- and capsaicin-evoked pain behaviors and the C-fiber-evoked action potential firing

activation may reduce aversion to pain [78]. Compared to D1-like receptors in the NAc, D2-like receptors have a higher affinity to DA and are activated preferentially [79, 80]. However, further studies are needed to shed light on the potential mechanisms of D1- and D2-like receptors in pain modulation.

3.3. Prefrontal Cortex (PFC). Studies over the past two decades have revealed the prominent role of the PFC in reward and pain modulation [81, 82]. As a region of the cerebral cortex located at the front of the frontal lobe, the PFC is a key structure contributing to critical brain functions such as memory, learning, attention, problem-solving, planning, and social behavior [83]. Recently, the important role of the DAergic signaling pathway from the VTA to the PFC on pain modulation has been proven [60, 84]. Anatomically, the PFC can be divided into the medial PFC (mPFC), dorsolateral PFC (dlPFC), ventrolateral PFC (vlPFC), orbitofrontal cortex, and caudal PFC [85]. Due to the potential pain modulating mechanisms of the DA system in the PFC, neuronal responses of the PFC were recorded using an extracellular recording unit in urethane-anesthetized rats. Applying a high-frequency stimulation (50 Hz, 250 μA, 100 μs square pluses, 30 s) to the VTA by a tungsten microelectrode (impedance 8-12 MΩ) suppressed nociceptive responses for an extended period in the rat PFC. Similarly, injection of a selective D2 receptor into the rat PFC produced long-lasting suppression of nociceptive responses, which was reversed by the blockade of D2 receptors. In contrast, the D1 antagonist/agonist was minimally effective in nociceptive responses [84].

The mPFC has a critical role in both reward and pain processing [86]. Projection of adrenergic neurons from VTA to mPFC (the DA inputs from VTA to mPFC) regulates the neural functions of mPFC (e.g., executive activities, excitability, and synaptic transmission) [87]. In chronic pain rodent models, the activity of neurons in the mPFC was reportedly reduced [88]. Optogenetic studies revealed that the activation of DA signaling from the VTA into the mPFC modulated hypersensitivity in mice with spared nerve injury neuropathic pain [89]. In summary, these studies suggest that the DA system in the mPFC may be a target for the relief of chronic pain.

DA modulation in the mPFC is also related to attention tasks for this region. Previous studies have proven the impairment of memory and attention by chronic pain [90]. In a rodent model, blocking the activity of D1 receptors in the mPFC impaired the attentional set-shifting task, whereas enhancing D1 receptor activity improved this performance [91, 92]. Based on these findings, clinical studies have shown that distraction tasks could decrease pain perception and relieve chronic back pain [93, 94]. Together, pain modulation of DA receptors in the mPFC may underlie distinct manners: D1 receptors tend to affect the cognitive aspect of pain (e.g., by regulating distraction), while D2 receptors may directly regulate the pain perception or nociceptive responses [83, 95]. Because of the complexity of the neuronal network, cellular receptor expression, DA concentration, and receptor affinity, it remains unclear as to how the DA system in the mPFC is involved in the pain modulation process.

3.4. Striatum. The dorsal striatum, which receives afferents from the sensorimotor cortex and DA-containing inputs

Table 2: The role of DA receptors on pain modulation in the brain.

Authors	Brain regions	Models	Drugs	Measurements	Main results
Moradi et al. [64]	VTA	Acute pain	D1 antagonist SCH23390 D2 antagonist sulpiride	Tail-flick test	(i) Blockage of the D1 and D2 receptors had a similar effect, as inhibiting the antinociception induced by carbachol
Taylor et al. [70] Siahposht-Khachaki et al. [73] Yazdi-Ravandi et al. [74] Martikainen et al. [29]	NAc	Acute pain and neuropathic injury (SNI and CCI)	D1 antagonist SCH23390 D1 agonist SKF38393 D2 antagonist sulpiride D2 agonist quinpirole	Formalin test Tail-flick test	(i) Neuropathic injury decreased the mRNA levels of both D2 and D1 receptors (ii) The blockade of D1- and D2-like receptors showed the similar pharmacological effects (iii) The activation of the D2 receptors had more profound analgesic effects
Sogabe et al. [84] Granon et al. [92] Fletcher et al. [91]	PFC	Acute pain In vitro	The same as above	Electrophysiological recording Attentional set-shifting task	(i) The D1 receptors tend to affect the cognitive aspect of pain, like via distraction (ii) The D2 receptors may directly regulate the pain perception or nociceptive responses (iii) The activation of the D2 receptors had more profound analgesic effects
Magnusson and Fisher [98] Ansah et al. [99] Saunier-Rebori and Pazo [101]	Striatum	Inflammatory pain	D1 antagonist SCH23390 D1 agonist SKF38393 D2 antagonist eticlopride D2 agonist quinpirole	Formalin test Jaw opening reflex	(i) The activation of the D2 receptors had antihypersensitive effect, but not D1 receptors
Hagelberg et al. [103, 104]	Striatum	Clinical chronic orofacial pain		PET	(i) Healthy male volunteers with a low D2 receptor, while D2 receptor availability of patients increased, which predicted a low synaptic DA concentration and a high capacity of recruiting pain inhibitory circuitry
Ben-Haim et al. [109] Li et al. [107] Tobaldini et al. [114]	PAG	Acute pain	DA agonist apomorphine D2 antagonist eticlopride D1 antagonist SCH-23390 Opiate heroin and morphine	Hot plate test Tail-flick test Mechanical paw-withdrawal test	(i) The analgesic effect of apomorphine was blocked by D2 antagonist, but not by D1 antagonist (ii) Blockage of the D1 and D2 receptors had a similar effect, as reducing the antinociception induced by the opioids (iii) The activation of D1 receptors could enhance the opioid- and D2-induced antinociception

from the pars compacta of the substantia nigra, has abundant D1 and D2 receptor expressions [96, 97]. Microinjection of a D1 antagonist (SCH-23390) or a D1 agonist (SKF-38393) into the dorsolateral striatum was reportedly not effective in formalin-induced nociception. Conversely, a D2 antagonist (eticlopride) could enhance the formalin-induced nociception, while a D2 agonist (quinpirole) exerted an opposite effect [98]. A similar result was found in neuropathic conditions in rats with unilateral ligation of the tibial and common peroneal nerves [99]. The antihypersensitive effect is induced by striatal D2 receptors and involved in inhibiting the impulse discharge of, presumably, pronociceptive neurons in the rostral ventromedial medulla, which is an important structure in descending pain modulation [100]. The antihypersensitive effect can be reversed by spinal administration of a D2 receptor antagonist [99]. Microinjection of quinpirole into the striatum inhibited the jaw opening reflex (JOR, an indicator of pain), evoked by tooth pulp stimulation, in a dose-dependent manner. This effect was blocked by haloperidol (a D2 receptor antagonist), whereas SKF-38393 left the JOR amplitude unaffected. Intrastriatal microinjection of quinpirole significantly reduced the responses of Aβ-

and C-fiber afferents associated with inhibition of the JOR [101]. Thus, it is possible that striatal D2 receptors attenuate pain-related responses through final descending sensory pathways.

Notably, evidence from human studies also indicated that striatal D2 receptors are involved in the regulation of pain [102]. A previous PET study showed that healthy male volunteers with low D2 receptor availability in the right putamen exhibited a high cold-pain threshold, while a low heat-pain modulatory capacity was associated with low D2 receptor availability in the left putamen [103]. Similarly, D2 receptor availability in the left putamen of patients with chronic orofacial pain increased [104]. Such results concur with experimental animal studies. More specifically, a high level of synaptic DA can lead to low availability of D2 receptors, a high cold-pain threshold, and a low response capacity to conditioning stimulation [103]. In other words, the high availability of D2/D3 receptors predicts a low synaptic DA concentration and a high capacity of recruiting pain inhibitory circuitry [96]. In addition, previous reports also demonstrated that striatal D2 receptors may influence pain-related responses not only through descending modulation of sensory pathways but also through supraspinal action on nonsensory factors [96, 97, 102]. For instance, the responses of the subject's attitude toward pain were negatively correlated with baseline striatal D2/D3 receptor availability [105]. Thus, subjects with high availability of striatal D2/D3 receptors, probably indicating low extracellular endogenous DA levels, rate the same stimulus as more painful than subjects with low striatal D2/D3 receptor availability [106].

3.5. Periaqueductal Gray (PAG). The midbrain PAG, a region full of opioid receptors, plays a significant role in the modulation of nociception. A subpopulation of DAergic neurons (A10-dc) known to be involved in the modulation of endogenous pain exists in the ventrolateral PAG (vlPAG), which projects locally within the PAG or to forebrain regions [107, 108]. Electrical stimulation of the PAG led to pain relief in animal models [109, 110]. Also, impairment of dopaminergic neurons of the PAG reduced antinociception induced by opioids [111]. In another study, enhanced levels of tyrosine hydroxylase following induction of CCI resulted in an enhanced level of DA in the PAG [112].

Microinjection of (–) apomorphine (DA agonist) into the ventral PAG (vPAG) was shown to increase the latency to lick the hind paw in the hot plate test in a dose-dependent manner. This effect was blocked by pretreatment with eticlopride (D2 antagonist), but not SCH-23390 (D1 antagonist). Apomorphine infusion into the outside of the vPAG had no marked analgesic effect [113]. In contrast, the findings of another study showed that administration of D1 receptor antagonist SCH-23390 in PAG dose-dependently attenuated analgesia induced by opiates (e.g., heroin and morphine). The effect was observed by the behaviors integrated supraspinal response (examined by hot plate test), but not the simple spinal reflex (examined by the tail-immersion test) [111]. Additionally, several studies have found that injection of both D2-like and D1-like receptor antagonists (raclopride and SCH-23390, respectively) into the PAG reduced antinociception induced by the activation of μ-opioid receptors [114]. Selective activation of D2-like receptors within the PAG significantly reduced allodynia, which was also blocked by GABAA receptor agonist (muscimol), opioid receptor antagonist (naloxone), and D2-like receptor antagonist (raclopride). Although the analgesic effect induced by activating D1-like receptors in the PAG was tiny and transient, it enhanced the antinociceptive effects of D2-like receptors [114]. Notably, treatments with all drugs had no significant influence on the locomotion of rats observed in open-field tests. Overall, these findings indicate that the activation of D2 receptors may induce the antinociceptive effects directly, while the activation of D1 receptors may participate synergically in the opioid-induced and D2-induced antinociception [111, 114].

In short, D2-like receptors may exert a higher analgesic potency, but D1-like receptors act in different manners with distinct mechanisms in the mentioned regions (Table 2). However, more studies should be designed to thoroughly investigate the role of DA receptors in antinociception and the underlying mechanisms.

4. Discussion and Conclusions

Complaints about acute and chronic pain reflect that pain management is poorly served by existing treatments. Developing novel analgesics with superior efficacy, diminished adverse effects, and lower abuse liability is urgent. Previous studies showed that the DAergic system plays a critical role in pain modulation [21, 115], suggesting that targeting DA receptors may be a novel treatment strategy for chronic pain. Therefore, we reviewed the role of DA receptor subtypes in the pain processes, particularly D1 and D2 receptors, throughout the central nervous system.

The evidence from studies on the spinal cord and brain cortex consistently indicated that more potent analgesic effects are related to D2 receptors, while the role of D1 receptors on pain modulation varies between different parts of the nervous system. Firstly, D1 receptors are mainly located postsynaptically, while D2 receptors are in both post- and presynaptic regions. Presynaptic DA receptors are characterized by higher sensitivity (5- to 100-fold) than those located in postsynaptic parts [116]. Therefore, compared to the D1 receptors, D2 receptors have a higher affinity for DA and require lower concentrations of DA to be activated. Secondly, D2 receptor signaling has an inhibitory effect, and the activation of D2 receptors decreases a neuron's firing rate, resulting in the network requiring more stimuli to initiate DA transmission [21]. For instance, in the spinal cord, D2 receptors play an analgesic role by reducing the intensity of the sensory input, like depressed C-fiber-evoked field potentials [55]. However, D1 receptors mediate neuronal excitation, which relies on the complex neuronal network between regions and a higher DA level.

In addition to the more potent analgesic efficacy of D2 receptors, D1 family receptors may play a more important role than D2 family receptors in mediating the facilitation of abuse-related intracranial self-stimulation (ICSS; one experimental procedure evaluated abuse-related effects of

drugs) [117]. High-efficacy D1 agonists SKF-82958 and A77636 produced facilitation of abuse-related ICSS depending on dosage and time. Lower efficacy D1 ligands and all D2/3 ligands failed to facilitate ICSS at any dose or pretreatment time. Besides, D2 receptor agonists are long prescribed and well tolerated, which are excellent features of clinical medicine [55].

Notably, although mounting evidence has revealed the antinociceptive effects of D2-like receptors, their analgesic efficacy is not as high as other drugs [55, 115]. Fortunately, a few studies have suggested that D2 receptors establish complex interactions with opioid receptors and could potentiate the analgesic effects of μ-opioid receptor agonists. For instance, coadministration of 1 μmol/L through spinal infusion was insufficient to alter potentials evoked by electrical C-fiber stimulation but could dramatically enhance the potential inhibition effects of DAMGO ([D-Ala^2,N-MePhe^4,Gly-ol]-enkephalin; a μ-opioid receptor agonist) and reduced its half-maximal inhibitory concentration (IC50) by 2-fold in a rat model of peripheral nerve injury [55]. Furthermore, the IT administration of quinpirole in lower doses remarkably augmented the antinociception effects of DAMGO (8-fold) in both inflammatory and neuropathic models of pain, assessed by mechanonociception and thermonociception behavioral tests [118]. Systemic administration of *R*-VK4-40, a highly selective D3 receptor antagonist, produced mild antinociceptive effects without altering locomotion, as observed in the open-field test or rotarod locomotor performance. In rats, this substance diminished the rewarding potency of oxycodone (the most commonly abused prescription opioid) and mitigated its tolerance and dependence without compromising its analgesic effects [119]. Thus, targeting the D2-like receptors may have the potential to enhance the analgesic property and alleviate the adverse effects of opioids.

Moreover, as previous reviews focused more on the role of the two subfamilies of DA receptors in the spinal cord and hypothalamus, the present review provides a more comprehensive summary on this topic by including the spinal cord and different brain regions. Indeed, some other regions (e.g., the hippocampus and amygdala), which are also involved in pain modulation, were excluded from the review due to the shortage of relevant studies, making it difficult to deduce a reliable conclusion. Moreover, even though we summarized the mutual promotion between the D2 receptor agonists and the opioids, whether chronic exposure to coadministration of D2-like receptor agonists and opioids could decrease the side effects of long-term opioid use remains unknown.

In summary, due to the vital role of the dopaminergic system on pain modulation, exploiting the multimodal analgesic regimens that target different DA receptors attracts more attention. Thus, we reviewed relevant studies to clarify the potential analgesic features of the DA receptor subtypes, especially D1 and D2 receptors, and summarized as follows: (1) D1 receptors act in different manners with distinct mechanisms in several regions, including the spinal cord, striatum, nucleus accumbens (NAc), and periaqueductal gray (PAG); (2) compared with D1 receptors, D2 receptors may exert a higher analgesic potency. Considering the superadditive or synergistic interactions between the D2 receptors and the opioid receptors, the agonist of D2 receptor may work as an adjuvant to potentiate the analgesic effect and reduce the side effects of opioids [55, 118].

Data Availability

All the researches involved in the present review are available in standard databases such as Web of Science, PubMed, and MEDLINE.

Conflicts of Interest

All authors declare no competing interests.

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References

[1] R. B. Fillingim, "Individual differences in pain: understanding the mosaic that makes pain personal," *Pain*, vol. 158, no. 1, pp. S11–S18, 2017.

[2] J. Lovich-Sapola, C. E. Smith, and C. P. Brandt, "Postoperative pain control," *The Surgical Clinics of North America*, vol. 95, no. 2, pp. 301–318, 2015.

[3] R. Melzack, "Pain and the neuromatrix in the brain," *Journal of Dental Education*, vol. 65, no. 12, pp. 1378–1382, 2001.

[4] D. A. Fishbain, J. E. Lewis, and J. Gao, "The pain–suffering association, a review," *Pain Medicine*, vol. 16, no. 6, pp. 1057–1072, 2015.

[5] X. Li and L. Hu, "The role of stress regulation on neural plasticity in pain chronification," *Neural Plasticity*, vol. 2016, Article ID 6402942, 9 pages, 2016.

[6] Y. H. Tu, J. Cao, Y. Z. Bi, and L. Hu, "Magnetic resonance imaging for chronic pain: diagnosis, manipulation, and biomarkers," *Science China Life Sciences*, 2020.

[7] K. Siebenhuener, E. Eschmann, A. Kienast et al., "Chronic pain: how challenging are DDIs in the analgesic treatment of inpatients with multiple chronic conditions?," *PLoS One*, vol. 12, no. 1, article e0168987, 2017.

[8] H. Li, X. Li, Y. Feng, F. Gao, Y. Kong, and L. Hu, "Deficits in ascending and descending pain modulation pathways in patients with postherpetic neuralgia," *NeuroImage*, vol. 221, article 117186, 2020.

[9] Q. Su, Y. Song, R. Zhao, and M. Liang, "A review on the ongoing quest for a pain signature in the human brain," *Brain Science Advances*, vol. 5, no. 4, pp. 274–287, 2019.

[10] B. G. Oertel and J. Lotsch, "Clinical pharmacology of analgesics assessed with human experimental pain models: bridging basic and clinical research," *British Journal of Pharmacology*, vol. 168, no. 3, pp. 534–553, 2013.

[11] S. S. Negus, "Core outcome measures in preclinical assessment of candidate analgesics," *Pharmacological Reviews*, vol. 71, no. 2, pp. 225–266, 2019.

[12] J. M. Scheiman and C. E. Hindley, "Strategies to optimize treatment with NSAIDs in patients at risk for gastrointestinal

and cardiovascular adverse events," *Clinical Therapeutics*, vol. 32, no. 4, pp. 667–677, 2010.

[13] J. M. Scheiman and A. M. Fendrick, "Practical approaches to minimizing gastrointestinal and cardiovascular safety concerns with COX-2 inhibitors and NSAIDs," *Arthritis Research & Therapy*, vol. 7, Supplement 4, pp. S23–S29, 2005.

[14] A. M. Rayar, N. Lagarde, C. Ferroud, J. F. Zagury, M. Montes, and M. Sylla-Iyarreta Veitia, "Update on COX-2 selective inhibitors: chemical classification, side effects and their use in cancers and neuronal diseases," *Current Topics in Medicinal Chemistry*, vol. 17, no. 26, pp. 2935–2956, 2017.

[15] A. B. Seidenberg and Y. H. An, "Is there an inhibitory effect of COX-2 inhibitors on bone healing?," *Pharmacological Research*, vol. 50, no. 2, pp. 151–156, 2004.

[16] K. Yukata, C. Xie, T. F. Li et al., "Teriparatide (human $PTH_{1\text{-}34}$) compensates for impaired fracture healing in COX-2 deficient mice," *Bone*, vol. 110, pp. 150–159, 2018.

[17] P. Lavand'homme and A. Steyaert, "Opioid-free anesthesia opioid side effects: tolerance and hyperalgesia," *Best Practice & Research. Clinical Anaesthesiology*, vol. 31, no. 4, pp. 487–498, 2017.

[18] H. Khademi, F. Kamangar, P. Brennan, and R. Malekzadeh, "Opioid therapy and its side effects: a review," *Archives of Iranian Medicine*, vol. 19, no. 12, pp. 870–876, 2016.

[19] J. Hjsted, O. Ekholm, G. P. Kurita, K. Juel, and P. Sjgren, "Addictive behaviors related to opioid use for chronic pain: a population-based study," *Pain*, vol. 154, no. 12, pp. 2677–2683, 2013.

[20] N. Vadivelu, A. M. Kai, V. Kodumudi, J. Sramcik, and A. D. Kaye, "The opioid crisis: a comprehensive overview," *Current Pain and Headache Reports*, vol. 22, no. 3, p. 16, 2018.

[21] S. Huang, S. L. Borgland, and G. W. Zamponi, "Dopaminergic modulation of pain signals in the medial prefrontal cortex: challenges and perspectives," *Neuroscience Letters*, vol. 702, pp. 71–76, 2019.

[22] L. Tiemann, H. Heitmann, E. Schulz, J. Baumkotter, and M. Ploner, "Dopamine precursor depletion influences pain affect rather than pain sensation," *PLoS One*, vol. 9, no. 4, article e96167, 2014.

[23] R. A. Serafini, K. D. Pryce, and V. Zachariou, "The mesolimbic dopamine system in chronic pain and associated affective comorbidities," *Biological Psychiatry*, vol. 87, no. 1, pp. 64–73, 2020.

[24] M. Pecina, M. Martinez-Jauand, T. Love et al., "Valence-specific effects of BDNF Val66Met polymorphism on dopaminergic stress and reward processing in humans," *The Journal of Neuroscience*, vol. 34, no. 17, pp. 5874–5881, 2014.

[25] D. J. Scott, C. S. Stohler, C. M. Egnatuk, H. Wang, R. A. Koeppe, and J. K. Zubieta, "Individual differences in reward responding explain placebo-induced expectations and effects," *Neuron*, vol. 55, no. 2, pp. 325–336, 2007.

[26] M. N. Baliki, B. Petre, S. Torbey et al., "Corticostriatal functional connectivity predicts transition to chronic back pain," *Nature Neuroscience*, vol. 15, no. 8, pp. 1117–1119, 2012.

[27] B. Cagnie, I. Coppieters, S. Denecker, J. Six, L. Danneels, and M. Meeus, "Central sensitization in fibromyalgia? A systematic review on structural and functional brain MRI," *Seminars in Arthritis and Rheumatism*, vol. 44, no. 1, pp. 68–75, 2014.

[28] P. B. Wood, J. C. Patterson 2nd, J. J. Sunderland, K. H. Tainter, M. F. Glabus, and D. L. Lilien, "Reduced presynaptic dopamine activity in fibromyalgia syndrome demonstrated with positron emission tomography: a pilot study," *The Journal of Pain*, vol. 8, no. 1, pp. 51–58, 2007.

[29] I. K. Martikainen, E. B. Nuechterlein, M. Pecina et al., "Chronic back pain is associated with alterations in dopamine neurotransmission in the ventral striatum," *The Journal of Neuroscience*, vol. 35, no. 27, pp. 9957–9965, 2015.

[30] A. Nebe and G. Ebersbach, "Pain intensity on and off levodopa in patients with Parkinson's disease," *Movement Disorders*, vol. 24, no. 8, pp. 1233–1237, 2009.

[31] A. Q. Rana, D. Qureshi, W. Sabeh et al., "Pharmacological therapies for pain in Parkinson's disease - a review paper," *Expert Review of Neurotherapeutics*, vol. 17, no. 12, pp. 1209–1219, 2017.

[32] C. A. Rabinak and M. J. Nirenberg, "Dopamine agonist withdrawal syndrome in Parkinson disease," *Archives of Neurology*, vol. 67, no. 1, pp. 58–63, 2010.

[33] M. Dourado, H. Cardoso-Cruz, C. Monteiro, and V. Galhardo, "Effect of motor impairment on analgesic efficacy of dopamine D2/3 receptors in a rat model of neuropathy," *Journal of Experimental Neuroscience*, vol. 10, pp. 51–57, 2016.

[34] N. Cobacho, J. L. De la Calle, J. R. Gonzalez-Escalada, and C. L. Paino, "Levodopa analgesia in experimental neuropathic pain," *Brain Research Bulletin*, vol. 83, no. 6, pp. 304–309, 2010.

[35] M. Jaber, S. W. Robinson, C. Missale, and M. G. Caron, "Dopamine receptors and brain function," *Neuropharmacology*, vol. 35, no. 11, pp. 1503–1519, 1996.

[36] J. M. Beaulieu and R. R. Gainetdinov, "The physiology, signaling, and pharmacology of dopamine receptors," *Pharmacological Reviews*, vol. 63, no. 1, pp. 182–217, 2011.

[37] S. Panchalingam and A. S. Undie, "Optimized binding of [35S]GTPgammaS to Gq-like proteins stimulated with dopamine D1-like receptor agonists," *Neurochemical Research*, vol. 25, no. 6, pp. 759–767, 2000.

[38] J. E. Lachowicz and D. R. Sibley, "Molecular characteristics of mammalian dopamine receptors," *Pharmacology & Toxicology*, vol. 81, no. 3, pp. 105–113, 1997.

[39] H. K. Kleitz, C. A. Cornil, J. Balthazart, and G. F. Ball, "Species differences in the relative densities of D1- and D2-like dopamine receptor subtypes in the Japanese quail and rats: an in vitro quantitative receptor autoradiography study," *Brain, Behavior and Evolution*, vol. 73, no. 2, pp. 81–90, 2009.

[40] C. Carcenac, M. Favier, Y. Vachez et al., "Subthalamic deep brain stimulation differently alters striatal dopaminergic receptor levels in rats," *Movement Disorders*, vol. 30, no. 13, pp. 1739–1749, 2015.

[41] M. Puopolo, "The hypothalamic-spinal dopaminergic system: a target for pain modulation," *Neural Regeneration Research*, vol. 14, no. 6, pp. 925–930, 2019.

[42] R. D'Mello and A. H. Dickenson, "Spinal cord mechanisms of pain," *British Journal of Anaesthesia*, vol. 101, no. 1, pp. 8–16, 2008.

[43] A. Tamae, T. Nakatsuka, K. Koga et al., "Direct inhibition of substantia gelatinosa neurones in the rat spinal cord by activation of dopamine D2-like receptors," *The Journal of Physiology*, vol. 568, no. 1, pp. 243–253, 2005.

[44] A. Almanza, K. Simón-Arceo, U. Coffeen et al., "A D2-like receptor family agonist produces analgesia in mechanonociception but not in thermonociception at the spinal cord level in rats," *Pharmacology, Biochemistry, and Behavior*, vol. 137, pp. 119–125, 2015.

[45] S. Barasi and K. N. Duggal, "The effect of local and systemic application of dopaminergic agents on tail flick latency in the rat," *European Journal of Pharmacology*, vol. 117, no. 3, pp. 287–294, 1985.

[46] T. S. Jensen and D. F. Smith, "Dopaminergic effects on tail-flick response in spinal rats," *European Journal of Pharmacology*, vol. 79, no. 1-2, pp. 129–133, 1982.

[47] Q. S. Liu, J. T. Qiao, and N. Dafny, "D_2 dopamine receptor involvement in spinal dopamine- produced antinociception," *Life Sciences*, vol. 51, no. 19, pp. 1485–1492, 1992.

[48] X. Gao, Y. Zhang, and G. C. Wu, "Effects of dopaminergic agents on carrageenan hyperalgesia after intrathecal administration to rats," *European Journal of Pharmacology*, vol. 418, no. 1-2, pp. 73–77, 2001.

[49] N. Cobacho, J. L. de la Calle, and C. L. Paino, "Dopaminergic modulation of neuropathic pain: analgesia in rats by a D2-type receptor agonist," *Brain Research Bulletin*, vol. 106, pp. 62–71, 2014.

[50] A. Stuchlik, L. Rehakova, L. Rambousek, J. Svoboda, and K. Vales, "Manipulation of D2 receptors with quinpirole and sulpiride affects locomotor activity before spatial behavior of rats in an active place avoidance task," *Neuroscience Research*, vol. 58, no. 2, pp. 133–139, 2007.

[51] S. A. Sharples, K. Koblinger, J. M. Humphreys, and P. J. Whelan, "Dopamine: a parallel pathway for the modulation of spinal locomotor networks," *Frontiers in Neural Circuits*, vol. 8, p. 55, 2014.

[52] O. Lapirot, C. Melin, A. Modolo et al., "Tonic and phasic descending dopaminergic controls of nociceptive transmission in the medullary dorsal horn," *Pain*, vol. 152, no. 8, pp. 1821–1831, 2011.

[53] R. A. N. Pértile, M. E. Corvino, R. C. N. Marchette et al., "The quinpirole hypolocomotive effects are strain and route of administration dependent in SHR and SLA16 isogenic rats," *Behavior Genetics*, vol. 47, no. 5, pp. 552–563, 2017.

[54] W. Galbavy, E. Safaie, M. J. Rebecchi, and M. Puopolo, "Inhibition of tetrodotoxin-resistant sodium current in dorsal root ganglia neurons mediated by D1/D5 dopamine receptors," *Molecular Pain*, vol. 9, p. 1744-8069-9-60, 2013.

[55] Z. Aira, T. Barrenetxea, I. Buesa, J. C. Gomez-Esteban, and J. J. Azkue, "Synaptic upregulation and superadditive interaction of dopamine D2- and μ-opioid receptors after peripheral nerve injury," *Pain*, vol. 155, no. 12, pp. 2526–2533, 2014.

[56] K. Kawamoto, K. Otsuguro, M. Ishizuka, and S. Ito, "Inhibitory effects of dopamine on spinal synaptic transmission via dopamine D1-like receptors in neonatal rats," *British Journal of Pharmacology*, vol. 166, no. 2, pp. 788–800, 2012.

[57] J. Cheriyan and P. L. Sheets, "Altered excitability and local connectivity of mPFC-PAG neurons in a mouse model of neuropathic pain," *The Journal of Neuroscience*, vol. 38, no. 20, pp. 4829–4839, 2018.

[58] G. Descalzi, V. Mitsi, I. Purushothaman et al., "Neuropathic pain promotes adaptive changes in gene expression in brain networks involved in stress and depression," *Science Signaling*, vol. 10, no. 471, p. eaaj1549, 2017.

[59] N. S. Narayanan, D. J. Guarnieri, and R. J. DiLeone, "Metabolic hormones, dopamine circuits, and feeding," *Frontiers in Neuroendocrinology*, vol. 31, no. 1, pp. 104–112, 2010.

[60] Y. Tu, Y. Bi, L. Zhang, H. Wei, and L. Hu, "Mesocorticolimbic pathways encode cue-based expectancy effects on pain," *The Journal of Neuroscience*, vol. 40, no. 2, pp. 382–394, 2020.

[61] M. Watanabe, M. Narita, Y. Hamada et al., "Activation of ventral tegmental area dopaminergic neurons reverses pathological allodynia resulting from nerve injury or bone cancer," *Molecular Pain*, vol. 14, p. 174480691875640, 2018.

[62] K. Kami, F. Tajima, and E. Senba, "Activation of mesolimbic reward system via laterodorsal tegmental nucleus and hypothalamus in exercise-induced hypoalgesia," *Scientific Reports*, vol. 8, no. 1, article 11540, 2018.

[63] F. del-Fava, R. H. Hasue, J. G. Ferreira, and S. J. Shammah-Lagnado, "Efferent connections of the rostral linear nucleus of the ventral tegmental area in the rat," *Neuroscience*, vol. 145, no. 3, pp. 1059–1076, 2007.

[64] M. Moradi, M. Yazdanian, and A. Haghparast, "Role of dopamine D2-like receptors within the ventral tegmental area and nucleus accumbens in antinociception induced by lateral hypothalamus stimulation," *Behavioural Brain Research*, vol. 292, pp. 508–514, 2015.

[65] M. Moradi, Z. Fatahi, and A. Haghparast, "Blockade of D1-like dopamine receptors within the ventral tegmental area and nucleus accumbens attenuates antinociceptive responses induced by chemical stimulation of the lateral hypothalamus," *Neuroscience Letters*, vol. 599, pp. 61–66, 2015.

[66] F. Ambroggi, A. Ghazizadeh, S. M. Nicola, and H. L. Fields, "Roles of nucleus accumbens core and shell in incentive-cue responding and behavioral inhibition," *The Journal of Neuroscience*, vol. 31, no. 18, pp. 6820–6830, 2011.

[67] J. J. Walsh and M. H. Han, "The heterogeneity of ventral tegmental area neurons: projection functions in a mood-related context," *Neuroscience*, vol. 282, pp. 101–108, 2014.

[68] R. Ito and A. Hayen, "Opposing roles of nucleus accumbens core and shell dopamine in the modulation of limbic information processing," *The Journal of Neuroscience*, vol. 31, no. 16, pp. 6001–6007, 2011.

[69] S. Koyanagi, S. Himukashi, K. Mukaida, T. Shichino, and K. Fukuda, "Dopamine D2-like receptor in the nucleus accumbens is involved in the antinociceptive effect of nitrous oxide," *Anesthesia and Analgesia*, vol. 106, no. 6, pp. 1904–1909, 2008.

[70] B. K. Taylor, C. Joshi, and H. Uppal, "Stimulation of dopamine D2 receptors in the nucleus accumbens inhibits inflammatory pain," *Brain Research*, vol. 987, no. 2, pp. 135–143, 2003.

[71] A. Haghparast, M. Ghalandari-Shamami, and M. Hassanpour-Ezatti, "Blockade of D1/D2 dopamine receptors within the nucleus accumbens attenuated the antinociceptive effect of cannabinoid receptor agonist in the basolateral amygdala," *Brain Research*, vol. 1471, pp. 23–32, 2012.

[72] G. Faramarzi, M. Zendehdel, and A. Haghparast, "D1- and D2-like dopamine receptors within the nucleus accumbens contribute to stress-induced analgesia in formalin-related pain behaviours in rats," *European Journal of Pain*, vol. 20, no. 9, pp. 1423–1432, 2016.

[73] A. Siahposht-Khachaki, P. Pourreza, S. Ezzatpanah, and A. Haghparast, "Nucleus accumbens dopamine receptors mediate hypothalamus-induced anti-nociception in the rat formalin test," *European Journal of Pain*, vol. 21, no. 7, pp. 1285–1294, 2017.

[74] S. Yazdi-Ravandi, Y. Razavi, A. Haghparast, M. Goudarzvand, and A. Haghparast, "Orexin A induced antinociception in the ventral tegmental area involves D1 and D2 receptors in the nucleus accumbens," *Pharmacology, Biochemistry, and Behavior*, vol. 126, pp. 1–6, 2014.

[75] D. E. Selley, M. F. Lazenka, L. J. Sim-Selley et al., "Attenuated dopamine receptor signaling in nucleus accumbens core in a rat model of chemically-induced neuropathy," *Neuropharmacology*, vol. 166, article 107935, 2020.

[76] J. D. Hakim, J. Chami, and K. A. Keay, "μ-Opioid and dopamine-D2 receptor expression in the nucleus accumbens of male Sprague-Dawley rats whose sucrose consumption, but not preference, decreases after nerve injury," *Behavioural Brain Research*, vol. 381, article 112416, 2020.

[77] H. N. Harris and Y. B. Peng, "Evidence and explanation for the involvement of the nucleus accumbens in pain processing," *Neural Regeneration Research*, vol. 15, no. 4, pp. 597–605, 2020.

[78] T. Hikida, S. Yawata, T. Yamaguchi et al., "Pathway-specific modulation of nucleus accumbens in reward and aversive behavior via selective transmitter receptors," *Proceedings of the National Academy of Sciences of the United States of America*, vol. 110, no. 1, pp. 342–347, 2013.

[79] M. L. Perreault, A. Hasbi, M. Alijaniaram et al., "The dopamine D1-D2 receptor heteromer localizes in dynorphin/enkephalin neurons," *The Journal of Biological Chemistry*, vol. 285, no. 47, pp. 36625–36634, 2010.

[80] E. K. Richfield, J. B. Penney, and A. B. Young, "Anatomical and affinity state comparisons between dopamine D_1 and D_2 receptors in the rat central nervous system," *Neuroscience*, vol. 30, no. 3, pp. 767–777, 1989.

[81] M. Lee, T. R. Manders, S. E. Eberle et al., "Activation of corticostriatal circuitry relieves chronic neuropathic pain," *The Journal of Neuroscience*, vol. 35, no. 13, pp. 5247–5259, 2015.

[82] W. W. Peng, Z. Y. Tang, F. R. Zhang et al., "Neurobiological mechanisms of TENS-induced analgesia," *NeuroImage*, vol. 195, pp. 396–408, 2019.

[83] W. Y. Ong, C. S. Stohler, and D. R. Herr, "Role of the prefrontal cortex in pain processing," *Molecular Neurobiology*, vol. 56, no. 2, pp. 1137–1166, 2019.

[84] S. Sogabe, Y. Yagasaki, K. Onozawa, and Y. Kawakami, "Mesocortical dopamine system modulates mechanical nociceptive responses recorded in the rat prefrontal cortex," *BMC Neuroscience*, vol. 14, no. 1, p. 65, 2013.

[85] P. L. Gabbott, T. A. Warner, P. R. Jays, P. Salway, and S. J. Busby, "Prefrontal cortex in the rat: projections to subcortical autonomic, motor, and limbic centers," *Journal of Comparative Neurology and Psychology*, vol. 492, no. 2, pp. 145–177, 2005.

[86] C. Wang, C. Bao, J. Gao, Y. Gu, and X. W. Dong, "Pain modulates neural responses to reward in the medial prefrontal cortex," *Human Brain Mapping*, vol. 41, no. 5, pp. 1372–1381, 2020.

[87] D. J. Lodge, "The medial prefrontal and orbitofrontal cortices differentially regulate dopamine system function," *Neuropsychopharmacology*, vol. 36, no. 6, pp. 1227–1236, 2011.

[88] J. Dale, H. Zhou, Q. Zhang et al., "Scaling up cortical control inhibits pain," *Cell Reports*, vol. 23, no. 5, pp. 1301–1313, 2018.

[89] S. Huang, Z. Zhang, E. Gambeta et al., "Dopamine inputs from the ventral tegmental area into the medial prefrontal cortex modulate neuropathic pain-associated behaviors in mice," *Cell Reports*, vol. 31, no. 12, article 107812, 2020.

[90] C. P. Mao, Q. L. Zhang, F. X. Bao, X. Liao, X. L. Yang, and M. Zhang, "Decreased activation of cingulo-frontal-parietal cognitive/attention network during an attention-demanding task in patients with chronic low back pain," *Neuroradiology*, vol. 56, no. 10, pp. 903–912, 2014.

[91] P. J. Fletcher, C. C. Tenn, J. Sinyard, Z. Rizos, and S. Kapur, "A sensitizing regimen of amphetamine impairs visual attention in the 5-choice serial reaction time test: reversal by a D1 receptor agonist injected into the medial prefrontal cortex," *Neuropsychopharmacology*, vol. 32, no. 5, pp. 1122–1132, 2007.

[92] S. Granon, F. Passetti, K. L. Thomas, J. W. Dalley, B. J. Everitt, and T. W. Robbins, "Enhanced and impaired attentional performance after infusion of D1 dopaminergic receptor agents into rat prefrontal cortex," *The Journal of Neuroscience*, vol. 20, no. 3, pp. 1208–1215, 2000.

[93] S. J. Bantick, R. G. Wise, A. Ploghaus, S. Clare, S. M. Smith, and I. Tracey, "Imaging how attention modulates pain in humans using functional MRI," *Brain*, vol. 125, no. 2, pp. 310–319, 2002.

[94] C. Villemure and M. C. Bushnell, "Cognitive modulation of pain: how do attention and emotion influence pain processing?," *Pain*, vol. 95, no. 3, pp. 195–199, 2002.

[95] J. M. Leyrer-Jackson and M. P. Thomas, "Subtype-specific effects of dopaminergic D2 receptor activation on synaptic trains in layer V pyramidal neurons in the mouse prefrontal cortex," *Physiological Reports*, vol. 5, no. 22, article e13499, 2017.

[96] N. Hagelberg, S. K. Jääskeläinen, I. K. Martikainen et al., "Striatal dopamine D2 receptors in modulation of pain in humans: a review," *European Journal of Pharmacology*, vol. 500, no. 1-3, pp. 187–192, 2004.

[97] A. Pertovaara and H. Wei, "Dual influence of the striatum on neuropathic hypersensitivity," *Pain*, vol. 137, no. 1, pp. 50–59, 2008.

[98] J. E. Magnusson and K. Fisher, "The involvement of dopamine in nociception: the role of D_1 and D_2 receptors in the dorsolateral striatum," *Brain Research*, vol. 855, no. 2, pp. 260–266, 2000.

[99] O. B. Ansah, H. Leite-Almeida, H. Wei, and A. Pertovaara, "Striatal dopamine D_2 receptors attenuate neuropathic hypersensitivity in the rat," *Experimental Neurology*, vol. 205, no. 2, pp. 536–546, 2007.

[100] Y. Z. Bi, Z. X. Wei, Y. Z. Kong, and L. Hu, "Supraspinal neural mechanisms of the analgesic effect produced by transcutaneous electrical nerve stimulation," *Brain Structure and Function*, vol. 226, no. 1, pp. 151–162, 2021.

[101] B. T. Saunier-Rebori and J. H. Pazo, "Inhibition of jaw opening reflex and single neurons in the trigeminal subnucleus caudalis by activation of striatal D2 dopamine receptors," *Neuropharmacology*, vol. 51, no. 2, pp. 263–271, 2006.

[102] A. C. Barcelo, B. Filippini, and J. H. Pazo, "The striatum and pain modulation," *Cellular and Molecular Neurobiology*, vol. 32, no. 1, pp. 1–12, 2012.

[103] N. Hagelberg, I. K. Martikainen, H. Mansikka et al., "Dopamine D2 receptor binding in the human brain is associated with the response to painful stimulation and pain modulatory capacity," *Pain*, vol. 99, no. 1, pp. 273–279, 2002.

[104] N. Hagelberg, H. Forssell, S. Aalto et al., "Altered dopamine D2 receptor binding in atypical facial pain," *Pain*, vol. 106, no. 1, pp. 43–48, 2003.

[105] K. Ledermann, J. Jenewein, H. Sprott et al., "Relation of dopamine receptor 2 binding to pain perception in female fibromyalgia patients with and without depression - a [^{11}C]

raclopride PET-study," *European Neuropsychopharmacology*, vol. 26, no. 2, pp. 320–330, 2016.

[106] I. K. Martikainen, N. Hagelberg, S. K. Jaaskelainen, J. Hietala, and A. Pertovaara, "Dopaminergic and serotonergic mechanisms in the modulation of pain: *in vivo* studies in human brain," *European Journal of Pharmacology*, vol. 834, pp. 337–345, 2018.

[107] C. Li, J. A. Sugam, E. G. Lowery-Gionta et al., "Mu opioid receptor modulation of dopamine neurons in the periaqueductal gray/dorsal raphe: a role in regulation of pain," *Neuropsychopharmacology*, vol. 41, no. 8, pp. 2122–2132, 2016.

[108] N. E. Taylor, J. Pei, J. Zhang et al., "The role of glutamatergic and dopaminergic neurons in the periaqueductal gray/dorsal raphe: separating analgesia and anxiety," *eNeuro*, vol. 6, no. 1, 2019.

[109] S. Ben-Haim, Z. Mirzadeh, and W. S. Rosenberg, "Deep brain stimulation for intractable neuropathic facial pain," *Neurosurgical Focus*, vol. 45, no. 2, article E15, 2018.

[110] S. L. Owen, A. L. Green, D. D. Nandi, R. G. Bittar, S. Wang, and T. Z. Aziz, "Deep brain stimulation for neuropathic pain," *Acta Neurochirurgica. Supplement*, vol. 97, Part 2, pp. 111–116, 2007.

[111] J. A. Flores, F. el Banoua, B. Galán-Rodríguez, and E. Fernandez-Espejo, "Opiate anti-nociception is attenuated following lesion of large dopamine neurons of the periaqueductal grey: critical role for D1 (not D2) dopamine receptors," *Pain*, vol. 110, no. 1, pp. 205–214, 2004.

[112] D. Mor, J. W. Kang, P. Wyllie et al., "Recruitment of dorsal midbrain catecholaminergic pathways in the recovery from nerve injury evoked disabilities," *Molecular Pain*, vol. 11, 2015.

[113] P. J. Meyer, M. M. Morgan, L. B. Kozell, and S. L. Ingram, "Contribution of dopamine receptors to periaqueductal gray-mediated anti-nociception," *Psychopharmacology*, vol. 204, no. 3, pp. 531–540, 2009.

[114] G. Tobaldini, R. A. Reis, N. F. Sardi et al., "Dopaminergic mechanisms in periaqueductal gray-mediated anti-nociception," *Behavioural Pharmacology*, vol. 29, no. 2 and 3, pp. 225–233, 2018.

[115] V. Mitsi and V. Zachariou, "Modulation of pain, nociception, and analgesia by the brain reward center," *Neuroscience*, vol. 338, pp. 81–92, 2016.

[116] J. Mlost, A. Wasik, and K. Starowicz, "Role of endocannabinoid system in dopamine signalling within the reward circuits affected by chronic pain," *Pharmacological Research*, vol. 143, pp. 40–47, 2019.

[117] M. F. Lazenka, L. P. Legakis, and S. S. Negus, "Opposing effects of dopamine D1- and D2-like agonists on intracranial self-stimulation in male rats," *Experimental and Clinical Psychopharmacology*, vol. 24, no. 3, pp. 193–205, 2016.

[118] J. Mercado-Reyes, A. Almanza, P. Segura-Chama, F. Pellicer, and F. Mercado, "D2-like receptor agonist synergizes the μ-opioid agonist spinal antinociception in nociceptive, inflammatory and neuropathic models of pain in the rat," *European Journal of Pharmacology*, vol. 853, pp. 56–64, 2019.

[119] C. J. Jordan, B. Humburg, M. Rice et al., "The highly selective dopamine D_3R antagonist, *R*-VK4-40 attenuates oxycodone reward and augments analgesia in rodents," *Neuropharmacology*, vol. 158, article 107597, 2019.