Opioidergic Modulation of Striatal Circuits, Implications in Parkinson's Disease and Levodopa Induced Dyskinesia

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The functional organization of the dorsal striatum is complex, due to the diversity of neural inputs that converge in this structure and its subdivision into direct and indirect output pathways, striosomes and matrix compartments. Among the neurotransmitters that regulate the activity of striatal projection neurons (SPNs), opioid neuropeptides (enkephalin and dynorphin) play a neuromodulatory role in synaptic transmission and plasticity and affect striatal-based behaviors in both normal brain function and pathological states, including Parkinson's disease (PD). We review recent findings on the cell-type-specific effects of opioidergic neurotransmission in the dorsal striatum, focusing on the maladaptive synaptic neuroadaptations that occur in PD and levodopa-induced dyskinesia. Understanding the plethora of molecular and synaptic mechanisms underpinning the opioid-mediated modulation of striatal circuits is critical for the development of pharmacological treatments that can alleviate motor dysfunctions and hyperkinetic responses to dopaminergic stimulant drugs.

Keywords: opioids, dopamine, striatum, Parkinson's disease, signaling pathway, synaptic plasticity

INTRODUCTION

Opioidergic signaling is involved in several functional aspects of the peripheral and central nervous system and due to the broad distribution of opioid receptors throughout the brain, its activation modulates different neural circuits. Opiate drugs are widely used as analgesic to induce antinociception and to treat pain disorders. However, edonic effects of opiates induce addictive behaviors that entail the involvement of opioidergic system in reward processes (1, 2). Opioid receptors and the endogenous opioid peptides Enkephalin (Enk) and Dynorphin (Dyn) are expressed at striatal circuits, where the opioid system modulates the activity of spiny projection neurons (SPNs) during movement control in both a healthy state and in motor disorders such as Parkinson's disease (PD). In PD, functional changes in striatal pathways are associated with a reorganization of molecular and synaptic mechanisms that counteract the loss of dopaminergic cells. However, aberrant neuroadaptations in the striatal circuit can be responsible for critical aspects of PD, as observed in levodopa-induced dyskinesia (LID). It is still unclear what role opioid transmission plays in striatal circuity and how this system affects neural reorganization, both in PD and in response to dopaminergic treatment. Here, we review recent findings on

the cell-type-specific effects of opioid transmission in the dorsal striatum, including the signaling pathways, synaptic and behavioral effects mediated by opioid ligands, as well as their interactions with dopaminergic transmission in both a PD state and in response to dopaminergic treatment with levodopa (L-DOPA).

ANATOMY AND PHYSIOLOGY OF THE BASAL GANGLIA

The basal ganglia (BG) comprise a distributed group of nuclei that include the striatum, which is composed by the caudate and putamen (CPu), the globus pallidus, with the pars externa (GPe) and interna (GPi), the subthalamic nucleus (STN); and the substantia nigra pars compacta (SNpc) and pars reticulata (SNpr). The Striatum and the STN represent the main input nuclei of the BG, while the GP and SNpr are the two output structures projecting to the thalamus and brainstem (3–7). The BG nuclei's connectivity to cortical regions provides a complex network of sensorimotor, limbic and associative information, conferring on the BG a pivotal role in the control of movement as well as in associative learning, emotion and reward-related behavior (8).

Nearly 95% of the striatum is composed of striatal projection neurons (SPNs), which are GABA (γ-aminobutyric acid)-ergic neurons that relay inhibitory efferent transmission and are rich in dopaminergic receptors (DR). These neurons are classified in two subtypes based on their projection targets, neuropeptides expression and DR subtypes (9). SPNs that express the neuropeptide Dyn and bear D1 excitatory receptors (D1Rs) (10) belong to what is termed the direct striatonigral pathway (dSPNs), projecting directly to the GPi/SNpr. On the other hand, SPNs expressing Enk and bearing D2 inhibitory receptors (D2Rs) project to the GPi/SNpr indirectly through the GPe, as part of the indirect striatopallidal pathway (iSPNs) (9, 11). In a healthy state (see **Figure 1A**), the activation of the direct pathway promotes movement execution by reducing the neural firing of the GPi/SNpr to the thalamus and boosting glutamatergic thalamocortical transmission. In parallel, activation of the indirect pathway reduces movement initiation, exciting GPi/SNpr transmission by inhibiting the GPe and activating the STN, ultimately leading to the inhibition of thalamocortical transmission (4, 12, 13). The concomitant activation of both striatofugal pathways maintains a balance between the direct and indirect pathways, activating specific and voluntary actions through the direct pathway and inhibiting involuntary movements through the indirect pathway (13, 14).

Excitatory corticostriatal transmission on SPNs is modulated by dopaminergic input from the SNpc through "diffusion-based volume transmission," where dopamine (DA) diffuses away from the synapse to reach extrasynaptic receptors and regulate excitability of SPNs (15). However, sparse release sites defined as active zone have been identified in the striatal DA axons to allow for a fast DA release and to generate a localized DA signal (16). Once released, DA exerts a dual effect on striatal neurons (17), exciting the direct pathway by binding to D1Rs and inhibiting

the indirect pathway by binding to D2Rs. DA discharge from the dopaminergic neurons of the SNpc is crucial for the initiation and execution of motor sequences (14, 18).

THE OPIOIDERGIC SYSTEM: PEPTIDES AND RECEPTORS

Enk, Dyn and β-endorphin belong to family of endogenous peptides produced through the proteolytic cleavage of protein precursors such as preproenkephalin-A (PPENK), which forms six copies of methionine-Enk (Met-Enk) and one copy of leucine-Enk; preproenkephalin-B (also known as preprodynorphin), which produces Dyn and endorphin; and finally, proopiomelanocortin, which produces β-endorphin. The endogenous peptides have different degrees of selectivity for the opioid receptors; Enk binds δ opioid receptors (DORs) and μ opioid receptors (MORs), Dyn is selective for κ-opioid receptors (KORs), and β-endorphin binds MORs (1).

Opioid receptors (ORs) are seven-transmembrane receptors and belong to a superfamily of G protein-coupled receptors (GPCRs) with inhibitory activity ($G\alpha_{i/o}$) on cellular excitability and synaptic transmission (1). OR activity promotes the activation of G-protein-coupled inwardly rectifying K^+ channels, inhibits Ca^+ channels and adenylyl cyclase (AC), and reduces neurotransmitter release and neural activity (19, 20). ORs are broadly distributed in the brain, with some structures exhibiting higher expression of a specific type of receptor, while others have three overlapping receptors that can interact locally with one another in synergistic or antagonistic ways (21).

A broad distribution of MORs has been observed in the thalamus, amygdala and locus coeruleus (1), and in the thalamic afferents to the striatum (22). MOR expression has also been observed in CPu striosomal compartments that project to the SNpc (23) (**Figure 2**). Specifically, MORs are expressed in striosomes both on dSPNs enriched in Dyn precursor and on iSPNs (24), where they colocalize with D2Rs in dendrites (25). MORs are also expressed on striatal cholinergic interneurons (26, 27).

DORs are abundant in layers II, III, IV and V of the cerebral cortex and in the striosomes and matrix compartments of the CPu, with a higher dorsolateral distribution than ventromedial (28). On a cellular level, DORs are expressed within the nucleus and in the somatodendritic area on iSPNs, but not on dSPNs (24, 29).

KORs are predominantly found in the medial sector of the CPu and in the nucleus accumbens and showed a higher coexpression with D1Rs (24). They are also localized presynaptically in the nigrostriatal afferents of the SNpc.

OPIOID RECEPTOR SIGNALING

The activation of opioidergic GPCRs by endogenous opioid peptides or exogenous agonists leads to the dissociation of Gα/βγ subunits that stimulate various intracellular effectors. The inhibitory activity of opioid receptors includes several processes that are selectively initiated by the Gα and Gβγ protein
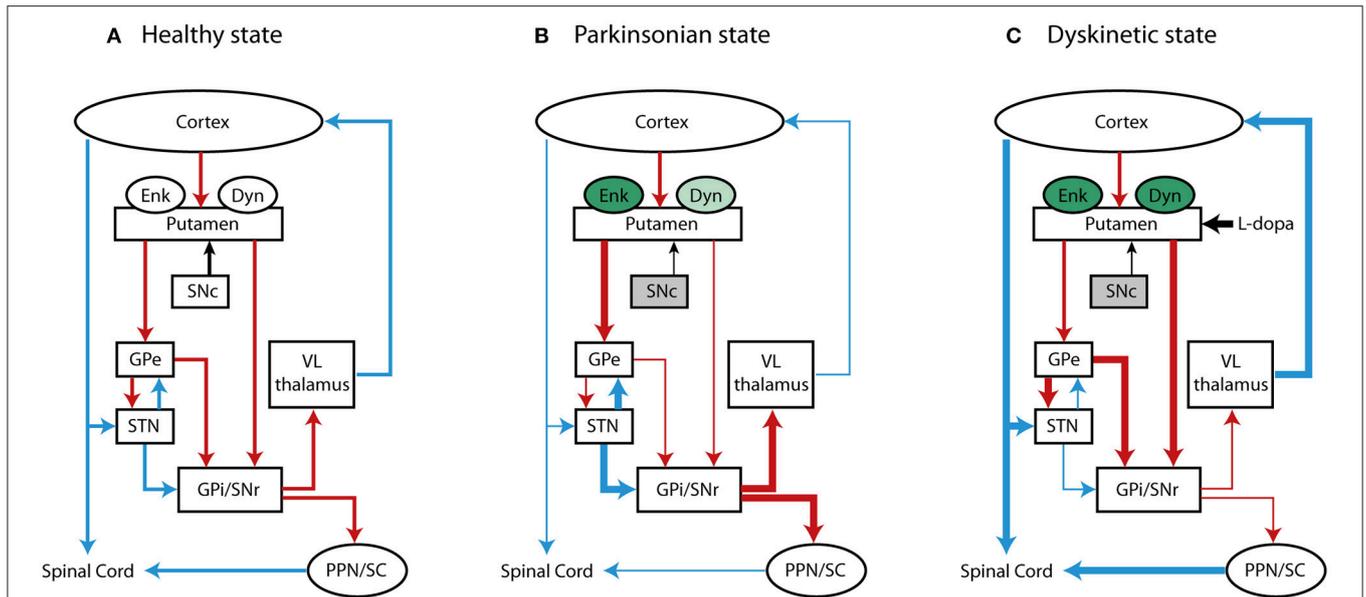
FIGURE 1 | Basal ganglia motor loop in **(A)** normal, **(B)** PD, and **(C)** LID condition. The schematic represents the direct, indirect and hyperdirect pathways projecting to the thalamus and spinal cord and the changes of expression of opiod peptides, Enk and Dyn. Red, blue and black lines indicate GABA-ergic, glutamatergic and dopaminergic projections, respectively. Changes in the rate of neural transmission are indicated with thick (increased activity) and thin (decreased activity) lines. Changes in the expression of Enk and Dyn are depicted in green (increased levels) and light green (decreased levels). The gray color of substantia nigra pars compact (SNc) is representative of PD state due to the loss of dopaminergic cells.
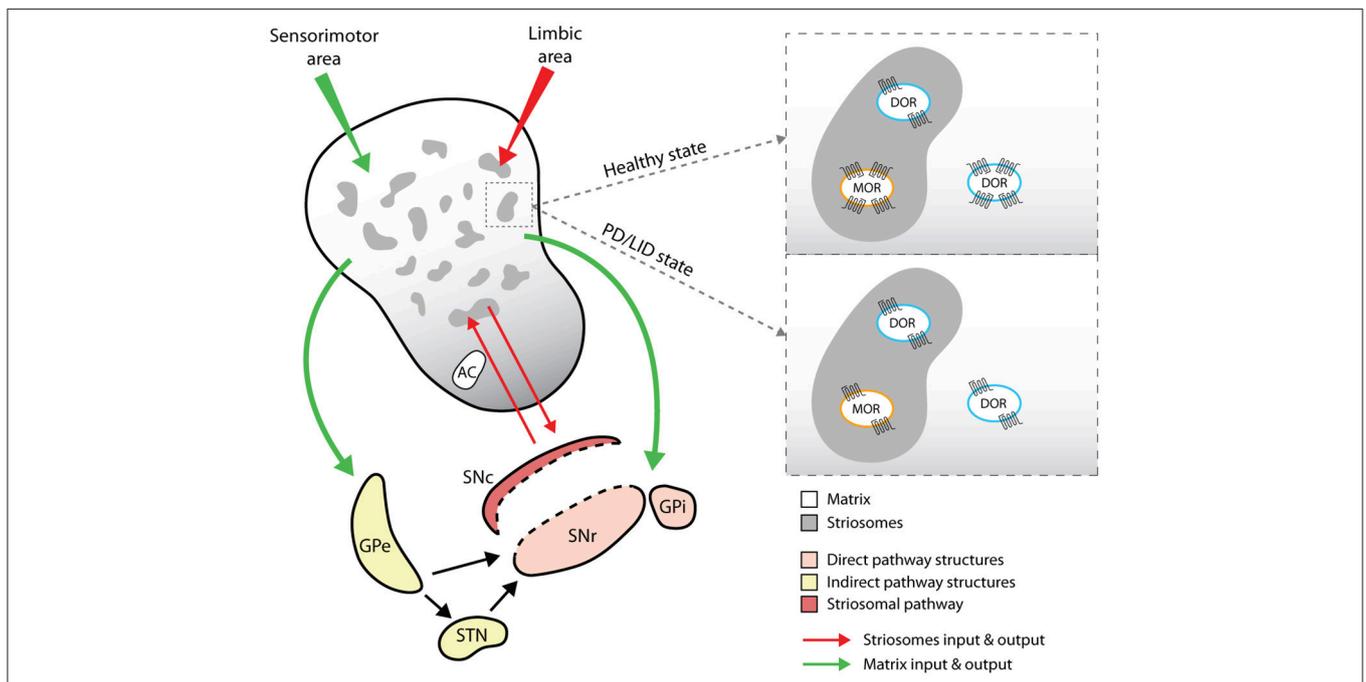

FIGURE 2 | Representative cartoon of opioid receptors distribution and expression in striosomes and matrix compartments of the dorsal striatum. The drawing shows the different input and output pathways related to the striosomes (red lines) and matrix compartments (green lines) and the changes in the expression levels of MOR and DOR. GPe (globus pallidus pars externa) and STN (subthalamic nucleus) indicate the indirect pathway targets; SNr (substantia nigra pars reticulata) and GPi (globus pallidus pars interna) indicate the direct pathway targets; SNc (substantia nigra pars compacta) is the target of the specific pathway arising from the striosomal compartments.

subunits. The **Gα** subunit inhibits AC by decreasing intracellular cyclic adenosine monophosphate (cAMP) levels and activates the inward-rectifier K^+ channel, leading to the hyperpolarization of the cellular membrane and the inhibition of neural activity (30). The inhibition of AC and cAMP by the Gα subunit can also lead to a reduction of Ca^{2+} conductance (31), although this reduction is predominately induced by the direct binding of **Gβγ** subunit to the channel, and the consequent decrease in neurotransmitter release. Indeed, activation of KORs on the nigrostriatal afferents of the SNpc reduces the release of DA and influences the kinetics of the DA transporter (32, 33). Intrastriatal injection of a MOR agonist alters extracellular DA levels in the shell and core of the nucleus accumbens and in the rostral and caudal subregions of the dorsal striatum, where the reduction is thought to be due to presynaptic activation of MORs on DA terminals (34, 35). Activation of MORs on striatal cholinergic interneurons reduces Ach release and decreases cholinergic interneurons excitability (26, 27).

Besides inhibiting the AC /cAMP, opioid receptors shape several other cellular responses. The interaction with different G proteins, β-arrestins or kinases, can promote the activation of different effectors or signaling pathways (36), or prompt the internalization and desensitization of receptor functional activity (19, 37), with significant changes in behavior (38). The direct activation of opioid receptors and the release of Gβγ subunits can promote the activation of mitogen-activated protein kinases (MAPKs) (19, 39). Notably, activation of MAPK can be also mediated by binding of DA to D1R. In the dorsal striatum of PD animal models, pulsatile replacement of DA, for example by L-DOPA treatment, leads to an overstimulation of the direct striatonigral pathway that promotes the activation of MAPK and its downstream effectors, such as extracellular signal-regulated kinases ERK1/2 or transcription factors (40–42). Increased levels of phosphorylated ERK (p-ERK) or immediate early genes are associated with aberrant cellular responses and dysfunctional behaviors in PD and LID state (43–45). Therefore, opioidergic and dopaminergic receptors could both activate postsynaptic signaling cascades that converge to ultimately promote an increase of proteins and transcriptional factors that affect striatal-based behaviors. However, it is still unclear whether alterations of the striatal motor function arise from a synergic activity of the dopaminergic and opioidergic system or if opioid transmission only modulates the molecular and synaptic mechanisms mediated by dopaminergic transmission.

COMPARTMENT-SPECIFICITY LOCALIZATION OF OPIOID RECEPTORS IN THE DORSAL STRIATUM

Beyond the classical division of the striatum into the direct and indirect pathways, this structure is also subdivided into striosomes (defined as striatal bodies) and matrix compartments (**Figure 2**), which are defined according to neurotransmitter and receptor segregation, afferent and efferent connections (46), signaling cascade activation (47) and neurophysiological features (48). Striosomes represent about 10–15% of the dorsal striatum

and are mainly localized in the medial sector of the CPu (29, 49), where they are characterized by acetylcholinesterase (AchE)-poor zones and by immunoreactivity against Enk, substance P and GABA (50). The matrix compartment comprises 85% of the remaining striatum. It is rich in AchE, contains calcium-binding proteins such as parvoalbumin and calbindin, and is directly affiliated with the sensorimotor system (51). Both striosomes and matrix contain dSPNs and iSPNs, although dSPNs are more prevalent in the striosomal compartment and project predominantly to dopaminergic neurons in the SNpc (50, 52).

The matrix and striosomal compartments also receive inputs from different cortical areas; striosomes are related to the limbic area, whereas the matrix is associated with sensorimotor and associative areas (53) (see **Figure 2**). Overall, this complex striatal subdivision, together with a discrete distribution of neuromodulators between matrix and striosomes compartments, reflects that SPNs functional activity might differ in compartment-specific manner and affect different striatal-based behaviors (54).

While dSPNs and iSPNs are broadly distributed in both striosomes and matrix, opioid-mediated synaptic transmission seems to segregate (46), perhaps due to the different distributions of opioid receptors on dSPNs and iSPNs in these compartments. For example, application of MOR and DOR agonists reduces GABAergic synaptic responses in both dSPNs and iSPNs predominantly in the striosomal compartment, but not in the matrix (29, 48). Specifically, the binding of Enk to DORs located on iSPNs collaterals that synapse on dSPNs, suppresses the inhibition of dSPNs only in the striosomes, but not in matrix, leading to strengthened striosomal dSPNs responses to corticostriatal inputs (29). The behavioral implications of this connectivity might be relevant in PD, where changes in the levels of the endogenous opioid Enk might promote or reduce dSPNs response to cortical inputs, thereby affecting the release of DA through the striatonigral pathway (29).

OPIOID-MEDIATED NEUROTRANSMISSION AND SYNAPTIC PLASTICITY IN THE DORSAL STRIATUM

The first neurophysiological studies on the opioid-mediated neurostransmission at striatal circuits investigated the role of these neuropeptides in the modulation of glutamatergic inputs mainly arising from the cortex. These studies showed that MOR and DOR agonists inhibited glutamatergic inputs to the striatum (55) and more specifically, selective MOR agonists reduced the excitatory inputs at the corticostriatal level in both striosomes and matrix compartments (48, 56). In addition, the application of exogenous MOR and DOR agonists or the release of endogenous opioids induced long-term depression (LTD) on striatal SPNs in both the DLS and the dorsomedial striatum (DMS). Specifically, MOR activation inhibited thalamostriatal excitatory inputs, whereas the activation of DOR inhibited corticostriatal inputs; these results indicate the specificity of opioid-mediated synaptic plasticity in the dorsal striatum (22). Interestingly, applying an exogenous KOR agonist induced LTD more selectively in the

TABLE 1 | Summary of opioid-mediated neurotransmission and synaptic plasticity in the dorsal striatum.

Activation of opioid receptors	Distribution	Signal
MOR	Thalamostriatal afferents	↓EPSCs (22)
	Striosomal dSPN and iSPN	↓IPSCs (29, 48)
	Cholinergic interneurons	↓ACh release (26, 27)
DOR	Nigrostriatal terminal	↓ DA release (34, 35)
	iSPN striosomal collaterals	↓ IPSCs (29)
	Corticostriatal afferents	↓ EPSCs (22)
KOR	Presynaptic nigrostriatal afferents	↓ DA release (33)
		LTP (57)
	Striatal SPNs in DLS	LTD (22)

According to the specific distribution of opioid receptors, changes in neurotransmitter release or synaptic plasticity are observed in response to exogenous and endogenous opioid agonists. ESPCs, excitatory postsynaptic currents; ISPCs, inhibitory postsynaptic currents; Ach, acetylcholine; DA, dopamine; LTP, long term potentiation; LTD, long term depression.

DLS than in the DMS, suggesting subregional specificity of KOR-mediated synaptic plasticity (22) (**Table 1**). This subregional difference between the DLS and DMS might be related to their distinct functional roles in motor control. Behavioral studies demonstrate that the DLS is more connected to the control of body movements rather than to more general control of locomotor activity (58, 59). In PD animals treated with L-DOPA, higher levels of Dyn precursor (PDYN) mRNA, selective for KOR binding, are expressed in the DLS than the DMS (60–62). Moreover, higher PDYN mRNA expression in the lateral striatal portion of the DA-denervated hemisphere correlates only with the severity of dyskinesia, instead of with locomotor variables that define animals' spontaneous motion (60, 62).

Opioids have been shown to regulate striatal LTD (22). In contrast, their effect on long-term potentiation (LTP) in the dorsal striatum remains unexplored. Most of the studies that have attempted to characterize the role of opioids in LTP have examined different functional areas, such as the ventral tegmental area (63), hippocampus or C-fiber of the spinal dorsal horn (64). A recent study investigated the effect of KOR activation on LTP in the corticostriatal pathway (57), and demonstrated that applying Dyn reduced the release of DA, as expected by binding to KOR on DA nigrostriatal terminals. Moreover, selective activation of the D1R-SPNs that promote the co-release of Dyn also led to impared corticostriatal LTP, likely due to the KOR-mediated reduction in DA release from the nigrostriatal pathway (57) (**Table 1**).

OPIOID NEURONTRANSMISSION IN PARKINSON'S DISEASE AND LEVODOPA-INDUCED DYSKINESIA

The broad distribution of opioid receptors in the striatum and their interplay with dopaminergic transmission point at critical role for opioidergic neuropeptides in modulating striatal activity and motor control, in particular, both in healthy and pathological states, such as in PD. This is a progressive neurodegenerative disorder characterized by the loss of dopaminergic cells in the

SNpc, which results in motor deficits (i.e., bradykinesia, rest tremor, rigidity, and postural and gait impairment) (65, 66). PD patients develop these symptoms only after a significant depletion of striatal DA– by 60 to 80% (67) – likely because of compensatory DA production by surviving neurons or unknown compensatory mechanisms within or outside of the BG (68). Furthermore, the loss of dopaminergic neurons in the SNpc results in a functional imbalance in the two major output pathways of the striatum: hypoactivity in the direct circuit and hyperactivity in the indirect circuit. This imbalance leads to an overstimulation of the GPi/SNpr which decreases thalamic input to motor cortical areas, resulting in reduced movement and classical Parkinson's symptoms (**Figure 1B**).

Various animal models of PD are used to better understand the disease's pathophysiology, but none of them fully exhibit all PD symptoms, nor do they develop a neurodegenerative state similar to that in PD patients. For this reason, the most suitable animal model depends on the scientific question being investigated (69). Parkinsonian motor deficits due to DA depletion or DA neuronal death are usually recreated in animals through the injection of selective neurotoxins such as 6-hydroxydopamine (6-OHDA) in rat and 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) in mouse or primate, while specific molecular events and protein aggregation are investigated using genetic models of PD-related mutations (70).

PD symptoms can be alleviated with dopaminergic treatments that aim to replace the DA deficiency in the nigrostriatal pathway. No curative treatments exist for PD patients, and currently available therapies are symptomatic. To date, L-DOPA remains the most effective drug for exogenous dopaminergic replacement and for counteracting PD symptoms. However, as the disease progresses and dosages of L-DOPA increase, many patients develop disabling complications, including severe fluctuations in motor function (on-off phenomena) and abnormal involuntary movements called L-DOPA-induced dyskinesia (LID) (71, 72). The pathophysiology of LID has been associated with aberrant activation of the direct striatal pathway and with increased levels of the endogenous opioid neuropeptides Enk and Dyn (**Figure 1C**). It is still unclear whether opioid transmission can affect the neural reorganization of striatal pathways, and if changes in opioid expression might have a compensatory or synergistic effect on striatal-based behaviors in PD and LID.

OPIOID PEPTIDE EXPRESSION IN PD AND LID

Several studies have been conducted in animal models to investigate changes in the expression of endogenous opioids in the dorsal striatum and their association with motor impairment and dyskinetic movements. Indeed, DA and its binding to D1Rs and D2Rs can modulate the striatal levels of mRNA expression of Dyn and Enk neuropeptide precursors (PDYN and PPENK). Changes in PDYN and PPENK mRNA levels have been observed in PD, where DA transmission is lost, and in LID, during the exogenous replacement of DA (**Figure 1**).

In the striatum of 6-OHDA and MPTP animal models (60, 62, 73, 74), as well as in PD patients (75), the levels of PPENK mRNA expression are increased, irrespective of L-DOPA treatment. The levels of PPENK mRNA remain highly expressed in PD animals also given chronic L-DOPA treatment (76) as well as in PD patients affected by dyskinesia (77), suggesting persistent adaptive changes in the Enk peptide (78).

In contrast, nigrostriatal DA denervation leads to a reduction in the levels of PDYN mRNA (60, 62, 79, 80) that increase under L-DOPA therapy compared to untreated or non-dyskinetic states, consistently across different study models (62, 76, 78, 81). These observations suggest that the expression of opioidergic neuropeptides involved in the modulation of BG output is strictly regulated by striatal DA levels, likely also through the activation of postsynaptic transcription factors that ultimately can promote the expression of multiple genes, including those for opioidergic peptides.

In addition, in dyskinetic PD rat model, high levels of both PPENK and PDYN are overall correlated with L-DOPA-induced locomotor alterations. While there is a more specific association between high levels of PDYN mRNA and dyskinetic movements (60), on the other hand, high expression of PPENK mRNA is also correlated with locomotor hyperactivity, beyond dyskinesia (62). These observations suggest that Enk and Dyn might play different roles in striatal-based behavioral effects and in locomotor alterations in response to dopaminergic treatment.

OPIOID RECEPTOR EXPRESSION IN PD AND LID

Along with different levels of opioidergic peptides expression, alterations in the levels of opioidergic receptor immunoreactivity have been observed in both PD patients and animal models. Piccini et al. (82) found reduced opioid receptor binding in the caudate of PD patients, and in the putamen and thalamus of dyskinetic PD patients compared to non-dyskinetic. Similar observations have been described in animal studies, although some differences were found across the various models.

Striatal levels of MOR binding and μ-immunoreactivity were reduced in PD rats (83) and in MPTP-lesioned macaques treated with L-DOPA (80), as well as in PD patients undergoing chronic L-DOPA therapy (84). Lower levels of DOR binding are expressed in the GP and striatal areas of 6-OHDA dyskinetic rats, while an increase of δ-immunoreactivity occurs in the motor and premotor cortex (83) (**Figure 2**). Consistent with these results, PD patients treated with L-DOPA have reduced levels of DOR binding compared with control patients (84). KOR binding levels are decreased in the striatal areas of dyskinetic PD rats and in the GP of PD rats with and without LID (83); low κ-immunoreactivity is observed only in the GP structure of MPTP-denervated macaques with and without dyskinesia (80).

Even though the exposure to L-DOPA treatment in PD animals and PD patients leads to a reduction in opioid receptor binding levels, Chen and colleagues (85) assessed G protein-coupled receptor signaling as a marker of MOR, DOR and KOR activity in MPTP-lesioned non-human primates. Interestingly,

TABLE 2 | Summary of opioidergic drugs used as pharmacological intervention to counteract parkinsonian symptoms and dyskinetic movements in PD animal model.

Opioidergic drugs	Opioid receptor targets	Function	Effect
Cyprodine ADL5510	MOR	Antagonist	↓ LID (86, 87)
Naltrindole	DOR	Antagonist	↓ LID (86, 88) Akinesia (89)
SNC-80	DOR	Agonist	↑ Kinesia in PD state (90–92)
nor-BNI	KOR	Antagonist	No effect on LID (86)
U50,488	KOR	Agonist	↓ LID (93) ↑ Akinesia
Nalbuphine	KOR-MOR	Agonist-antagonist	↓ LID (94)
Naloxone	KOR-MOR-DOR	Antagonist	↓ LID (95, 96)

nor-BNI, nor-binaltorphimine; LID, levodopa-induced dyskinesia; PD, Parkinson disease.

they found a hyperactive transduction signal mediated by all three opioid receptors in the striatum. This suggests that in the parkinsonian state under L-DOPA treatment, although the levels of receptor binding can be decreased, the response to activation of opioid receptors is in fact enhanced.

PHARMACOLOGICAL IMPLICATIONS OF OPIOIDS IN MOTOR FUNCTION

Elucidating the role of opioidergic transmission in the molecular mechanisms that control motor function is complex, not only due to the striatum's neural heterogeneity, but also because of the broad distribution of opioid receptors throughout the brain. The activation of opioid-mediated postsynaptic signaling cascades likely depends on several factors, including opioid agonists and their response to ORs, the type of ORs activated, and whether receptor stimulation is acute or chronic. Systemic administration of opioidergic drugs might affect different neural circuits and modulate behavioral aspects beyond locomotor activity. Therefore, pharmacological approaches used to distinguish the neural pathways in the control and alteration of movement should be considered critically.

Considering the enhanced expression of endogenous opioid peptides in the striatum of PD animal models and in PD patients, selective agonists and antagonists to ORs have been used to counteract akinesia in PD and to reduce the development of dyskinesia in response to L-DOPA treatment (**Table 2**). MOR antagonists (cyprodine and ADL5510) alleviated LID in MPTP-lesioned non-human primates without interfering with the antiparkinsonian effects of L-DOPA (86, 87). A selective DOR antagonist (naltrindole) has a similar effect, reducing dyskinetic movements in MPTP-lesioned marmoset and 6-OHDA rats treated with L-DOPA (86, 88), although there is an akinetic effect on motor activity in a PD model without DA treatment (89). A selective DOR agonist (SNC-80) increased locomotor activity in naive and PD animals, but its potential therapeutic applications

are limited by its convulsive effects (90–92). In contrast, a κ-receptor antagonist (norBNI) did not induce any anti-dyskinetic effect in MPTP-lesioned macaques (86); yet a selective κ-receptor agonist (U50, 488) reduced LID in PD rats and monkeys, but impaired the anti-parkinsonian effects of L-DOPA treatment (93). In line with these effects, the synthetic opioid analgesic nalbuphine, acting as both a KOR agonist and a MOR antagonist, reduced LID in a non-human primate model of PD and decreased the levels of specific molecular markers associated with the development of dyskinesia (94). Also noteworthy is the effect of the non-selective antagonist naloxone, which reduced LID in 6-OHDA rats (95, 96), although results in MPTP-lesioned macaques and PD patients were inconclusive (97, 98).

The literature makes it clear that different pharmacological responses are expected across animal models and in human patients, likely due to the greater neural organization and connectivity in primates and humans. The lost of DA in PD and its exogenous replacement by L-DOPA lead to changes in the expression of opioid peptides and receptor immunoreactivity that reflect a strong interaction between dopaminergic and opioidergic systems in the BG motor circuit. However, it is still debated whether changes in the opioid transmission occur to compensate for DA denervation and L-DOPA treatment, or whether these changes interact with the molecular and synaptic mechanisms associated with altered neural responses in motor diseases.

CONCLUDING REMARKS

The recent advances in understanding the striatal functionality highlight the strong impact of opioidergic transmission to modulate synaptic plasticity and cellular responses of the SPNs. The studies here reviewed, demonstrate that opioid receptors have a regional (ventral vs. dorsal striatum), compartmental (striosomes vs. matrix) and cellular (dSPNs vs. iSPNs) specificity that affects the striatal activity in response to different inputs. Such specificity reflects the complexity of striatal organization

and the efforts to find selective opioidergic treatments that can modulate specific neural pathways. Although the literature points out the inhibitory effect of opioid agonists on synaptic transmission and neurotransmitters release, it is still debated how opioid receptors interact with dopaminergic receptors and whether they share common mechanisms to activate postsynaptic signaling cascades and downstream effectors. The interaction between opioidergic and dopaminergic pathways becomes crucial in PD and LID where the high levels of endogenous opioids occurs in parallel with aberrant dopaminergic transmission, and are associated with altered striatal-based behaviors. Since the broad distribution of opioid receptors throughout the brain, pharmacological approaches should aim to selectively target defined receptor subtypes, in a cell-type- and input-specific manner. The use of chemogenetic or optogenetic approaches are therefore crucial to dissect opioidergic neurotransmission within the striatum and its interaction with dopaminergic system. This would be instrumental to develop specific pharmacological treatments able to restore maladaptive changes without interfering with other neuronal pathways.

AUTHOR CONTRIBUTIONS

SS wrote the manuscript. RT conceived the review contribution, supervised the writing and critically edited the manuscript.

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