Review

MOLECULAR PAIN

Molecular Pain
Volume 17: 1–11

DOI: 10.1177/17448069211999025
journals.sagepub.com/home/mpx
SAGE

Cellular and synaptic mechanisms for Parkinson's disease-related chronic pain

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Abstract

Parkinson's disease is the second most common neurodegenerative disorder after Alzheimer's disease. Chronic pain is experienced by the vast majority of patients living with Parkinson's disease. The degeneration of dopaminergic neuron acts as the essential mechanism of Parkinson's disease in the midbrain dopaminergic pathway. The impairment of dopaminergic neurons leads to dysfunctions of the nociceptive system. Key cortical areas, such as the anterior cingulate cortex (ACC) and insular cortex (IC) that receive the dopaminergic projections are involved in pain transmission. Dopamine changes synaptic transmission via several pathway, for example the D2-adenly cyclase (AC)-cyclic AMP (cAMP)-protein kinase A (PKA) pathway and D1-G protein-coupled receptor kinase 2 (GRK2)-fragile X mental retardation protein (FMRP) pathway. The management of Parkinson's disease-related pain implicates maintenance of stable level of dopaminergic drugs and analgesics, however a more selective drug targeting at key molecules in Parkinson's disease-related pain remains to be investigated.

Keywords

Parkinson's disease, pain, dopamine, cortex

Date Received: 3 February 2021; Revised: 3 February 2021; Accepted: 9 February 2021

Introduction

Parkinson's disease is a complex, multi-system neurodegenerative disorder. In addition to the motor symptoms, the non-motor symptoms of Parkinson's disease such as emotional disorder, cognitive deterioration and chronic pain are gaining more and more clinical attention.[1] Different forms of pain are common in 30–95% of patients with Parkinson's disease, including acute pain and chronic pain.[2,3] Pain exists from early to late stage of Parkinson's disease and has an impact on the quality of life.[4] However, the exact neuronal and synaptic mechanism of Parkinson's disease-related pain is still unclear. In this review, we will explore basic mechanisms, especially those changes that may be responsible for Parkinson's disease-related pain.

Parkinson's disease-related central changes

Parkinson's disease is a progressive neurodegenerative disease characterized by selective loss of dopaminergic neurons in the midbrain. Considering the important role of dopamine as a central neurotransmitter and modulator, clinical symptoms in various brain functions are likely due to the loss of the function of dopamine neurons. There are several major possibilities. First, the loss of dopamine neurons leads to the decrease of dopamine in the synaptic transmission. Dopaminergic signaling pathways may be downregulated or upregulated. Second, dopamine is known to play key roles in central plasticity by activating intracellular signaling pathways,

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such as long-term potentiation (LTP) of excitatory transmission. Loss of dopamine may reduce or block the plasticity. Third, dopamine affects local inhibitory transmission. Changes of inhibitory transmission alter excitatory transmission along the pathway. The loss of dopamine may cause tonic inhibition or disinhibition within local circuits. Finally, dopamine may have long term impact on neuronal/synaptic structures. Loss of dopamine may also lead to long-term structure changes or losses in the brain. Due to wide-spread projections of dopamine in the central nervous system, it is very likely that the impact of Parkinson's disease is significant.

Parkinson's disease-related pain

Pain is a prevalent symptom in Parkinson's disease. In clinic, most patients with Parkinson's disease are suffering pain. Patients with Parkinson's disease suffer from a range of different pain syndromes, varying in their cause, origin, location and chronicity.[3,5] These include musculoskeletal pain, articular/arthritic pain, neuropathic pain and radicular pain.[6] Musculoskeletal pain typically seems to be related to motor symptoms of Parkinson's disease, such as rigidity, akinesia, postural abnormalities and dystonia. Painful joints are common in pain syndromes of Parkinson's disease, most frequently at the shoulders, hips, knees and ankles. Additionally, pain might even precede the onset of motor symptoms by several years.[7] Therefore, it is worthy to discover the connection between the pathological changes of Parkinson's disease and the basic mechanism of pain, especially chronic pain.

Cortical mechanisms for chronic pain

Cortical areas including the anterior cingulate cortex (ACC) and insular cortex (IC) play significant roles in the processing of nociceptive information in the brain. Excitation of cortical synapse is thought to be a key synaptic mechanism for chronic pain and its related emotional anxiety.[8,9] At least four different synaptic mechanisms might contribute to chronic pain: (i) presynaptic enhancement of the release of glutamate; (ii) postsynaptic enhancement of glutamate receptor-mediated responses; (iii) recruitment of previously silent synapses, synaptic trafficking insertion of AMPA receptors (AMPARs); and (iv) structural changes in synapses. Potentiated excitatory synapses through LTP are induced by presynaptic and postsynaptic mechanisms.[10] Intracellular mechanisms for pre-LTP and post-LTP have been investigated (Figure 1). Inhibition of the induction of LTP or expression of LTP in ACC or IC reduces or blocks chronic pain in different animal models.[11,12] Induction of postsynaptic LTP requires the activation of NMDA receptors (NMDARs) and L-type voltage-gated calcium channels (L-VGCCs).[8] Presynaptic kainate receptors are necessary for the induction of presynaptic LTP, and the expression of presynaptic LTP may require the activity of hyperpolarization-activated cyclic nucleotide-gated (HCN) channels. Among various signaling pathways, calcium-stimulated adenylyl cyclase subtype 1 (AC1) plays important roles in both forms of LTP.[10,13]

Long-term depression (LTD)

The other form of synaptic plasticity, long-term depression (LTD) was also proved to be involved in mechanisms of chronic pain. Early studies in the cerebellum reported that LTD forms the basis of physiological functions.[14] Two major forms of LTD have been characterized in the rodent ACC.[15] One of them requires the activation of mGluR1 and L-VGCCs,[16] independent of NMDARs has only a minor effect on the induction of this form of LTD.[17] However, the other NMDAR-dependent form of LTD in the ACC require both GluN2A- and GluN2B and an increase in postsynaptic Ca^{2+} and CaM levels.[18,19] In animal models of chronic pain, low-frequency stimulation failed to induce LTD, providing a disinhibition mechanism for chronic pain in the cortex.[16,17] In the IC, the induction of LTD required the activation of the mGluR5 and L-VGCC. Protein phosphatase 1/2A and endocannabinoid signaling are also critical for the induction of LTD in the IC.[20,21] A recent study found that peripheral nerve injury prevented LTD induction in the ACC due to the downregulation of Casp3. Restoration of cingulate LTD rescues peripheral pain hypersensitivity.[22] This further supported the view that cortical LTD is involved in the mechanism of chronic pain.

Alterations in pain-related cortical areas in patients with Parkinson's disease

Brain imaging is widely used for prediction or measure Parkinson's disease, for example the functional magnetic resonance imaging (fMRI) and positron emission topography (PET). Human imaging studies found that pain-related cortical areas are affected in patients with Parkinson's disease. PET studies found that in patients with Parkinson's disease without pain symptom in the off-medication state, the activation by pain stimulation in the right IC, and left ACC significantly increased.[23] Those areas also show focal hot spots of increased [18F] dopa utilization in early disease. These may be due to compensatory mechanisms to maintain dopamine transmission.[24] When used PET imaging to compare dopamine D2 receptor availability, patients with Parkinson's disease with mild cognitive impairment demonstrated more reductions in D2 receptor binding in the IC and ACC compared to healthy control.[25] Computed

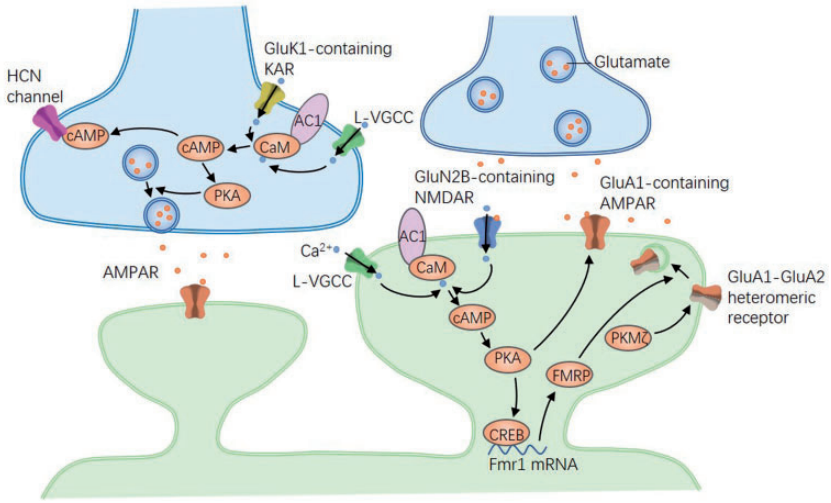

Figure 1. Two forms of long-term potentiation (LTP) in the anterior cingulate cortex (ACC). Two forms of LTP were recorded in the cortical areas that modulate pain: the postsynaptic LTP and presynaptic LTP in the ACC. Induction of postsynaptic LTP requires the activation of postsynaptic NMDARs, and the maintenance of postsynaptic LTP expression requires the postsynaptic activity of a PKC isoform PKMζ. AC1 is crucial for the induction of postsynaptic LTP in the ACC. Activation of cyclic AMP-dependent PKA drives the insertion of Ca^{2+}-permeable AMPARs. PKA also translocates to the nucleus, where it phosphorylates the transcription factor CREB, leading to the synthesis of several downstream plasticity proteins, including FMRP (encoded by gene Fmr1). PKMζ may maintain LTP by upregulating GluA1-GluA2 heteromers. In addition, increased levels of FMRP may enhance the postsynaptic function of AMPARs and NMDARs. Presynaptic KAR and AC1 activation are necessary for the induction, and the expression of presynaptic LTP may require the activity of HCN channels. cAMP binds to the HCN channel to increase its sensitivity, and PKA enhances vesicle fusion. NMDARs, NMDA receptors; AMPARs, AMPA receptors; PKC, protein kinase C; AC1, adenylyl cyclase 1; PKA, protein kinase A; cAMP, cAMP response element-binding protein; FMRP, fragile X mental retardation protein; HCN, hyperpolarization-activated cyclic nucleotide-gated; KARs, kainate receptors.

tomography revealed subtle gray matter atrophy in the ACC, and temporal neocortex in patients with Parkinson's disease with normal cognition compared to healthy control.[26] These studies further demonstrated that the ACC and IC play important roles in Parkinson's disease.

Unlike fMRI and PET, the higher temporal resolution of electroencephalogram (EEG) allows for a more accurate recording of the Parkinson's disease processes. Compared to healthy controls, de novo patients with Parkinson's disease showed a widespread increase of power in the theta (5–7 Hz) and low alpha bands (8–10 Hz), as well as a decrease of beta (14–30 Hz) and gamma (over 30 Hz) power in sculp EEG.[27] The fine analysis of the frequency spectrum ranging from slow delta wave (1–4 Hz) to high frequency gamma oscillations enables precise connectivity studies.[3,28] General slowing of background activity, excessive synchronization of beta activity, and disturbed movement-related gamma oscillations of EEG were observed in cortico-subcortical and cortico-cortical motor loops in patients with Parkinson's disease.[28] It has also been reported that non-motor symptoms in Parkinson's disease are associated with oscillatory activity in all frequency ranges, including theta (impulse control disorders), alpha (depression), beta (cognitive impairment), and gamma (cognitive inflexibility). In patients with Parkinson's disease, the amplitude of endogenous component N2 and exogenous component P2 of event related potential was significantly lower in several brain structures including the cingulate gyrus and insula. These results suggest that in patients with Parkinson's disease there is an abnormal nociceptive input processing in the central nervous system.[29] A recent study about the anticipation of pain in patients with Parkinson's disease reported that, during the anticipation to noxious stimuli, EEG source localisation reported an increased activation in the mid-cingulate cortex and supplementary motor area in the Parkinson's disease group compared to the healthy control group, indicating enhanced cortical activity before noxious stimulation. The Parkinson's disease group was also more sensitive to the laser and required a lower voltage level to induce pain.[30] EEG investigations of Parkinson's disease provide another evidence that cortical areas such as cingulate cortex and insula play significant roles in Parkinson's disease-related pain.

Modulation of excitatory synaptic transmission by dopamine

As shown in Figure 2, dopamine system is known to affect pain-related pathways, especially those involved in pain perception such as ACC, IC and PFC and somatosensory cortices.[31] For patients with certain

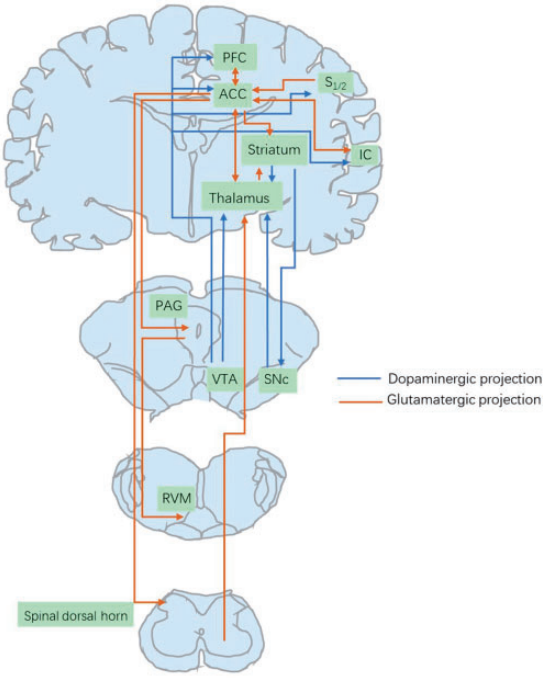

Figure 2. Major top-down corticospinal network for Parkinson-related chronic pain in the body. Proposed network that may explain pain among patients of Parkinson's disease. ACC neurons receive glutamatergic inputs (red arrows) from various cortical and subcortical structures. These inputs convey nociceptive information through the thalamus, as well as other cortical regions such as the PFC, $S_{1/2}$ and IC. Neurons in the deep layers of the ACC also send their glutamatergic projections directly or indirectly (via PAG and RVM) to the dorsal horn of the spinal cord. Neurons in the VTA/SNc send their ascending dopaminergic projections (blue arrows) to structures in midbrain (e.g., thalamus, striatum) and cortical areas (e.g., ACC, PFC, IC). PFC, prefrontal cortex; $S_{1/2}$, somatosensory cortex; IC, insular cortex; PAG, periaqueductal grey; RVM, rostroventral medulla; VTA, ventral tegmental area; SNc, substantia nigra pars compacta.

peripheral disorders, these brain changes will manifest sensory transmission, and results in different forms of discomfort and pain. Dopamine is a key neurotransmitter in the central nervous system. The substantia nigra pars compacta (SNc) and ventral tegmental area (VTA) send ascending dopaminergic projections to various subcortical targets such as the striatum, nucleus accumbens and cortical areas including the PFC, ACC and IC (Figure 2). Thus, the effect of dopamine on these cortical areas may play important roles in the Parkinson's disease-related pain.

It has been reported that dopamine affects excitatory synaptic transmission in cortical areas. In the superficial layer of the ACC in adult mice, bath application of dopamine caused a significant, rapid and reversible dose-related inhibition of evoked EPSCs (eEPSC). Additionally, dopamine exerted mixed effects on spontaneous EPSCs (sEPSCs) and miniature EPSCs (mEPSCs).[32] Selectively inhibiting postsynaptic G protein-coupled receptor (GPCR), which acts as downstream of postsynaptic dopamine receptor, completely abolished the inhibitory effects of dopamine. Application of selective D1- and D2-receptor antagonists individually proved that inhibition of dopamine on eEPSCs is mediated by postsynaptic D1- and D2-receptors.[33]

In the PFC, cumulative evidences have been reported that dopamine participates in the modulation of synaptic plasticity. Within a specific range of concentration, background dopamine concentration dependently facilitates LTP in the PFC of rats.[34] Additionally, dopamine D1 receptor activation facilitates LTP induction. The fragile X mental retardation protein (FMRP) is required for this dopaminergic facilitation of LTP.[35] However, in the PFC of human patients and animal models of Parkinson's disease, LTP failed to be induced.[36–38] Therefore, it is less likely that downregulation of dopamine caused synaptic changes via LTP under the condition of Parkinson's disease. As for the LTD, coactivation of dopamine D1-, D2-receptors and groups I and II mGluRs is sufficient for the induction of LTD in rat PFC. This requires the postsynaptic activation of mitogen-activated protein kinases. The difference between the role of dopamine in LTP and LTD is that, LTD can be induced even when the background dopamine level is very low.[39] There are few reports about the role of dopamine in the synaptic plasticity in the ACC and IC, but it is possible that the degeneration of endogenous dopamine interferes the cortical LTD thus cause long-term changes in the nociceptive pathway.

Regulation of inhibitory transmission by dopamine

In the ACC, the proper GABAergic inhibitory innervation of excitatory pyramidal cells is also reported to be important for nociceptive processes. Inhibitory interneurons can be classified as fast-spiking (FS) and non-FS cells based on their firing patterns. Previous studies found that dopamine depressed inhibitory transmission between FS interneurons and pyramidal neurons but enhanced inhibition between non-FS interneurons and pyramidal cells in the prefrontal areas.[40] Dopamine activity increased the frequency of both miniature and spontaneous inhibitory postsynaptic currents (IPSCs).[41] Furthermore, dopamine activity enhanced the amplitude of evoked and unitary IPSCs from FS interneurons. Notably, the amplitude of evoked IPSCs was enhanced by the activation of D1-like receptor-mediated pathways. These results suggest that dysfunction of D1-like receptor-mediated regulation of glutamatergic excitatory and GABAergic inhibitory synaptic transmission onto

pyramidal cells of the ACC may contribute to the pathophysiology of Parkinson's disease.

Intracellular signaling pathways of dopamine

Presynaptically released dopamine interact with postsynaptic dopamine receptor family D1-D5 receptors, which is also a kind of GPCR. D1 and D2 receptors are the two widely-expressed subtypes in the brain. D1 receptors displaying the most widespread distribution and highest expression levels. The expression of D3, D4, and D5 receptors is more restricted and weaker than that of D1 and D2 receptors.[42] D1-D5 receptors could be divided into two major classes based on their structural, pharmacological, and signaling properties. D1-like receptor comprises of D1 and D5 receptors, D2-like receptor is composed of D2, D3, and D4 receptors. D1-like receptors stimulate the G proteins $G\alpha_s$ and $G\alpha_{olf}$, which are positively coupled to ACs, leading to the production of cyclic adenosine monophosphate (cAMP) and the activation of protein kinase A (PKA). By contrast, D2-like receptors activate $G\alpha_i$ and $G\alpha_o$ proteins, which inhibit AC and limit PKA activation.

In the ACC of adult mice, our previous studies have found that the inhibitory effect of dopamine is dose-dependent. A greater inhibition was observed when a potent D1 antagonist SCH23390 was applied. However, application of D2 antagonist sulpiride blocked the inhibition of eEPSCs by dopamine. Possible postsynaptic interaction of dopamine with both D1 and D2 components yields a D2-mediated inhibition of AMPA/KA eEPSCs that is exacerbated by the inhibition of the D1 system. This is in accordance with a D2 inhibitory tone by inhibiting AC-cAMP-PKA pathway[32] (Figure 3). The AC-cAMP-PKA pathway in the ACC and IC is activated in chronic pain.[15,43,44] Therefore, we can infer that, in the condition of Parkinson's disease, when the concentration of dopamine decreased due to the neurodegeneration of midbrain dopaminergic neurons, D2-mediated inhibition might be alleviated, thus the AC-cAMP-PKA pathway is disinhibited.

Aside from the disinhibition of AC-cAMP-PKA pathway, previous studies have identified FMRP as a key messenger for dopamine modulation in the prefrontal areas[35] (Figure 3). FMRP is an RNA-binding protein that controls translational efficiency and regulates synaptic plasticity. In cultured $Fmr1^{-/-}$ PFC neurons, the surface expression and phosphorylation of AMPA GluR1 receptor in response to D1 receptor stimulation were reduced. Furthermore, in $Fmr1^{-/-}$ mice, D1 receptor signaling was impaired, D1 receptor was

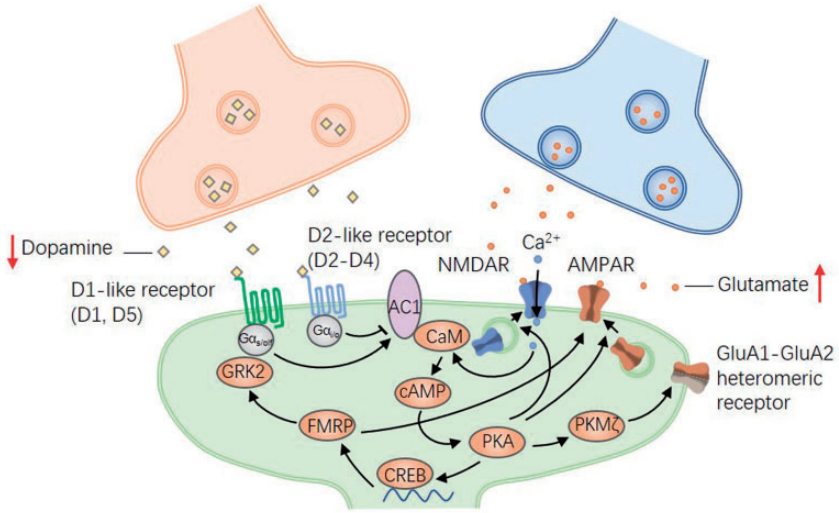

Figure 3. Schematic of dopamine postsynaptic signaling pathways. Schematic shows the dopamine postsynaptic signaling pathways in cortical neurons. Once combined with dopamine released by dopaminergic projections, D1-like receptors stimulate the G proteins $G\alpha_s$ and $G\alpha_{olf}$, which activates the AC-cAMP-PKA pathway. By contrast, D2-like receptors activate $G\alpha_i$ and $G\alpha_o$ proteins, which inhibit AC-cAMP-PKA activation. D2-mediated inhibition of AMPAR EPSCs involves inactivation of AC-cAMP-PKA pathway. This pathway is activated by D1 signaling to promote upregulation of AMPAR surface expression and conductance via phosphorylation. The FMRP interacted with GRK2 and modulated D1 signaling pathway. Both the AC-cAMP-PKA pathway and FMRP play significant roles in the presynaptic and postsynaptic mechanisms of chronic pain in pain related cortices. When the presynaptic dopamine decreased, the AC-cAMP-PKA pathway would be disinhibited, and enhanced the nociceptive transmission. CaM, calmodulin; cAMP, cyclic AMP; CREB, cAMP response element-binding protein; FMRP, fragile X mental retardation protein (encoded by Fmr1); GRK2, G protein-coupled receptor kinase 2; HCN, hyperpolarization-activated cyclic nucleotide-gated; L-VGCC, L-type voltage-gated calcium channel; PKA, protein kinase A; PKMζ, protein kinase Mζ.

hyperphosphorylated at serine sites and subcellular G protein-coupled receptor kinase 2 (GRK2) was redistributed. FMRP interacted with GRK2, and pharmacological inhibition of GRK2 rescued D1 receptor signaling in $Fmr1^{-/-}$ neurons. Finally, D1 receptor agonist partially rescued hyperactivity and enhanced the motor function of $Fmr1^{-/-}$ mice. This may provide insights into the cellular and molecular mechanisms in cortical areas underlying pain in Parkinson's disease.

As an important structure in the nociception, spinal cord also receives dopaminergic projection. Activation of D1/D5 receptors induces LTP of C-fiber evoked potentials, and the effect is dependent on the new protein synthesis and cAMP signaling. Whereas activation of D2 receptor depresses the C-fiber responses.[45] Consistently, it has been shown spinal dopaminergic projections control the transition to pathological pain via a D1/D5-mediated mechanism.[46] In an animal model of Parkinson's disease, D2 receptor activation relieves pain hypersensitivity by inhibiting superficial dorsal horn neurons, while the activation of the D1/D5 receptor failed to obtain such phenomenon.[47] Therefore, spinal D2 receptor signalling pathway may play significant roles in Parkinson's disease related pain.

Animal models for studying Parkinson's disease-related pain

Animal models are an essential tool to study human diseases, not only to enable a thorough investigation into the mechanisms involved in the pathogenesis of a disease but also to help in the development of therapeutic strategies. By using animal models of Parkinson's disease, the striatal dopamine deficiency was associated with symptoms of Parkinson's disease for the first time. However, the mechanisms involved in Parkinson's disease are remain elusive to this day. It is therefore important to develop animal models to understand the pathogenesis of Parkinson's disease and to develop therapeutic strategies to treat it. The table lists up some animal models of Parkinson's disease (Table 1). The neurodegenerative models are most commonly used among all the different models. In the neurotoxic models, 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP)-treated mice showed remarkably shorter nociceptive response latencies compared to saline-treated mice and the subcutaneous injection of L-3,4-dihydroxyphenylalanine (L-DOPA) partially reversed pain hypersensitivity induced by MPTP treatment.[48] 6-hydroxydopamine (6-OHDA)-treated rats exhibit reduced nociceptive thresholds.[49] However, the time window of MPTP-treated model for test is limited, while the 6-OHDA-lesioned rat provides a stable model with persistent hypersensitivity. These models will not only help to discover the potential cellular and molecular mechanisms underlying pain in Parkinson's disease, but they may also be used to test the efficacy of novel analgesics or nonpharmacological therapies.

Clinical treatment of Parkinson's disease-related pain

In order to cure the pain symptom of Parkinson's disease, pharmacological interventions are applied via two main approaches, typical dopaminergic compensation approaches for Parkinson's disease and nondopaminergic analgesics.

Effect of dopaminergic therapies

Some types of pain are the result of insufficient dopaminergic stimulation, even related to motor symptoms of Parkinson's disease. Therefore, rescuing dopaminergic pathways could be the first step in the management of pain in Parkinson's disease.[67] It was reported that the precursor of dopamine, levodopa, reduced pain during the on-state of the pain symptom. Dopamine agonists may also have the potential in treating Parkinson's disease-related pain.[50] A double-blind, placebo-controlled trial supported the beneficial effect of rotigotine on fluctuation-related pain, which is commonly used in the treatment of Parkinson's disease.[51] Safinamide, the inhibitor of an enzyme involved in metabolism of dopamine, monoamine oxidase type B (MAO-B), also appear to have a beneficial effect on Parkinson's disease related pain.[52] Furthermore, antiparkinson medications were reported to be effective in treating sophisticated pain symptoms such as pain related to motor symptoms, as well as neuropathic pain.

Effect of current analgesics

Common analgesics such as opioids (oxycodone/naloxone, codeine and morphine) has been proved effective to reduce different types of pain in patients with Parkinson's disease.[53] Non-steroidal anti-inflammatory drugs have been reported in patients with Parkinson's disease as effective drugs against their pain.[54] Acetaminophen is generally recommended, as reported by clinical experience with other neurological diseases.[67] Tramadol and oxycodone are a complementary therapy for analgesics.[55] In patients with Parkinson's disease with combined depression and pain, combined serotonin and noradrenaline reuptake-inhibitors such as duloxetine have been suggested for pain modulation.[56] However, these analgesics are not selectively designed for the Parkinson's disease-related pain. A more selective drug targeting at key molecules in the synaptic

Table 1. Summary of animal models used for the study of Parkinson's disease.

Models		Potential mechanisms	Animals	Features	Behaviors	References
Pharmacological Model	Reserpine model	Monoamine depletion in nerve terminals	Rat	A model of tardive dyskinesia	Hypokinesia, akinesia, and even catalepsy	57
Neurotoxic Models	6-OHDA model	Neurodegeneration by oxidative stress	Rat Mouse Zebrafish	Stable lesions, allow long-term studies	Asymmetric circling motor behavior	58-60
	MPTP model	Selective degeneration of the dopamine nigrostriatal pathway	Rat Mouse Monkey	The best characterized and most widely-used model	Bradykinesia, rigidity, and postural abnormalities	61-63
Environmental Toxins Models	Paraquat	Dose-dependent decrease in dopaminergic nigral neurons	Rat Mouse	Helped to determine the involvement of environmental exposures	Decreased locomotor activity	64
	Rotenone	Progressive formation of cytoplasmic inclusions and loss of nigral dopamine neurons	Rat Mouse	Produced most of key features of Parkinson's disease	Motor behavioral impairment	65,66
Transgenic Models	α-synuclein	Overexpressing human α-synuclein	Mouse Drosophila	An excellent model system for studying the formation of α-synuclein-positive protein aggregates	Motor impairments	68,69
	Parkin	Alteration of dopamine release or metabolism	Mouse Drosophila	Associated with autosomal recessive juvenile Parkinson's disease, one of the most common familial forms of Parkinson's disease	Bradykinesia, rigidity and resting tremor	70,71
	Ubiquitin carboxyl-terminal hydrolase L1	Increase polyubiquitination of mono- or diubiquitinated α-synuclein	Mouse	Associated with gracile axonal Dystrophy syndrome	Tremor and ataxia	72
Ubiquitin proteasome system (UPS) impairment model		Selective loss of striatal dopaminergic terminals	Mouse	UPS impairment could produce features similar to Parkinson's disease	Motor deficits	73
The 3-nitrotyrosine model		Loss of striatal tyrosine hydroxylase-positive terminals, loss of dopaminergic neurons in substantia nigra and motor abnormalities	Mouse	Used to understand mechanisms of Parkinson's disease etiology and had the potential for use in screening putative antioxidant therapies	Increased net ipsilateral turning behavior	74

mechanism of Parkinson's disease-related pain remains to be found.

Conclusion and future directions

As an important kind of suffering symptoms in Parkinson's disease, pain is found to be prevalent in patients. In cortical areas such as the ACC and IC, the degeneration of dopaminergic neurons acts as the key mechanism of Parkinson's disease and its related pain. Animal models have been created to investigate the mechanisms of pain syndromes. Current pharmacological therapies for Parkinson's disease-related pain mainly consists of dopaminergic drugs for motor symptoms and analgesics. Future study will focus on the synaptic mechanisms of the Parkinson's disease-related pain in cortical areas by using appropriate animal models. The difference between chronic pain and Parkinson's disease-related pain remains to be further investigated. Key molecules for the mechanism will be discovered as potential drug targets for alleviating or eliminating pain in patients with Parkinson's disease.

Acknowledgments

The authors would like to thank Emily England for English editing.

Author Contributions

JSL, QYC, XC, XHL, ZZ, QL, YL, MZ, PYX and MZ drafted the manuscript and finished the final version of the manuscript. All authors read and approved the final manuscript.

Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding

The author(s) disclosed receipt of the following financial support for the research, authorship, and/or publication of this article: XC was supported by National Natural Science Foundation of China (81901282) and Guangdong Basic and Applied Basic Research Foundation (2019A1515011189). PYX was supported by National Key R&D Program of China (2016YFC1306601, 2017YFC1310300, 2017YFC1306002), National Natural Science Foundation of China (81870992, 81870856, U1603281), Technology project of Guangzhou (2018-1202-SF-0019) and Key project of Guangzhou Health Commission (2019-ZD-09). MZ was supported by Grants 36 from the Canadian Institute for Health Research (CIHR) project Grants (PJT-148648 and 419286).

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