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

Jing-Shan Lu1,2, Qi-Yu Chen1,2,3, Xiang Chen4, Xu-Hui Li1,2,3, Zhaoxiang Zhou2, Qin Liu4, Yuwan Lin4, Miaomiao Zhou4, Ping-Yi Xu4, and Min Zhuo1,2,3*

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 neurons 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-adenyly 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

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,
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. These include musculoskeletal pain, articular/arthritic pain, neuropathic pain and radicular pain. 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. 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 noiceptive information in the brain. Excitation of cortical synapse is thought to be a key synaptic mechanism for chronic pain and its related emotional anxiety. At least four different synaptic mechanisms might contribute to chronic pain: (i) presynaptic enhancement of the release of glutamate and its related emotional anxiety; (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. 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. Induction of postsynaptic LTP requires the activation of NMDA receptors (NMDARs) and L-type voltage-gated calcium channels (L-VGCCs). 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. 

**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. Two major forms of LTD have been characterized in the rodent ACC. One of them requires the activation of mGluR1 and L-VGCCs, independent of NMDARs has only a minor effect on the induction of this form of LTD. However, the other NMDAR-dependent form of LTD in the ACC require both GluN2A- and GluN2B and an increase in postsynaptic Ca2+ and CuM levels. In animal models of chronic pain, low-frequency stimulation failed to induce LTD, providing a disinhibition mechanism for chronic pain in the cortex. 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. 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. 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 tomography (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. 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. 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. Computed
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. 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 scalp EEG. The fine analysis of the frequency spectrum ranging from slow delta wave (1–4 Hz) to high frequency gamma oscillations enables precise connectivity studies. General slowing of background activity, excessive synchronization of beta activity, and disturbed movement-related gamma oscillations of EEG were observed in corticobulbar and cortical-motor loops in patients with Parkinson’s disease. 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. 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 midcingulate 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. 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. For patients with certain
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). 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. 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 $G_{as}$ and $G_{olf}$, 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 $G_i$ and $G_o$ 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 (Figure 3). The AC-cAMP-PKA pathway in the ACC and IC is activated in chronic pain. 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 (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](https://example.com/f3.png)

**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 $G_{as}$ and $G_{olf}$, which activates the AC-cAMP-PKA pathway. By contrast, D2-like receptors activate $G_i$ and $G_o$ 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; PKM, 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<sup>−/−</sup> neurons. Finally, D1 receptor agonist partially rescued hyperactivity and enhanced the motor function of Fmr1<sup>−/−</sup> 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.<sup>45</sup> Consistently, it has been shown spinal dopaminergic projections control the transition to pathological pain via a D1/D5-mediated mechanism.<sup>46</sup> 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.<sup>47</sup> 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.<sup>38</sup> 6-hydroxydopamine (6-OHDA)-treated rats exhibit reduced nociceptive thresholds.<sup>49</sup> 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.<sup>67</sup> 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.<sup>50</sup> 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.<sup>51</sup> 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.<sup>52</sup> 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.<sup>53</sup> Non-steroidal anti-inflammatory drugs have been reported in patients with Parkinson’s disease as effective drugs against their pain.<sup>54</sup> Acetaminophen is generally recommended, as reported by clinical experience with other neurological diseases.<sup>67</sup> Tramadol and oxycodone are a complementary therapy for analgesics.<sup>55</sup> 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.<sup>56</sup> 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 pathway will be required to improve the analgesics for Parkinson’s disease-related pain.
| Models                        | Potential mechanisms                                           | Animals       | Features                                      | Behaviors                                 | References |
|------------------------------|-----------------------------------------------------------------|---------------|-----------------------------------------------|-------------------------------------------|------------|
| Pharmacological Model        | Reserpine model                                                 | Rat           | A model of tardive dyskinesia                 | Hypokinesia, akinesia, and even catalepsy | 57         |
| Neurotoxic Models            | 6-OHDA model                                                    | Rat, Mouse, Zebrafish | Stable lesions, allow long-term studies        | Asymmetric circling motor behavior       | 58-60      |
|                              | MPTP model                                                      | Rat, Mouse, Monkey | The best characterized and most widely-used model | Bradykinesia, rigidity, and postural abnormalities | 61-63      |
| Environmental Toxins Models  | Paraquat                                                        | Rat, Mouse    | Helped to determine the involvement of environmental exposures | Decreased locomotor activity             | 64         |
|                              | Rotenone                                                        | Rat, Mouse    | Produced most of key features of Parkinson’s disease | Motor behavioral impairment              | 65,66      |
| Transgenic Models            | α-synuclein                                                     | Mouse, Drosophila | An excellent model system for studying the formation of α-synuclein-positive protein aggregates | Motor impairments                        | 68,69      |
|                              | Parkin                                                          | 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                       | Mouse         | Associated with gracile axonal dystrophy syndrome | Tremor and ataxia                        | 72         |
|                              | Ubiquitin proteasome system (UPS) impairment model             | Mouse         | UPS impairment could produce features similar to Parkinson’s disease | Motor deficits                           | 73         |
|                              | The 3-nitrotyrosine model                                       | 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.

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Min Zhuo

https://orcid.org/0000-0001-9062-3241

References

1. Armstrong MJ, Okun MS. Diagnosis and treatment of Parkinson disease: a review. J Am Med Assoc 2020; 323: 548–560.
2. Antonini A, Tinazzi M. Targeting pain in Parkinson’s disease. Lancet Neurol 2015; 14: 1144–1145.
3. Georgiev D, Lange F, Seer C, Kopp B, Jahanshahi M. Movement-related potentials in Parkinson’s disease. Clin Neurophysiol 2016; 127: 2509–2519.
4. Blanchet PJ, Brefel-Courbon C. Chronic pain and pain processing in Parkinson’s disease. Prog Neuro-Psychoph 2018; 87: 200–206.
5. Sophie M, Ford B. Management of pain in Parkinson’s disease. CNS Drugs 2012; 26: 937–948.
6. Wasner G, Deuschl G. Pains in Parkinson disease-many syndromes under one umbrella. Nat Rev Neurol 2012; 8: 284–294.
7. Hawkes CH, Del Tredici K, Braak H. A timeline for Parkinson’s disease. Parkinsonism Relat Disord 2010; 16: 79–84.
8. Zhuo M. Cortical excitation and chronic pain. Trends Neurosci 2008; 31: 199–207.
9. Bliss TV, Collingridge GL, Kaang BK, Zhuo M. Synaptic plasticity in the anterior cingulate cortex in acute and chronic pain. Nat Rev Neurol 2016; 17: 485–496.
10. Koga K, Descalzi G, Chen T, Ko HG, Lu JS, Li S, Son J, Kim T, Kwak C, Huganir RL, Zhao MG, Kaang BK, Collingridge GL, Zhuo M. Coexistence of two forms of LTP in ACC provides a synaptic mechanism for the interactions between anxiety and chronic pain (vol 85, pg 377, 2015). Neuron 2015; 86: 1109–1109.
11. Zhuo M. Contribution of synaptic plasticity in the insular cortex to chronic pain. Neuroscience 2016; 338: 220–229.
12. Li XH, Miao HH, Zhuo M. NMDA receptor dependent long-term potentiation in chronic pain. Neurochem Res 2019; 44: 531–538.
13. Li XH, Chen QY, Zhuo M. Neuronal adenylyl cyclase targeting central plasticity for the treatment of chronic pain. Neurotherapeutics. Epub ahead of print 15 September 2020. DOI: 10.1007/s13311-020-00927-1.
14. Toyoda H, Zhao MG, Zhuo M. NMDA receptor-dependent long-term depression in the anterior cingulate cortex. Rev Neurosci 2006; 17: 403–413.
15. Bliss TV, Collingridge GL, Kaang BK, Zhuo M. Synaptic plasticity in the anterior cingulate cortex in acute and chronic pain. Nat Rev Neurol 2016; 17: 485–496.
16. Wei F, Li P, Zhuo M. Loss of synaptic depression in mammalian anterior cingulate cortex after amputation. J Neurosci 1999; 19: 9346–9354.
17. Kang SJ, Liu MG, Chen T, Ko HG, Baek GC, Lee HR, Lee K, Collingridge GL, Kaang BK, Zhuo M. Plasticity of metabotropic glutamate receptor-dependent long-term depression in the anterior cingulate cortex after amputation. J Neurosci 2012; 32: 11318–11329.
18. Toyoda H, Zhao MG, Xu H, Wu LJ, Ren M, Zhuo M. Requirement of extracellular signal-regulated kinase/
| Page | Reference |
|------|-----------|
| 19. | Toyoda H, Zhao MG, Zhuo M. Roles of NMDA receptor NR2A and NR2B subtypes for long-term depression in the anterior cingulate cortex. *Eur J Neurosci* 2005; 22: 485–494. |
| 20. | Liu MG, Koga K, Guo YY, Kang SJ, Collingridge GL, Kaang BK, Zhao MG, Zhuo M. Long-term depression of synaptic transmission in the adult mouse insular cortex in vitro. *Eur J Neurosci* 2013; 38: 3128–3145. |
| 21. | Liu MG, Zhuo M. No requirement of TRPV1 in long-term potentiation or long-term depression in the anterior cingulate cortex. *Mol Brain* 2014; 7: 27. |
| 22. | Wang YJ, Liu MG, Wang JH, Cao W, Wu C, Wang ZY, Liu L, Yang F, Feng ZH, Sun L, Zhang F, Shen Y, Zhou YD, Zhuo M, Luo JH, Xu TL, Li XY. Restoration of cingulate long-term depression by enhancing non-apoptotic caspase 3 alleviates peripheral pain hypersensitivity. *Cell Rep* 2020; 33: 108369. |
| 23. | Brefel-Courbon C, Payoux P, Thalamas C, Ory F, Quelven E, Tinazzi M, Antonini A, Bovi T, Pasquin I, Steinmayr M, Bockova M, Rektor I. Impairment of brain functions in patients with early Parkinson’s disease. *Brain* 2007; 130: 2001–2010. |
| 24. | Kumakura Y, Danielsen EH, Gjedde A, Grander G, Bartenstein P, Cumming P. Elevated [F-18]FDOPA utilization in the basal ganglia: a positron emission tomography study of patients with early Parkinson’s disease. *Neuroimage* 2010; 49: 2933–2939. |
| 25. | Christopher L, Duff-Canning S, Koshimori Y, Segura B, Boileau I, Chen R, Lang AE, Houle S, Rusjan P, Strafella AP. Salience network and parahippocampal dopamine dysfunction in memory-impaired Parkinson disease. *Ann Neurol* 2015; 77: 269–280. |
| 26. | Kunst J, Marecek R, Klobusiakova P, Balazova Z, Anderkova L, Nemcova-Ellmarkova N, Rektorova I. Patterns of grey matter atrophy at different stages of Parkinson’s and Alzheimer’s diseases and relation to cognition. *Brain Topogr* 2019; 32: 142–160. |
| 27. | Stoffers D, Bosboom J LW, Deijen JB, Wolters EC, Berendse HW, Stam CJ. Slowing of oscillatory brain activity is a stable characteristic of Parkinson’s disease without dementia. *Brain* 2007; 130: 1847–1860. |
| 28. | Bockova M, Rektor I. Impairment of brain functions in Parkinson’s disease reflected by alterations in neural connectivity in EEG studies: a viewpoint. *Clin Neurophysiol* 2019; 130: 239–247. |
| 29. | Tinazzi M, Antonini A, Bovi T, Pasquin I, Steinmayr M, Moretto G, Fiaschi A, Ottaviani S. Clinical and [123I]FP-CIT SPET imaging follow-up in patients with drug-induced parkinsonism. *J Neurol* 2009; 256: 910–915. |
| 30. | Martin SL, Jones AKP, Brown CA, Kobylecki C, Silverdale MA. A neurophysiological investigation of anticipation to pain in Parkinson’s disease. *Eur J Neurosci* 2020; 51: 611–627. |
| 31. | Zhao MG, Toyoda H, Lee YS, Wu LJ, Ko SW, Zhang XH, Jia YH, Shum F, Xu H, Li BM, Kaang BK, Zhuo M. Roles of NMDA NR2B subtype receptor in prefrontal long-term potentiation and contextual fear memory. *Neuron* 2005; 47: 859–872. |
| 32. | Darvish-Ghane S, Yamanaka M, Zhuo M. Dopaminergic modulation of excitatory transmission in the anterior cingulate cortex of adult mice. *Mol Pain* 2016; 12. Epub ahead of print 19 June 2016. DOI: 10.1177/1744806916648153. |
| 33. | Darvish-Ghane S, Quintana C, Beaulieu JM, Martin LJ. D1 receptors in the anterior cingulate cortex modulate basal mechanical sensitivity threshold and glutamatergic synaptic transmission. *Mol Brain* 2020; 13:121. |
| 34. | Kolomiets B, Marzo A, Caboche J, Vanhoutte P, Otani S. Background dopamine concentration dependently facilitates long-term potentiation in rat prefrontal cortex through postsynaptic activation of extracellular signal-regulated kinases. *Cereb Cortex* 2009; 19: 2708–2718. |
| 35. | Wang H, Wu LJ, Kim SS, Lee FJ, Gong B, Toyoda H, Ren M, Zhang YZ, Xu H, Liu F, Zhao MG, Zhuo M. FMRP acts as a key messenger for dopamine modulation in the forebrain. *Neuron* 2008; 59: 634–647. |
| 36. | Andersen AH, Smith CD, Slevin JT, Kryscio RJ, Martin CA, Schmitt FA, Blonder LX. Dopaminergic modulation of medial prefrontal cortex deactivation in Parkinson depression. *Parkinsons Dis* 2015; 2015: 513452. |
| 37. | Matheus FC, Rial D, Real JJ, Lemos C, Ben J, Guaita GO, Pita IR, Sequeira AC, Pereira FC, Walz R, Takahashi RN, Bertoglio LJ, Da Cunha C, Cunha RA, Prediger RD. Decreased synaptic plasticity in the medial prefrontal cortex underlies short-term memory deficits in 6-OHDA-lesioned rats. *Behav Brain Res* 2016; 301: 43–54. |
| 38. | Okano M, Takahata K, Sugimoto S, Selegeline recovers synaptic plasticity in the medial prefrontal cortex and improves corresponding depression-like behavior in a mouse model of Parkinson’s disease. *Front Behav Neurosci* 2019; 13:176. |
| 39. | Bai J, Blot K, Tzavara E, Nosten-Bertrand M, Giros B, Otani S. Inhibition of dopamine transporter activity impairs synaptic depression in rat prefrontal cortex through over-stimulation of D1 receptors. *Cereb Cortex* 2014; 24: 945–955. |
| 40. | Gao WJ, Wang Y, Goldman-Rakic PS. Dopaminergic modulation of perisomatic and peridendritic inhibition in prefrontal cortex. *J Neurosci* 2003; 23: 1622–1630. |
| 41. | Satoh H, Suzuki H, Saitow F. Downregulation of dopamine D1 receptors in the anterior cingulate cortex modulate basal mechanical sensitivity and glutamatergic synaptic transmission. *Front Behav Neurosci* 2012; 6: 121. |
| 42. | Tritsch NX, Sabatini BL. Dopaminergic modulation of synaptic transmission in cortex and striatum. *Neuron* 2012; 76: 33–50. |
| 43. | Song Q, Zheng HW, Li RH, Huganir RL, Kuner T, Zhuo M, Chen T. Selective phosphorylation of AMPA receptor contributes to the network of long-term potentiation in the anterior cingulate cortex. *J Neurosci* 2017; 37: 8534–8548. |
| 44. | Yamanaka M, Matsuura T, Pan H, Zhuo M. Calcium-stimulated adenyl cyclase subtype 1 (AC1) contributes to LTD in the insular cortex of adult mice. *Heliyon* 2017; 3: e00338. |
45. Yang HW, Zhou LJ, Hu NW, Xin WJ, Liu XG. Activation of spinal d1/d5 receptors induces late-phase LTP of C-fiber-evoked field potentials in rat spinal dorsal horn. J Neurophysiol 2005; 94: 961–967.

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

47. Tang DL, Luan YW, Zhou CY, Xiao C. D2 receptor activation relieves pain hypersensitivity by inhibiting superficial dorsal horn neurons in parkinsonian mice. Acta Pharmacol Sin. Epub ahead of print 23 July 2020. DOI: 10.1038/s41401-020-0433-3.

48. Park J, Lim CS, Seo H, Park CA, Zhuo M, Kaang BK, Lee K. Pain perception in acute model mice of Parkinson’s disease induced by 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP). Mol Pain 2015; 11:28.

49. Buhidma Y, Rukavina K, Chaudhuri KR, Duty S. Hallmarks of Reserpine as a Model for Parkinson’s Disease: New Perspectives to a Long-Standing Model. J Neurochem 2020; 90: 841–1171.

50. Leao AH, Sarmento-Silva AJ, Santos JR, Ribeiro AM and Silva RH. Molecular, Neurochemical, and Behavioral Hallmarks of Reserpine as a Model for Parkinson’s Disease: New Perspectives to a Long-Standing Model. Brain Pathol 2015; 25: 377–390. 2015/03/03. DOI: 10.1111/bpa.12253.

51. Ulusoy A, Sahin G and Kirik D. Presynaptic dopaminergic compartment determines the susceptibility to L-DOPA-induced dyskinesia in rats. Proc Natl Acad Sci U S A 2010; 107: 13159–13164. 2010/07/10. DOI: 10.1073/pnas.1003432107.

52. Blandini F, Armentero MT and Martignoni E. The 6-hydroxydopamine model: news from the past. Parkinsonism Relat Disord 2008; 14 Suppl 2: S124–129. 2008/07/04. DOI: 10.1016/j.parkreldis.2008.07.015.

53. Vijayanathan Y, Lim FT, Lim SM, Long CM, Tan MP, Majeed ABA and Ramasamy K. 6-OHDA-Lesioned Adult Zebrafish as a Useful Parkinson’s Disease Model for Dopaminergic Neuroregeneration. Neurotoxin Res 2017; 32: 496–508. 2017/07/15. DOI: 10.1007/s12640-017-9778-x.

54. Jackson-Lewis V and Przedborski S. Protocol for the MPTP mouse model of Parkinson’s disease. Nat Protoc 2007; 2: 141–151. 2007/04/03. DOI: 10.1038/nprot.2006.342.

55. Bezard E, Imbert C, Deloire X, Bioulac B and Gross CE. A chronic MPTP model reproducing the slow evolution of Parkinson’s disease: evolution of motor symptoms in the monkey. Brain Res 1997; 766: 107–112. 1997/08/22. DOI: 10.1016/s0006-8993(97)00531-3.

56. Chiueh CC, Markey SP, Burns RS, Johannessen JN, Jacobowitz DM and Kopin JJ. Neurochemical and behavioral effects of 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) in rat, guinea pig, and monkey. Psychopharmacol Bull 1984; 20: 548–553. 1984/01/01.

57. Berry C, La Vecchia C and Nicotera P. Parauquat and Parkinson’s disease. Cell Death Differ 2010; 17: 1115–1125. 2010/01/23. DOI: 10.1038/cdd.2009.217.

58. Cannon JR, Tapias V, Na HM, Honick AS, Drolet RD and Greenamyer JT. A highly reproducible rotenone model of Parkinson’s disease. Neurobiol Dis 2009; 34: 279–290. 2009/04/23. DOI: 10.1016/j.nbd.2009.01.016.

59. Pan-Montojo F, Anichtchik O, Dening Y, Knels L, Pursche S, Jung R, Jackson S, Gille G, Spillantini MG, Reichmann H and Funk RH. Progression of Parkinson’s disease pathology is reproduced by intragastric administration of rotenone in mice. PLoS One 2010; 5: e8762. 2010/07/26. DOI: 10.1371/journal.pone.0008762.

60. Singleton AB, Farrer M, Johnson J, Singleton A, Hague S, Kachergus J, Hulihan M, Peuralinna T, Dutra A, Nussbaum R, Lincoln S, Crawley A, Hanson M, Maraganore D, Adler C, Cookson MR, Muenter M, Baptista M, Miller D, Blancato J, Hardy J and Gwinn-Hardy K. alpha-Synuclein locus triplication causes Parkinson’s disease. Science 2003; 302: 841. 2003/11/01. DOI: 10.1126/science.1090278.

61. Kara E, Kiely AP, Proukakis C, Giffin N, Love S, Hehir J, Rantell K, Pandraud A, Hernandez DG, Nacheva E, Pittman AM, Nalls MA, Singleton AB, Revesz T, Bhatia KP, Quinn N, Hardy J, Holton JL and Houlden H. A 6.4 Mb duplication of the alpha-synuclein locus causing frontotemporal dementia and Parkinsonism: phenotype-genotype correlations. JAMA Neurol 2014; 71: 1162–1171. 2014/07/09. DOI: 10.1001/jamaneurol.2014.994.

62. Lucking CB, Durr A, Bonifati V, Vaughan J, De Michele G, Gasser T, Harhangi BS, Meco G, Benfelle P, Wood NW, Agid Y, Brice A, French Parkinson’s Disease Genetics Study G and European Consortium on Genetic Susceptibility in Parkinson’s D. Association between early-onset Parkinson’s disease and mutations in the parkin gene. N Engl J Med 2000; 342: 1560–1567. 2000/05/29. DOI: 10.1126/NEJM200005253422103.

63. Periquet M, Latouche M, Lohmann E, Rawal N, De Michele G, Ricard S, Teive H, Fraix V, Vidalhmet N, Nicholl D, Barone P, Wood NW, Raskin S, Deleuze JF, Agid Y, Durr A, Brice A, French Parkinson’s Disease Genetics Study G and European Consortium on Genetic Susceptibility in Parkinson’s D. Parkin mutations are frequent in patients with isolated early-onset parkinsonism. Brain 2003; 126: 1271–1278. 2003/05/24. DOI: 10.1093/brain/awg136.

64. Ardley HC, Scott GB, Rose SA, Tan NG and Robinson PA. UCH-L1 aggresome formation in response to proteasome impairment indicates a role in inclusion formation in Parkinson’s disease. J Neurochem 2004; 90: 379–391. 2004/07/02. DOI: 10.1111/j.1471-4159.2004.02485.x.

65. Forloni G, Terreni L, Bertani I, Fogliarino S, Invernizzi R, Mariani C, Franceschi M, Tabaton M and Bertoli A. Protein misfolding in Alzheimer’s and Parkinson’s disease: genetics and molecular mechanisms. Neurobiol Aging 2002; 23: 957–976. 2002/10/24. DOI: 10.1016/s0197-4580(02)00076-3.
66. Pennathur S, Jackson-Lewis V, Przedborski S and Heinecke JW. Mass spectrometric quantification of 3-nitrotyrosine, ortho-tyrosine, and o,o’-dityrosine in brain tissue of 1-methyl-4-phenyl-1,2,3, 6-tetrahydropyridine-treated mice, a model of oxidative stress in Parkinson’s disease. *J Biol Chem* 1999; 274: 34621–34628. 1999/11/27. DOI: 10.1074/jbc.274.49.34621.

67. Rukavina K, Leta V, Sportelli C, Buhidma Y, Duty S, Malcangio M, Ray Chaudhuri K. Pain in Parkinson’s disease: new concepts in pathogenesis and treatment. *Curr Opin Neurol* 2019; 32: 579–588.

68. Singleton AB, Farrer M, Johnson J, Singleton A, Hague S, Kachergus J, Hulihan M, Peuralinna T, Dutra A, Nussbaum R, Lincoln S, Crawley A, Hanson M, Maraganore D, Adler C, Cookson MR, Muenter M, Baptista M, Miller D, Blancato J, Hardy J, Gwinn-Hardy K. alpha-Synuclein locus triplication causes Parkinson’s disease. *Science* 2003; 302: 841.

69. Kara E, Kiely AP, Proukakis C, Giffin N, Love S, Hehir J, Rantell K, Pandraud A, Hernandez DG, Nacheva E, Pittman AM, Nalls MA, Singleton AB, Revesz T, Bhatia KP, Quinn N, Hardy J, Holton JL, Houlden H. A 6.4 Mb duplication of the alpha-synuclein locus causing fronto-temporal dementia and Parkinsonism: phenotype-genotype correlations. *JAMA Neurol* 2014; 71: 1162–1171.

70. Lucking CB, Durr A, Bonifati V, Vaughan J, De Michele G, Gasser T, Harhangi BS, Meco G, Denefle P, Wood NW, Agid Y, Brice A. French Parkinson’s Disease Genetics Study G, European Consortium on Genetic Susceptibility in Parkinson’s D. Association between early-onset Parkinson’s disease and mutations in the Parkin gene. *N Engl J Med* 2000; 342: 1560–1567.

71. Periquet M, Latouche M, Lohmann E, Rawal N, De Michele G, Ricard S, Teive H, Fraix V, Vidalhiet M, Nicholl D, Barone P, Wood NW, Raskin S, Deleuze JF, Agid Y, Durr A, Brice A. French Parkinson’s Disease Genetics Study G, European Consortium on Genetic Susceptibility in Parkinson’s D. Parkin mutations are frequent in patients with isolated early-onset parkinsonism. *Brain* 2003; 126: 1271–1278.

72. Ardley HC, Scott GB, Rose SA, Tan NG, Robinson PA. UCH-L1 aggresome formation in response to proteasome impairment indicates a role in inclusion formation in Parkinson’s disease. *J Neurochem* 2004; 90: 379–391.

73. Forloni G, Terreni L, Bertani I, Fogliarino S, Invernizzi R, Assini A, Ribizzi G, Negro A, Calabrese E, Volonte MA, Mariani C, Franceschi M, Tabaton M, Bertoli A. Protein misfolding in Alzheimer’s and Parkinson’s disease: genetics and molecular mechanisms. *Neurobiol Aging* 2002; 23: 957–976.

74. Pennathur S, Jackson-Lewis V, Przedborski S, Heinecke JW. Mass spectrometric quantification of 3-nitrotyrosine, ortho-tyrosine, and o,o’-dityrosine in brain tissue of 1-methyl-4-phenyl-1,2,3, 6-tetrahydropyridine-treated mice, a model of oxidative stress in Parkinson’s disease. *J Biol Chem* 1999; 274: 34621–34628.