Pathophysiology and clinical management of pain in Parkinson’s disease: Differences in efficacy of dopamine agonists and deep brain stimulation

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Abstract
Although different types of pain may be present from the early stage of Parkinson’s disease (PD), musculoskeletal pain related to an impaired motor status is most commonly encountered in clinical practice. Levodopa is widely for the treatment of PD and can substantially improve symptoms. However, prolonged treatment with levodopa can induce serious motor complications, which in turn may trigger or aggravate pain. It has been reported that dopamine agonists, when used in conjunction with levodopa, significantly improve levodopa–induced motor complications. A randomized placebo controlled study has demonstrated that transdermal rotigotine improves pain related to motor fluctuations. Deep brain stimulation (DBS) is a promising method of improving levodopa–induced complications in advanced PD patients, and subthalamic DBS has been shown to be particularly beneficial for nonmotor symptoms including pain. While newer effective methods are expected to be in development for PD–related pain, here, we review current approaches to pain management in PD.

Keywords
Parkinson’s disease; Pain; Dopamine agonist; Deep Brain Stimulation

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Introduction
Parkinson’s disease (PD) is generally characterized as a movement disorder that results from dopamine depletion in the nigrostriatal pathway. However, neural degeneration is not only limited to the dopaminergic system, and
PD patients may suffer from various nonmotor symptoms (NMSs) including pain. About 40 – 85% of PD patients may suffer from different types of pain, which significantly worsens their quality of life. There is a body of evidence to suggest that chronic pain may reorganize neural networks and disturb physiological functions, which negatively affect motor outputs, posture, mood, behavior, as well as cognitive functions. Therefore, adequate management of pain symptoms is crucial in PD treatment.

Pain in PD results from both the pathological activation or sensitization of nociceptors and a decrease in pain threshold due to somatosensory dysfunction. Reviewers have variously classified pain in PD patients into different types, and all have emphasized musculoskeletal pain as the most common type encountered in clinical practice. Here, we simplify Wasner’s four-tier taxonomy for PD-related pain and present the incidence rate as well as the basic characteristics of each subtype in Table 1. Musculoskeletal pain related to the motor status of patients and treatment-induced motor complications accounted for up to 90% of PD-related pain (Table 1). Thus, adequate management of motor symptoms including dystonia and rigidity, and prevention of levodopa-induced motor complications significantly benefit in most patients.

Levodopa, the precursor of dopamine, is the most effective drug currently available to improve motor and nonmotor symptoms. It relieves pain not only by improving motor status but also increasing pain threshold. However, intermittent administrations of levodopa induce serious complications related to the sensitization of motor and nonmotor pathways, involving even central inhibitory pain circuits. Therefore, management of pain related to motor fluctuations remains a challenge to clinical practitioners. Dopamine agonists are another drug category used for dopamine replacement, which signifi-
cantly prevent levodopa–induced complications. However, their efficacy in pain management differs depending on the pharmacological profile of each agent. Deep brain stimulation (DBS) has also been shown to be very effective in improving levodopa–induced motor fluctuations in advanced PD patients, and provides significant benefits in the managements of nonmotor symptoms including pain. In this review, we discuss the analgesic characteristics of the most commonly used dopaminergic medications and DBS in PD patients.

Pathophysiology of pain in PD

Pain is perceived through a mechanism that consists of sensory, affective and cognitive components, and multiple structures are involved in its modulation. Bushnell et al. have described in detail in their review the circuits that underlie the sensory and emotional processing of pain, and their central modulations. Hache et al., on the other hand, reviewed the contribution of neurotransmitters to pain modulation. On the base of these reviews, here, we combine the neural pathways with monoaminergic neurotransmission, which is involved in pain processing, and illustrate dynamic pain modulation in healthy individuals in Fig.1. In the spinal cord, dorsal horn neurons relay peripheral afferents through the spinothalamocortical tract to somatosensory cortices, which encode pain perception, and through spinoparabrachial projections to the amygdala, which in turn encodes the unpleasant feeling of pain. The basal ganglia (BG) receives multisensory inputs from the cortical and subcortical brain structures that integrate sensory information and organize behavioral responses to external and internal stimuli. The descending projections from the prefrontal cortex (PFC) and limbic system, which includes the insular and cingulate cortices, on the other hand, modulate the periaqueductal gray (PAG) matter depending on cognitive and emotional factors. The PAG matter is an important nociception modulation site that sends outputs to the locus ceruleus and raphe nuclei that connect with the spinal cord dorsal horn neurons.

Monoaminergic neurotransmitters, including noradrenaline and serotonin released from brainstem nuclei, and dopamine released from midbrain dopaminergic neurons enforce the central modulations of nociceptive inputs and sensory gating. In healthy individuals, their overall nervous system is endowed with monoaminergic–rich neurotransmitters that ensure intact pain inhibition. In PD, Lewy bodies excessively accumulate in the brainstem from the very early stage of disease progression and spread to functionally related brain areas through synaptic interconnections. These not only interfere with neuronal activities but also induce neuronal degeneration in the brainstem and consequently in the substantia nigra and/or the spinal cord. Therefore, monoaminergic transmissions may be severely impaired in PD, resulting in dysfunctional somatosensory processing and central pain inhibition. Thus, PD patients are more vulnerable to nociceptive stimulation, and chronic pain often precedes the motor deficits that are characteristic of the disease.

Chronic nociceptive stimuli, on the other hand, reduce the activity of painful muscle groups as well as impair proprioception that in turn exacerbates movement disorders. Moreover, imbalanced sensory and affective
inputs, and impaired central modulations result in alterations of neuronal networks and, as a consequence, induce or/aggravate mood and cognitive dysfunction\(^9,^{43}\). There is clinical evidence that also demonstrates a correlation of chronic pain with anxiety, depression, and abnormal behaviors\(^{25,36}\). In conclusion, chronic pain not only manifests as a nonmotor symptom in PD, but can also significantly worsen the quality of life of patients.

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Fig. 1 Illustration of pain afferent and inhibitory pain pathways, and monoaminergic neurotransmission.

In healthy individuals, their overall nervous system is endowed with monoaminergic–rich neurotransmitters released from brainstem nuclei as well as midbrain dopaminergic neurons, which enforce the central modulations of nociceptive inputs and sensory gating. In the spinal cord, dorsal horn neurons relay peripheral afferents through the spinothalamocortical tract to somatosensory cortices, which encode pain perception, and through spinoparabrachial projections to the amygdala, which in turn encodes the unpleasant feeling of pain and is powerfully inhibited by the central pain inhibitory system. The basal ganglia receives multisensory inputs from the cortical and subcortical brain areas, integrates sensory information, and organizes behavioral responses to external and internal stimuli. The descending inhibitory projections from the prefrontal cortex and the limbic system including the cingulate and insular cortices, on the other hand, modulate the PAG matter depending on cognitive and emotional factors. The PAG matter sends outputs to the locus ceruleus and raphe nuclei, which are connected to the spinal cord dorsal horn neurons that regulate peripheral nociceptive stimuli.

Abbreviations: PFC, prefrontal cortex; IC, insular cortex; ACC, anterior cingulate cortex; PAG, periaqueductal gray; BG, basal ganglia; TH, thalamus; hTH, hypothalamus; SNC, substantia nigra compacta; VTA, ventral tegmental area; RVM, rostral ventromedial medulla; LC, locus ceruleus; PB, parabrachial nucleus; AMY, amygdala.
Management of chronic pain in PD

Dopamine, by stimulating overall dopamine receptors as well as interacting with other neurotransmitters, plays a crucial role in the pain inhibitory system. There are two subclasses of dopamine receptors: D1–like receptors (i.e., D1 and D5 receptors), and D2–like receptors (i.e., D2, D3, and D4 receptors)\(^\text{15,16}\). D1–like dopamine receptors are highly expressed in the striatum, nucleus accumbens, substantia nigra, olfactory bulb, amygdala, and frontal cortex\(^\text{46}\). D1 receptors are located postsynaptically and activate dopamine–receptive cells that enhance the release of different neurotransmitters including acetylcholine, GABA, glutamine and serotonin, which leads to an increase in interconnections between related structures\(^\text{31,62,74}\). The D2–like dopamine receptors, on the other hand, are expressed at highest levels in the striatum, nucleus accumbens, and olfactory tubercle\(^\text{59}\). They are expressed both postsynaptically, in which they inhibit the activity of dopamine target cells, and presynaptically, in which they inhibit dopamine release on dopaminergic neurons\(^\text{59}\). Because multiple cortical and subcortical areas are involved in pain modulation, and the expression patterns of dopamine receptors in these areas vary, a synergic regulation of different brain structures by balanced stimulation of a wide spectrum of dopamine receptors is essential in central pain suppression. Thus, dopamine replacement therapy not only assuages musculoskeletal and dystonic pain related to motor functions, but it also significantly alleviates central neuropathic pain\(^\text{32,78}\).

Levodopa

Levodopa (l–DOPA, 1–3,4–dihydroxyphenylalanine) is converted to dopamine by aromatic acid decarboxylase (AADC) in dopaminergic, serotonergic, and histaminergic neurons, and replenishes broad regions of the brain with higher concentrations of dopamine\(^\text{6,90}\). Dopamine not only induces a balanced modulation of dopaminergic systems, but it is also a precursor of noradrenaline and increases serotonin concentrations\(^\text{18,66}\). Thus, levodopa administration can markedly ameliorate PD symptoms by modulating all monoaminergic neurotransmissions. In addition to motor recovery, there is evidence to demonstrate that levodopa can restore pain thresholds in PD patients\(^\text{22}\). Although levodopa is clinically effective in controlling PD symptoms, prolonged use induces motor fluctuations and dyskinesia, which in turn might trigger or aggravate other types of pain\(^\text{14,45}\). Sensitization in central neural circuits induced by progressive loss of dopaminergic innervations and nonphysiological overstimulation of dopamine receptor D1 is postulated to be responsible for levodopa–related complications\(^\text{24,44}\). Continual delivery of levodopa has been demonstrated to show promising benefits in controlling levodopa–induced side effects, but limitations in its clinical application still have to be resolved\(^\text{3}\).

Dopamine agonists

Dopamine agonists (DA) directly stimulate dopamine receptors (DRs) and show different clinical benefits depending on their discrete affinity to each DR subtype (Fig.2). Pramipexole and ropinirole show selective affinity to D2–like receptors (Fig.2) and have been shown to significantly inhibit levodopa–induced motor complications\(^\text{71,75}\). Although they demonstrate significant benefits in improving motor functions, these agonists have a greater risk associated with the induction of some nonmotor symp-
Symptoms, such as somnolence, edema, hallucination and impulse control disorder. Moreover, although some basic research has shown that D2 receptors are involved in pain modulation in experimental animals, there is no evidence that D2-selective agonists indeed relieve pain syndromes in PD. Another dopamine receptor agonist available is rotigotine, which binds uniformly and shows a high affinity to the D1, D2, D3, D4, and D5 receptors as well as selected adrenergic and serotonergic receptors. A single daily application of a rotigotine transdermal patch (RTP) maintains a stable plasma concentration over 24 hours, and improves motor fluctuations by significantly reducing "Off" time. In addition to improvements in motor disturbances, RTP alleviates nonmotor symptoms including pain. Rascol et al. investigated the effects of RTP on PD-related chronic pain as a primary outcome in a randomized placebo controlled pilot study. In their study, overall improvements in pain, particularly significant relief in motor fluctuation related pain, were observed. Therefore, the therapeutic benefits of RTP in PD patients may extend beyond the significant reduction of motor complications to relief across different types of pain.

Deep brain stimulation (DBS)

The basal ganglia (BG) receives multisensory inputs from the cortical and subcortical brain areas including the frontal, parietal and insular cortices, and the hippocampal regions. These structures integrate sensory information and organize behavioral responses to external and internal stimuli. The BG plays a critical role in pain processing, and alterations...
of neural activities in the BG have been suggested as a pathophysiological mechanism of PD. Thus, interventions targeting the BG with the aim of reversing its abnormal neuronal activities have been postulated to have a modulatory effect on pain symptoms in PD patients. Although different BG structures can be selected for stimulation, the efficacy of DBS of the subthalamic nucleus (STN-DBS) for PD-related pain is the most well understood. There is evidence to show that STN-DBS significantly reduces overall pain but its efficacy varies across the different subtypes of pain symptom. Oshima et al. followed up a cohort of 69 PD patients for one year after STN-DBS surgery, and they reported that STN-DBS is more effective in alleviating musculoskeletal and dystonic pain, but patients with somatic and radicular/peripheral neuropathic pain had a higher risk of deterioration after surgery. Jung et al. followed up the changes in pain symptoms in 24 patients over eight years after STN-DBS surgery. They reported that although STN-DBS demonstrated a persistent beneficial effect in relieving pain, new musculoskeletal pain developed in most patients. STN-DBS is considered to modulate BG circuitry and cortical regions related to sensory integration, and emotional and motivational–affective behavior. Thus, STN-DBS with the principal aim to improve motor function may also have variable effects on pain depending on the location, characteristics and origin of the pain, as well as modify the emotional and cognitive conditions of a patient. The globus pallidus internus (Gpi) is another main target for DBS in PD, and a study showed that both unilateral and bilateral stimulations reduce dystonia, muscle cramps, and sensory symptoms including pain. Although there are fewer reports on Gpi-DBS with regard to pain modulation in the literature, it has been shown to significantly reduce motor symptoms and improve the ability of patients to perform everyday tasks, which results in improvements in pain and overall quality of life.

Conclusions

In PD patients, pain may be present at any stage of the disease and have significant detrimental effects on their quality of life. However, in clinical practice, pain symptoms are often overlooked, as treatments usually focus on the management of motor symptoms. With regard to pain relief, the RTP was demonstrated to provide overall relief of chronic pain, which in turn leads to improvements in the quality of life. It is considered that reduction of levodopa-induced motor complications contributes toward these beneficial effects. Regarding surgical intervention, DBS, particularly stimulation of the subthalamic nucleus, also alleviates pain of different pathologies by reducing levodopa-induced motor complications. With regard to managing pain in PD, greater priority to the appropriate selection of a drug or DBS protocol would be helpful in mitigating pain symptoms and improving the quality of life of PD patients.

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