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Cortical synaptic mechanism for chronic pain and anxiety in Parkinson's disease

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BACKGROUND

Parkinson's disease (PD) is a common movement disorder and represents the second most common neurodegenerative disease after Alzheimer's disease.[1,2] A serious problem is that PD prevalence and incidence showed an actual increase.[3] The main neuropathological finding is degeneration of dopaminergic neurons in the midbrain, especially substantia nigra.[4] Although PD is predominantly considered as a motor disorder, nonmotor manifestations have gained increasing attention, such as pain and anxiety.[5,6] Both pain and anxiety symptoms severely affect the life quality of PD patients. Pain is a prevalent nonmotor symptoms in PD, leading to increased disability and reduced health-related quality of life. Most patients with PD are suffering pain. PD patients suffer from a range of different pain syndromes, varying in their cause, origin, location and chronicity. The most frequent pain syndromes in PD are musculoskeletal pain, neuropathic radicular pain, dystonia-related pain, akathisia discomfort, and primary central parkinsonian pain. There are 30%–95% of patients with PD suffering from different forms of pain, including acute pain and chronic pain.[7]

Anxiety is another frequent nonmotor symptom in PD. The prevalence of anxiety in PD is about 40%.[6] Although anxiety is a frequent worsening factor of the disease and is associated with lower quality of life,[8, 9] the underlying mechanisms remain largely unknown.

In clinical treatment of Parkinson's disease-related pain, typical dopaminergic drugs for PD and common analgesics are applied to relieve the symptom. A recent study showed that a cognitive behavioral therapy was effective to treat anxiety in PD.[10] However, there are few selectively clinical treatments for PD-related chronic pain and anxiety. Therefore, it is worthy to discover the connection between the pathological changes of Parkinson's disease and the basic mechanism of chronic pain and anxiety.

ACC, CHRONIC PAIN AND ANXIETY

Among several cortical regions, the anterior cingulate cortex (ACC) has been demonstrated to play important roles in sensory perception and emotional responses.[11] Human imaging and *in vivo* electrophysiological recordings of animals show that neurons in the ACC are activated by noxious sensory stimuli. In addition, inhibiting central plasticity in the ACC produces analgesic effects in different animal models of chronic pain.[11] Increased activity in the ACC has been reported in patients with anxiety disorders,[12] and Li *et al.* reported that oxytocin in the ACC attenuates emotional anxiety by inhibiting presynaptic long-term potentiation (LTP).[13]

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On the other hand, clinical studies of human brain imaging have documented the interaction between pain and anxiety, indicating the ACC is a more important region for such an interaction.[14] Moreover, Koga *et al.* demonstrated that injury triggered pre- and post-LTP in the anterior cingulate cortex and that the two forms of LTP may converge to mediate interaction between anxiety and pain.[15]

LTP and long-term depression (LTD) are two forms of synaptic plasticity that have been studied in the sensory and emotion function.[16] In the cortical areas, increasing evidence suggests that LTP and LTD are causally related to chronic pain, including the ACC.[11, 17] Excitatory synaptic transmission in the ACC undergoes both pre- and postsynaptic LTP in different animal models of chronic pain and anxiety.[18] At the synaptic level, changes in the properties and abundance of a-amino-3-hydroxy-5-methyl-4-isoxazole-propionic acid (AMPA)-type glutamate receptors are major mechanisms underlying various forms of synaptic plasticity, including LTP and LTD.[11] Furthermore, inhibiting or blocking ACC LTP produced significantly reduction of behavioral sensory sensitization and injury-related anxiety in non-PD mice.[15]

In summary, ACC is a key cortical region in the researches of chronic pain, anxiety, and their interaction. The synaptic plasticity of ACC neuron is likely the key cellular mechanism.

ALTERATIONS OF ACC IN PD PATIENTS

Most previous PD basic studies paid more attention to midbrain areas, especially substantia nigra pars compacta. However, less is known about the alterations of ACC in PD patients.

By using positron emission tomography (PET), pain thresholds and cerebral activity were assessed before and after nociceptive stimulation.[19] The regional cerebral blood flow (rCBF) in the right ACC was significantly increased in PD patients with pain. In pain-free PD patients, pain was associated with a significant rCBF increase in the right prefrontal cortex, bilateral posterior insula and left ACC. However, PD patients with pain had a higher pain activation only in the right ACC, but not prefrontal cortex and posterior insula, than pain-free PD patients. The study suggests that ACC may play a more important role in PD-related pain than other cortical areas.

As another nonmotor symptom, anxiety also attracted an increasing attention. A voxel-based morphometry (VBM) study reported that symptoms of anxiety in PD are associated with reduced gray matter volume of the left precuneus and ACC.[20, 21] Moreover, a PET study showed that putamen functional connectivity with ACC was altered in PD patients with anxiety disorder.[22] The anatomical and functional changes indicated that ACC is involved in PD-related anxiety.

PD ANIMAL MODELS WITH CHRONIC PAIN AND ANXIETY

Animal models are an essential aid in studying human diseases. They are widely used to study the pathogenetic mechanisms and the therapeutic target in human diseases. 1-Methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) model and 6-hydroxydopamine (6-OHDA) model are two classical animal models in PD studies.

Chronic pain is a commonly occurring nonmotor symptom of PD. A previous study found that MPTP-treated mice showed remarkably shorter nociceptive response latencies compared to saline-treated mice.[23] 6-OHDA-treated rats also exhibited thermal hyperalgesia and reduced nociceptive threshold.[24] Our recent study confirmed that MPTP-treated and 6-OHDA-treated mice exhibited thermal hyperalgesia and mechanical pain hypersensitivity.[25] In studies of anxiety symptom, MPTP-treated mice showed increased anxiety in the marble-burying test,[26] and the 6-OHDA injection also induced anxiety-like behavior in the elevated plus maze.[27]

Therefore, we believe that MPTP-induced and 6-OHDA-induced PD models are appropriate models to study the chronic pain and anxiety symptoms of PD patients. In addition, it is important to develop transgenic models to understand the nonmotor symptoms of Parkinson's disease and develop therapeutic strategies to treat it.

ALTERATIONS OF ACC IN PD ANIMAL MODELS

Our recent study reported that ACC was activated bilaterally in MPTP-treated mice.[25] By local infusion of muscimol, inactivation of the ACC reversed the chronic pain and anxiety symptoms in MPTP-treated mice, suggesting that ACC activity at least partially contribute to chronic pain and emotional anxiety in PD model mice. Furthermore, the motor impairment in MPTP-treated mice was not affected by ACC microinjection of muscimol, indicating that ACC is relatively selective involved in sensory and emotional functions of PD model mice.

Considering the activation of ACC in both PD patients and the PD model mice, there are reasons to believe that ACC may participate in the regulation of PD-related chronic pain and anxiety.

PERSPECTIVES

The presynaptic and postsynaptic excitatory transmissions of ACC neurons are enhanced in MPTP-treated mice.[25] The results are similar to ACC plastic changes reported in previous studies in different chronic pain animal models.[28, 29] As a novel target for chronic pain, adenylyl cyclase 1 (AC1) has been proved to be essential for the presynaptic enhancement of glutamate release and postsynaptic potentiation.[30] As a selective inhibitor of AC1, NB001 has an estimated 50% inhibitory concentration (IC50) of 10 μmol/L on HEK293 cells expressing AC1. Moreover, NB001 produces powerful analgesic effects in different animal models of chronic pain.[31, 32] The current findings strongly suggest that NB001 is potentially used for the treatment of chronic pain in PD patients.

Recent years, increasing evidence suggested that pre-LTP in ACC is closely associated with anxiety behavior.[13, 15] However, current drugs are not targeted at pre-LTP but rather focus on modulating transmission or release of glutamate. Thus, inhibiting pre-LTP may provide a unique target to treat anxiety in PD patients.

In summary, we hypothesized that the activation of ACC plays an important role in PD-related pain and anxiety. AC1 has the potential to treat PD-related chronic pain, and the mechanism of PD-related anxiety may be further clarified by targeting pre-LTP. Further studies of PD-related chronic pain and anxiety would focus on cortex regions and investigate the cellular and synaptic mechanisms.

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Conflict of Interest

None declared.

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