RESEARCH HIGHLIGHT

Dopamine in Parkinson's Disease: Precise Supplementation with Motor Planning

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Parkinson's disease (PD) is the second most common neurodegenerative disorder which mainly affects the motor system. The pathological characteristics of PD include the loss of dopaminergic neurons in the substantia nigra region and dopamine depletion in the striatum.

Dopamine functions as a neurotransmitter that is involved in motor control, executive functions, motivation, arousal, reinforcement, and reward [1]. The ongoing tonic levels of dopamine release in the dorsal striatum are thought to be important for the regulation of movement. Because of the dopamine depletion in the striatum, movement is affected in PD. The typical motor symptoms consist of poverty of movement, tremor at rest, rigidity, and postural instability. Meanwhile, pre-motor symptoms, including hyposmia, constipation, depression, and REM sleep behavior disorder, have been suggested to precede these typical motor symptoms by years [2]. It is usually proposed to alleviate these symptoms *via* boosting the levels of dopamine in PD. However, this may not be the case.

Recently, Joaquim Alves da Silva and colleagues implanted 16-channel movable electrode bundles coupled to a fiber-optic cannula just above the substantia nigra pars compacta (SNc) in mice, and investigated the activity of photo-identified SNc dopamine neurons in relation to movement initiation [3]. They found that the activity of dopamine neurons before movement initiation was

transient and not very action-specific. After the specific expression of archaerhodopsin in SNc neurons and the delivery of light unpredictably for periods of 15 s, they found that movement initiation was significantly impaired when dopamine neurons in the SNc were inhibited during immobility. The effect of inhibition was so rapid that 5 s of inhibition was sufficient to impair movement initiation. However, no significant change was found in the vigor of movement when SNc dopamine neurons were inhibited after movement initiation. Also, mice did not stop during the inhibition, indicating that the probability and vigor of future movements is modulated by the activity of dopamine neurons before movement initiation. However, the activity of these neurons is less critical for the maintenance and vigor of ongoing movements. Furthermore, they found that, when the animals were immobile, brief activation of the dopamine neurons was sufficient to promote movement initiation. And SNc dopamine activity before the initiation of movement was not critical for the execution of ongoing action sequences. These results suggested that the transient changes of dopamine act as a fast system to increase the probability and vigor of movement initiation by modulating the excitability of striatal projection neurons. This is in accord with recent studies showing that dopamine secretion is rapid and mediated by sparse and specialized active zone-like release sites [4]. And about 30% of dopamine varicosities have been found to contain these active zone-like sites, which were identified by super-resolution microscopy.

The most widely used treatment for PD is levodopa, which passes through the blood-brain barrier and is readily converted to dopamine. However, the long-term use of levodopa usually leads to complications such as involuntary movements, also called dyskinesias, fluctuations in the effectiveness of the medication, and neuroleptic malignant

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syndrome. The withdrawal of levodopa for some time reduces the dyskinesias and fluctuations [5]. A role for dopamine in gating and invigorating movements would explain the side-effects in PD patients who are continuously supplied with levodopa. All these findings highlight that closed-loop deep-brain stimulations in the cortical areas related to motor planning, which transiently modulate the basal ganglia circuitry, may be more efficient with fewer side-effects in PD patients. Of course, this needs to be confirmed by more clinical studies.

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