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Rebound Excitability Mediates Motor Abnormalities in Parkinson's Disease

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Parkinson's disease (PD) is a debilitating disorder resulting from loss of dopamine neurons. In dopamine deficient state, the basal ganglia increases inhibitory synaptic outputs to the thalamus. This increased inhibition by the basal ganglia output is known to reduce firing rate of thalamic neurons that relay motor signals to the motor cortex. This 'rate model' suggests that the reduced excitability of thalamic neurons is the key for inducing motor abnormalities in PD patients. We reveal that in response to inhibition, thalamic neurons generate rebound firing at the end of inhibition. This rebound firing increases motor cortical activity and induces muscular responses that triggers Parkinsonian motor dysfunction. Genetic and optogenetic intervention of the rebound firing prevent motor dysfunction in a mouse model of PD. Our results suggest that inhibitory synaptic mechanism mediates motor dysfunction by generating rebound excitability in the thalamocortical pathway.

Keywords: Parkinson's disease, thalamus, basal ganglia, rebound firing, T-type Ca²⁺ channels

The brain generates motor signals to organize a spectrum of behavior, ranging from simple to complex. In 1950s, Eccles and colleagues established a simple motor circuit model in the spinal cord: principal motor neurons transmit motor signals that trigger muscle contractions by releasing the excitatory neurotransmitter, acetylcholine, whereas local interneurons inhibit this excitatory mechanism by releasing γ -aminobutyric acids (GABA). In higher motor circuits in the brain, some GABA-producing neurons play predominant roles in the control of motor behavior, suggesting that relevant motor information can also be relayed via inhibitory synaptic mechanisms.

The basal ganglia - that play a critical role in action selection, patterning and coordination - consist predominantly (96%) of inhibitory neurons and produce mainly inhibitory outputs. The activity of these inhibitory neurons is modulated by dopamine; in dopamine-deficient states, their inhibitory input to target areas is increased and may contribute to motor dysfunction in Parkinson's disease (PD) and L-DOPA-responsive dystonia. Given that patients with dopamine deficiency show multiple motor abnormalities - such as akinesia, rigidity, tremor, and gait abnormalities - the inhibitory input provides by the basal ganglia conveys diverse motor information.

Pioneering studies have suggested how enhanced inhibitory synaptic transmission from the basal ganglia exerts pathological effects. According to the rate model, inhibitory input decreases overall firing rate in target neurons, thereby interfering with their motor functions Albin et al., 1989; DeLong, 1990;). In a second model, inhibited neurons generate low-threshold burst firing, that depend on the activation of T-type Ca^{2+} channels and exert a strong post-synaptic impact. A third model posits that rhythmic inhibition induces oscillations, that synchronizes target neurons at specific frequencies and may result in abnormal processing of motor information. However, because PD patients show phenomena consistent with all three of these hypotheses, it has been challenging to uncover the key mechanism involved. The lack of a robust mouse model that precisely mimics the physiological and behavioral consequences of dopamine deficiency has limited analysis of the circuit-based functions of diverse basal ganglia outputs.

Here we used optogenetic approach to control the activity of specific inhibitory inputs (GPM, globus pallidus medial) to the ventro lateral thalamus (VL) and examined the effects of such manipulation in wild-type (WT) mice and in a mouse model of dopamine deficiency. Through this approach, we found that in the VL thalamus, T-type Ca^{2+} currents (I_T) are involved in neither the generation of low-threshold burst firing nor inhibition-induced oscillations. We instead propose that T-type Ca^{2+} channels induce rebound firing that induces PD-like motor abnormalities, such as akinesia, rigidity, and tremor, the severity of which is proportional to the number of neurons with rebound firing. In CaV3.1-KO mice lacking I_T , rebound firing is reduced and fails to induce motor responses (Fig. 1). In a mouse model of PD, reduction of rebound excitability of thalamic neurons by genetic and optogenetic means abolishes motor abnormalities.

What is the physiological role of rebound firing of VL neurons? Considering that the VL area has a somatotopic relationship with the cortex, the production of rebound firing in many VL neurons may, in turn, increase muscle tone in many body parts simultaneously. Maintenance of muscle tension against gravity is critical during resting postures. It is interesting to note that PD patients also show non-specific recruitment of muscles that may lead to whole-body rigidity and tremors, especially during the resting state. In conjunction with our results indicating a postulated role for coincident rebound firing in body stabilization, this may indicate that abnormal potentiation of rebound firing may produce PD condition by causing abnormal recruitment of muscles.

Finally, our study sheds light on how to cure PD. First, reducing the inhibitory synaptic inputs to the thalamus could reduce rebound excitation. Second, direct reduction of rebound firing of VL neurons by blockade of CaV3.1 may also relieve motor symptoms. Revealing the precise molecular mechanisms underlying the inhibition-induced rebound excitability may provide clues to novel therapeutic targets, particularly for neurological disorders associated with enhanced inhibition.

Fig. 1 Excitatory motor signals in the thalamus generate multiple PD-like motor symptoms. In low dopamine condition, enhanced basal ganglia inputs to the thalamus generate rebound firing (rebound excitation) in many thalamic neurons. Suppression of rebound firing by CaV3.1 KO or direct inhibition of thalamic activity rescue PD-like motor problems.

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