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Research Article

Levodopa-Induced Dyskinesia: Striatal Activity in Parkinsonism pathophysiological Mechanisms

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Abstract

Levodopa-induced dyskinesia is one of the most difficult problems facing patients with Parkinson's disease. With more treatment options available for Parkinson's disease, physicians need to understand the pathogenetic mechanisms underlying levodopa-induced dyskinesia. Better understanding of the pharmacological actions of dopaminergic drugs in the basal ganglia will lead to better management of patients with levodopa-induced dyskinesia.

The therapeutic and preventative strategies for LID include using a lower dosage of levodopa, employing dopamine agonists as initial therapy in Parkinson's disease, amantadine, atypical neuroleptics, and neurosurgery. LID can adversely affect the quality of life and increase the cost of healthcare.

Keywords

Striatum, Basal ganglia, Parkinson'sdisease, Dopamine, Levodopa, Dyskinesia, Electrophysiology, Optogenetics.

Introduction

Levodopa is the most effective drug for treating Parkinson's disease (PD), but its long-term use is complicated by motor fluctuations and dyskinesia.Dyskinesia may be mild at the beginning but may progress to become a disabling symptom and may interfere with quality of life. Different types of movement disorders are seen in levodopa-induced dyskinesia (LID) including chorea, ballism, dystonia, myoclonus, or combination of any of these movements. These dyskinesias are seen in the neck, facial muscles, jaw, tongue, hip, shoulder, trunk, and limb or may appear as involuntary flexion of toes.

The average firing rate of medium spiny neurons increased as axial dyskinesias developed, and both medium spiny neurons and fast spiking interneurons were modulated around axial dyskinesias. We also found that delta field potential power increased in the striatum with dyskinesia, and that this increased delta power coupled with striatal neurons.

Secondly, we studied the role of the two main types of dopamine receptors. We pharmacologically inhibited either the D1 or D2 receptors while recording from neuronal ensembles in the striatum and measuring LIDs in high temporal resolution. We found that inhibiting the D1, but not the D2, receptor led to a decrease in axial dyskinesias.

Action selection relies on the coordinated activity of striatal direct and indirect pathway medium spiny neurons (dMSNs and iMSNs, respectively). Loss of dopamine in Parkinson's disease is thought to disrupt this balance. While dopamine replacement with levodopa may restore normal function, the development of involuntary movements (levodopa-induced dyskinesia [LID]) limits therapy. How chronic dopamine loss and replacement with levodopa modulate the firing of identified MSNs in behaving animals is unknown. Using optogenetically labeled striatal single-unit recordings, we assess circuit dysfunction in Parkinsonism and LID. Counter to current models, we found that following dopamine depletion, iMSN firing was elevated only during periods of immobility, while dMSN firing was dramatically and persistently reduced.

Most notably, we identified a subpopulation of dMSNs with abnormally high levodopa-evoked firing rates, which correlated specifically with dyskinesia. These findings provide key insights into the circuit mechanisms underlying Parkinsonism and LID, with implications for developing targeted therapies.

Pathophysiology Of Lid

Despite significant advances, the pathogenesis of LID remains incompletely understood. It is known that dyskinesias appear only after dopaminergic therapy and there is a time lag between the start of treatment and the emergence of LID.

Several possible mechanisms, both peripheral and central, have been proposed. They include reduced buffering capacity of the remaining intact neurons, dietary proteins, role of D3 receptors, and the role of glutamate receptors. While dietary proteins and gastric absorption have some relevance in producing fluctuations and "wearing off" associated with chronic levodopa therapy, central mechanisms are of greater importance for the genesis of LID.

It is suggested that pulsatile (as opposed to a continuous, physiological) stimulation of the postsynaptic receptors due to intermittent administration of levodopa leads to downstream changes in proteins and genes, causing alterations in striatal output in a way that promotes dyskinesias. Disinhibition of the primary and associated motor cortex secondary to increased outflow (pallidothalamocortical motor pathway) may account for LID.

Results

The standard model also predicts that dopamine loss, as occurs in PD, causes opposing changes in the activity of MSNs: persistently reduced dMSN and increased iMSN firing rates. Indirect support for this model derives from recordings in downstream basal ganglia nuclei in patients and parkinsonian primates.

However, direct evidence for bidirectional regulation of striatal MSN firing by dopamine in awake, behaving parkinsonian animals is lacking.

As a corollary of this model, dopamine replacement with levodopa is postulated to improve motor symptoms by rebalancing striatal dMSN and iMSN activity. In addition, the prevailing hypothesis is that long-term levodopa treatment causes excessive direct pathway activity.

Dopamine Receptor-Specific Agonists Mimic the Effects of Levodopa

While these results point toward bidirectional dysregulation of dMSNs and iMSNs as an underlying feature of LID, levodopa-evoked dopamine release may directly or indirectly influence dMSN and iMSN firing through the activation of D_1-like (D1R) and D_2-like (D2R) dopamine receptors located on several microcircuit elements (Gerfen and Surmeier, 2011). We sought to assess how selective activation of D1R or D2R compared to combined activation with levodopa. Remarkably, we found that the administration of the selective D1R agonist SKF-81297 (SKF) also produced bidirectional regulation of striatal neurons, much like levodopa (On MSN: 0.10 ± 0.05 Hz [Park] versus 2.20 ± 0.39 Hz [SKF], n = 23, N = 5, $p < 0.0001$, Wilcoxon; Off MSN: 0.93 ± 0.33 Hz [Park] versus 0.19 ± 0.08 Hz [SKF], n = 9, N = 5, $p = 0.004$, Wilcoxon), while evoking robust dyskinesia and contralesional rotations A–S2E). Administration of the selective D2R agonist quinpirole (Quin) also produced bidirectional regulation of striatal neurons, albeit with more modest firing rate changes in activated neurons (On MSN: 0.18 ± 0.05 Hz [Park] versus 0.76 ± 0.10 Hz [Quin], n = 19, N = 6, $p < 0.0001$, Wilcoxon; Off MSN: 1.22 ± 0.39 Hz [Park] versus 0.18 ± 0.05 Hz [Quin], n = 12, N = 6, $p < 0.0001$, Wilcoxon), while evoking contralesional rotations and more modest dyskinesia F–S2J). highlighting the effects of dopamine receptor activation on striatal microcircuitry through both direct regulation of MSNs and indirect modulation of synaptic (local inhibitory and/or extrastriatal excitatory) inputs.

Experimental Model and Subject Details

Animals

Hemizygous BAC transgenic mice expressing Cre recombinase under the control of the Drd1a (D1-Cre, GENSAT BAC transgenic EY217) or Adora2a (A2a-Cre, GENSAT BAC transgenic KG139) regulatory elements were used to restrict expression of Cre-dependent constructs to direct and indirect pathway striatal neurons, respectively. All mice were on a C57BL/6 background and housed under a 12-h light/dark cycle with food and water *ad libitum*. Male and female mice were used.

Pharmacology

Levodopa (Sigma Aldrich), in combination with benserazide (Sigma Aldrich), was dissolved in normal saline and administered daily (5 days per week) by i.p. injection. A dose of 2.5-5.0 mg/kg of levodopa (plus 1.25-2.5 mg/kg benzeraside) typically elicited dyskinetic movements and contralesional rotations. Lower doses of levodopa (0.5-2.5 mg/kg) were administered in some sessions to elicit therapeutic behavioral responses (defined as increased contralateral rotations) without dyskinesia (sub-dyskinetic dose; The D1R-selective agonist SKF-81297 or the D2R-selective agonist Quinipriole.

In Vivo Electrophysiology

During each recording session, the animal was placed in the open-field while tethered via a lightweight, multiplexed headstage cable (Triangle Biosystems) attached to a low-torque electrical commutator (Dragonfly) to allow free movement. The animal's gross behavior was recorded by video tracking software (Noldus Ethovision). Fine behavior was manually scored by the experimenter (AIM score). Behavioral measurements were synchronized with simultaneous electrophysiological recordings via TTL pulses triggered by the video tracking software and recorded by the electrophysiology system (MAP system, Plexon). Animals were habituated to tethering and i.p. injections (saline) prior to pharmacological experiments.

In parkinsonian animals, a typical recording session consisted of a 30 minute baseline period during which animals displayed ipsilesional biased rotations, followed by i.p. injection of levodopa.

Contralesional rotations and levodopa-induced dyskinesia (LID) typically began within 10 minutes of injection, lasted between 30-120 minutes and terminated spontaneously.

Discussion

In routine clinical practice, attempts should be made to prevent LID. This is possible, particularly in younger and biologically fit older patients by using dopamine receptor agonists as initial monotherapy to control symptoms of Parkinson's disease. This strategy may work for a long time in some patients. However, a proportion of patients do not tolerate dopamine agonists and the majority of patients eventually need levodopa for symptom control. Levodopa should not be withheld in patients with late- onset Parkinson's disease with significant symptoms, as the risk of LID is substantially low in these patients.

Conclusion

Dyskinesias, such as those seen in levodopa-treated patients with Parkinson's disease, represent the abnormal release of fragments of movements that quite often resemble or are within the normal motor repertoire. It is therefore interesting and conceptually appealing to think that prefrontal areas that are normally involved in the initiation of voluntary actions could also participate in LIDs.

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