Parkinson’s Disease (PD) is characterized by some typical dopamine-dependent motor symptoms:

- Slow movements (bradykinesia)
- Too little movement (hypoakinesia)
- Rigidity
- Resting tremor

Dopamine depletion impairs the processing of motor information in cortico-basal ganglia networks:

- Degeneration of dopamine (DA) neurons in the substantia nigra
- Caudate nucleus
- Putamen
- Striatum
- Nigra

The basal ganglia:

- Cerebral cortex glutamatergic synapses
- Striatum GABAergic synapses
- Globus pallidus (GP)
- The internal segment of the GP (GPI) sends out signals to the rest of the brain (via the thalamus and the brainstem)
Mechanisms of L-DOPA-induced dyskinesia in Parkinson’s Disease
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Dopamine replacement therapy for Parkinson’s disease

- L-DOPA (L-3,4-dihydroxyphenylalanine)
  - The precursor of dopamine (DA)
  - Crosses the blood-brain barrier
  - Administered as oral tablets 3-8 times a day
  - Converted to DA by Aromatic Amino acid Decarboxylase (AADC)
  - DA can be stored in vesicles by neurons expressing Vesicular Monoamine Transporter 2 (VMAT2)
  - Nigrostriatal nerve terminals are the main source of both AADC and VMAT2 in an intact striatum

L-DOPA is the most effective drug for PD, although it produces complications

L-DOPA-induced dyskinesias in Parkinson’s disease

- Peak-dose dyskinesia
  - Mainly choreiform movements of the upper part of the body
  - Occur 1-4 hours after the administration of L-DOPA
  - Usually non-disabling

- Complex dyskinesias
  - Complex relationship with the timing of L-DOPA administration
  - Complex movements, often including dystonic components
  - Usually disabling
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Why does the motor response to L-DOPA change over the time?

- **Postsynaptic hypothesis:**
  - Molecular and structural changes in the postsynaptic neurons alter their response to DA
- **Presynaptic hypothesis:**
  - Degeneration of nigrostriatal DA terminals
  - Loss of presynaptic storage capacity for DA
  - L-DOPA is immediately converted to DA (dyskinesia)
  - DA is rapidly eliminated (wearing-off fluctuations)

- **Postsynaptic hypothesis:**
  - Molecular and structural changes in the postsynaptic neurons alter their response to DA

Pre-synaptic mechanisms of LID investigated in PD patients

L-DOPA-induced DA release in the striatum as studied with positron emission tomography (PET) using the tracer [11C]-raclopride, which binds to D2 receptors.

- PET scans show [11C]-raclopride binding in the striatum (white).
- PD patient at baseline.
- One hour after L-DOPA tablet.
- Peak DA release ("change in RAC BP") is larger in dyskinetic patients compared with PD patients with a stable motor response to L-DOPA ("stable group").

Pre- and post-synaptic mechanisms of LID investigated in animal models of PD

- 6-hydroxodopamine (6-OHDA) is injected in the nigrostriatal fiber pathway to remove the striatal dopaminergic innervation.
- The lesion is most often performed on one side of the brain only (unilateral).
- The animal develops bradykinesia and hypokinesia on the contralateral side of the body.

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Rats with unilateral 6-OHDA lesions develop LID on the contralateral side of the body

Daily treatment with L-DOPA (6-10 mg/kg) for 2-3 weeks produces abnormal involuntary movements (AIMs) of axial, limb, and orolingual muscles

Not all animals develop AIMs when treated with the above L-DOPA regimen. We can thus compare dyskinetic and non-dyskinetic rats having the same PD-like lesion.

L-DOPA induces larger peak levels of dopamine in the striatum in dyskinetic rats

Striatal dopamine (DA) levels as studied with microdialysis in freely-moving rats

Extracellular DA levels

L-DOPA induces larger peak levels of dopamine in the striatum in dyskinetic rats.

In 6-OHDA lesioned rats, serotonin neurons are the main source of L-DOPA-induced DA release

Serotonin neurons play a causal role in LID in the rat

LID is blocked by serotonin lesions

LID aggravated by serotonin neuron grafts

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Low doses of 5-HT1a and 1b serotonin receptor agonists blunt L-DOPA-induced DA efflux

When coadministered with L-DOPA, 5-HT1A and 5-HT1B receptor agonists blunt peak extracellular levels of DA and improve dyskinesia.

Lindgren et al., 2010, J Neurochem. 112: 1465-76

When coadministered with L-DOPA, 5-HT1A and 5-HT1B receptor agonists blunt peak extracellular levels of DA and improve dyskinesia.

cp: CP94253, 5-HT1B agonist

Modified from Carta et al., 2007, Brain 130: 1819-33
dpat: 8-OH-DPAT, 5-HT1A agonist

The density of serotonin axon terminals in the striatum correlates positively with LID severity
Levels of radioligand binding to the serotonin transporter (SERT) as a index of 5-HT innervation density

PET imaging data from PD patients support a role for serotonin neurons as a source of DA release in LID
PET study using both [11C]-raclopride to assess DA release and [11C]-DASB (which binds to the SERT) to assess serotonin innervation density

Buspirone, a compound with 5-HT1a agonistic activity, blunt peak DA release in human LID

Levels of [11C]-DASB binding correlated with dyskinesia severity (AIM scores) in PD patients with mild-moderate (MM)LID

PET study using both [11C]-raclopride to assess DA release and [11C]-DASB (which binds to the SERT) to assess serotonin innervation density

Levels of [11C]-DASB binding correlated with dyskinesia severity (AIM scores) in PD patients with mild-moderate (MM)LID
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Presynaptic mechanisms, interim summary

- Nigrostriatal dopamine (DA) denervation causes:
  - Dysregulation of DA release/DA re-uptake in the striatum
  - L-DOPA is handled by cells other than dopaminergic neurons
  - DA release from serotonin neurons is causally linked with LID
- Serotonin innervation density in the striatum
  - A susceptibility factor for peak-dose LID

But these presynaptic factors are just one side of the coin, as dopamine receptor agonists can induce dyskinesias too!

Post-synaptic mechanisms of LID: zooming in on striatal neurons

Dopamine denervation causes profound molecular and structural changes in the cells of the striatum

SPNs have spiny dendrites, on which DA and glutamate inputs interact

High expression of certain genes in SPN in regions related to the AIM subtypes induced by L-DOPA

*Δ*FosB colocalizes with PDyn mRNA

Dyskinetic rat, lateral striatum

Andersson et al., 1999, Neurobiol. Dis. 6: 461-474
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The upregulation of ∆FosB and related genes is caused by high levels of ERK1/2-mediated signaling

- Transiently activated
  - ERK1/2: Extracellular signal-regulated kinases 1 and 2
  - Phosphorylates many targets in the cell membrane, in the cytosol, in the nucleus, e.g.
  - MSK-1: a histone kinase, involved in chromatin remodelling

- Persistently upregulated
  - ∆FosB: stable transcription factor of the AP1-family
  - Regulates other genes, e.g.: PDyn: Prodynorphin, opiod neurotransmitter in the direct pathway

Andersson et al., 1999, Neurobiol Dis. 6: 461-474
Westin et al., 2007, Biol. Psychiatry, 62: 800-810
Rylander et al., 2009, JPET 330: 227-235

Transiently activated ERK1/2 phosphorylates many targets in the cell membrane, in the cytosol, and in the nucleus, e.g., MSK-1, a histone kinase involved in chromatin remodeling.

Persistently upregulated ∆FosB, a stable transcription factor of the AP1-family, regulates other genes, e.g., PDyn, a prodynorphin opiod neurotransmitter in the direct pathway.

The upregulation of pERK1/2 and ∆FosB by L-DOPA is mediated by the D1 dopamine receptor

Genetic inactivation of dopamine D1 but not D2 receptors inhibits L-DOPA-induced dyskinesia and histone activation.

- Genetic inactivation of D1 prevents both LID and the upregulation of pERK1/2 and DFosB.

Darmopil et al., 2009, Biol. Psychiatry 66: 603-613

Antagonism of metabotropic glutamate receptor type 5 (mGluR5) attenuates ERK1/2 signaling and LID

- Reduced development of dyskinesia and improved motor dexterity during L-DOPA treatment.

Mela et al., 2007, J Neurochem 101: 483-498
Rylander et al., 2009, JPET 330: 227-235

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mGluR5 antagonists produce significant anti-dyskinetic effects also in PD patients

Molecular and structural changes hand-in-hand?

Dendritic atrophy of striatal medium-spiny neurons in post-mortem putamen from PD patients

Spiny projection neurons show loss and gain of spines in PD and LID

- Reduced density of spines following 6-OHDA lesion
- Trend towards return to normal spine densities following chronic L-DOPA treatment
- Increased number of very large (“mushroom”) spines in SPN in dyskinetic rats
- These spines were found to receive several glutamatergic synaptic contacts from the cortex
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Spiny projection neurons show dendritic atrophy and changes in excitability in PD and LID

Post-synaptic mechanisms involved in LID

- Nigrostriatal dopamine (DA) denervation causes:
  - Altered signaling properties of DA receptors
  - Structural and physiological changes of SPN, associated with altered corticostriatal connectivity
- L-DOPA treatment causes:
  - Pulsatile stimulation of supersensitive DA receptors
  - Abnormal activation of intracellular signaling pathways downstream of the D1 receptor in SPN
  - Additional changes in the structure of SPN and their connectivity

Key mechanisms of L-DOPA-induced dyskinesia

- Non-dopaminergic systems affected by DA denervation and DOPA treatment modulate these events

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M. Angela Cenci

Basal Ganglia Pathophysiology Unit, Lund University, Lund, Sweden
Daniella Rylander
Jenny Westin
Alessandra Recchia
Ann-Christin Lindh
Marin Lundblad
Malin Andersson
Mery Pharmaceuticals, Frankfurt, Germany
Wojciech Danysz
Flora Meia
Andrzej Dekundy
Northwestern University, Chicago, IL
D. James Surmeier
Steve Graves
Josh Plotkin

Sahlgrenska Academy, Gothenburg, Sweden
Hanna Iderberg
Hanne Lindgren
Veronica Francardo
Eliabet Ohlin
Kristina Abarca
Queen Square Brain Bank, London, UK
Andrew Lees
Sean O’Sullivan

Merz Pharmaceuticals, Frankfurt, Germany
Hans Nissbrandt
Daniel Andersson

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