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Applied Translational Medicine

Drug-Induced Movement Disorders: Back Translation from the Clinic and Moving Forward from Animal Models

Bruce H. Morimoto, PhD

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Dyskinesia: Movement Disorders

- Dyskinesia
  - Derived from Greek:
    - *Kinesi* refers to motion, movement or action
    - *Dys-* meaning negation
  - Voluntary muscle control is impaired
- Dystonia—chronic muscle contraction
- Akathisia—loss of voluntary muscle control (unable to sit still)
- Parkinsonism—loss of muscle function

History of Drug-Induced Movement Disorders

- Early in the1960s, doctors were prescribing neuroleptic drugs to treat schizophrenia
- Noticed patients experienced small, repetitive and compulsive movements (facial muscles)
- This drug-induced disorder was recognized in 1964 and termed Tardive Dyskinesia

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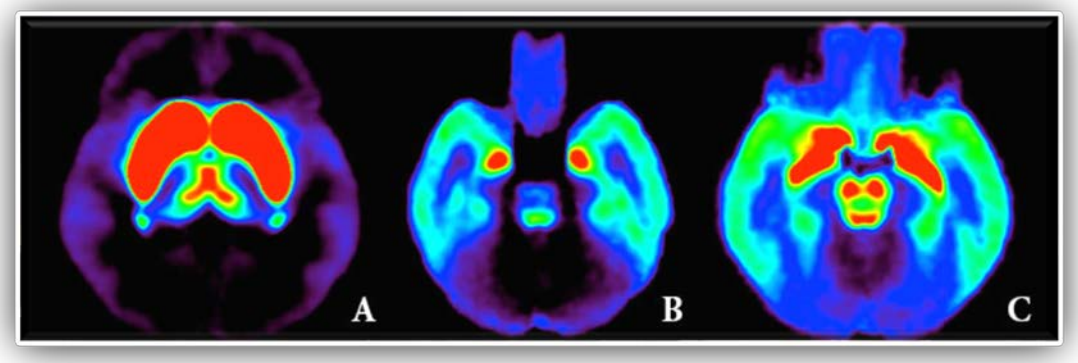
More History…

- Prior to 2000, acid reflux and gastroparesis was treated with Cisapride
  - Classical hERG blocker
  - QT prolongation, TdP
  - Withdrawn from market
- Metoclopramide (developed in mid-1960s) was considered a “safer” alternative to Cisapride
- Tardive dyskinesia emerged as a side-effect of Metoclopramide treatment

Clinical Observations Lead to Common Connection

- Neuroleptics and Metaclopride→ common pharmacology, namely Dopamine
- Correlation of dyskinesia with strength of D2 antagonism



These are 18F-Fallypride PET images of dopamine D2 type receptors, averaged across several normal subjects. There are high levels of these receptors (red color) in deep brain structures and lower levels in the cortex. These include the basal ganglia and thalamus (A), amygdala and temporal cortex (B), and substantia nigra (C). These regions are concerned with movement, emotion and cognition. From: Univ Alabama Birmingham, Prof Robert Kessler, MD

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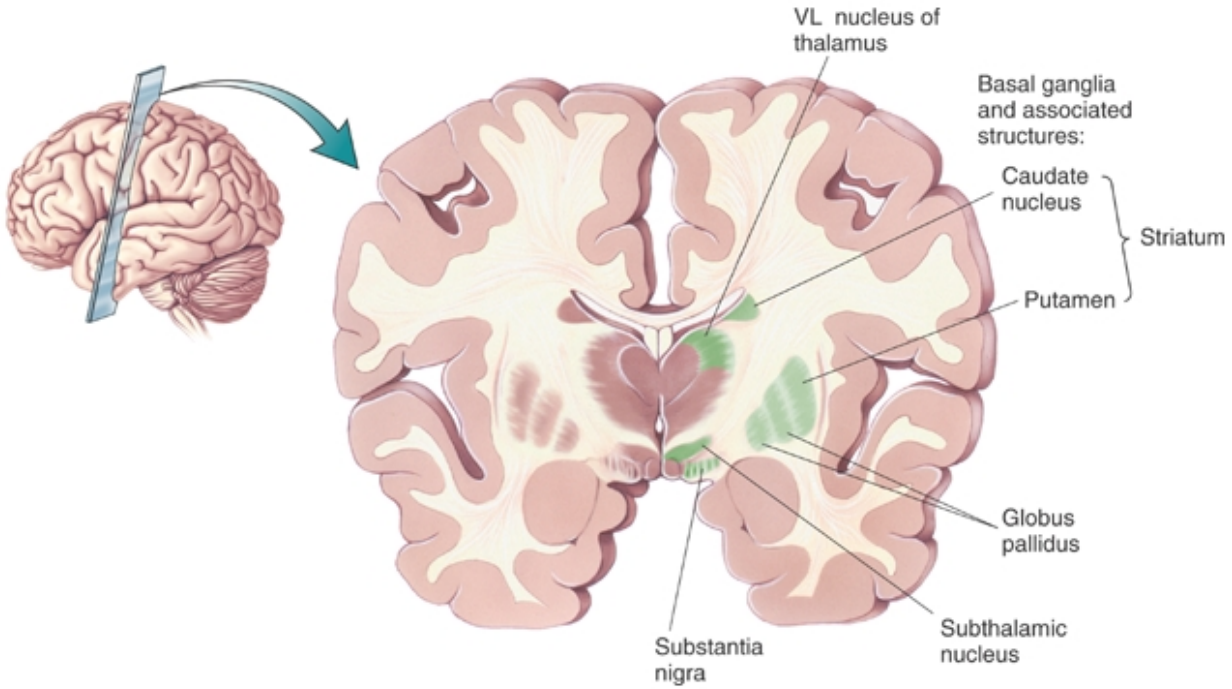
The Basal Ganglia

- Basal Ganglia: Selection and initiation of willed movements



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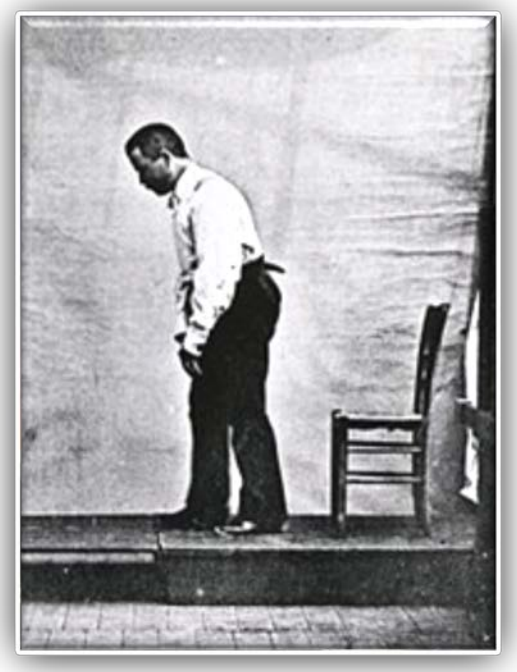
Parkinson Disease (PD): Movement Disorder

- Second most common neurodegenerative disease (after AD)
- 7 million people affected world-wide
- Prevalence increases with age
- Mean age of onset is 60 years but…many cases of early onset is 30 years of age
- Resting tremor, abnormal posture and gait, paralysis and diminished muscle strength—progressive deterioration



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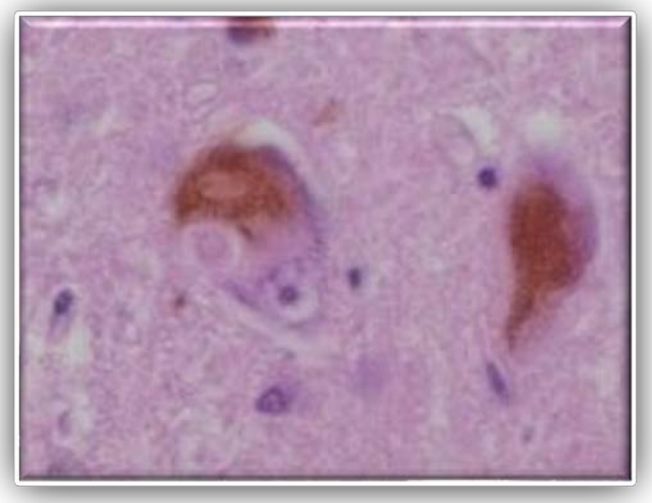
Clinical Manifestations

- Tremor
  - Rest tremor (unlike action tremor when affected limb is being used)
  - Unilateral in hand. Spreads contralaterally as the disease progresses
  - Tremor can be in legs, lips, jaw, tongue, rarely in the head
- Bradykinesia
  - Slowness of movement (major cause of disability)
  - Starts distally…buttoning clothes, tying shoelaces, double clicking mouse
  - In legs, results in dragging or shuffling steps

Cause of Parkinson Disease?

- Frederick Lewy (1912) discovered inclusion pathology in substantia nigra, later called Lewy bodies
- 1950s recognition that a loss of neurons in the substantia nigra (midbrain) and dopamine deficiency in the basal ganglia
- 1997 Alpha-synuclein protein component of Lewy bodies



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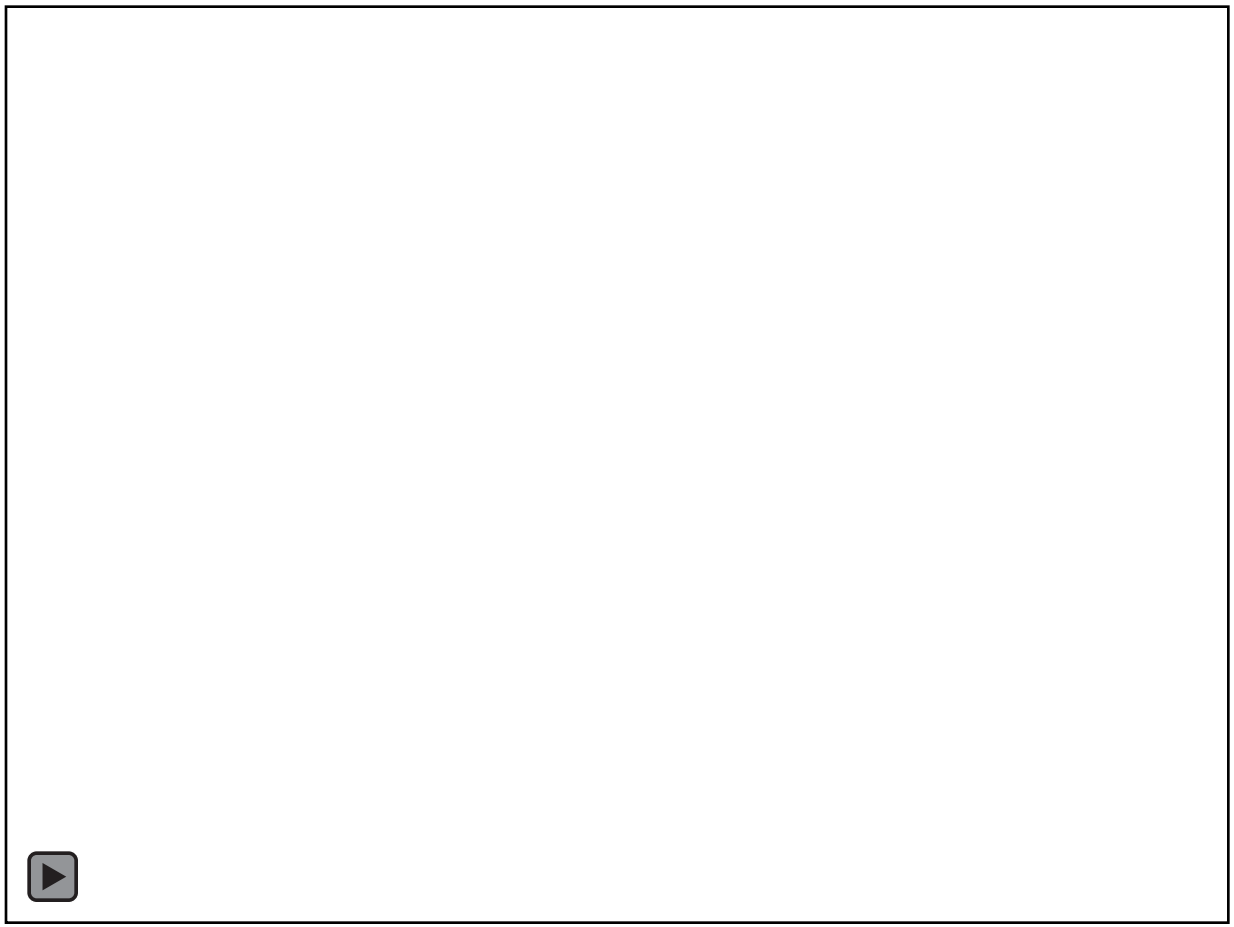
Treatment of Parkinson Disease?

- Cause?
  - Loss of dopamine neurons
  - Decreased dopaminergic transmission
- Treatment?
  - Dopamine “replacement” therapy
    - MAO-B inhibitors (prevent degradation of dopamine)
    - Levodopa (L-DOPA) - dopamine precursor

L-DOPA → dopamine
(DOPA decarboxylase in dopaminergic neurons)

PD Treated with L-DOPA



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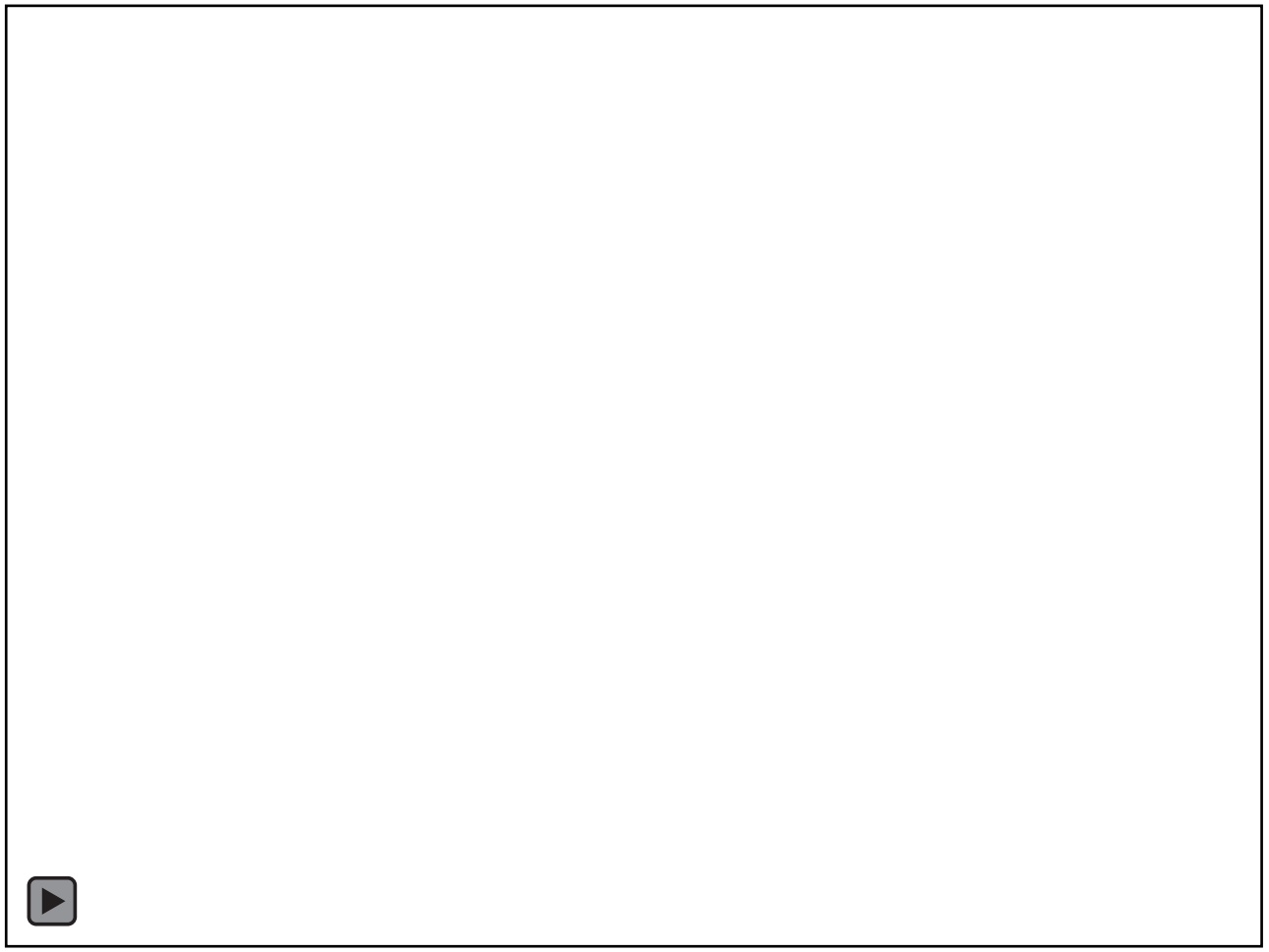
The Dark Side of L-DOPA…Dyskinesia

- Chronic L-DOPA therapy (5-10 yrs) can lead to dyskinesia in more than half of PD patients
- Commonly coincides with peak plasma concentrations L-DOPA
- Mechanism thought to involve alterations in pre- and post-synaptic signal transduction in the nigro-striatal pathway
- Can be as debilitating as PD itself…

Example: L-DOPA-Induced Dyskinesia



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What Have These Clinical Observations Taught Us?

- Blockage of dopamine receptors
  - >70% D2 blockage
  - >80% high risk
    - Note: 80% loss of nigrostriatal dopamine receptors produced clinical Parkinson symptoms
- Subcortical brain regions involved (basal ganglia and thalamus)
- Loss of dopamine neurotransmission leads to motor or extrapyramidal effects

Mechanism: Complex and Not Fully Understood

- Receptor dissociation or off-rate
  - Rapid off-rate correlates with low potential
  - Characteristic of atypical antipsychotics
- May involve other neurotransmitter systems
  - Serotonin 5HT2A blockage enhances dopamine release which may compete/compensate for D2 blockage
  - Ratio of 5HT2A to D2 in basal ganglia predictive for extrapyramidal symptoms

More Potential Mechanisms

- Synaptic remodeling
  - Chronic blockage of pre-synaptic DA receptors enhances EAA neurotransmission
  - May cause neurotoxic stress in striatum which destroys the output neurons
  - Receptor desensitization-internalization
  - Continuous D2 receptor occupancy can result in receptor upregulation and trigger distinct drug-induced neuroadaptation

Prospective Testing: What to Look Out for?

- Receptor screens: Cerep, Eurofins-Panlabs
  - Dopamine receptor interaction
  - D2-receptor antagonism—flag
- General motor deficits: Open-field activity (rodent)
  - Spontaneous locomotor activity
  - Total distance traveled, vertical activity, stereotypy, time spent in central region

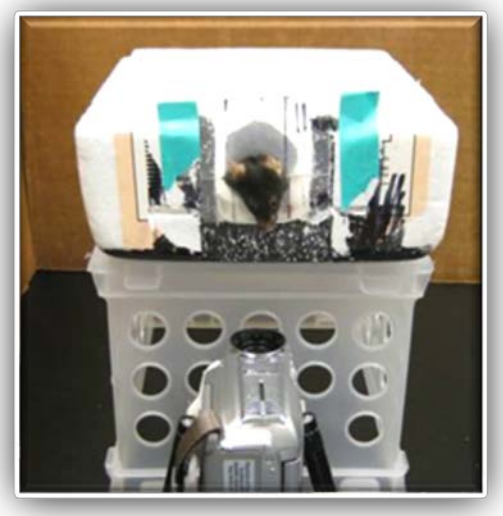
Specialized Testing

- Catalepsy (simple animal test) - failure to correct from imposed posture
  - Measure latency to correct
  - Bar test: hind paws on bench with forepaws on elevated bar

  - Wire grid: 50 degree incline, forelimb spread
- Observation: dose required to induce catalepsy occurs when ~65-70% D2 receptor occupancy

Vacuous Chewing Movements (VCM)

- Quantify orofacial movements (rat, NHP)
- Animals placed in individual cages to visualize mouth
- Count number of VCMs
- Reasonable validation with slow-releasing antipsychotics, but there is a population of animals that do not develop VCMs



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Questions?

bruce.morimoto@celerion.com