Harvard-MIT Division of Health Sciences and Technology
HST.151: Principles of Pharmocology
Instructor: Dr. David Standaert

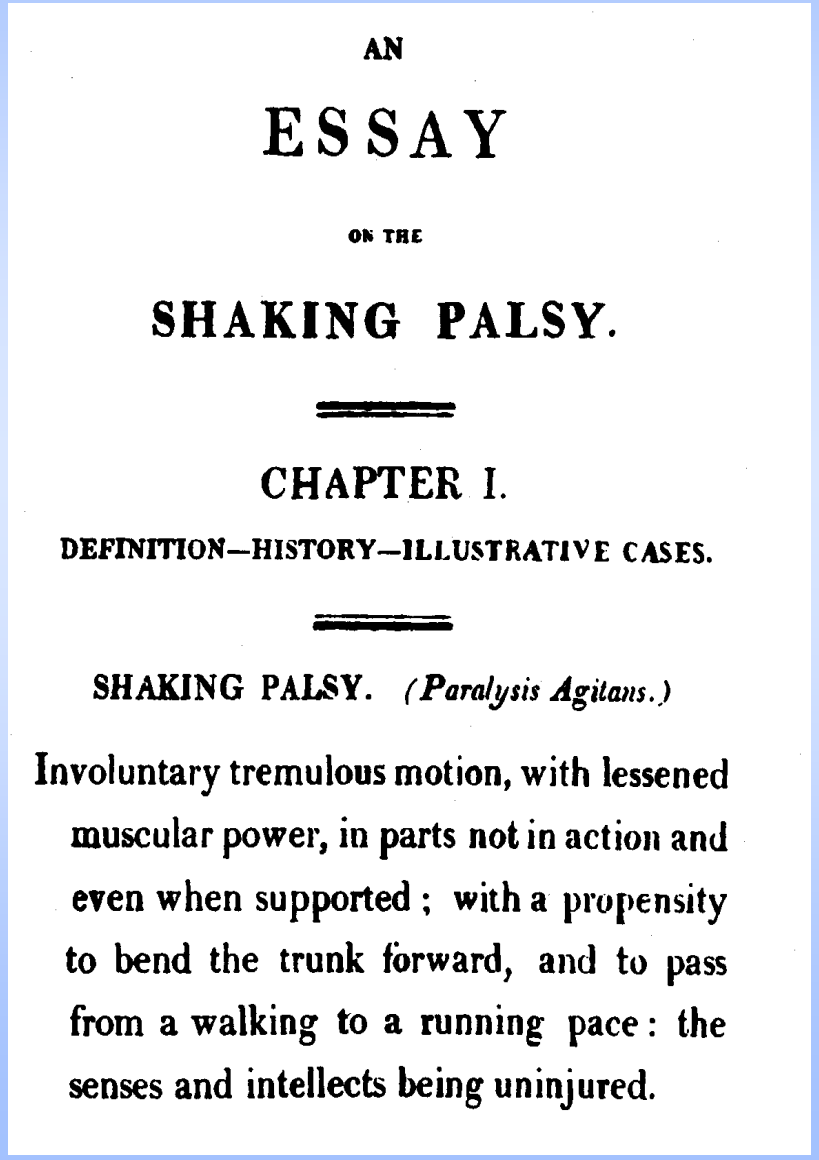
Treatment of Parkinson's Disease and Movement Disorders

David G. Standaert, M.D., Ph.D.
Massachusetts General Hospital
Harvard Medical School

Movement Disorders

- Parkinson's Disease
- Tremor
- Chorea
- Ballism
- Dystonia
- Tic Disorders

Parkinson's disease



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ON THE

SHAKING PALSY.

CHAPTER I.

DEFINITION—HISTORY—ILLUSTRATIVE CASES.

SHAKING PALSY. *(Paralysis Agitans.)*

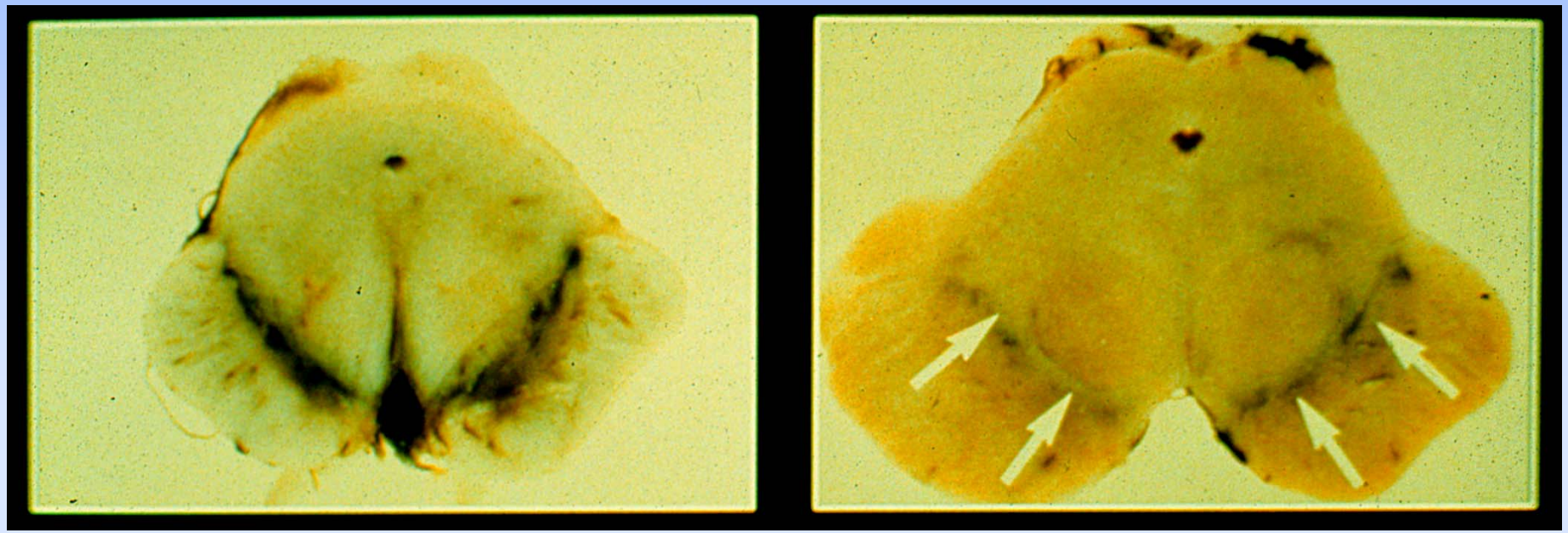
Involuntary tremulous motion, with lessened muscular power, in parts not in action and even when supported; with a propensity to bend the trunk forward, and to pass from a walking to a running pace: the senses and intellects being uninjured.

- Described by James Parkinson, 1817
- Most common disorder of movement
- Affects 3% of the population over the age of 65 years
- About 500,000 patients in the US

“Cardinal Features” of Parkinson’s Disease

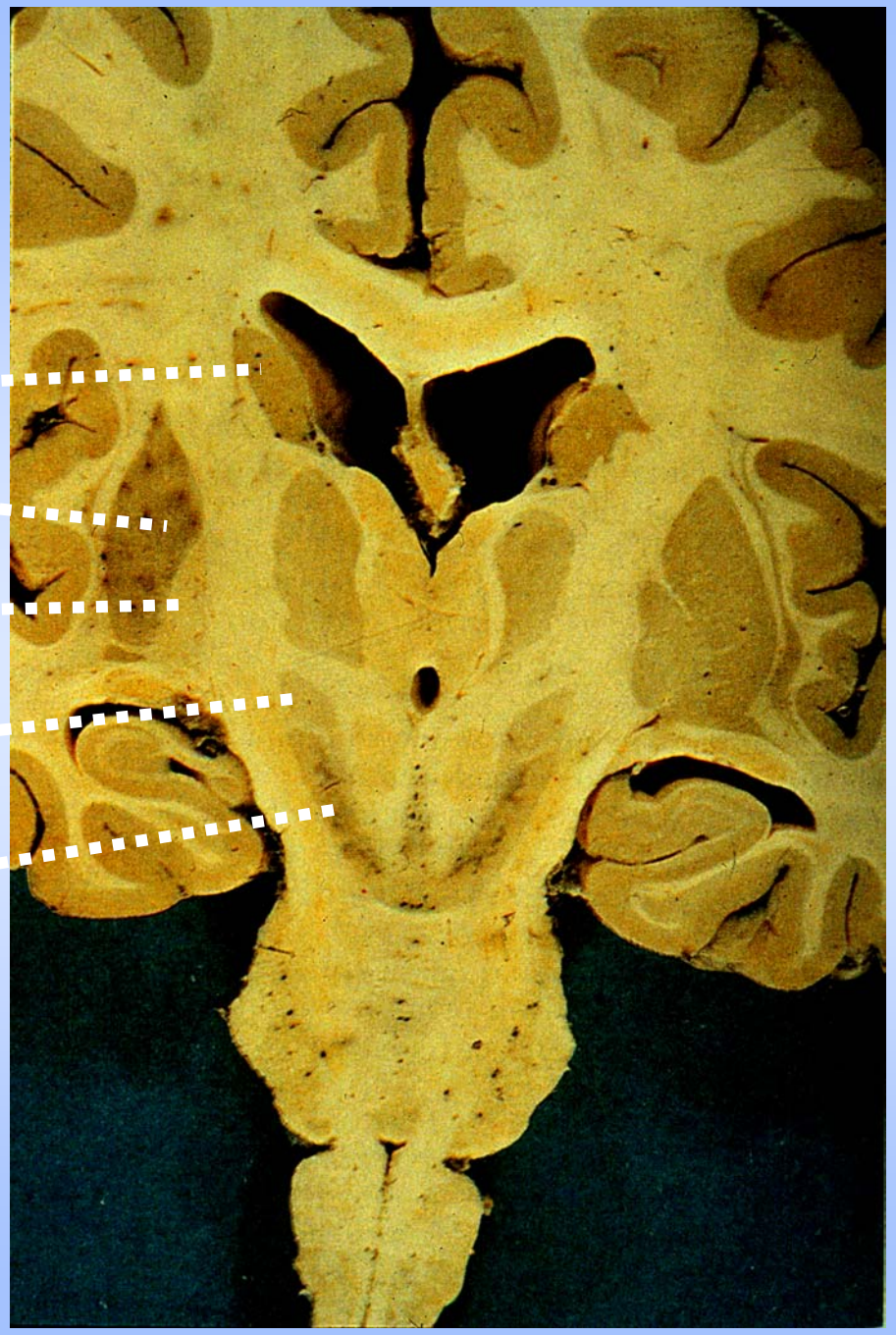
- Tremor
- Rigidity
- Bradykinesia
- Postural Instability

Normal Parkinson's

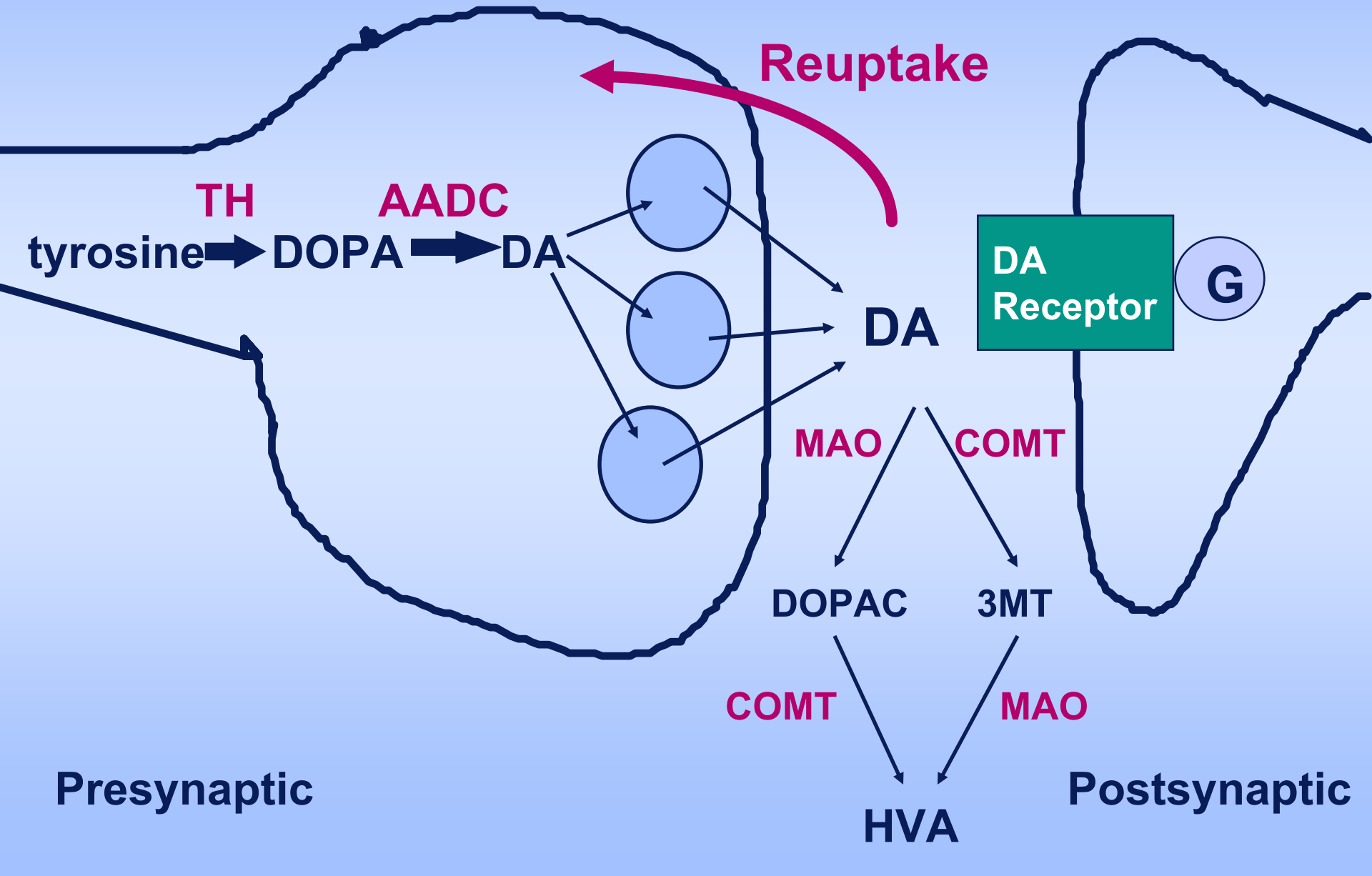


- Loss of dopamine neurons from the *substantia nigra pars compacta*
- Leads to deficiency of dopamine in the caudate and putamen ("striatum").

Human basal ganglia



The Dopaminergic Synapse



Dopamine Receptors

- **Classical Pharmacology:**
  - **D1 - stimulates cAMP formation**
  - **D2 - inhibits cAMP formation**
- **Molecular Pharmacology:**
  - **Family of at least 5 receptor proteins**
  - **All have 7 transmembrane regions, typical of G-protein coupled receptors**
  - **d1 and d2 are abundant in striatum, correspond to classically identified sites**
  - **Others primarily extrastriatal, likely account for many of the side effects of dopaminergic drugs**

Pharmacological Approaches to Treatment of Parkinson's Disease

- **Symptomatic treatments**
  - most are based on dopamine augmentation
- **"Neuroprotective" treatments**
  - none presently proven
  - most current studies are based on "oxidative stress hypothesis"

The "Oxidative Stress" hypothesis

- Proposes that dopamine cell death is caused by the reactive free radicals produced by the catabolism of dopamine
- suggests that treatments which reduce catabolism of dopamine should slow the progress of the disease

Levodopa therapy

- also called L-DOPA, L-dihydroxyphenylalanine
- Works by replacing biosynthetic precursor:

- Usually given with carbidopa, an inhibitor of peripheral AADC - prevents nausea.
- Adverse effects: peripheral, central
- Most important limitation of treatment is the development of “complications of levodopa therapy” - wearing off and dyskinesias

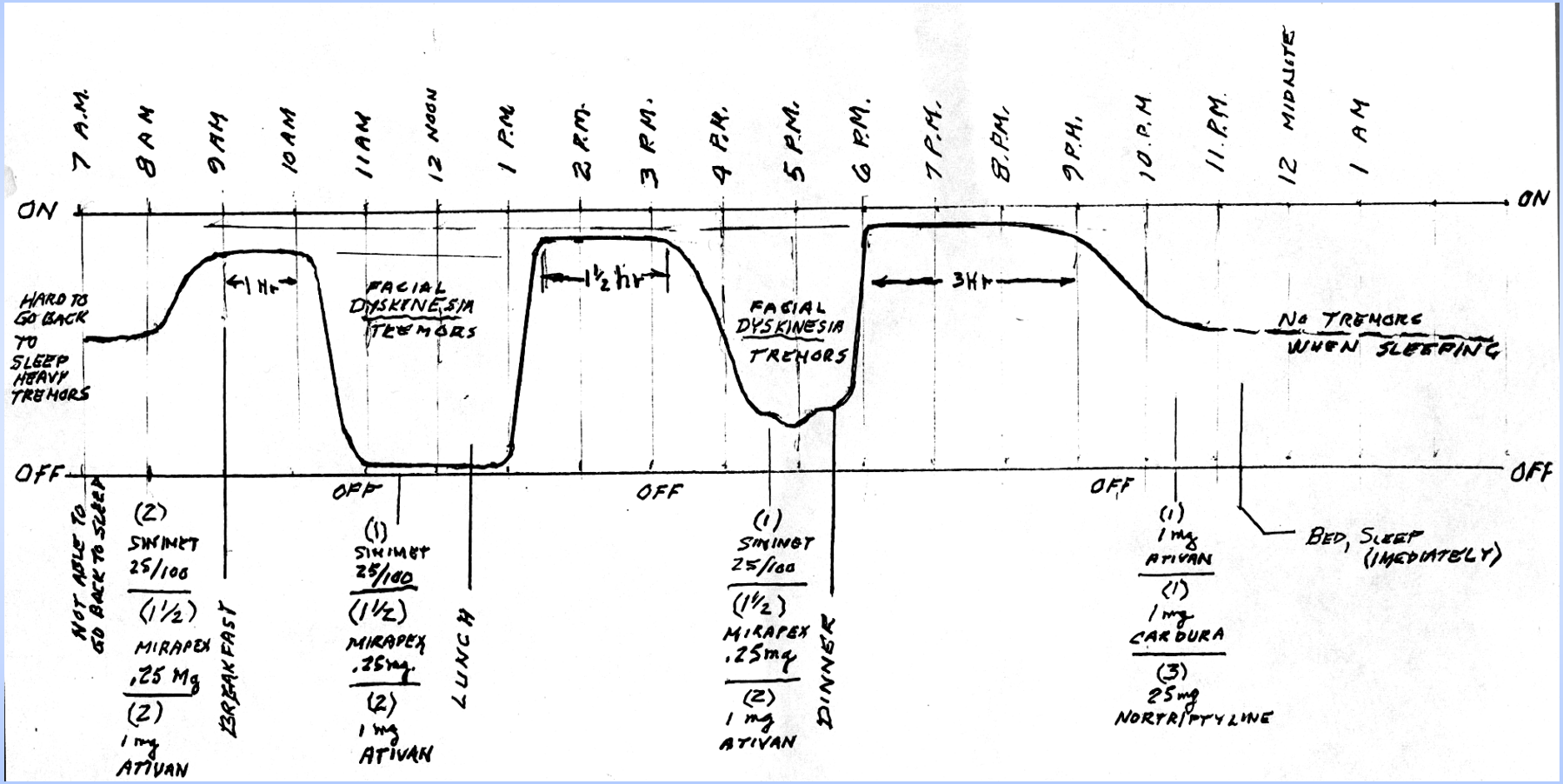
Levodopa Therapy of Parkinson's Disease

- **1950's: Arvid Carlsson discovers that dopamine is a neurotransmitter, reserpine replicates features of Parkinson's**
- **1960: Deficiency of dopamine in postmortem PD described by Enringer and Hornykeiwicz**
- **1961: Effect of levodopa in PD reported by Birkmayer and Hornykeiwicz**
- **1967: Long term treatment of PD with levodopa described by Cotzias et al.**
- **2000: Carlsson, Kandel and Greengard awarded Nobel prize**

Motor complications of levodopa therapy

- **Fluctuations:** variations in mobility related to medication dose and interval.
- **Wearing-off:** loss of efficacy at the end of a dosing interval
- **Dyskinesias:** excessive, involuntary movements

Motor complications - a patient's view



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What causes fluctuations, wearing off, and dyskinesias?

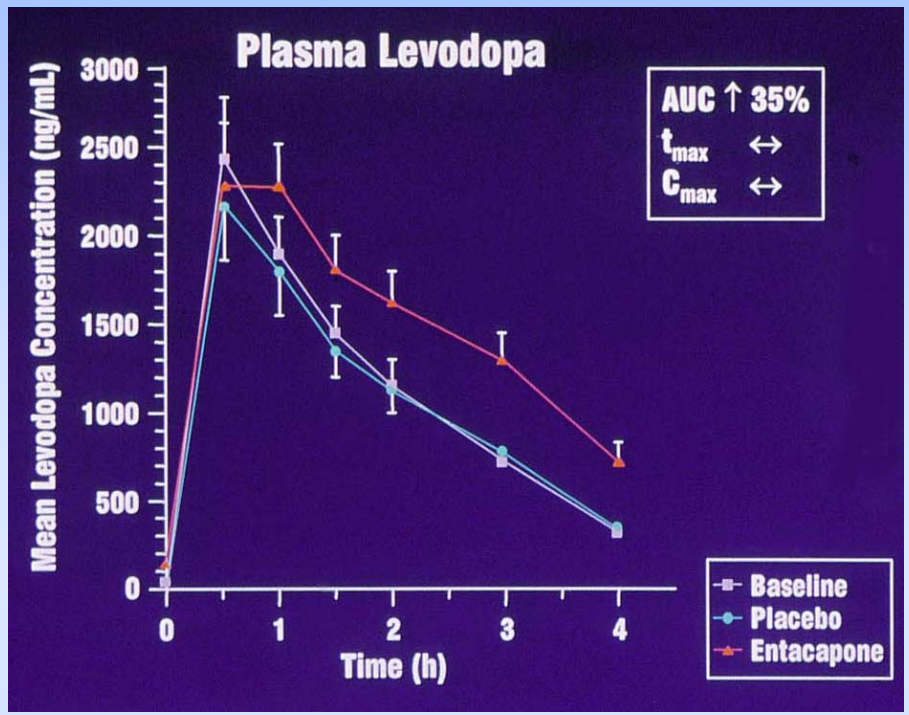
- Not explained by simple DA receptor upregulation
- Loss of “buffering capacity” is an important factor
- Clinical and experimental data suggests that variations in plasma levodopa levels have an important “inductive” effect
- Role of NMDA glutamate receptors

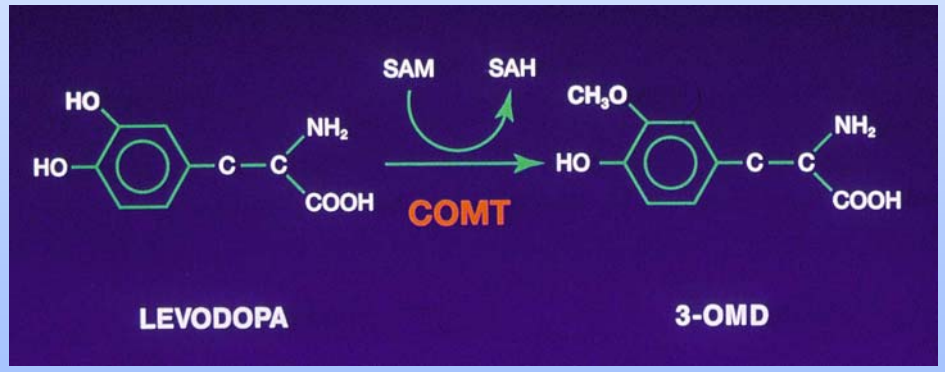
Dopamine Agonists

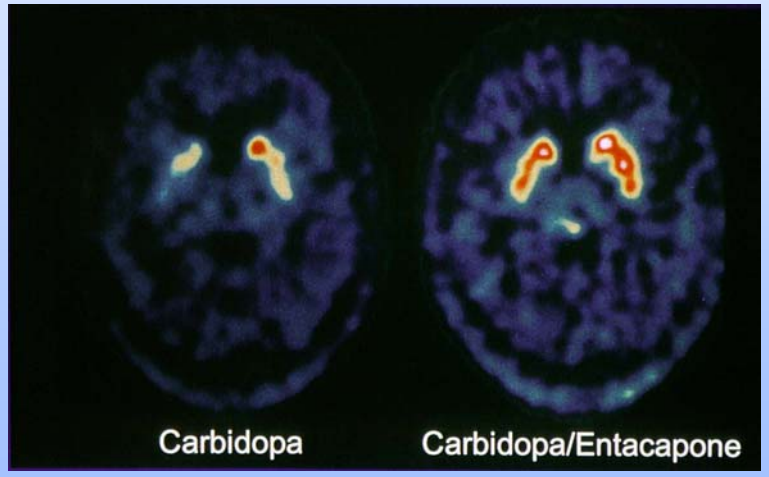
- Act directly at postsynaptic DA receptors
- Longer half life - less wearing off
- Older Agents:
  - bromocriptine - d2 agonist, partial d1 antagonist
  - pergolide - d1 and d2 agonist
- Newer Agents - d2/d3 agonists
  - pramipexole (Mirapex®)
  - ropinirole (Requip®)

COMT Inhibitors

- **Entacapone, tolcapone**
- **Inhibitors of the enzyme *catechol-O-methyl transferase***
- **Slow breakdown of levodopa and dopamine**





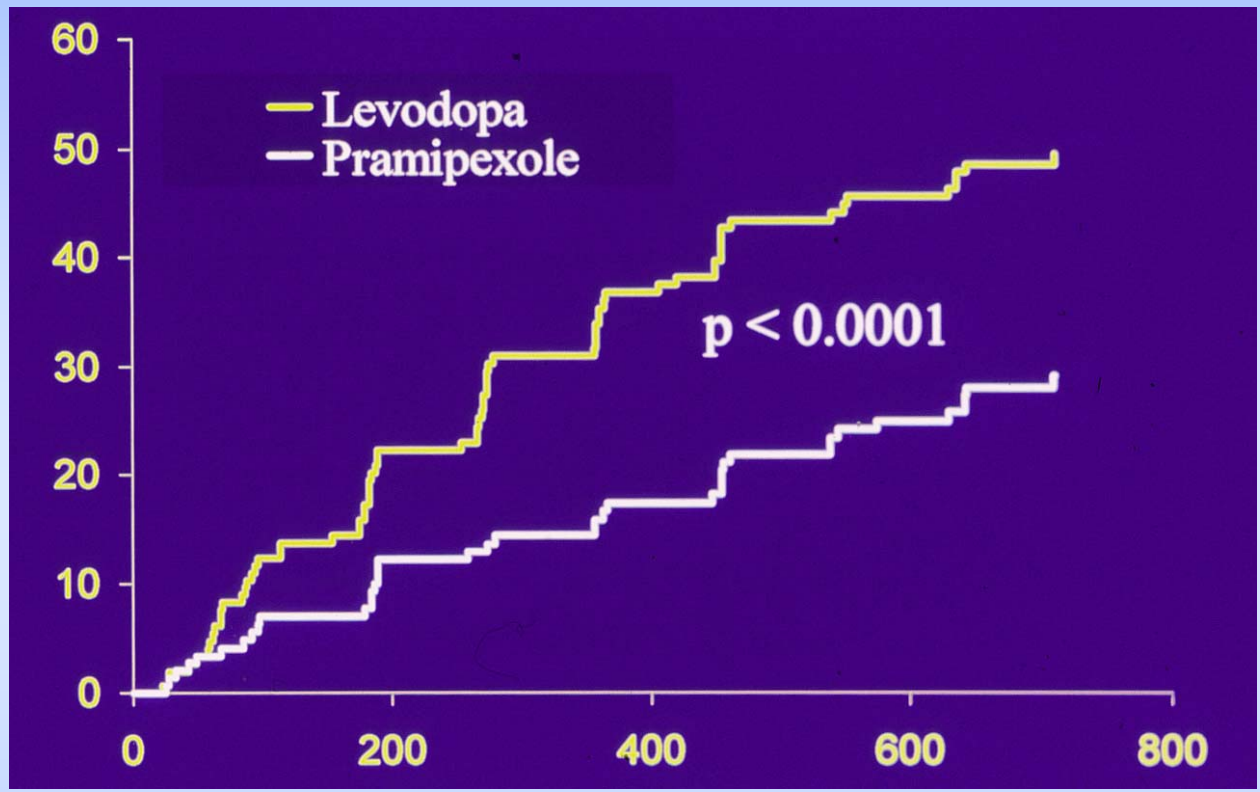


Motor complications of levodopa: prevention?

- Hypothesis: “non-physiologic” replacement of dopamine by oral levodopa underlies the development of motor complications
- Dopamine agonists: a “more physiologic” replacement ?

CALM-PD: Wearing Off or Dyskinesias

- Randomized trial comparing levodopa to pramipexole as initial treatment for PD
- 301 patients, followed for 2 years

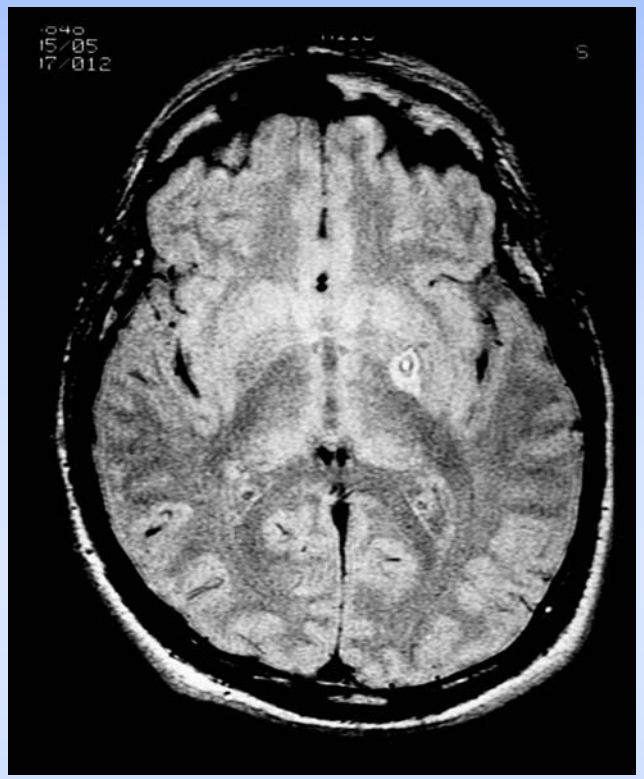


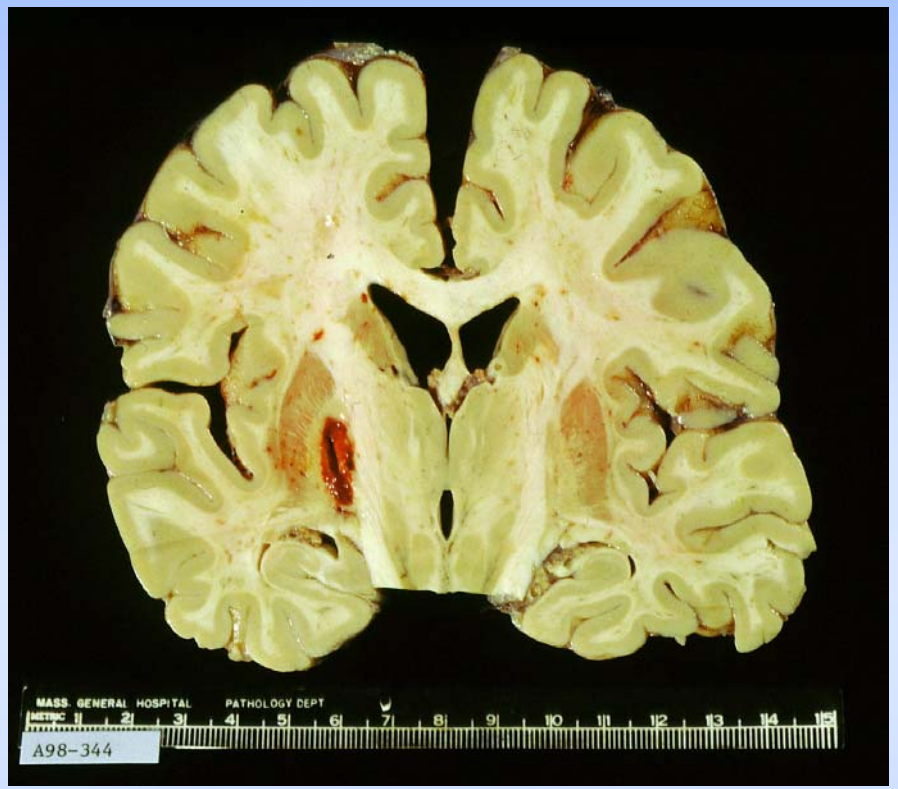
- **Less wearing off and dyskinesias in patients treated with a dopamine agonist instead of levodopa/carbidopa**

Dopamine agonists as initial therapy

- Initial treatment with pramipexole or ropinirole instead of levodopa reduces development of wearing off or dyskinesias.
- But this comes at a price:
  - Increased fatigue and somnolence
  - Increased hallucinations in the elderly
  - ? Reduced efficacy
  - Increased cost

Pallidotomy

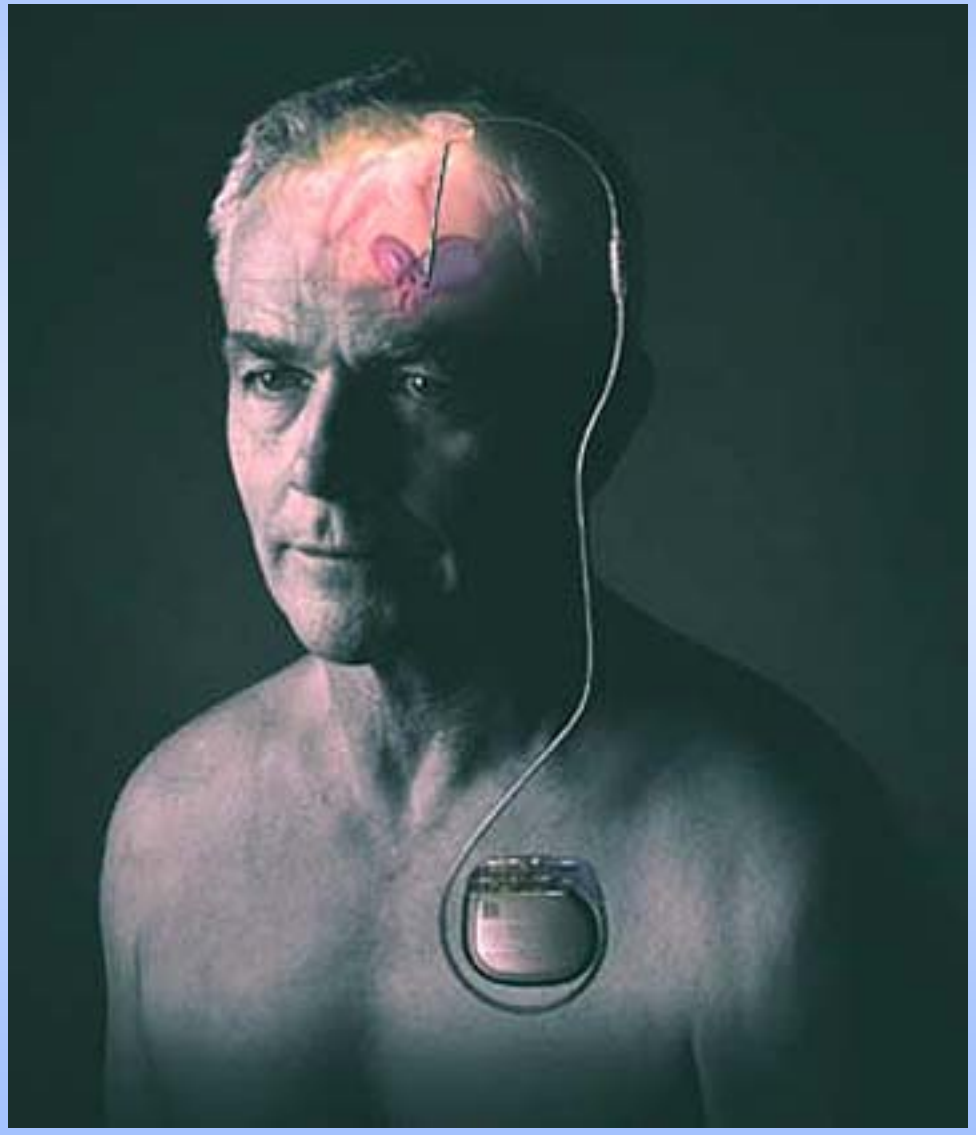




- Surgical lesion of the globus pallidus
- Effect can be long-lasting (>3 years), but underlying disease continues to progress

Deep Brain Stimulation

- Recently FDA-approved
- Implanted into subthalamic nucleus, to control all symptoms of PD
- Require periodic adjustment, battery changes, carry risk of infection, surgical complications



Dopamine receptor antagonists

- Principal application is treatment of psychosis
- Also used as antiemetics
- "Typical" antipsychotics
  - Distinguished by potency at D2 receptors and degree of sedation
  - May cause movement disorders -
    - Akathisia
    - Dystonia
    - Tardive Dyskinesia
    - "Neuroleptic Malignant Syndrome"
- "Atypical" antipsychotics
  - clozapine - d4 antagonist. Effective in refractory psychosis, but causes seizures, neutropenia
  - Resperidone, olanzapine, quetiapine

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