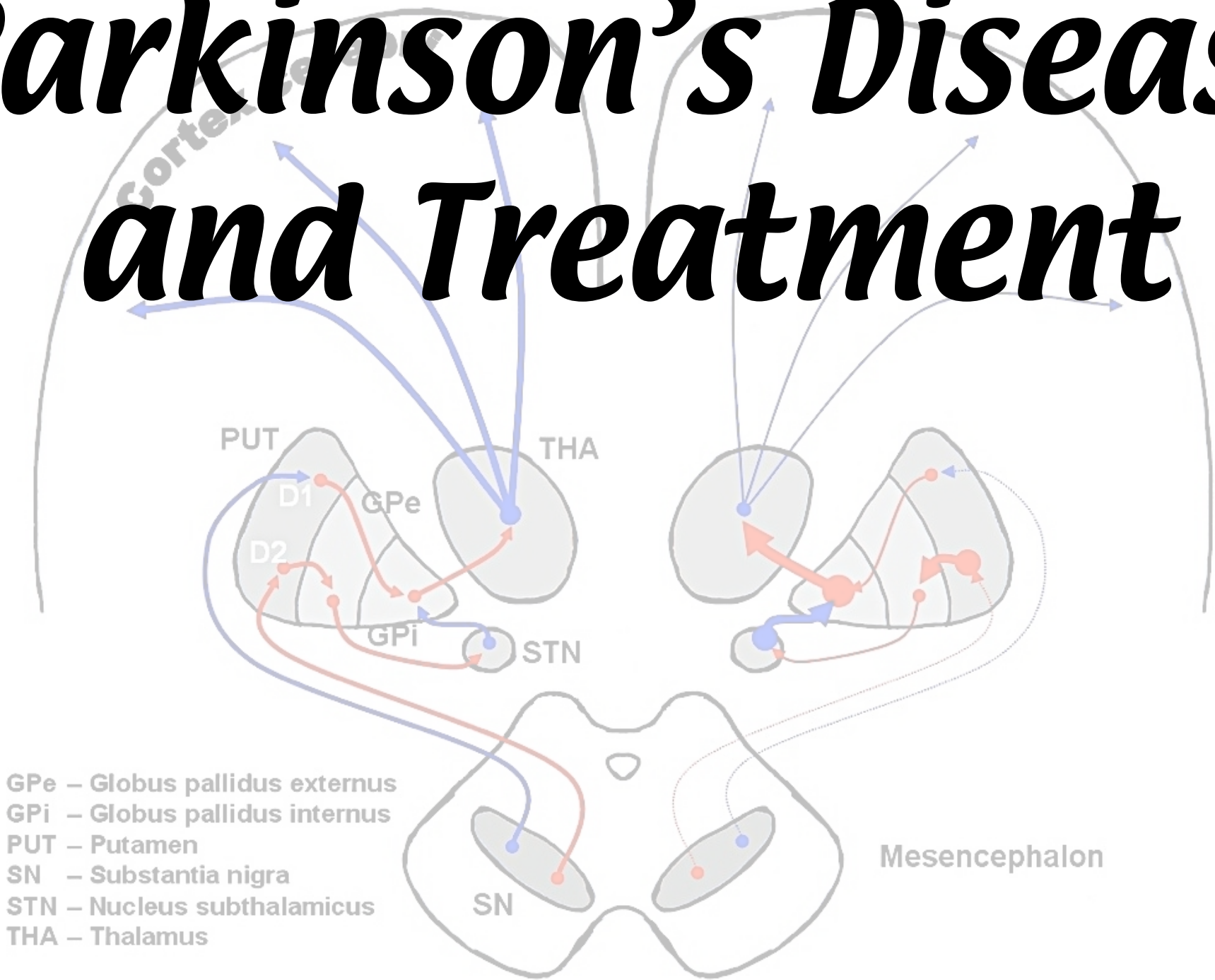
Parkinson's Disease and Treatment



Introduction

- The shaking palsy (Parkinson - 1817)
- A prevalent, progressive neurodegenerative disease
- Biochemical lesion - neurodegeneration
- No cure, no means to prevent the degeneration of neurons
- Treatment based on knowledge of biochemical lesion

Parkinson's Disease

- PD affects over 1 million Americans.
- It is second only to Alzheimer's disease as the most common degenerative disease of neurons.
- Symptoms generally appear in middle age and continue becoming more and more severe with age.
- There is no cure available.
- Drug therapy can maintain functional mobility for years (prolongs/improves quality of life).

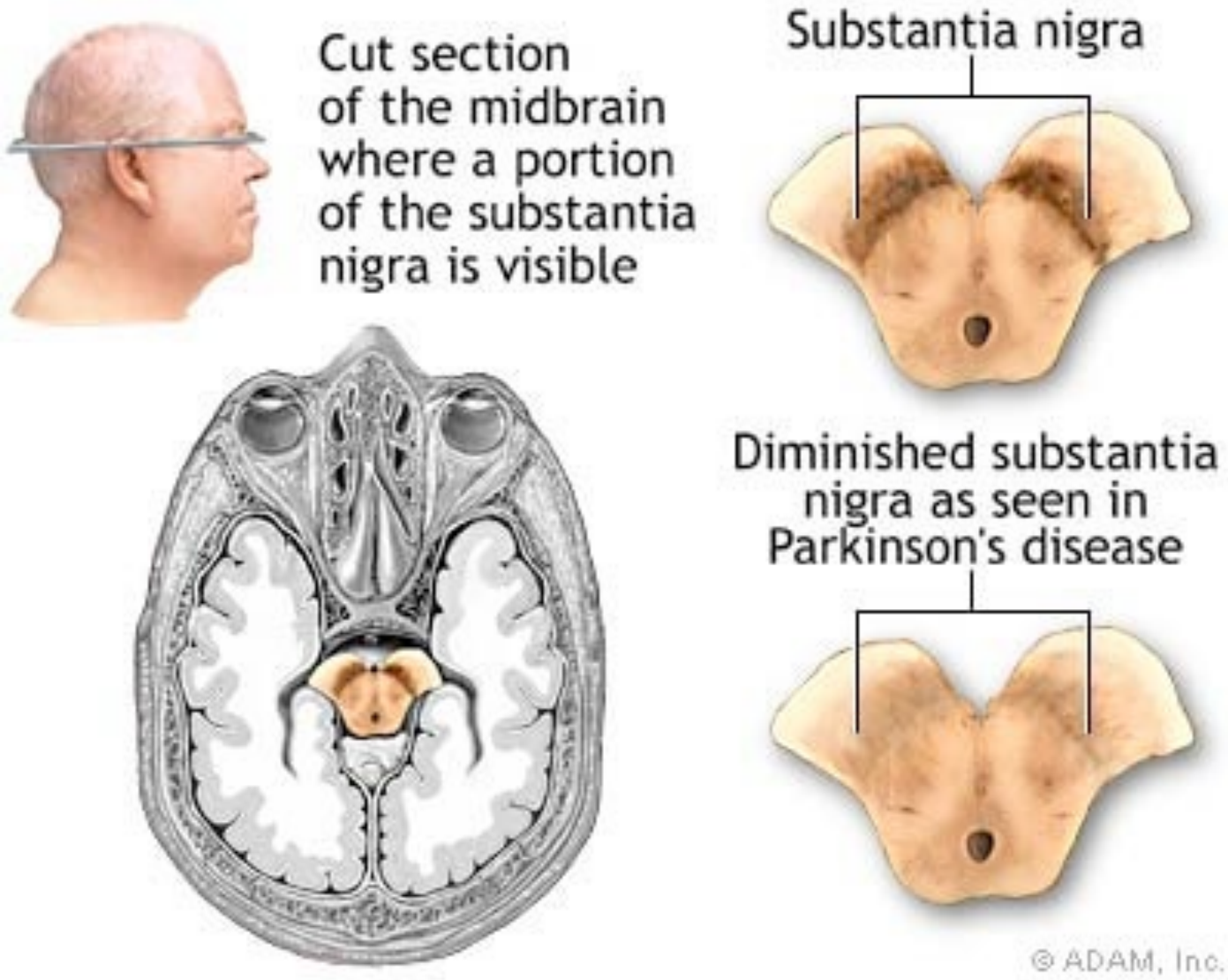
Symptoms

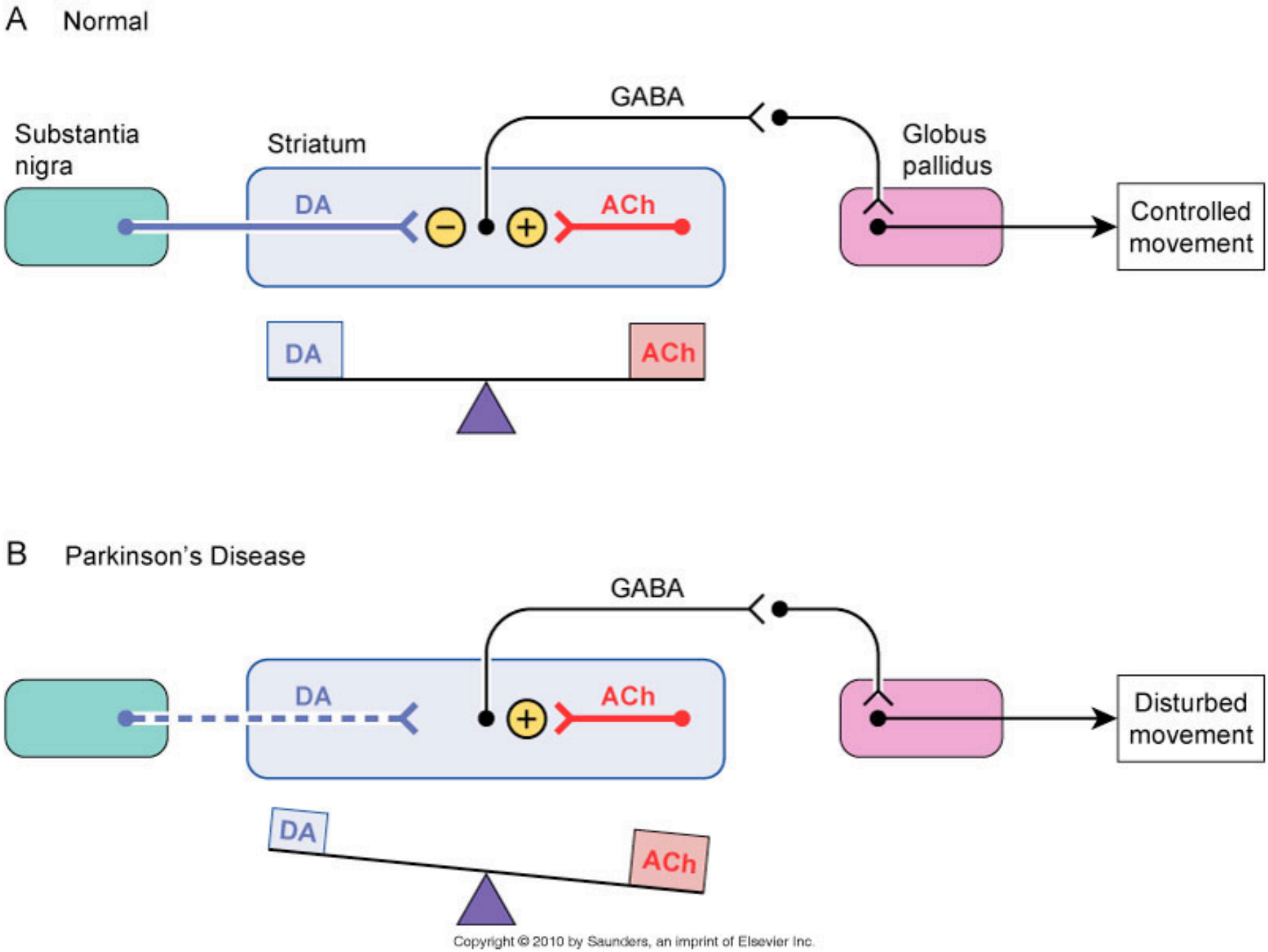
- Tremor
- bradykinesia
- Rigidity
- Postural effect
- Dementia

Causes

- Genetics?
- Environment?
- Drug induced
- Environmental toxins?
- Parkinsonism and MPTP (1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine)

Substantia nigra

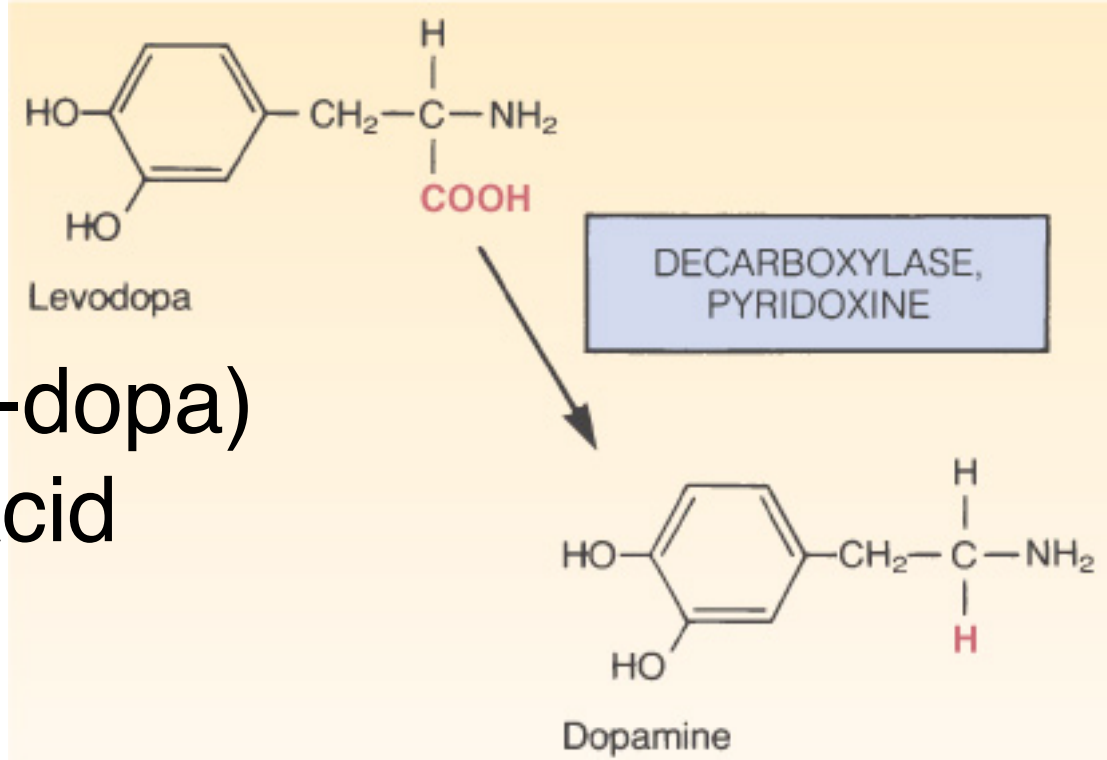




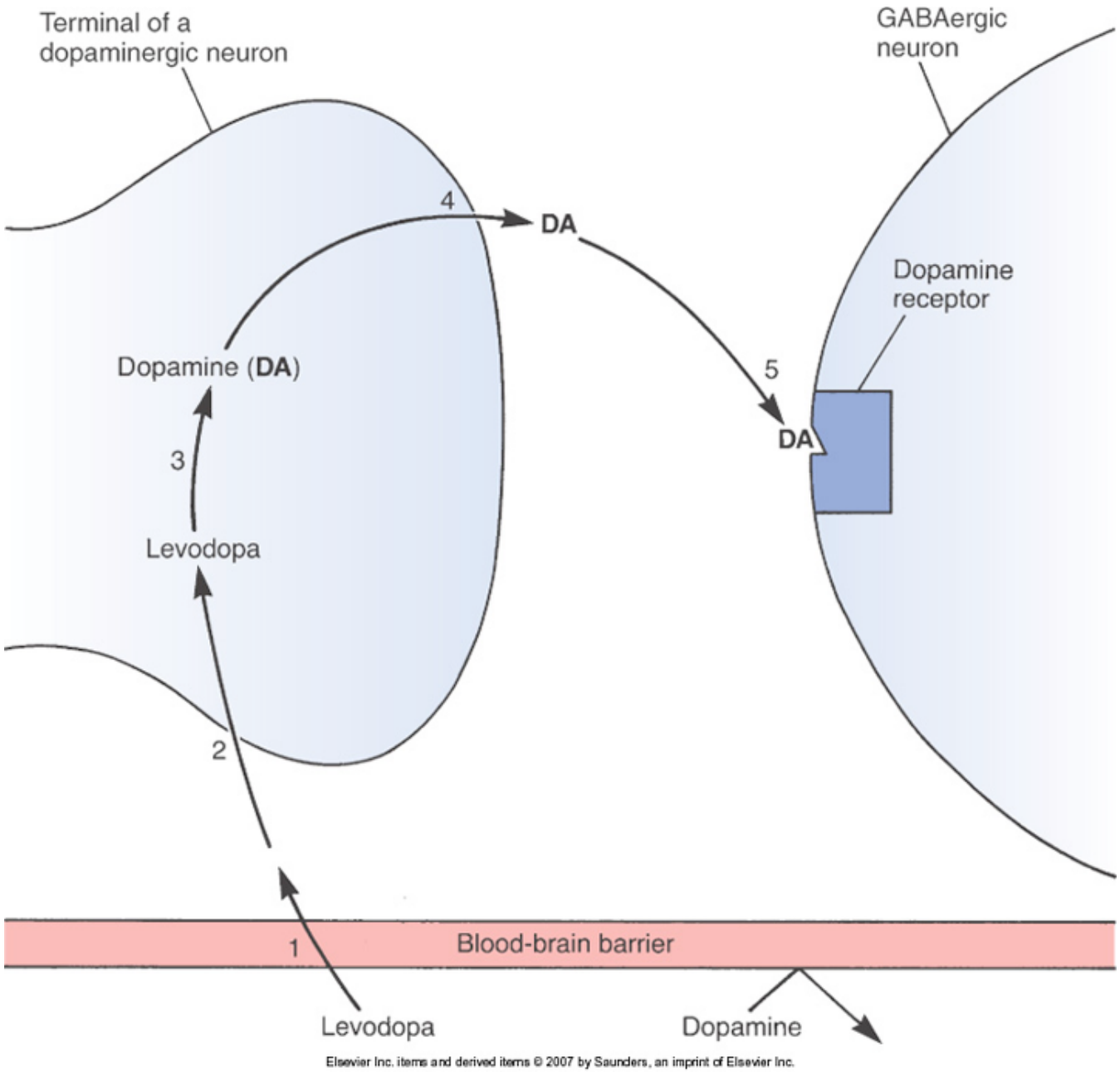
Dopamine restoration in brain

- Need to restore dopamine in brain
- Blood brain barrier for dopamine

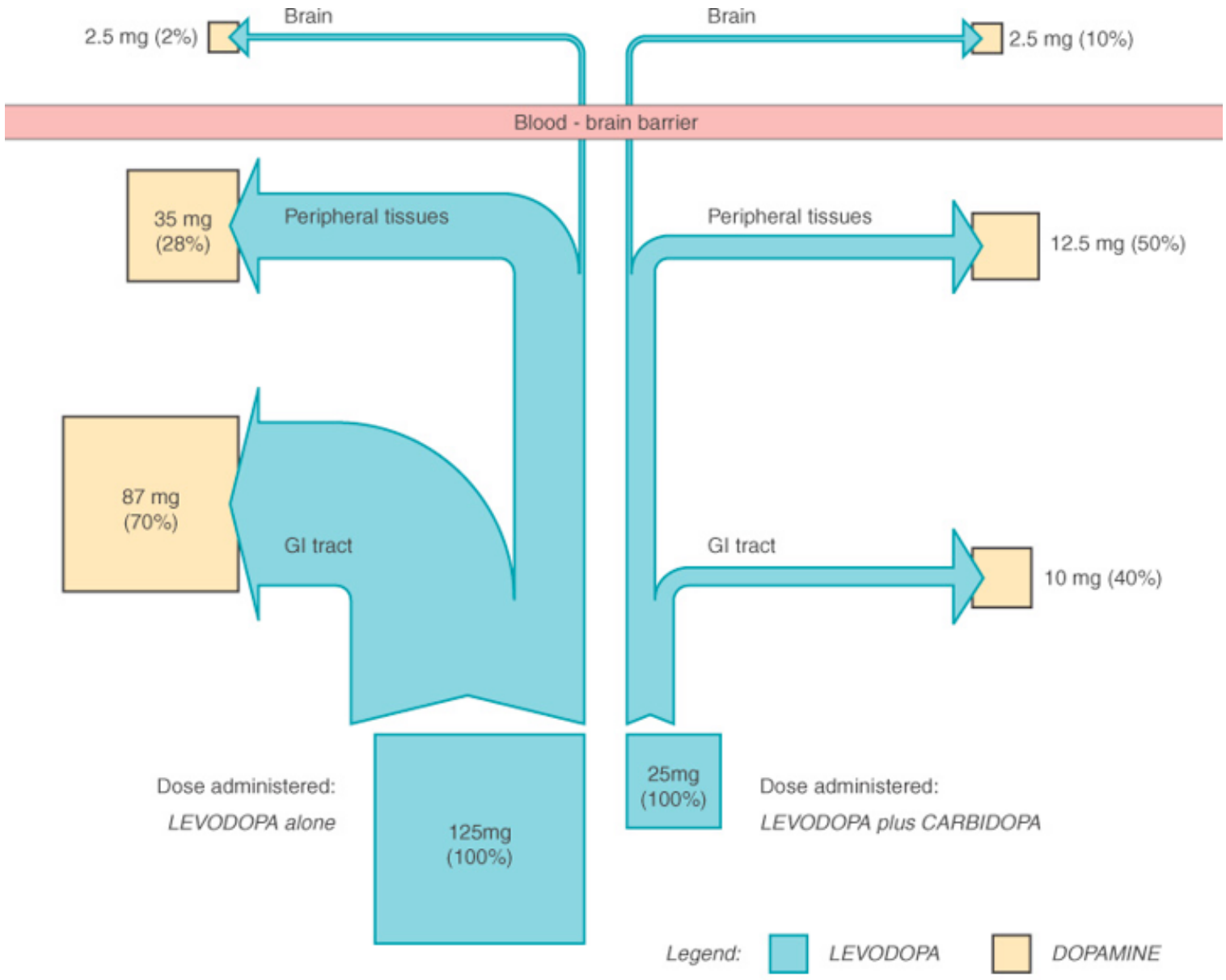
- Levodopa as a precursor to dopamine
- Decarboxylation to dopamine
- Use of Levodopa (L-dopa)
- Aromatic L-Amino Acid decarboxylase



Dopamine restoration in brain

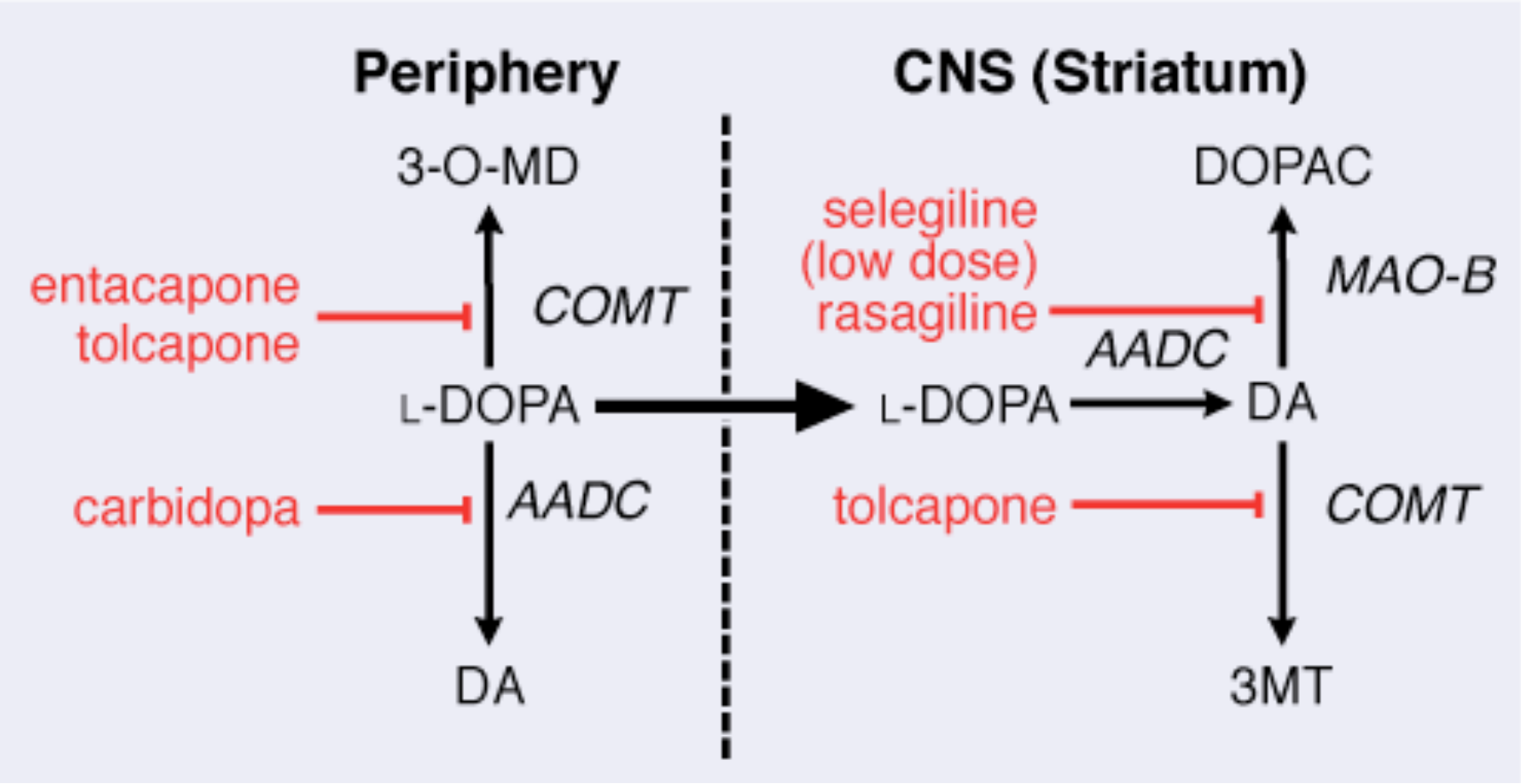


Central availability



(Data in the figure are extrapolated from Nutt JG, Fellman JH. *Pharmacokinetics of levodopa*. Clin Neuropharmacol 7:35, 1984.)

Preservation of L-DOPA and striatal dopamine



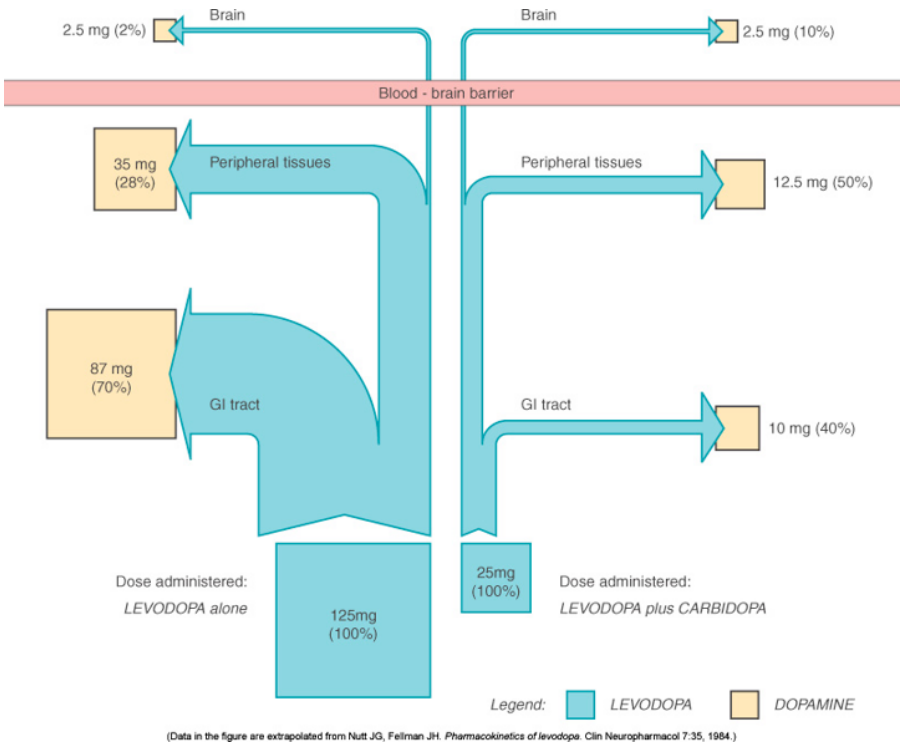
COMT: Catechol-O-methyltransferase
AADC: Aromatic L-amino acid decarboxylase
DOPAC: 3,4- dihydroxyphenylacetic acid
3MT: 3-methoxyltyramine
3-O-MD: 3-O-methyl DOPA
DA: Dopamine
MAO-B: Monoamine oxidase-B

Side effects

- Peripheral decarboxylation produces peripheral side-effects
- Generally dose-dependent and reversible
- Gastrointestinal (Caution: Don't use phenothiazines for nausea)
- Cardiac irregularities (ß-adrenergic receptors)
- Behavioral disturbances (role of dopamine)
- Special care: cardiac arrhythmias, major psychoses
- Abnormal involuntary movements - a serious side effect, no tolerance, may limit the dose

L-Dopa/Carbidopa therapy

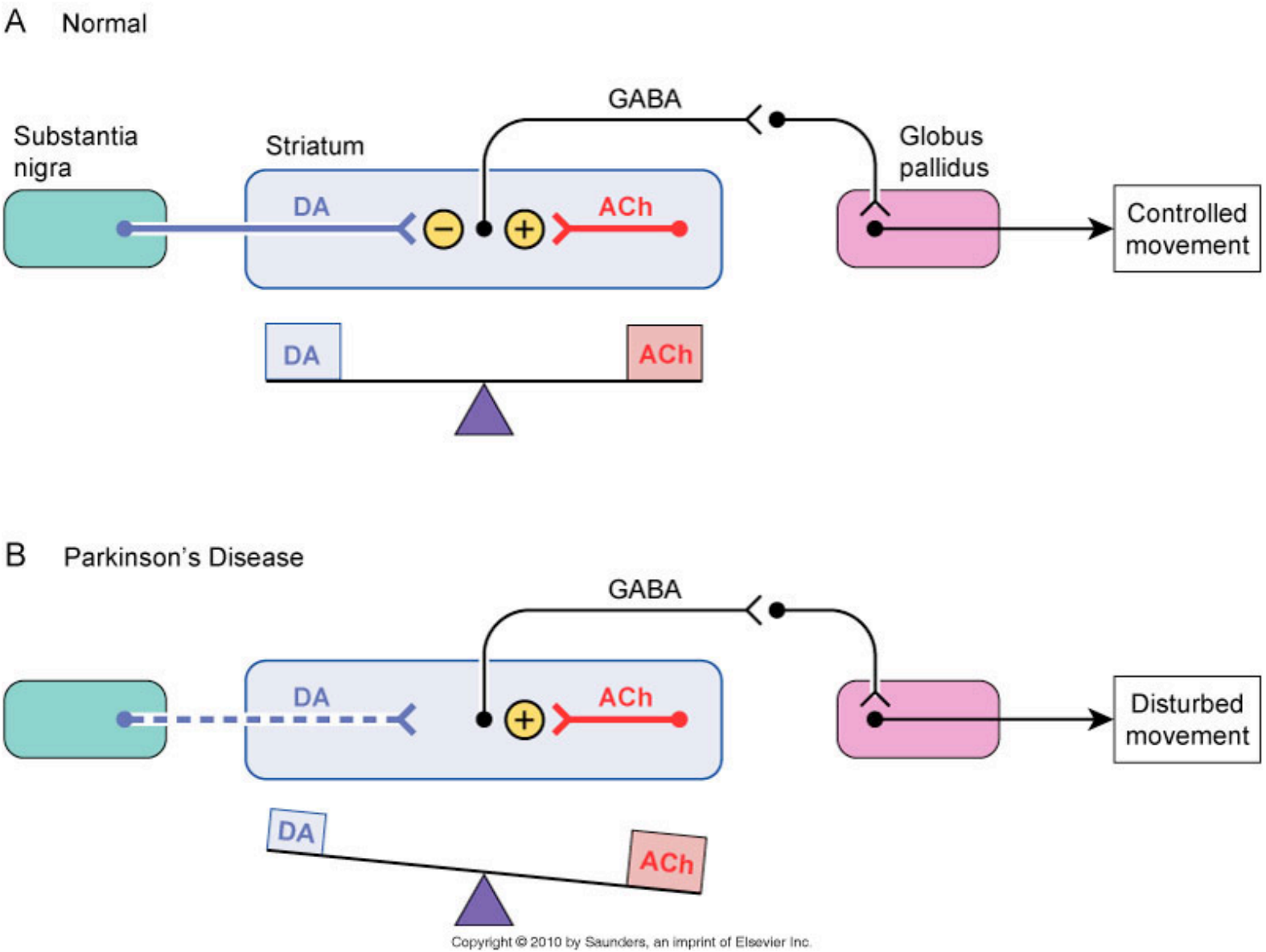
- Generally a combination of levodopa and carbidopa given



- Gradual increase in dose
- Careful Individual titration needed
- Complications of dyskinesias
- Limitations with respect to long-term treatment
- Not a cure

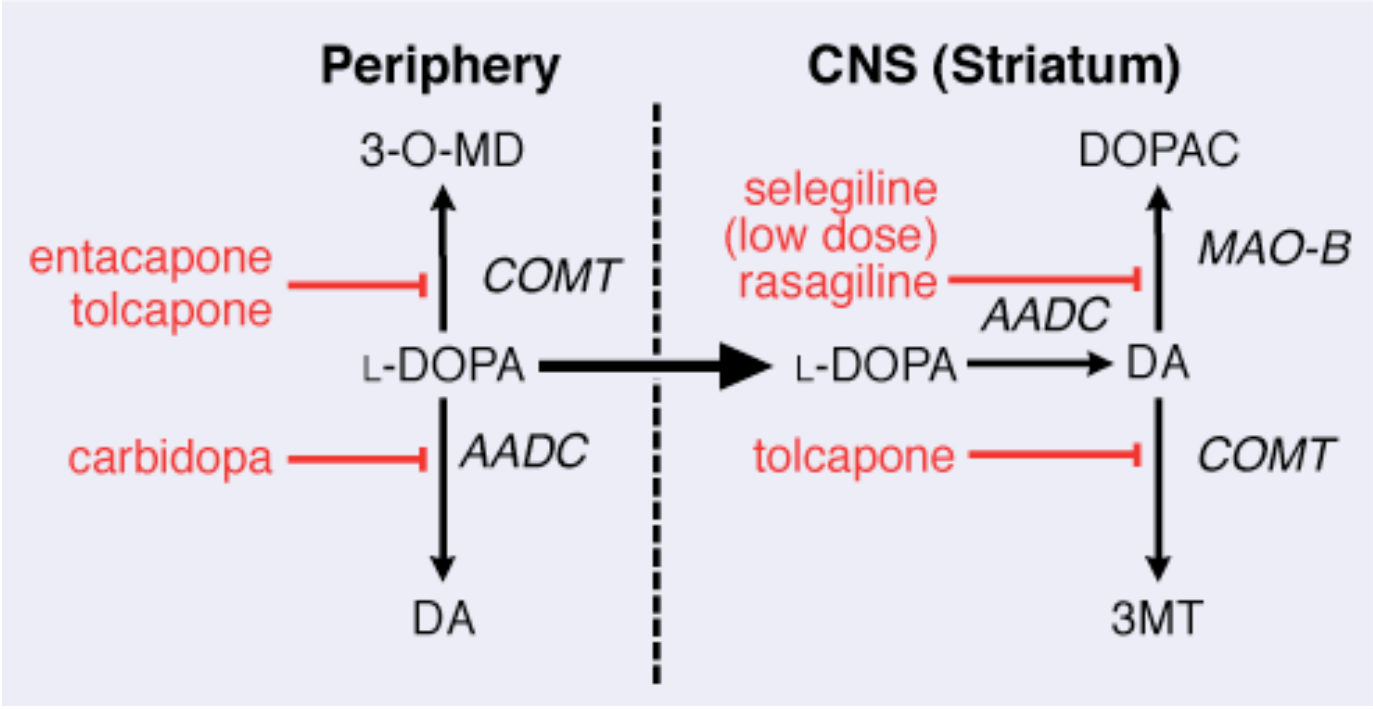
Other drugs

- Dopaminergic agonists - pramipexole, ropinirole
- Anticholinergic drugs - benztropine, trihexyphenidyl

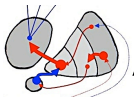


Other drugs

- Selegiline & Rasagiline:
  - Selective inhibition of MAO-B
  - MAO-B present predominantly in the striatum
  - Inhibition of the breakdown of dopamine by MAO-B
- Entacapone: catechol-o-methyl transferase inhibitors - inhibition of dopamine degradation



Other drugs



- Amantadine: blockade of NMDA receptors - treatment of levodopa-induced dyskinesias

Effectiveness of the treatment

- Effective relief from symptom for several years
- Implications of protection from progressive neurodegeneration

A possibility to prevent cell death?

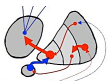
- Implications of protection from neurodegeneration

MPTP Induced Parkinsonism

- A major advance in 1979 - the case of a young man
- Link with MPTP
- The "Frozen Addict" patients

PHOTOGRAPH BY RUSS LEE in *The Case of the Frozen Addicts*, © Pantheon Books, 1995

Insights from MPTP induced Parkinsonism



- Parallels in symptoms, pathology, treatment, complications
- Dopamine depletion without symptoms
- Animal models using MPTP
- Environmental toxins and Parkinson's Disease
- Rotenone and Parkinson's disease

The objectives of the lecture on Parkinson's Disease (PD) are to understand:

- **The pathology underlying PD**
- **The role of dopaminergic neurotransmission in PD**
- **Drug treatments available to reduce the symptoms of PD, including levodopa-carbidopa therapy and other drugs that may be useful**
- **Enzymatic pathways involved in Dopamine synthesis and its breakdown.**
- **MPTP induced Parkinsonism and the role of environmental toxins in PD**