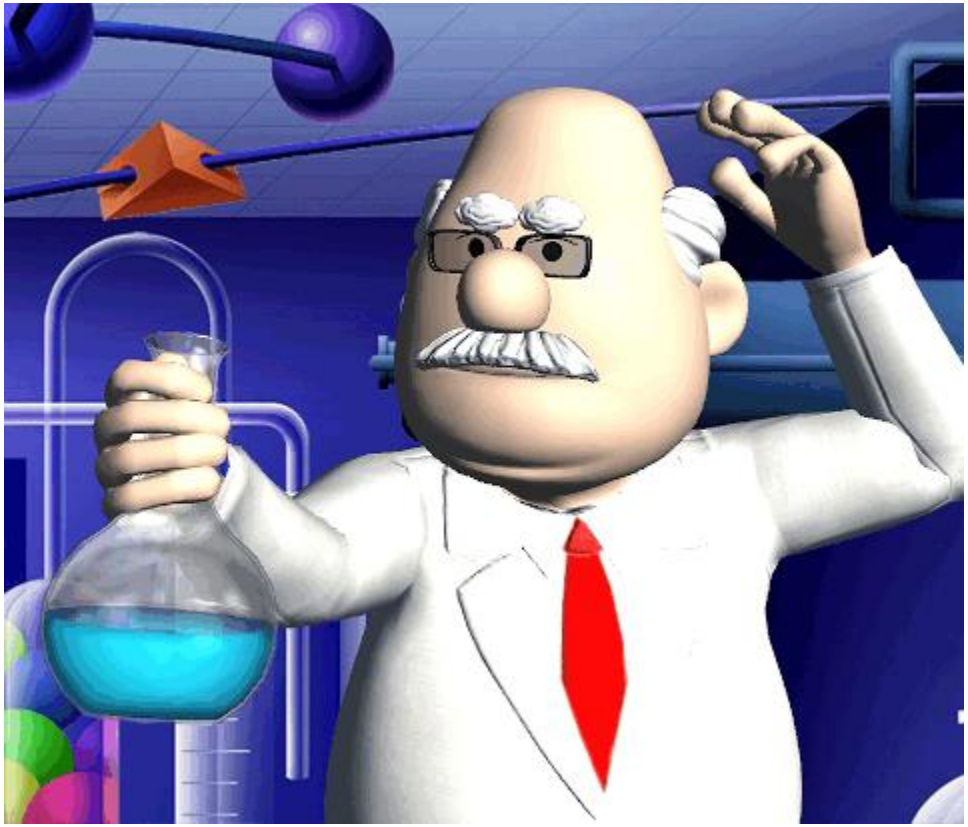
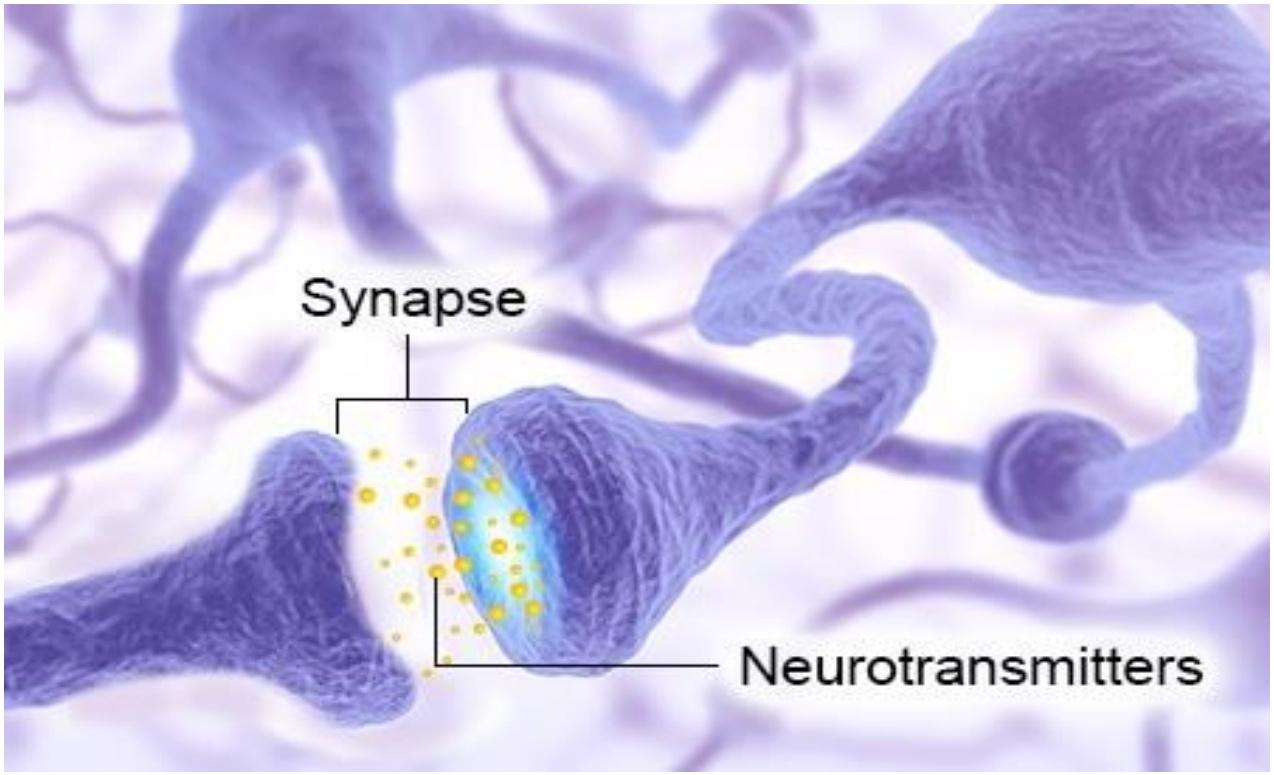
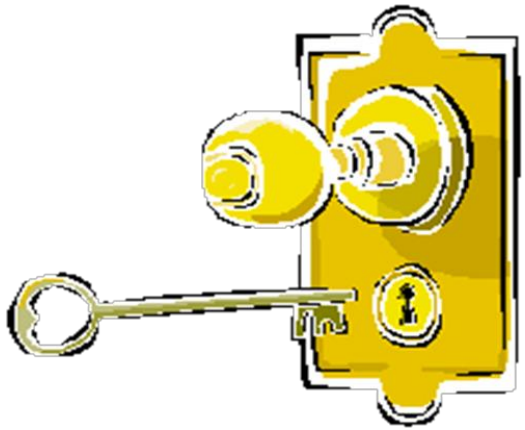
How were medicines for treating the motor symptoms of Parkinson disease discovered? How do the medicines work ?

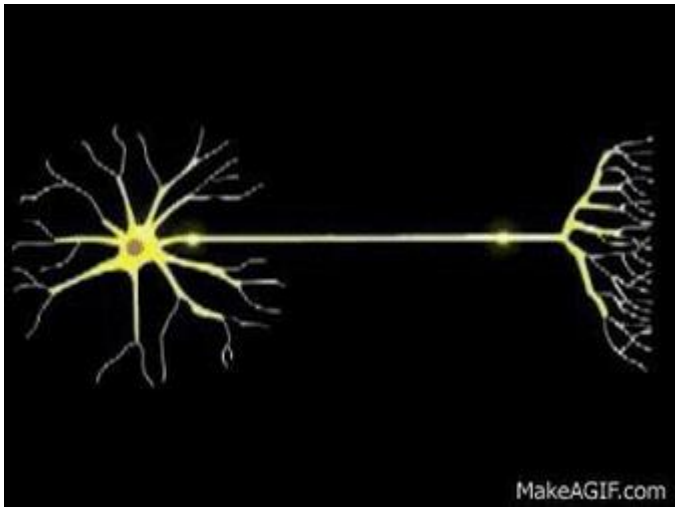


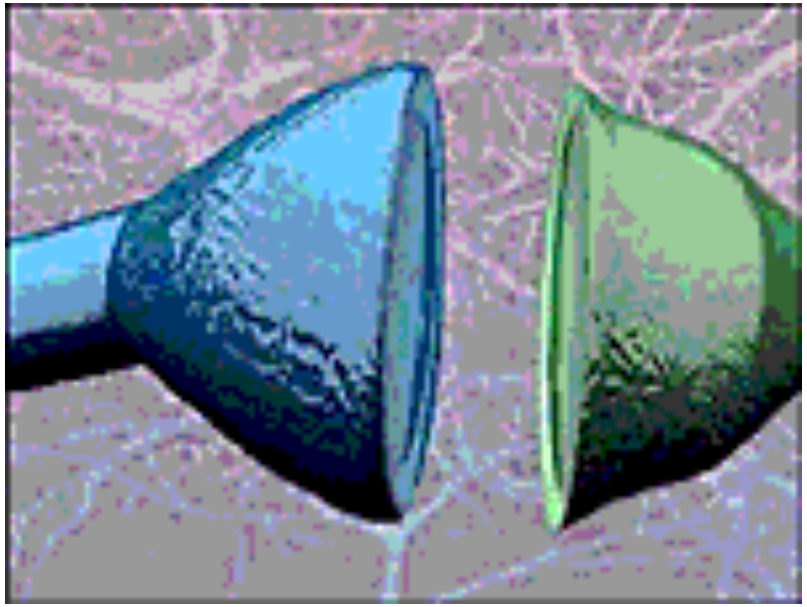
1950s neurotransmitter research

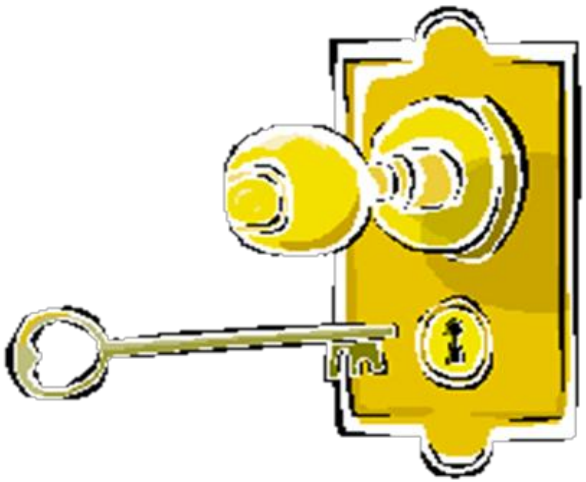




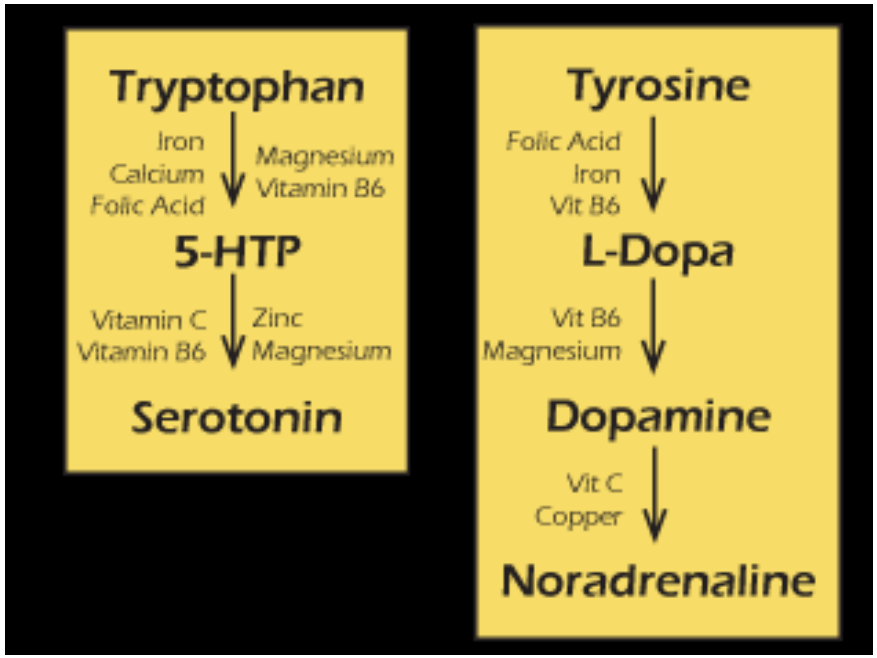
1950s neurotransmitter research







1950s: **Serotonin** and **noradrenaline** were known to be “neurotransmitters” in the brain



Dopamine was thought to be an unimportant chemical that was merely needed for the production of norepinephrine.

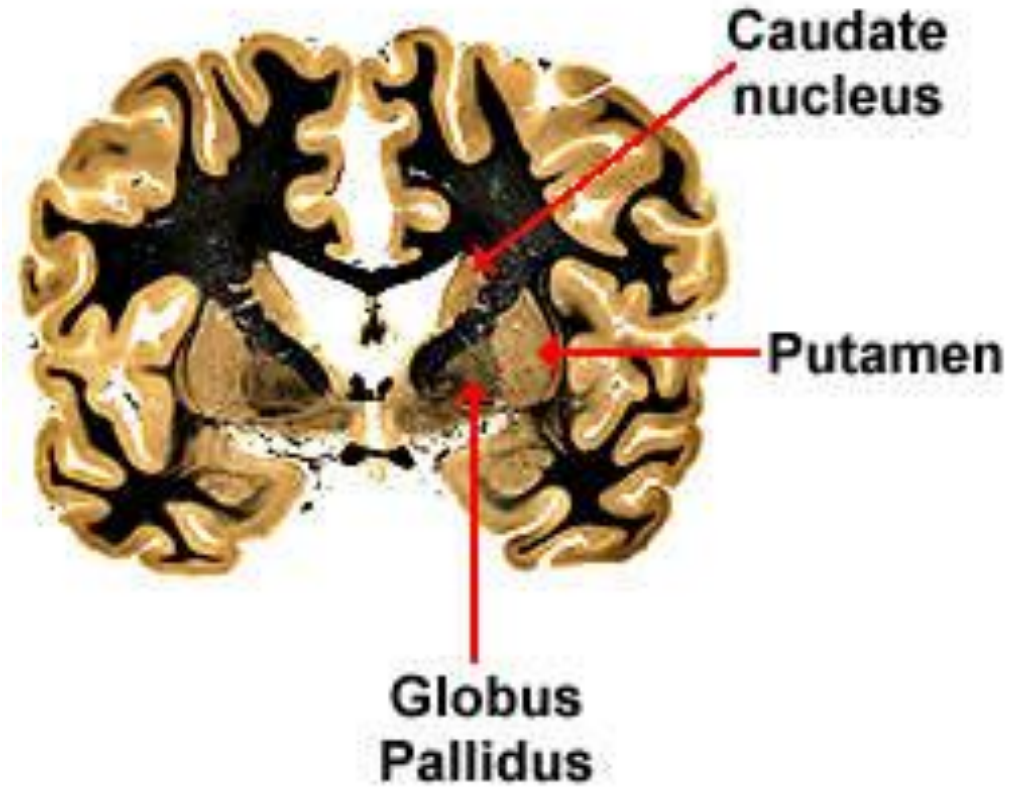
1950s reserpine, “parkinsonism”, dopamine


NATURE November 30, 1957

3,4-Dihydroxyphenylalanine and 5-Hydroxytryptophan as Reserpine Antagonists

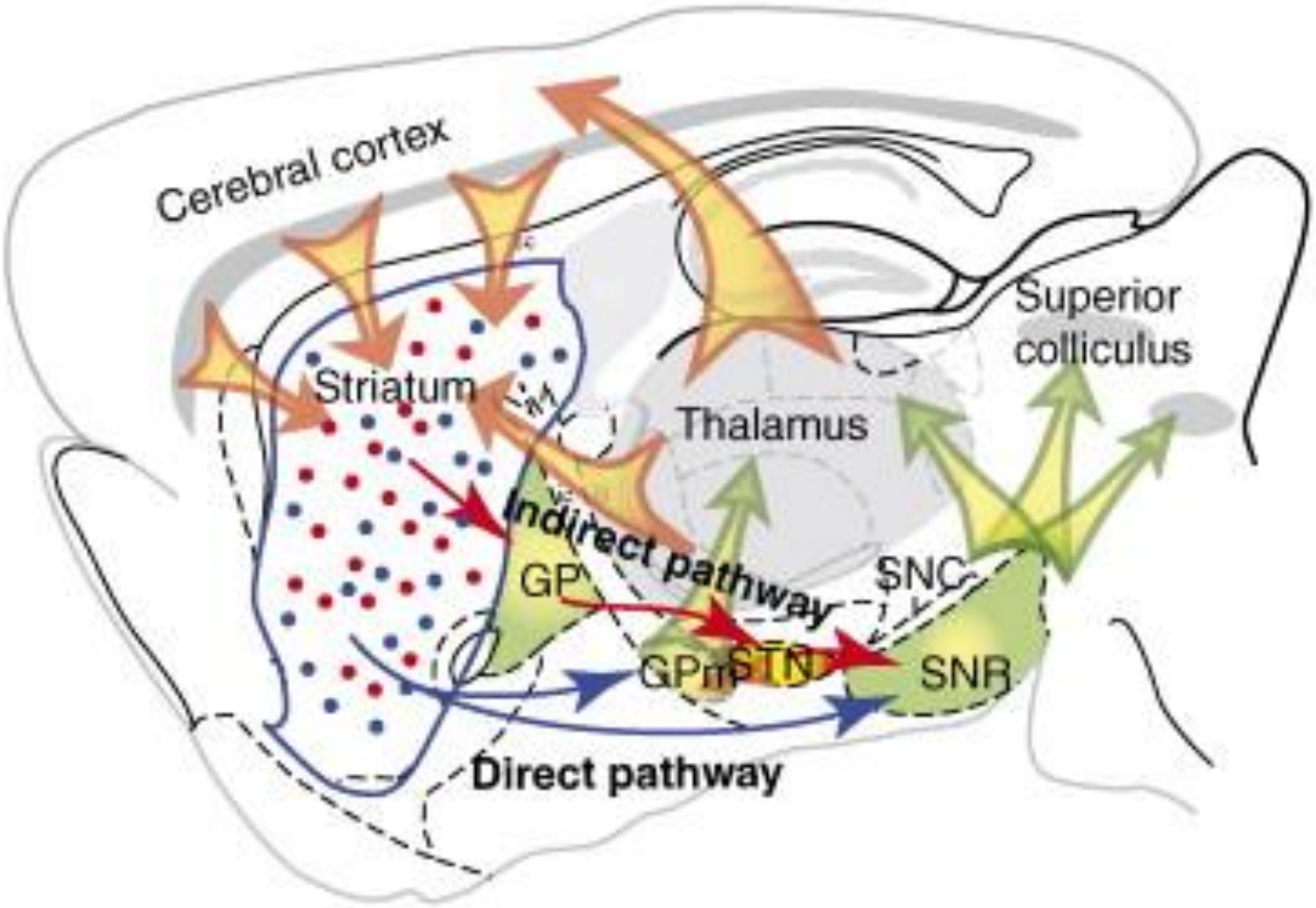
Antihypertensive Activity of Hexahydro-1-Azepinecarbothioamides

1958 discovering the importance of dopamine

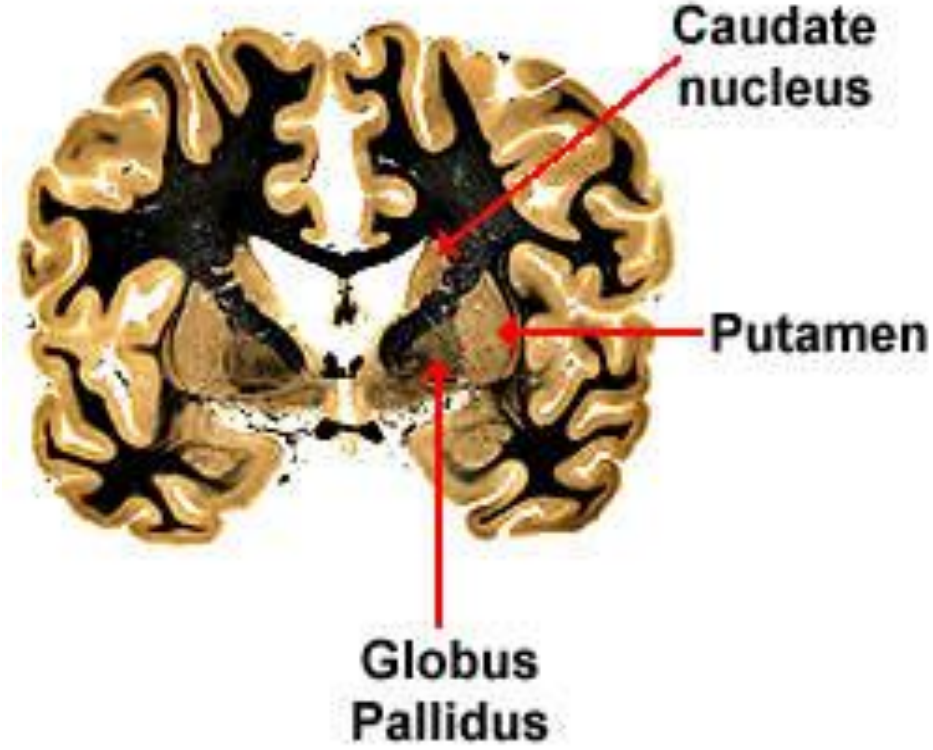


dopamine is a **neurotransmitter**
and is highly concentrated in the "**striatum**"
(caudate and putamen)

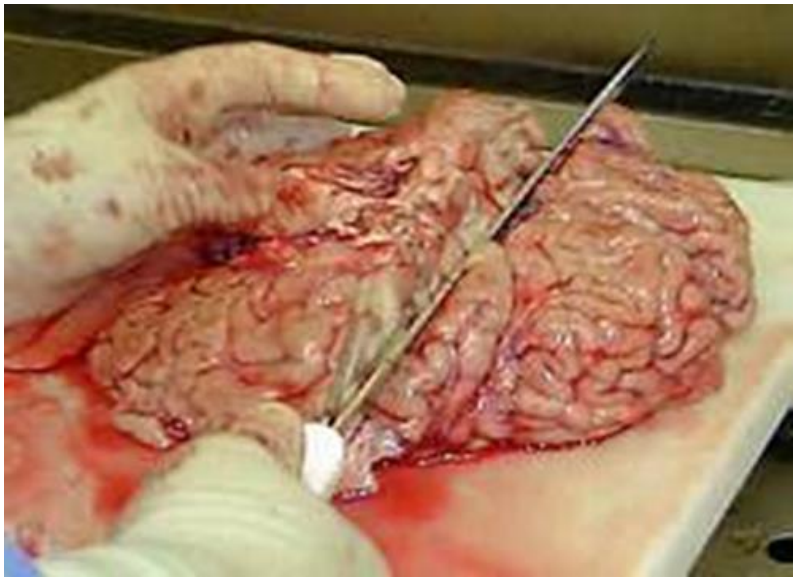
Control of movement



A major function of the **striatum** is to
“facilitate complex sequences of movements”
It was apparent that the striatum was not performing its function well in persons with Parkinson disease.



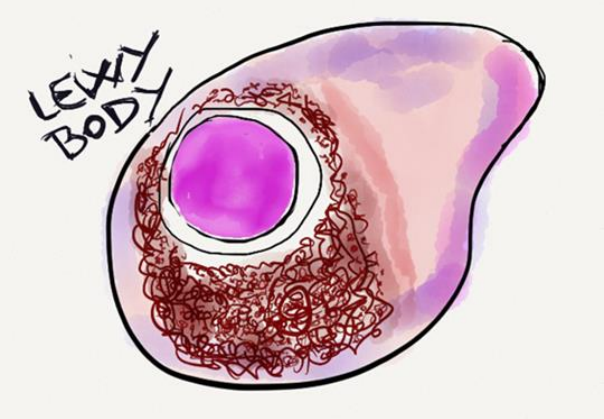
1960 Post-mortem neurochemistry of PD

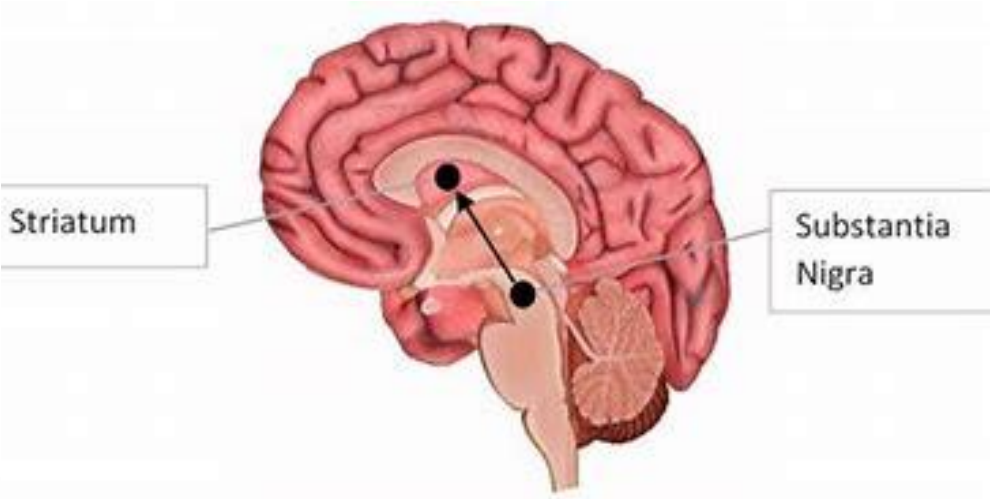


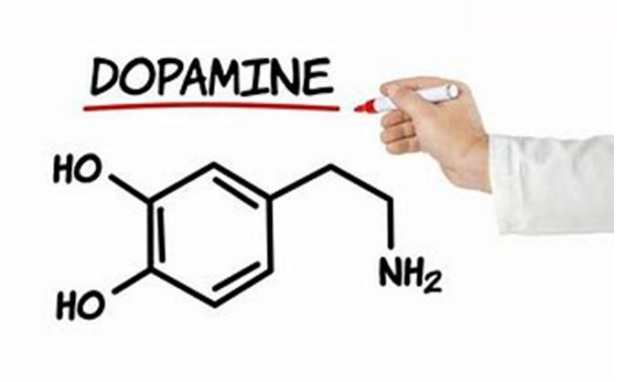
Studying autopsy specimens, Dr. H. found **severe loss of dopamine in the striatum** in **PD patients**, but **not** in persons with other neurologic disorders.

Dr. Oleh Hornykiewicz

1960 Dr. H. speculated that the damaged nerve cells in the substantia nigra were the cells that normally produce dopamine

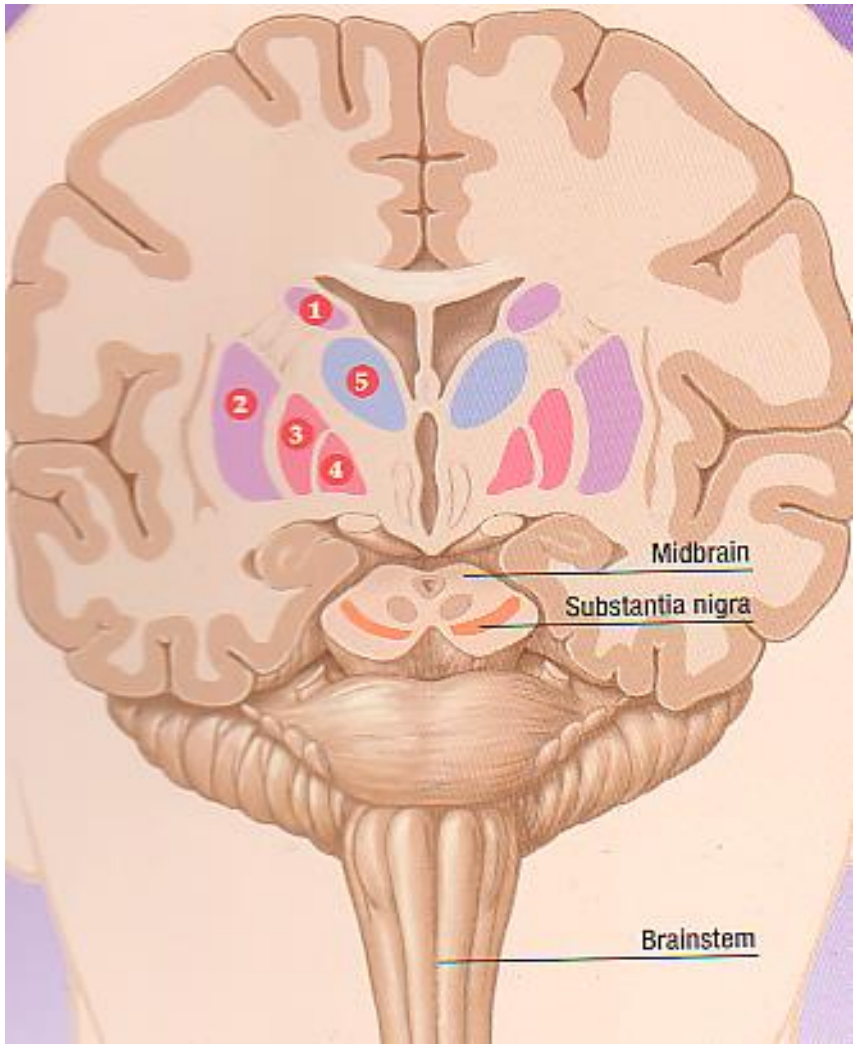


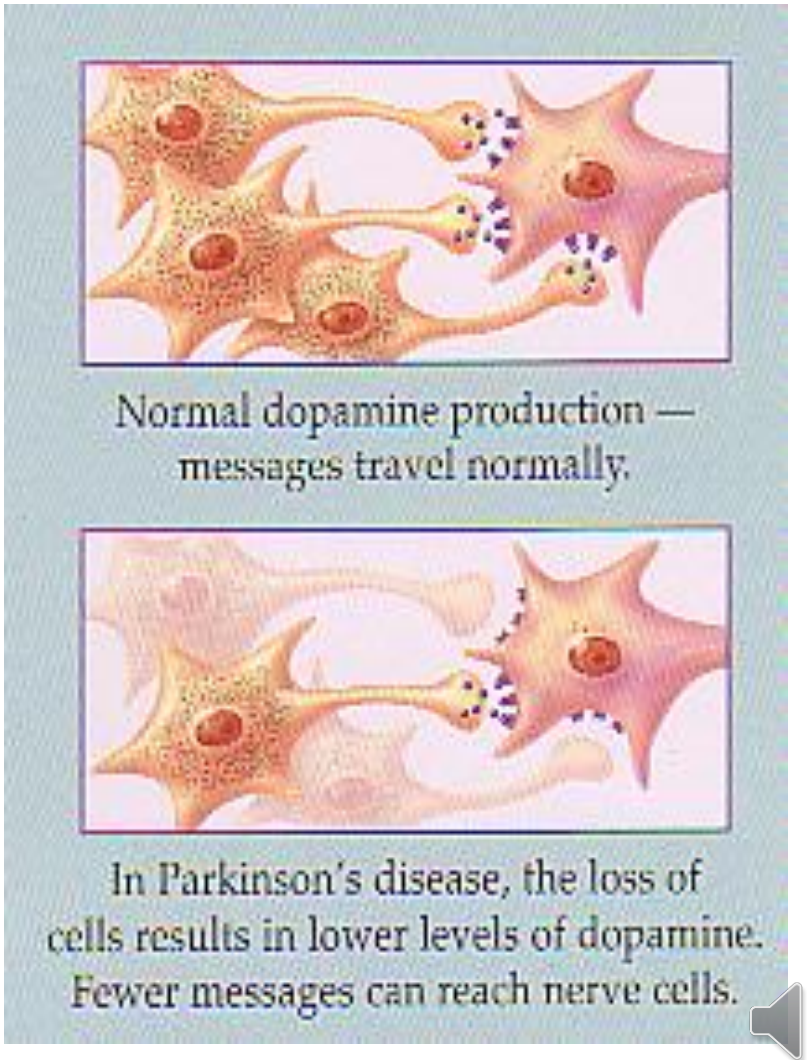




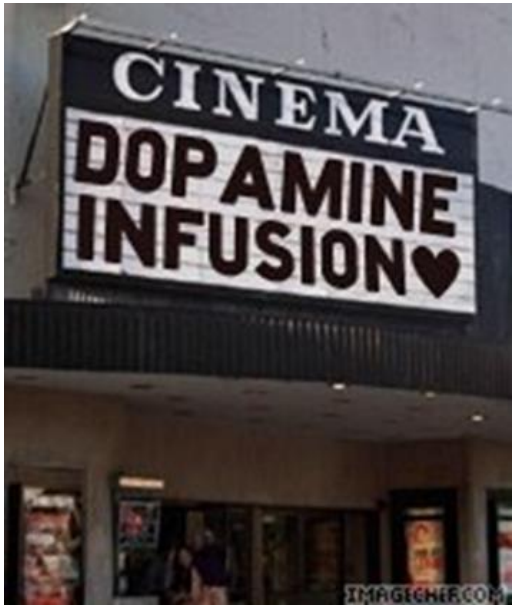
The model of PD in the late 1960s :

“nerve cells that produce dopamine degenerate in Parkinson disease”:

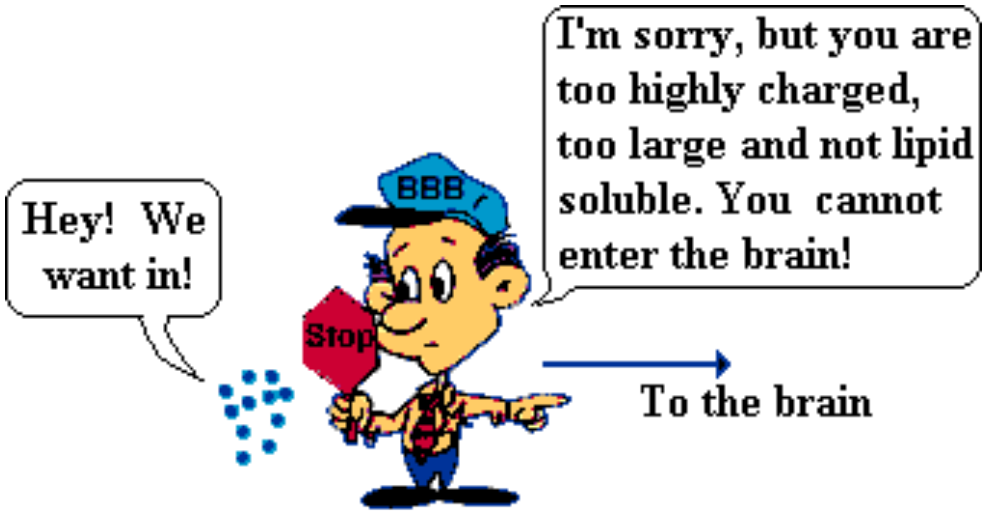


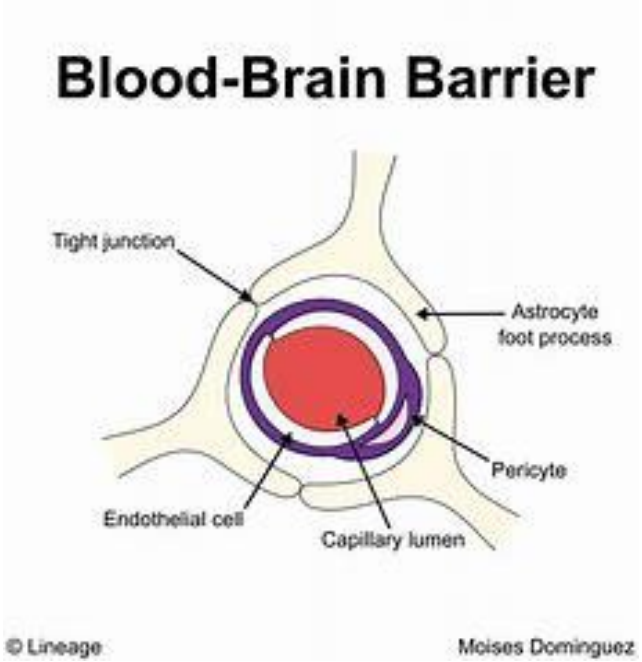


If the brain needs more dopamine, why not give oral dopamine ?



The “blood brain barrier” prevents certain types of chemicals from getting into the brain

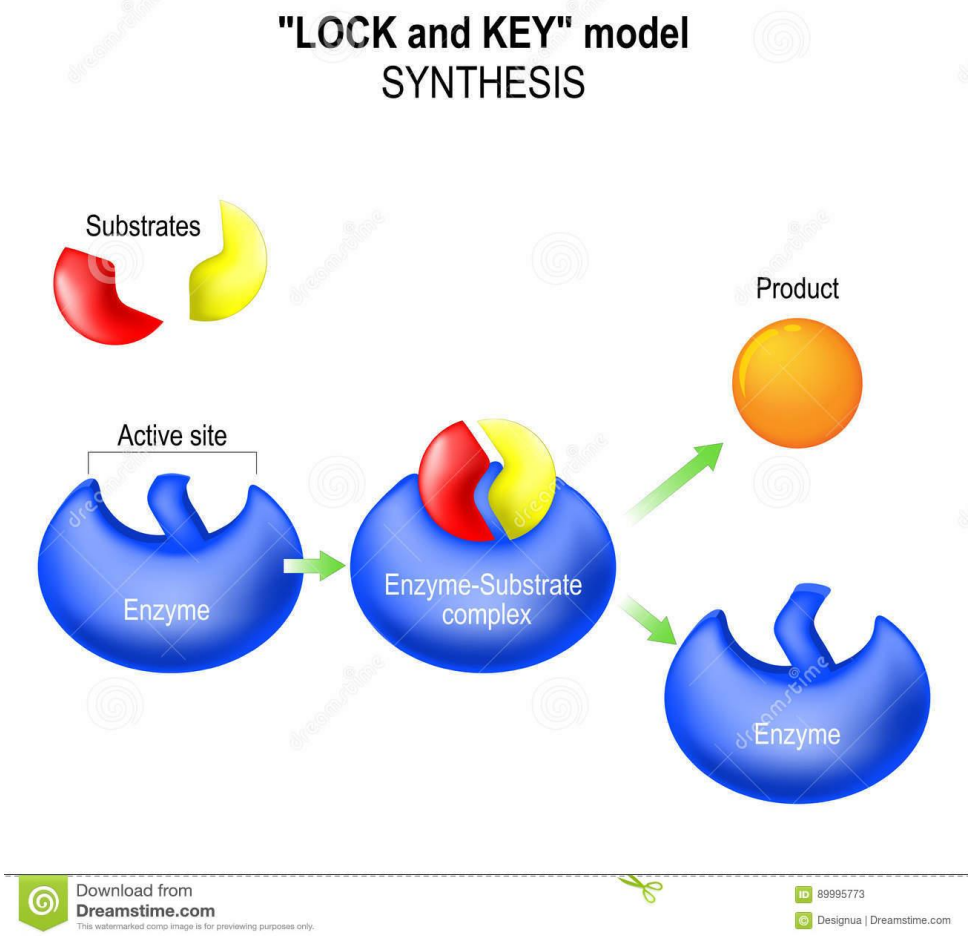




Orally administered dopamine cannot enter the brain from the bloodstream.

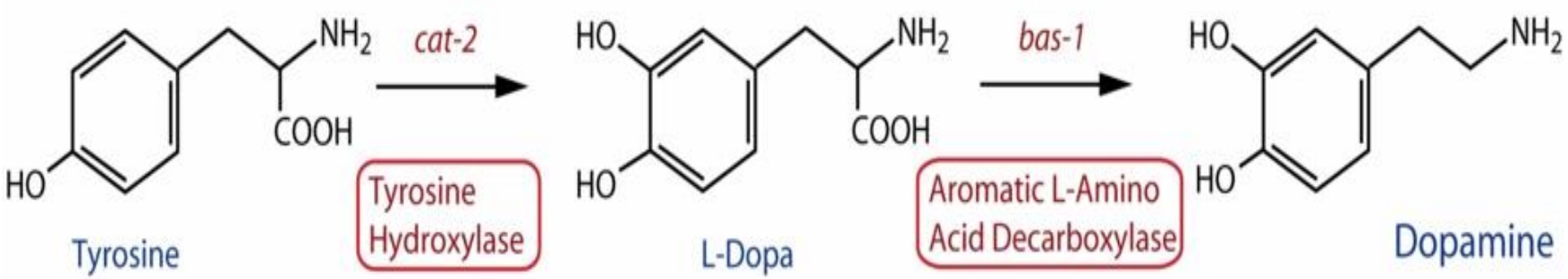
Oral dopamine is also very nauseating and poorly tolerated.

How does the brain make dopamine ?



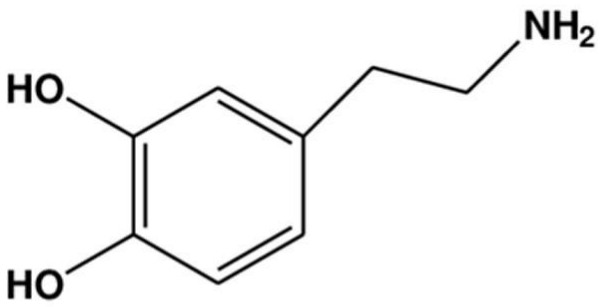
Enzymes assist in chemical synthesis.

How does the brain make dopamine ?



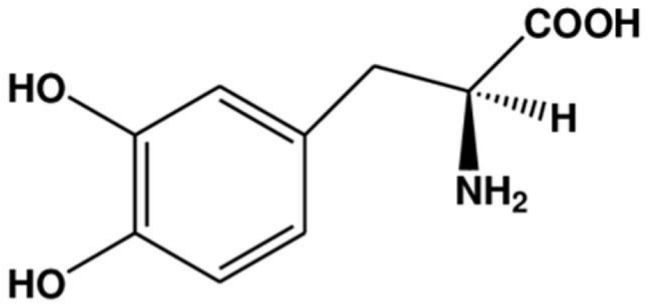
- The amino acid **tyrosine** (which is very prevalent in the diet, but can also be synthesized in the absence of dietary sources) is converted to **levodopa**
- **Levodopa** (for which there are very few dietary sources) is converted to **dopamine**

Unlike oral dopamine, oral levodopa can enter the brain.



Dopamine

Too Polar
Cannot cross blood brain barrier



Levodopa

Non-polar
Can cross blood brain barrier

Could anything be done to help?

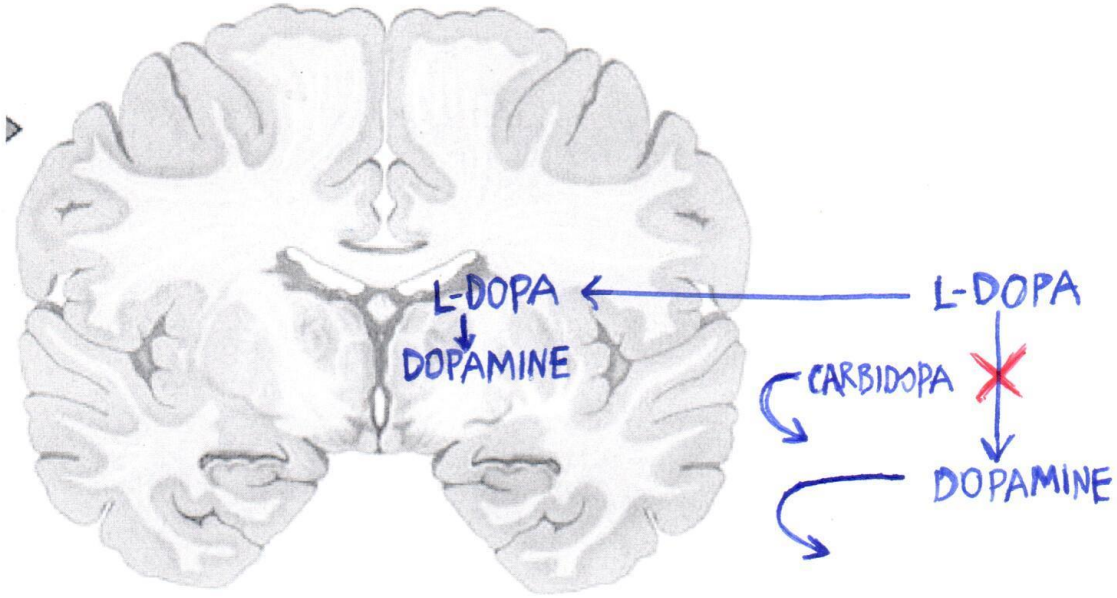
L-dopa (levodopa) in the treatment of Parkinson disease:

- L-dopa was shown to be effective in treating the motor symptoms of Parkinson disease

George Cotzias et. al.

NEJM 1969; 280: 337-345

- An “amazing breakthrough”: neurodegenerative diseases were previously thought to be “untreatable” and “hopeless”



Why **CARBIDOPA** and **LEVODOPA ?**

Combining carbidopa with levodopa blocks dopamine production outside the brain, reducing side effects of and allowing more levodopa to enter the brain.

carbidopa/levodopa was marketed in1971 as **sinemet**:

"*sin*" (*sans*) = without "*emet*" (*emesis*) = vomiting

Carbidopa/levodopa in Parkinson disease

All patients with PD improve with levodopa therapy

- Walking better
- Writing better
- Less stiffness
- Less tremor
- Move more quickly

These benefits persist over the course of the illness.

"refractory" Parkinson disease tremors

- Tremors may not respond as dramatically to levodopa therapy as other symptoms
- Tremors are obtrusive, and a patient whose tremor is controlled 90% of the time may focus on the residual 10%, reporting "poor tremor control"
- **Tremor wax and wane, often exacerbated by**

  stress

  anxiety

  excitement

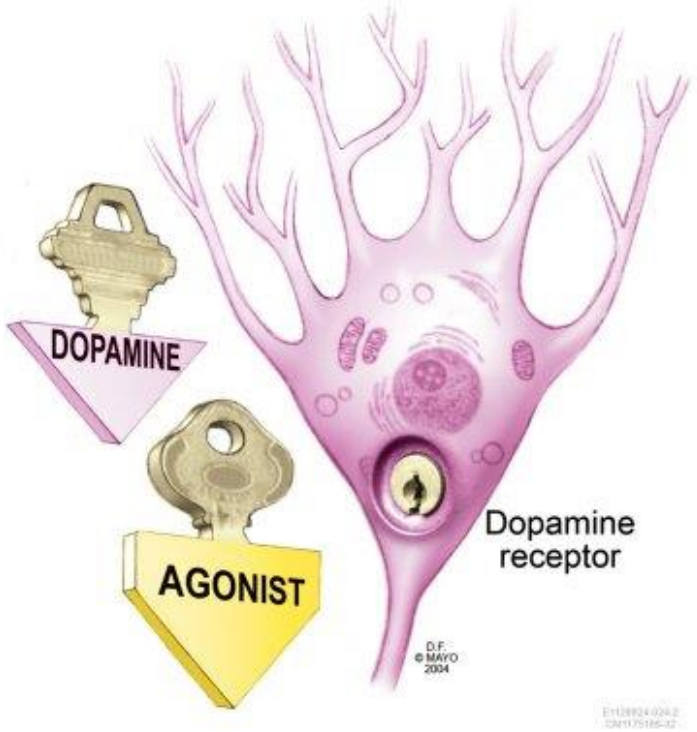
Soon after the introduction of levodopa, **"dopamine receptor agonists"** were developed

Current dopamine agonists commonly used to treat Parkinson disease:

ropinirole

pramipexole

rotigotine transdermal patch



"Dopamine agonists" directly stimulate dopamine receptors without actually inducing dopamine synthesis.

Treating the motor symptoms of Parkinson disease:

What treatment should be recommended for every person with Parkinson disease?

Treating the motor symptoms of Parkinson disease:

EXERCISE !

Long term outcomes are better in PD patients who participate in exercise programs on a regular basis. Exercise helps patients maintain mobility, dexterity, and balance, and also has potential benefits for mental health.

"Symptomatic treatment": When should medication for treating the motor symptoms of Parkinson disease be initiated?

- **People with very mild symptoms do not necessarily have to be started on medication.**

However, if symptoms
- interfere with employment, or
- interfere with daily activity, or
- impair balance, or
- cause embarrassment

starting medication to reduce the motor symptoms of PD should not be delayed.

There was a controversy regarding which medication should recommended for the initial treatment of PD:

carbidopa / levodopa or a **dopamine agonist ?**

The jury is in, and the verdict is:

carbidopa/levodopa !

"the differences in favor of initial levodopa treatment are significant and persistent"

Lancet 2014; 384: 1196-1205

Levodopa in Parkinson disease

Still the <u>most effective</u> drug treatment for PD

It is the *gold standard* against which new therapies must be measured

No other medical therapy currently available provides benefits superior to what can be achieved with levodopa.

Comparison of dopaminergic medications

Carbidopa/levodopa:

Benefits for motor symptoms:

+++++

Common side effects:

- Nausea
- Orthostatic hypotension
- Dyskinesias

Less common side effects:

- Somnolence
- Hallucinations

Dopamine agonists:

Benefits for motor symptoms:

+++

Common side effects:

- Nausea
- Orthostatic hypotension
- Impulse control disorders
- Somnolence
- Hallucinations
- Leg swelling

Many carbidopa/levodopa doses are available

- 10/100
- 25/100
- 25/250
- CR 25/100
- CR 50/200
- ER 23.75/95 (rytary)
- ER 36.25/145 (rytary)
- ER 48.75/195 (rytary)
- ER 62.25/245 (rytary)

One size does not fit all !

People may require a total dose anywhere from only 150mg/day to well over 1000mg/day of levodopa to optimally control their motor symptoms.

The “do’s” and “don’ts” of treating Parkinson disease

Avoid over-medication!

- **Take divided doses, and find the lowest dose that controls the target symptoms.**
- **Over-medication can trigger serious side effects.**

The “do’s” and “don’ts” of treating Parkinson disease

Avoid under-medication!

- **Under-medication leads to increased disability**
- **Doses and time intervals between doses should be individualized and titrated.**
- **There is no reason to arbitrarily restrict the dose** (but do not take more than is needed to control symptoms).
- **Compliance** !

Despite misinformation you might read online, I can reassure you that: **Levodopa is not "toxic"**

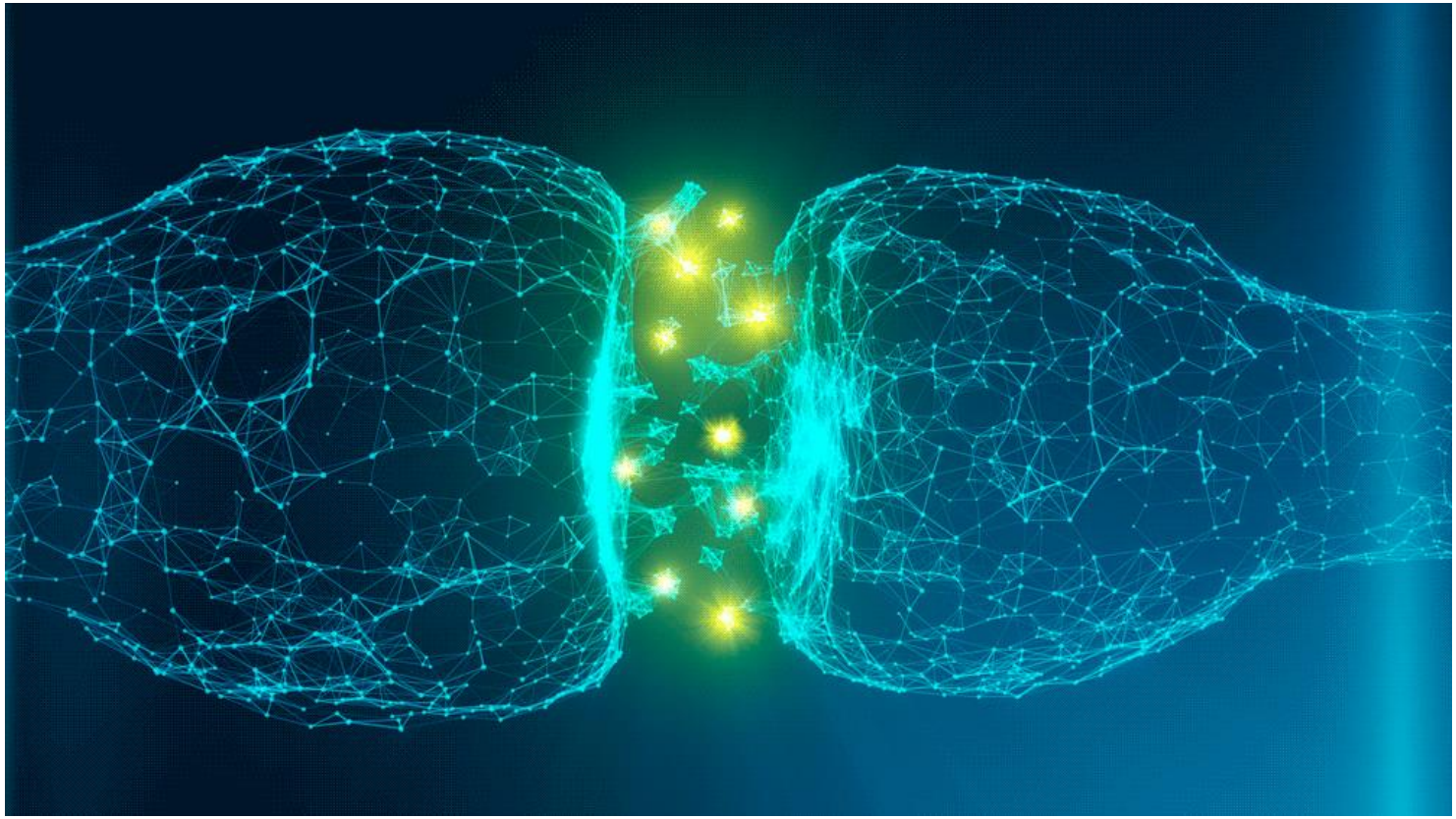
Levodopa does not "stop working"

Delaying treatment when PD motor symptoms are significant makes no sense:

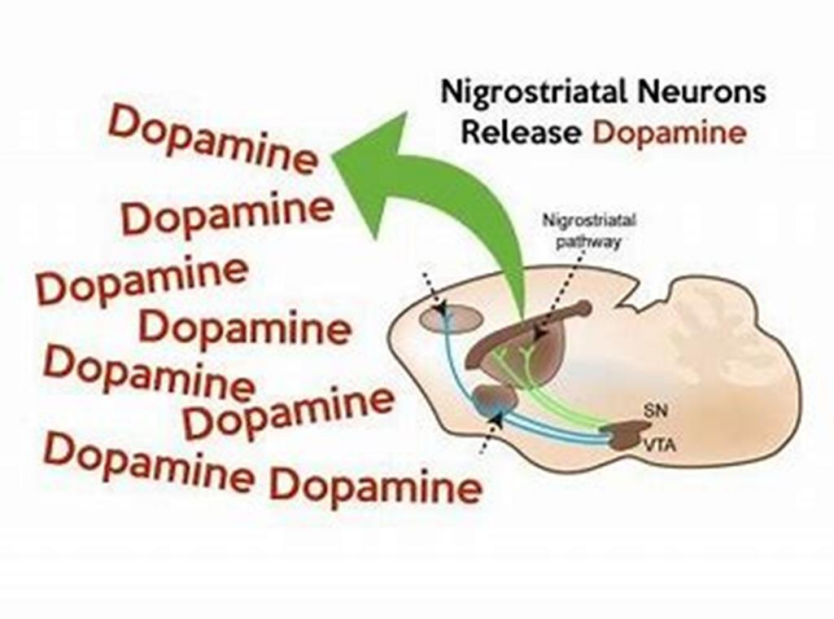
you cannot save the

"best response" for later

How is dopamine released in the striatum ?



Role of dopamine in facilitating movement

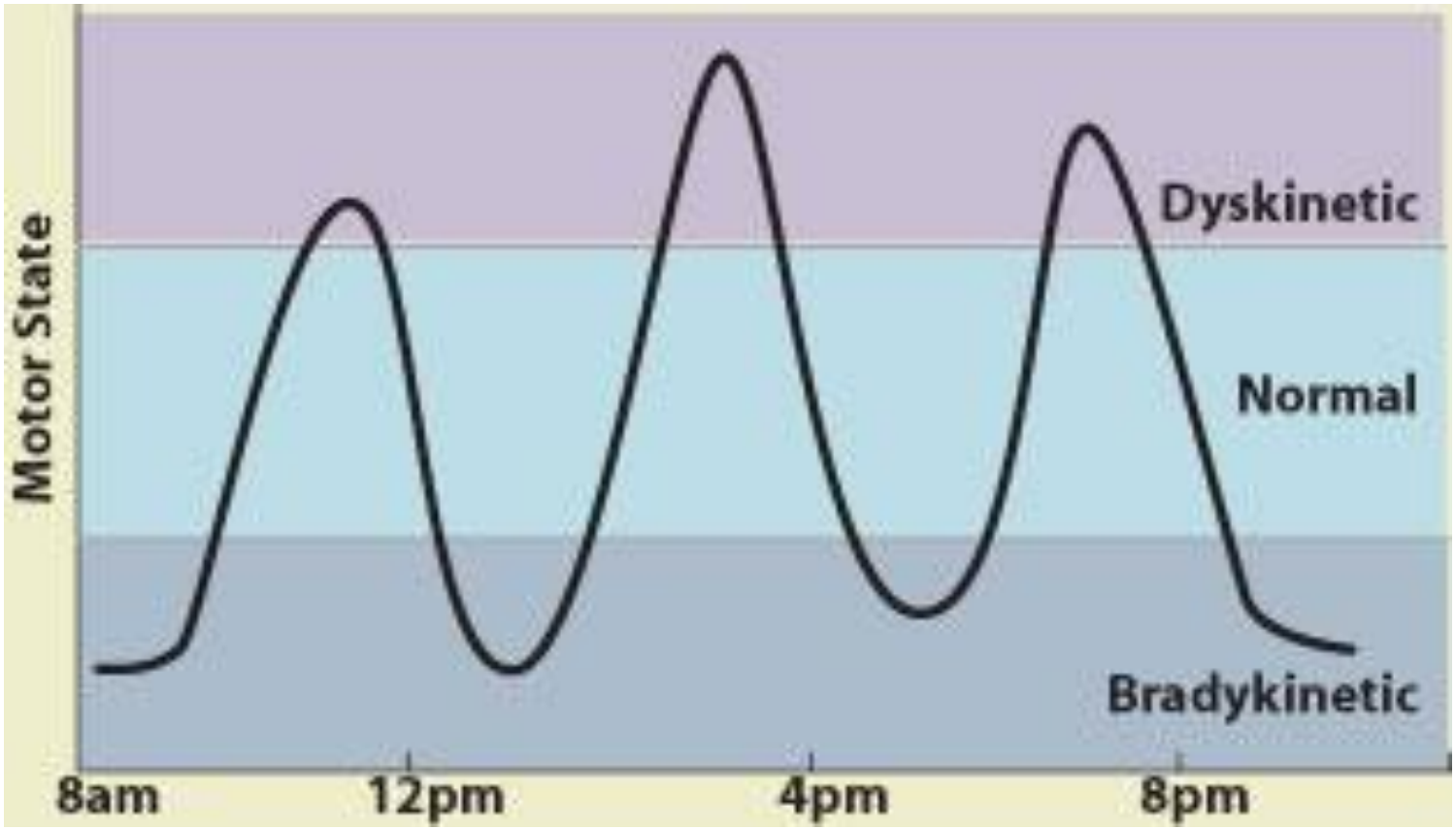


Dopaminergic modulation of the striatum is mainly "tonic" (steady and continuous): a neuro-modulator

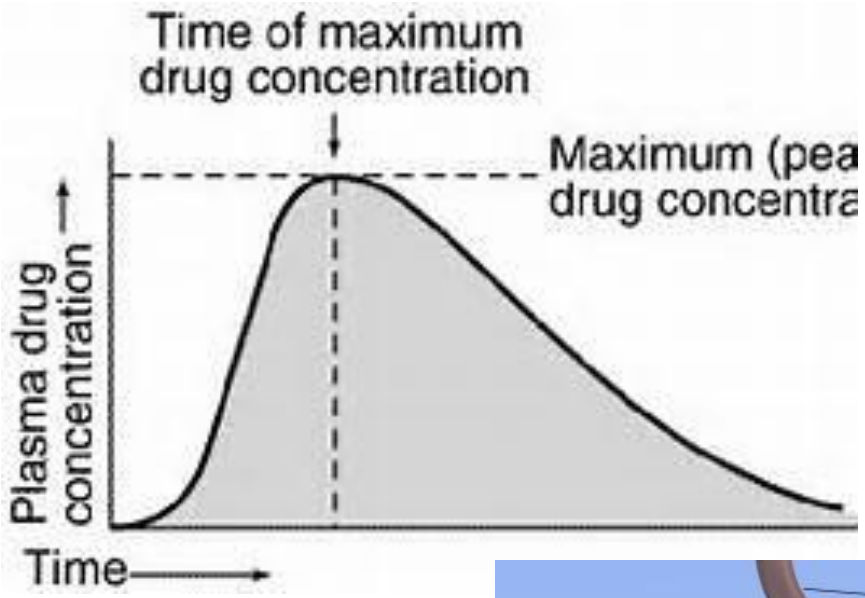
- it is not tightly linked to specific motor events.

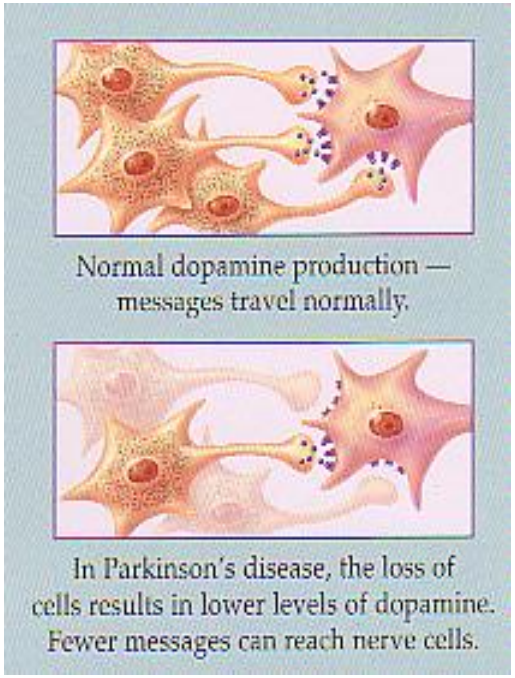
A **steady continuous supply of dopamine** is needed to keep the motor system "en garde", "in tune", and ready to act.

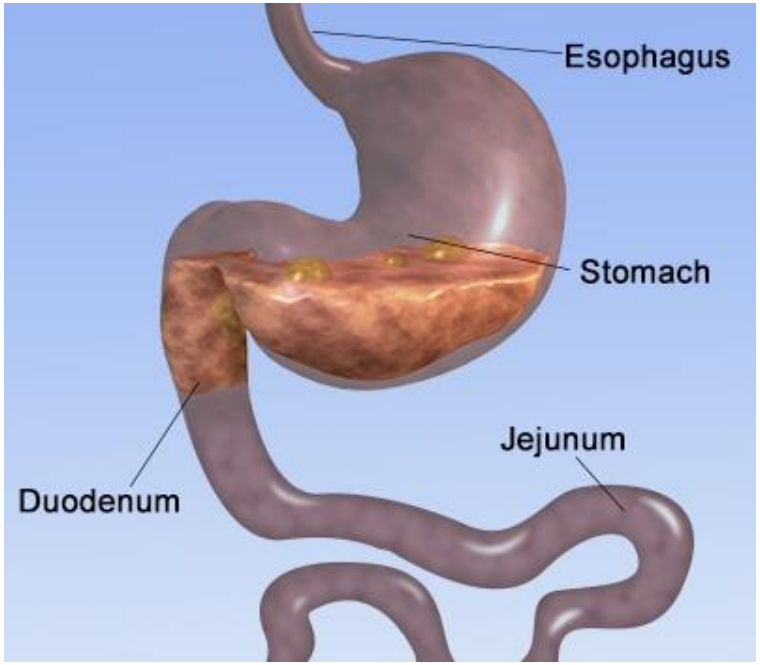
Fluctuations in response to levodopa can occur several years after diagnosis



Why might symptoms fluctuate ?

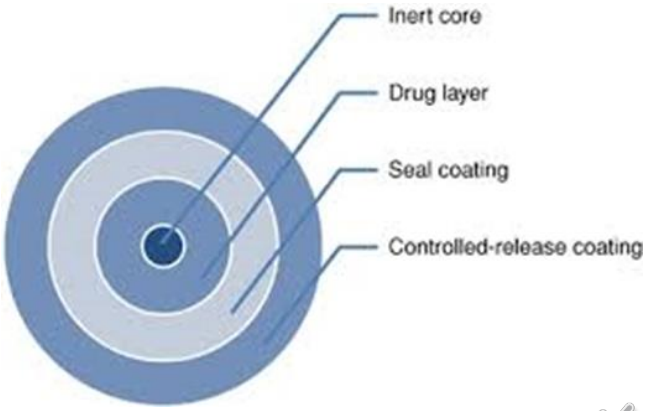






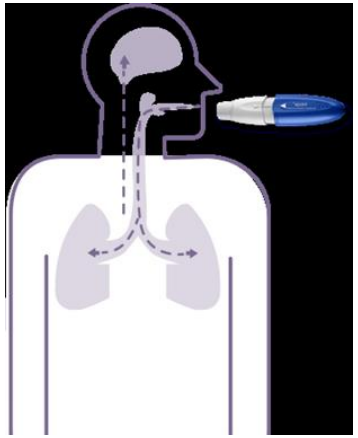
Strategies to adjust carbidopa/levodopa to minimize “fluctuations”:

- Re-time the doses of administration
- Carbidopa / levodopa CR
- Extended release (rytary)



Novel delivery systems of levodopa:

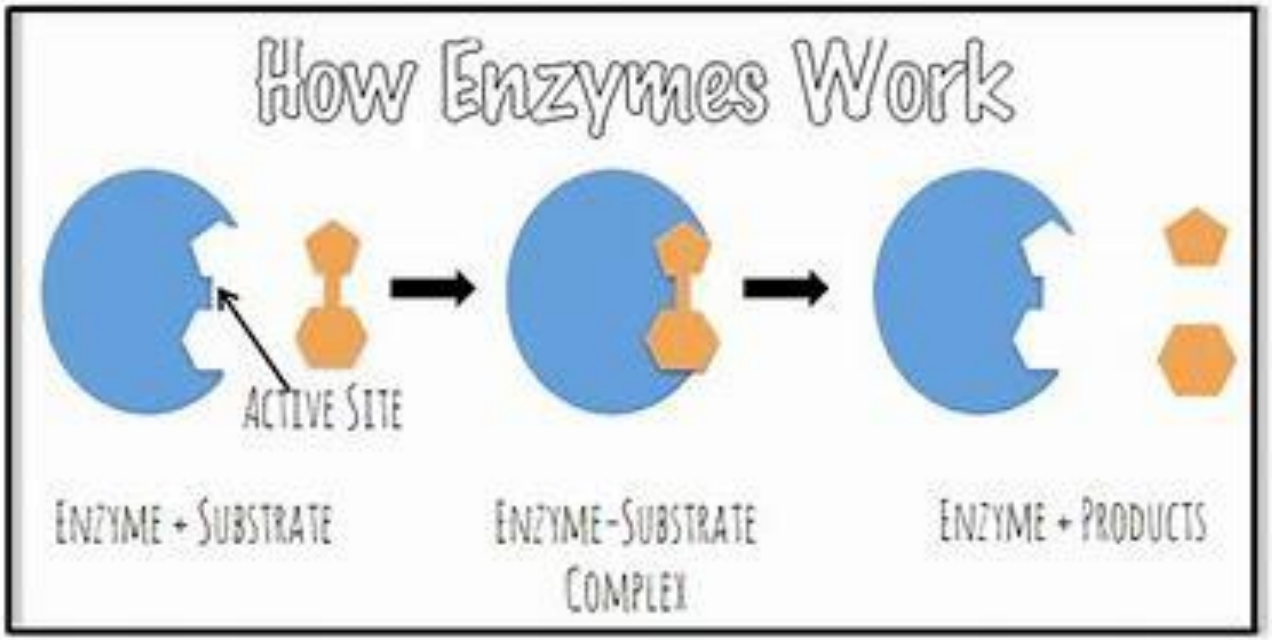
- **“rescue dose” of oral carbidopa /levodopa**
- **Inhaled levodopa (inbrija)**
- Transdermal administration ?



In some cases additional medications are necessary

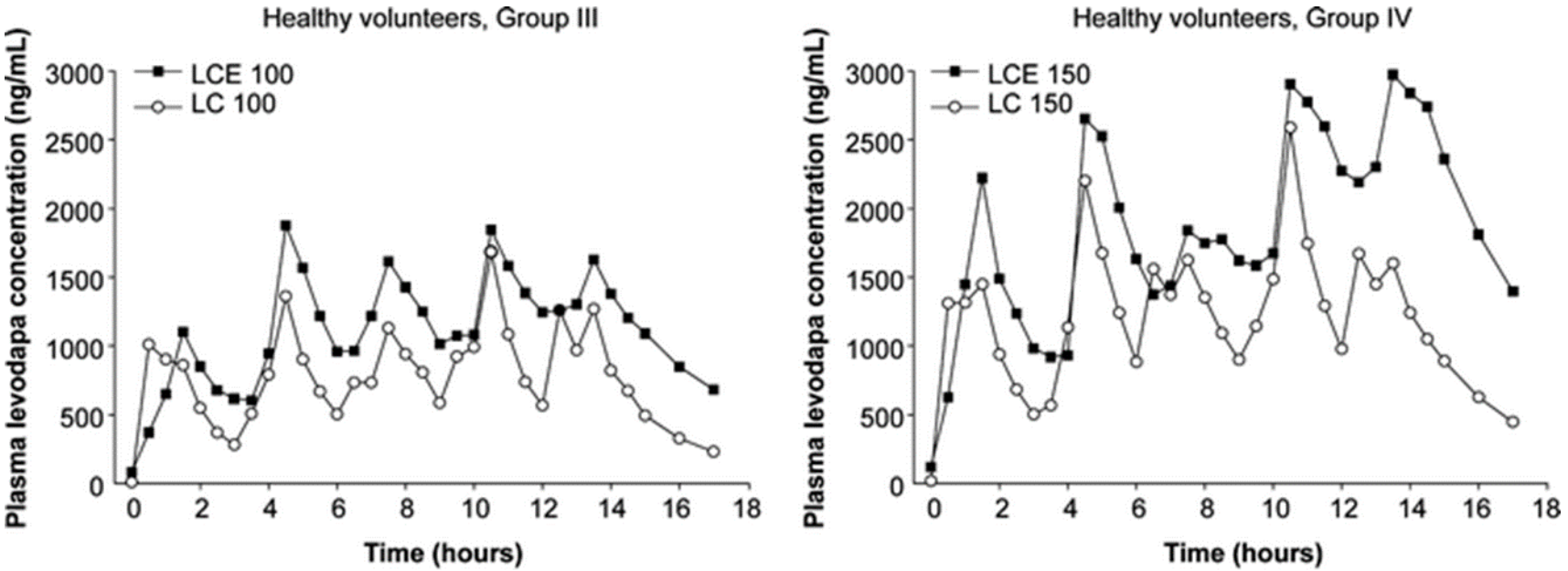
I need another medicine !?!?

There are enzymes that metabolize (break down) levodopa and dopamine:



- Catechol-O-methyl transferase (COMT)
- Monoamine oxidase type B (MAOb)

Blocking these enzymes will modestly enhance and prolong the effect of levodopa:



LCE=levodopa/carbidopa/entacapone; LC=levodopa/carbidopa

- **COMT inhibitors**
  - **entacapone**
  - **tolcapone**
  - **opicapone**
- **MAOb inhibitors**
  - **selegiline**
  - **rasagiline**
  - **safinamide**

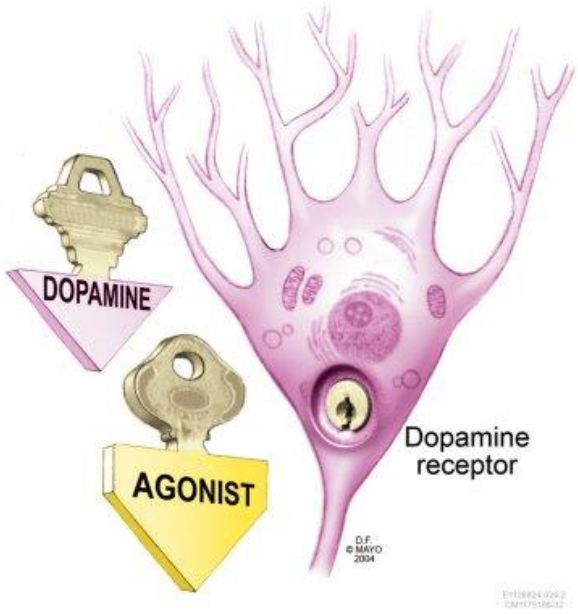
Alternative ways to stimulate the dopamine receptors

"dopamine agonists"

ropinerole

pramipexole

rotigotine patch

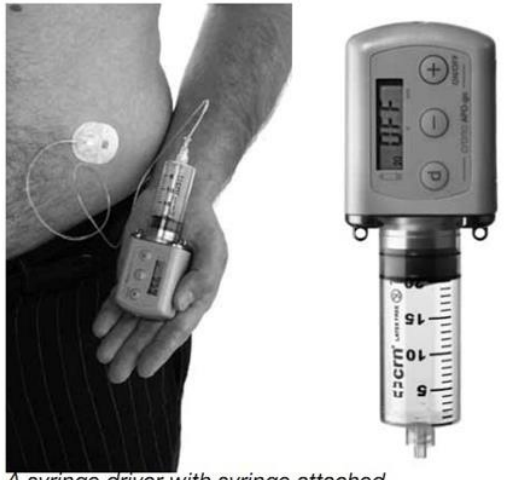


Have a longer "half life" and can be added to reduce fluctuating symptoms or dyskinesias

Watch out for side effects!

Apomorphine

a highly effective dopamine agonist



A syringe driver with syringe attached

Dopamine is not the only neurotransmitter affected by Parkinson disease.

Acetyl choline ("cholinergic:) pathways:

- **Blockers can reduce tremor**

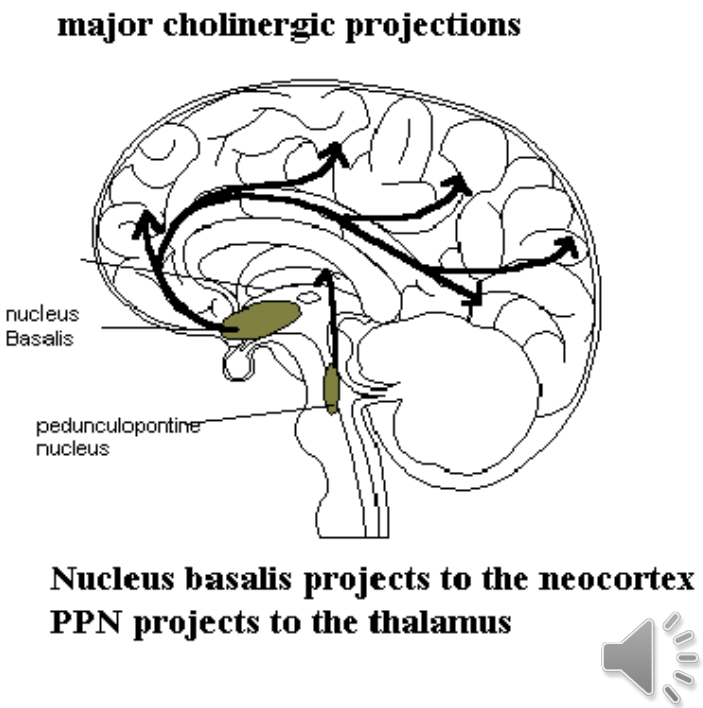
  benztropine

  trihexyphenidyl

- **Enhancers can improve cognitive function**

  rivastigmine

  donepezil



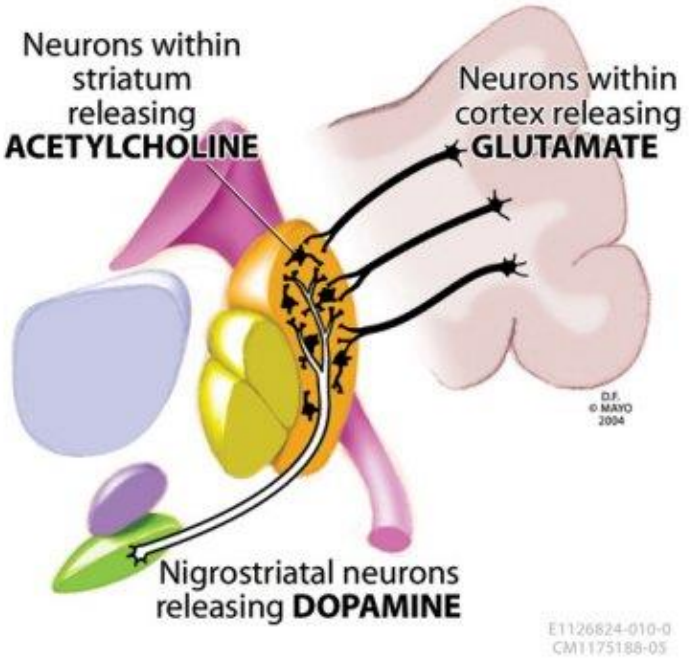
Dopamine is not the only neurotransmitter affected by Parkinson disease.

- **Adenosine 2A blockers**

  istradefylline

- **Glutamine / acetyl choline**

  amantadine



Treatment of dyskinesias:

Dyskinesias reflect excessive dopaminergic brain stimulation in patients with PD

- Usually mild and no treatment is necessary
- If significant:

decrease levodopa doses

or

add amantadine

We try to avoid “polypharmacy” if possible

But:

- **Complex medication schedules are sometimes necessary.**
- **Compliance is imperative.**

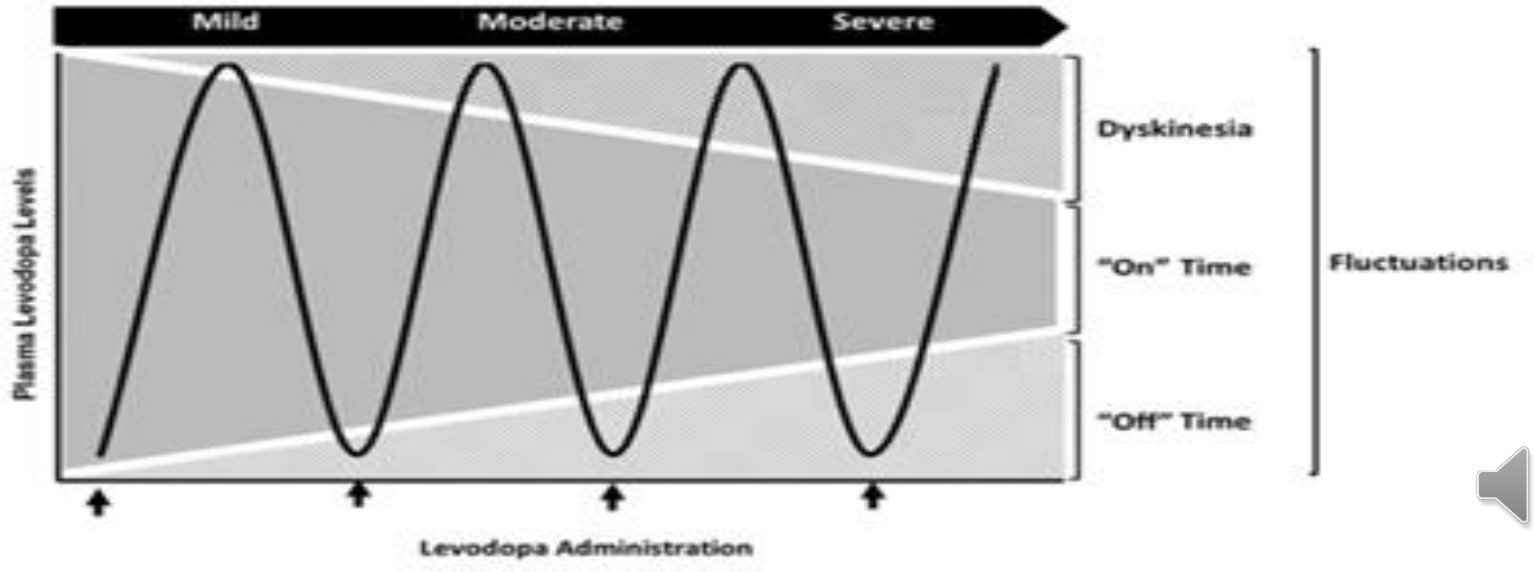
Complex medication schedules might be needed for PD patients with significant “fluctuations”

for example:

	7am	10am	1pm	4pm	7pm	10pm	1am	4am
Carbidopa-levodopa 25/100	1 ½	1 ½	1 ½	1	1		(1)	(1)
Carbidopa-levodopa ER 25/100						1		
Ropinerole 4mg	1		1		1			
Entacapone 200mg	1	1	1	1	1	1		
Selegiline 5mg	1		1					
Amantadine 100mg	1			1				

Extended release carbidopa/levodopa (rytary) might decrease the amount of polypharmacy, but the high cost of this medication limits its availability for all patients.

.



The “pill question”

Patients should be able to name their medications, doses, and intake times:

- **Inaccurate reporting suggests non-compliance or confusion**
- **Inaccurate reporting suggests that the patient cannot take their medications reliably or safely on their own**

YOU SHOULD KNOW YOUR MEDS!

Bring a list of <u>all</u> your medications to each office visit !

What happens when you stimulate the dopaminergic system in Parkinson disease?

The “good”:

- The cardinal motor features of Parkinson disease improve

The “bad”:

- Dyskinesias
- Fluctuating symptoms
- Mild hallucinations

The “ugly”:

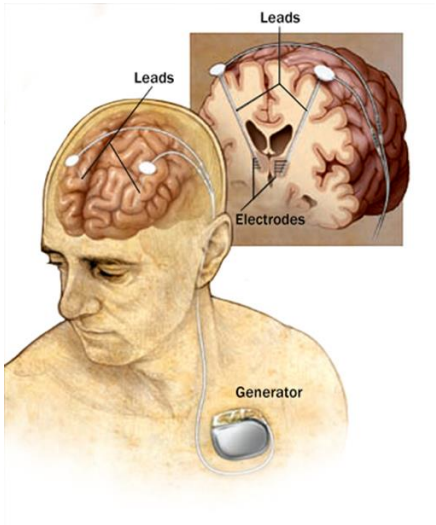
- Impulse control disorders
- Severe hallucinations
- Delusions / full blown psychosis
- Dopamine dysregulation syndrome

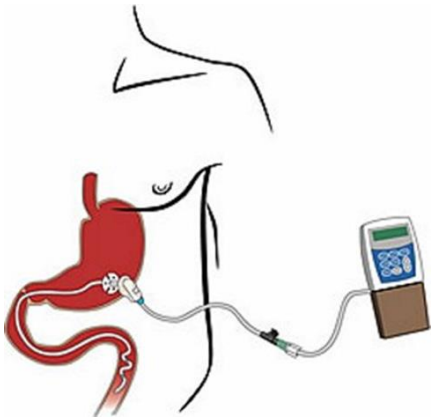
When adjusting oral therapies does not provide adequate control, surgical therapies can reduce motor fluctuations in PD

- **"deep brain stimulation" (DBS)**

  and

- **continuous carbidopa/levodopa gel infusion into the jejunum (duopa)**





have become important therapeutic options that improve the quality of life for carefully selected patients.

What is the goal for treating the motor symptoms in Parkinson disease?

- **To completely eliminate tremor and all other motor symptoms at all times**

(this would be nice, but is seldom possible)

or

- **To keep people functioning in the mainstream of life**

(a realistic goal)

Aiming for "perfection" increases the risk of over-medication and significant side effects.

In conclusion:

- Many effective options are available to control motor symptoms
- There are many effective options to treat the “non-motor” symptoms
- Active research will likely lead to new insights and improved treatments
- There is much you should do in addition to taking medication:

  exercise programs

  improve mental health