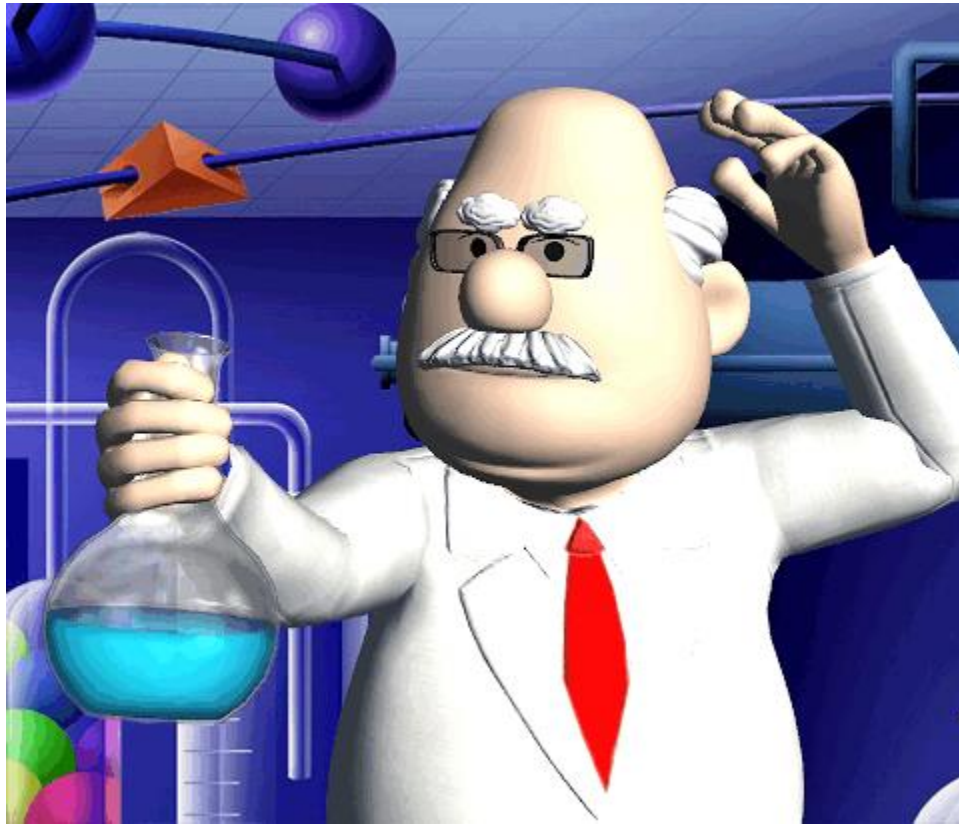
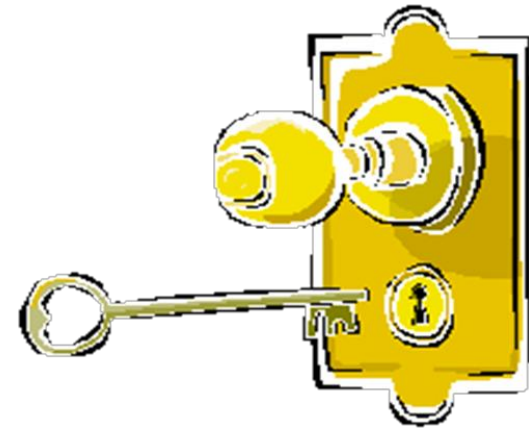
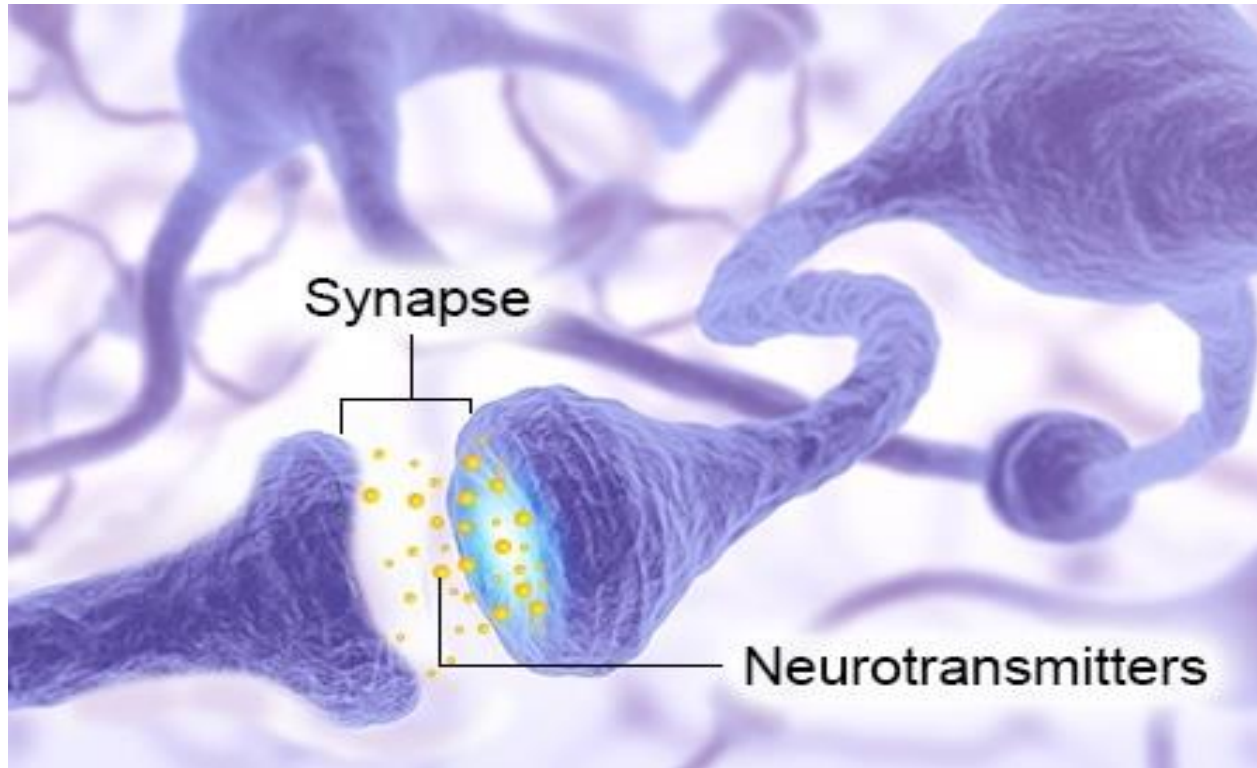


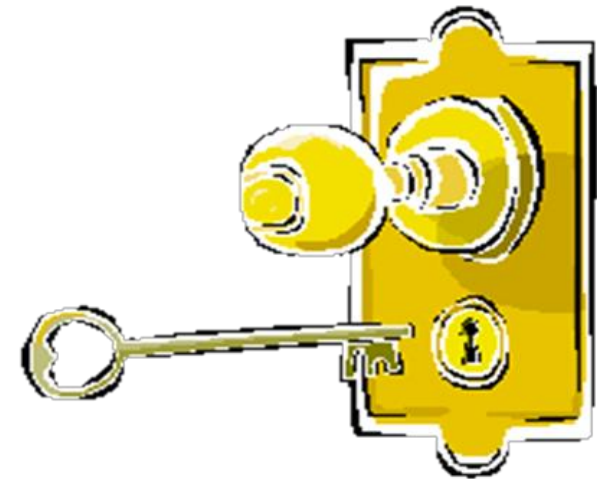
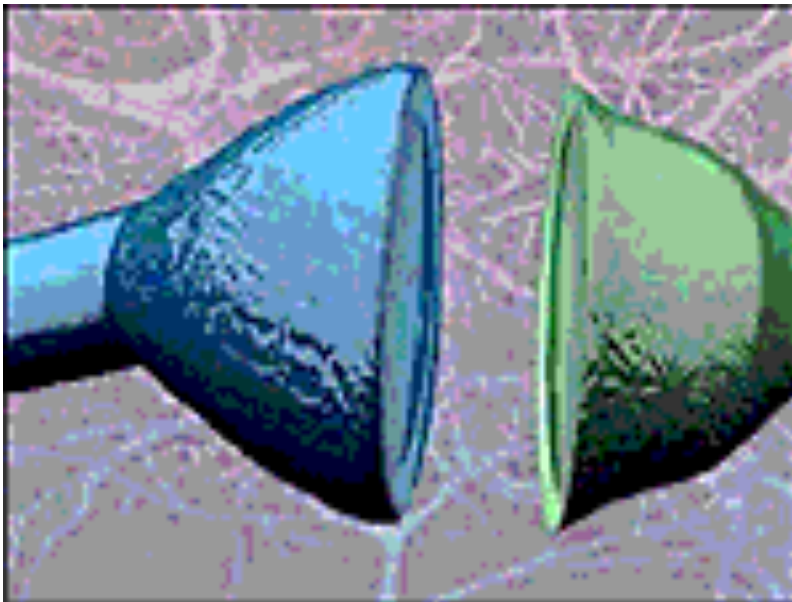
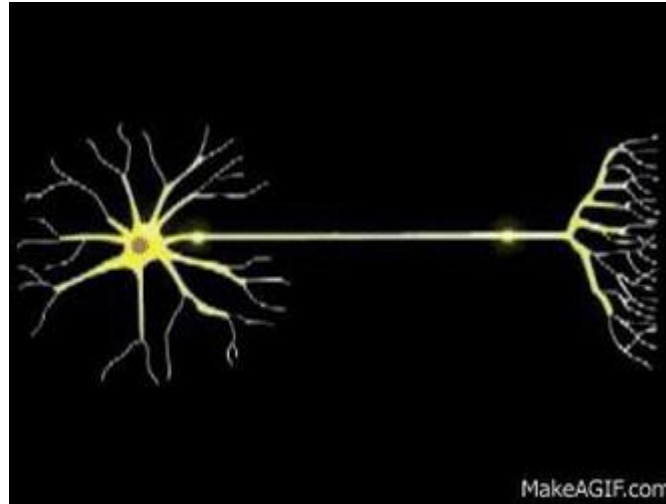
# How were medicines for treating the motor symptoms of Parkinson disease discovered? How do the medicines work ?



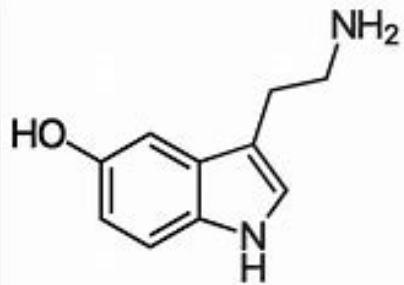
# 1950s neurotransmitter research



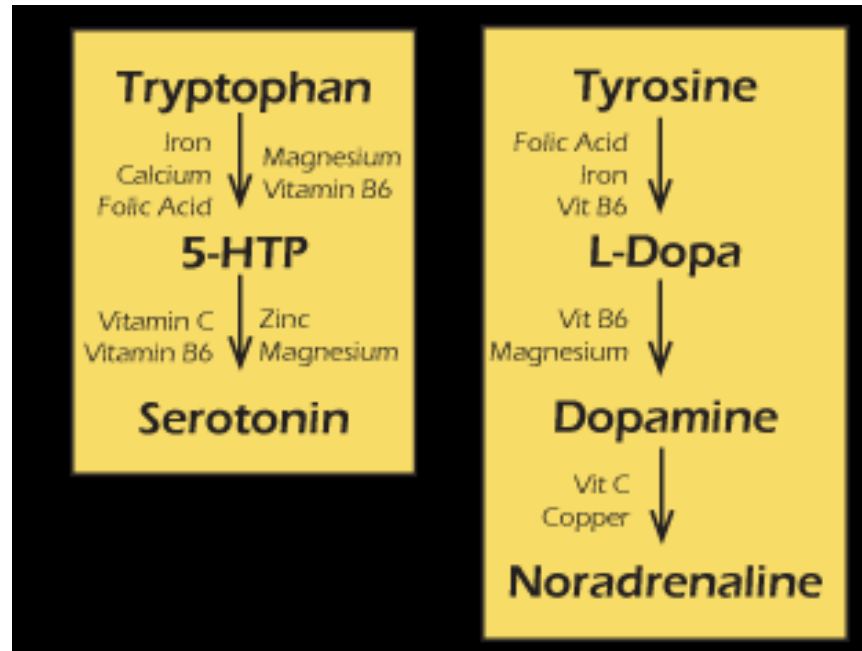
# 1950s neurotransmitter research



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



*Serotonin*



alamy stock photo

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



# 1950s reserpine, "parkinsonism", dopamine

1280

plaid elements a homogeneous population as to their dopaminergic and serotonergic content.

This work was aided by a grant of the Belgian F.N.R.S.

R. LEGRAND  
Belgian Centre of Genetic and Differentiation,  
Department of Human and Comparative Anatomy,  
University of Ghent.

*J. Pharm. Med. (Lond.)*, **1957**, *1*, 1280.  
*Science*, **1957**, *125*, 1280.  
*Ann. N.Y. Acad. Sci.*, **1957**, *107*, 1280.

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

The depletion by reserpine of storage in the body of 3-hydroxytryptophan ("serotonin") and of the catecholamine is now well established\*. In the adrenergic system, the peripheral part of the sympathetic system does not function owing to lack of the essential part of the adrenergic system. However, it remains to be proved to what extent the central action of reserpine may be attributed to changes in brain catecholamine and/or 5-hydroxytryptophan. If lack of amine were responsible for the central action of reserpine, administration of the amine in the form of amine salts or their precursors should counteract these effects, provided that the amine were capable of entering the brain. However, 3-hydroxytryptophan has been shown not to penetrate the blood-brain barrier readily, and difficulty may be overcome by administering the amine as a precursor by administering the amine as a precursor. Preliminary experiments in the laboratory have shown that in the presence of 3,4-dihydroxyphenylalanine, which is the precursor of the catecholamine (dopamine, noradrenaline, and adrenaline), behaves similarly.

Experiments were performed on mice (male) weighing about 18 gm., which received an intraperitoneal injection of reserpine (20-40 mgm. per kgm.). After about 16 hr., when the animals were markedly tranquilized and showed symptoms of the typical 3,4-dihydroxytryptophan, 3,4-dihydroxyphenylalanine, or a mixture of both, was administered.

A dramatic effect of 3,4-dihydroxyphenylalanine in animals which had received reserpine in a dose of 2 mgm. per kgm. intraperitoneally 4 hr. earlier. Within 10-12 min. after the injection of 3,4-dihydroxyphenylalanine the tranquillization as well as the motor depression caused by reserpine had disappeared completely. If the animal had received 3,4-dihydroxyphenylalanine (100 mgm. per kgm. intraperitoneally) about 2 hr. before the 3,4-dihydroxytryptophan, the dose of the latter required to antagonize the effects of reserpine was markedly reduced. This suggests the possibility that the effect of 3,4-dihydroxytryptophan was when administered about two hours after the reserpine was in some way related to it. (The experiments, as in the case of 3,4-dihydroxytryptophan, did not give as consistent results as in the case of 3,4-dihydroxyphenylalanine. In normal saline solution, which was likewise markedly potentiated by reserpine treatment.

A full account of these experiments will be published elsewhere.

LEONIE CROOK  
MARGOT LEVINE  
TON MARRAS  
Department of Pharmacology,  
University of London,  
Lond.  
June 19

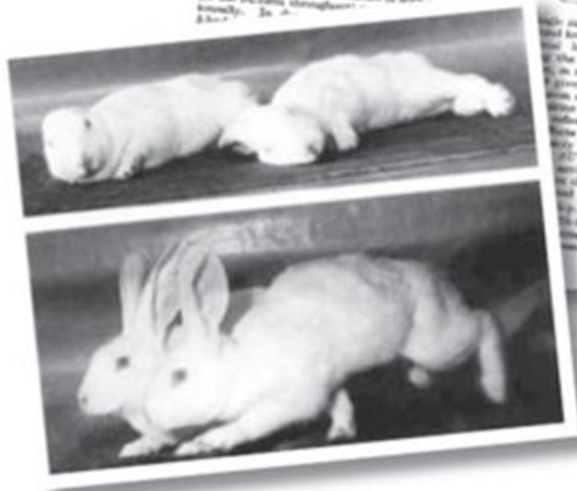
\*H. H. K. Lee, *J. Pharm. Med. (Lond.)*, **1957**, *1*, 1280.  
\*H. H. K. Lee, *J. Pharm. Med. (Lond.)*, **1957**, *1*, 1280.  
\*H. H. K. Lee, *J. Pharm. Med. (Lond.)*, **1957**, *1*, 1280.  
\*H. H. K. Lee, *J. Pharm. Med. (Lond.)*, **1957**, *1*, 1280.

**Antihypertensive Activity of Hexahydro-1-Asp/serpinamide**

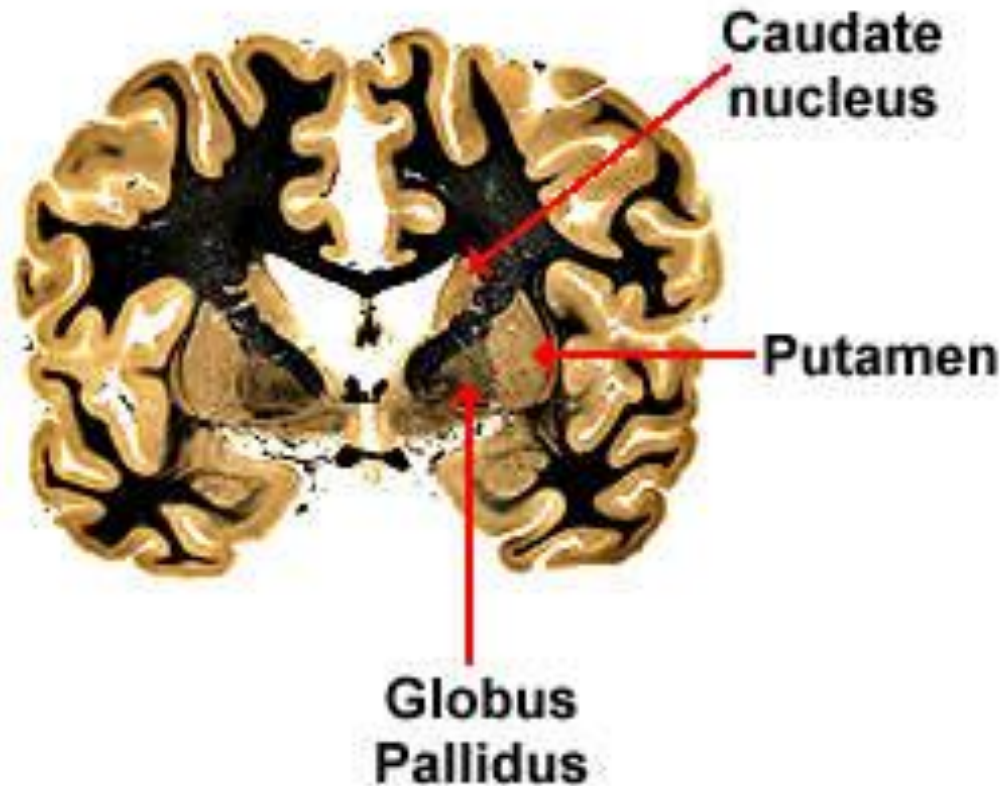
HEXAHYDRO-1-ASP/SERPINAMIDE (I), designated as 627-6029, has been studied for its effect on the cardiovascular system of the dog.

C1CCN(C1)C(=O)N (I)

High intravenous doses of 20 mgm./kgm. of this compound lowered the arterial pressure of reserpine-treated hypertensive dogs while not totally abolishing the blood pressure of normotensive dogs. In normotensive animals 20 mgm./kgm. of given intraperitoneally stimulated the arterial pressure and also markedly augmented cardiac output and also markedly augmented cardiac output. These animals were also in most and had a very low to six weeks following surgery. 627-6029 was orally active and had a marked antihypertensive effect in the normotensive, hexahydroserpinamide was also given hexahydroserpinamide was given 100-150 mgm. i.v.  $n=7$   $t=47.0$   $P<0.01$ ;  $M$ , 10-12;  $S$ , 10-12 per cent.  $t=10.0$ ;  $C$ , 7.1-8.1;  $M$ , 10-12;  $S$ , 10-12. The mechanism of this action with hydroxy-



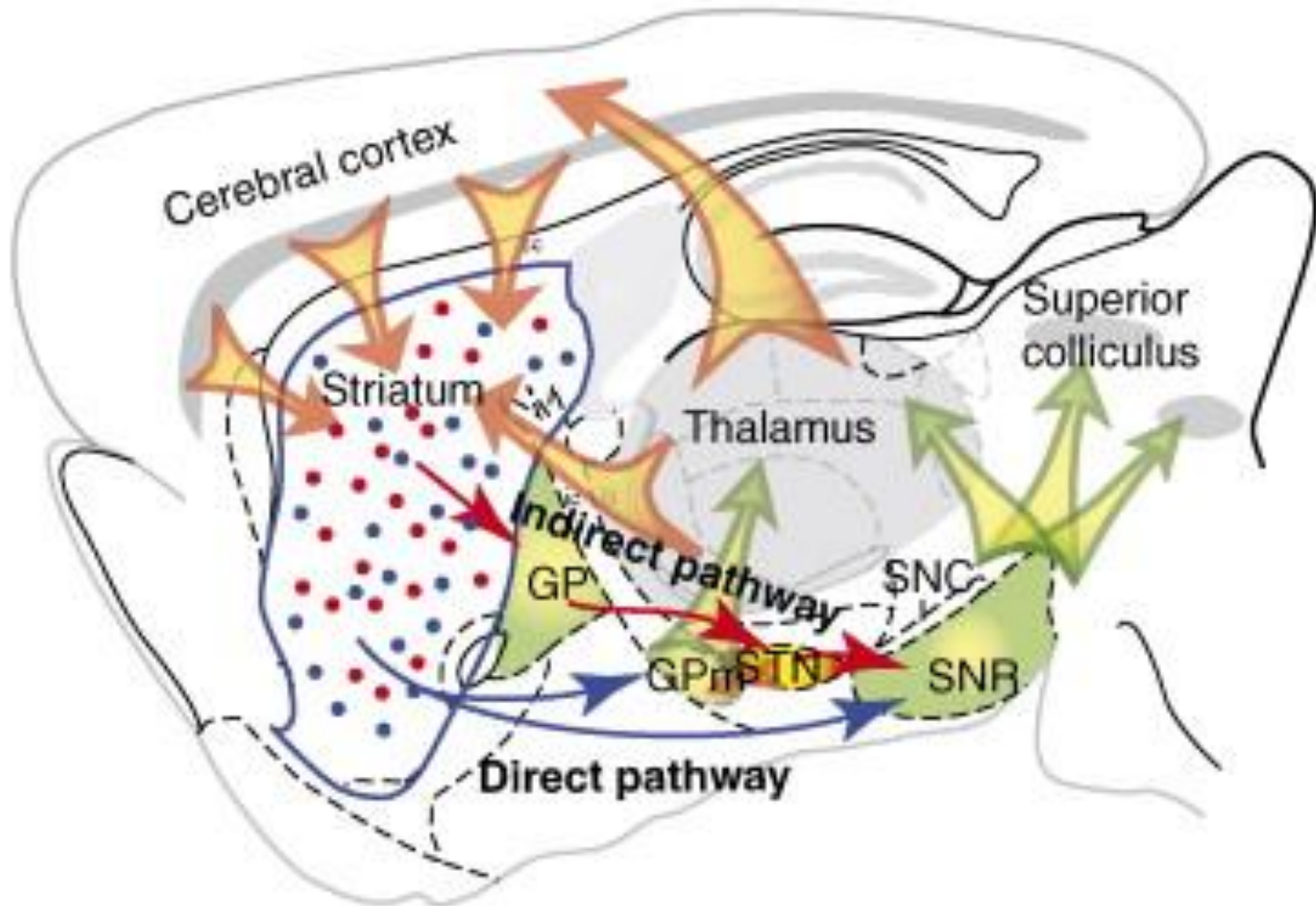
# 1958 discovering the importance of dopamine



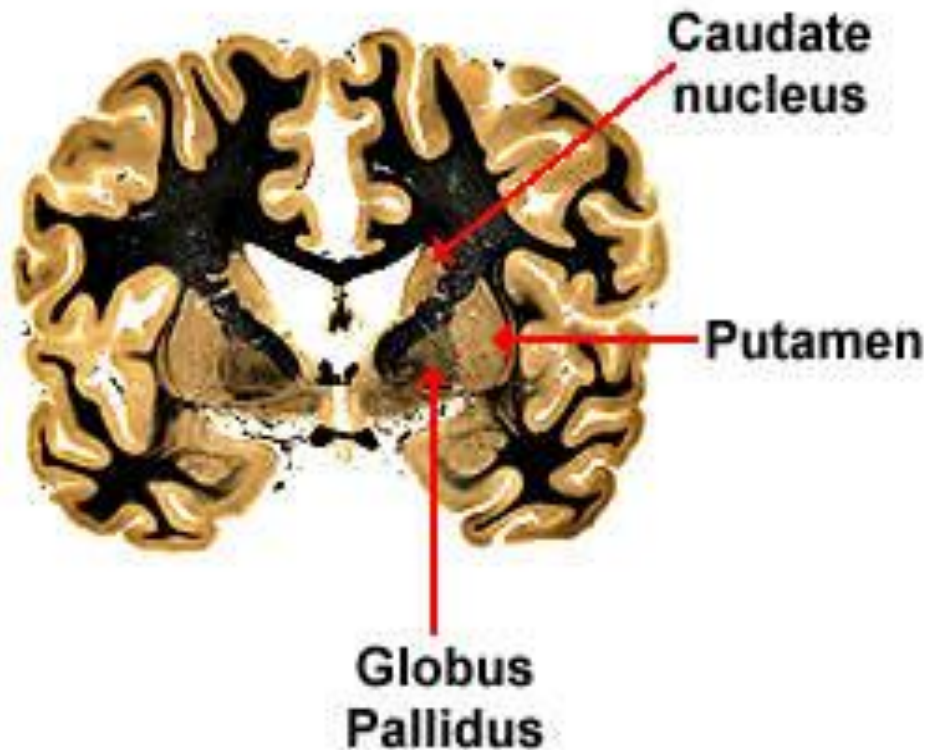
**dopamine is a neurotransmitter**  
and is highly concentrated in the “**striatum**”  
(caudate and putamen)



# 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.





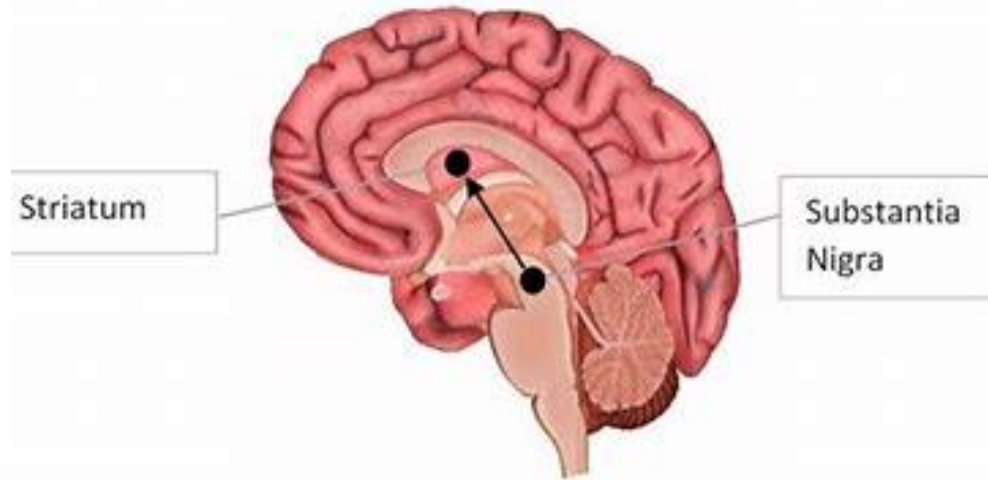
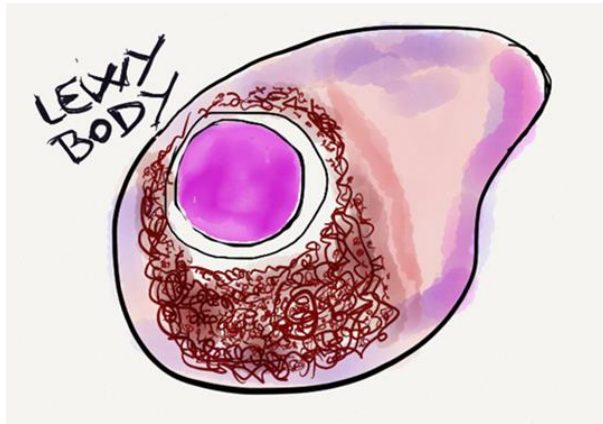
## 1960 Post-mortem neurochemistry of PD



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

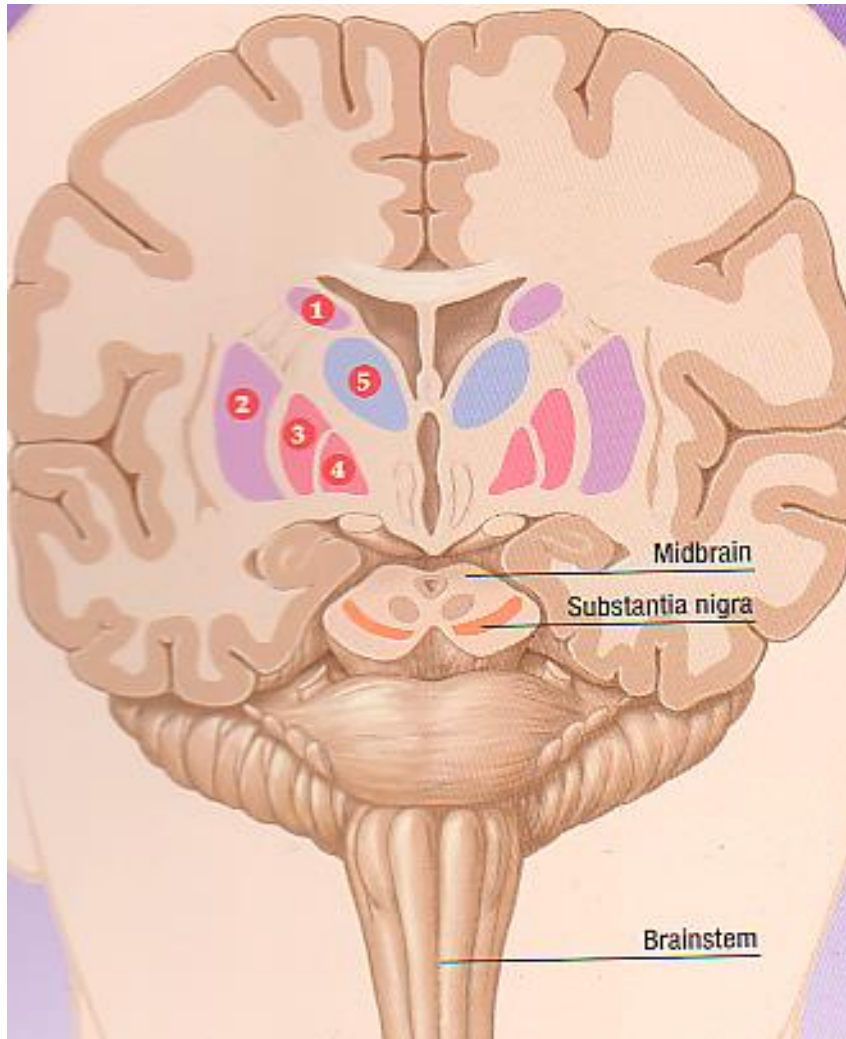


**1960 Dr. H. speculated that the damaged nerve cells in the substantia nigra were the cells that normally produce dopamine**



The model of PD in the late 1960s :

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



Normal dopamine production —  
messages travel normally.



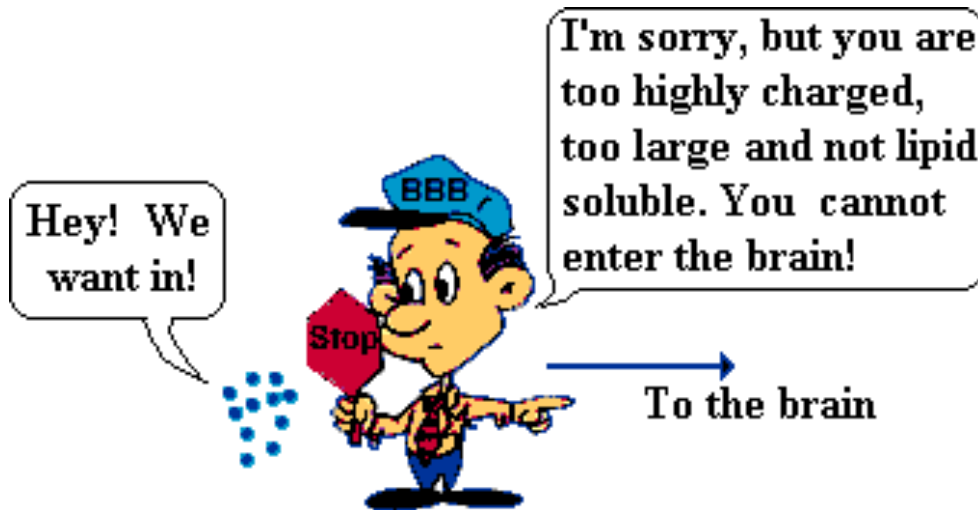
In Parkinson's disease, the loss of  
cells results in lower levels of dopamine.  
Fewer messages can reach nerve cells.



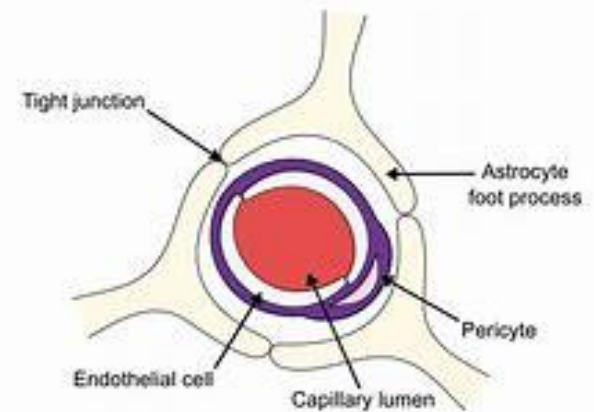
# If the brain needs more dopamine, why not give oral dopamine ?



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



## Blood-Brain Barrier



© Lineage

Moises Dominguez

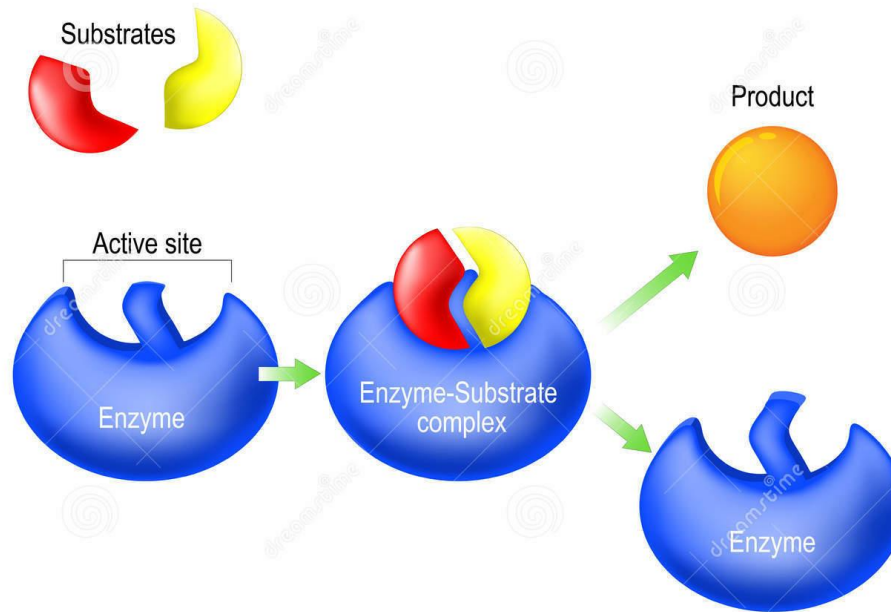
**Orally administered dopamine cannot enter the brain from the bloodstream.**

Oral dopamine is also very nauseating and poorly tolerated.



# How does the brain make dopamine ?

"LOCK and KEY" model  
SYNTHESIS



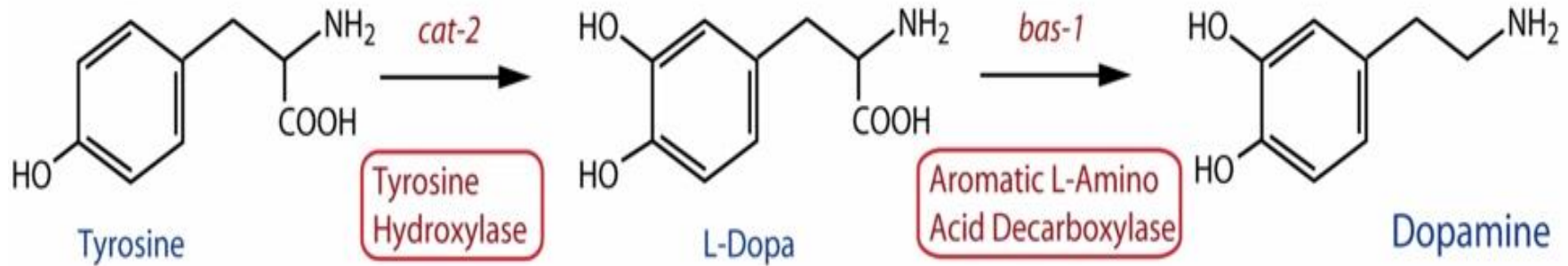
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## Enzymes assist in chemical synthesis.



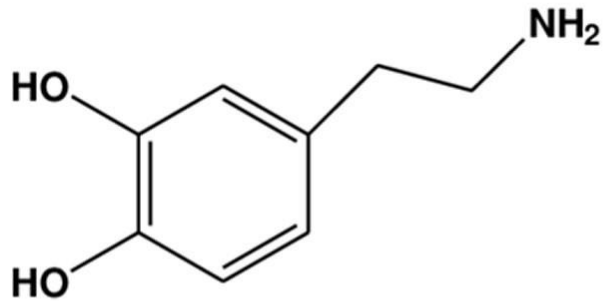
# How does the brain make dopamine ?



- 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**

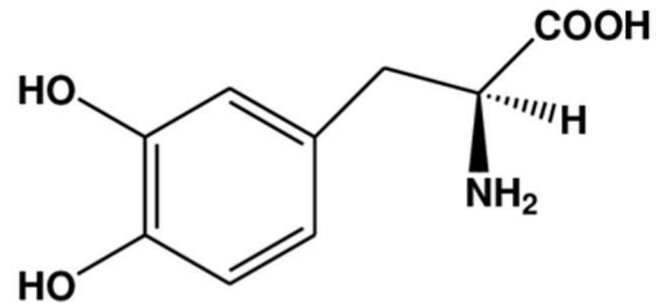


# Unlike oral dopamine, oral levodopa can enter the brain.



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:

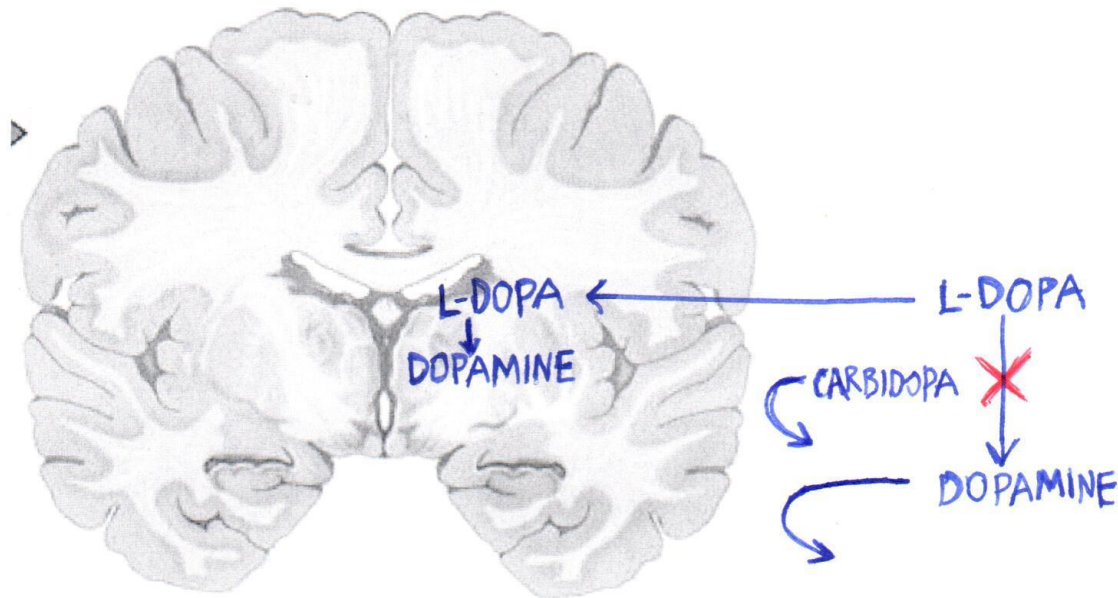
- L-dopa was shown to be effective in treating the motor symptoms of Parkinson disease

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 in 1971 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

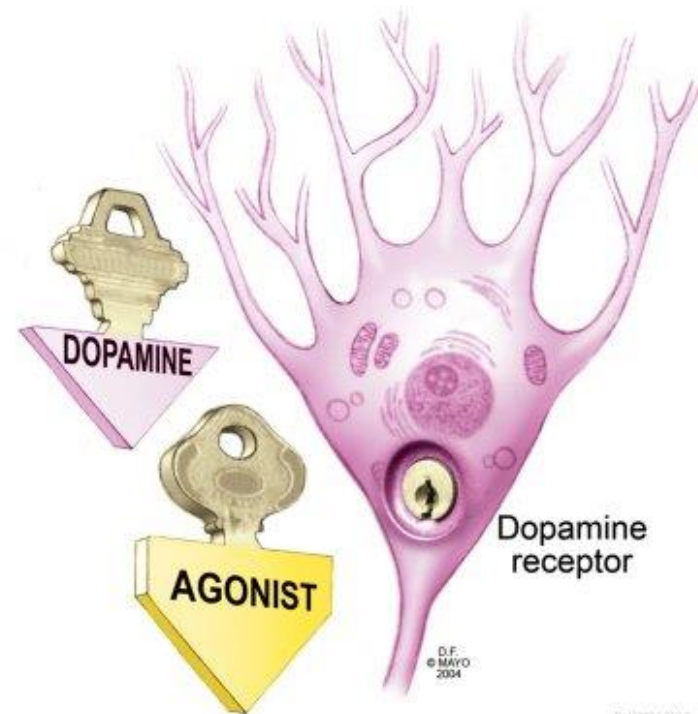
Current dopamine agonists commonly  
used to treat Parkinson disease:

**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 be 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 most effective 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

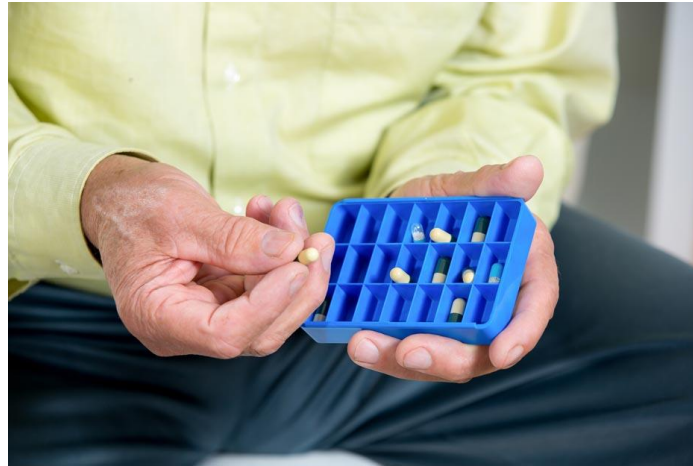


## Avoid over-medication!

- 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”**

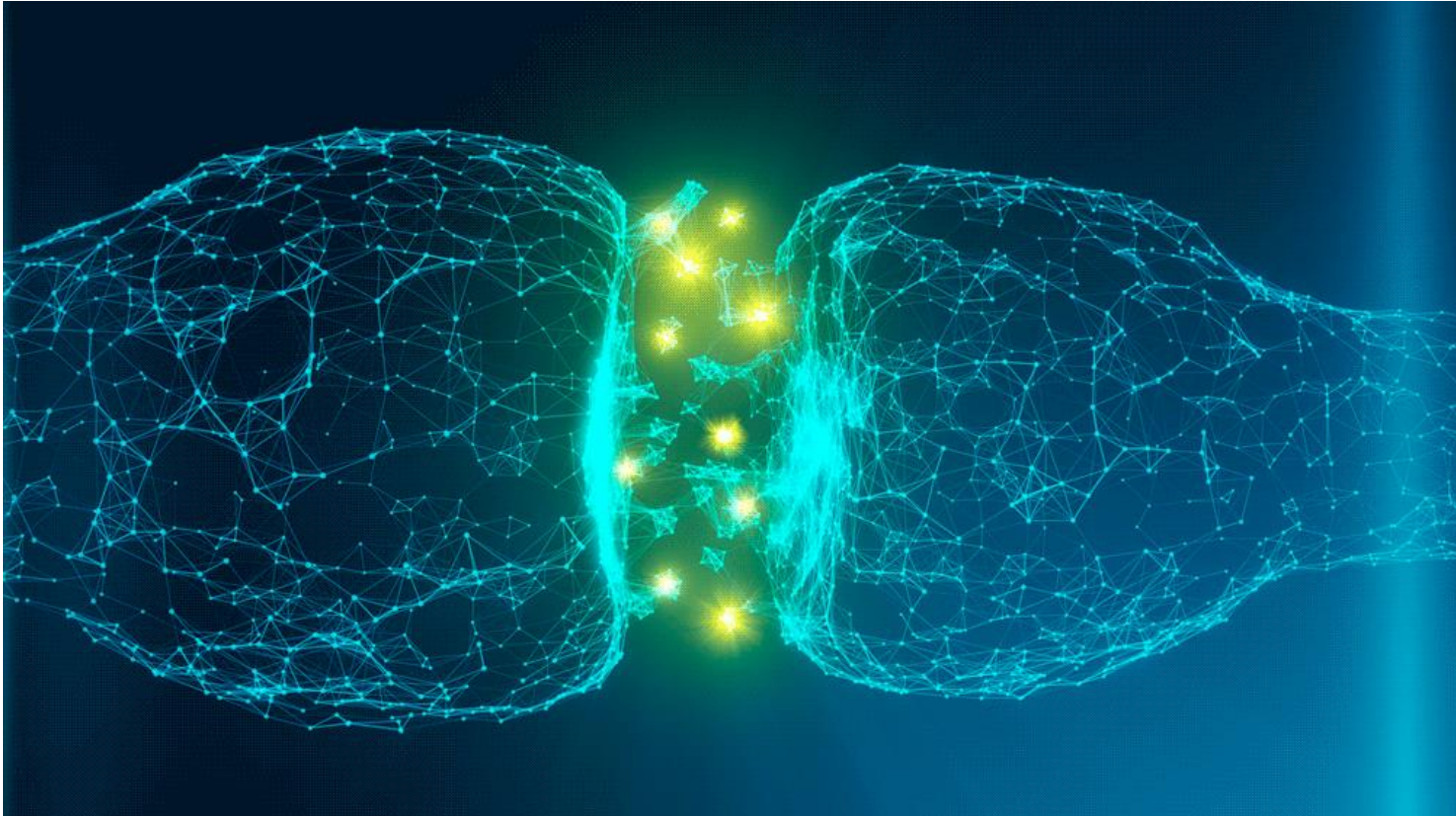


Delaying treatment when PD motor symptoms are significant makes no sense:

**you cannot save the**  
**“best response” for later**

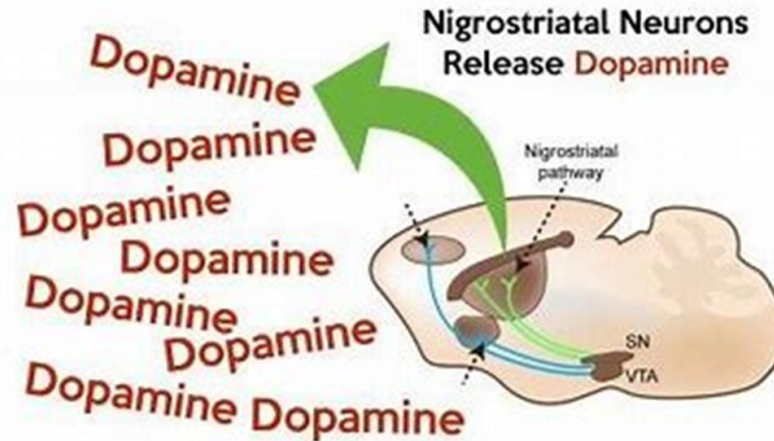


# How is dopamine released in the striatum ?





# Role of dopamine in facilitating movement

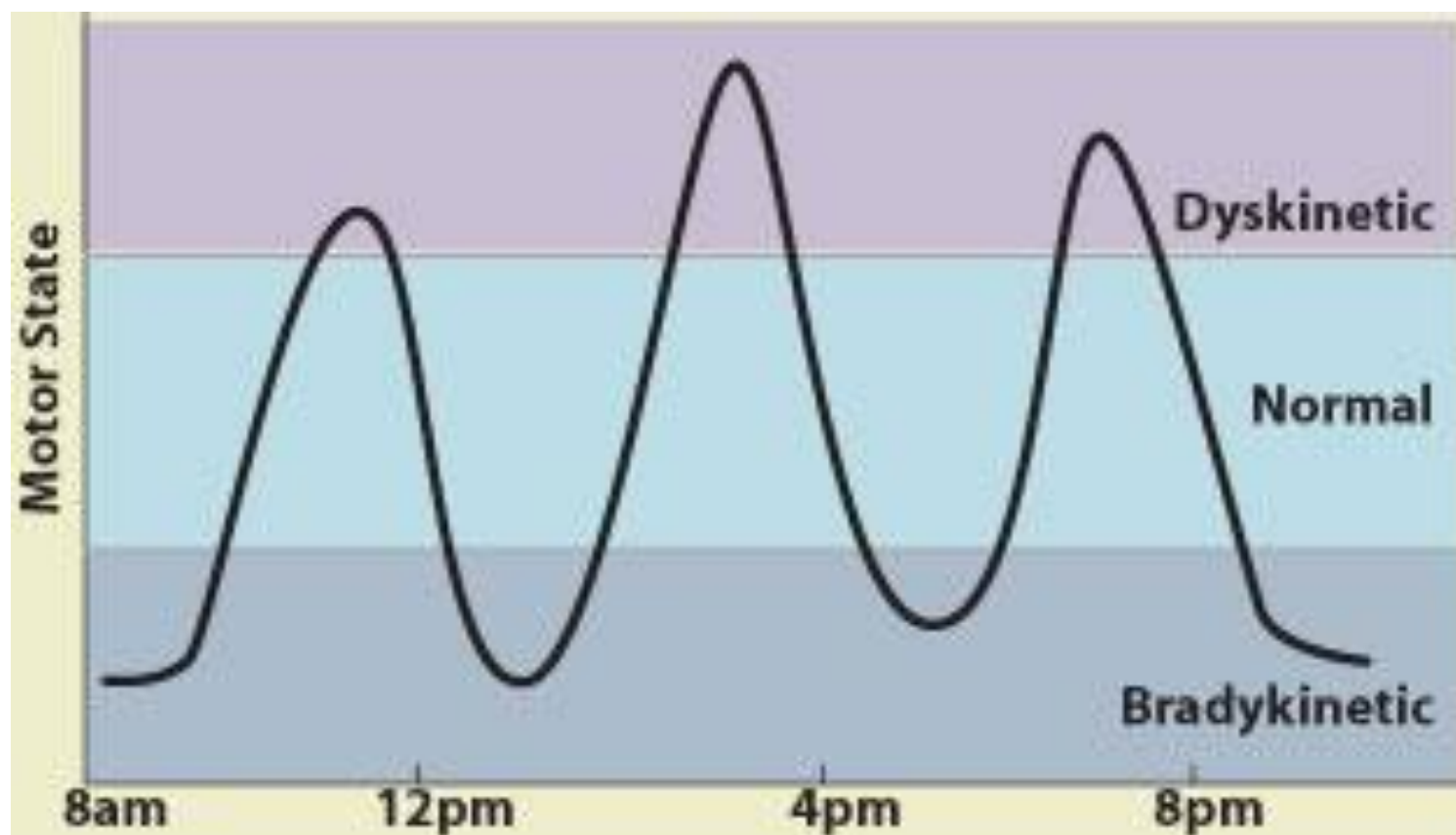


Dopaminergic modulation of the striatum is mainly “tonic” (steady and continuous): a neuro-modulator  
- it is not tightly linked to specific motor events.

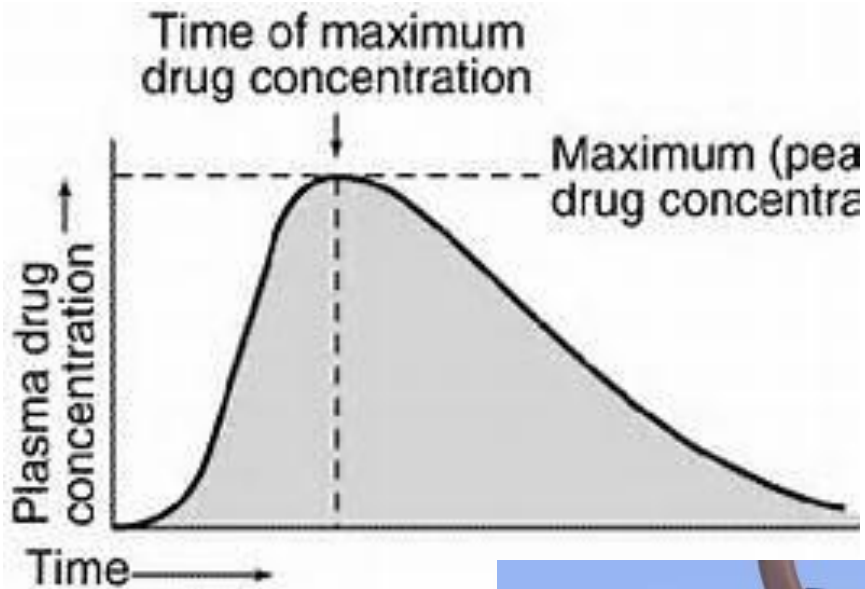
**A steady continuous supply of dopamine** is needed to keep the motor system “en garde”, “in tune”, and ready to act.



# Fluctuations in response to levodopa can occur several years after diagnosis



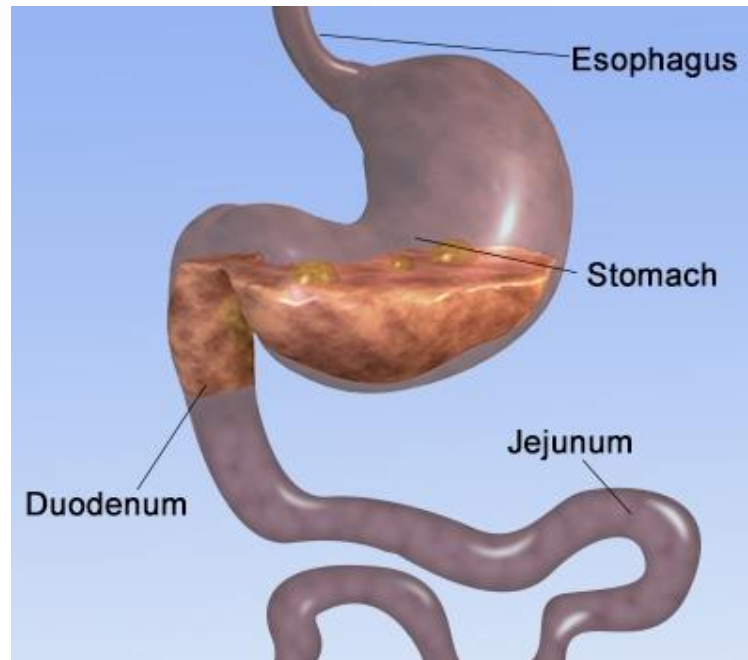
# Why might symptoms fluctuate ?



Normal dopamine production — messages travel normally.

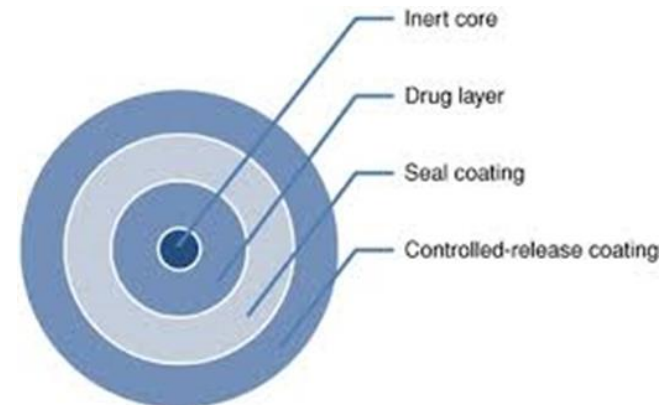


In Parkinson's disease, the loss of cells results in lower levels of dopamine. Fewer messages can reach nerve cells.



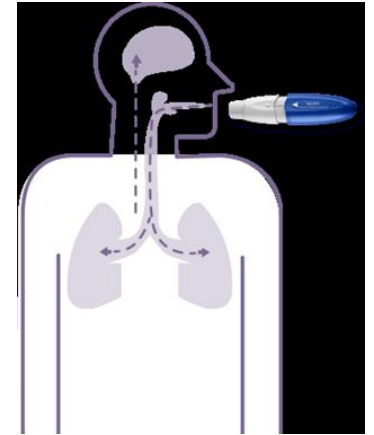
# Strategies to adjust carbidopa/levodopa to minimize “fluctuations”:

- 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 ?

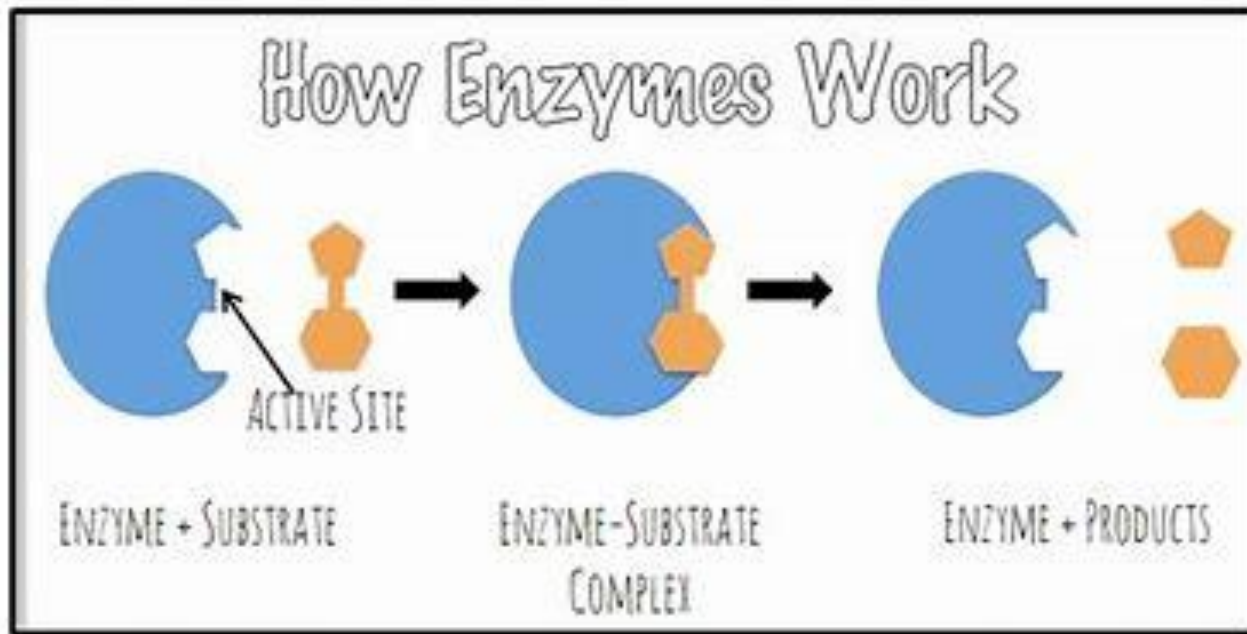


In some cases additional medications are necessary

**I need another medicine !?!?**



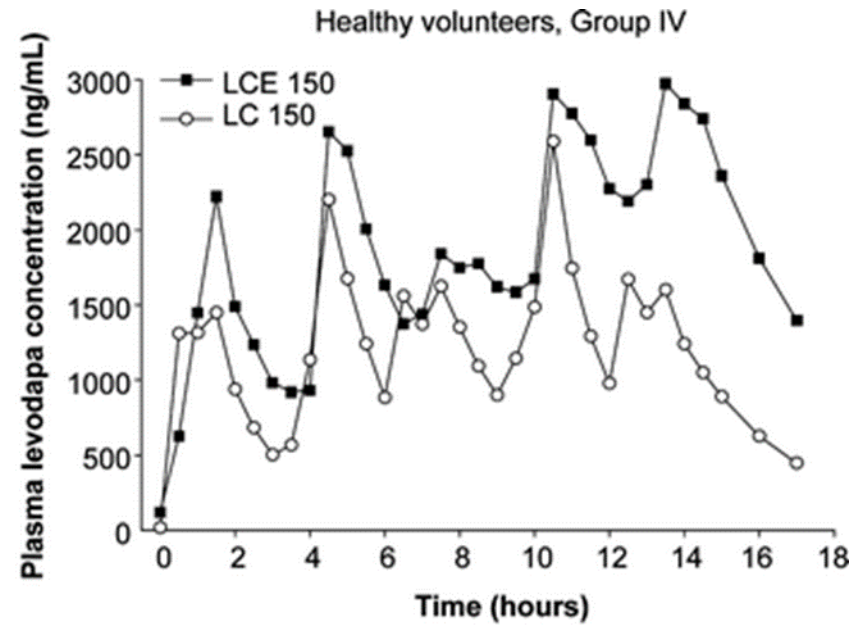
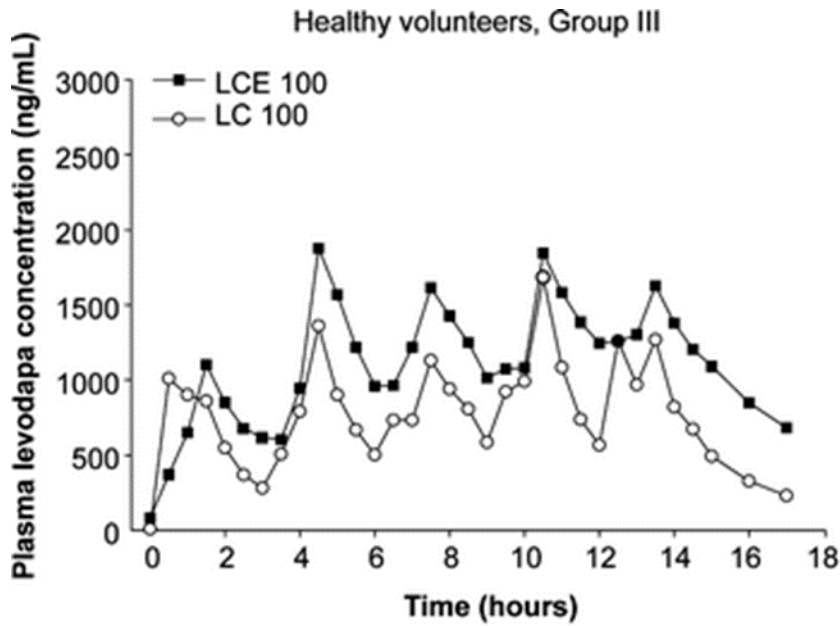
**There are enzymes that metabolize (break down) levodopa and dopamine:**



- **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”

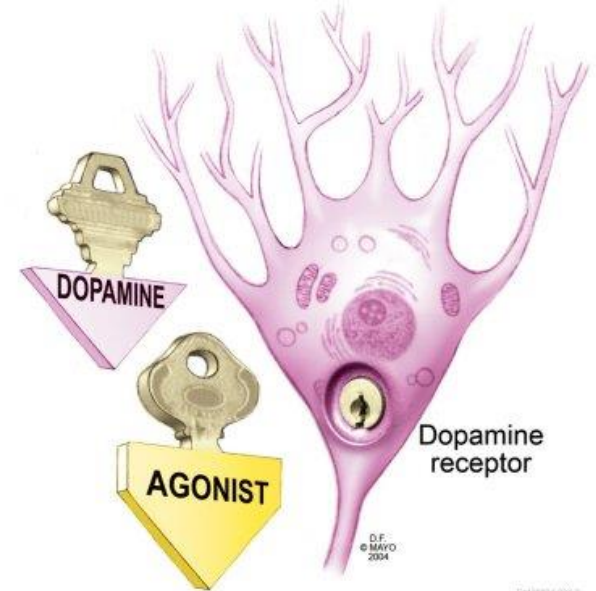
ropinerole

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

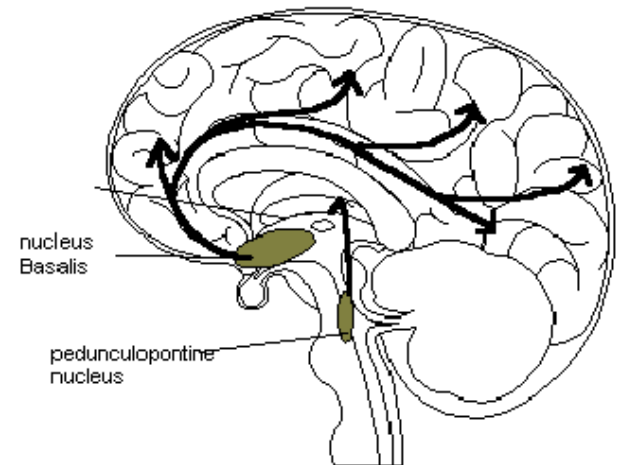
trihexyphenidyl

- **Enhancers can improve cognitive function**

rivastigmine

donepezil

major cholinergic projections

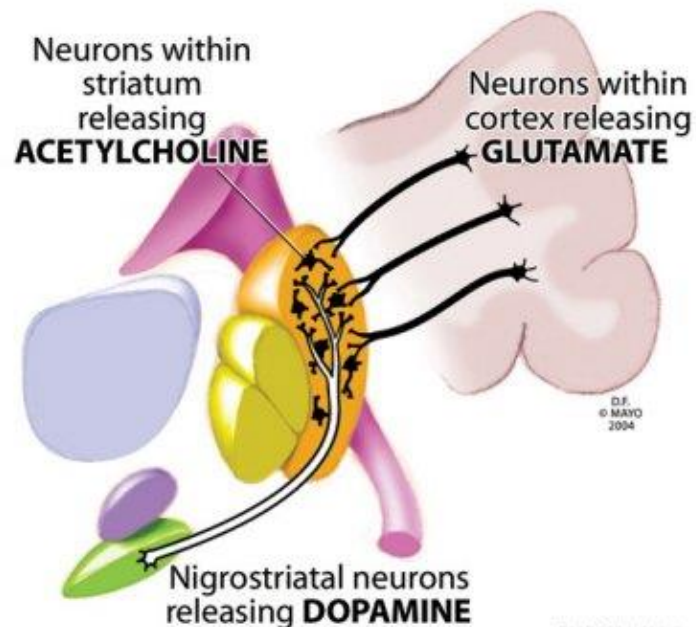


Nucleus basalis projects to the neocortex  
PPN projects to the thalamus



# Dopamine is not the only neurotransmitter affected by Parkinson disease.

- **Adenosine 2A blockers**  
    istradefylline
- **Glutamine / acetyl choline**  
    amantadine



E1126824-010-0  
CM1175188-05



# 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.**

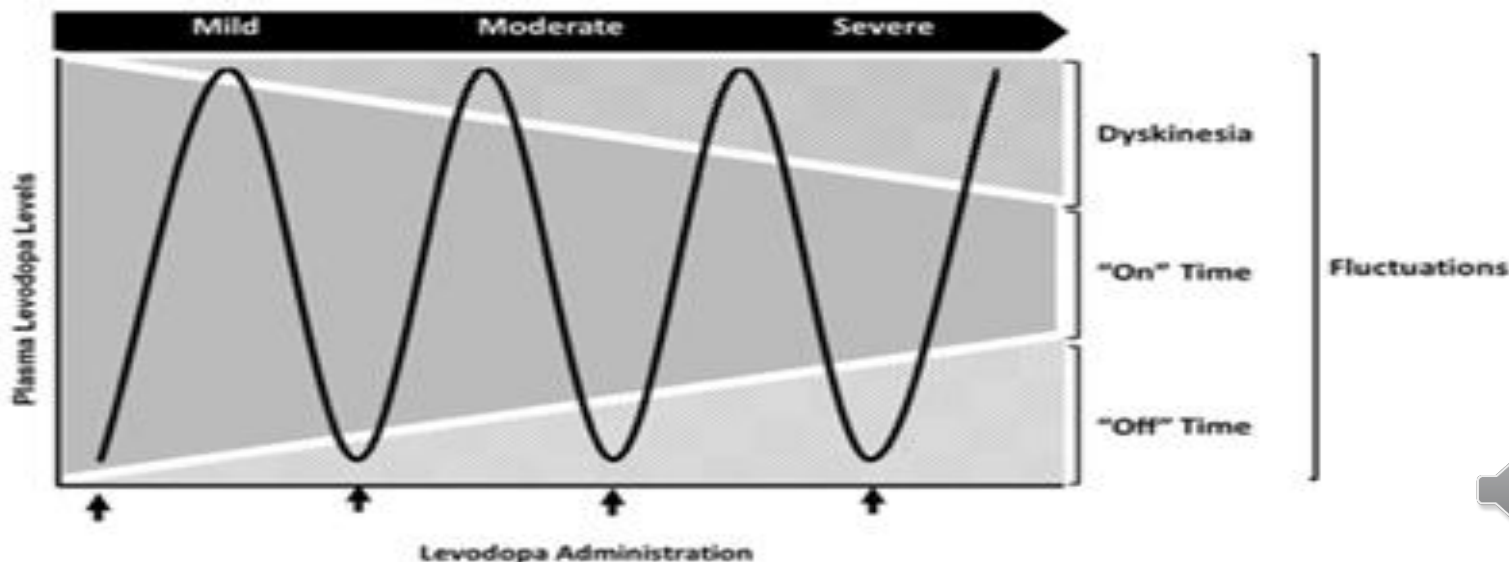


# Complex medication schedules might be needed for PD patients with significant “fluctuations”

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 all 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”:

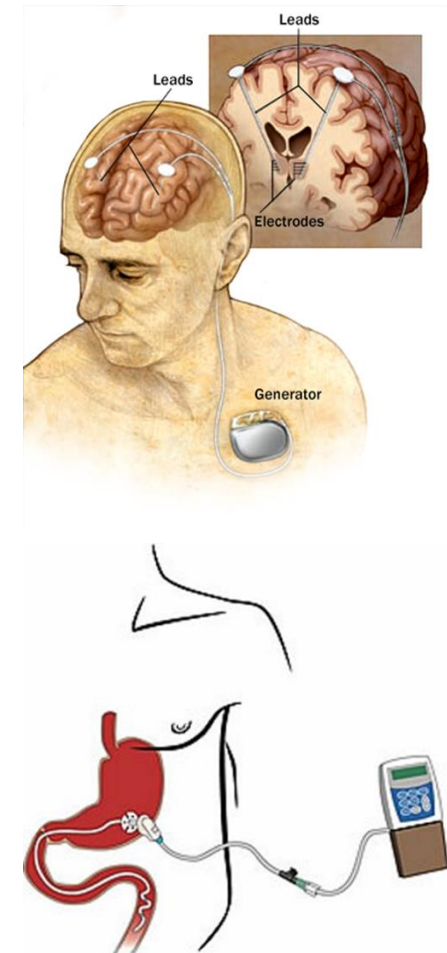
- Impulse control disorders
- Severe hallucinations
- Delusions / full blown psychosis
- Dopamine dysregulation syndrome



# 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**

