

Parkinson's disease

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DEFINITION

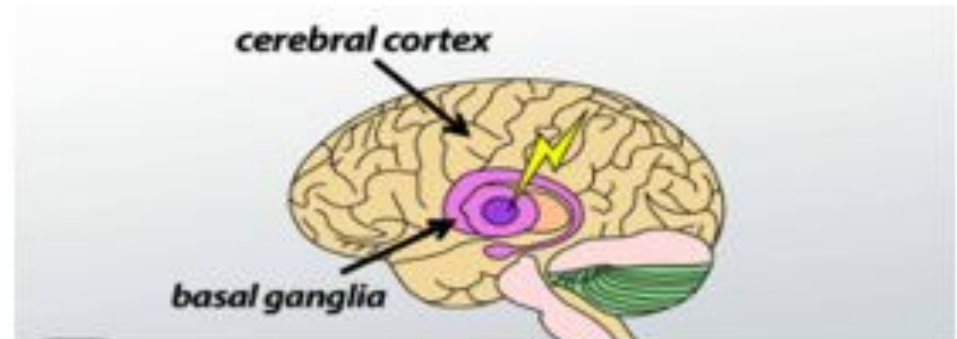
- Parkinson's disease is a neurodegenerative disorder, which leads to progressive deterioration of motor function due to loss of dopamine-producing brain cells.

OVERVIEW

- 2nd most common neurodegenerative disease after Alzheimer's disease
- Age-related, progressive disorder
- Dopamine, critical modulator of striatal output, is markedly decreased PD = control fine skillful movements



- Loss of dopaminergic input to basal ganglia
- **Basal ganglia** responsible for **motor control**, motor learning, executive functions and behaviors, and emotions
- Result in imbalance with dopamine and acetylcholine



- PD is estimated to affect 100-180 in 100,000
- Annual incidence of 4-20 per 100,000
- Rising prevalence with age
- Male: Female ratio is 3:2

- Genetic influence is most pronounced in individuals who develop symptoms at a younger age
- Risk factors for the disease, shown in various studies, include a history of carbon monoxide poisoning, residing in a rural area, exposure to pesticides or herbicides

Oxidative stress theory

- Increased iron level
- Increased aluminum levels
- Reduced glutathione levels
- Evidence of oxidative damage to
 - Lipids, DNA, proteins, tyrosine-containing molecules

- Oxidative stress
- Mitochondrial dysfunction
- Excitotoxicity

- Mitochondria dysfunction a **loss of efficiency** in the **electron transport chain** and **reductions in the synthesis** of high-energy molecules (**ATP**), is a characteristic of **aging**, and essentially, of all **chronic diseases**. include **neurodegenerative diseases**
- Excitotoxicity **excessive activation** of neuronal amino acid receptors
- **Cell death** resulting from the **toxic actions** of **excitatory amino acids**.

genetics

- Young onset <40yrs
- Juvenile onset <20yrs
- Parkin mutations: parkin gene
- Mutations in the alpha synuclein and ubiquitin carboxy hydrolase: seen in autosomal dominant PD

proteins maintain normal neurotransmitter release

Genetic influence is most pronounced in individuals who develop symptoms at a younger age

Pathology

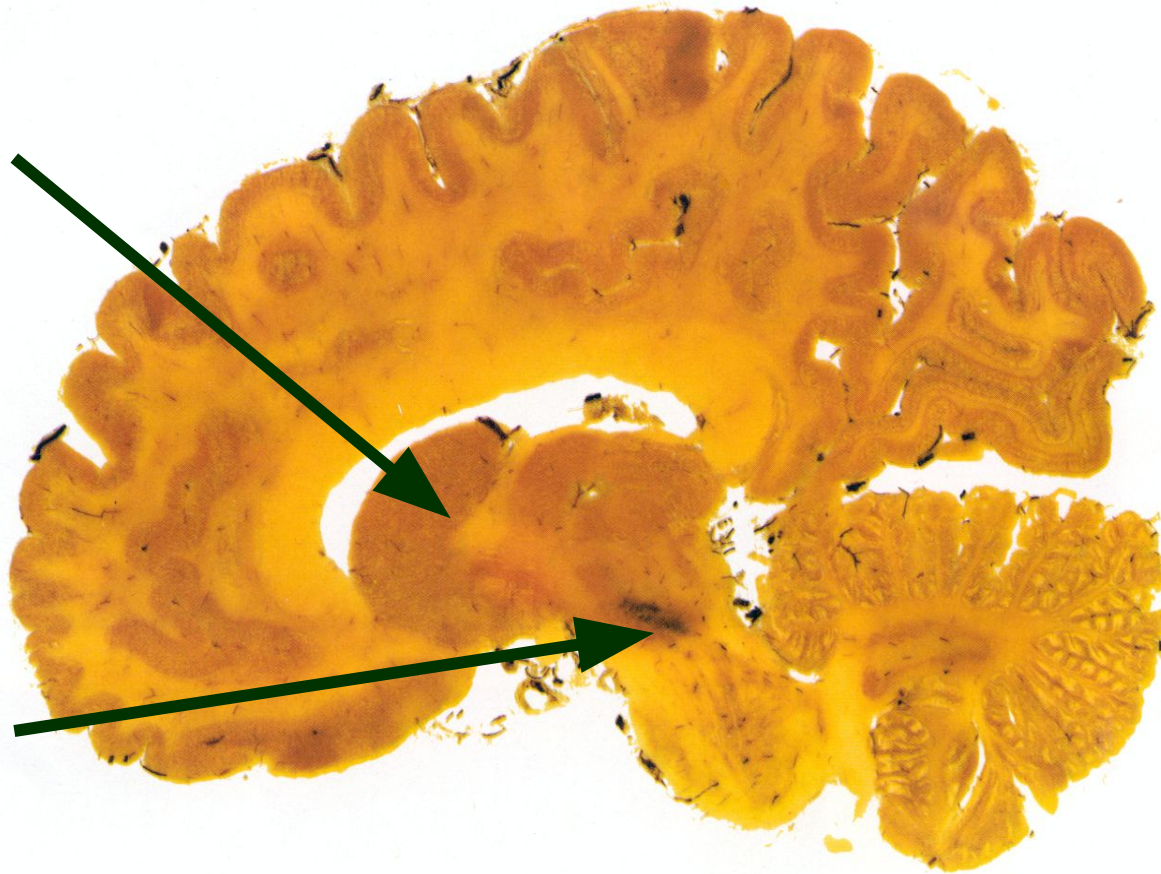
- Loss of dopaminergic (DA) cells located in substantia nigra: most symptoms do not appear striata DA levels decline by at least 70-80%

Pathophysiology

- Degeneration of substantia nigra
- Reduced production of dopamine

Nigrostriatal Dopaminergic Neurons

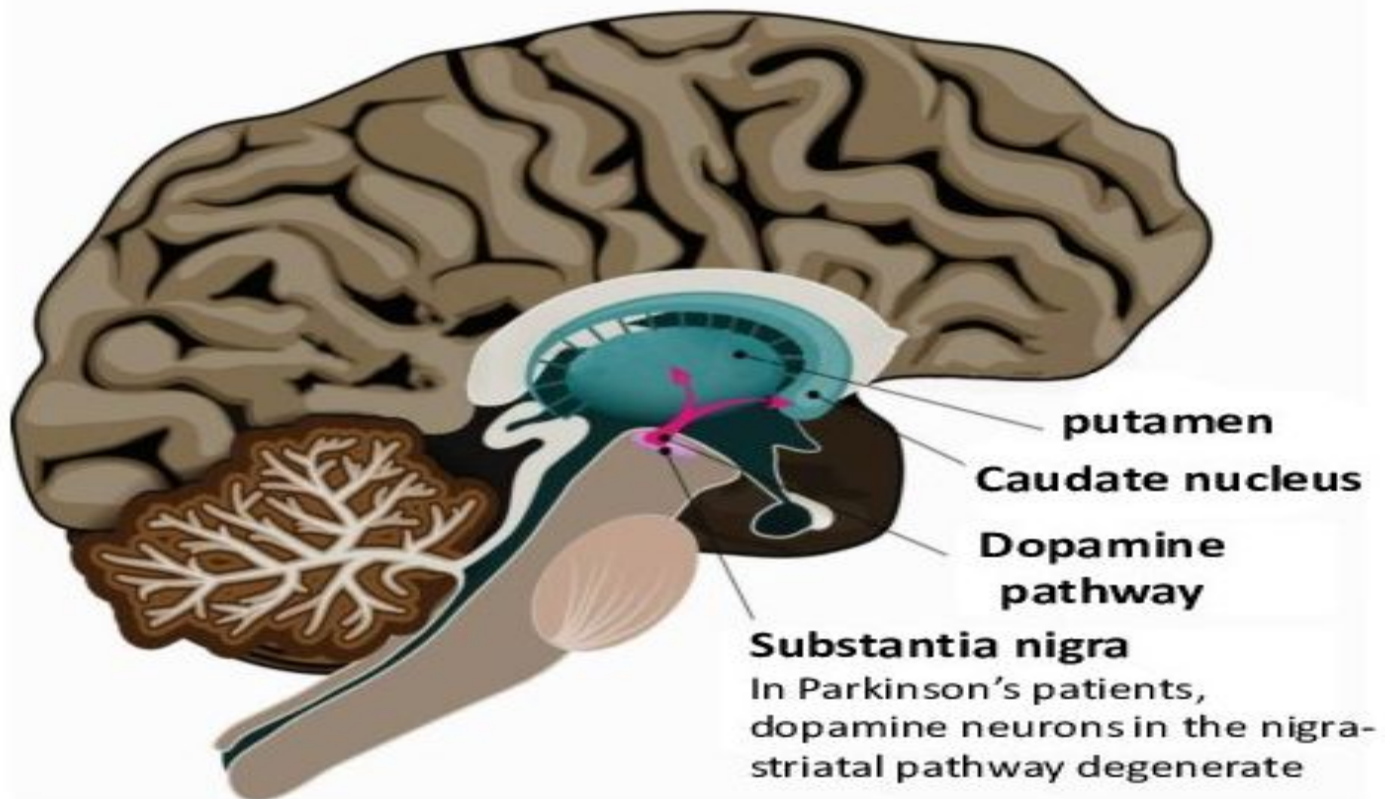
Striatum



Substantia nigra

- Substantia nigra critical brain region for the production of dopamine
- Depletion of the neurotransmitter dopamine in the corpus striatum. This depletion results from the **death of dopaminergic neurons that project from the substantia nigra to the striatum**

PARKINSON'S DISEASE



Cardinal features of Parkinson's disease

Parkinson's disease is a clinical syndrome consisting of four cardinal features:

- ▶ Bradykinesia
- ▶ Muscular rigidity
- ▶ Resting tremor
- ▶ Postural instability



Onset usually asymmetric

Bradykinesia

- Slowed voluntary movements
- Less arm swing when walking
- Reduced facial expression, less blinking
- Identify by rapid alternating movements during examination

Secondary Symptoms

- ◆ Depression
- ◆ Emotional Changes
(Irritable, pessimistic,
fearful, become
dependent or isolated)
- ◆ Memory Loss (slower
thought processes)
- ◆ Swallowing
Difficulties
- ◆ Speech Problems
- ◆ Bladder/Bowel Prob's
- ◆ Excessive sweating
- ◆ Sleep Disturbance

Motor impairments

Non-motor impairments



Bradikinesia

Cognitive impairment



Hypersalivation

Sleeping disorders



Postural imbalance

Mood disturbances



Tremor

Gastrointestinal issues



Muscular rigidity

Sweat and olfactory disorders



Walking difficulties

Anxiety and depression



Freezing of movements

Pain



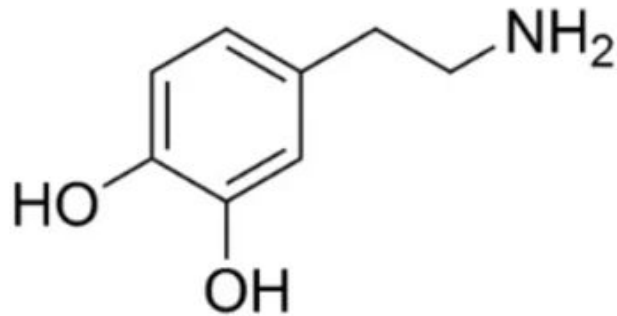
Causes

- ◆ Basal Ganglia and Substantia Nigra cell death or dysfunction
- ◆ These neurons produce the neurotransmitter (neuro-chemical) dopamine
- ◆ Dopamine is responsible for the transmission of signals associated with smooth, controlled, muscular activity from the substantia nigra to the corpus striatum

- ◆ PD “occurs” when these neurons die or fail to function properly.
- ◆ Without enough dopamine, neurons in the corpus striatum do not function in the usual coordinated manner.
- ◆ The result is an inability to direct or control the body’s movements normally.
- ◆ Typical PD pt. has an 80% reduction of dopamine producing cells.

Theories about cell death

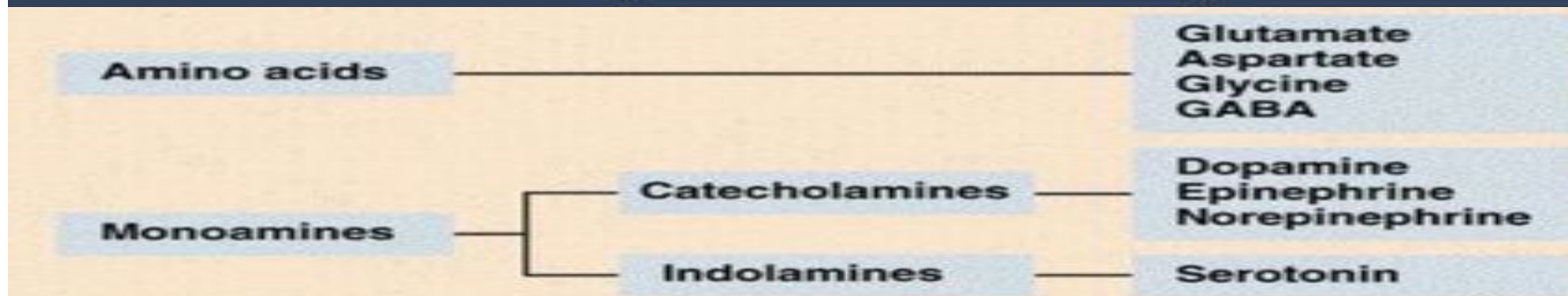
- ◆ Nerve cells are damaged by free radicals - unstable molecules generated by normal chemical reactions.
- ◆ Free radicals lack one electron and attempt to replace it by reacting with nearby molecules in a process called oxidation.
- ◆ Damage is normally controlled by other chemicals called antioxidants.
- ◆ Not understood yet what mechanistic event prevents this “checks and balances” procedure to take place.



3,4-DIHYDROXYPHENYLETHYLAMINE

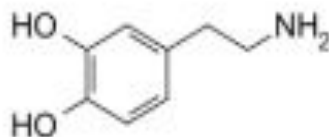
DOPAMINE

- Dopamine is a monoamine neurotransmitter that upon binding to a dopamine receptor releases a variety of downstream signals.



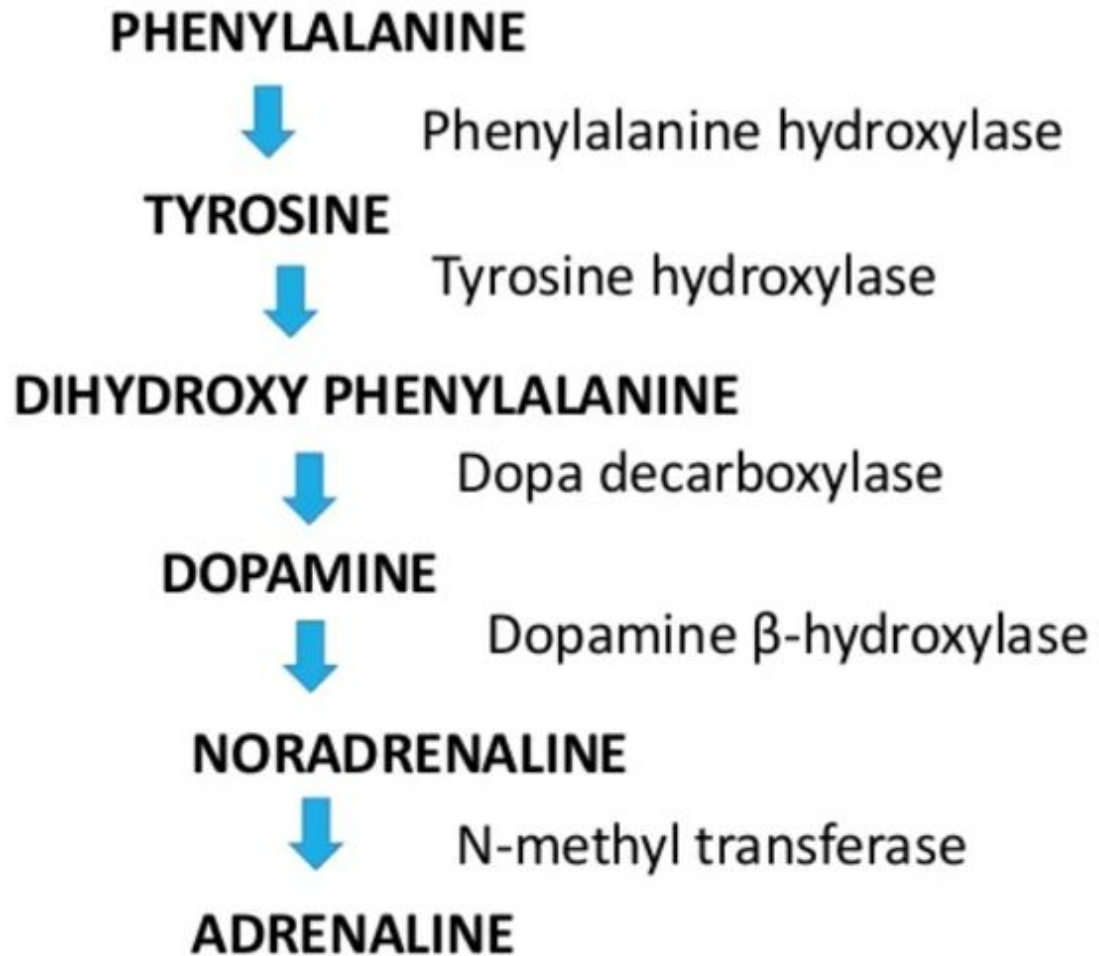
Introduction

- Dopamine belongs to the family of catecholamines



- Hormones Epinephrine and Norepinephrine (other catecholamines) are derived from Dopamine
- Significant role in learning, goal-directed behavior, regulation of hormones, motor control

SYNTHESIS & METABOLISM



The primary and minor metabolic pathways:

- Primary: L-Phenylalanine $\rightarrow$ L-Tyrosine $\rightarrow$ L-DOPA $\rightarrow$ Dopamine
- Minor: L-Phenylalanine $\rightarrow$ L-Tyrosine $\rightarrow$ *p*-Tyramine $\rightarrow$ Dopamine

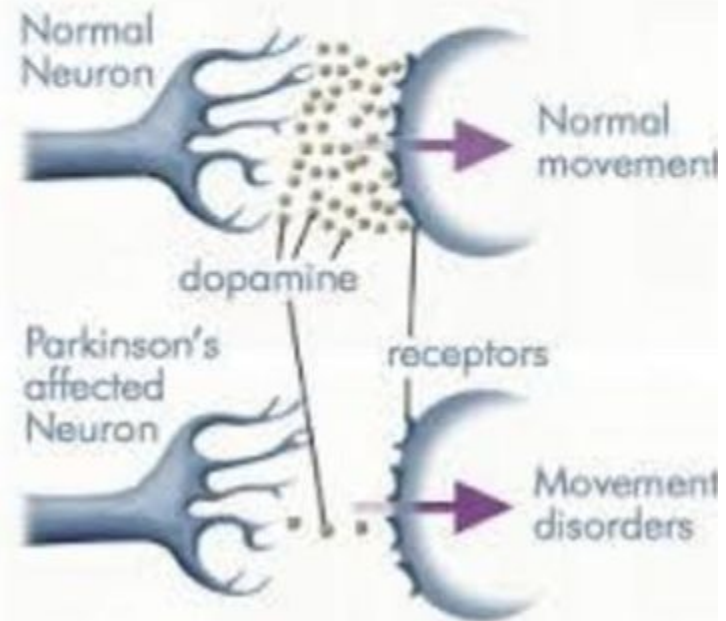
Malfunction of Dopamine

- Malfunction of Dopamine and muscle movement
 - When dopamine receptors are blocked, or not enough dopamine is produced, a person will find muscle coordination difficult
 - People who do not produce enough dopamine develop Parkinson
 - Parkinson is degenerative – this means that it progressively gets worse. A person with Parkinson's Disease will gradually produce less and less dopamine over time

- Caused by the loss of dopamine synthesising neurones.
- Loss of dopamine can affect control and coordination of movement.
- Dopamine cannot be given as a treatment as it cannot cross the blood brain barrier.
- Patients are given drugs such as L-dopa but they have unpleasant side effects.
- Research into the use of stem cells to treat PD is currently underway.

Parkinson's

Dopamine levels in a normal and a Parkinson's affected neuron.



Pharmacological Treatments

- Levadopa/carbidopa – increase available DA
- COMPT inhibitors – prevent the breakdown of DA
New class of Parkinson's medications by inhibiting the enzyme catechol-o-methyl-transferase (COMT), prevent peripheral degradation of Dopamine
- Anticholinergics – restore balance of Ach and DA.

Significance of Dopaminergic Pathways

- ▶ Mesolimbic Pathway

- Associated with **pleasure, reward and goal directed behavior**

- ▶ Mesocortical Pathway

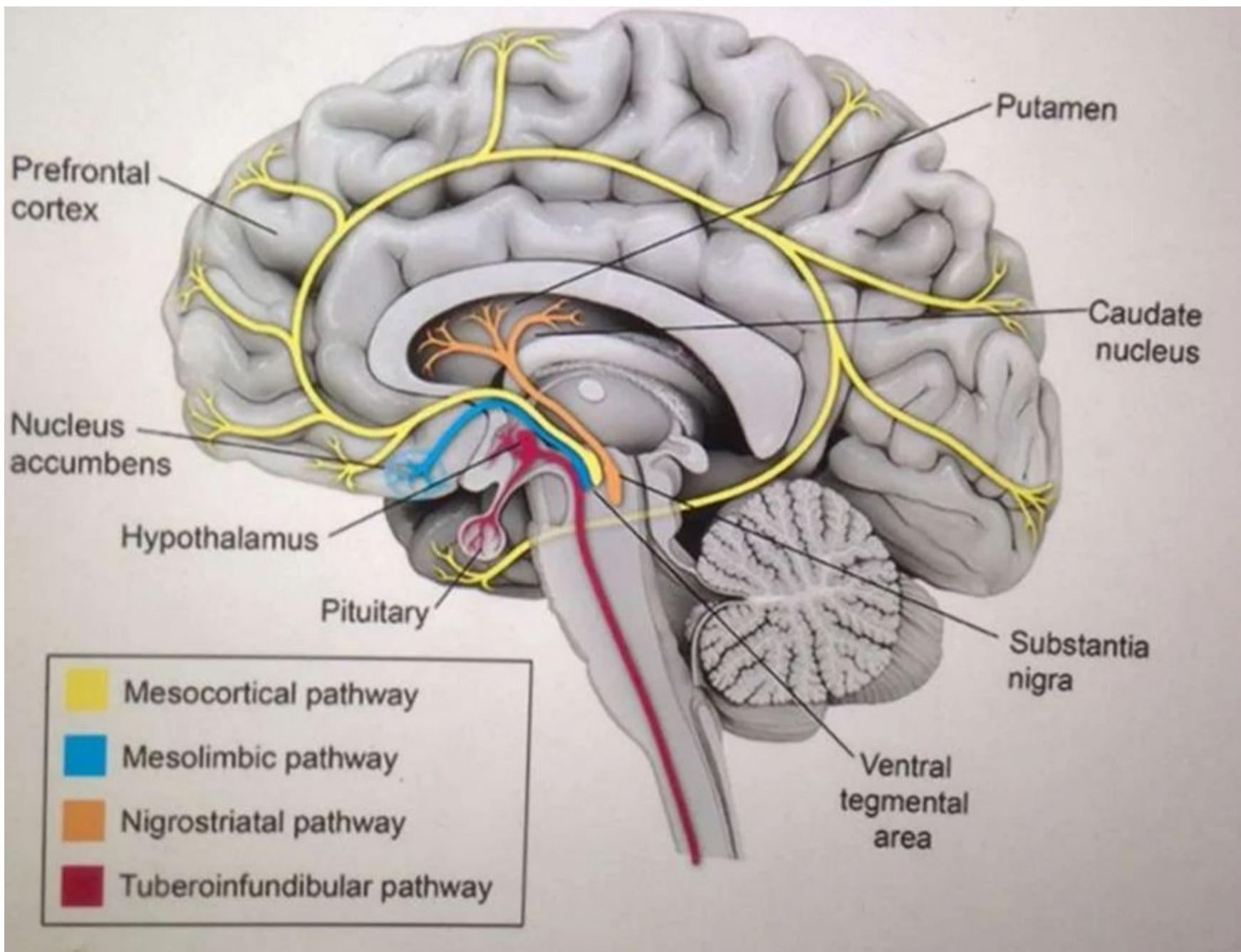
- Associated with **motivational and emotional responses**

- ▶ Nigrostriatal Pathway

- Involved in **coordination of movement** (part of basal ganglia motor loop)

- ▶ Tuberoinfundibular Pathway

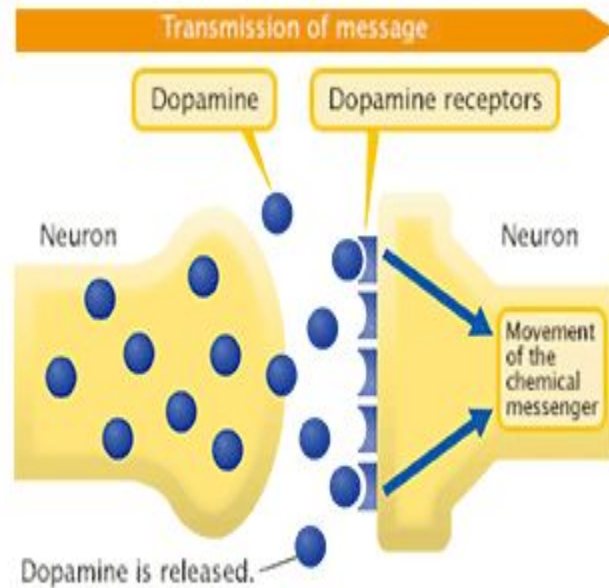
- **Regulates secretion of prolactin** by pituitary gland and involved in maternal behavior



- Some drugs are known as dopamine **agonists**.
- Dopamine **agonists**- bind to dopamine receptors in place of dopamine and directly stimulate those receptors.
- Dopamine **antagonists** - drugs that bind but don't stimulate dopamine receptors.
 - can prevent or reverse the actions of dopamine by keeping dopamine from attaching to receptors.

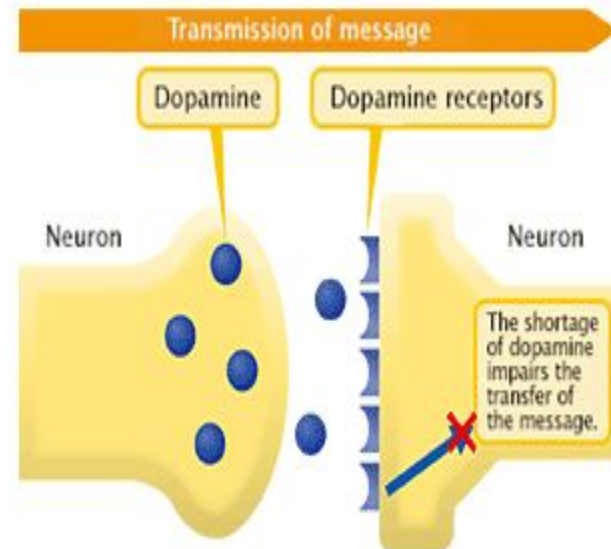
Agonists	Antagonists	Other drugs (Inhibitors)
Agonists bind to and stimulate receptors mimicking the neurotransmitter. e.g. L-dopa in Parkinson's	Antagonists bind to specific receptors blocking the action of the neurotransmitter. e.g. Beta-blockers for anxiety	Inhibitors inhibit the enzyme involved in degradation or re-uptake of the neurotransmitter. e.g. Cholinesterase inhibitors for Alzheimer's

Transfer of messages in normal neurons



The message is transmitted smoothly, as there is a lot of dopamine.

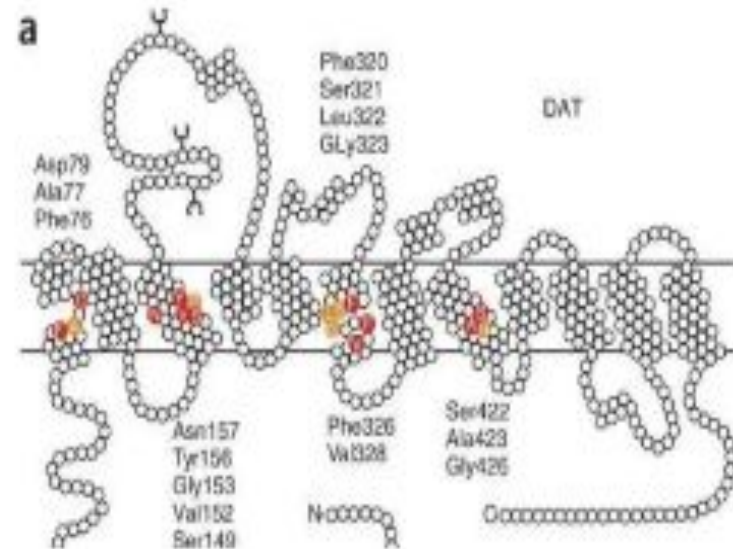
In Parkinson's disease



The shortage of dopamine impairs the transfer of the message.

Dopamine Transporter

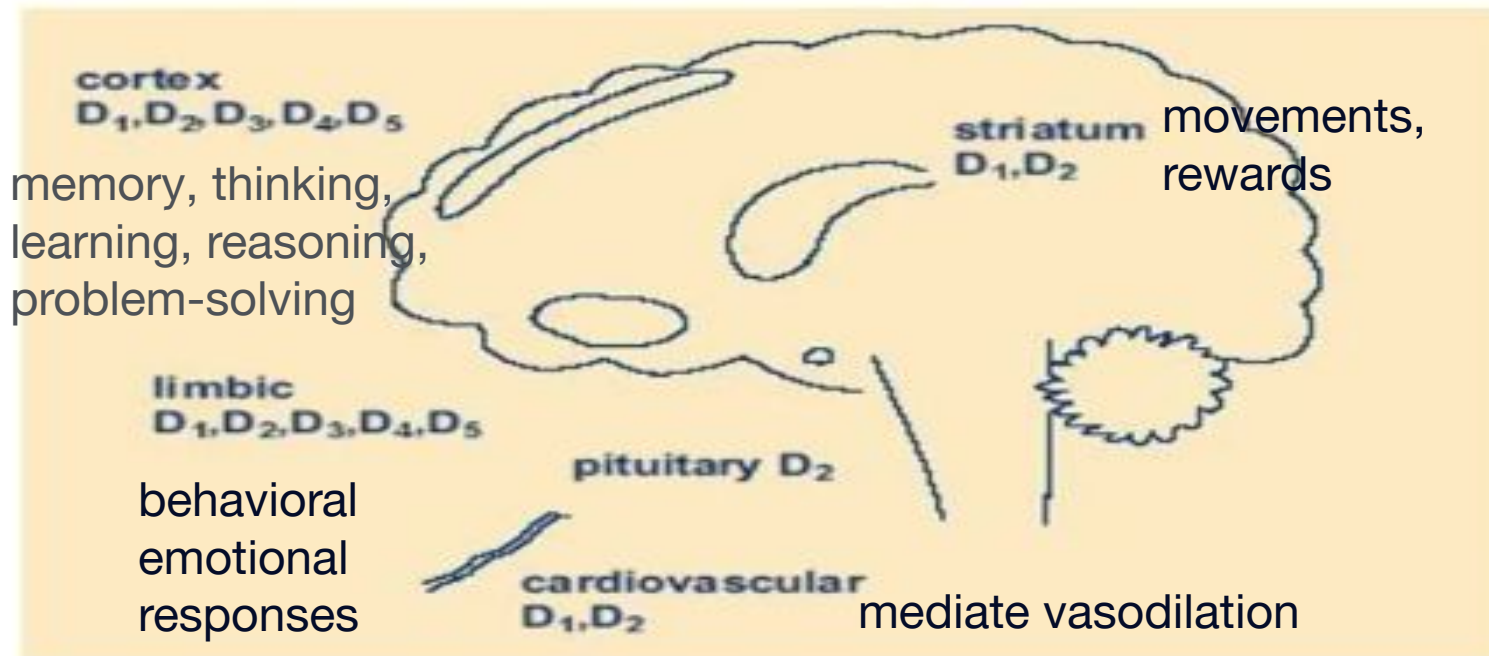
- High affinity DA-uptake sites – terminating transmitter action and homeostasis
- 619 amino acid protein
- Uses energy provided by Na^+ gradient generated by Na^+ / K^+ transporting ATPase
- The dopamine transporter (DAT) controls dopamine neurotransmission by driving reuptake of extracellular transmitter into presynaptic neurons.
- Recaptures DA soon after its release, modulating the concentration in the synapse



Dopamine Receptors

- There are five types of dopamine receptors. D1, D2, D3, D4, D5.

LOCATION AND DISTRIBUTION



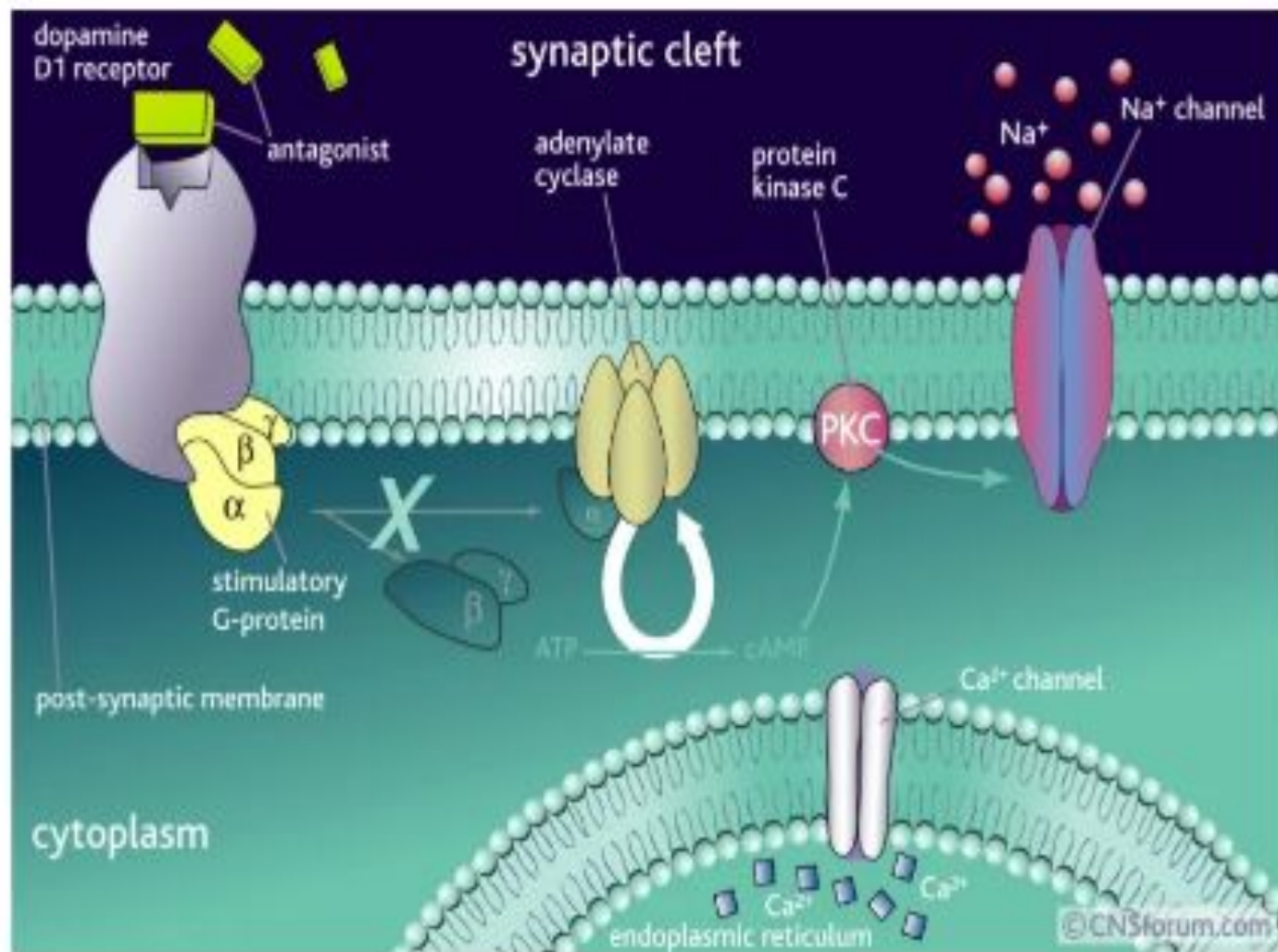
Functions of Dopamine receptors

Functions	Type of receptors involved
Locomotion	D1, D2, D3
Learning and memory	D1, D2
Cognition	D3, D4, D5
Attention, impulse control, decision making, motor learning, sleep, reproductive behaviors and the regulation of food intake	D1, D2, D3, D4, D5
hormonal regulation, such as the regulation of prolactin secretion; renin secretion; aldosterone secretion	D2 D1 D2
regulation of renal function; blood pressure regulation; vasodilation; and gastrointestinal motility	D1, D2, D4

Dopamine Receptors

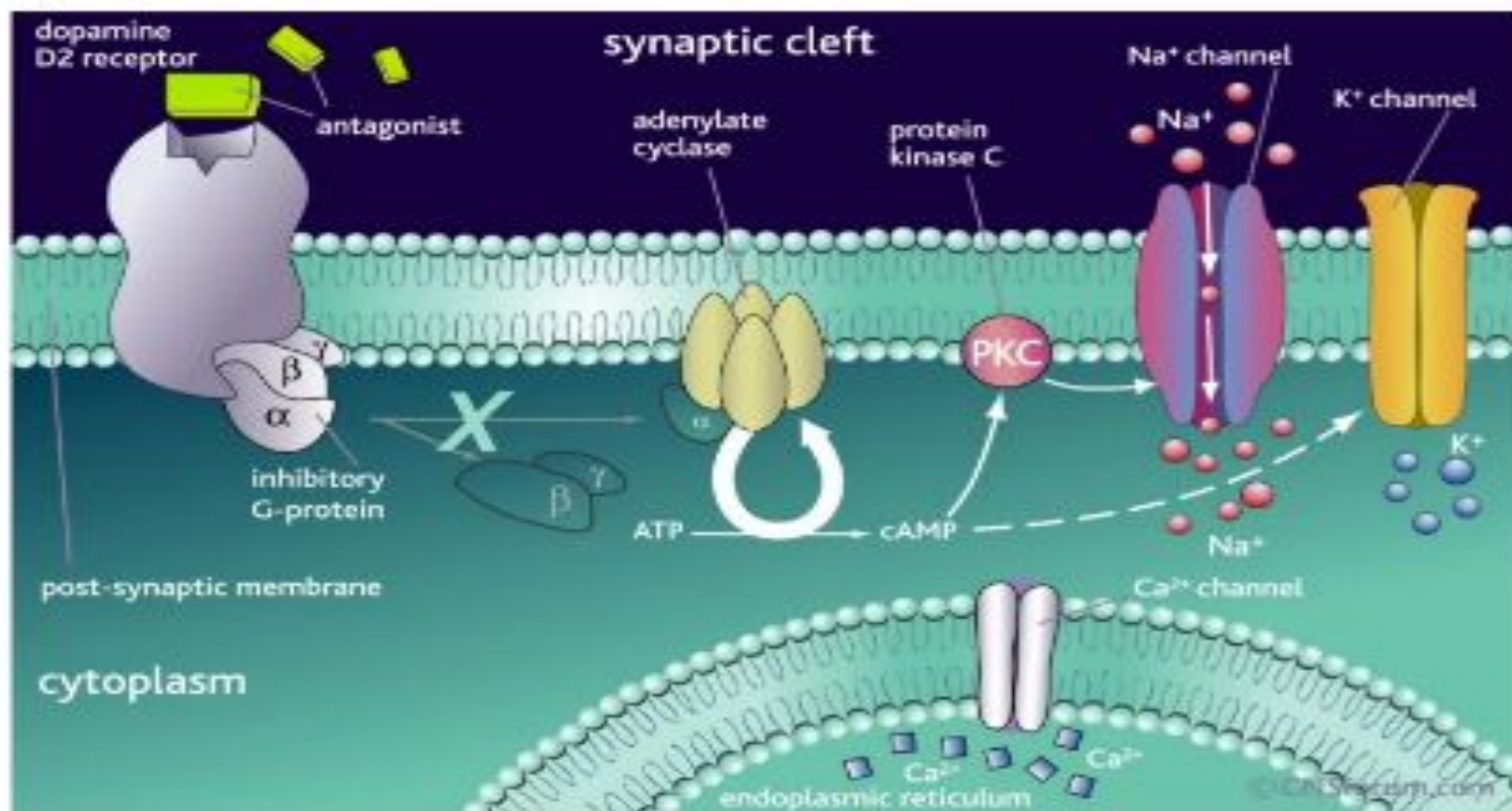
- Metabotropic G-protein coupled receptors
- D_1 – like family:
 - Includes subtypes D_1 and D_5
 - Activation is coupled to G_s ; activates adenylyl cyclase which leads to increase in concentration of cAMP
- **D1 and D5 receptors couple to G_s stimulatory sites and activate adenylyl cyclase.**
- **Adenylyl cyclase enzyme that catalyzes the conversion of ATP to cAMP**
- **cAMP, an intracellular second messenger, activates protein kinase by dissociating its regulatory subunit from the catalytic subunit**
- **Mediate excitatory neurotransmission.**

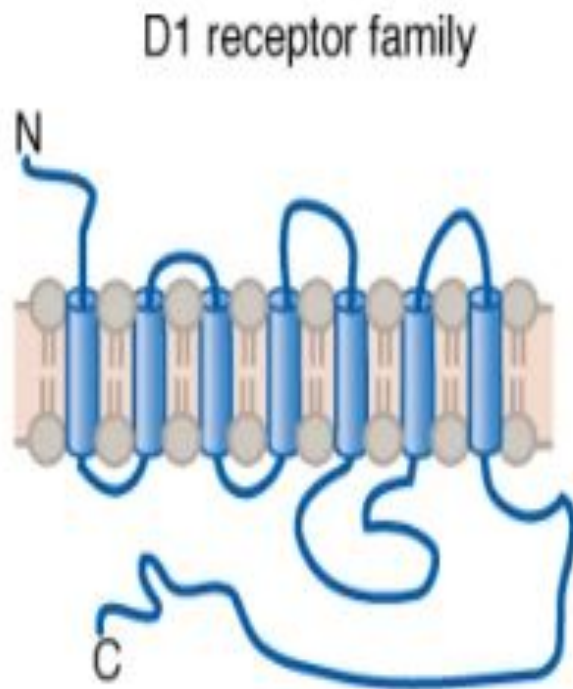
Dopamine Receptors



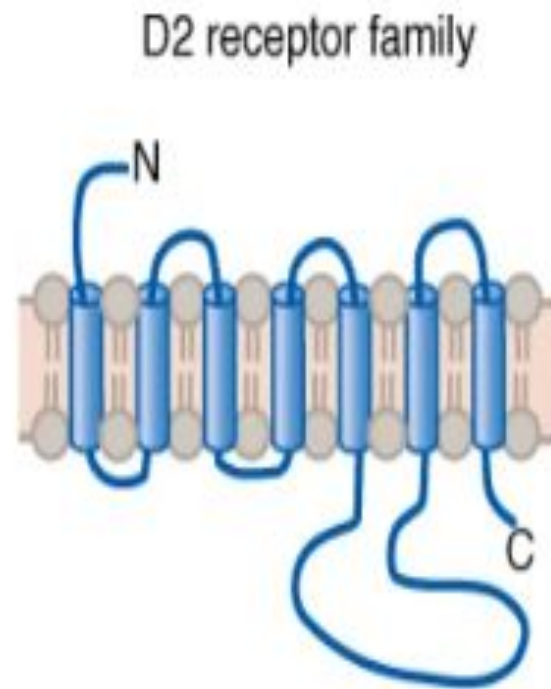
- D_2 – like family:
 - Includes D_2 , D_3 and D_4
 - Activation is coupled to G_{ai} ; inhibits adenylyl cyclase leading to decrease in concentration of cAMP
 - **Mediate inhibitory neurotransmission**

Dopamine Receptors



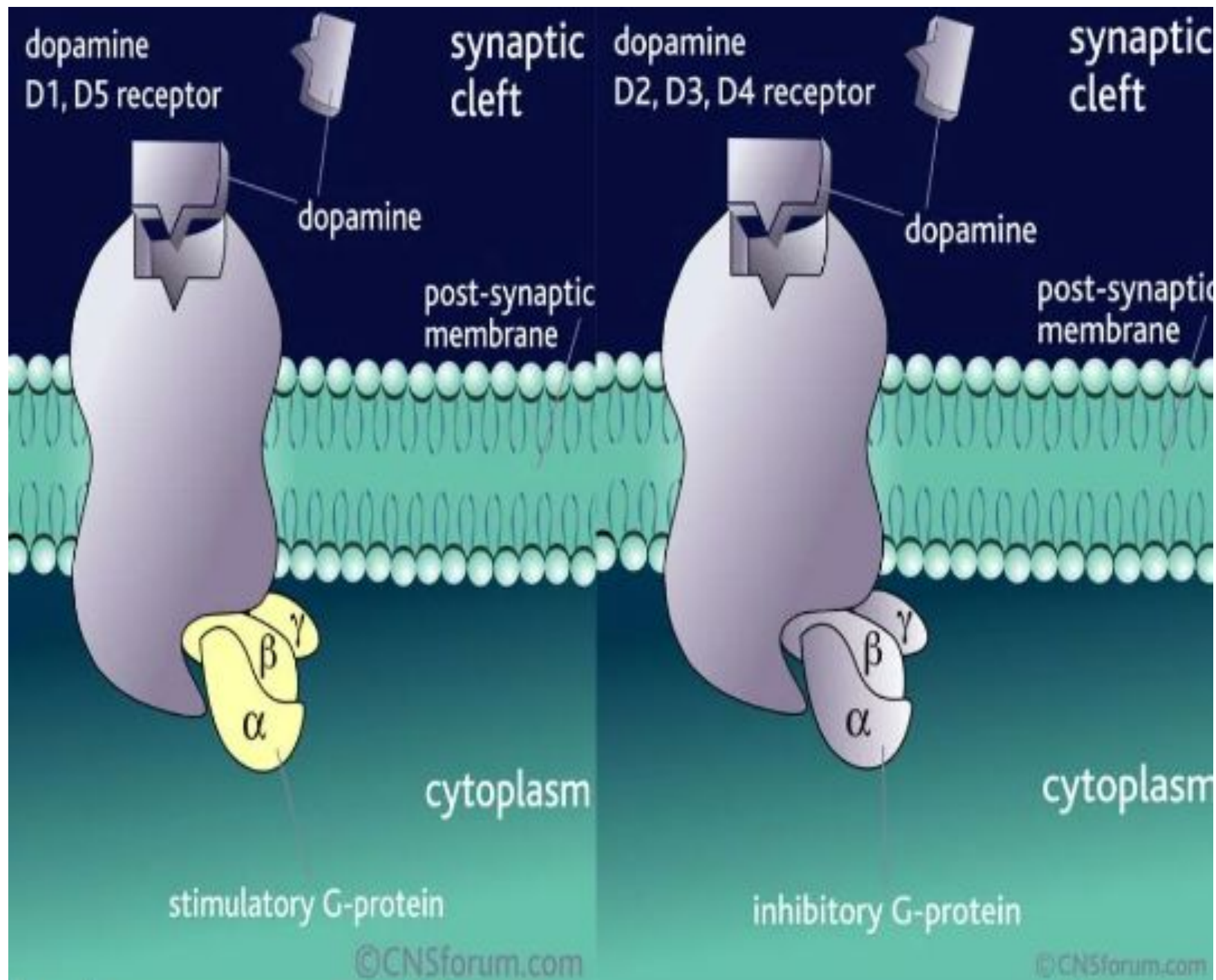


↑ cyclic AMP



↓ cyclic AMP
↑ K⁺ currents
↓ voltage-gated Ca²⁺ currents

D1 and D2 receptor subtypes are found at 10-100 times the levels of the D3, D4, D5 subtypes



Literature Review:

Parkinson Disease patients:

Demonstrated **significantly higher GABA levels** in the basal ganglia, which correlated with the degree of gait disturbance

Parkinson Disease patients:

- would show **increased GABA** levels in the basal ganglia and **decreased glutamate** in the prefrontal cortex
- Lead to more pronounced **abnormalities in the GABA and glutamate** levels would correlate positively with the **severity** of the axial symptoms of PD.