Physiology Team

LECTURE 26

Physiology of BASAL Ganglia and Regulatory Mechanism

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OBJECTIVES

At the end of this lecture, student should be able to describe:

1-appreciate different nuclei of basal ganglia
2-know different neurotransmitters that have a role in basal ganglia functions
3-appreciate general functions of basal ganglia
4-diagnose basal ganglia disorders

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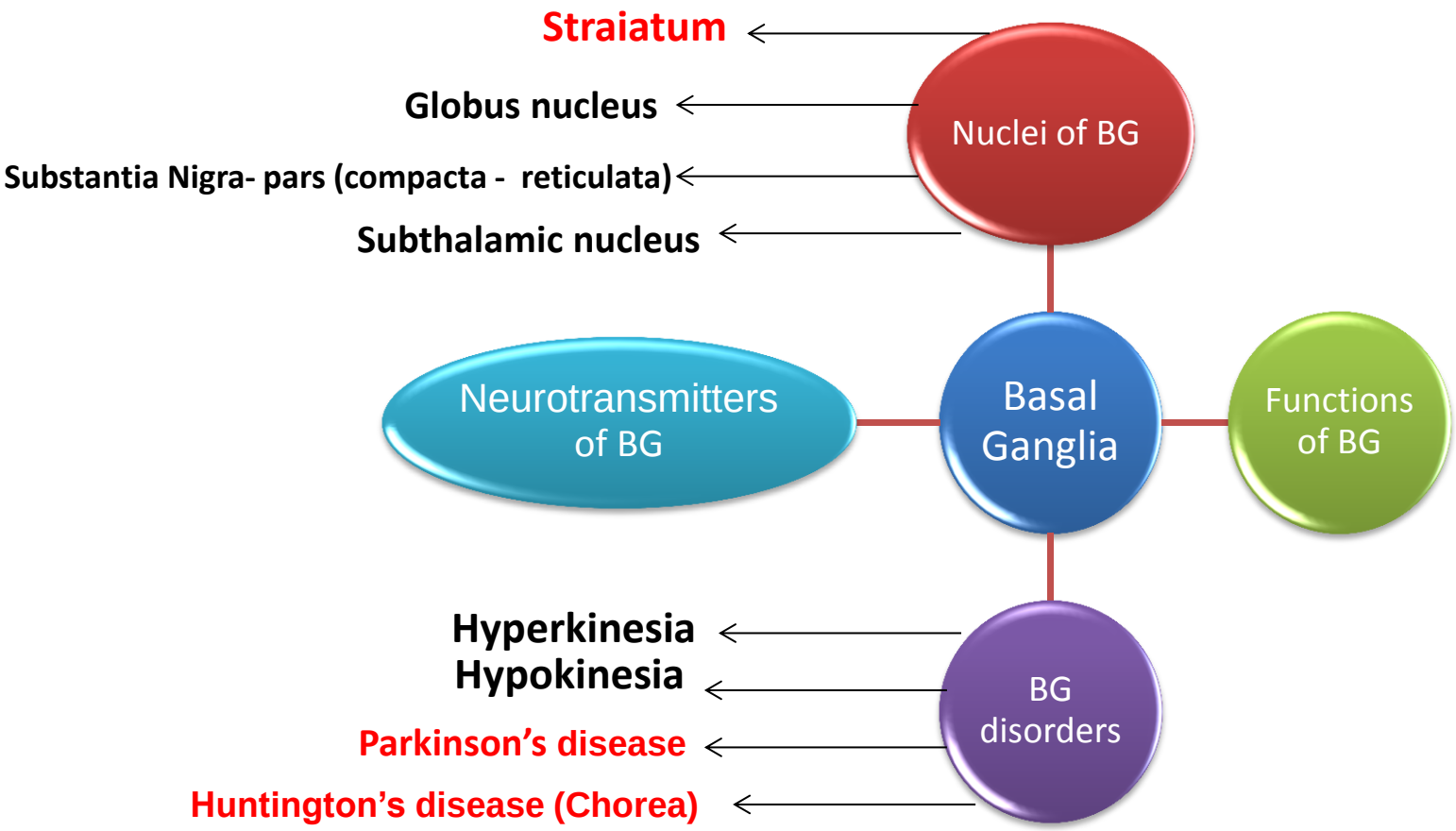
MIND MAP



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INTRODUCTION

- Basal ganglia are subcortical nuclei of grey matter located in the interior part of cerebrum near about base, base of the forebrain
- Basal ganglia is part of brain not part of cerebrum.
- Play a role in action selection, decision of possible behaviors to execute at a given time

Metabolic characteristics of basal ganglia:

- High Oxygen consumption .
- High Copper content .
- Wilsons disease (Copper intoxication):
  Ceruloplasmin is low,
  Lenticular degeneration .

Note: wilsons disease is in some feature of Parkinson's disease.

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The four principle nuclei of the basal ganglia Are the

1- Striatum

- caudate nucleous
- putamn nucelous
- Ventral striatum

2- globus pallidus

3- substantia Nigra- pars compacta,reticulata

4- subthalamic nucleus

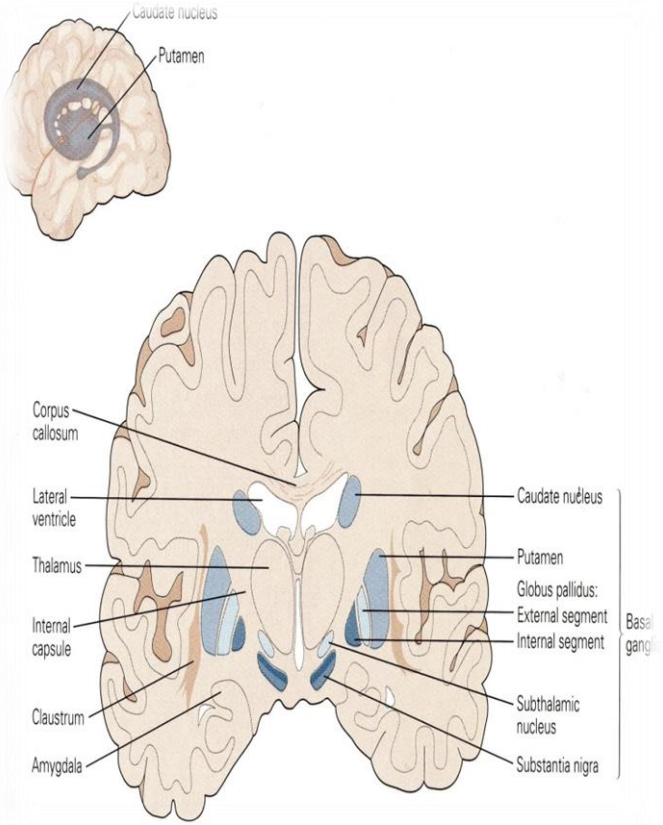

Table 12–3. The basal ganglia.

Lenticular nucleus	Caudate nucleus	Striatum
	Putamen	Striatum
	Globus pallidus (pallidum)	
	Subthalamic nucleus (body of Luys)	
	Substantia nigra	

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The striatum

The striatum consists of *three* subdivisions, the:

1. Caudate nucleus
2. Putamen
3. Ventral striatum (which includes the nucleus accumbens): Could be included in the striatum so, the striatum consests mainly of caudate & putamn nuclei

Internal capsule: a major collection of fibers that separates the caudate nucleus and putamen.

Basic Circuits of basal ganglia (functions of basal ganglia)

1- A motor loop (putamen circuit)

concerned with learned movment.

Putamen circuit is inhibitory

2- Cognitive loop (Caudate circuit)

concerned with cognitive control of sequences of motor pattern. Basically it is concerned with motor intentions.

Note: cognition means thinking process using sensory input with information already stored in memory

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3- Limbic loop

involved in giving motor expression to emotions like, smiling, aggressive or submissive posture

4- Occulomotor loop

concerned with voluntary eye movement [saccadic movement]

Note: submissive posture means without thinking

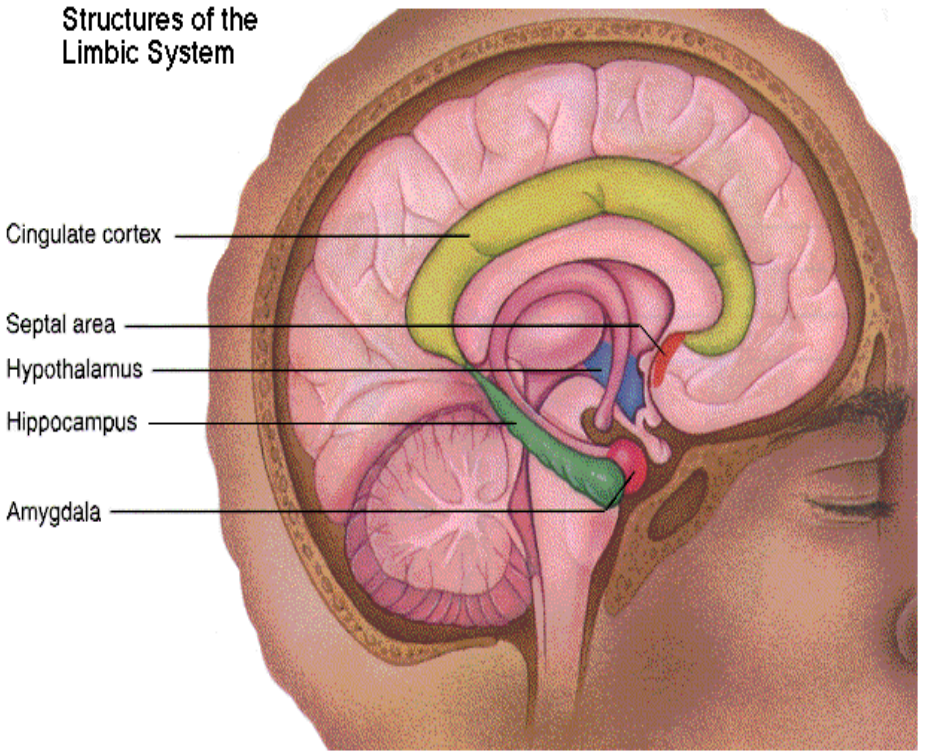
- Basal Ganglia has connection with limbic loop & occulomotor so, if there is defect in basal ganglia you will find defect in the limbic loop and occulomotor loop.

FUNCTIONS OF THE LIMBIC SYSTEM

The doctor said this slide is just For our information

If there is defect in basal ganglia you will find defect in these functions because it is connected to limbic system

- **Cingulate cortex:**
  - Coordination of sensory signals
  - Emotion
- **Septal area:**
  - Sexual arousal
- **Hippocampus:**
  - Long-term memory development
- **Amygdala:**
  - Aggression and fear
- **Hypothalamus:**
  - Endocrine regulation
  - Body temperature
  - Regulation of thirst and hunger
  - Regulation of circadian rhythms



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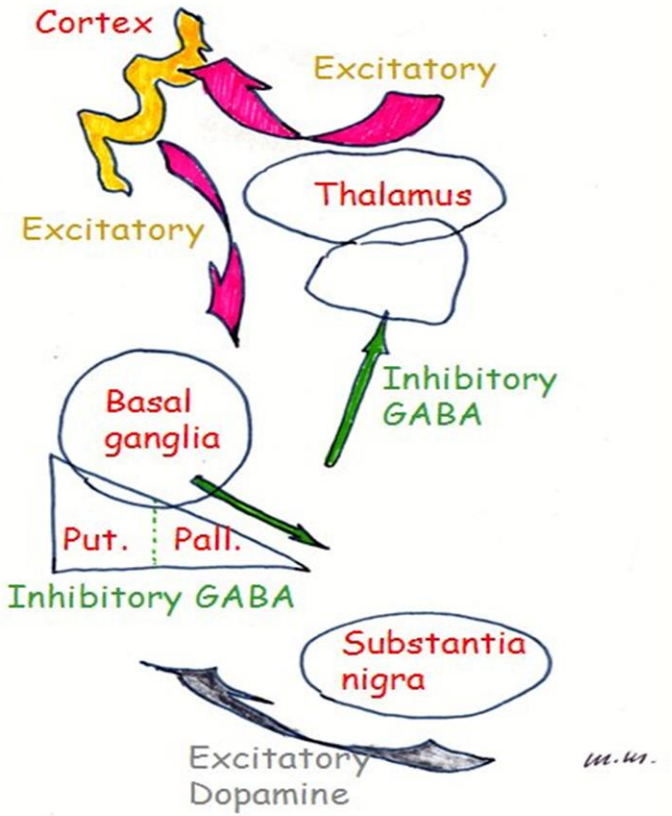
Functional Considerations on Basal Ganglia

Basal ganglia exert influence on the motor activity by way of the thalamic neurons which project onto the frontal cortex. Neither basal ganglia or brain stem nuclei project directly to spinal levels.

The striatum is the receptive component of the basal ganglia. Output of basal ganglia arises from the globus pallidus and the substantia nigra. Disinhibition is the model proposed for basal ganglia mechanism. The spiny neurons, main striatal efferents, are GABAergic. They inhibit the nigro and pallido fugal fibers which themselves GABAergic are also inhibitory. There is a double inhibitory chain. This double inhibitory chain gives rise to a disinhibition which allows excitatory inputs to control the cells' firing at the cortical motor system.

The substantia nigra with its dopaminergic system gives a major feedback to the striatum. In Parkinson, the lack of Dopamine causes a release of inhibition of GABA to Gpe.



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Notes from previous slide

Basal ganglia & cerebeullum are important motor structure which control the motor movement.

If the person has basal ganglia defect or cerebeullum defect he don't have paralysis but his movement is uncontrolled

Why not paralysis?!

Because the motor area in frontal lobe in cerebral cortex is not affected)

- **Motor Area is different from the basal ganglia & cerebellum So, the person can move but there is defect in the control of movement (Because he will lose the inhibition which coming from the basal ganglia from striatum (caudate & putamen)**
- **These nuclei (Caudate & putamen) send inhibitory impulses to the cortex via the thalamus.**

The striatum
(Putamen & Caudate)

Putamen circuit	Caudate circuit
Indirect **Inhibitory**	**Direct** **Excitatory**
From Cerebral cortex (Prefrontal, premotor, primary motor area, somatosensory area)	From Cerebral cortex (Prefrontal, premotor, primary motor area, somatosensory area)
To putamen	To caudate nucleus
Via globus pallidus subthalamic nucleus	**(Because it's direct pathway)**
Thalamus	Thalamus
Executes skilled motor activities. E.g. cutting paper with a scissor, hammering on nail, shooting a basket ball & like throwing a base ball.	Has instinctive function which works without thinking & need quick response. e.g. response after seeing a lion.

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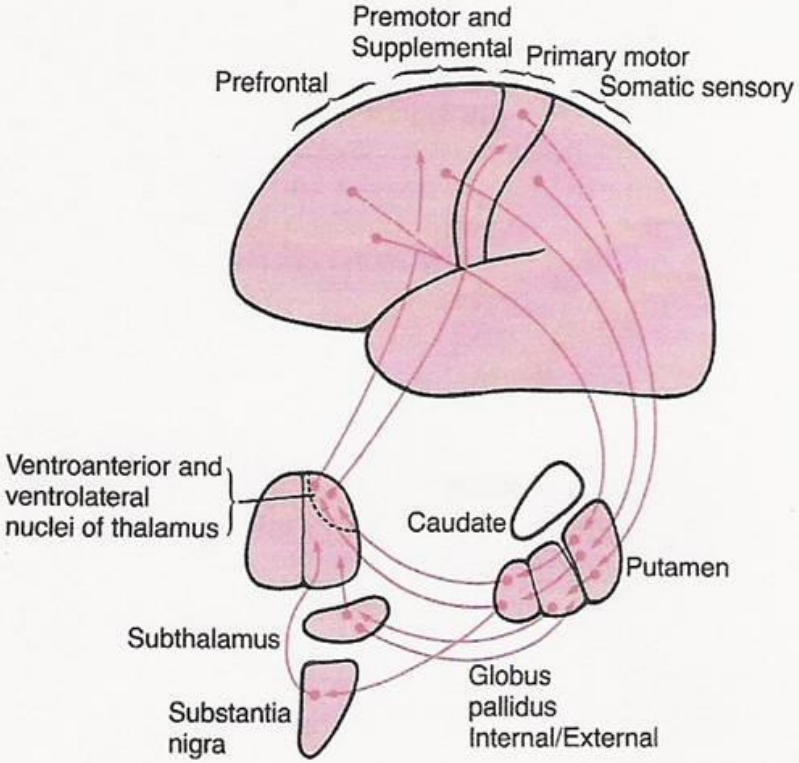
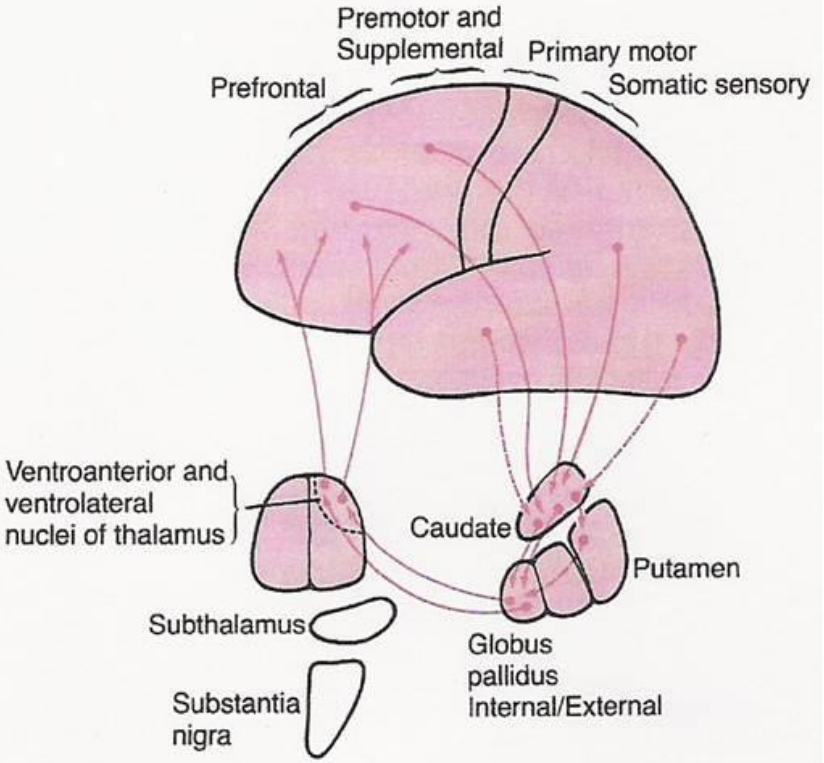
The striatum
(Putamen & Caudate)



The Putamen Circuit

Figure 38–14 The *putamen circuit* through the basal ganglia for subconscious execution of learned patterns of movement.



The Caudate Circuit

Figure 38–15 The *caudate circuit* through the basal ganglia for cognitive planning of sequential and parallel motor patterns to achieve specific conscious goals.

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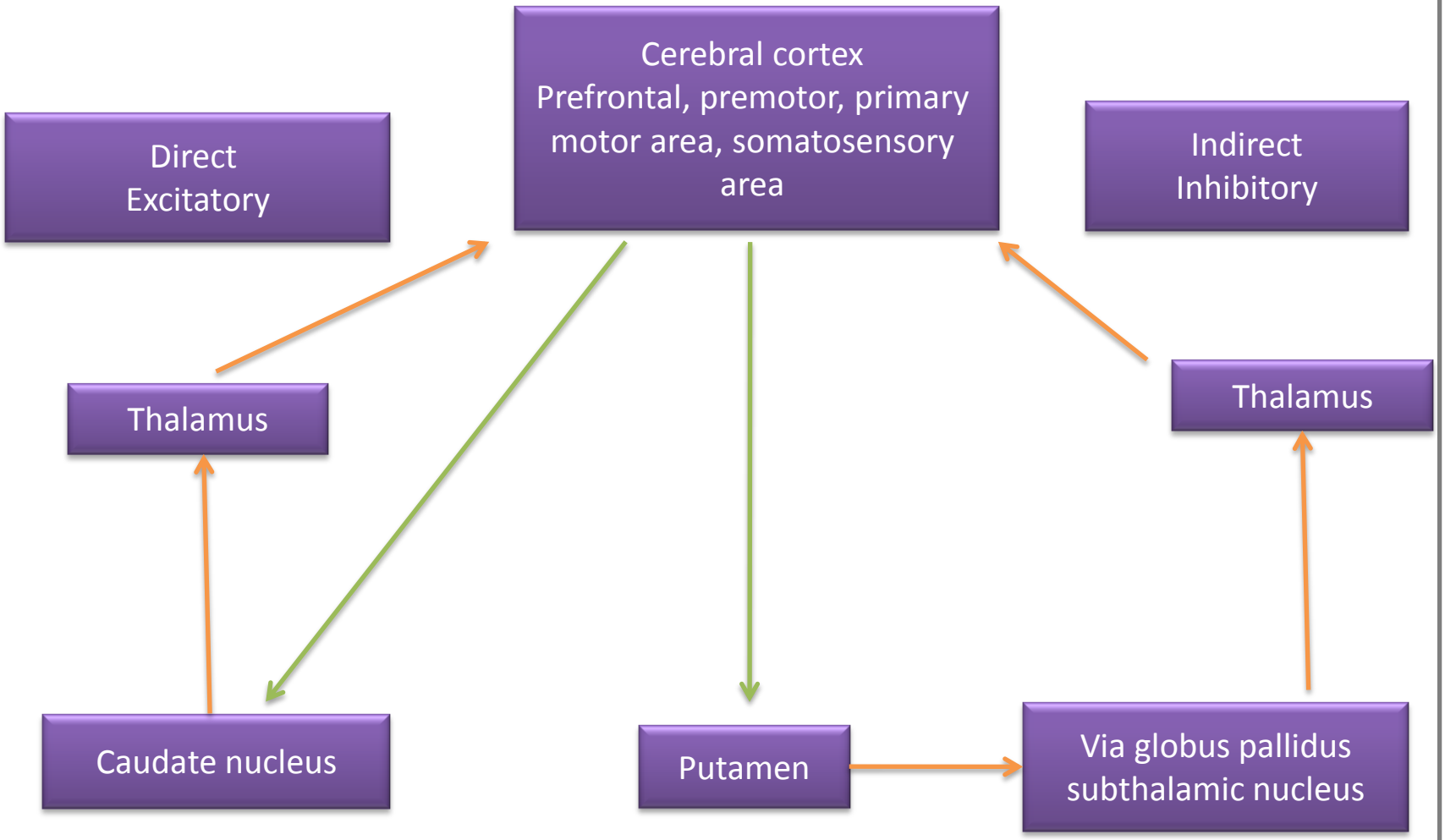

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AFFERENT TO BASAL GANGLIA

✧ Cortico-striatal pathway .

✧ Centro-medial nucleus – thalamus .

Important Notes:

- Nearly all inputs arrive at the caudate and putamen.
- All outputs go out from the internal segment of globus pallidus or from substantia nigra pars reticulata.
- Parallel pathways in BG function in general motor control, eye movements, cognitive functions, and emotional functions.

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INPUTS

origin	Ends	Neurotransmitters
Cerebral Cortex	All lobes have projections to striatum	Glutamate **(Excitatory)**
Substantia nigra - pars compacta -	Striatum	Dopamine (Either **Inhibitory or Excitatory**)
Thalamus (Intralaminar nuclei)	Striatum	Glutamate (**Excitatory**)
Raphe nuclei (Median RF)	Basal ganglia	Serotonin

Note: ALL of these signals will go to the basal ganglia to inform the basal ganglia about movement (Control Movement)

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Basal ganglia Input

1. Parietal cortex (primary and secondary somatosensory information, secondary visual information),
2. Temporal cortex (secondary visual and auditory information),
3. Cingulate cortex (limbic and emotional status information),
4. Frontal cortex (primary and secondary motor information),
5. Prefrontal cortex.

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There are connections inside the BG also called (intrinsic BG connections), before it gives a signal to control the movements

*It could be Direct or Indirect Pathways **WHY ?!**

Because the connections & Neurotransmitters are different.

	Direct Pathway	Indirect Pathway
FROM	striatum	Striatum
TO	Globus Pallidus **internal** segment and substantia nigra pars reticulata.	Globus Pallidus **external** segment to subthalamus, to GP* internal segment to VA/VL** thalamus.
NET EFFECT	Excitation of thalamus	Inhibition of thalamus
MOVEMENT	Facilitation of movement	Inhibition of movement

***GP=Globus Pallidus**
****VL= Ventrolateral of thalamus**
****VA=Ventroanterior of thalamus**

next slide will help you in regards the pathways ☺

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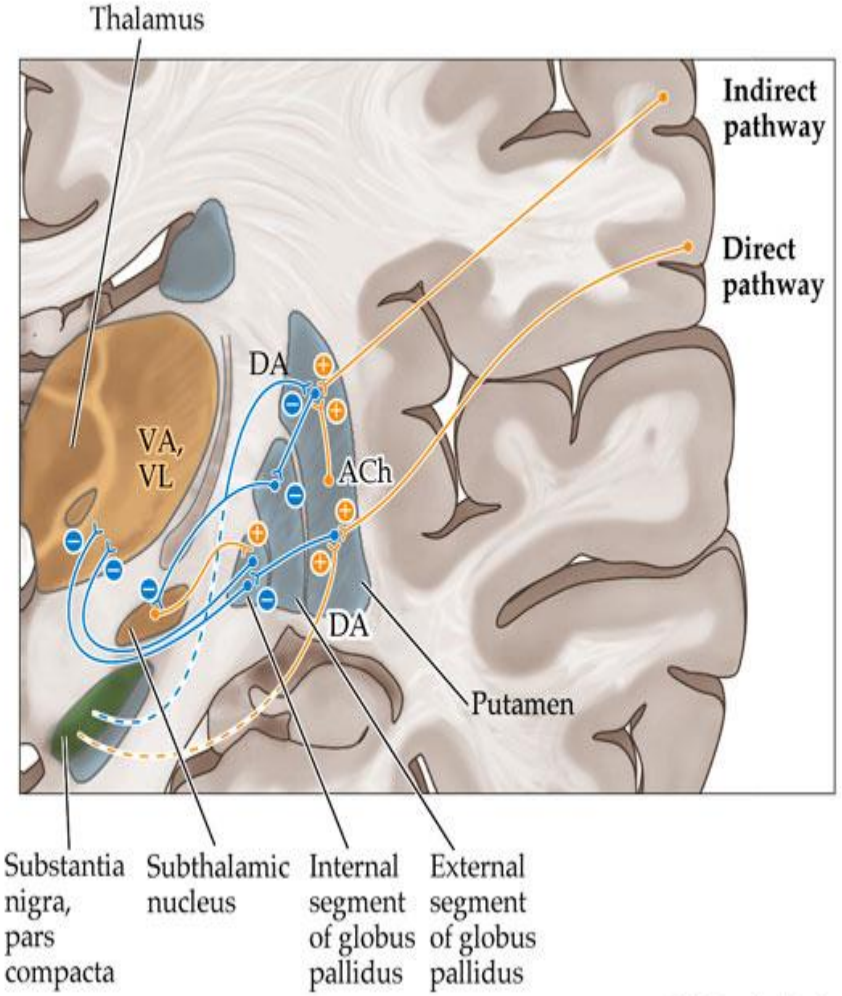

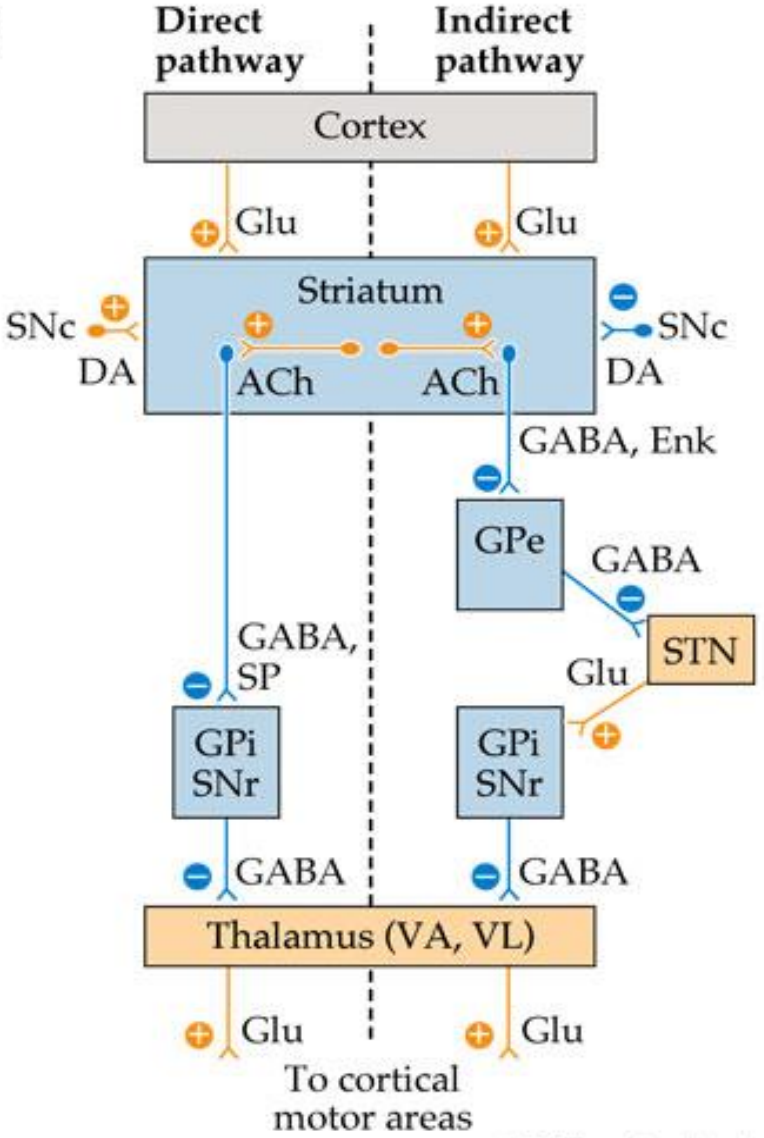

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Further details on next slide

OUTPUTS

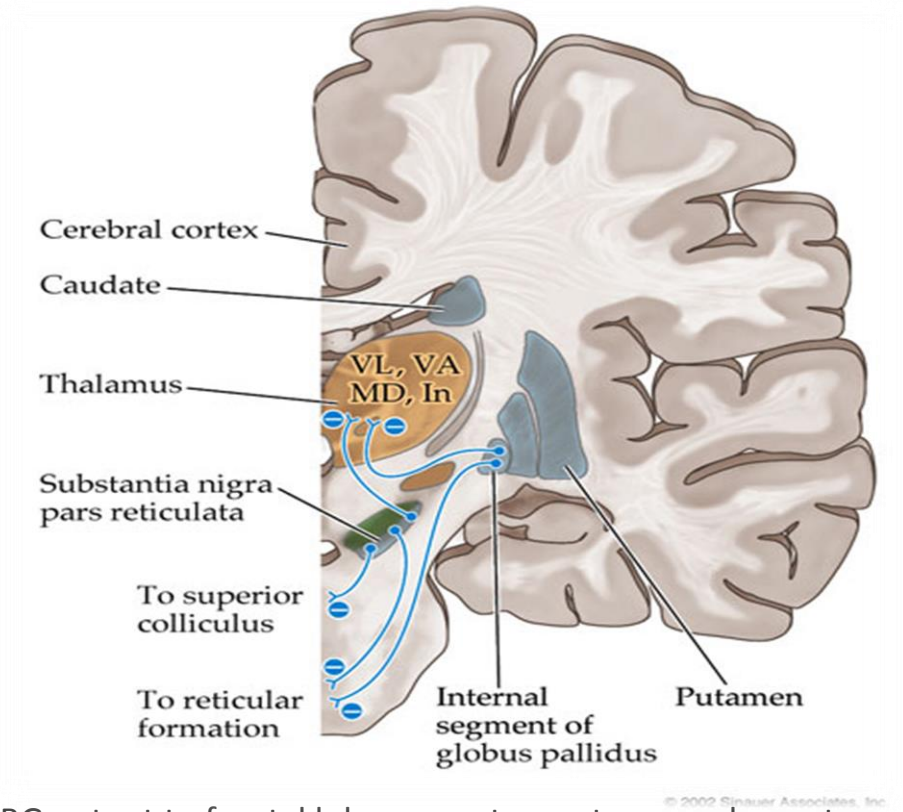
From Basal Ganglia

1) Substantia nigra pars reticulata in BG

2) Globus pallidus internal segment in BG

Neurotransmitters of BOTH is
GABA (Inhibitory)

to VL and VA of the thalamus



- VL/VA thalamus carries BG output to frontal lobe premotor cortex, supplementary motor cortex, and primary motor cortex.
- SN and GP also project to **MD* thalamus** (limbic connections).
- SN and GP also project to **pontomedullary RF** to modulate **reticulospinal tract.**
- SN projects to **superior colliculus** to modulate **tectospinal tract.**
- ✓ **By these paths BG control both medial and lateral motor systems.**

***MD= Medial dorsal nucleus.**

Neurotransmitters of basal ganglia

Dopamine pathway	Gama amino butyric acid pathway	Acetylcholine pathway	Glutamate
• **from substantia nigra** • To caudate nucleus and putamen. • **Note: Dopamine is exciatatory & Inhibitory but mainaly it is Inhibitory**	• from caudate nucleus and putamen to globus pallidus and substantia nigra • **Note: GABA & Serotonin are inhibitory transmitters.**	• from cortex to the caudate nucleus to putamen.	• that provide the excitatory signals that balance out the large no. of the inhibitory signals transmitted specially by the dopamin

Dopamine: excites areas of caudate/putamen with D_1 receptors to promote the direct pathway, inhibits areas of caudate/putamen with D_2 receptors to inhibit the indirect pathway

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Go through it briefly, girl's doctor did not explain it deeply as in boy's slide

Dopamine: Neuromodulatory neurotransmitter, excites areas of the caudate/putamen with D_1 receptors to promote the direct pathway, inhibits areas of the caudate/putamen with D_2 receptors to inhibit the indirect pathway

Glutamate: Excitatory neurotransmitter

Subthalamic nucleus projects glutamate to stimulate the ventrolateral thalamus. Ventrolateral thalamus projects glutamate to stimulate the primary localized motor cortex

GABA: Inhibitory neurotransmitter:

Caudate/Striatum (direct) projects GABA to inhibit the Gp_i GP_i projects GABA to inhibit the ventrolateral nucleus Caudate/Striatum (indirect) projects GABA to inhibit the GP_e

GP_e projects GABA to inhibit the subthalamic nucleus

FUNCTIONS OF BASAL GANGLIA:

- **1.Voluntary motor activities**
  - Plan, Programming (discharge before movement begins)
  - Initiate
  - Maintain (Tone)
- **2. Regulatory**
  - Cognitive (thinking)* (Lesion will disrupt performance)
  - Emotional functions**
  - Voluntary control of eye movement***
- **3.Procedural learning**
- **4.Routine behavior (habits)**

* Because of Caudate nucleus.
** Because of limbic system.
***Because of Occulomotor loop.

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"Notes from Dr. Fawzia"

What is the difference between the function of Basal Ganglia & Cortex ?!

Both of them are control motor movement*Basal Ganglia firing before the cortex : That's why when there is basal ganglia defect there is tremor.

- If the cortex fire before Basal Ganglia the movement will be randomaly & not controlled.

Another functions of BG:

1) Motor control of the final common pathway .
2) Muscle tone (Lesion will increase the muscle tone)
3) Speech, lesion of left caudate results in disturbed speech dysarthria

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- The BG sends signals to the cortex → there is movement.
- Then the Cortex will move according to the BG signals

- BG will control the Movement **not** the Cortex .
- **Why BG control the movement ?!** To identify the distance & the velocity.

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Basal Ganglia Disorders

Hyperkinesia

- **Chorea:** rapid involuntary "dancing" movements
- **Athetosis:** Continuous, slow writhing movements.
- **Ballism (Hemiballismus):** Involuntary flailing, intense & violent movements

Hypokinesia

Parkinson's disease

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Watch these videos for Patients who are suffering from Hyperkinesia diseases

1) SYDENHAM'S CHOREA IN 10 YEAR OLD BOY:

http://www.youtube.com/watch?v=vqu5RtDh9sw

1) ATHETOSIS:

http://www.youtube.com/watch?v=I63SobW58J0

1) BALLISM (HEMIBALLISMUS):

http://www.youtube.com/watch?v=t9jcccWzVPs

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PARKINSON DISEASE

Causes	Etiology
✓ Parkinson's disease results from the degeneration of dopaminergic neurons in the substantia nigra ✓ These neurons project to other structures in the basal ganglia ✓ The basal ganglia includes the striatum, substantia nigra, globus pallidus and subthalmus	✓ Remain largely unknown ✓ Heredity have a limited role ✓ Defective gene responsible for a rare condition called autosomal recessive juvenile parkinsonism (teens and 20s) ✓ Oxidative stress theory (environmental origin)

PARKINSON DISEASE

Pathogenesis	Neurotransmitter Imbalance
✓ Dopaminergic neuron degeneration **decreased** activity in the **direct pathway** and **increased** activity in the **indirect pathway** ✓ As a result thalamic input to the motor area of the cortex is reduced and ✓ Patient exhibits rigidity and bradykinesia	✓ Basal ganglia normally contains balance of dopamine and acetylcholine ✓ Balance necessary to regulate posture, muscle tone and voluntary movement ✓ Inhibition of dopaminergic activity leads to excessive cholinergic activity ✓ In Parkinson's, lack inhibitory dopamine and thus an increase in excitatory acetylcholine

Excitation imbalance Inhibition
loss of dopamine inhibition of putamen
increases in inhibitory output to GBes
decreases inhibitory output of STN
increases excitatory output GBis
increases inhibitory output to thalamus
reduces excitatory drive to cerebral cortex

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PARKINSON DISEASE

Symptoms

1) resting tremor
2) Rigidity
3) akinesia (difficulty in initiation of movement)
4) bradykinesia (slowness in the execution of movement)

These symptoms are due to :

1) loss of function of the basal ganglia which is involved in the coordination of body movement.
2) degeneration of dopaminergic neurons

Steve Alten (American author) and Muhammad Ali (American boxer) are diagnosed with Parkinson's disease.

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Hypokinesia

1) Akinesia:

Difficulty in initiating movement .

2) Bradykinesia:

Slowness of movement .

Features:

- ✓ Akinesia –Bradykinesia are marked.
- ✓ Absence of associated unconcious movements (swinging of are during walking) .
- ✓ Facial expression is masked.(because of increase muscle stiffness &has a connections with limbic system)
- ✓ Rigidity (Increase tone of the muscle)
- ✓ Tremors (static Tremor)
- ✓ Rigidity agonists and antagonists (spasticity).

Lead-pipe rigidity

cogwheel-catches (mixture of tremor and rigidity) .

Tremors . At Rest , 8Hz of antagonists.

PHARMACOLOGY PART

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Pharma lecture Not related to Physiology refer to pharma

***Anti-Parkinson drugs:**

Drugs used are to increase levels of dopamine or to inhibit the actions of acetylcholine in the brain.

***Treatment Strategies for Parkinson's Disease:**

Symptomatic	Neuroprotective
➢ Improve motor symptoms ➢ Reduce medication side effects ➢ Improve non-motor symptoms • Depression • Bowel/bladder problems • Mentation	➢ Slow disease progression ➢ Reverse brain cell damage

***Drug Therapy:**

L-DOPA
Cholinergic
Pallidectomy (extirpation of the globus pallidus.)

***Electrical stimulation of Globus pallidus**

***Tissue transplants** (In Substantia Nigra)

***Drugs increase dopamine levels**

▪Levodopa, Selegiline , Amantadine , Carbidopa Tolcapone

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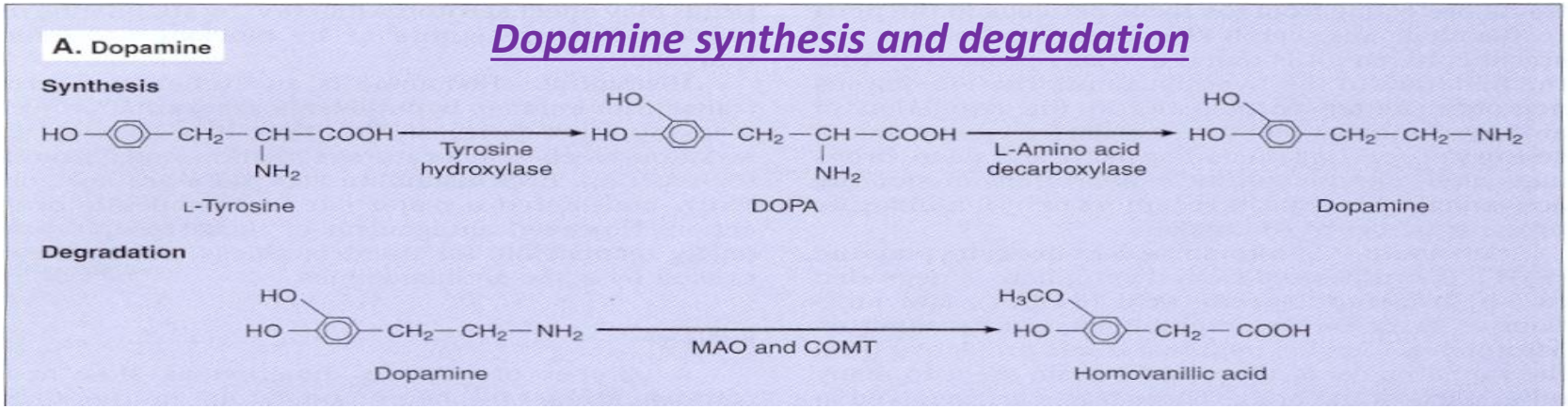
Levodopa

- L-dopa or Dihydroxyphenyalanine
- Biosynthetic precursor of dopamine
- Increase dopamine in the brain
- Main treatment used to decrease motor dysfunction
- Absorbed from proximal duodenum
- Protein-restricted diet
- Vit B6 should not be co-administrated with L-dopa
- L-dopa exhibits a large first-pass effect
- Only about 1% reaches brain tissue



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Huntington's disease (Chorea)

*Reverse Parkinson's disease.

Characterized by loss of GABAergic medium spiny projection neurons in the striatum.

Caused by glutamate-induced neurotoxicity .

Loss of GABAergic neurons that project of GP leads to disinhibition of thalamic nuclei and increase output to motor area of the cortex

Symptoms consistent with excess dopaminergic activity

- ✓ D2 receptor antagonist such as haloperidol and chlorpromazine have some effect at controlling the excess movement and some aspects of the psychiatric dysfunction
- ✓ Diazepam potentiates GABA and may reduce excess movement but only in the early stages of the disease
- ✓ Depression and impulsive behaviours may respond to antidepressant or propranolol (β-adrenergic antagonist)

Huntington's Disease (Chorea)

- **Rare**
  - onset 30-40s (Unlike Parkinson's disease that start at old age)
  - early as 20s(earlier than Parkinson's disease)
- **Degeneration of Striatum**
  - Caudate
  - Putamen
- **GABA & ACh neurons**

- Hereditory , autosomal dominant .
- Disease of caudate & putamen.
- **Jerky** movement of hands toward end of reaching an object .
- **Chorea**
- **Slurred** speech and incomprehensive .
- Progressive **Dementia**
- Loss of GABA – Cholinergic neurons .

The loss of **GABAergic** neurons leads to **chorea**

Loss of **Dopaminergic** neurons leads to **Parkinson"s disease** .

Important

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SUMMARY

- ✓ BG play important motor function in starting and stopping motor functions and inhibiting unwanted movement.
- ✓ It changes the timing and scales the intensity of movements.
- ✓ Putamen circuit is inhibitory. Executes skilled motor activities for example cutting paper with a scissor, hammering on nail, shooting a basket ball & like throwing a base ball.
- ✓ Putamen circuit has indirect connection to cortex via thalamus.while caudate has direct connection to the cortex from thalamus
- ✓ Caudate circuit is excitatory, has instinctive function which works without thinking and need quick response. e.g. response after seeing a lion.
- ✓ [Note: effects of basal ganglia on motor activity are generally inhibitory.]
- ✓ Lesions of the basal ganglia produce effects on contra lateral side of the body
- ✓ Damage to basal ganglia does not cause paralysis. However it results in abnormal movements

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QUESTIONS

1) Parkinson disease tremors are the result of which condition?

A. dopamine excess
B. Norepinephrine deficiency
C. epinephrine excess
D. dopamine deficiency

2) The following are basal ganglia terms except which one?

A. caudate nucleus
B. Putamen
C. Hippocampus
D. globus pallidus

3) What is the most significant neurotransmitter in the basal ganglia?

A. Norepinephrine
B. Epinephrine
C. Acetylcholine
D. Dopamine

4) The basal ganglia are mainly related to ---------functions:

A.Motor
B.Sensory
C.Mental
D.Autonomic

Key Answers :

1	2	3	4
D	C	D	A

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THE END

If there are any Problems or Suggestions,
Feel free to contact:

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THANK YOU