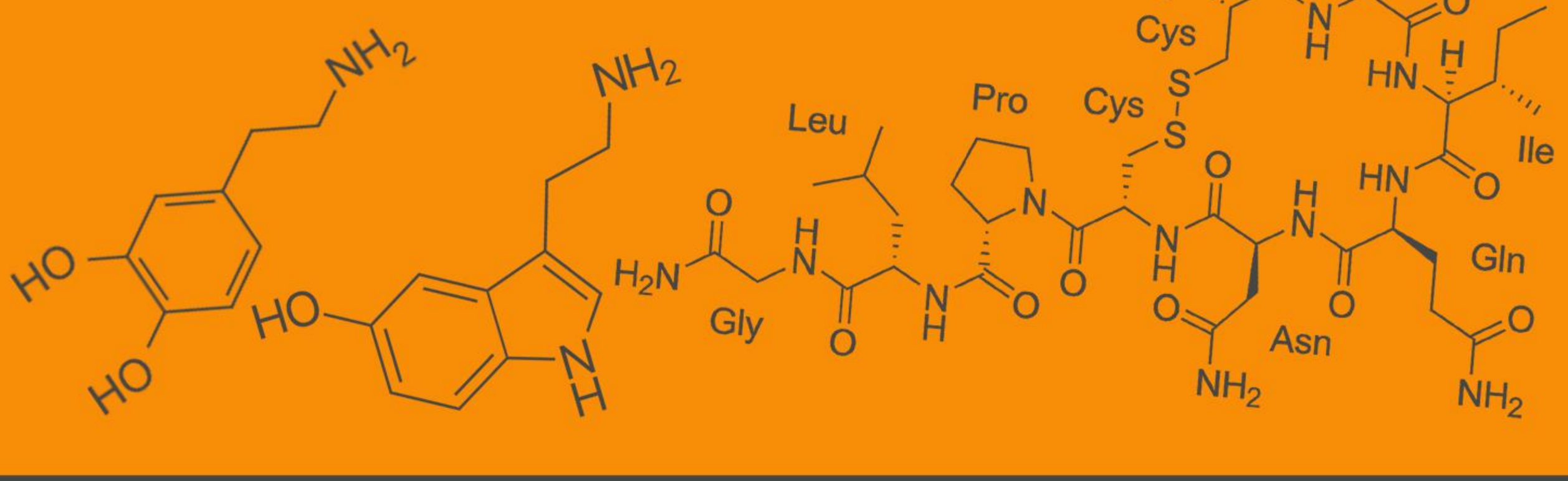
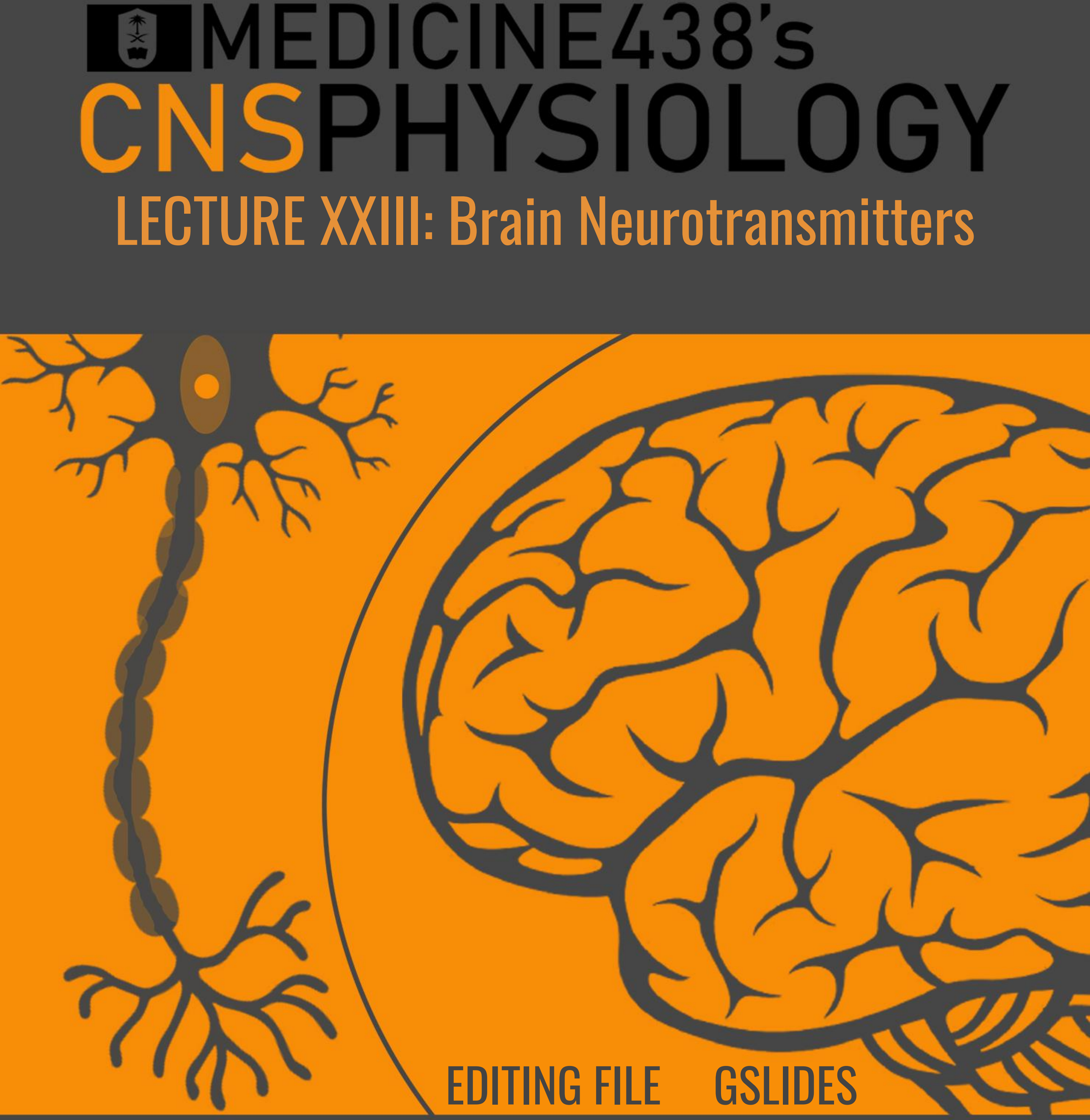


MEDICINE438's CNS PHYSIOLOGY

LECTURE XXIII: Brain Neurotransmitters



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1 Brain neurotransmitters

Lecture Twenty Three

OBJECTIVES

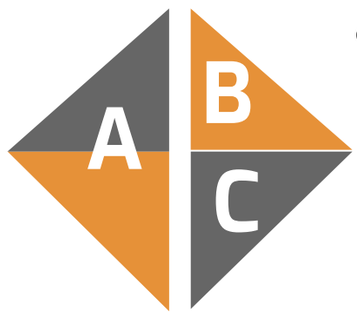
- Describe the functions of glutaminergic system
- Describe the functions of NTs of the brain (the noradrenergic & serotonergic cholinergic, dopaminergic, GABAergic systems)
- Appreciate that many drugs and CNS disorders affect function of brain neurotransmitters

Reviewed by Razan AlRabah & Ibrahim AlDakhil

Brain Neurotransmitters

Chemical substances released by electrical impulses into the synaptic cleft from synaptic vesicles of presynaptic membrane.

- Diffuses to the postsynaptic membrane.



- Binds to and activates the receptors.
- Leading to initiation of new electrical signals or inhibition of the postsynaptic neuron.

Classification of Neurotransmitters			
Amines			
Acetylcholine (ACh)	Dopamine (DA)	Norepinephrine (NE)	Epinephrine
Serotonin (5-HT)		Histamine	
Amino Acids			
Gamma-aminobutyric acid (GABA)	Glycine	Glutamate	Aspartate
Neuroactive Peptides - partial list			
bradykinin	beta-endorphin	bombesin	calcitonin
cholecystokinin	enkephalin	dynorphin	insulin
gastrin	Substance P	neurotensin	glucagon
secretin	somatostatin	motilin	vasopressin
oxytocin	prolactin	thyrotropin	Angiotensin II
Sleep peptides	galanin	Neuropeptide Y	Thyrotropin-releasing hormone
Gonadotropnin-releasing hormone	Growth hormone-releasing hormone	Luteinizing hormone	Vasoactive intestinal peptide
Soluble Gases			
Nitric Oxide (NO)		Carbon Monoxide	

Major Brain Neurotransmitters:

1. Ach.
2. Glutamate.
3. GABA
4. Norepinephrine (NE)/Epinephrine.
5. Serotonin.
6. Dopamine

2 Brain neurotransmitters

Lecture Twenty Three

Classes of Receptors:

- **Metabotropic:** Transmembrane receptor which acts through a secondary messenger.
- **Ionotropic:** Ligand gated ion channel

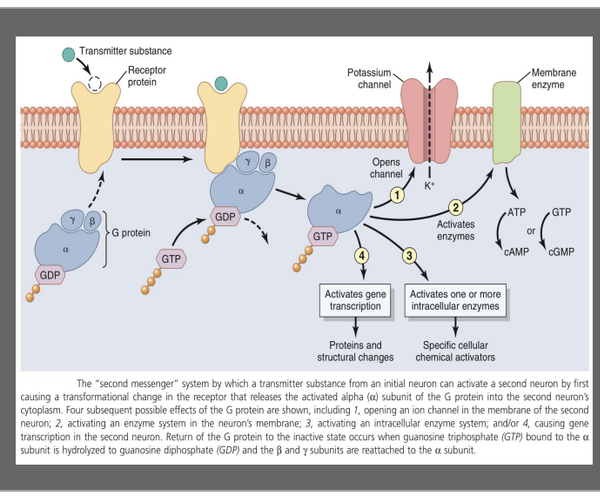
BOX 23-1: GUYTON AND HALL

- **ionotropic receptors:** usually of two types:

A) Cation channels: allow sodium, potassium and/or calcium ions to pass. Neurotransmitter that opens these channels (allowing positively charged ions to enter which excite the neuron) is called an excitatory transmitter, example are acetylcholine receptors on skeletal muscles.

B) Anion channels: mainly allow chloride ions to pass. Neurotransmitters that open these channels are called inhibitory transmitters. Examples are GABA receptors.

- The ion channel usually opens within a fraction of a millisecond and closes equally rapidly.
- **metabotropic receptors:** by activating a second messenger systems.It provides a prolonged postsynaptic neu ronal excitation or inhibition that many functions of the nervous system require, like memories.
- The most common type of second messenger systems is G protein



The "second messenger" system by which a transmitter substance from an initial neuron can activate a second neuron by first causing a transformational change in the receptor that releases the activated alpha (α) subunit of the G protein into the second neuron's cytoplasm. Four subsequent possible effects of the G protein are shown, including *1*, opening an ion channel in the membrane of the second neuron; *2*, activating an enzyme system in the neuron's membrane; *3*, activating an intracellular enzyme system; and/or *4*, causing gene transcription in the second neuron. Return of the G protein to the inactive state occurs when guanosine triphosphate *(GTP)* bound to the α subunit is hydrolyzed to guanosine diphosphate *(GDP)* and the β and γ subunits are reattached to the α subunit.

Cholinergic System:

- Acetylcholine is the major neurotransmitter in the peripheral nervous system.
- It's the second most common neurotransmitter in the brain.
- In the brain, cholinergic (ACh producing) neurons are present mainly in 2 areas:

1) **Basal Forebrain**[1] (mainly Nucleus Basalis of Myenert and septal nuclei)
2) **Mesopontine tegmental area** which is also called ponto-mesencephalic cholinergic complex

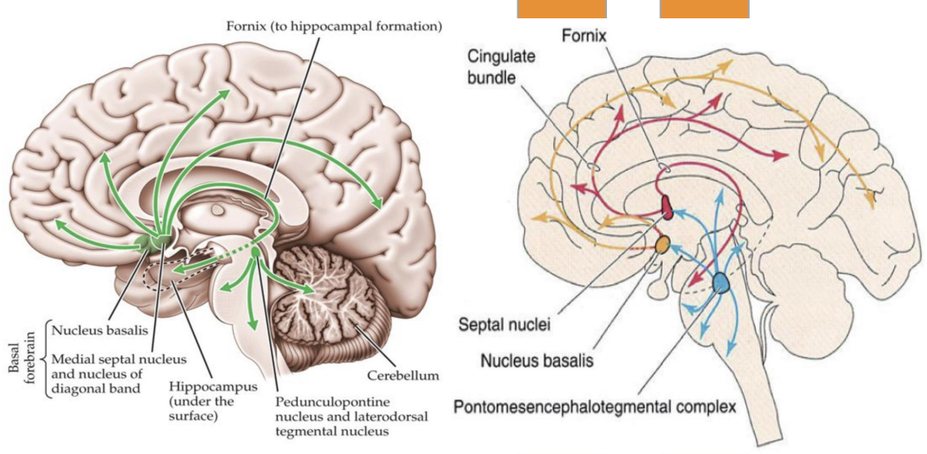


Figure 23-1

Acetylcholine Receptors:

Acts on 2 cholinergic receptors:

1. **Nicotinic (ionotropic)**
   - <u>The muscle-type:</u> can be selectively blocked by *curare*[2]
   - <u>The neuronal-type:</u> blocked by *hexamethonium*[3]
   - Excitatory
2. **Muscarinic (metabotropic)** (antagonist- Atropine):
   - Excitatory or inhibitory[4]
   - Five subtypes (M1-M5): all are found in the brain but **M1** is abundant.
   - **M1** receptors most involved in **cognitive functioning** (evidence from Knockout mice and pharmacologic human studies with M1 Blocking drugs)
   - M2 blocking agents may facilitate cognition in animals (but these drugs are not being used in humans at this point).
   - M3 receptors do not seem to play much of a role in cognition (animal studies).
   - M4 and M5 functions in the brain are unknown.

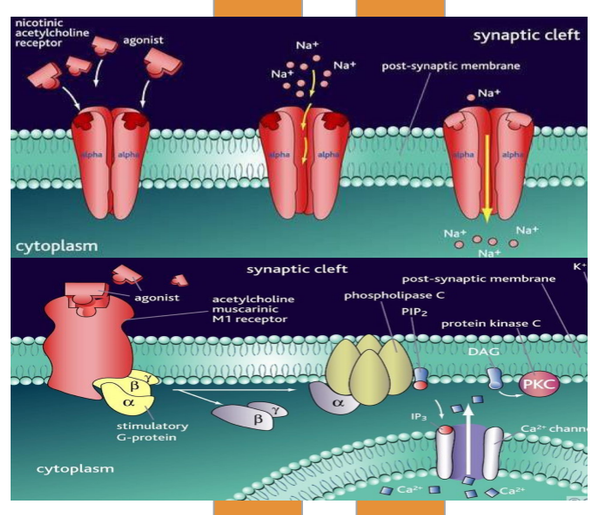


Figure 23-2

FOOTNOTES

1. The basal forebrain structures are located in the forebrain to the front of and below the striatum. They include the ventral basal ganglia (including nucleus accumbens and ventral pallidum), nucleus basalis, diagonal band of Broca, substantia innominata, and the medial septal nucleus.
2. A muscle relaxant used in anesthesia
3. It was formerly used to treat disorders, such as chronic hypertension, of the peripheral nervous system, which is innervated only by the sympathetic nervous system. The non-specificity of this treatment led to discontinuing its use
4. In most instances, acetylcholine has an excitatory effect; however, it is known to have inhibitory effects at some peripheral parasympathetic nerve endings, such as inhibition of the heart by the vagus nerves.

3 Brain neurotransmitters

Lecture Twenty Three

Ach Functions

ACh is associated with:

- Learning (high levels)
- Memory (high levels)
- Alertness
- Thought
- Sleep (low levels, except during REM Sleep)
- Speed of information processing in the brain
- Production of myelin sheath
- Muscular coordination

Ach Disorders

- Alzheimer's Disease: the most common form of dementia
- Associated with acetylcholine loss
- Damage to Ach producing cells in the basal forebrain.
- Ach levels are disturbed in:

1. Bipolar disorder (episodes of depression followed by mania "elevated mood")
2. Mood swings
3. Depression
4. Deficiencies in Ach can lead to myasthenia gravis

- Inhibitors of acetylcholinesterase in the brain are the main drugs used to treat Alzheimer's disease.

Glutaminergic System

1. **Glutamate is the most commonly found neurotransmitter in the brain** (king of NTs, ~50% neurons).
2. Glutamate is the major **excitatory** neurotransmitter of the brain and spinal cord, responsible for 75% of the excitatory transmission in the brain
3. **Glutamate** (can cause excitotoxicity) is *converted* in astrocytes into **glutamine** (not toxic) and passed onto glutaminergic neurons. To decrease the toxicity of Glutamate
4. Wide spread, but high levels in hippocampus; hypo function of NMDA receptors in this area and prefrontal cortex is associated with **schizophrenia**

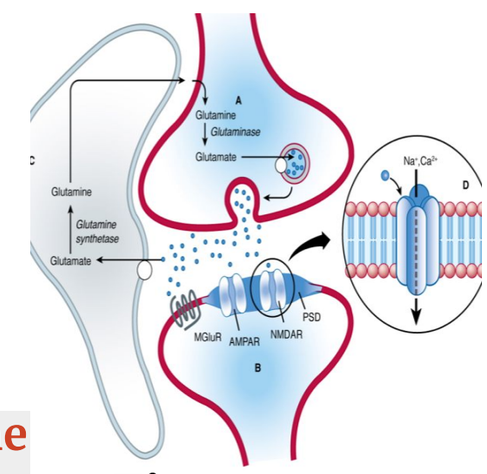


Figure 23-3

Glutamate Receptors

Are widely distributed in the brain; they are of two types:

Metabotropic receptors	Ionotropic receptors
(**G protein**- coupled receptors): mGluR	**ligand-gated ion channels** Three types:
Found in **hippocampus**, **cerebellum** and the **cerebral cortex**	**AMPA receptors** (α-amino-3-hydroxy-5-methylisoxazole- 4-propionate)
Act through second messengers which activate biochemical cascades, leading to modification of other proteins such as ion channels.	**Kainate receptors** (kainite is an acid isolated from seaweed)
	NMDA receptors (for N-methyl D-aspartate); play a role in long term potentiation so they are involved in learning and memory

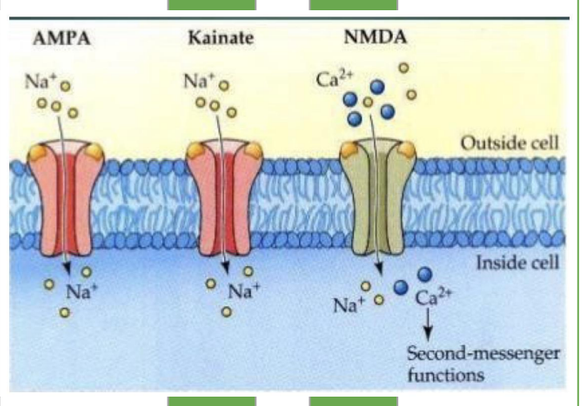


Figure 23-4

NMDA Receptors

Permits passage of Na+ and large amounts of Ca2+. They are unique:

- Glycine is essential for their normal response to glutamate
- The channel is blocked by **Mg2+ ion** at normal membrane potentials
- This blockade is removed by **depolarization** (caused by AMPA)
- Excitatory postsynaptic potential induced by activation of NMDA receptor is slower than that elicited by activation of *AMPA* and *kainate* receptors
- Glutamate NMDA receptor involved in Long-Term Potentiation & memory storage.

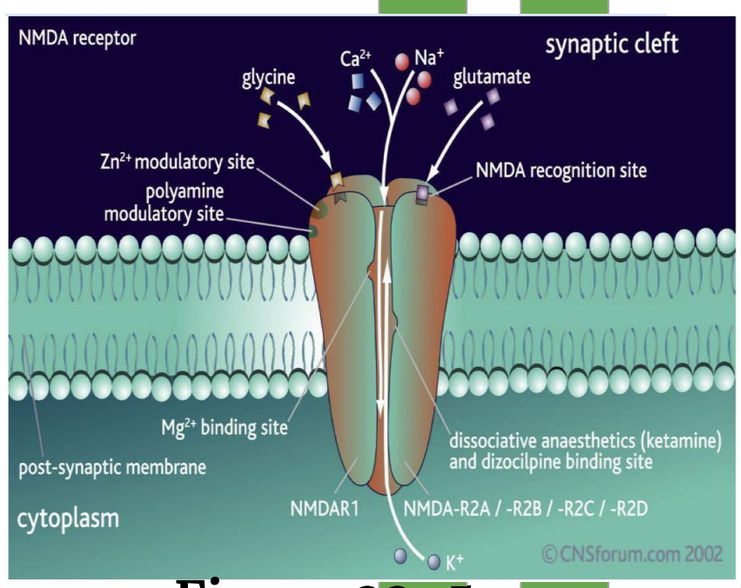


Figure 23-5

Functions Of Glutamate

- Glutamic acid (and aspartic acid): are major excitatory NTs in CNS.
- Learning and memory

Disorders Of Glutamate

- **Excess** Glutamate activity is implicated in some types of epileptic seizures
- Under some pathological conditions, such Stroke, ALS (Amyotrophic Lateral Sclerosis)[1], autism, and Alzheimer's disease, it acts as an excitotoxin, producing excessive influx of **calcium** into the neurons and causing **neuronal death.**

Glutamate is an important factor in neuronal cell degeneration:

- Motor neuron disease
- Huntington's disease[2]
- Parkinson's disease
- Alzheimer's disease

Reduced level in:

- Stroke
- Autism
- Intellectual disability
- Alzheimer's disease

GABAergic System

- GABA is the main inhibitory neurotransmitter in the central nervous system (CNS).
- GABAergic inhibition is seen at all levels of the CNS (Hypothalamus, hippocampus,cerebral cortex and cerebellar cortex).
- GABA interneurons are abundant in the brain, with 50% of the inhibitory synapses in the brain being GABA mediated
- Formed by decarboxylation of glutamate.
- Three types of GABA receptors: GABA A ,B & C.
- **GABA A & B** receptors are widely distributed in CNS.
- **GABA C** are found in retina only
- **GABA B** are metabotropic (G-protein) in function.
- GABA A and C receptors (ionotropic) have multiple binding sides (for benzodiazepine and barbiturates).
- The channel is a Cl-channel (not Na)

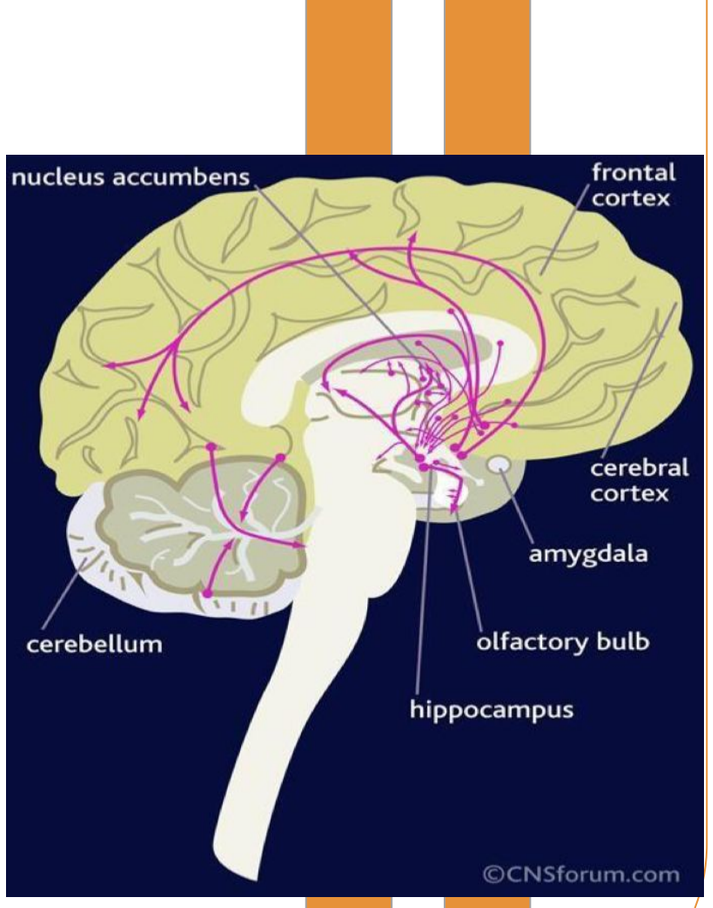


Figure 23-6

Functions of GABAergic System

- Presynaptic inhibition
- GABAA receptors in CNS are chronically stimulated to regulate neuronal excitability.

Disorders of GABA:

under activity of GABA leads to seizures. While over activity of glutamate leads to seizures

Alcohol, barbiturates, progesterone and deoxycorticosterone also in part work by increasing GABA activity

FOOTNOTES

1. Amyotrophic lateral sclerosis (ALS), also known as motor neurone disease (MND), is a specific disease that causes the death of neurons controlling voluntary muscles. It's characterized by stiff muscles, muscle twitching, and gradually worsening weakness.
2. Huntington's disease (HD), also known as Huntington's chorea, is an inherited disorder that results in the death of brain cells. The hallmark symptom is uncontrolled movement of the arms, legs, head, face and upper body.
3. A barbiturate is a drug that acts as a central nervous system depressant, and can therefore produce a wide range of effects, from mild sedation to death. Barbiturates are effective as anxiolytics, hypnotics "commonly known as sleeping pills", and anticonvulsants.

Noradrenergic System

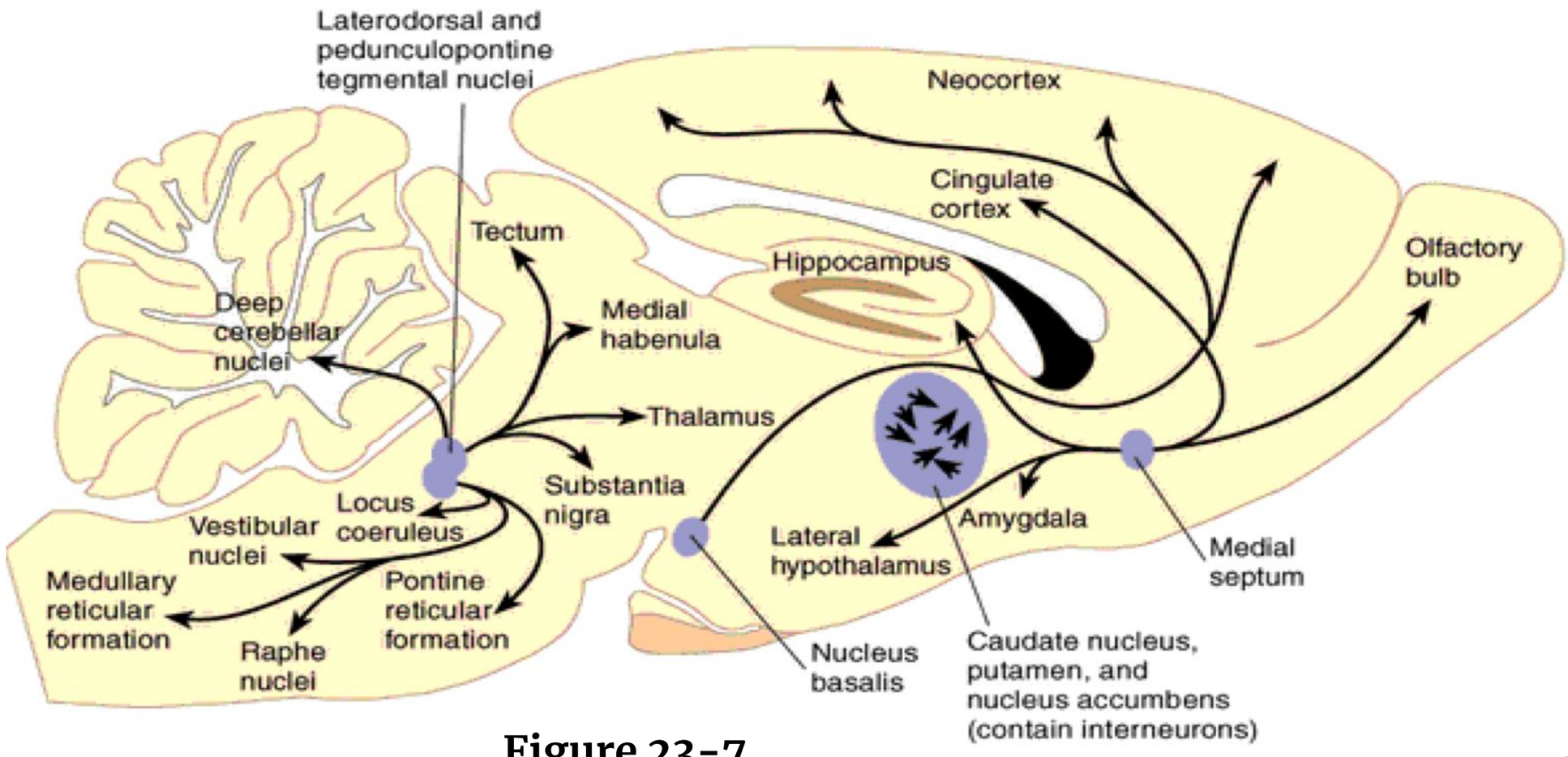


Figure 23-7

- Norepinephrine (NE): is a catecholamine that is synthesized from Dopamine.
- It is released from sympathetic nerves, the adrenal medulla and brainstem neurons.
- It acts on both α and β adrenergic receptors (G-protein-coupled receptors)
- NE is believed to play a role in both learning and memory.
- The Noradrenergic System has a very wide spread projection system
- **Locus ceruleus** is activated by stress and coordinates responses via projections to thalamus, cortex, hippocampus, amygdala, hypothalamus, autonomic brainstem centers, and the spinal cord.
- Nucleus Coeruleus is located in the pons, involved in physiological responses to stress and panic.
- **Locus coeruleus** neurons fire as a function of vigilance and arousal
- Irregular firing during **quiet wakefulness**
- Sustained activation during **stress**
- Their firing decreases markedly during **slow-wave sleep** and virtually disappears during **REM sleep.**

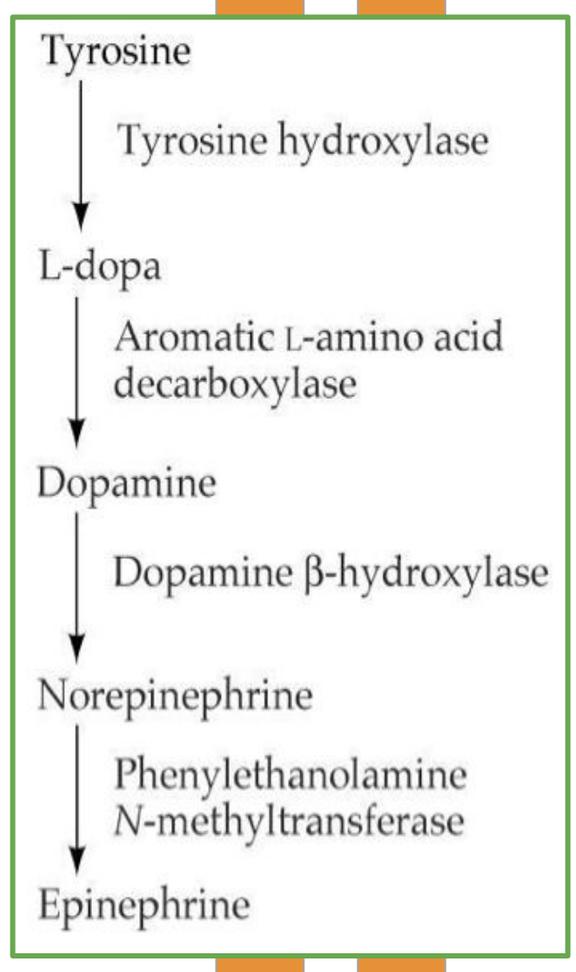


Figure 23-8

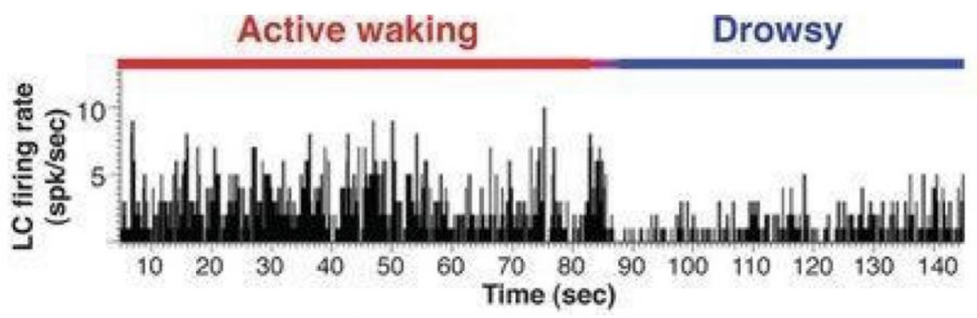


Figure 23-9

Functions of Norepinephrine

- Sleep
- Attention/Vigilance
- It constitutes part of the RAS (Reticular Activating System)
- Fight or flight response (reaches much higher levels during situations of stress or danger)
- Learning
- Enhances formation and retrieval of memory
- Aggressive behaviour

Disorders of Norepinephrine:

- Depression (decreased levels of NE)
- Withdrawal from some drugs of abuse (NE imbalance + other NTs)
- Anxiety and other stress-related disorders such as panic disorder. (High levels of NE)

6 Brain neurotransmitters

Lecture Twenty Three

Serotonin

1. Serotonin is synthesized from the amino acid tryptophan, which is abundant in meat
2. Our bodies cannot make tryptophan (must get from diet)
3. Tryptophan deprivation alters brain chemistry and mood
4. There is only a few 100,000`s of 5-HT neurons in human brain
5. There is 7 classes serotonin receptors in different parts of CNS (most are metabotropic, except **5-HT3**)
6. Mice in which the gene for **5-HT2 C** receptors has been knocked out are obese. These receptors are responsible for reducing the appetite. If blocked, it may result in obesity

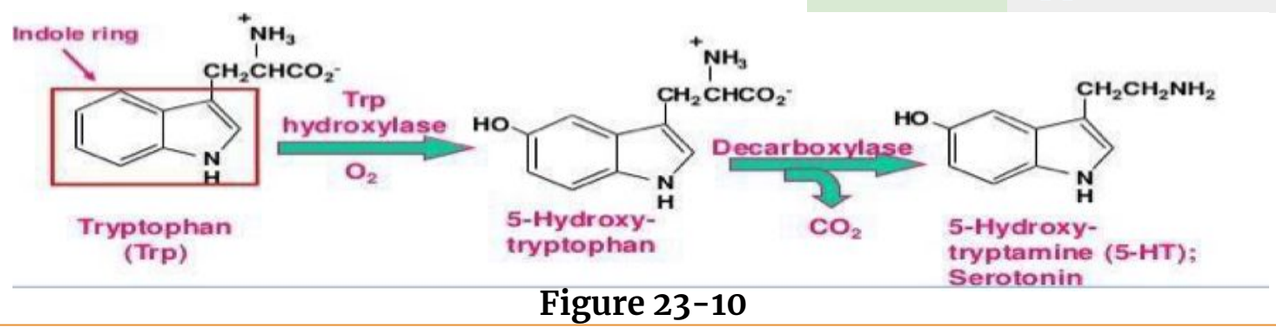


Figure 23-10

Serotonin pathways in the brain

- The principal centers for serotonergic neurons are the rostral and caudal **Raphe nuclei**
- Axons ascend to the cerebral cortex (induces Sleep), limbic and basal ganglia.
- **Serotonergic nuclei in the Brainstem** send descending axons which terminate in the medulla & spinal cord (suppress pain).

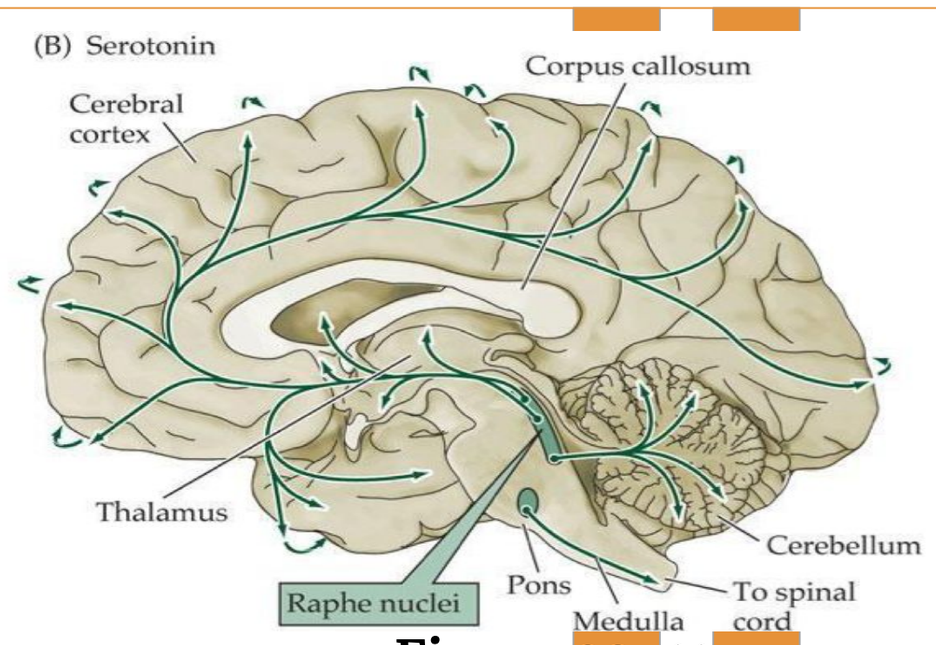


Figure 23-11

Serotonin (5-HT) Functions

- Improved mood
- Decrease appetite
- Sleep

Disorders of Serotonin:

- Depression (low levels)
- Anxiety (high levels)

- Drugs (e.g. Prozac "fluoxetine" is a selective serotonin reuptake inhibitor, an antidepressant) that prolong serotonin's actions, relieve symptoms of depression & obsessive disorders
- The major neurotransmitter which is associated with depression is Serotonin.

Dopamine

- Dopamine is a catecholamine that is synthesized from tyrosine.
- Five dopaminergic receptors (D1-D5).
- **Overstimulation of D2 receptors** is thought to be related to schizophrenia

Disorders of Dopamine:

- Parkinson's Disease.
- Schizophrenia

- Cocaine **elevate** activity at dopaminergic synapses.

Dopaminergic Pathway

Dopamine is transmitted via three major pathways:

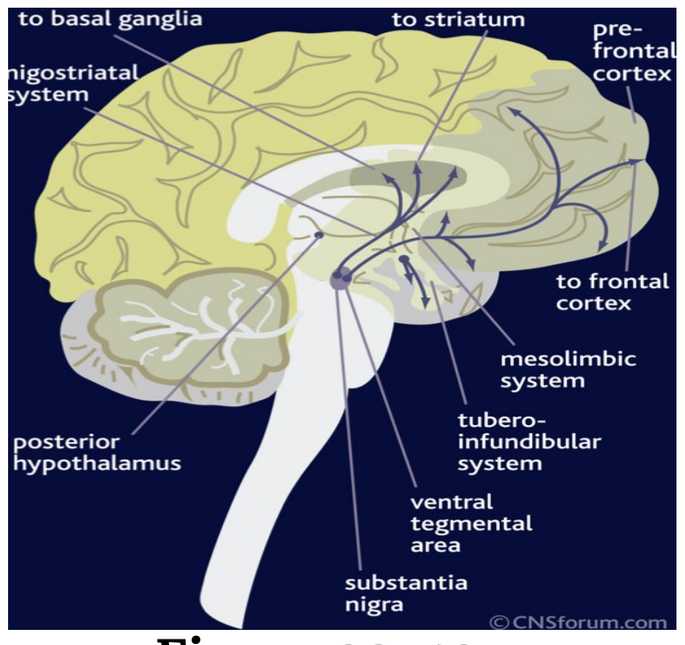


Figure 23-12

1

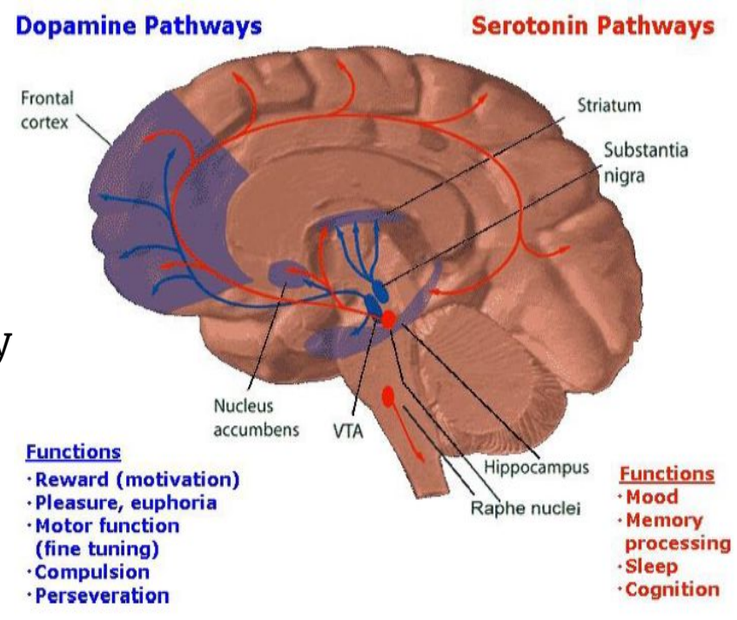
The first (Nigro-striatal system) extends from the **substantia nigra** to the **caudate nucleus-putamen (neostriatum)** and is concerned with sensory stimuli and movement.

- Dysfunction is connected to Parkinson's disease

2

The second pathway project to the **mesolimbic forebrain**

- Related to cognitive, reward and emotional behavior
- Dysfunction is connected to hallucinations and schizophrenia



3

The third pathway, known as the **tuberoinfundibular system** It is concerned with:

- Regulation of secretion of prolactin[1] from the anterior pituitary gland[2]
- Maternal behavior (nurturing)

★ You only need to know the effects, receptors, and functions.

Figure 23-13

Neurotransmitter	Postsynaptic effect	Derived from	Site of synthesis	Postsynaptic receptor	Fate	Functions
Acetylcholine (ach)	Excitatory	Acetyl coA + Choline	- Cholinergic nerve endings - Cholinergic pathways of brainstem	1. Nicotinic 2. Muscarinic	Broken by acetylcholinesterase	- Cognitive function e.g. memory - Peripheral action e.g. cardiovascular system
Catecholamines: 1. Epinephrine (adrenaline)	Excitatory In some but inhibitory in other	Tyrosine produced in liver from phenylalanine	Adrenal medulla and some CNS cells	Excites both α and β receptors	1. Catabolized to inactive product through COMT & MAO in liver 2. Reuptake into adrenergic nerve endings 3. Diffusion away from nerve endings to body fluid	For details refer ANS. e.g. fight or flight, on heart, BP, gastrointestinal activity etc.
2. Norepinephrine	Excitatory	Tyrosine, found in pons. Reticular formation, locus coerules, thalamus, midbrain	Begins inside axoplasm of adrenergic nerve ending is completed inside the secretory vesicles	α1 α2 β1 β2		Norepinephrine controls attention & arousal, sleep/wake cycle.
3. Dopamine	Excitatory	Tyrosine	CNS, concentrated in basal ganglia and dopamine pathways e.g. nigrostriatal, mesocorticolimbic and tubero-hypophyseal pathway	D1 to D5 receptor		Sensory motor Cognitive / emotional behavior Endocrine Hypothalamic Decreased dopamine in parkinson's disease.

FOOTNOTES

1. Prolactin is a hormone produced in the pituitary gland. Its primary role is to promote breast milk production (lactation). It affects many different hormones in the body. Present in both men and women.
2. Dopamine released at this site inhibits the secretion of prolactin from anterior pituitary gland lactotrophs by binding to D2 receptors. Some antipsychotic drugs block dopamine in the tuberoinfundibular pathway, which can cause an increase in the amount of prolactin in the blood (hyperprolactinemia).

8 Brain neurotransmitters

Lecture Twenty Three

Neurotransmitter	Postsynaptic effect	Derived from	Site of synthesis	Postsynaptic receptor	Fate	Functions
Serotonin (5HT)	Excitatory	Tryptophan	CNS,Gut (chromaffin cells) platelets & retina	5-HT 1 to 5-HT7 - 5-HT2A receptor mediates platelet aggregation & smooth muscle contraction	Inactivated by MAO to from 5-hydroxyindole acetic acid (5-HIAA) in pineal body it is converted to melatonin	Mood control,sleep,pain feeling, temperature, BP & hormonal activity
Histamine	Excitatory	Histidine	Hypothalamus	Three types H1 H2 H3 receptors found in peripheral tissues & the brain	Enzyme diamine oxidase (histaminase) cause breakdown	Arousal ,pain threshold, blood pressure, blood flow control, gut secretion, allergic reaction (involved in sensation of itch)
Glutamate	Excitatory 75% of excitatory transmission in the brain	By reductive amination of krebs cycle intermediate α-ketoglutarate	Brain & spinal cord e.g. Hippocampus	Ionotropic and metabotropic receptors. Three types of ionotropic receptors e.g. NMDA, AMPA and kainate receptors.	It is cleared from the brain ECF by Na + dependent uptake system in neurons and neuroglia.	Long term potentiation involved in memory and learning by causing Ca++ influx.
Aspartate	Excitatory	Acidic amines	Spinal cord	Spinal cord	Aspartate & Glycine form an excitatory / inhibitory pair in the ventral spinal cord	
Gama-amino-butyric-acid (GABA)	Major inhibitory mediator	Decarboxylation of glutamate by glutamate decarboxylase (GAD) by GABAergic neuron	CNS	- GABA A increases the Cl - conductance - GABA B is metabotropic works with G – protein - GABA transaminase catalyzes. - GABA C found exclusively in the retina.	Metabolized by transamination to succinate in the citric acid cycle.	- GABA – A causes hyperpolarization (inhibition) - Anxiolytic drugs like benzodiazepine cause increase in Cl- entry into the cell & cause soothing effects. - GABA – B cause increase conductance of K+ into the cell.
Glycine	Inhibitory	simple amino acid having amino group and a carboxyl group attached to a carbon atom	Spinal cord	Glycine receptor makes postsynaptic membrane more permeable to Cl- ion.	Deactivated in the synapse by simple process of reabsorption by active transport back into the presynaptic membrane	Glycine is inhibitory transmitted found in the ventral spinal cord. It is inhibitory transmitter to Renshaw cells.

QUIZ

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1. Which of the following is involved in Long-term potentiation and memory storage:

A) AMPA receptors
B) Kainate receptors
C) NMDA receptors

2. What is the most important neurotransmitter to be involved in Parkinson's disease?

A) Norepinephrine
B) GABA
C) Dopamine

3. Which of the following is inhibitory neurotransmitter?

A) Norepinephrine
B) Epinephrine
C) GABA

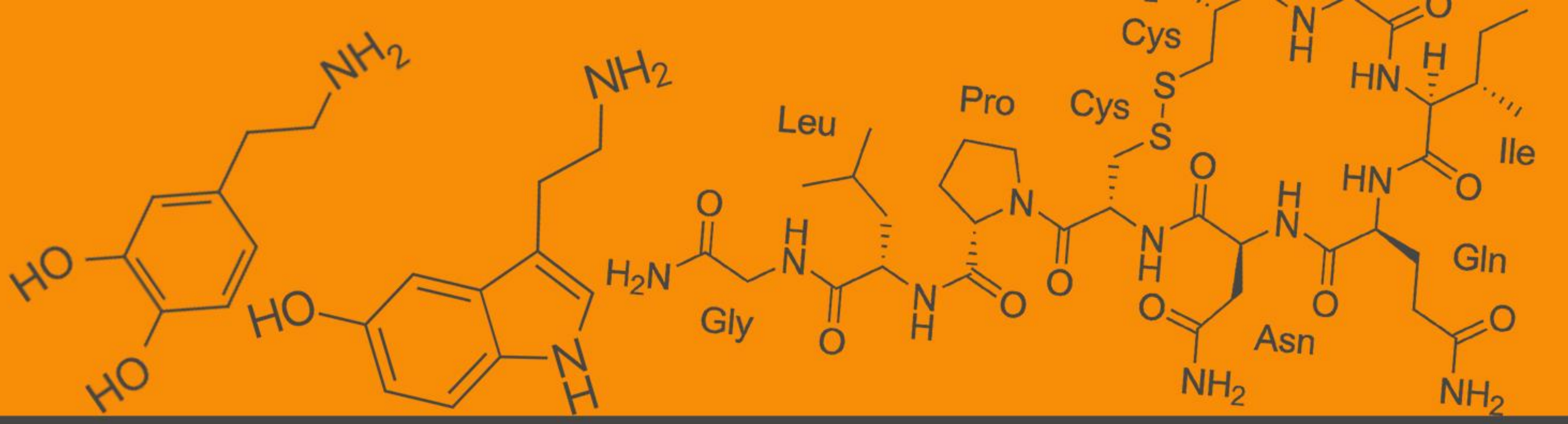
4. What is the major cholinergic output of the CNS?

A) The basal forebrain
B) Locus coeruleus
C) Raphe nuclei

5. Dysfunction of which of the following dopaminergic pathways can lead to schizophrenia and hallucinations?

A) Nigro-striatal system
B) Project to the mesolimbic forebrain
C) Tuberoinfundibular system

ANSWER KEY: C, C, C, A, B



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