24

Brain Neurotransmitter

PHYSIOLOGY
CNS Block
Team 443

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Editing File

Objectives

1. Describe the functions of glutamergic system.
2. Describe the functions of NTs of the brain (the noradrenergic & serotonergic cholinergic, dopaminergic, GABAergic systems).
3. Appreciate that many drugs and CNS disorders affect function of brain neurotransmitters.

From team (439):

Male's doctor: The **Function of each Neurotransmitter** (& it's related system)
is the **Most Important Objective** of this Lecture

Brain Neurotransmitters:

- Chemical substances released by electrical impulses into the synaptic cleft from synaptic vesicles of presynaptic membrane.
- **Diffuses to the postsynaptic membrane.**(function: either excite or inhibit the postsynaptic membrane, depending on the type of receptor)
- Binds to and activates the receptors.
- Leading to initiation of new electrical signals or inhibition of the postsynaptic neuron. EPSP or IPSP

Classification of Neurotransmitters

Amines

Male doctor did not focus on it

- Acetylcholine (ACh)
- Dopamine (DA)
- Norepinephrine (NE)
- Epinephrine
- Serotonin (5-HT)
- Histamine

Amino Acids

- Gamma-aminobutyric acid (GABA)
- Glycine
- Aspartate
- Glutamate

Neuroactive Peptides - (Partial list!)

- bradykinin
- cholecystokinin
- gastrin
- secretin
- oxytocin
- Sleep peptides
- Gonadotropin-releasing hormone
- beta-endorphin
- enkephalin
- Substance P
- somatostatin
- prolactin
- galanin
- Growth hormone-releasing hormone
- bombesin
- dynorphin
- neurotensin
- motilin
- thyrotropin
- Neuropeptide Y
- Vasoactive intestinal peptide
- calcitonin
- insulin
- glucagon
- vasopressin
- Angiotensin II
- Thyrotropin-releasing hormone
- Luteinizing hormone

Soluble Gases

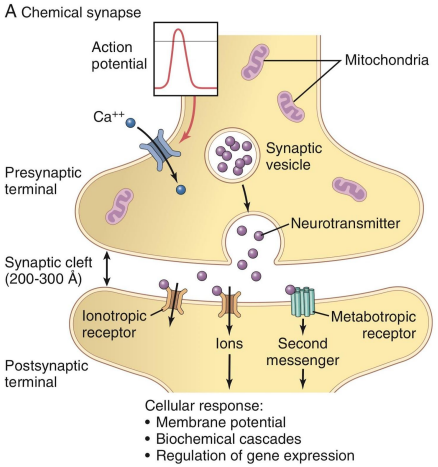
Their effect doesn't last long

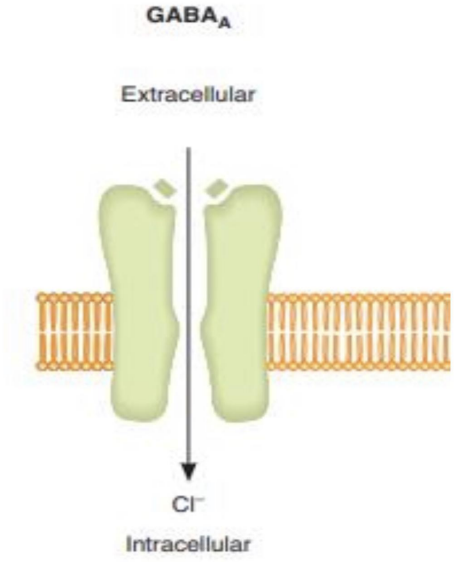
- Nitric Oxide (NO)
- Carbon Monoxide

Classes of receptors

Guyton: Receptor activation controls the opening of ion channels in the postsynaptic cell in one of two ways:
(1) by gating **ion channels directly and allowing passage of specified types of ions** through the membrane.
(2) by **activating a "second messenger" that is not an ion channel** but instead is a molecule that protrudes into the cell cytoplasm and activates one or more substances inside the postsynaptic neuron. These second messengers increase or decrease specific cellular functions.

Neurotransmitter receptors that **directly gate ion channels are often called ionotropic** receptors, whereas those that **act through second messenger systems are called metabotropic receptors.**





either open or close channels

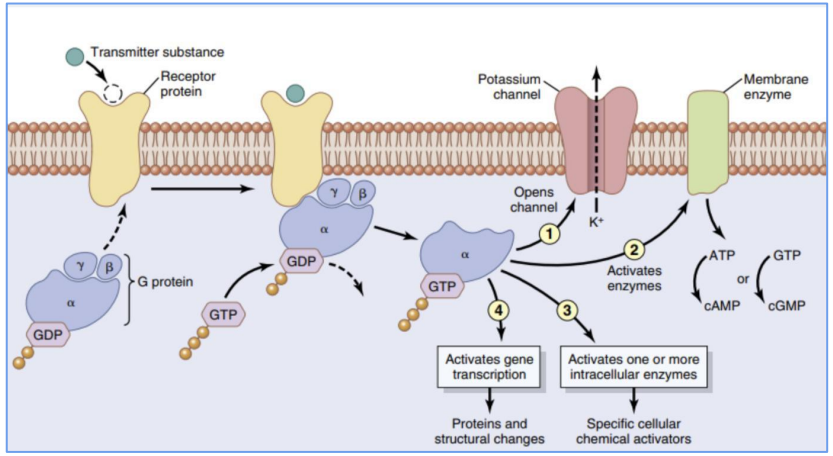
Classes of Receptors

Ionotropic

Ligand gated ion channel.
Fast and short lived

Metatropic

Transmembrane receptor which acts through a secondary messenger.(G protein)
important for memory



secondary messenger acts in 4 ways :
1-Opens channel
2-Activates enzymes
3-Activates I or more intracellular enzymes for specific cellular chemical activators
4-Activates gene transcription for protein and structural changes

Important

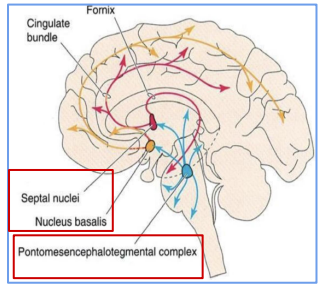
Neurotransmitters we gonna discuss:

1	Ach (Acetylcholine)
2	Glutamate
3	GABA (Gamma Aminobutyric acid)
4	Norepinephrine (NE)/ Epinephrine (Adrenaline).
5	Serotonin
6	Dopamine

Cholinergic system : Ach

Overview

- Acetylcholine is the major neurotransmitter in the **peripheral nervous system.**
  (Extensively collected in the brain & spinal cord).
- In the brain, cholinergic (ACh producing) neurons are present mainly in 2 areas:
  1) **Basal Forebrain** (**namely Nucleus Basalis** of Meynert and **septal nuclei**). It starts in the basal forebrain
  2) **Mesopontine tegmental area** which is also called **pontomesencephalic cholinergic complex.**



Male slides

Receptors

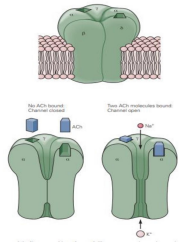
1- Nicotinic (ionotropic)
opens Na channels

- **Excitatory.**
- 2 types:

1. The muscle-type: can be selectively blocked by curare.
2. The neuronal-type blocked by hexamethonium.

2- Muscarinic (metabotropic) (antagonist-Atropine)

- **Excitatory or inhibitory.**
- Five subtypes (M1-M5): M1,M4 and M5 are found In the CNS 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.

Important

Ach Functions & Disorders

Functions

- ACh is associated with **Thought, Memory, Muscular coordination, Speed of information processing** in the brain and **Production of myelin sheath.**
- ACh influences mental processes such as:
  High levels during: Learning, memory, alertness, and REM (rapid eye movement sleep).
  Low levels during: Sleeping **(Except REM).**

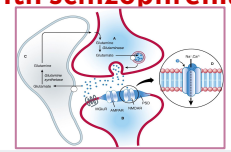
Disorders

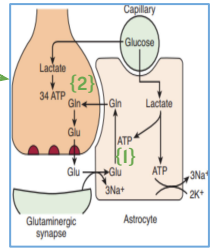
- **Alzheimer's Disease**: the most common form of dementia. Associated with **acetylcholine loss.**
- Ach levels are disturbed in/ Damage to Ach producing cells in the basal forebrain is associated with some psychiatric disorders:
  1. Bipolar disorder.
  2. Mood swings.
  3. Depression.
  4. Mental attention.
- **Inhibitors of acetylcholinesterase** in the brain are the main drugs used to treat Alzheimer's disease.

Glutaminergic System: Glutamate

Overview

- Glutamate is the **most commonly** found neurotransmitter in the brain (king of NTs, ~50% neurons).
- Glutamate is the **major excitatory** **neurotransmitter of the brain and spinal cord,** responsible for 75% of the excitatory transmission in the brain.
- Glutamate (can cause **excitotoxicity**) is converted in astrocytes into glutamine{1} (not toxic) and passed onto glutaminergic neurons{2}.
- Wide spread, but high levels in hippocampus; **hypofunction of NMDA receptors** in this area and prefrontal cortex **is associated with schizophrenia.**
- Glutamate is synthesized from glutamine by the help of glutaminase enzyme present in the presynaptic vesicles.
- Upon stimulation, glutamate is released stimulating NMDA receptors.
- The remaining unused glutamate will be reconverted to glutamine and the cycle repeats.





Glutamate Functions & Disorders

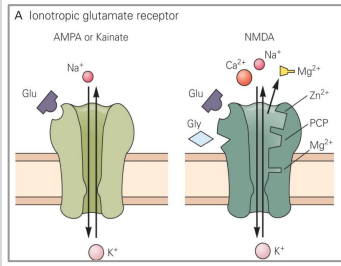
Functions	❖ Glutamic acid (and aspartic acid): are major excitatory NTs in CNS. ❖ Glutamate NMDA receptor **involved in Long-Term Potentiation & memory storage.**(discussed in next slide) ❖ Important role in Learning and memory.
Disorders	❖ Excess Glutamate activity is implicated in some types of **epileptic seizures.** ❖ Under some pathological conditions, such Stroke, ALS (Amyotrophic Lateral Sclerosis), autism ,Huntington's disease, and Alzheimer's disease, it acts as an excitotoxin, **producing excessive influx of calcium** into the neurons and causing neuronal death. ❖ **Reduced level in :** Stroke, Autism, Intellectual disability, Motor neuron disease, Huntington's disease, Parkinson's disease and **Alzheimer's disease.**

Glutaminergic System: Glutamate

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

1- Metabotropic receptors:

- (G protein- coupled receptors): mGluR.
- Found in hippocampus, cerebellum and the cerebral cortex.
- Act through second messengers which activate biochemical cascades, leading to modification of other proteins such as ion channels.



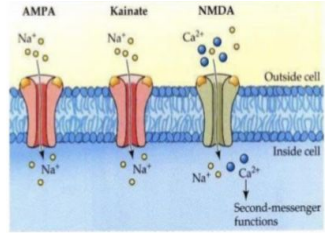
2- Ionotropic Receptors (ligand-gated ion channels) Three types:

AMPA

(α-amino-3-hydroxy-5-methyl isoxazole- 4-propionate).

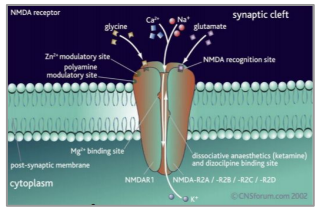
Kainate

Kainate receptors (kainite is an acid isolated from seaweed).

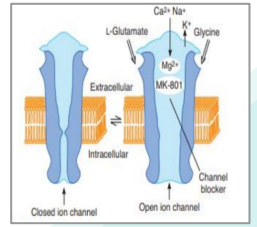


NMDA
Dr:هذا الي يهمني

(for N-methyl D-aspartate); play a role in long term potentiation so they are involved in learning and memory storage.
Permits passage of Na+ and large amounts of Ca2+. They are unique:



- The channel(NMDA)is blocked by Mg2+ ion at normal membrane potentials.(at resting state)
- This blockade is removed by depolarization (caused by AMPA). (that will lead to influx of Ca inside NMDA receptors,that will lead to activation of enzymes that will increase the number of AMPA receptors and that will lead to activation of NMDA receptors again and the cycle goes on. this whole process is called long term potentiation and this is important for memory storage)
- Excitatory postsynaptic potential induced by activation of NMDA receptor is slower than that elicited by activation of AMPA and kainate receptors.
- Glycine is essential for their normal response to glutamate.

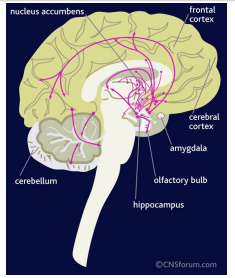


441:باختصار NMDA تحتاج الى glutamate أكثر من AMPA، فاذا كان الGlutamate قليل بيفعل AMPA وشوي بس بيروح ل NMDA فما راح تفتح بشكل كامل، فمب سامحه للصوديوم والكالسيوم بالدخول بشكل كافي وبتتقفل بالماغنيسيوم. لكن لو كان الGlutamate كثير بيفعل الاثنين ،واذا كان الglutamate كثير مره بيدخل كالسيوم كثير وممكن يؤدي الى exotoxicity.

GABAergic System: Gamma Aminobutyric acid (GABA)

Overview

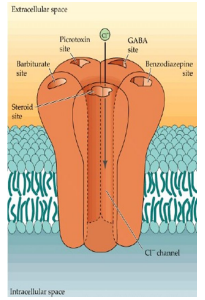
- GABA is the **main inhibitory** neurotransmitter in the central nervous system (CNS).
- GABAergic inhibition is seen at all levels of the CNS (Hypothalamus, hippocampus,cerebral cortex and cerebellar cortex).
- GABA interneurons are **abundant** in the brain, with 50% of the inhibitory synapses in the brain being GABA mediated.
- Formed by decarboxylation of glutamate.



Receptors

Three types of GABA receptors: GABA A ,B & C.

- GABA **A & B** receptors are widely distributed in CNS. .(details of function next slide)
- GABA **C** are found in **retina** only. (See has same pronunciation as C :ربط)
- GABA **B** are metabotropic **(G-protein)** in function.
- **GABA A and C receptors (ionotropic) have multiple binding sides (for benzodiazepine and barbiturates).** (drugs)
- **The channel is a Cl-channel (not Na).** Hyperpolarization because it's inhibitory.



GABA Functions & Disorders

Male slides

Functions

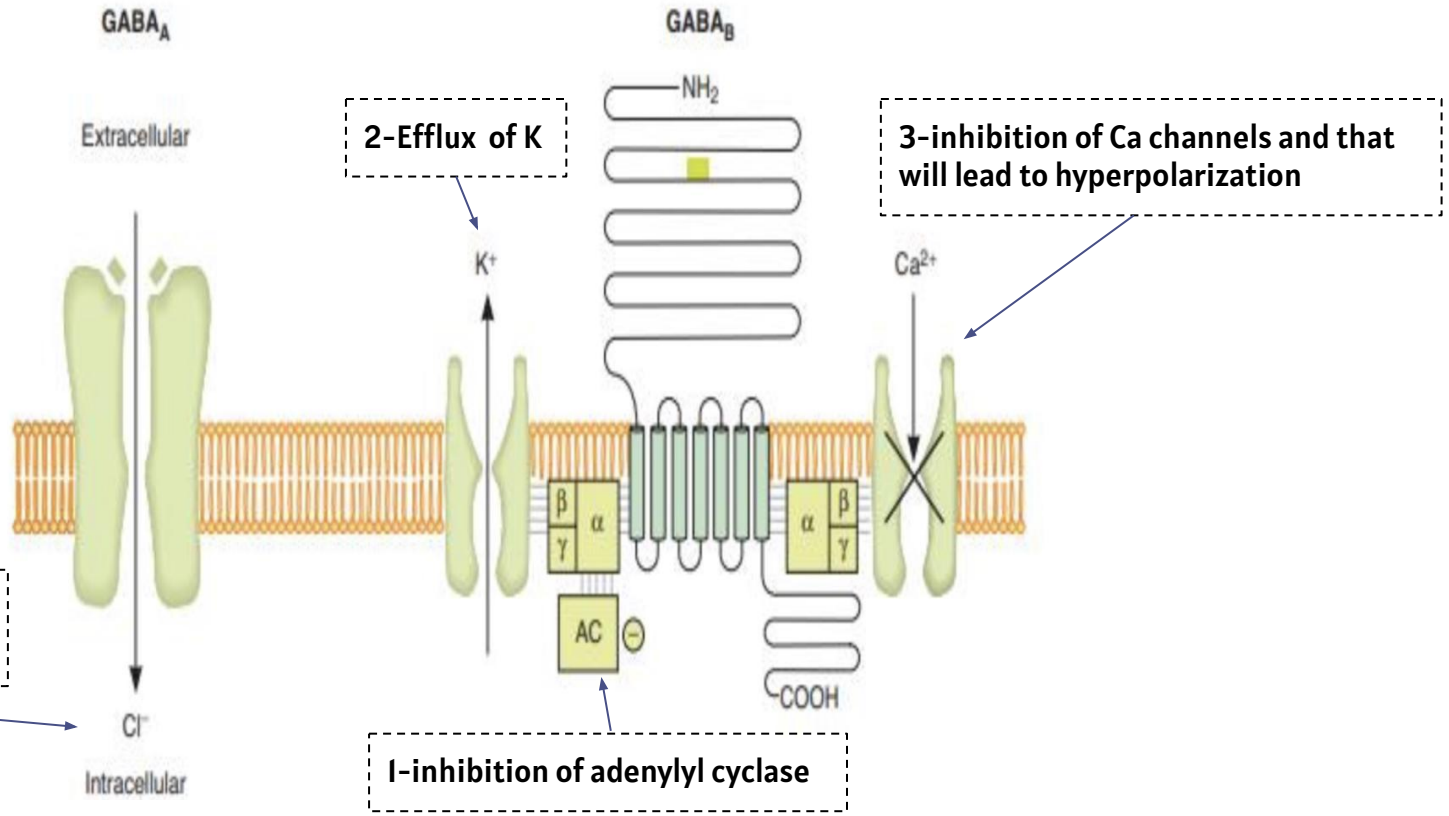
- Presynaptic inhibition.
- GABA receptors in CNS are chronically stimulated to regulate neuronal excitability.

Disorders

- Under activity of GABA leads to seizures.
- **Alcohol, barbiturates, progesterone and deoxycorticosterone also in part work by increasing GABA activity.**

Extra:GABA receptors A and B

GABA B is metatropic works by G protein



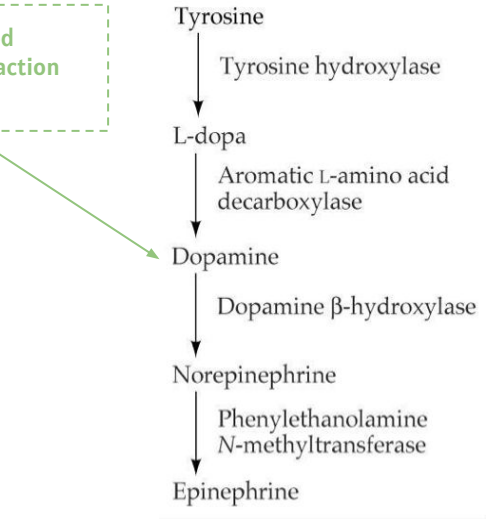
GABA A is Ionotropic, when it is stimulated it will lead to influx of Cl

Norepinephrine System

Overview

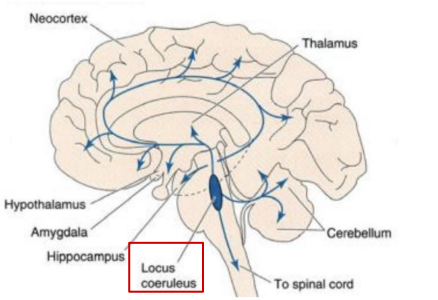
- Norepinephrine (NE): is a catecholamine that is synthesized from Dopamine.
- It is released from sympathetic nerves, the adrenal medulla and brainstem neurons.
- It acts on both α and β adrenergic receptors (G-protein-coupled receptors)
- NE is believed to play a role in both learning and memory.
- The Noradrenergic System has a very wide spread projection system

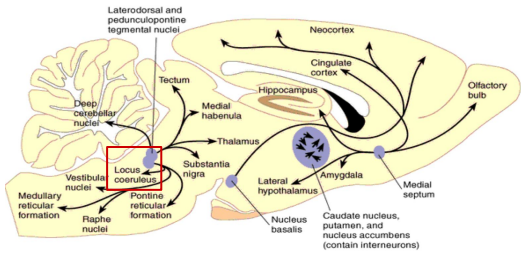
In places that need dopamine, the reaction will stop here

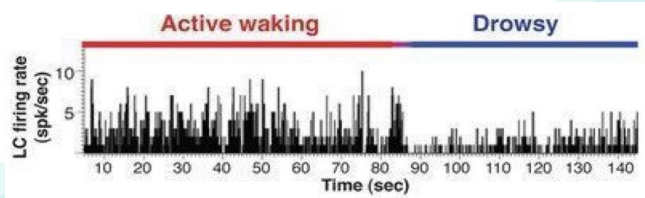


Locus coeruleus

- Major site for secretion of NE
- is a small nucleus located deep in the brainstem that provides the far-reaching noradrenergic neurotransmitter system of the brain
- 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 (تيقظ) 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.**







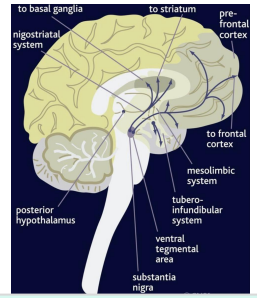
Norepinephrine System

Functions of Norepinephrine	Disorders of Norepinephrine
• Sleep • Attention/Vigilance,arousal • 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.	•Reduced levels in: Depression • Withdrawal from some drugs of abuse (NE imbalance + other NT). •High level in : Anxiety and other stress-related disorders such as panic disorder.

Dopamine

Overview

- Dopamine is a catecholamine that is synthesized from tyrosine.
- Five dopaminergic receptors (DI-D5).
- Overstimulation of **D2 receptors is thought to be related to schizophrenia.** (The main cause of Schizophrenia)
- D4 receptors have a greater affinity for the "atypical" antipsychotic drug clozapine



Dopaminergic Pathways:

Dopamine is transmitted via <u>three</u> major pathways:

The first (Nigro-striatal system)	extends from the **substantia nigra** to the caudate nucleus-putamen (neostriatum) and is concerned with **sensory stimuli and movement**/involved in **motor control**. - Dysfunction is connected to Parkinson's disease.
The second pathway	project to the mesolimbic forebrain, Related to **cognitive, reward, addiction** and **emotional behavior**. Dysfunction is connected to hallucinations and schizophrenia.
The third pathway (tuberoinfundibular system)	It is concerned with: Regulation of secretion of prolactin from the anterior pituitary gland. Related to **neuronal control of the hypothalamic -pituitary endocrine system**. (Part of pituitary:endocrine secretion /function) ● Maternal behavior (nurturing)

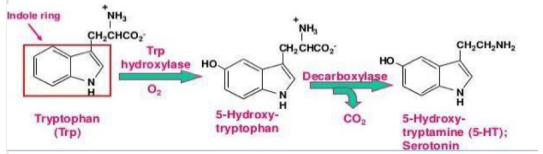
Dopamine

Functions of Dopamine	Disorders of Dopamine
❖ Addiction ❖ Perseveration ❖ Reward ❖ Pleasure, euphoria, emotional behaviour ❖ Motor function (fine tuning)	1-Schizophrenia increased subcortical release of dopamine at D2 receptors (results in hallucinations and delusions) 2-Parkinson's Disease decreased release of dopamine from substantia nigra Cocaine elevate activity at dopaminergic synapses.

Serotonin

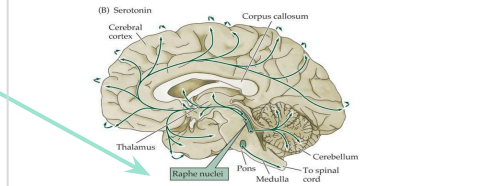
Overview

- Serotonin is synthesized from the amino acid tryptophan, which is abundant in meat
- Our bodies cannot make tryptophan (must get from diet)
- Tryptophan deprivation alters brain chemistry and mood
- There is only a few 100,000`s of 5-HT neurons in human brain
- There is 7 classes serotonin receptors in different parts of CNS (most are metabotropic, except 5-HT3)
- Mice in which the gene for 5-HT2 C receptors has been knocked out are obese
- 5-HT6 and 5-HT7 receptors (limbic system) , and the 5-HT6 receptors have a high affinity for antidepressant



Serotonin pathways in the brain

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



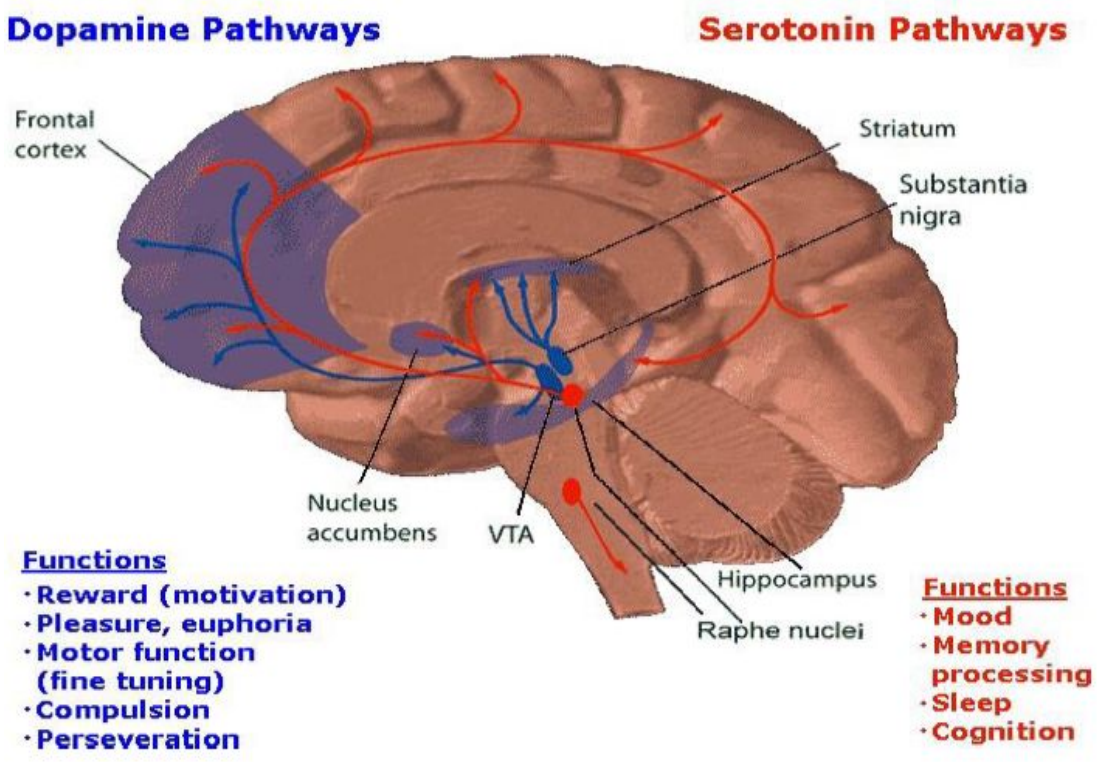
Important

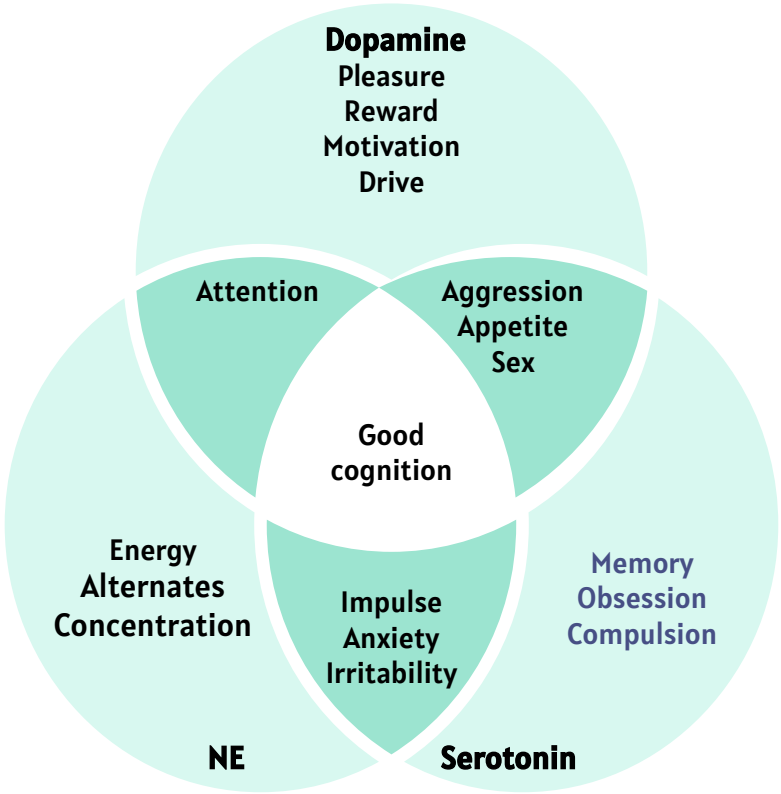
Functions of Serotonin (5-HT):	Disorders of Serotonin Low level in:
Improved mood	Depression (Low self-esteem)
Decrease appetite	Poor appetite (there is a mistake in female doctors slides, it should be increased)
Sleep	**Anxiety** Drugs (e.g.Prozac) that prolong serotonin's actions relieve symptoms of depression & obsessive disorders
	Poor memory & irritability

comparison

The picture is from female slides
The diagram is extra from 44I

Female slides





Neurotransmitters summary:

Neurotransmitter	Postsynaptic effect	Derived from	Site of synthesis	Postsynaptic Receptor	Fate	Function
Acetylcholine (ach)	Excitatory	Acetyl coA + Choline	●Cholinergic nerve ending ●Cholinergic pathways of brainstem	I.Nicotinic 2.Muscarinic	Broken by acetylcholinesterase	- Cognitive function e.g. memory - Peripheral action e.g. cardiovascular system
Catecholamines: **I. 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	I- 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 coeruleus, thalamus, midbrain	Begins inside axoplasm of adrenergic nerve ending is completed inside the secretory vesicles	αI α2 βI 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	DI to D5 receptor		Sensory motor Cognitive / emotional behavior Endocrine Hypothalamic Decreased dopamine in parkinson's disease. Increased dopamine concentration causes schizophrenia
Serotonin (5HT)	Excitatory	Tryptophan	CNS,Gut (chromaffin cells) platelets & retina	5-HT I to 5-HT7 5-HT2A receptor mediates platelet aggregation & smooth muscle contraction	Inactivated by MAO to from 5-hydroxyindoleacetic acid (5-HIAA) in pineal body it is converted to melatonin	Mood control,sleep,pain feeling, temperature, BP & hormonal activity

Neurotransmitters summary:

Neurotransmitter	Postsynaptic effect	Derived from	Site of synthesis	Postsynaptic Receptor	Fate	Function
Histamine (Not imp)	Excitatory	Histidine	Hypothalamus	Three types HI 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 (Not imp)	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 (Not imp))	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.

Functions & disorders summary from 441

Neurotransmitter	Function	Disorder
Acetylcholine	Thought, Memory, Muscular coordination alertness and REM sleep.	● Alzheimer's Disease ● Bipolar disorder. ● Mood swings. ● Depression. ● Mental attention.
Norepinephrine	Sleep Attention Part of the RAS Fight or flight response Learning & memory Aggressive behaviour	Depression Withdrawal from some drugs of abuse (NE imbalance + other NT) Anxiety and other stress-related disorders such as panic disorder.
Glutamate	❖ Major excitatory NTs in CNS ❖ Long-Term Potentiation & memory storage. ❖ Learning and memory	some types of epileptic seizures. Under some pathological conditions, it acts as an excitotoxin causing neuronal death. Alzheimer's disease Stroke, Autism, Intellectual disability, Motor neuron disease, Huntington's disease, Parkinson's disease
GABA	❖ Presynaptic inhibition ❖ regulate neuronal excitability.	❖ Under activity of GABA leads to seizures. Alcohol, barbiturates, progesterone and deoxycorticosterone also in part work by increasing GABA activity.
Serotonin	❖ Improved mood ❖ Decrease appetite ❖ Sleep	●Depression (Low self-esteem) ●Poor appetite ●Anxiety ●Drugs (e.g.Prozac) that prolong serotonin's actions relieve symptoms of depression & obsessive disorders Poor memory & irritability
Dopamine	❖ Reward ❖ Pleasure, euphoria ❖ Motor function (fine tuning) ❖ Compulsion ❖ Perseveration	❖ Schizophrenia (disrupted or low) ❖ Parkinson's Disease Cocaine elevate activity at dopaminergic synapses.

Disorders summary from 441

Disorders	Low levels of
Depression	Ach. Decreased NE Serotonin (5-HT)
Schizophrenia	Increased Dopamine Hypofunction of NMDA receptors in hippocampus and prefrontal cortex is associated with schizophrenia
Anxiety	Increased NE Serotonin (5HT)
Parkinson's	Glutamate Dopamine
Alzheimer	Ach Glutamate
Seizures	Decreased GABA Increased Glutamate

TEST YOURSELF !

Overstimulation of which Dopamine receptor cause Schizophrenia?

A) D1

B)D2

C)D3

D)D4

What neurotransmitter is released at the locus coeruleus nucleus? (From Male Dr)

A)Dopamine

B)Ach

C)GABA

D)Norepinephrine

Decreased level of brain serotonin is associated with .....

A)Depression

B)Self confidence

C)Hallucinations

D)Mania

Cholinergic system has a crucial role in .....

A)Appetite control

B)Desire and addiction

C)Learning and memory

D)Panic disorder management

1- B
2- D
3- A
4- C

SAQ

1)Enumerate Dopamine transmission pathways:

slide 13

2)What is the effect of Glutamate on post-synaptic neuron?

Excitatory 75% of excitatory transmission in the brain.

3)Mention three of Serotonin functions:

Mood control, sleep, pain feeling, temperature, BP, & hormonal activity

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