

Neurochemistry-Slide 8

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Introduction:

- It's the study of chemical inter-neuronal communication.
- Wilhelm and Santiago (late 19th century): brain consists of individual cells rather than a mass of cytoplasm.
- A search was initiated for the mediators of intercellular effects of communication.
- By the turn of the 20th century the effects of extracts of the adrenal glands on sympathetic nerve tissue was explained.
- Soon scientists discovered chemicals in the brain (neurotransmitters)
- Later Karl Lashley envisioned the entire basic apparatus of chemical neurotransmission (neurotransmitter + specific receptor molecules).
- In the middle of 20th century the major biogenic amine neurotransmitters were characterized and discoveries continue.

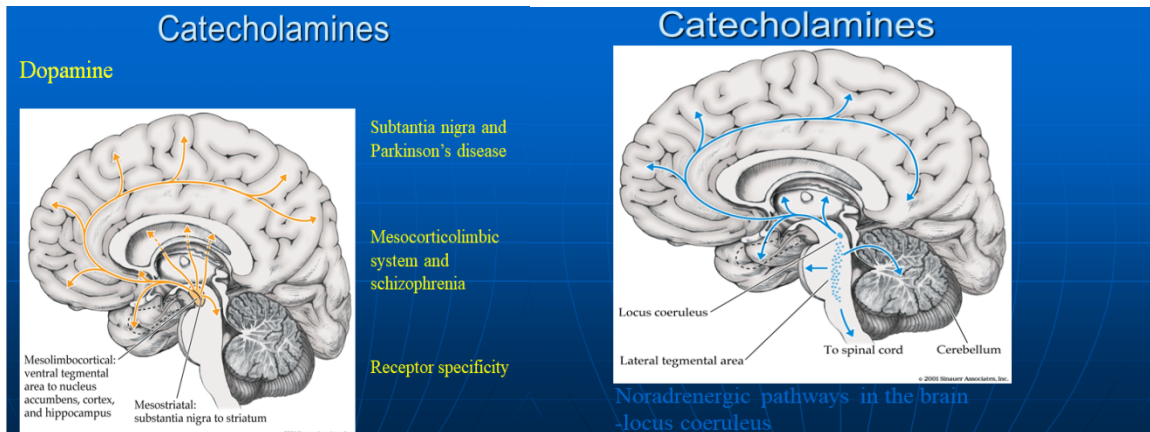
Criteria for Neurotransmitters:

- Synthesized in the neuron.
- Present in the pre-synaptic neuron and released on depolarization.
- When administered exogenously has the same effect as the endogenous neurotransmitter.
- A mechanism in the neuron /synaptic cleft acts to remove /deactivate the neurotransmitter.

Classification:

- Biogenic amines (catecholamines and indolamines) (best understood).
- Amino acids
- Peptides

1. Biogenic Amines



- The monoamines (Dopamine, Noradrenaline & Adrenaline) are products of the catecholamine synthetic pathway starting from the amino acid Tyrosine.
- The indolamines (serotonin, acetylcholine & histamine) are derived from distinct precursors.
- These neurotransmitters are very important in the etiology of psychiatric disorders.

a. Dopamine:

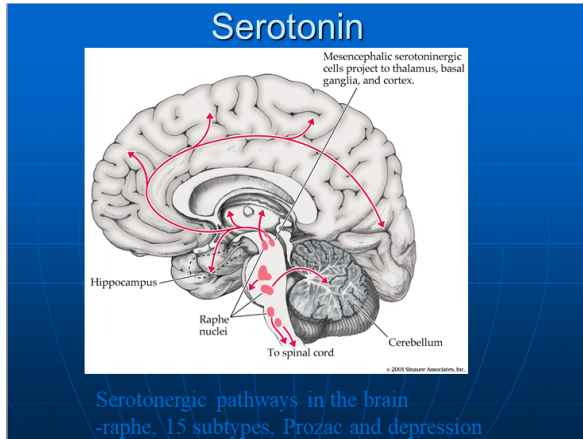
CNS dopaminergic tracts:

- Nigrostriatal-projects from substantia nigra to the corpus striatum (parkinsonism, depression).
- Mesolimbic-mesocortical tract, VTA to cortex (schiz.)
- Tuberoinfundibular (hypothalamic-pituitary) tract, cell bodies are in the arcuate nucleus and the periventricular area of the hypothalamus and projects to the infundibulum and the anterior pituitary. (prolactin, gynecomastia, galactorrhea).
- Medullary tract (vomiting)

Dopamine Receptor Types: (5 subtypes, 2 groups):

- D1+D5: stimulate the formation of cAMP, by activating the stimulatory G protein Gs, D5 has higher affinity for Dopamine than D1.

- D2, D3, D4: D2 inhibit the formation of cAMP by activating the inhibitory G protein G1, probably D3, D4 receptors act similarly.
- D2 are concentrated mainly in the striatum, D3 in the nucleus accumbens and D4 in the frontal cortex.



Dopamine theory of Schizophrenia: The theory grew from the observation that drugs which stimulate Dopamine can induce schizophrenic symptoms, and drugs which block Dopamine can improve schizophrenic symptoms. Dopamine may also be involved in the pathophysiology of mood disorders (amphetamine is an antidepressant and Levodopa cause mania)

b. Norepinephrine:

- The major concentration of the brain of noradrenergic cell bodies is in the locus ceruleus in the pons and projects to cerebral cortex, limbic system, thalamus and hypothalamus.
- The key enzyme involved in metabolism is MAO.

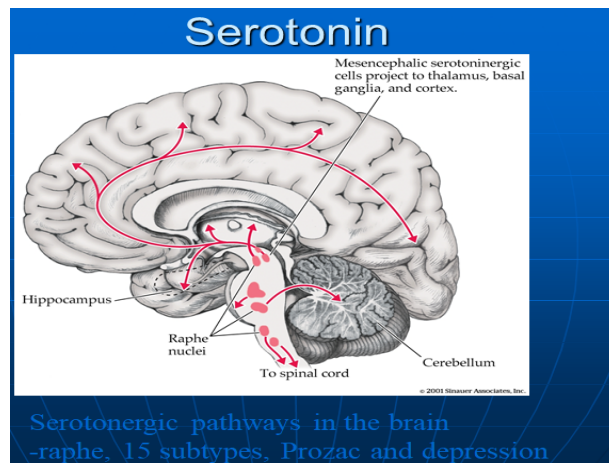
Adrenergic Receptors:

- Alpha adrenergic receptors : $\alpha_1(\alpha_{1a}, \alpha_{1b}, \alpha_{1d}), \alpha_2(\alpha_{2a}, \alpha_{2c}, \alpha_{2b}), \alpha_3$. They inhibit the formation of cAMP
- Beta adrenergic receptors ($\beta_1, \beta_2, \beta_3$) they stimulate the formation of cAMP
- The signal transduction of adr. Rec. are regulated by phosphorylation and changes in protein-protein interaction

- B1, b2 regulates the function of nearly every organ in the body often in antagonism to the effects of a receptors, b3 regulates energy metabolism, expressed in adipocytes, their activation reduces body fat.

b. Serotonin (5-HT):

- The major site of serotonergic cell bodies is the upper pons, midbrain (raphe nuclei, locus ceruleus) projects to basal ganglia, limbic system, and cerebral cortex.
- Precursor is Tryptophan.
- The enzyme involved in the metabolism of serotonin is MAO. Primary metabolite is 5HIAA
- Serotonin deficiency causes depression and over activity may be involved in the etiology of schizophrenia.



Serotonergic receptors:

- Seven types of serotonin receptors are now recognized 5HT1-5HT7 with numerous subtypes totaling 14 distinct receptors.
- Busirone, an anxiolytic, is 5HT1a agonist.
- Clozapine, an antipsychotic, is a 5HT2 antagonist
- Fluoxetine is a 5HT reuptake inhibitor (increase it) (antidepressant)

Biogenic amine theory of depression: states that depression is caused by reduced amount of biogenic amines (norepinephrine, 5HT, dopamine) in the brain or reduced sensitivity of their receptors. And mania is caused by increase of their amount.

2. Peptide Neurotransmitters:

- A peptide is a short protein made of less than 100 amino acids
- As many as 300 peptide neurotransmitters may be found in the human body.
- Endogenous opioids act on 3 receptors m, k d, and are believed to be involved in the regulation of stress ,pain and mood.
- Three classes of endogenous opioids: enkephalines, endorphines and dynorphines.
- Substance P(pain) Neurotensin (schizophrenia)
Cholecystokinin (schizophrenia, Eating disorder)
Somatostatin (Huntingtons chorea Alzheimers,)

3. Amino Acid Neurotransmitters:

- The two major amino acid neurotransmitters are:
-GABA (an inhibitory amino acid)
-Glutamate (an excitatory amino acid)

Some suggest that a simplified way to look at the brain is as a balance between just those two neurotransmitters, with all the biogenic amines and peptide neurotransmitters simply involved in modulating that balance.

- Benzodiazepines, Barbiturates and several anticonvulsants act primarily through GABA and PCP acts at glutamate receptors.

• Histamine:

- Neurons that release histamine as their neurotransmitter are located in the hypothalamus and projects to the cerebral cortex, the limbic system and thalamus
- There are 3 types of histamine receptors: H1,H2, H3
- Anti-allergic drugs act by blocking H1 receptors and causing sedation.
- H3 receptors are involved in vascular tone control

• Acetylcholine:

CNS cholinergic tracts :

- A group of cholinergic neurons in the nucleus basalis of Meynert projects to the cerebral cortex and limbic system.
- Other cholinergic neurons in the reticular system project to the cortex ,limbic system, hypothalamus and thalamus .
- Some patients with Alzheimer's, dementia or Down syndrome have specific degeneration of the neurons in the nucleus basalis of Meynert.
- Synthesized in the cholinergic axon terminal from acetylcoenzyme A and choline by the enzyme choline acetyltransferase and metabolized by acetylcholinesterase.
- Drugs used in the treatment of Alzheimer's and dementia are acetylcholinesterase inhibitors

Neuromodulators:

- ✓ In contrast to the characteristically immediate and short - lived effect of a neurotransmitter, a neuromodulator, as the name implies, modulates the response of a neuron to a neurotransmitter.
- ✓ The modulatory effect may be present for a longer time than is usual for a neurotransmitter molecule to be present.
- ✓ Thus, a neuromodulating substance may have an effect on a neuron over a long period of time, and that effect may be more involved with fine tuning than with activating or directly inhibiting the generation of an action potential.
- ✓ When a hormone co-exists and is co-secreted with a neurotransmitter, it may be referred to as a neuromodulator. Some hormones or neuromodulators have been shown to meet criteria for neurotransmitters themselves.
- ✓ A neurohormone is distinguished by the fact that it is released into the blood stream, rather than into the extraneuronal space in the brain.
- ✓ Once in the blood stream, the neurohormone can then diffuse into the extraneuronal space and have its effect on neurons.
- ✓ Hormone secretion is stimulated by the action of a neurohormone, a neuronal secretory product of neuroendocrine transducer cells of the hypothalamus.

Examples on Neurohormones:

- Corticotropin- releasing hormone – CRH – which stimulates adrenocorticotrop hormone – ACTH
- Thyrotropin- releasing hormone–TRH- which stimulates release of thyroid-stimulating-hormone– TSH.
- Gonadotropin–releasing hormone – GnRH –which stimulates release of luteinizing hormone – LH - and follicular stimulating hormone – FSH
- Growth- hormone-releasing hormone –GHRH - which stimulates release of the growth hormone.
- Somatostatin inhibits growth hormone.

Chemical signals cause the release of these neurohormones from the median eminence of the hypothalamus into the portal hypophyseal blood stream and their transport to the anterior pituitary to regulate the release of target hormone.

- Pituitary hormones in turn, act directly on target cells, e.g.: ACTH on the adrenal gland, or stimulate release of other hormones from peripheral endocrine organs.
- In addition, these hormones have feedback action that regulates neurohormone secretion and has effects in the brain itself, both directly and as modulators of neurotransmitter action (neuromodulation).

Past Paper Questions:

- All of the following are neurotransmitters except:
 - a- dopamine
 - b- Epinephrine
 - c- Norepinephrine
 - d- Vasopressin
 - e- Serotonin
- One of the following is not a biogenic amine: Thyroxine
- Modulators wrong ---> short duration
- Which of the following is false about neuromodulators?
 - a- released into the blood stream
 - b- Some meet the criteria of neurotransmitters
 - c- >>>short lived effect
 - d- Fine tune the effect of neurotransmitter
- Which of the following don't meet the criteria of a neurotransmitter?
 - a- synthesized in neuron
 - b- Present pre-synaptically and released upon depolarization
 - c- Similar effect if administered endogenously
 - d- Released to synaptic cleft
 - e- >>>remains without change after release
- Which of the following is not a biogenic amine?
 - a- serotonin
 - b- adrenaline
 - c- norepinephrine
 - d- dopamine
 - e- >>>somatostatin
- Which of the following is false?
 - >>> Dopamine deficiency results in psychosis
- True about Dopamine– tyrosine is its precursor
- True about neuromodulators – some satisfy the criteria of neurotransmitters
- Not a neurotransmitter– angiotensin
- Neuroreceptor =specific for neurotransmitter

- The following are criteria of a neurotransmitter except one
 - A – The molecule is synthesized in the neuron
 - B – The molecule is present in the pre-synaptic neuron
 - C – When given exogenously has the same effect as the endogenous substance.
 - D – Is released by depolarization
 - E – When released to the synaptic cleft remains there*

- The following statements are true about neurotransmitters except one
 - A – Tyrosine is the precursor of catecholamines.
 - B - The indolamines include serotonin and acetylcholine.
 - C –Dopamine deficiency is thought to cause psychosis *
 - D- MAO enzyme is involved in noradrenaline metabolism
 - E -A peptide is a short protein made of < 100 aminoacids

- The following are biogenic amines except
 - A- Dopamine.
 - B- Serotonin
 - C- Noradrenaline
 - D- Acetylcholine.
 - E- Neurotensin.*