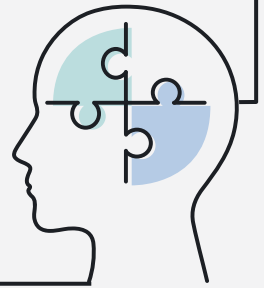
Neurochemistry



INTRODUCTION

- Neurochemistry is the study of chemical inter-neuronal communication .
- Wilhelm and Santiago in the late 19t century stated that the brain consists of individual cells (neurons) rather than a mass of cytoplasm .
- A search was initiated for the mediators of intercellular effects of e communication . (mediators) that allow them to communicate across synapses = neurotransmitters
- By the turn of the 20th century the effects of extracts of the adrenal glands on sympathetic nerve tissue was elucidated

- Soon scientists discovered chemical in the brain (neurotransmitters)
- Later Karl Lashley envisioned the entire basic apparatus of chemical neurotransmission (neurotransmitters + specific receptor molecules). neurotransmitter + specific receptor → chemical signaling.
- In the middle of 20th century the major biogenic amine neurotransmitters (e.g., dopamine, serotonin, norepinephrine) were characterized and discoveries continue.

Criteria for neurotransmitter

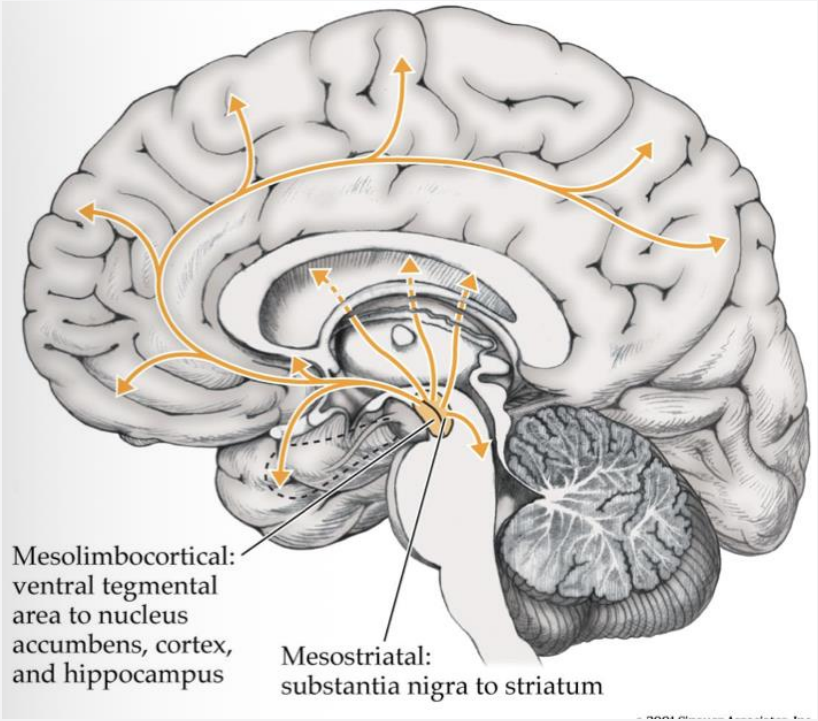
- The molecule is synthesized in the neuron.
- The mol. Is present in the pre-synaptic neuron and is released on depolarization.
- When administered exogenously has the same effect as the endogenous neurotransmitter.
- A mechanism in the neuron /synaptic cleft acts to remove /deactivate the neurotransmitter. inactivation mechanism (reuptake or enzymatic breakdown)

CLASSIFICATION

- **The major types of neurotransmitter in the brain are :**
- The biogenic amines(catecholamines and indolamines)→best understood .
- The amino acids .
- The peptides .

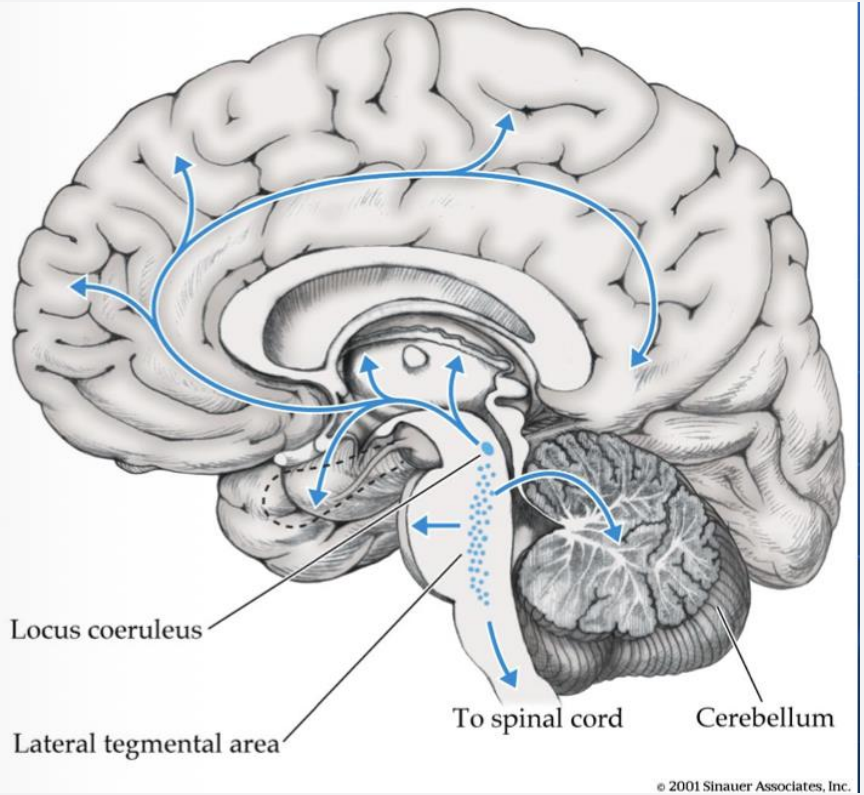
Catecholamines

Dopamine



- Subtantia nigra an Parkinson's disease
- Mesocorticolimbic system and schizophrenia :Overactivity ⟶ schizophrenia (positive symptoms)
- Receptor specificity : Acts via dopamine receptors (D1–D5) ⟶ different effects depending on receptor type

CATECHOLAMINES



- Noradrenergic pathways in the brain :
- Origin : locus coeruleus (pons)
- Neurotransmitter : NE
- Projection : diffuse ; cortex , limbic system , cerebellum , spinal cord

BIOGENIC AMINES

- The monoamines(Dopamine,Noradrenaline& Adrenaline) are products of the catechol amines 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 .

DOPAMINE

- CNS dopaminergic tracts : Nigrostriatal-pojects from substantia nigra to the corpus striatum(parkisonism. depression .).
- Mesolimbic-mesocortical tract,VTA to cortex (schizophrenia .)
- Tuberoinfundibular (hypthalmic-pituitary) tract , cell bodies are in the arcuate neucleus and the periventricular area of the hypothalamus and y to the infundibulum and the anterior pituitary .(prolactin, gynecomastia ,galactorea).
- Medullary tract (vomiting)

Dopamine receptors

Five subtypes, divided into two groups:

- **Group 1: D1-like receptors (D1 + D5)**
- Stimulate the formation of cAMP
- Act by activating the stimulatory G protein Gs
- D5 has higher affinity for dopamine than D1

- **Group 2: D2-like receptors (D2, D3, D4)**
- D2 inhibits the formation of cAMP
- Acts by activating the inhibitory G protein Gi
- D3 and D4 receptors probably act similarly

- **Distribution**
- D2: mainly concentrated in the striatum
- D3: mainly in the nucleus accumbens
- D4: mainly in the frontal cortex

Dopamine Theory of Schizophrenia

- This 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)

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

- a1 (a1a, a1b, a1d), a2 (a2a, a2c, a2b), a3
- They inhibit the formation of cAMP

Beta adrenergic receptors

- (b1, b2, b3)
- They stimulate the formation of cAMP

- The signal transduction of adr. recp. are regulated by phosphorylation and changes in protein-protein interaction

Functions

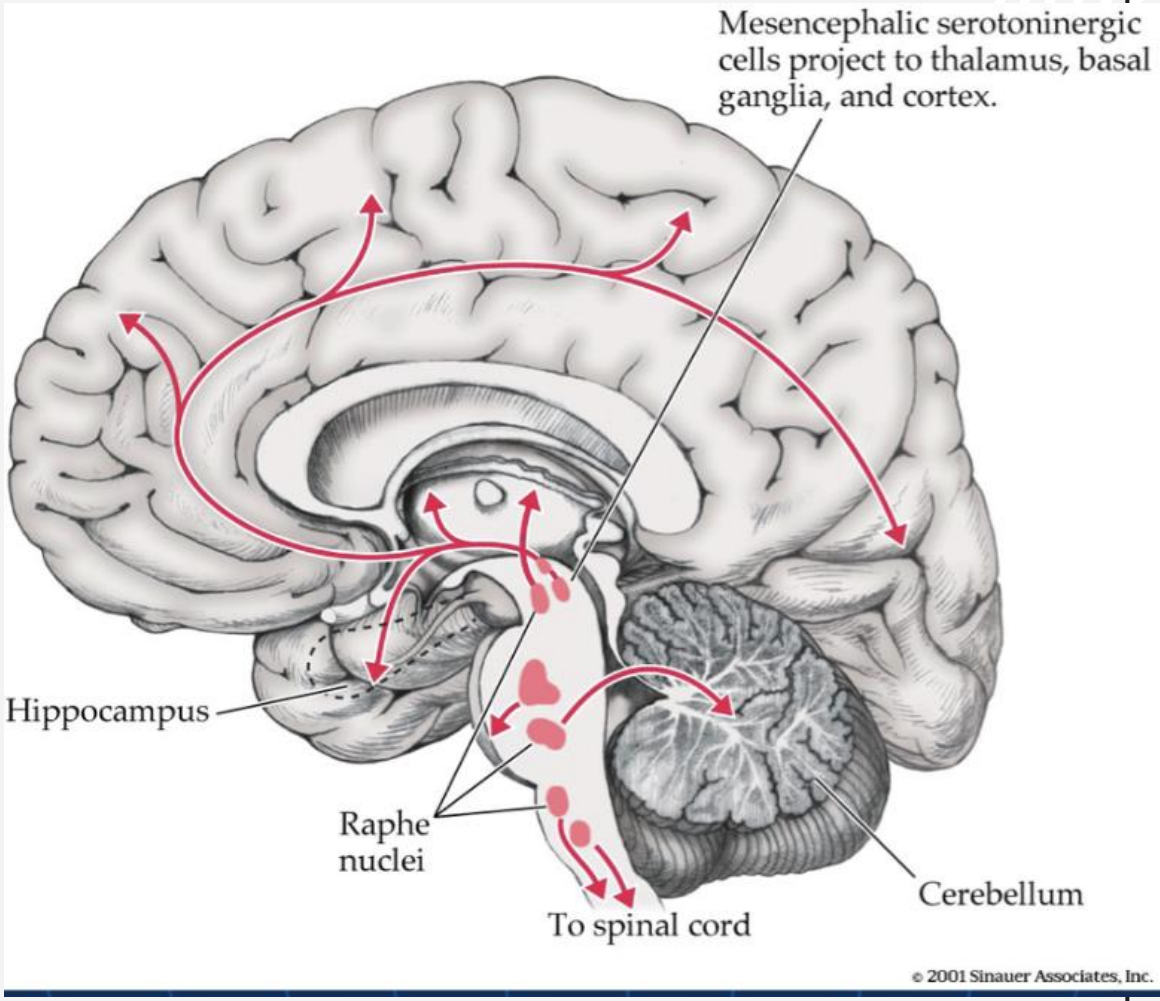
- B1, b2 regulates the function of nearly every organ in the body often in antagonism to the effects of a receptors
- b3 regulates energy metabolism, expressed in adipocytes, their activation reduces body fat

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, cerebral cortex.
- Its precursor is Tryptophan.
- The enzyme involved in the metabolism of serotonin is MAOa. primary metabolite 5HIAA.
- Serotonin deficiency causes depression and over activity may be involved in etiology of schizophrenia

SEROTONIN

- Serotonergic pathways in the brain -raphe, 15 subtypes, Prozac and depression



Serotonergic Receptors

- Seven types of serotonin receptors are now recognized 5HT1–5HT7, with numerous subtybes totaling 14 distinct receptors.

- Busirone is an anxiolytic is 5HT1a agonist
- Clozapine is an antipsychotic is 5HT2 antagonist
- Fluoxetine is 5HT reuptake inhibitor (increase it) is an antidepressant

The Biogenic Amines 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.

Peptide Neurotransmitters

- A peptide is a short protein made of less than 100 aminoacids.
- As many as 300 peptide neurotransmitters may be found in the human body

- Endogenous opioids, acts on 3 receptors m, k, d, are believed to be involved in the regulation of stress, pain and mood.
- Three classes end. opioids: encephalines, endorphines and dynorphines.

- Substance P (pain)
- Neurotensin (schiz.)
- Cholecystokinin (schiz. Eating disorder)
- Somatostatin (Huntingtons chorea Alzheimers,)

Amino Acid Neurotransmitters

- Amino acids are the building blocks of proteins.
- **The two major amino acid neurotransmitters are:**
- GABA, is an inhibitory amino acid.
- Glutamate is 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.

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 causes sedation.
- H3 receptors involved in vascular tone control

ACETYLCHOLINE

Central nervous system cholinergic tracts:

- **Nucleus Basalis of Meynert Pathway**
- A group of cholinergic neurons in the nucleus basalis of Meynert projects to the cerebral cortex and limbic system.

- **Reticular System Pathway**
- 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.

ACETYLCHOLINE

- Is 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 Alzheimers dementia are acetylcholinesterase inhibitors.

Cholinergic Receptors

- The two major subtybes of receptor are:

- **Muscarinic**
- Muscarinic, antagonized by atropine and anticholinergic drugs.

- **Nicotinic**

- Anticholinergic drugs can impair learning and memory in normal people.
- Acetylcholine may also be involved in mood and sleep disorders

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 long 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 co-secreted with a neurotransmitter, it may be referred to as a neuromodulator, although, 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 neurohormone, a neuronal secretory product of neuroendocrine transducer cells of the hypothalamus.

Neurohormones

Corticotropin-Releasing Hormone

- Corticotropin-releasing hormone (CRH) – which stimulates adrenocorticotropic hormone (ACTH).

Thyrotropin-Releasing Hormone

- Thyrotropin-releasing hormone (TRH) – which stimulates release of thyroid-stimulating hormone (TSH).

Gonadotropin-Releasing Hormone

- 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 regulate neurohormone secretion and effects in the brain itself, both directly and as modulators of neurotransmitter action (neuromodulation).