

Neurochemistry

Introduction

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

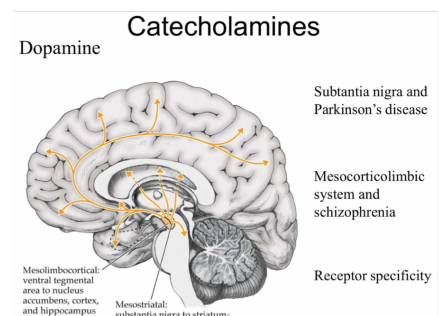
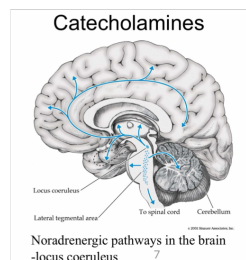
Criteria for neurotransmitter –

- 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.

Classification

The major types of neurotransmitters in the brain are:

- The biogenic amines(catecholamines and indolamines).best understood).
- The amino acids.
- The peptides.



Biogenic amines

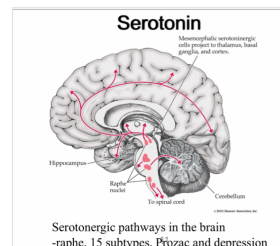
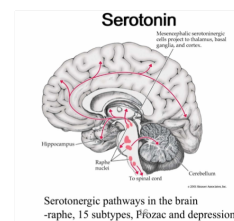
- The monoamines(Dopamine,Noradrenaline & Adrenenaline) are products of the catechol amines synthetic pathway starting from the amino acid Tyrosine .
- The indolamines (serotonin, acetylcholine & histamine)are derived from distinct precursors.
- These neurotransmitters are very important in the etiology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

Dopamine CNS dopaminergic tracts :

- Nigrostriatal-pojects from substantia nigra to the corpus striatum (parkinsonism.dep.).
- Mesolimbic-mesocortical tract,VTA to cortex (schiz.)
- Tuberoinfundibular(hypthalamic-pituitary) tract , cell bodies are in the arcuate neucleus and the periventricular area of the hypothalamus and pojects to the infundibulum and the anterior pituitary.(prolactin, gynecomastia, galactorea).
- Medullary tract (vomitting).

Dopamine receptors

- Five subtybes, Two groups.
- D1+D5:stimulate the formation of cAMP,by activating the stimulatory G protein G8,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 cocentrated mainly in the striatum ,D3 in the nucleus acumbens and D4 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 : α_1 (α_{1a} , α_{1b} , α_{1d}), α_2 (α_{2a} , α_{2c} , α_{2b}), α_3 . They inhibit the formation of cAMP.
- Beta adrenergic receptors (β_1 , β_2 , β_3) they stimulate the formation of cAMP.
- The signal transduction of adr.recp. are regulated by phosphorylation and changes in protein-protein interaction.
- β_1 , β_2 regulates the function of nearly every organ in the body often in antagonism to the effects of α receptors, β_3 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 the etiology of schizophrenia.

Serotonergic receptors

- Seven types of serotonin receptors are now recognized 5HT₁-5HT₇ with numerous subtypes totaling 14 distinct receptors.
- Buspirone is an anxiolytic is 5HT_{1a} 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 amino acids .
- As many as 300 peptide neurotransmitters may be found in the human body .
- Endogenous opioids, acts on 3 receptors μ, κ, δ , are believed to be involved in the regulation of stress ,pain and mood.
- Three classes end.opioids :encephalines, endorphines and dynorphines.
- Substance P (pain) Neotensin (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 neu.miters are: γ GABA ,is an inhibitory amino acid .and 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.
- 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 causes sedation .
- H3 receptors 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 projects to the cortex ,limbic system, hypothalamus and thalamus .
- Some pts.with Alzheimers dementia or Down syndrome have specific degeneration of the neurons in the neucleus basalis of Meynert.
- 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 ,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 is 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 include:

- Corticotropin- releasing hormone – CRH – which stimulates adrenocorticotrophic hormone – ACTH - .
- Thyrotropin- releasing hormone –TRH- which stimulates release of thyroid – stimulating hormone –TSH- .
- Gonadotropin –releasing hormone – GnRH –which stimulates release of leutinizing 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).