Monoamine Neurotransmitters

Outline

1. Definition
2. Criteria
3. Anatomical Features
4. Neurotransmitter action and receptors
5. Types
    - Acetylcholine
    - Serotonin
    - Dopamine
    - Epinephrine and Norepinephrine
    - Histamine

Definition

- Neurotransmitters are chemical signals released from presynaptic nerve terminals into the synaptic cleft.

- The subsequent binding of neurotransmitters to specific receptors on postsynaptic neurons (or other classes of target cells) transiently changes the electrical properties of the target cells, leading to an enormous variety of postsynaptic effects.

Criteria for a Neurotransmitter

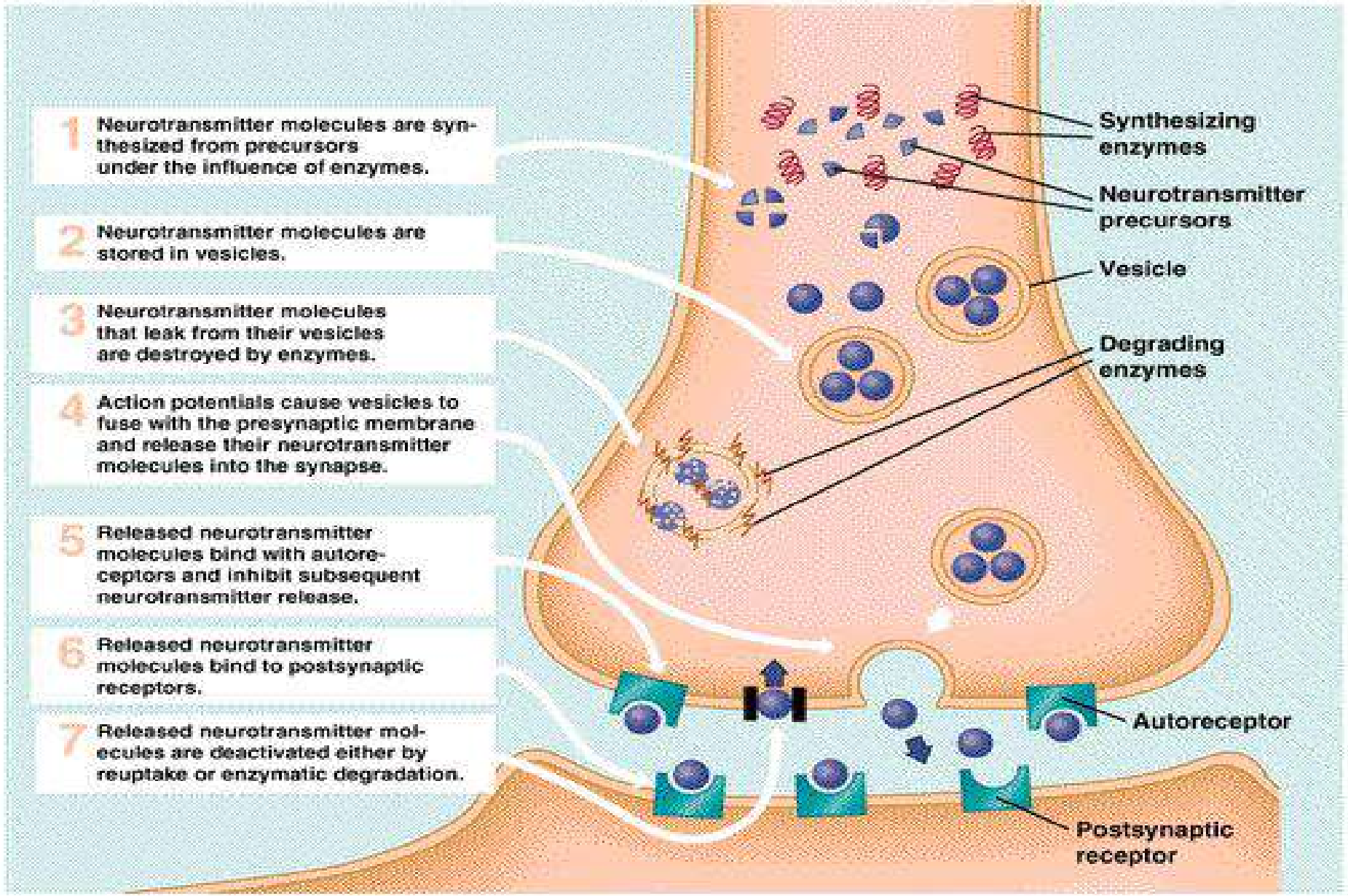
1. Molecule is synthesized in neuron
2. Molecule is present in presynaptic neuron & is released on depolarisation in physiologically significant amount
3. When administered exogenously as a drug, the exogenous molecule mimics the effect of endogenous neurotransmitter
4. A mechanism in neurons or synaptic cleft acts to remove or deactivate the neurotransmitter

Anatomical Features

- A cluster of cell bodies in subcortical or brainstem regions

- Long, extensively branched axonal processes into multiple cortical and limbic target regions

► Seven Processes in Neurotransmitter Action



Neurotransmitter Receptors

Neurotransmitter receptors produce intracellular effects by one of the two basic mechanisms :-

1. Via interactions with G-protein that couple receptors to intracellular effector systems

2. By providing channels through which ions flow when transmitters bind (ligand gated ion channels)

Neurotransmitter Receptors

- Whereas many receptor subtypes are located exclusively in post synaptic membranes , others are located presynaptically.

- Presynaptic auto-receptors often act to inhibit neurotransmitters release.

Types of Monoamine Neurotransmitters

1. Acetylcholine
2. Sertraline
3. Dopamine
4. Norepinephrine and Epinephrine
5. Histamine

Acetylcholine

- The first neurotransmitter identified in 1926, by Otto Loewi, a German-born pharmacologist and psychobiologist.
- He demonstrated that Acetylcholine carried a chemical signal from vagus nerve to the heart that slowed the cardiac rhythm.
- Nobel Prize in physiology and medicine [1936]

Two large clusters of cholinergic projection neurons are found within the brain

1. Basal Forebrain Complex (BFC)

- Medial septal nucleus
- Nucleus of diagonal band
- Substantia innomanata
- Preoptic field
- Nucleus basalis of Meynert [Alzheimers]

2. Mesopontine Complex : Pedunculopontine (PPN) and laterodorsal tegmental nuclei (LDT) of the midbrain and pons.

Synthesis and Metabolism

- Synthesis : Occurs in cholinergic axon terminals from Acetyl-CoA and choline by the enzyme choline acetyltransferase.

- Metabolism: In the synaptic cleft by acetylcholinesterase and the resulting choline is taken back in to the pre synaptic neuron and recycled to make new acetylcholine molecules and Butyrylcholinesterase is found in liver and plasma

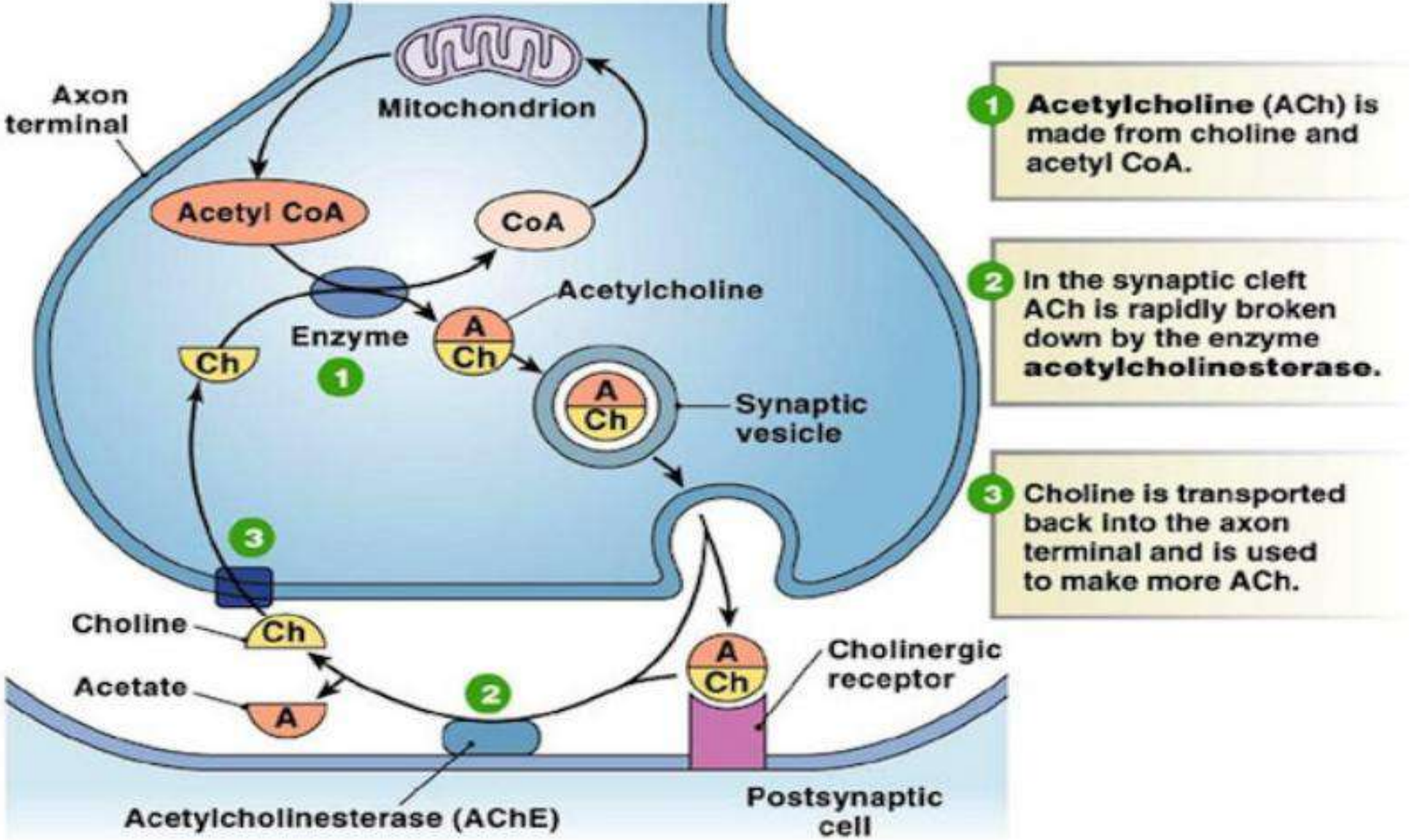


Fig. 8-22

Acetylcholine Receptors

Subtype	Primary Effectors	Proposed Clinical Relevance
M1	↑ PI Turnover	Regulation of cognition , seizures
M2	↓ AC	Regulation of cardiac function
M3	↑ PI Turnover	Regulation of smooth muscle contraction
M4	↓ AC	Target of antiparkinsonian anticholinergic drugs
M5	↑ PI Turnover	Unknown
NAChR	Cation selective ion channel	Regulation of tobacco use,seizures;possible cognitive enhancement

Nicotinic Receptors

They are of 2 types

1. N1 or Nm [NMJ]
2. N2 or Nn [Autonomic ganglia, CNS and Adrenal Medulla]

- A large proportion of nicotinic binding sites are found on pre-, peri- and extra synaptic sites in addition to the classic postsynaptic location.
- These various nicotinic acetylcholine receptor subunits are categorized into three general functional classes:
  (1) skeletal muscle subunits (α1, β1, δ, and ε), (2)standard neuronal subunits (α2–α6 and β2–β4), and (3) subunits capable of forming homomeric receptors (α7–α9)

Nicotinic receptors

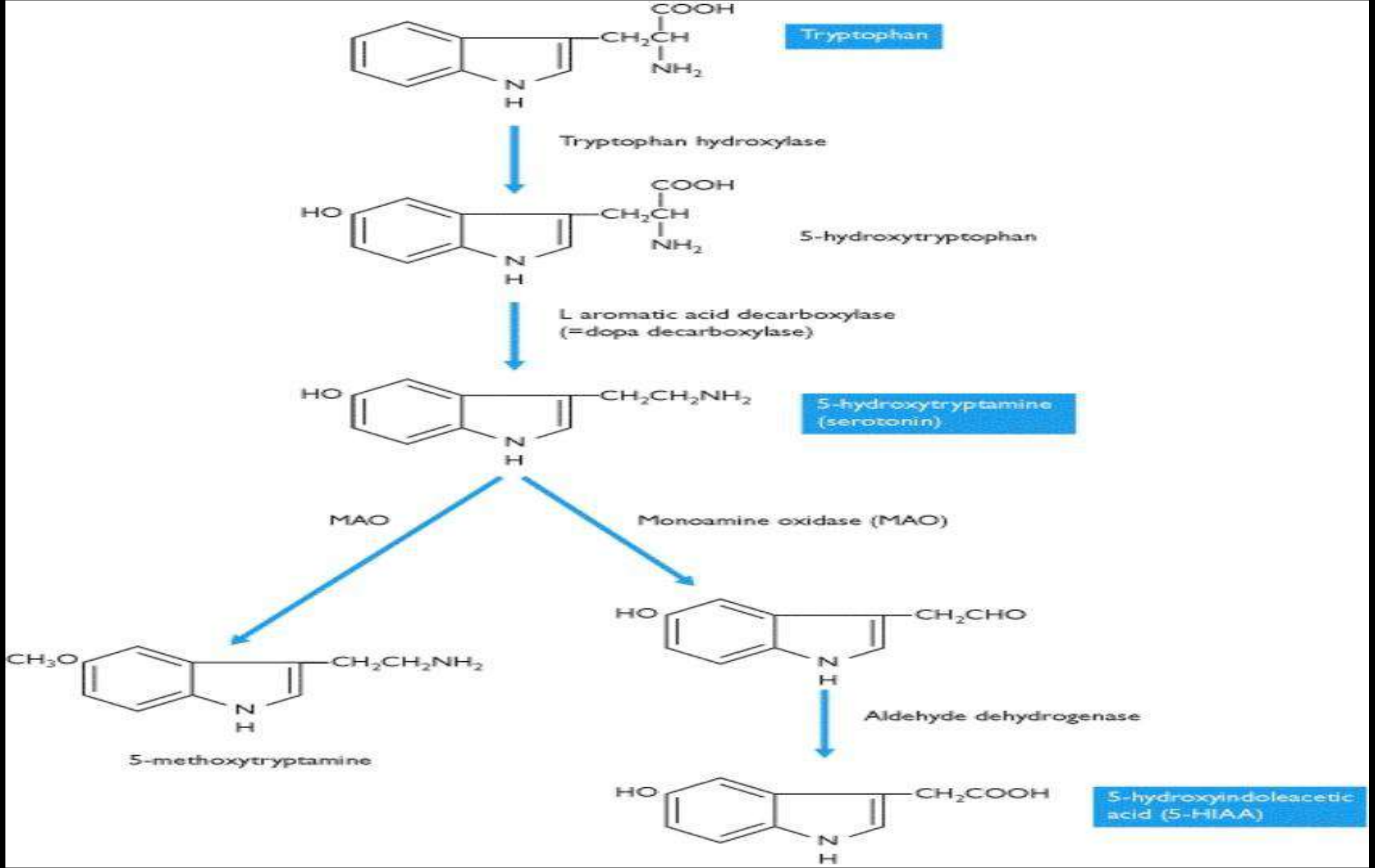
- Mutations in one of the nicotinic receptor subunit genes is responsible for a specific form of epilepsy, autosomal dominant frontal lobe epilepsy (ADNFLE)
- α7-nicotinic receptors have emerged as a potential therapeutic target for the treatment of neurocognitive dysfunctions in schizophrenia
- In Alzheimer disease and Parkinson disease, there is a significant loss of high affinity nicotinic receptor sites, which may contribute to the pathophysiological changes underlying the cognitive decline

Serotonin

- Vittorio Erspamer (30 July 1909 – 25 October 1999) was an Italian pharmacologist and chemist, known for the identification, synthesis and pharmacological studies of Serotonin.

- It is synthesized from the amino acid Tryptophan and does not cross the BBB

- The CNS contains less than 2% of the the serotonin in the body and peripheral serotonin is located in platelets, mast cells and enterochromaffin cells of the GI system


Tryptophan
Tryptophan hydroxylase
5-hydroxytryptophan
L aromatic acid decarboxylase
(=dopa decarboxylase)
5-hydroxytryptamine
(serotonin)
MAO
Monoamine oxidase (MAO)
5-methoxytryptamine
Aldehyde dehydrogenase
5-hydroxyindoleacetic
acid (5-HIAA)

Serotonergic Pathways

- Serotonin systems influence CNS activity at all levels of the neuraxis.
- Serotonergic neurons are clustered in midline raphe nuclei of the midbrain, pons, and medulla.
- These neurons project extensively throughout the brain and descend to the spinal cord .
- The majority of the serotonergic innervation of the forebrain arises from the dorsal and median raphe nuclei of the midbrain.

Serotonergic Pathways

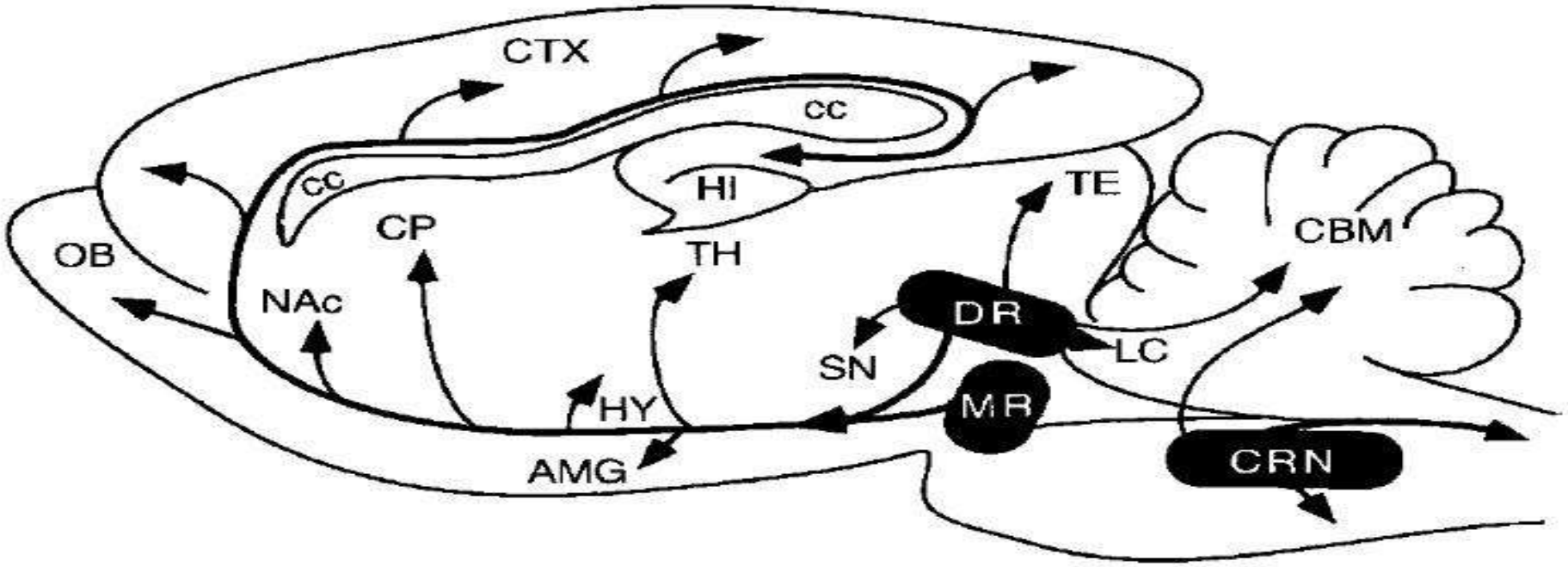


FIGURE 1.4–1. Brain serotonergic pathways (in rats). Serotonergic neurons are located in brainstem midline raphe nuclei and project throughout the neuraxis. (There is an approximate similarity between monoamine pathways in rats and in humans.) AMG, amygdala; CBM, cerebellum; cc, corpus callosum; CP, caudate putamen; CRN, caudal raphe nuclei; CTX, neocortex; DR, dorsal raphe nucleus; HI, hippocampus; HY, hypothalamus; LC, locus ceruleus; MR, median raphe nucleus; NAc, nucleus accumbens; OB, olfactory bulb; SN, substantia nigra; TE, tectum; TH, thalamus; TM, tuberomammillary nucleus of hypothalamus.

Serotonergic Pathways

- Ascending projections from these nuclei course through the medial forebrain bundle before diverging to many target regions.

- Whereas the median raphe nucleus provides the majority of the serotonergic innervation of the limbic system, the dorsal raphe nucleus provides the primary innervation of the striatum and thalamus.

- The caudal raphe serotonergic neurons project to the medulla, cerebellum, and spinal cord.

Serotonergic Receptors

Subtype	Primary Effector	Proposed Clinical Relevance
5-HT 1A,1B,1D,1E, 1F	↓ AC	Partial agonists (buspirone) anxiolytic,role in hippocampal neurogenesis;5-HT1B/D antagonists- antimigraine agents(triptans)
5-HT 2A,2B,2C	↑PI Turnover	2A antagonists ⟶ antipsychotic effects, 2A agonists ⟶ hallucinogens 2B agonism ⟶ cardiac valvulopathy; 2C agonists ⟶ under development as anorexigens , antiepileptics
5-HT 3	Na+ channel, cell membrane depolarisation	Agonists (ondansetron) are antiemetics.
5-HT 4	↑AC	Partial agonists used in IBS (tegaserod)
5-HT 5, 5-HT 6, 5-HT 7	↑AC	Unclear Unclear Antagonists -antidepressant potential

- Most serotonergic innervation of the cortex and limbic system arises from the dorsal and median raphe nuclei in the midbrain
- Projects through the medial forebrain bundle into target forebrain regions.
- The median raphe provides innervation to the limbic system
- The dorsal raphe nucleus innervate the striatum and thalamus primarily

5-HT_4 receptors :

- **modulate the release of neurotransmitters**
- **implicated in the serotonergic regulation of cognition and anxiety**

There is significant interest in the 5-HT_{1A} receptor as a modulator of both anxiety and depression. The downregulation of 5-HT_{1A} autoreceptors by the chronic administration of serotonin reuptake blockers has been implicated in their antidepressant effects, and SSRIs may produce some behavioral effects via increases in hippocampal neurogenesis mediated by postsynaptic 5-HT_{1A} receptor activation. In addition, partial 5-HT_{1A} receptor agonists such as buspirone (Buspar) display both anxiolytic and antidepressant properties.

5-HT_6 receptors

- **May contribute to the actions of the several antidepressant, antipsychotic, and hallucinogenic drugs.**
- **Expressed in the neocortex, hippocampus, striatum, and amygdala**

5-HT_7 receptor

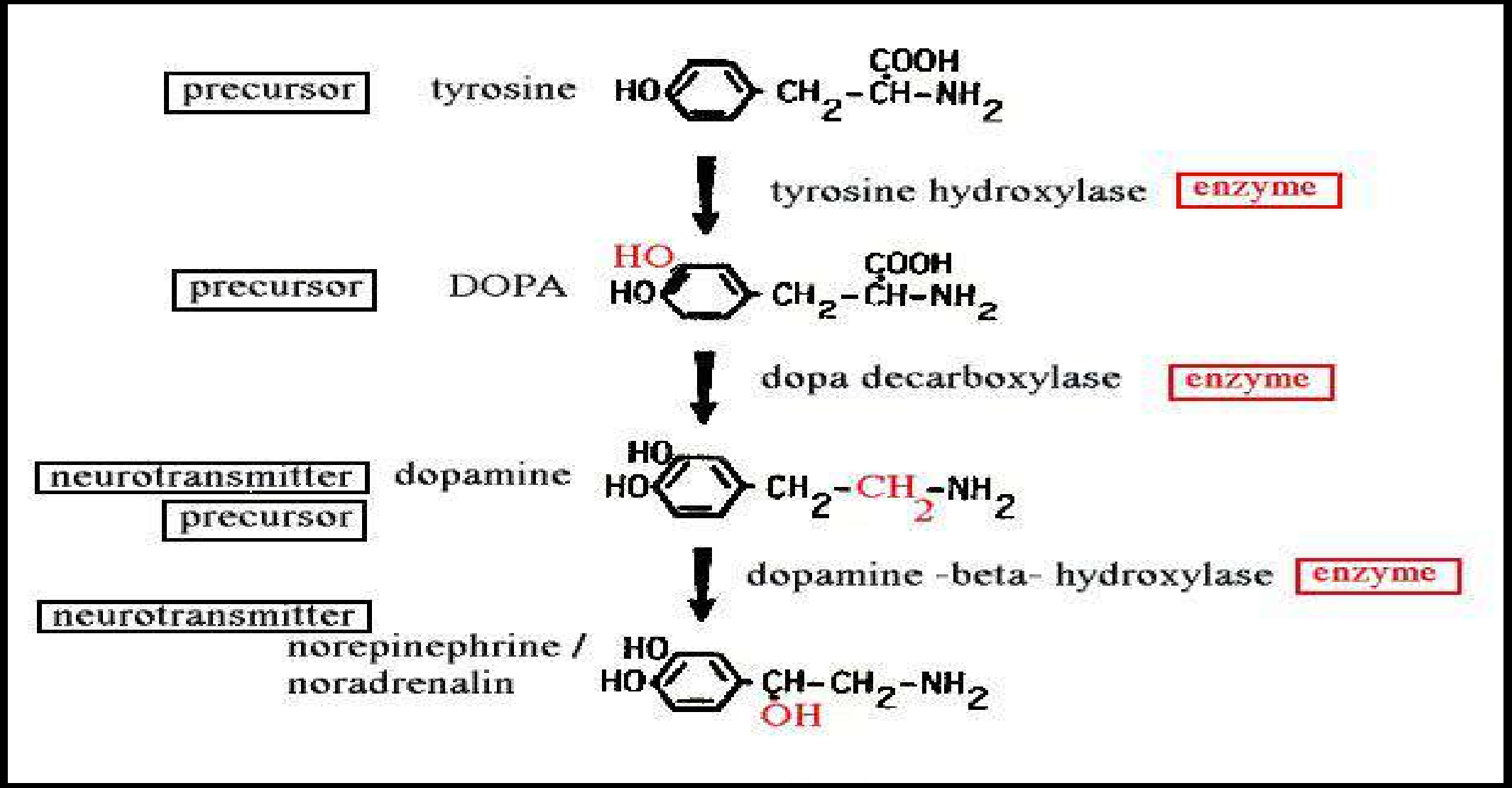
- **hypothalamus and thalamus.**
- **May contribute to the serotonergic modulation of circadian rhythms,**
- **drugs that block these receptors may have antidepressant effects.**

Dopamine

- The function of Dopamine as neurotransmitter was discovered in 1958 by Swedish Pharmacologist Arvid Carlsson.

- He was awarded the nobel prize in 2000 for showing that Dopamine is not just a precursor of Norepinephrine and Epinephrine but is a neurotransmitter as well

Dopamine Synthesis



Dopaminergic Pathways

There are the dopaminergic pathways in the brain

1. NIGROSTRIATAL DA pathway
2. MESOCORTICOLIMBIC DA pathway
3. TUBEROHYPOPHYSEAL pathway
4. THALAMIC DA pathway

Dopaminergic Pathways

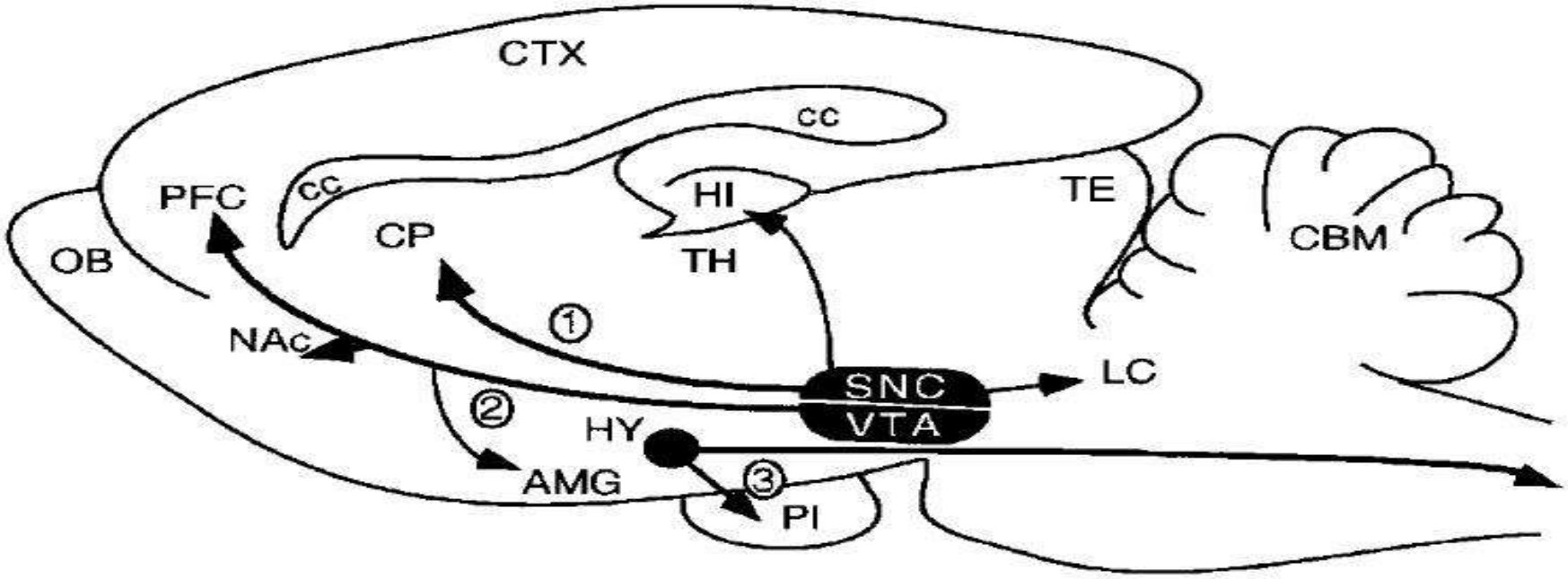


FIGURE 1.4–2. Brain dopaminergic pathways (in rats). The three principal dopaminergic pathways: (*1*) nigrostriatal pathway, (*2*) mesocorticolimbic pathway, and (*3*) tuberohypophyseal pathway. AMG, amygdala; CBM, cerebellum; cc, corpus callosum; CP, caudate putamen; CTX, neocortex; HI, hippocampus; HY, hypothalamus; LC, locus ceruleus; NAc, nucleus accumbens; OB, olfactory bulb; PFC, prefrontal cortex; PI, pituitary; SNC, substantia nigra pars compacta; TE, tectum; TH, thalamus; VTA, ventral tegmental area.

Dopamine

Dopamine is found in the CNS in 3 systems

1. Nigrostriatal
2. Mesocorticolimbic
3. Tuberohypophyseal

Peripherally, dopamine is also present in the olfactory bulb, kidney and retina.

Dopaminergic Receptors

Subtype	Primary Effector	Proposed Clinical Relevance
D1-like family (D1,D5)	↑ AC	D1 agonists used in Parkinson's disease
D2-like family (D2,D3,D4)	↓ AC	D2 antagonists are antipsychotics (e.g.,haloperidol) D3 agonists used in Parkinson's disease, restless legs syndrome (e.g.,pramipexole)

Adrenergic Amines

Norepinephrine-producing neurons are found in the pons and medulla namely :-

1. Locus ceruleus (LC)- found in the dorsal portion of the caudal pons.
2. Lateral tegmental noradrenergic nuclei (LTN)

These cells provide the major noradrenergic projections to the neocortex, hippocampus, thalamus, and midbrain tectum and regulate arousal state, vigilance and stress response

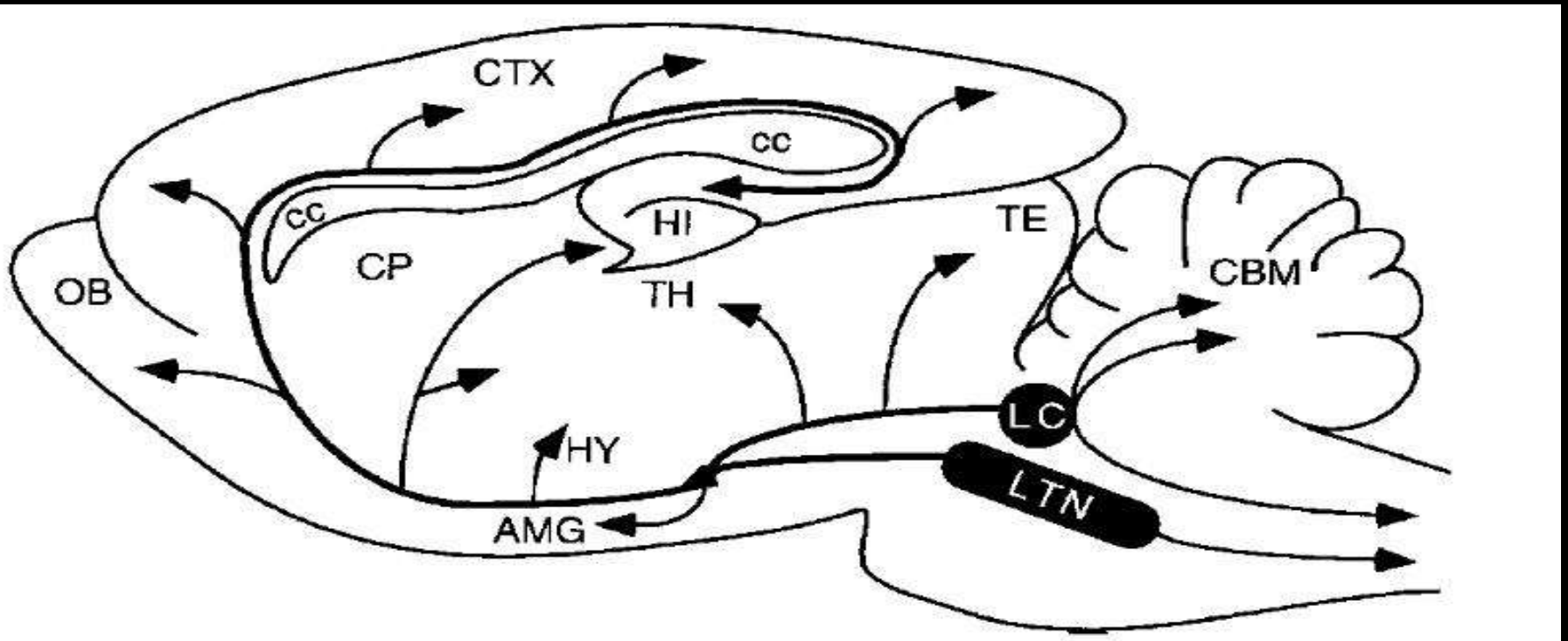
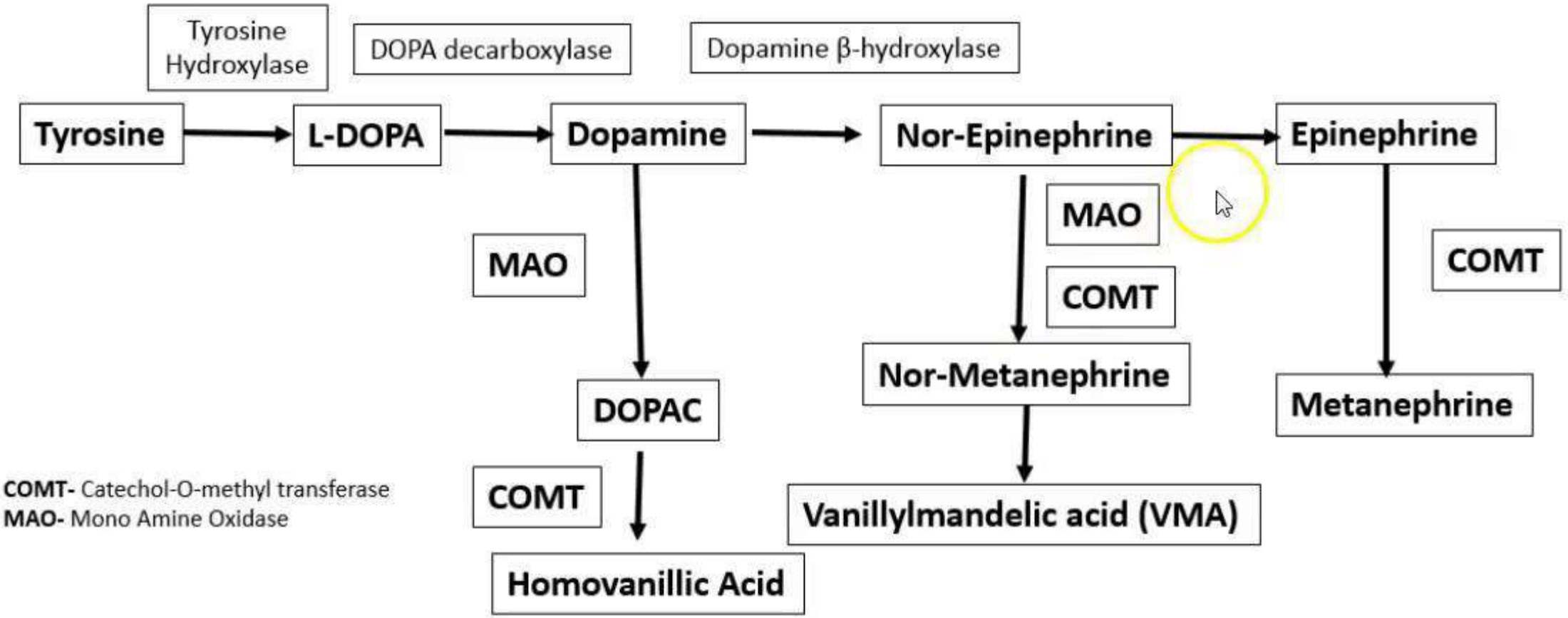


FIGURE 1.4–3. Brain noradrenergic pathways (in rats). Projections of noradrenergic neurons located in the locus ceruleus (LC) and lateral tegmental noradrenergic nuclei (LTN). AMG, amygdala; CBM, cerebellum; cc, corpus callosum; CP, caudate putamen; CTX, neocortex; HI, hippocampus; HY, hypothalamus; OB, olfactory bulb; TE, tectum; TH, thalamus.

Adrenergic Neurotransmission and Drugs affecting it

Synthesis and Metabolism of Catechol amines



Epinephrine/Norepinephrine Receptors

Subtype	Primary Effector	Proposed Clinical Relevance
α 1A,B,D	↑ PI Turnover	Antagonists used in management of prostate disease
α 2A,B,C	↓ AC	Agonists sedative and hypertensive
β1	↑ AC	Regulation of cardiac function , antagonists may be anxiolytic
β2	↑ AC	Agonists used as bronchodilators
β3	↑ AC	Possible role for agonists to treat obesity

Histamine

- Previously known as β-iminazolylethylamine
- It’s properties were first described in 1910 by the British scientists Henry H. Dale and P.P. Laidlaw.
- By 1913 the name Histamine came in use, combining forms of histo+amine, yielding "tissue amine"

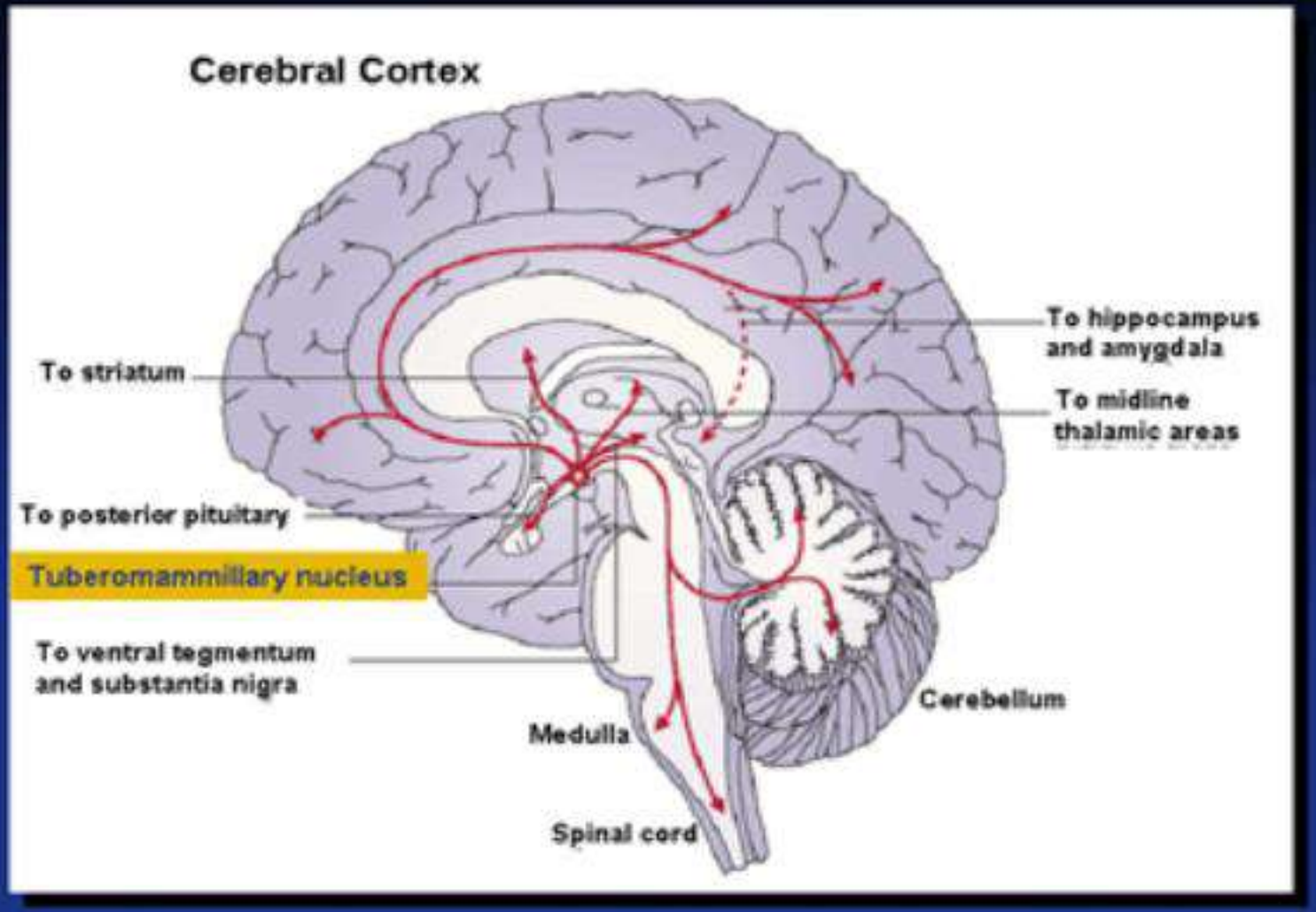
Synthesis

- Synthesized from histidine by the enzyme L Histidine Decarboxylase
- This enzyme is not normally saturated by substrate, so the synthesis is sensitive to histidine levels
- Thus peripheral administration of histidine elevates brain histamine levels.

Histamine Pathway

- Histaminergic cell bodies are located within the tuberomammillary nucleus of the posterior hypothalamus
- Ventral ascending projections course through the medial forebrain bundle and then innervate the hypothalamus, diagonal band, septum, and olfactory bulb.
- Dorsal ascending projections innervate the thalamus, hippocampus, amygdala, and Rostral forebrain
- Descending projections travel through the midbrain to the dorsal hindbrain and spinal cord.

Histamine Pathways in Brain Originate in the Tuberomammillary Nucleus (TMN)



Histamine

- TMN (tuberomammillary nucleus) has highest activity during wakeful state, slow firing in SW sleep , absence of firing in REM sleep.

- Hypothalamus receives the densest histaminergic innervation

Histamine receptors

Subtype	Primary Effector	Proposed Clinical Relevance
H1	↑ PI Turnover	Antagonists used as antiallergenic and anti-inflammatory agents , also promote sedation , weight gain
H2	↑ AC	Antagonists used to treat peptic ulcers, GI reflux and GI bleeding
H3	↓ AC	Antagonists proposed to treat sleep disorders, obesity ,dementia
H4	↓ AC	Possible role for antagonists as anti-inflammatory agents

Conclusion

- Neurotransmission is the communication b/w genomes of two neurons, through signal transduction cascade, leading to gene activation & biological response

- Understanding neurotransmitters, their receptor partners & other near/distant relations (transporters & transduction), is essential for our approaches to define & treat psychiatric disorders

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THE END