

BASICS OF NEUROBIOLOGY

NEUROTRANSMITTERS I.

ZSOLT LIPOSITS

Basics of Neurobiology: Neurotransmitters I.

DEFINITION AND CRITERIA OF NEUROTRANSMITTERS

NEUROTRANSMITTERS ARE ENDOGENOUS BIOACTIVE SUBSTANCES SYNTHESIZED BY NEURONS. THEY ARE RELEASED FROM THE CELLS, ACT VIA SPECIFIC RECEPTORS COUPLED TO THE MEMBRANE OF POSTSYNAPTIC TARGET STRUCTURES AND MODIFY THE ELECTRIC AND METABOLIC CONDITIONS OF THE AFFECTED CELLS.

CRITERIA OF CHEMICAL NEUROTRANSMITTERS:

1. THE SYNTHESIS OF THE CHEMICAL TRANSMITTER TAKES PLACE IN THE PRESYNAPTIC NEURON
2. THE SYNTHESIZED TRANSMITTER OR IT PRECURSOR IS STORED IN THE RELEASE COMPARTMENT OF THE CELL, MOST FREQUENTLY IN AXON TERMINALS
3. RELEASE OF THE NEUROTRANSMITTER INTO THE SYNAPTIC CLEFT UPON EXCITATION OF THE PRESYNAPTIC ELEMENT
4. BINDING OF THE TRANSMITTER TO ITS RECEPTOR/S/ THAT BELONG TO IONOTROPIC AND METABOTROPIC CLASSES
5. TERMINATION OF THE ACTION OF TRANSMITTERS AND ITS TRIGGERED MECHANISMS

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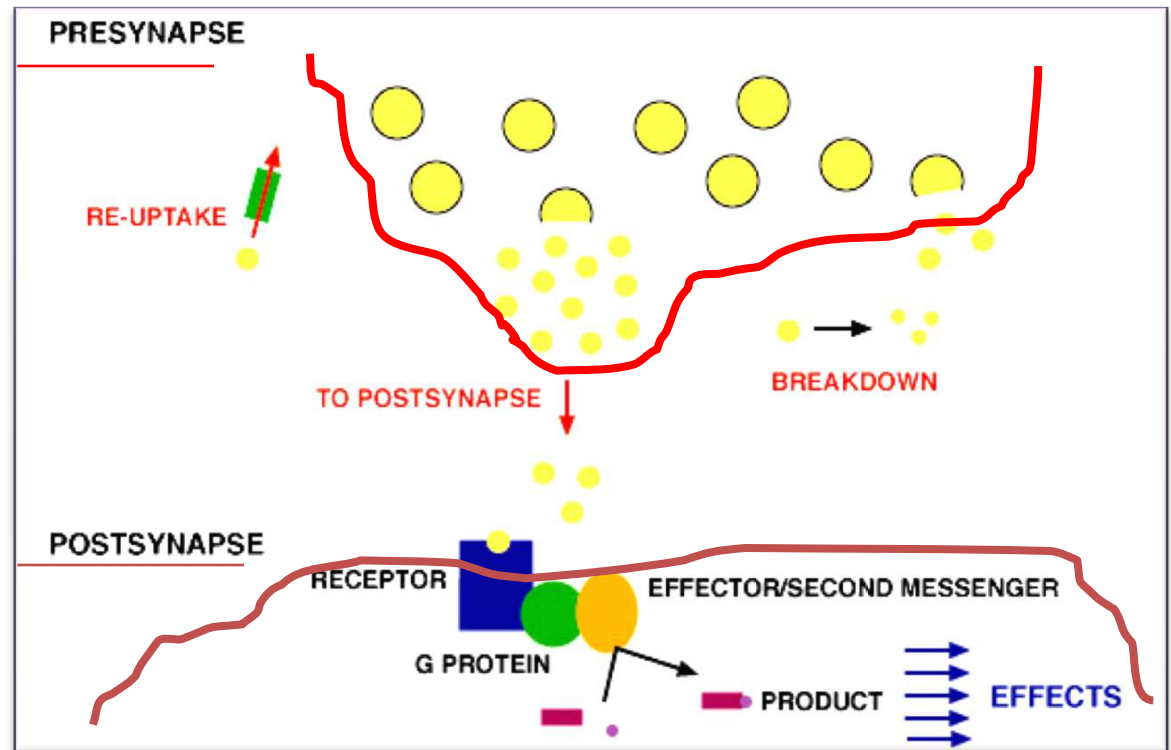
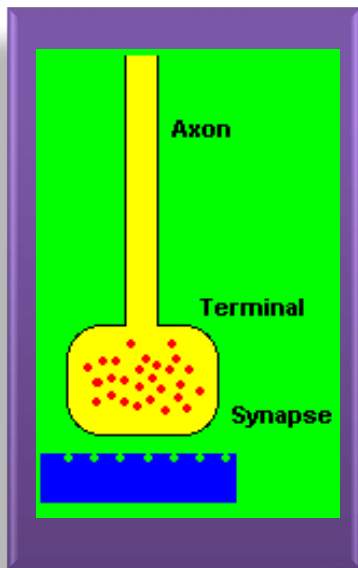
CLASSIFICATION OF NEUROTRANSMITTERS

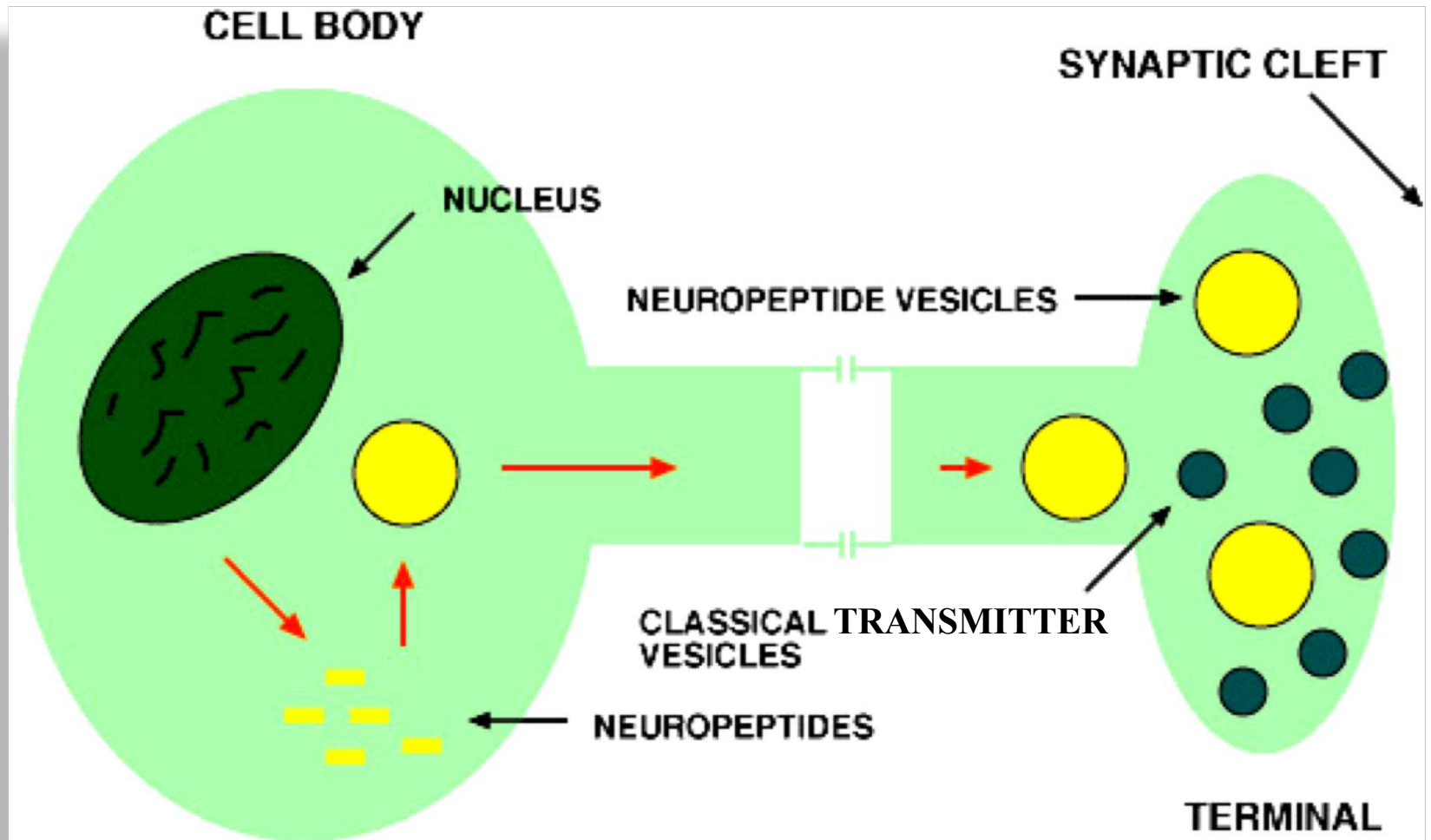
THE NEUROTRANSMITTERS BELONG TO TWO MAIN CATEGORIES, THE CLASSIC AMINE TYPE AND THE NON-CLASSIC PEPTIDE TYPE GROUPS

COMPARISON OF THE PRODUCTION OF CLASSIC AND NON-CLASSIC TRANSMITTERS

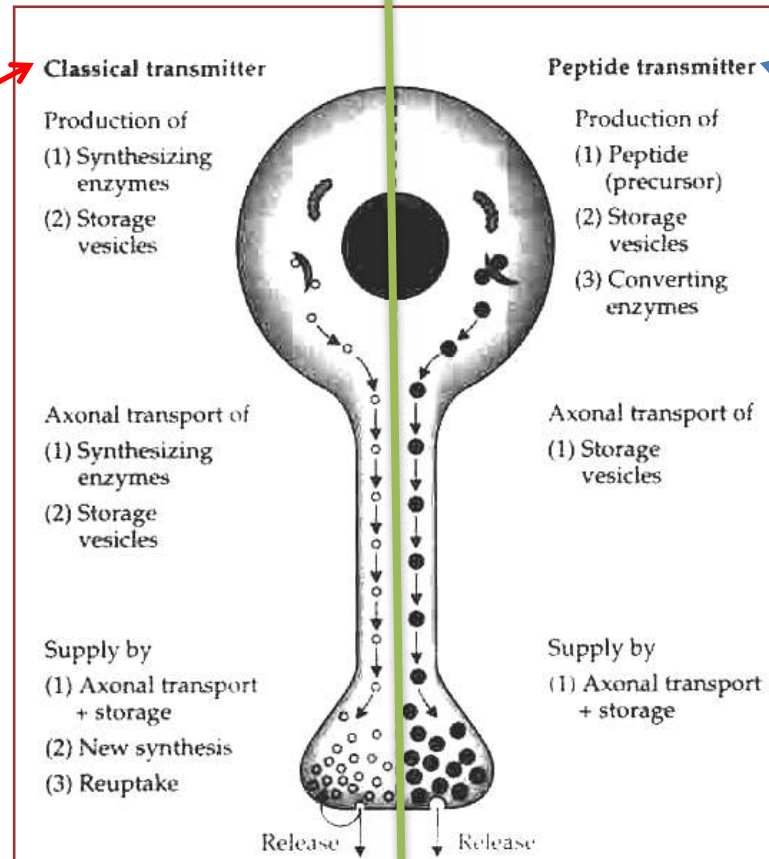
TYPE	CELL BODY	AXON	TERMINAL	EXAMPLE
AMINE	PRODUCTION OF 1. SYNTHESIZING ENZYMES 2. STORAGE VESICLES	AXONAL TRANSPORT OF 1. SYNTHESIZING ENZYMES 2. STORAGE VESICLES	SUPPLY OF CONSTITUENTS: 1. FROM CELL BODY 2. LOCAL SYNTHESIS 3. RE-UP TAKE	ACETYLCHOLINE GABA GLUTAMATE SEROTONIN NORADRENALINE
PEPTIDE	PRODUCTION OF 1. PEPTIDE PRECURSORS 2. CONVERTING ENZYMES 3. STORAGE VESICLES	AXONAL TRANSPORT OF STORAGE VESICLES	SUPPLY OF CONSTITUENTS FROM CELL BODY	ENKEPHALIN DYNORPHIN SUBSTANCE P VASOPRESSIN SOMATOSTATIN CHOLECYSTOKININ

Chemical transfer of information

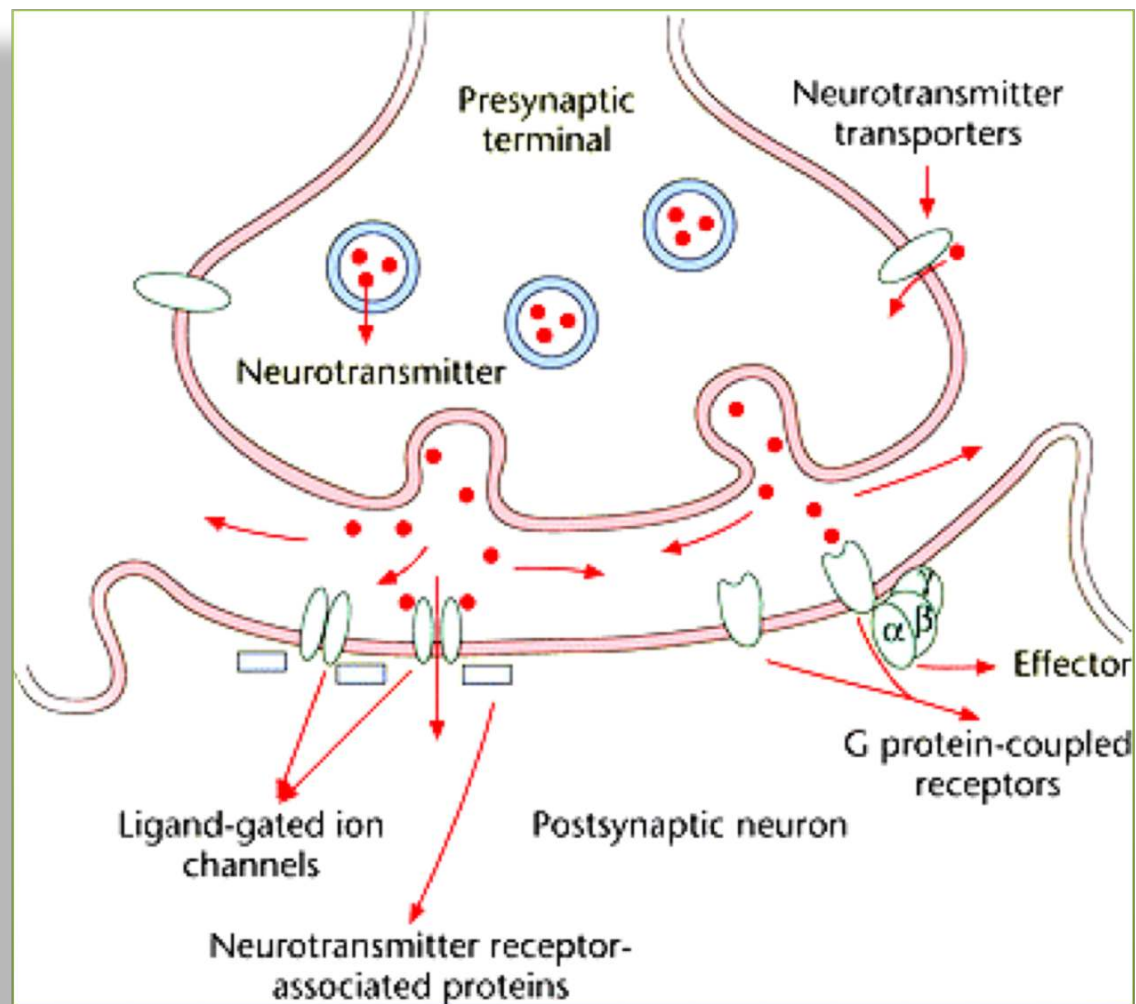




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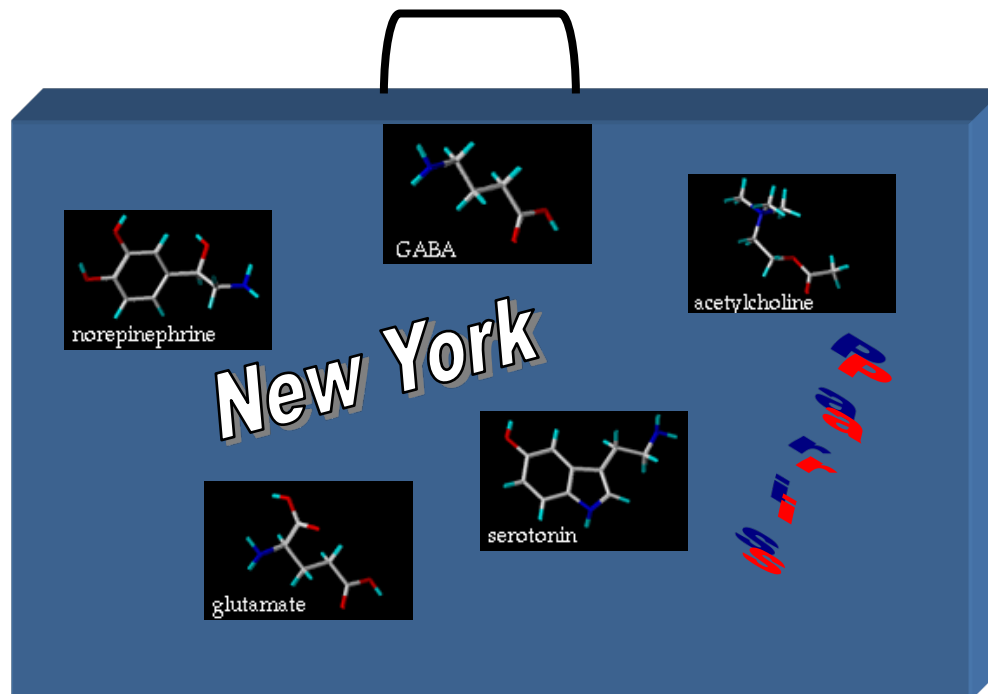


AMINE NEUROTRANSMITTERS

Table 1 Amine neurotransmitters

Neurotransmitter	Type of compound	Precursor
<i>Ester</i>		
Acetylcholine	Ester	Choline
<i>Amino acids</i>		
Glutamate	α Amino acid	α -Ketoglutarate (glutamine)
Glycine	α Amino acid	L-Serine
γ -Aminobutyric acid (GABA)	γ Amino acid	L-Glutamate
<i>Biogenic amines</i>		
Adrenaline (epinephrine)	Catecholamine	Noradrenaline
Noradrenaline (norepinephrine)	Catecholamine	Dopamine
Dopamine	Catecholamine	L-Tyrosine
Octopamine	Phenylamine	L-Tyrosine
5-Hydroxytryptamine (serotonin)	Indoleamine	L-Tryptophan
Histamine	Imidazoleamine	L-Histamine

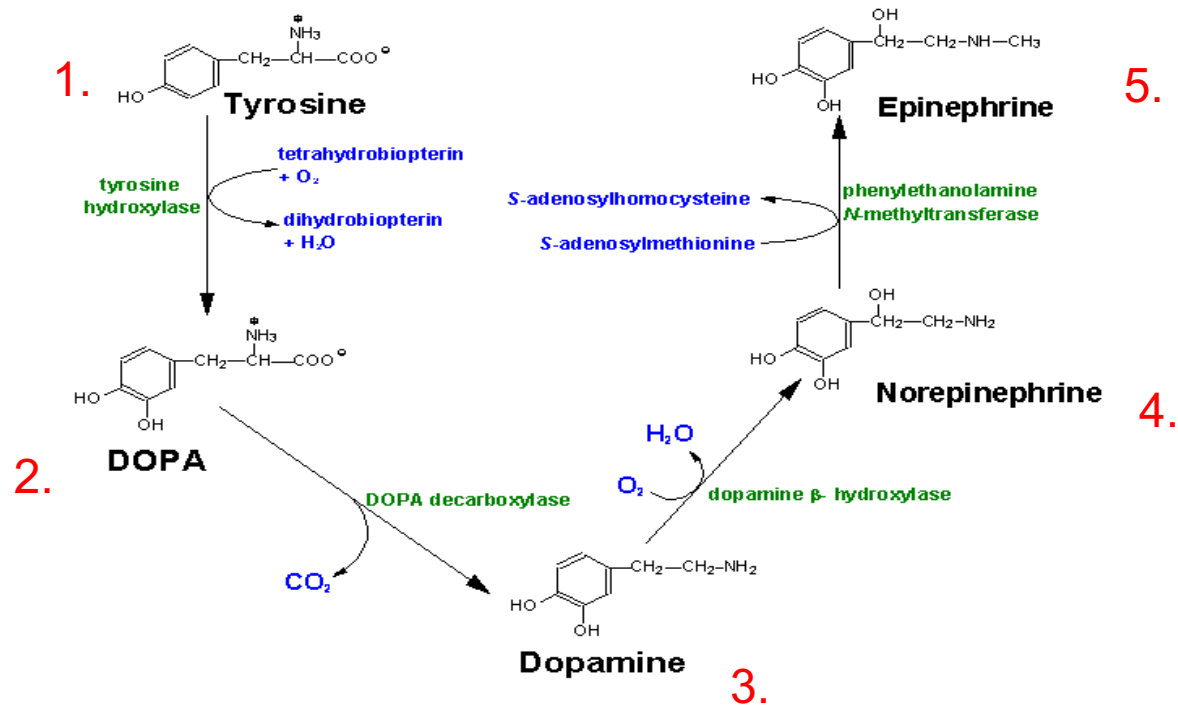
Transmitters



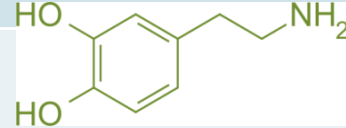
<http://themedicalbiochemistrypage.org/nerves.html>

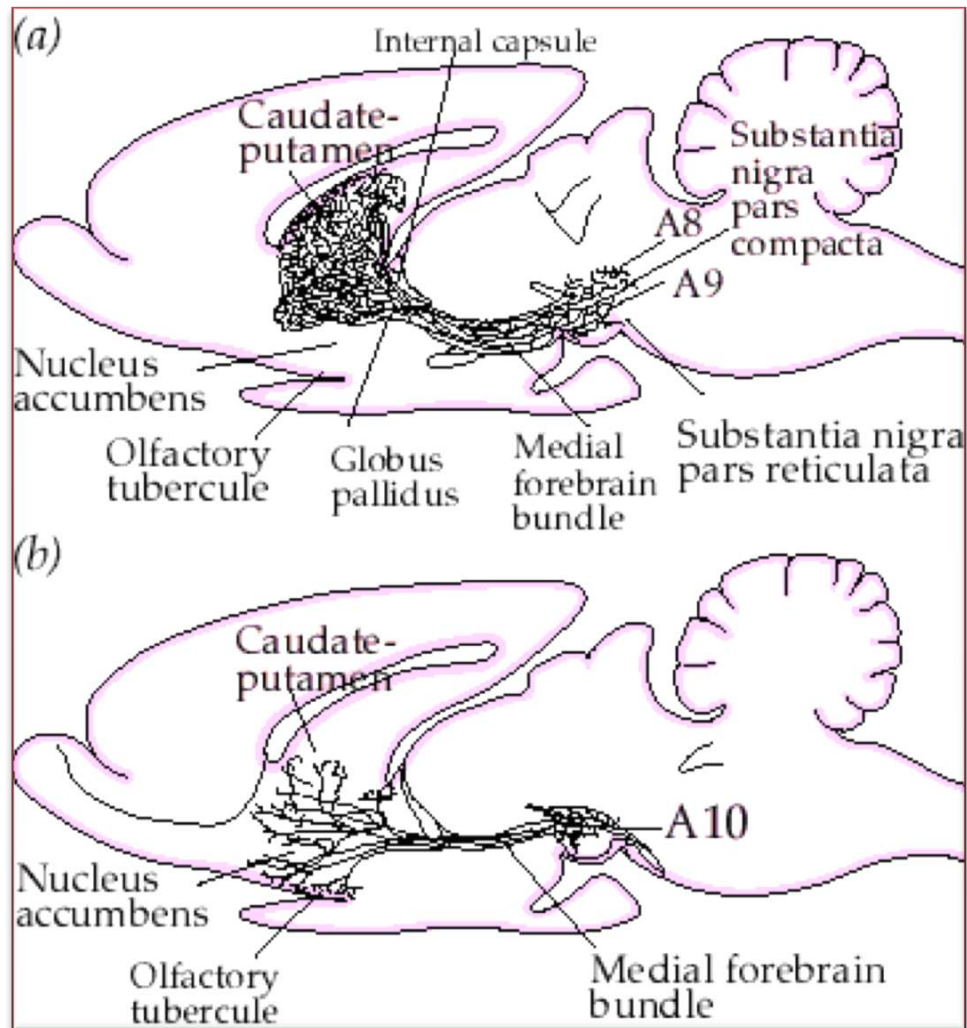
catecholamines

Synthesis



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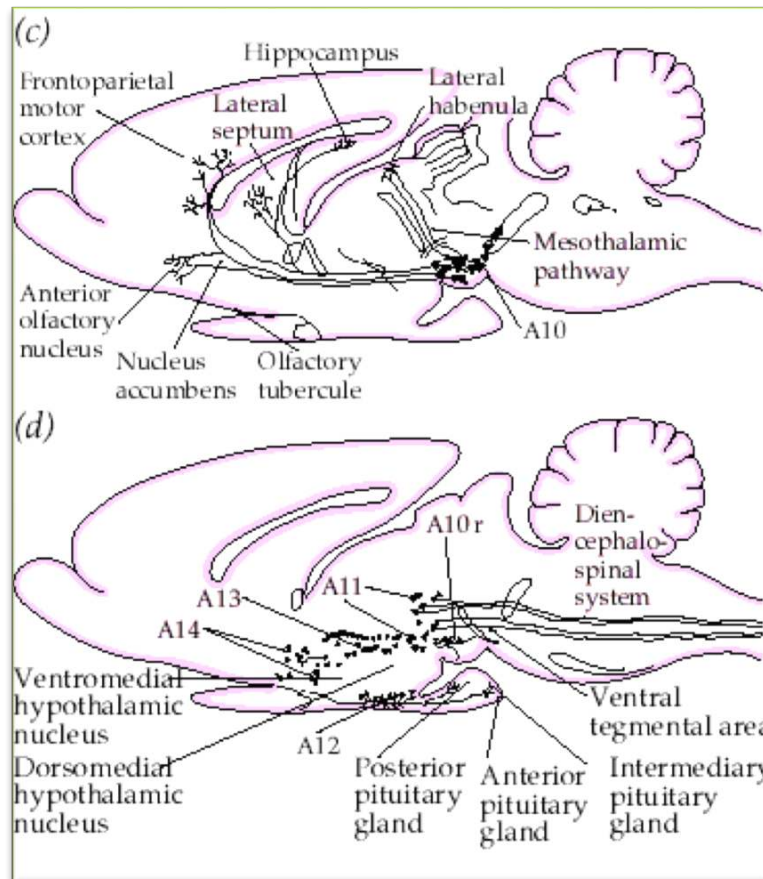
ATTRIBUTES	DESCRIPTION	
NAME	DOPAMINE	
CHEMICAL NAME, STRUCTURE	4-(2-AMINOETHYL)BENZENE-1,2-DIOL	
SYNTHESIS	DERIVATIVE OF:	L-DOPA
	SYNTHESIZING ENZYMES:	TYROSINE HYDROXYLASE (TH), DOPA DECARBOXYLASE
	REGULATION	TRANSCRIPTIONAL AND POST-TRANSCRIPTIONAL OF SYNTHESIZING ENZYMES
STORAGE	CELLULAR STRUCTURE TRANSPORTER	SYNAPTIC VESICLE VESICULAR MONOAMINE TRANSPORTER-2 (VMAT-2)
RELEASE	BY EXOCYTOSIS, PRESYNAPTIC REGULATION VIA AUTORECEPTORS (D2 FAMILY)	
INACTIVATION	BY MONOAMINE OXYDASE (MAO), CATECHOL-O-METHYL TRANSFERASE (COMT), DOPAMINE TRANSPORTER (DAT)	
RECEPTORS	D1-LIKE FAMILY: D1 AND D5 RECEPTORS, G PROTEIN-COUPLED D2-LIKE FAMILY: D2, D3 AND D4 RECEPTORS , G PROTEIN-COUPLED	
EXPRESSION IN BRAIN	IN NUCLEI OF THE BRAIN STEM AND HYPOTHALAMUS, MESOLIMBIC, MESOCORTICAL, NIGROSTRIATAL, TUBEROINFUNDIBULAR DOPAMINERGIC SYSTEMS	
SIGNIFICANCE	COGNITION, ATTENTION, MEMORY, PROBLEM SOLVING, REWARD, MOOD, PROLACTIN SECRETION, PARKINSON DISEASE, SCHIZOPHRENIA, AGING	



NIGRO-STRIATAL

DOPAMINE

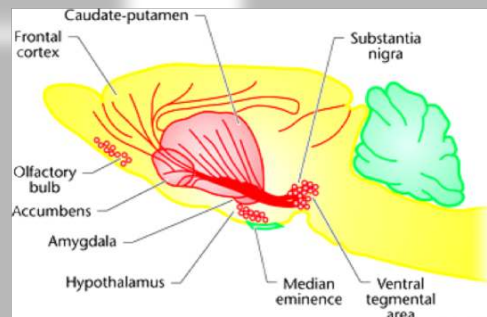
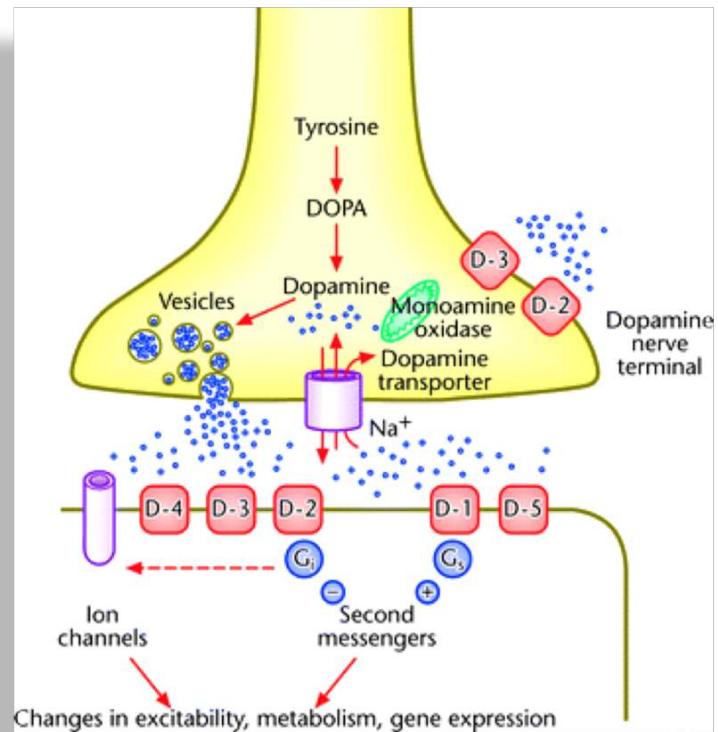
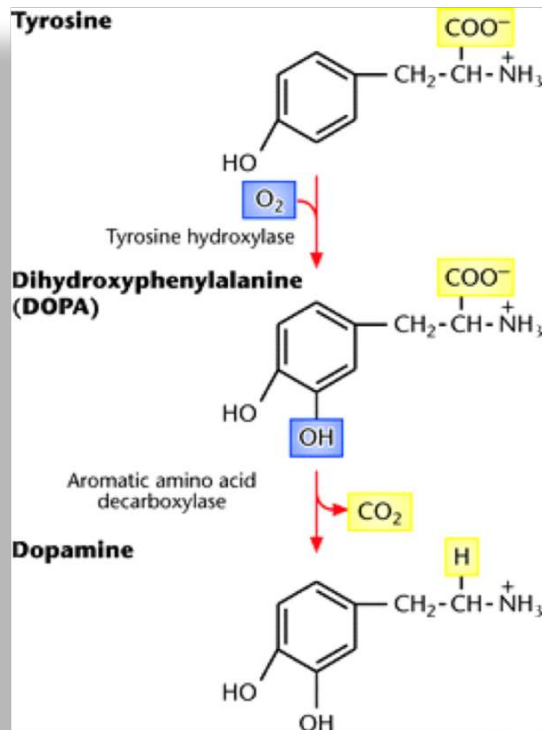
MESOLIMBIC



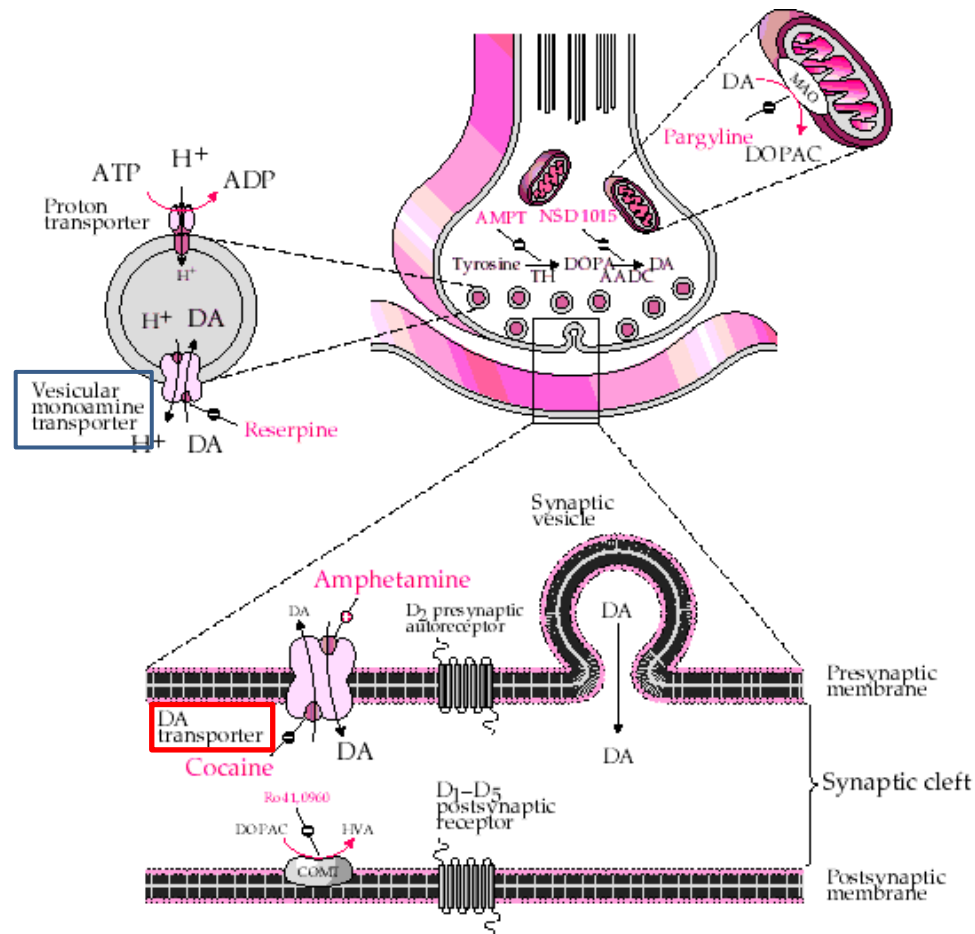
MESOTHALAMIC

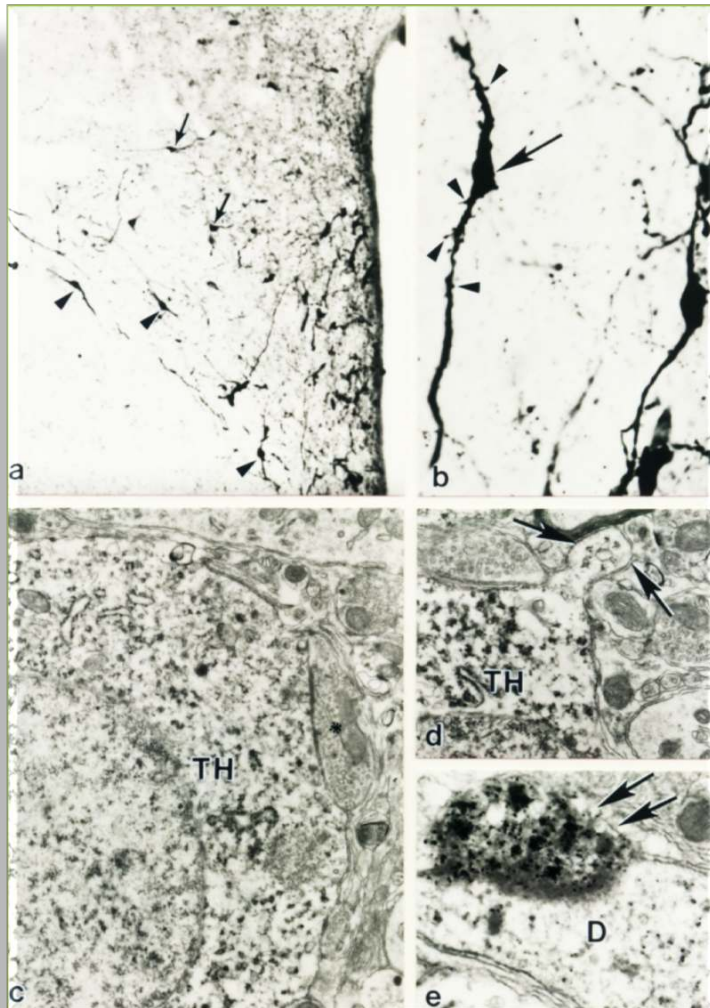
DOPAMINE

HYPOTHALAMIC



Dopaminergic synapse





TH-IR

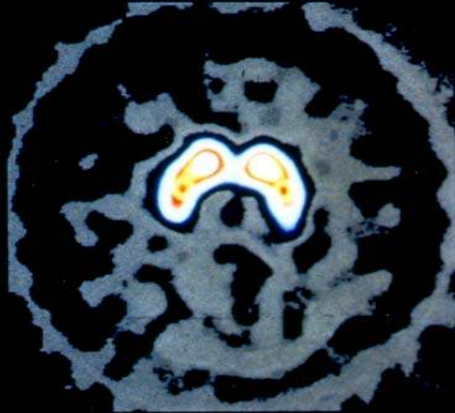
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DOPAMINERGIC NEURONS IN THE HYPOTHALAMUS



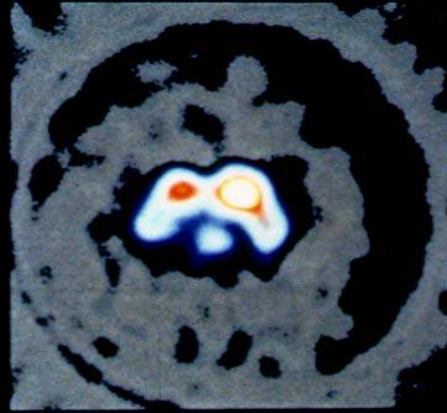
DOUBLE IMMUNOCYTOCHEMICAL LABELING REVEALS BLACK, DOPAMINERGIC NEURONS CONTACTING BROWN, CORTICOTROPIN-RELEASING HORMONE-SYNTHESIZING NEURONS IN THE PRAVENTRICULAR NUCLEUS

PD: SPECT Scan Images

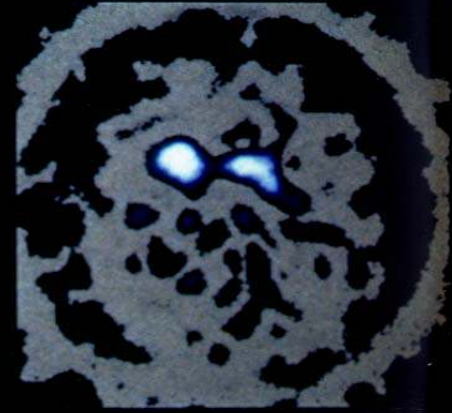


Healthy control

CONTROL



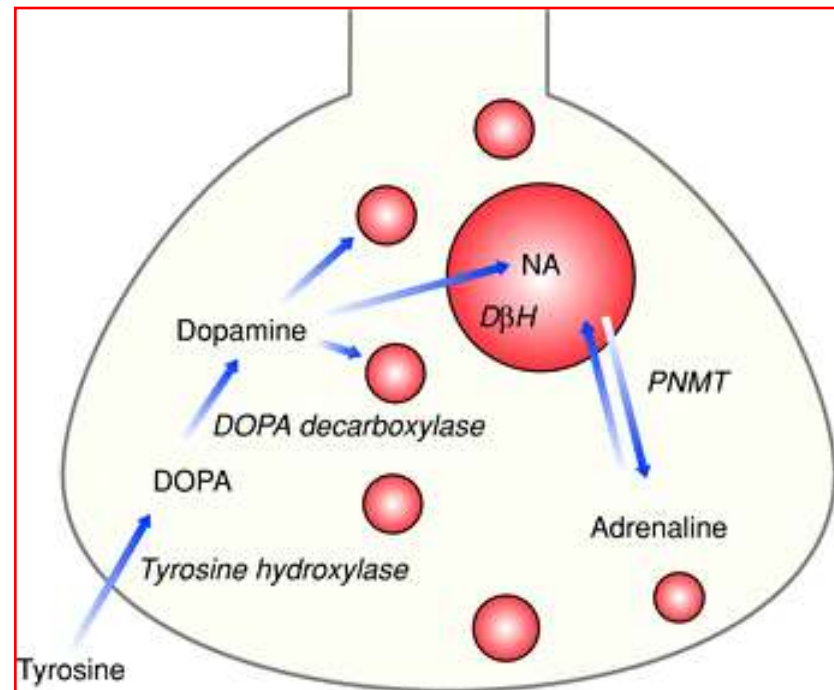
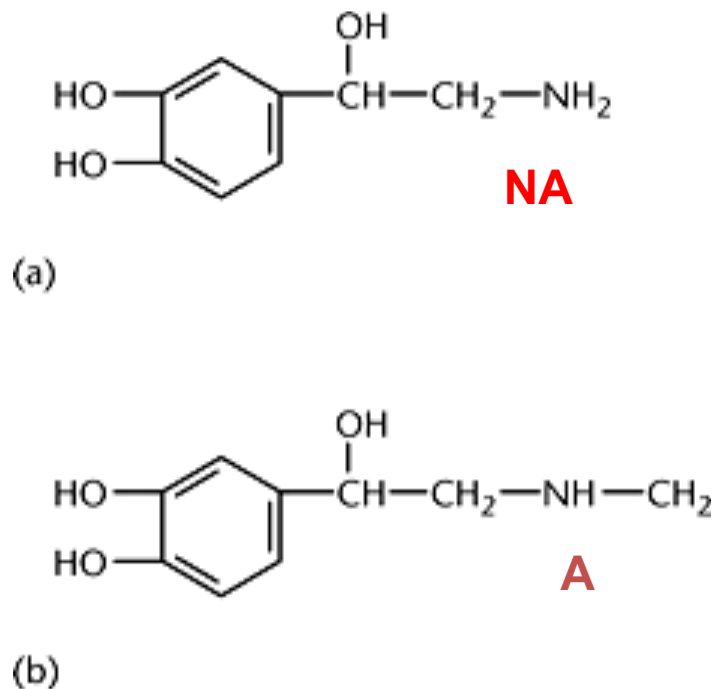
Hoehn-Yahr stage 1



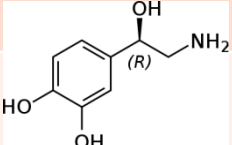
Hoehn-Yahr stage 4

PARKINSON DISEASE

NORADRENALINE AND ADRENALINE

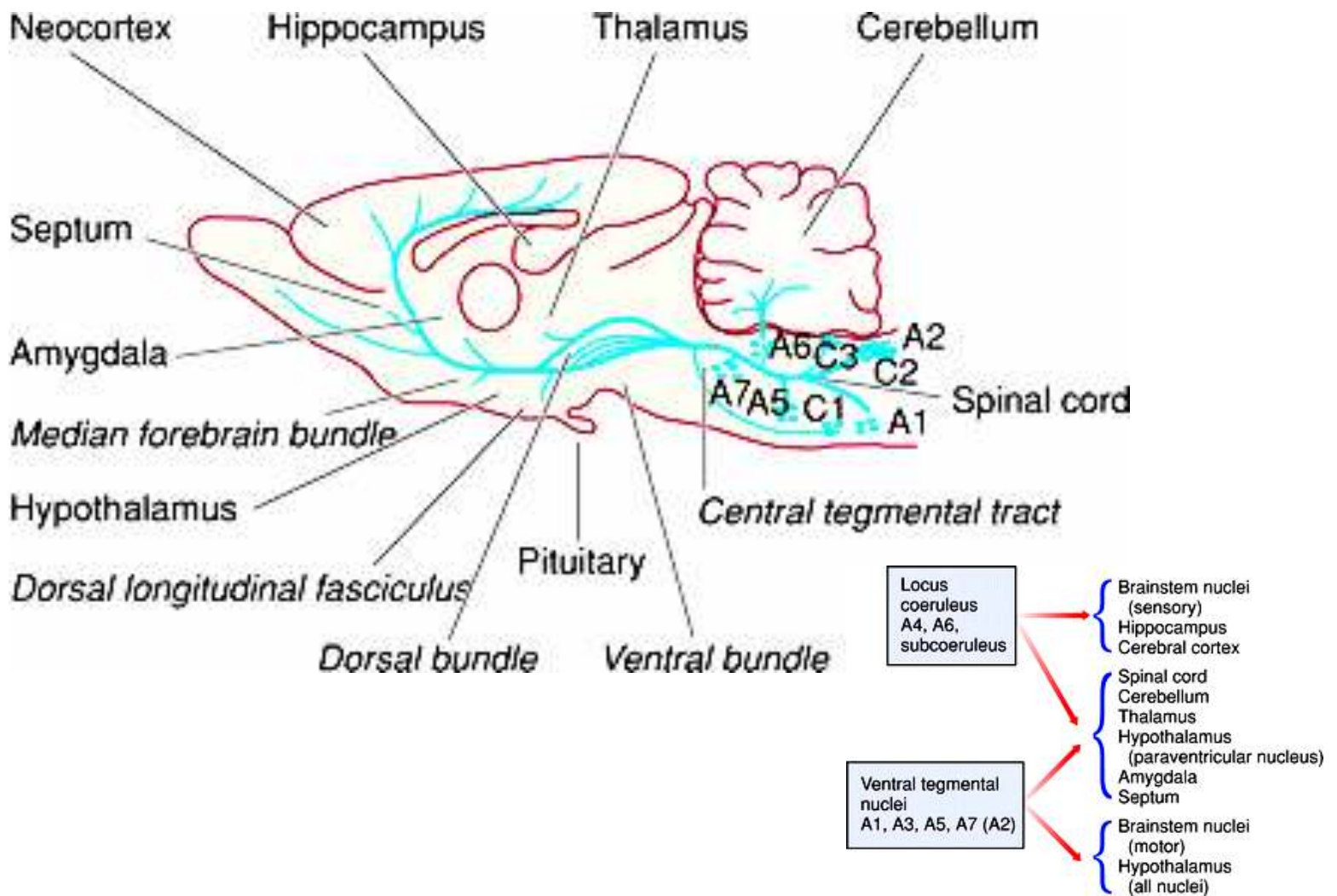


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ATTRIBUTES	DESCRIPTION	
NAME	NOREPINEPHRINE (NORADRENALINE, NE)	
CHEMICAL NAME, STRUCTURE	4-[(1R)-2-AMINO-1-HYDROXYETHYL]BENZENE-1,2-DIOL	
SYNTHESIS	DERIVATIVE OF:	DOPAMINE
	SYNTHESIZING ENZYME	DOPAMINE BETA-HYDROXYLASE
	REGULATION	TRANS-SYNAPTIC INDUCTION, GLUCOCORTICOIDS
STORAGE	CELLULAR STRUCTURE TRANSPORTER	SYNAPTIC VESICLE VESICULAR MONOAMINE TRANSPORTER-2 (VMAT-2)
RELEASE	BY EXOCYTOSIS, PRESYNAPTIC REGULATION VIA AUTORECEPTORS (ALPHA-2)	
INACTIVATION	BY MONOAMINE OXYDASE (MAO) , RE-UPTAKE BY NOREPINEPHRINE TRANSPORTER (NET)	
RECEPTORS	G PROTEIN-COUPLED RECEPTORS, ALPHA AND BETA TYPES IN THE BAIN: ALPHA 2 INHIBITS ADENYLYL CYCLASE, BETA 1 ACTIVATES IT	
EXPRESSION IN BRAIN	CELL GROUPS IN THE CAUDAL PART OF THE BRAIN STEM	
SIGNIFICANCE	ATTENTION, AROUSAL, STRESS, FEEDING REGULATION, ANTI DEPRESSION DRUG DEVELOPMENT	

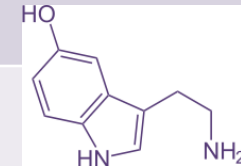
DISTRIBUTION OF CATECHOLAMINERGIC CELL GROUPS IN THE RODENT BRAIN

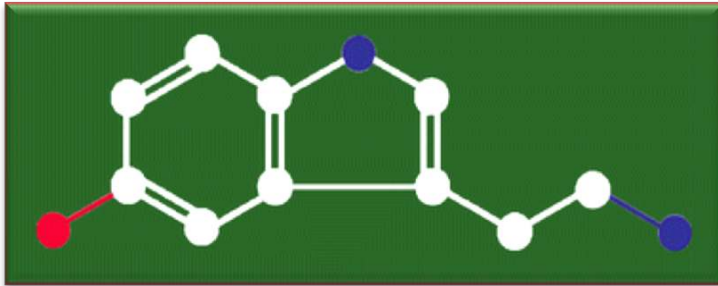




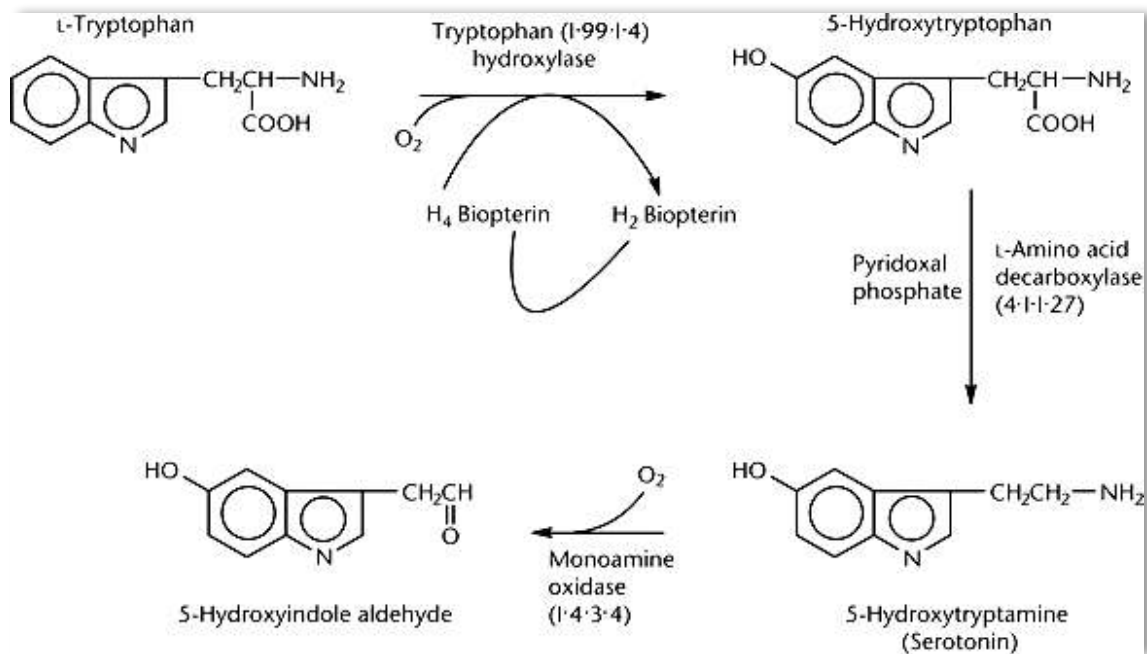
Basics of Neurobiology: Neurotransmitters I.

ATTRIBUTES	DESCRIPTION	
NAME	SEROTONIN	
CHEMICAL NAME, STRUCTURE	5-HYDROXYTRIPTAMINE (5-HT)	
SYNTHESIS	DERIVATIVE OF:	TRYPTOPHAN
	SYNTHESIZING ENZYMES:	TRYPTOPHAN HYDROXYLASE (TPH), AROMATIC L-AMINO ACID DECARBOXYLASE
	REGULATION	PRECURSOR CONCENTRATION, PHOSPHORYLATION OF TPH
STORAGE	CELLULAR STRUCTURE TRANSPORTER	SYNAPTIC VESICLE VESICULAR MONOAMINE TRANSPORTER-2 (VMAT-2)
RELEASE	BY EXOCYTOSIS, PRESYNAPTIC REGULATION VIA AUTORECEPTORS (5-HT _{1A})	
INACTIVATION	BY MONOAMINE OXYDASE (MAO) , RE-UPTAKE BY SEROTONIN TRANSPORTER	
RECEPTORS	LIGAND-GATED ION CHANNEL (5-HT ₃), G PROTEIN-COUPLED RECEPTORS (5-HT ₁₋₂ , 5-HT ₃₋₇)	
EXPRESSION IN BRAIN	RAPHE NUCLEI OF THE BRAINSTEM	
SIGNIFICANCE	AGGRESSION, OBSESSIVE-COMPULSIVE BEHAVIOR, FEEDING REGULATION, OBESITY, ANTI DEPRESSION DRUG DEVELOPMENT (SSRI)	

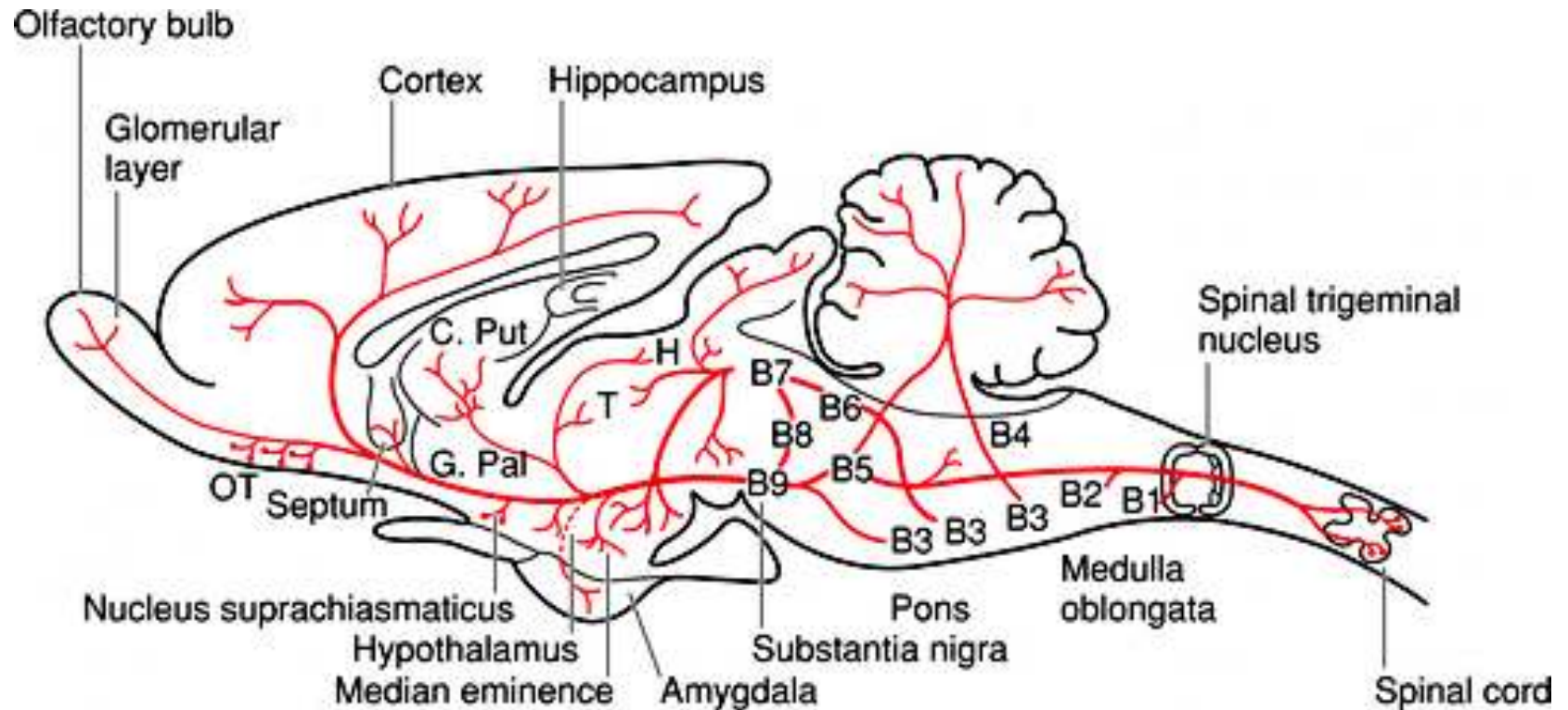




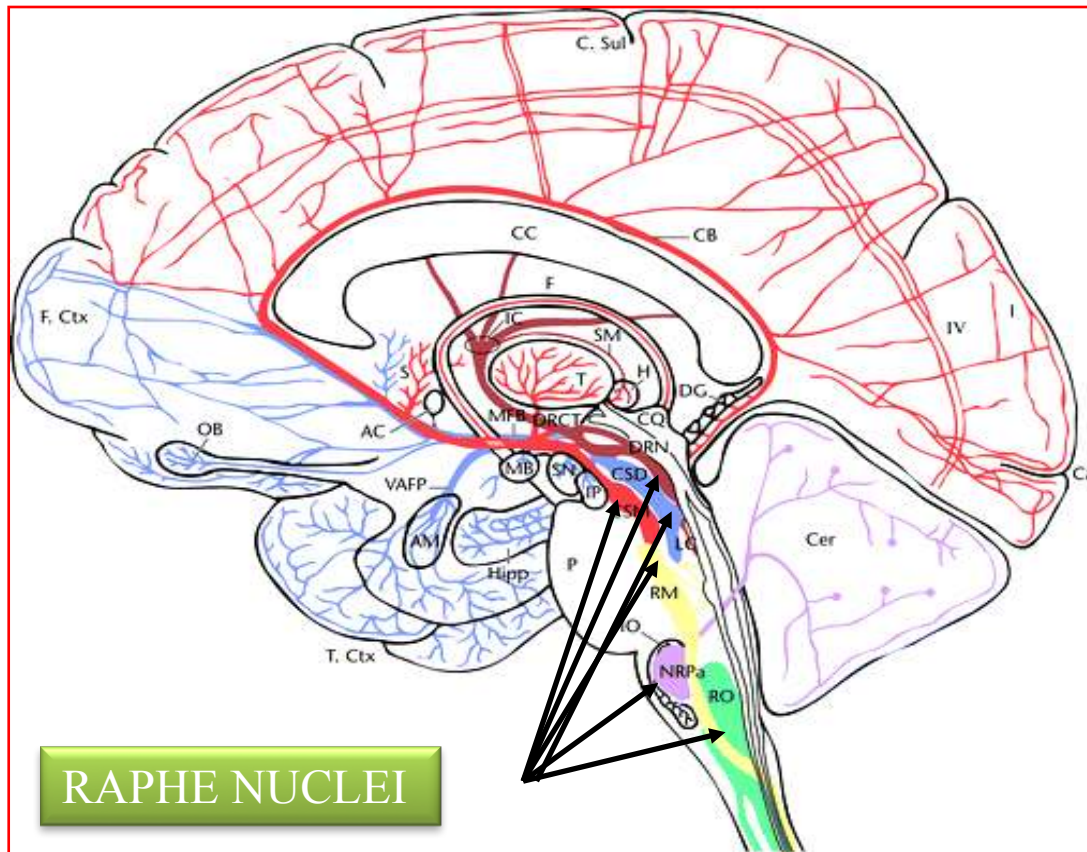
5HT



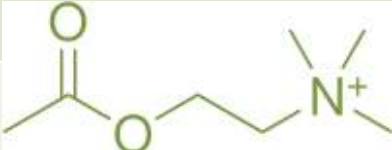
SEROTONERGIC GROUPS (B1-B9) AND THEIR PROJECTIONS IN RAT

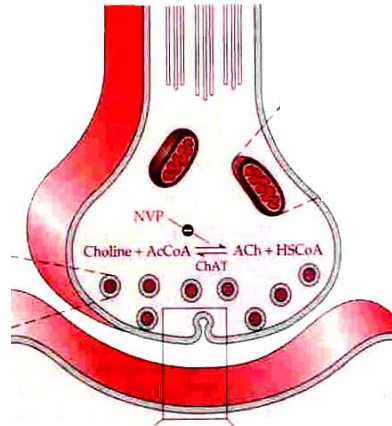


SEROTONERGIC SYSTEM OF THE HUMAN BRAIN

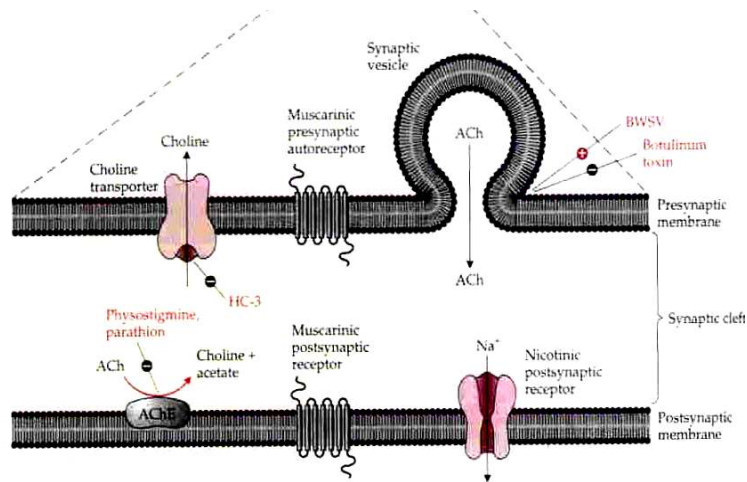


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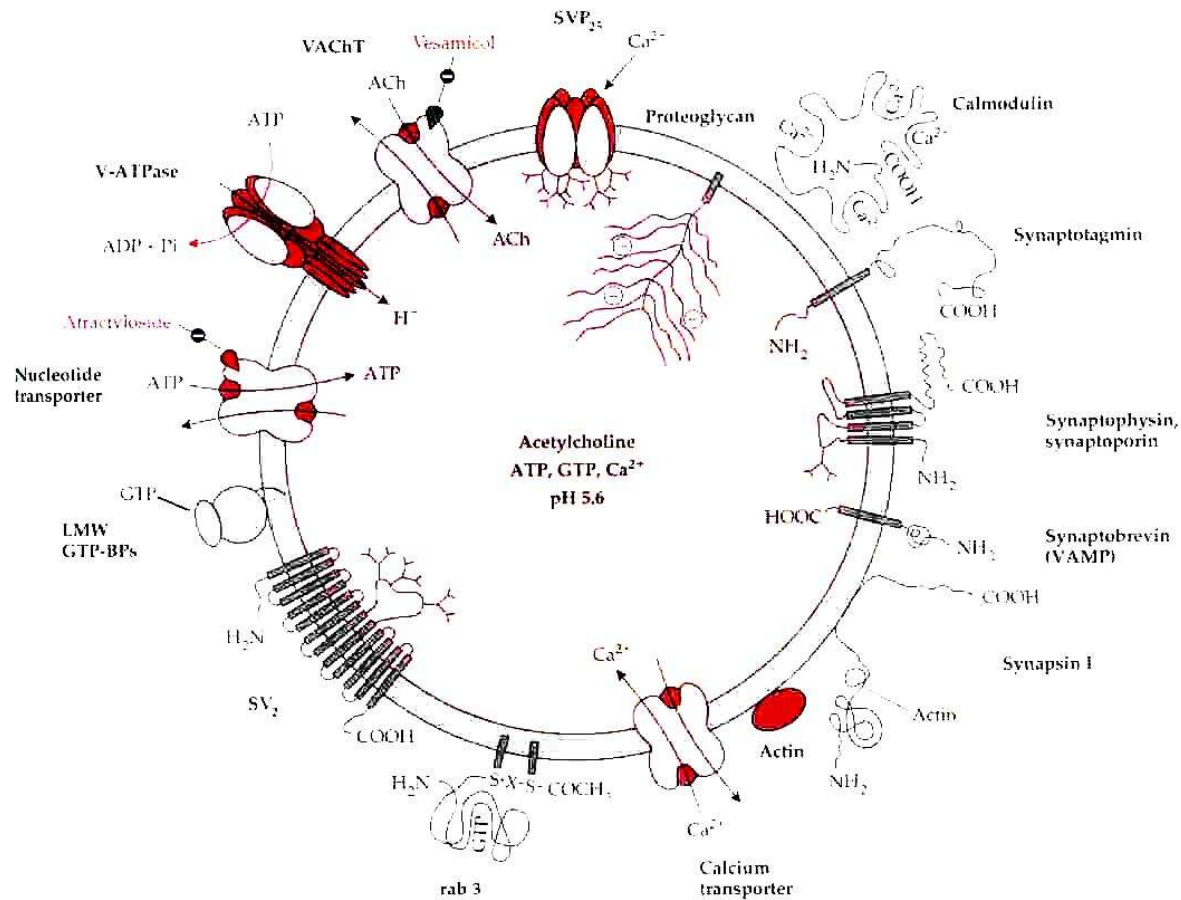
ATTRIBUTES	DESCRIPTION	
NAME	ACETYLCHOLINE (ACh)	
CHEMICAL NAME, STRUCTURE	2-ACETOXY- <i>N,N,N</i> -TRIMETHYLETHANAMINIUM	
SYNTHESIS	DERIVATIVE OF:	ESTER OF ACETIC ACID AND CHOLINE
	SYNTHESIZING ENZYME	CHOLINE ACETYLTRANSFERASE
	REGULATION	ACTIVITY, ALLOSTERIC INHIBITION, PRECURSOR AVAILABILITY
STORAGE	CELLULAR STRUCTURE TRANSPORTER	SYNAPTIC VESICLE VESICULAR ACh TRANSPORTER
RELEASE	BY EXOCYTOSIS, MINIATURE END-PLATE POTENTIALS, QUANTAL RELEASE	
INACTIVATION	ACETYLCHOLINESTERASE, CHOLINE TRANSPORTER	
RECEPTORS	NICOTINIC, IONOTROP, LIGAND-GATED ION CHANNEL, EXCITATORY MUSCARINIC, G PROTEIN-COUPLED, M1-M4	
EXPRESSION IN BRAIN	BASAL FOREBRAIN, HABENULA, BRAIN STEM	
SIGNIFICANCE	LEARNING, MEMORY, ATTENTION, AGING, ALZHEIMER DISEASE	



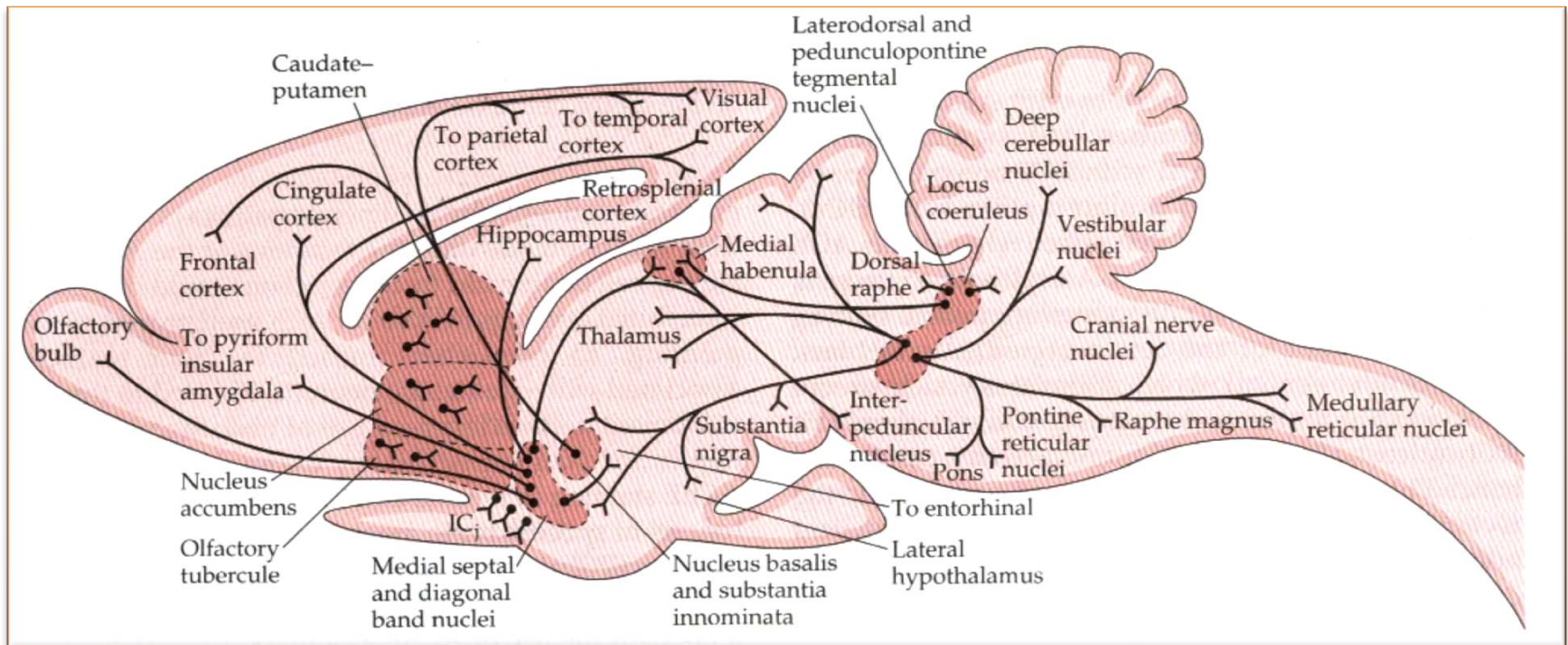
CHOLINERGIC SYNAPSE

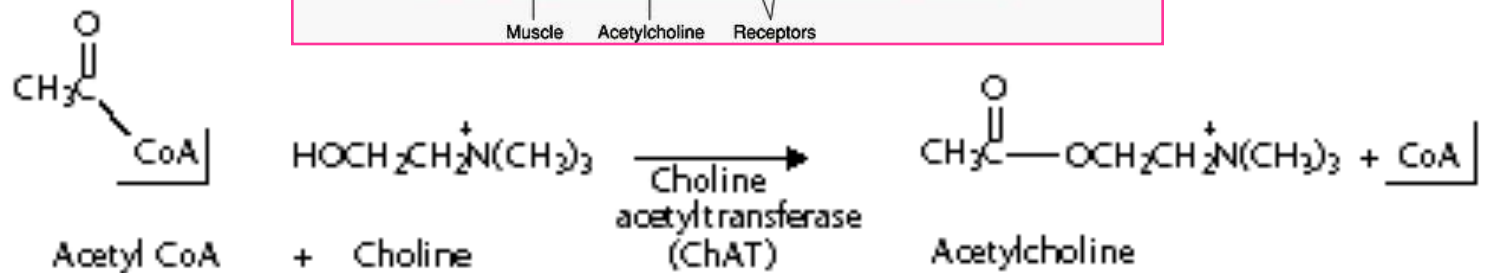
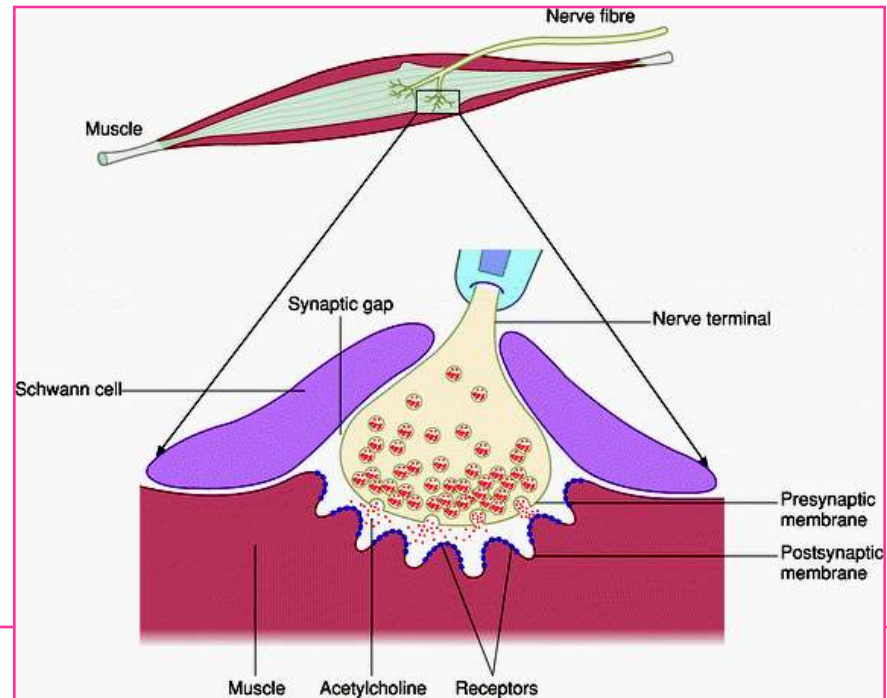


CHOLINERGIC VESICLE

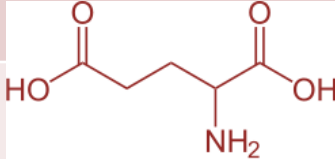


CHOLINERGIC SYSTEMS OF THE BRAIN

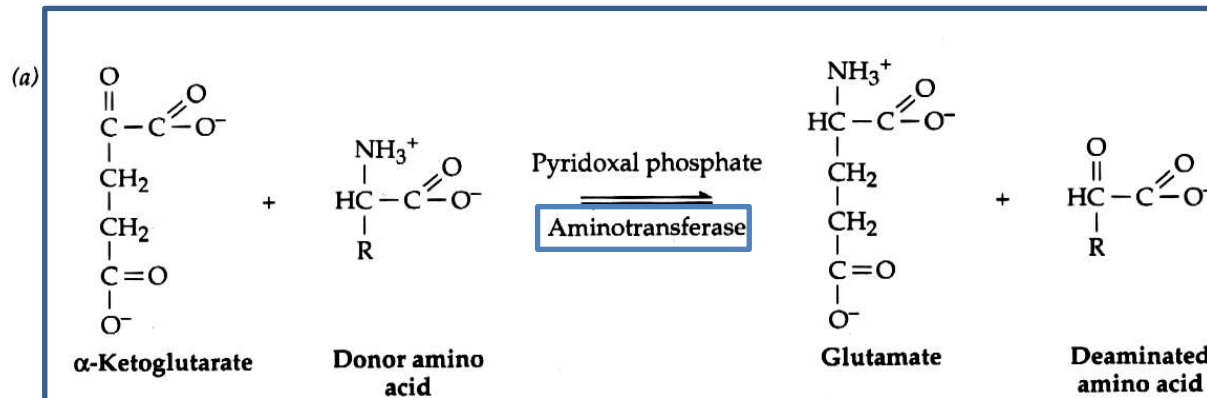




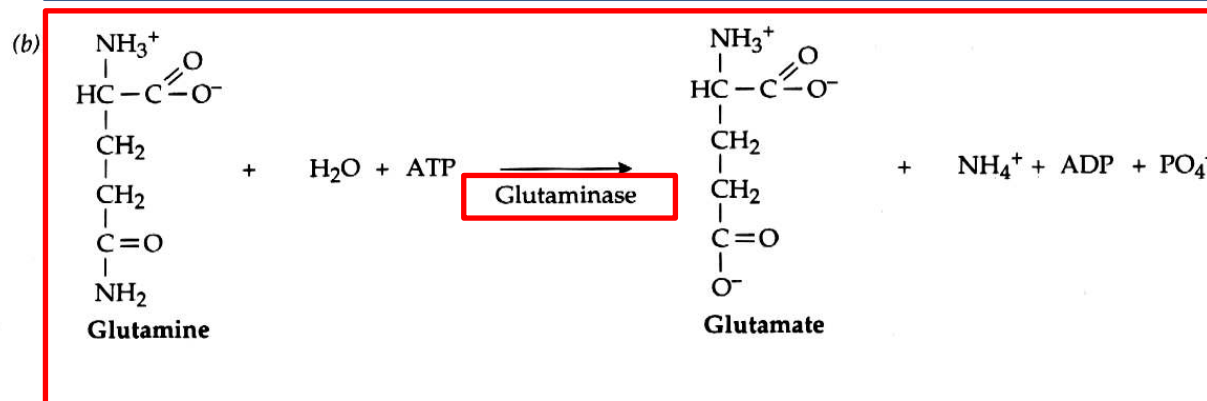
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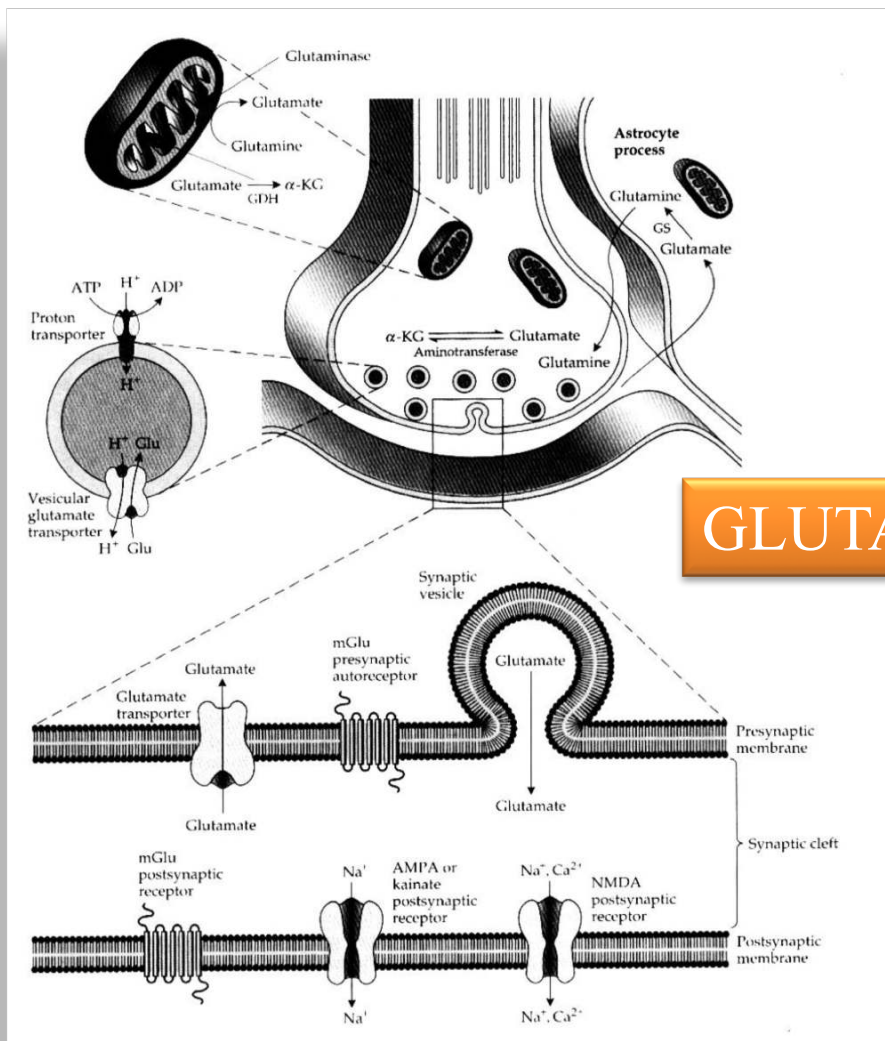
ATTRIBUTES	DESCRIPTION	
NAME	GLUTAMATE	
CHEMICAL NAME, STRUCTURE	GLUTAMIC ACID	
SYNTHESIS	DERIVATIVE OF:	ALPHA-KETOGLUTARATE AND GLUTAMINE
	SYNTHESIZING ENZYMES	AMINOTRANSFERASE, GLUTAMINASE
	REGULATION	THE GLUTAMINE-GLUTAMATE CYCLE (GLIA-NEURON)
STORAGE	CELLULAR STRUCTURE TRANSPORTER	SYNAPTIC VESICLE VESICULAR GLUTAMATE TRANSPORTER (VGLUT1-3)
RELEASE	BY EXOCYTOSIS, PRESYNAPTIC REGULATION VIA AUTORECEPTORS (mGluR2, mGluR3)	
INACTIVATION	NEURONAL AND GLIAL UPTAKE BY PLASMA MEMBRANE GLUTAMATE TRANSPORTERS	
RECEPTORS	IONOTROPIC, AMPA (GluR1-4), KAINATE (GluR5-7, KA1-2), NMDA (NR1, NR2A-2D) METABOTROPIC, G PROTEIN-COUPLED (mGluR1-7)	
EXPRESSION IN BRAIN	THROUGHOUT THE BRAIN	
SIGNIFICANCE	LEARNING, PLASTICITY, LONG TERM POTENTIATION, NEUROTOXICITY	

GLUTAMATE SYNTHESIS

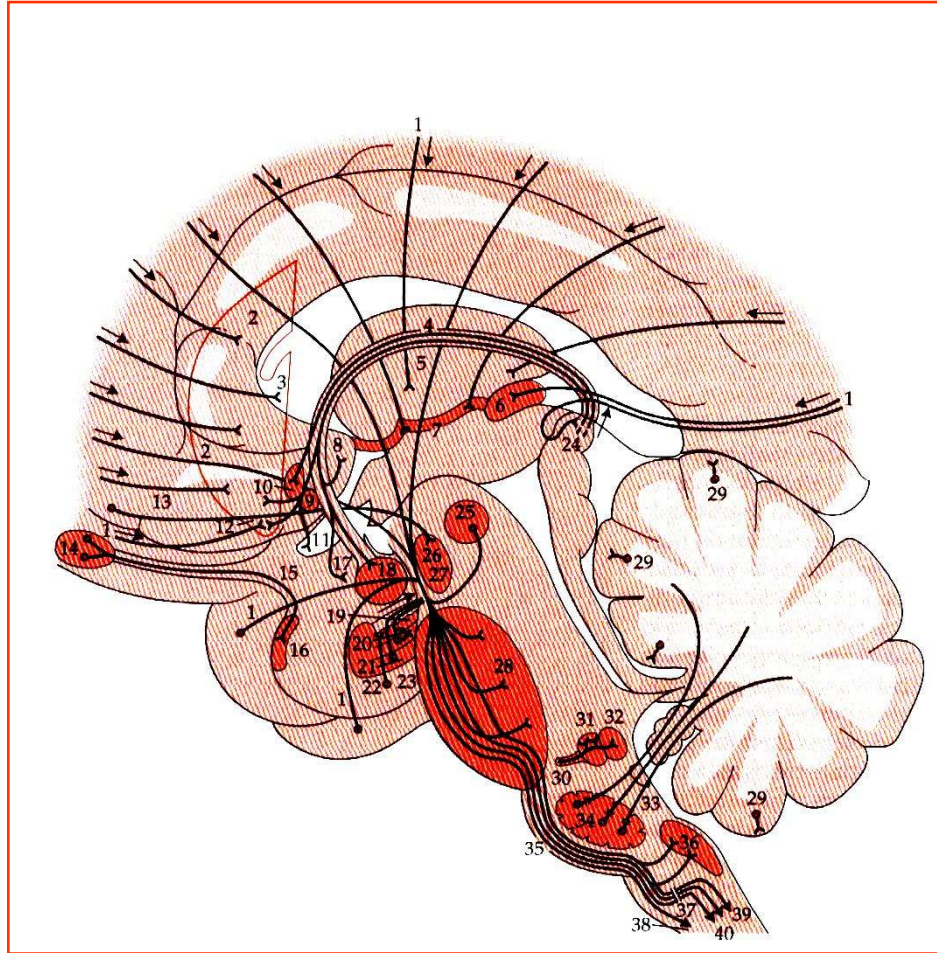


10.3 PATHWAYS OF GLUTAMATE SYNTHESIS. Glutamate is synthesized in neural tissues by two major pathways: (a) from α -ketoglutarate and donor amino acids by means of transamination, and (b) from glutamine by the action of the enzyme glutaminase.

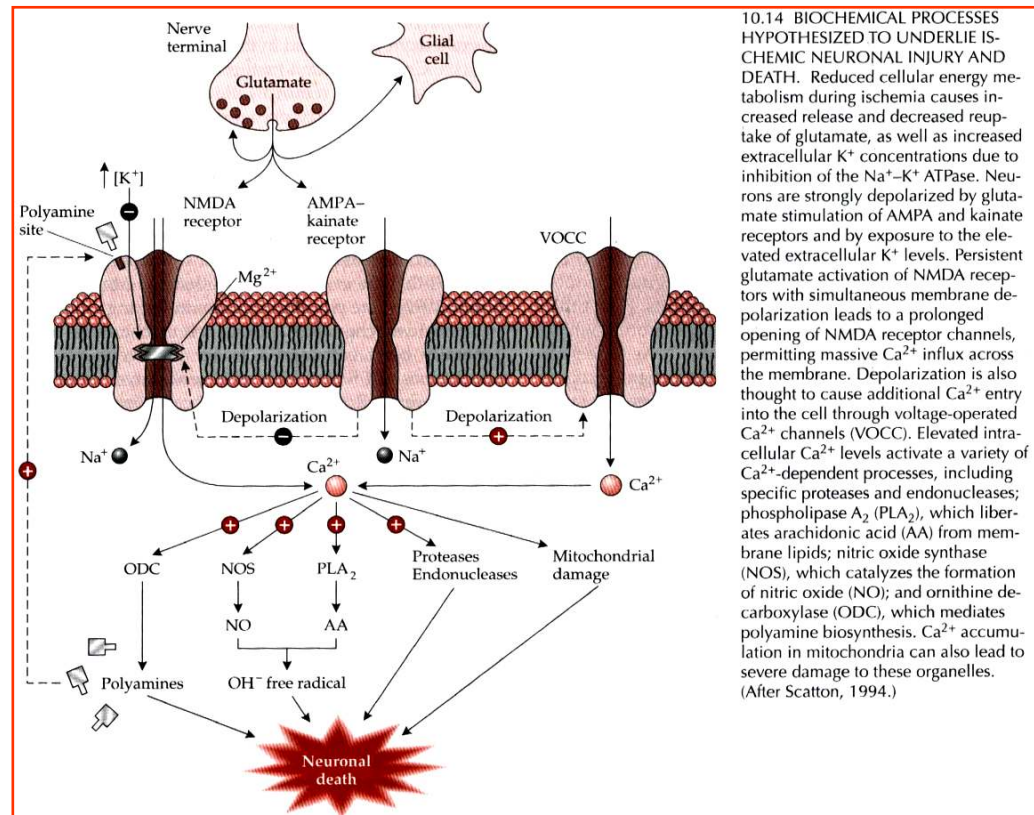


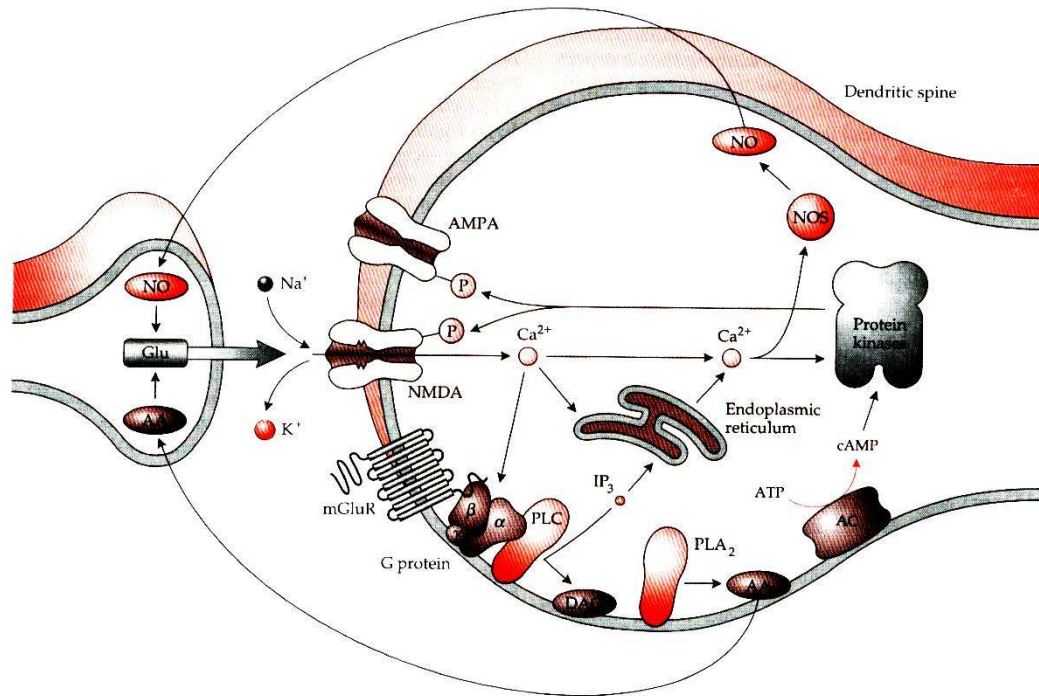


GLUTAMATERGIC SYNAPSE



GLUTAMATE NEUROTOXICITY

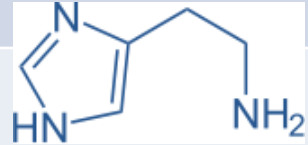




10.19 POSSIBLE MECHANISMS UNDERLYING LTP INDUCTION AND MAINTENANCE BY GLUTAMATE RECEPTOR ACTIVATION. LTP induction requires glutamate-stimulated Ca^{2+} influx through NMDA receptor channels. This process may be augmented by metabotropic glutamate receptor (mGluR) activation of phospholipase C (PLC), leading to inositol trisphosphate (IP_3) liberation and Ca^{2+} release from intracellular stores. LTP maintenance may involve the activation of protein kinases stimulated by Ca^{2+} and possibly other second messengers, including arachidonic acid (AA; liberated by phospholipase A_2 [PLA_2]) and cyclic AMP (cAMP; produced by adenylyl cyclase [AC]). These kinases phosphorylate several target proteins, probably including AMPA and NMDA receptors. There is some evidence that the biochemical cascade occurring postsynaptically also leads to the formation of one or more retrograde messengers, which may include nitric oxide (synthesized by nitric oxide synthase [NOS]) or arachidonic acid. (After Bliss and Collingridge, 1993.)

LTP

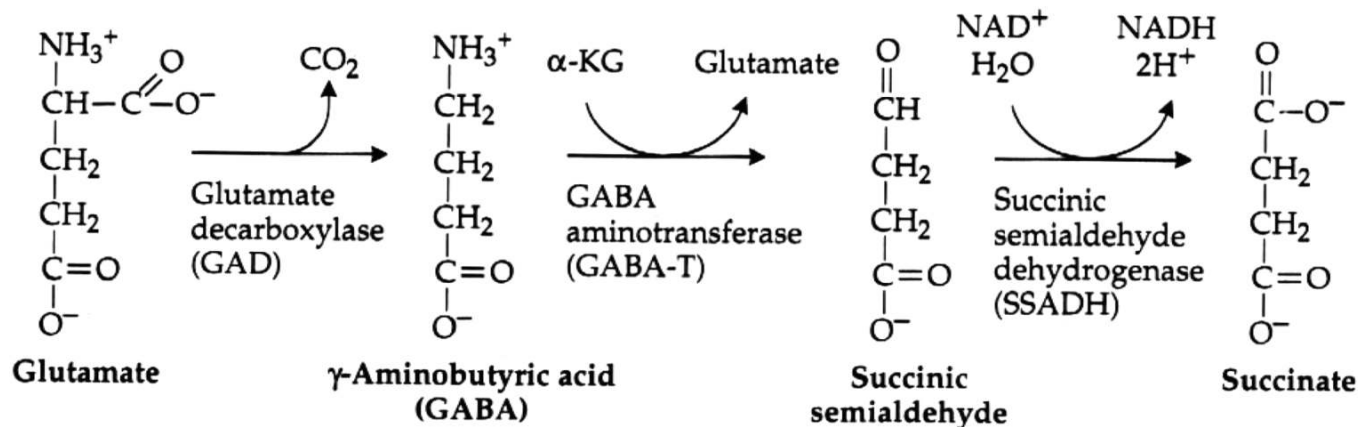
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ATTRIBUTES	DESCRIPTION	
NAME	HISTAMINE	
CHEMICAL NAME, STRUCTURE	2-(1H-IMIDAZOL-4-YL)ETHANAMINE	
SYNTHESIS	DERIVATIVE OF:	HISTIDINE
	SYNTHESIZING ENZYMES	L-HISTIDINE DECARBOXYLASE
	REGULATION	PRECURSOR AVAILABILITY
STORAGE	CELLULAR STRUCTURE TRANSPORTER	SYNAPTIC VESICLE VESICULAR MONOAMINE TRANSPORTER-2 (VMAT-2)
RELEASE	BY EXOCYTOSIS, AUTORECEPTORS	
INACTIVATION	HISTAMINE-N-METHYL TRANSFERASE, MAO-B	
RECEPTORS	HISTAMINE RECEPTORS 1-4	
EXPRESSION IN BRAIN	TUBERO-MAMMILLARY NUCLEI OF THE CAUDAL HYPOTHALAMUS (E1-5)	
SIGNIFICANCE	SLEEP-WAKING CYCLE, PSYCHOMOTOR PERFORMANCE	

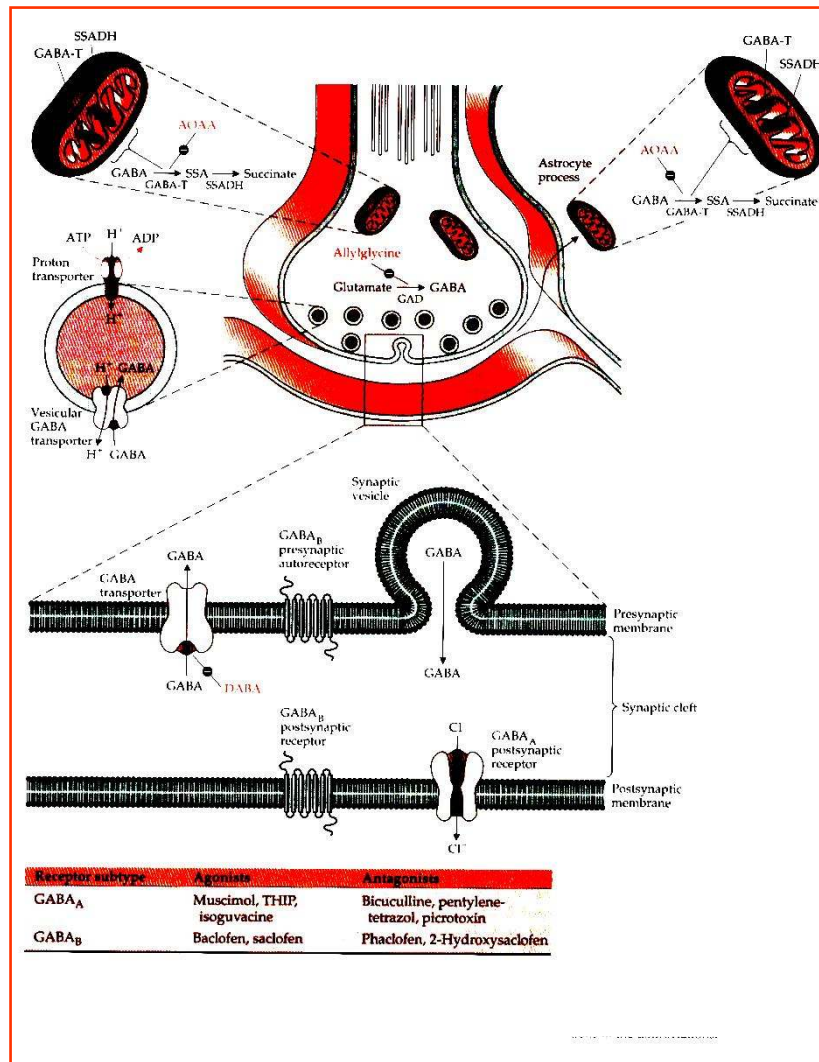
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ATTRIBUTES	DESCRIPTION	
NAME	GABA	
CHEMICAL NAME, STRUCTURE	GAMMA -AMINOBUTYRIC ACID 	
SYNTHESIS	DERIVATIVE OF:	L-GLUTAMATE
	SYNTHESIZING ENZYMES	GLUTAMATE DECARBOXYLASE (GAD)
	REGULATION	ENDPRODUCT
STORAGE	CELLULAR STRUCTURE TRANSPORTER	SYNAPTIC VESICLE VESICULAR GABA TRANSPORTER (VGAT)
RELEASE	BY EXOCYTOSIS, PRESYNAPTIC INHIBITION	
INACTIVATION	GABA AMINOTRANSFERASE	
RECEPTORS	GABA A, CHLORIDE CHANNEL, WITH VARIOUS BINDING SITES (GABA, PICROTOXIN, BARBITURATE, BENZODIAZEPINE, STEROID) GABA B	
EXPRESSION IN BRAIN	DIFFUSELY DISTRIBUTED CELL GROUPS IN THE ENTIRE NEUROAXIS	
SIGNIFICANCE	GENERAL INHIBITION AND COUNTERBALANCING OF EXCITATORY ACTIONS, ROLE IN EPILEPSY, ANXIETY AND CONVULSION	

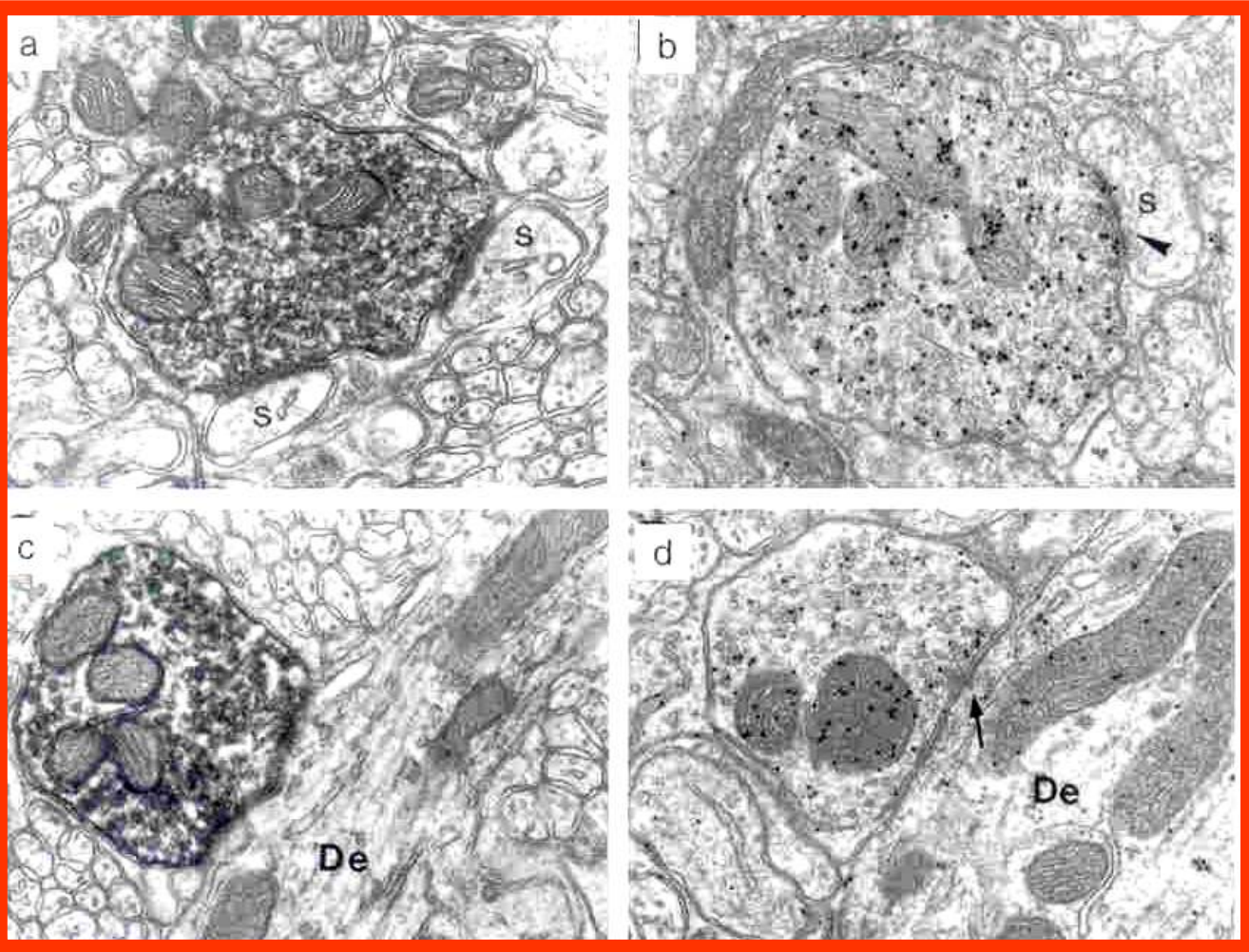
GABA SYNTHESIS AND METABOLISM

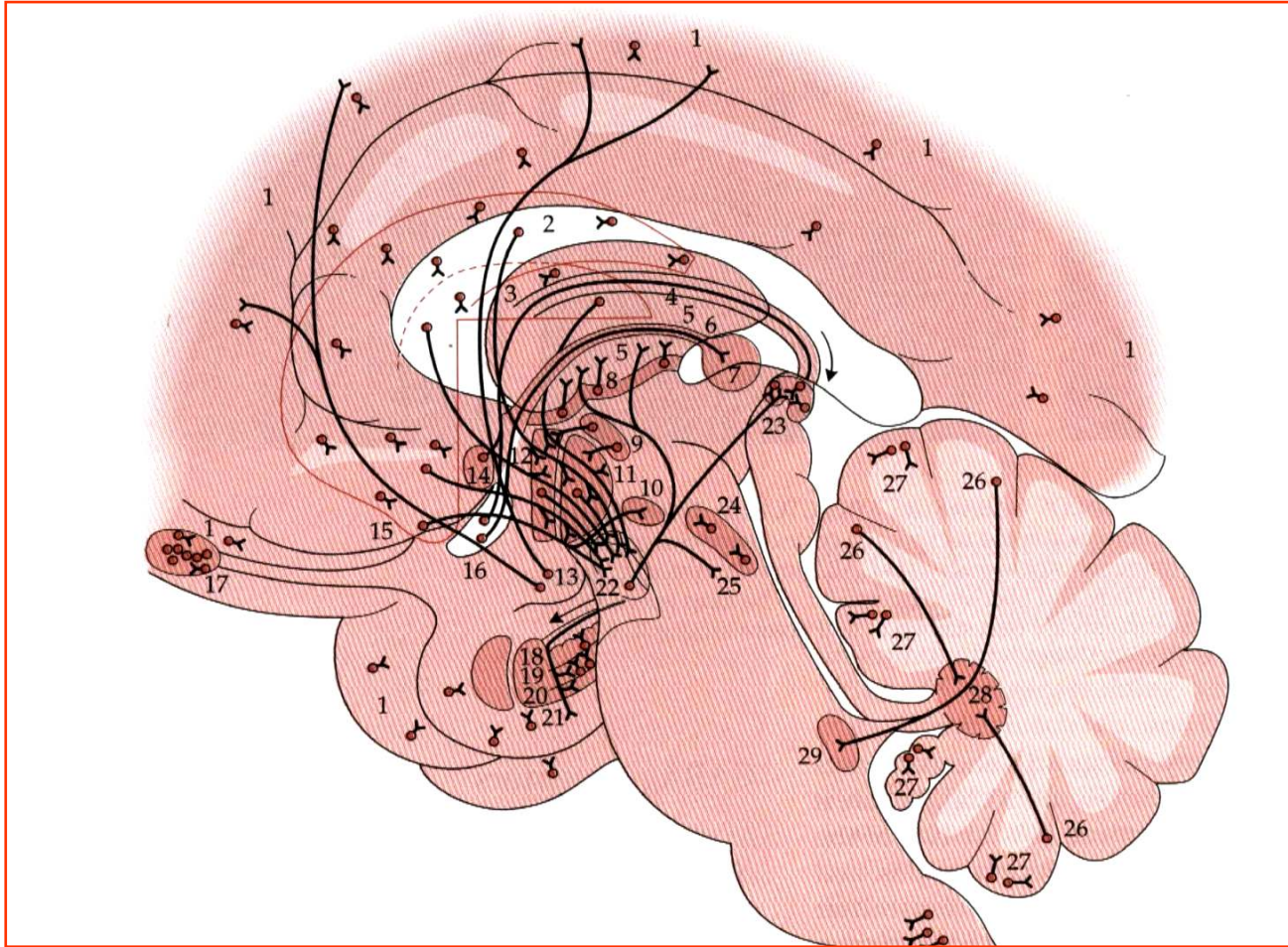


10.21 GABA SYNTHESIS AND METABOLISM. GABA is synthesized from glutamate by the enzyme glutamate decarboxylase (GAD). The breakdown of GABA is catalyzed by GABA aminotransferase (GABA-T), which forms succinic semialdehyde and regenerates the precursor glutamate from α -ketoglutarate (α -KG). Most of the succinic semialdehyde is converted to succinate, a citric acid cycle intermediate. This pathway is therefore often called the GABA shunt because it provides an alternate route (other than the citric acid cycle) by which succinate can be formed from α -KG.



GABAergic synapse





Basics of Neurobiology: Neurotransmitters I.

ATTRIBUTES	DESCRIPTION	
NAME	GLYCINE	
CHEMICAL NAME, STRUCTURE	AMINOETHANOIC ACID	
SYNTHESIS	DERIVATIVE OF:	SERINE
	SYNTHESIZING ENZYMES	SERINE HYDROXYMETHYLTRANSFERASE
	REGULATION	ENDPRODUCT
STORAGE	CELLULAR STRUCTURE TRANSPORTER	SYNAPTIC VESICLE VGAT/VIAAT
RELEASE	BY EXOCYTOSIS	
INACTIVATION	CONVERTED TO GLUTATHIONE, GLYCINE TRANSPORTERS (GLYT1 and GLYT2)	
RECEPTORS	CHLORIDE CHANNEL	
EXPRESSION IN BRAIN	MOST STUDIES IN THE SPINAL CORD, BRAIN IS A RISING FIELD	
SIGNIFICANCE	GENERAL INHIBITION AND COUNTERBALANCING OF EXCITATORY ACTIONS	

