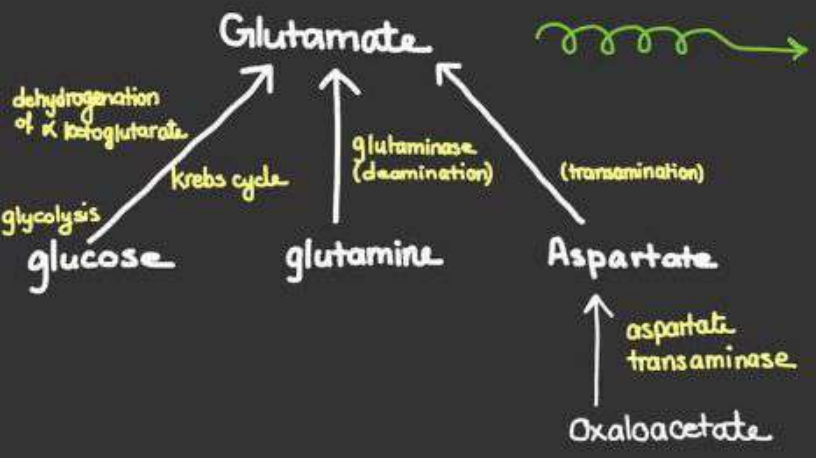
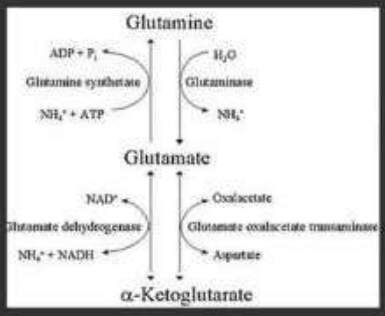
Glutamate & Aspartate

→ non essential amino acids
→ do not cross BBB (must be synthesized in neurons + glial cells)
→ excitatory neurotransmitters

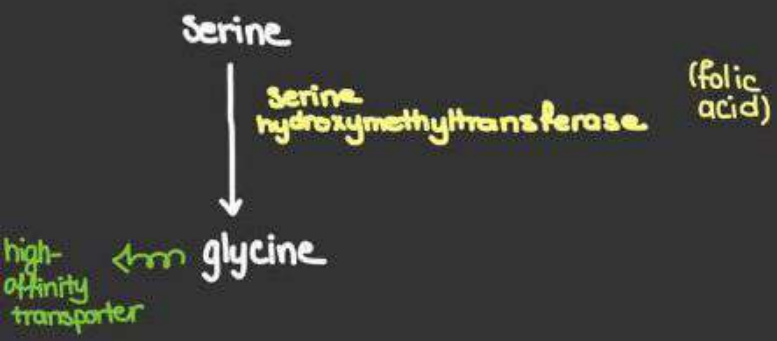


removal by high-affinity uptake systems in nerve terminals & glial cells
① excitatory amino acid carrier-1 (EAAC1)
② glutamate transporter-1 (GLT-1) & glutamate-aspartate transporter (GLAST)



Glycine

→ major inhibitory neurotransmitter in the spinal cord



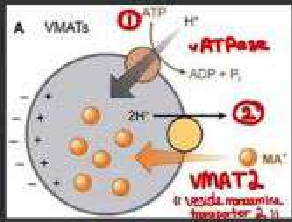
GABA

→ major inhibitory neurotransmitter of CNS (present in high con. in many brain regions)

GABA shunt (dual purpose of producing & conserving the supply)

Tyrosine – Derived Neurotransmitters

→ packaging of catecholamines into vesicles
↳ dopamine + NE



degredation may start with MAO and continue with COMT
أو العكس
→ Homovanillic acid (HVA)
SAM, vit B12, Folate يحتاج لـ

diet\ liver ↓ Phenylalanine hydroxylase ↓

tyrosine

↓ Cytosol — Rate limiting step !! — **tyrosine hydroxylase** (tetrahydrobiopterin) BH_4

DOPA

↓ cytosol — **DOPA decarboxylase** (pyridoxal phosphate) vit B6

Dopamine

↓ storage vesicles — **dopamine β-hydroxylase**

Norepinephrine

↓ leaking ((cytosol)) — **phenylethanolamine N-methyl transferase** (S-adenosylmethionine, vit B12 or folate)

Epinephrine

1- reuptake
2- liver [MAO, COMT]
3- postsynaptic neuron [COMT]
4- mitochondria [MAO]

Parkinson's disease
dopamine↓ ⇝ HVA↓

Regulation:

Short term
⊖ free cytosolic catecholamines
compete with BH_4 binding
⊕ depolarization
tight binding of BH_4 following phosphorylation by PKA, CAM kinase, PKC

long term
↑ amount of tyrosine hydroxylase & dopamine β-hydroxylase

Tryptophan – Derived Neurotransmitters

tryptophan

↓ **tryptophan hydroxylase** (BH_4)

5-hydroxy tryptophan

↓ **aromatic amino acid decarboxylase**

5-hydroxy tryptamine (Serotonin) — Doesn't cross BBB

antidepressants (SSRIs) ⊖ →
1- reuptake (plasma membrane Sertonin transporter SERT)
2- MOA ⇝ 5-hydroxy indoleacetic acid ⇝ urine

↓ in the pineal gland (SAM)

Melatonin
Sleep patterns
Seasonal & circadin rhythms
dark-light cycle

Acetylcholine

major neurotransmitter at NMJ

acytel group-CoA + choline ← diet \ membrane PL

pyruvate dehydrogenase

glucose → oxidation → Pyruvate → decarboxylation → acytel-CoA

choline acetyl-transferase

CoA

Cytoplasm

Ach

Sarin nerve gas ⊖ → acytelcholinestarse [paralysis]

acetic acid + choline

re uptake

Histamine

→ doesn't penetrate BBB (must be synthesized in the brain)

→ activates both postsynaptic & presynaptic receptors

Histidine → Histamine

histidine decarboxylase (Pyridoxal phosphate)

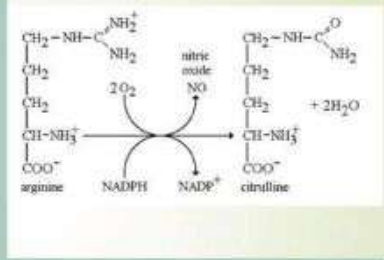
no recycling \ reuptake into presynaptic terminal

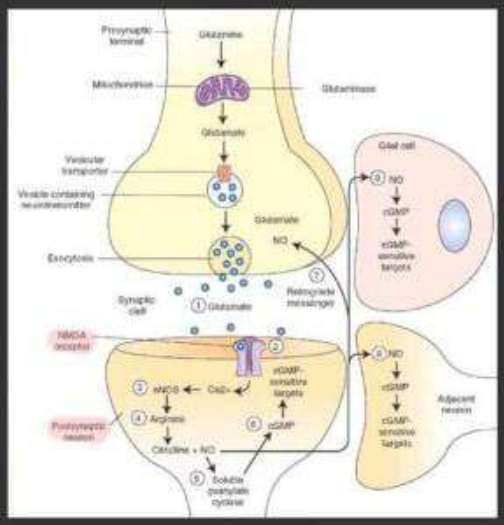
histamine methyltransferase → oxidation by MAO-B (brain)

diamine oxidase (histaminase) (periphral tissues)

NO

- Isoform I (nNOS or cNOS)
  - Neurons and epithelial cells
  - activated by the influx of extracellular calcium
- isoform II (iNOS)
  - Macrophages and smooth muscle cells
  - induced by cytokines
- and isoform III (eNOS)
  - Endothelial cells lining blood vessels
  - activated by the influx of extracellular calcium
- All three isoforms require BH2 as a cofactor and nicotinamide adenine dinucleotide phosphate (NADPH) as a coenzyme





not stored in vesicles, not released by Ca-dependent exocytosis (it diffuses), decays spontaneously, doesn't interact with receptors, retrograde messenger