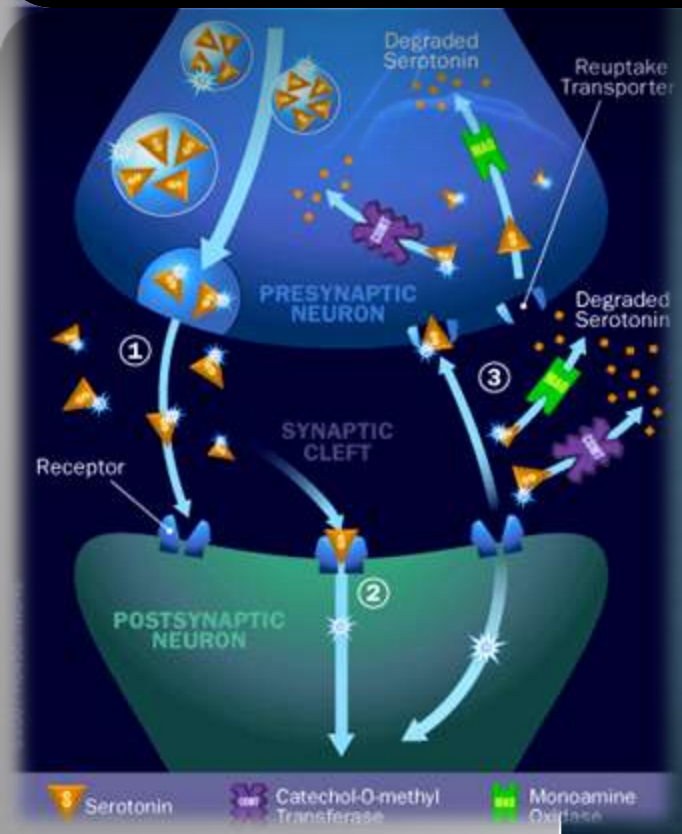


NEUROTRANSMITER

Disusun oleh:

Dr. Dian Apriliana R, M.Med.Ed.

SASARAN PEMBELAJARAN

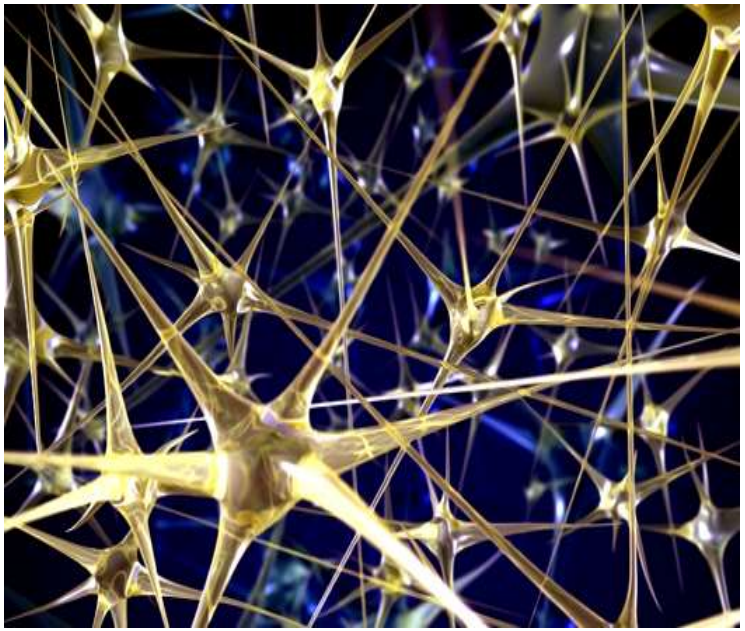
- Menjelaskan definisi dan persyaratan neurotransmitter
- Menjelaskan biosintesis dan biodegradasi neurotransmitter
- Mengetahui kaitan gangguan biosintesis dan biodegradasi neurotransmitter dengan kondisi klinis pasien

PENDAHULUAN

- Apa fungsi otak?
- Bagaimana otak bisa mengendalikan tubuh kita?
- Tersusun atas apa saja?

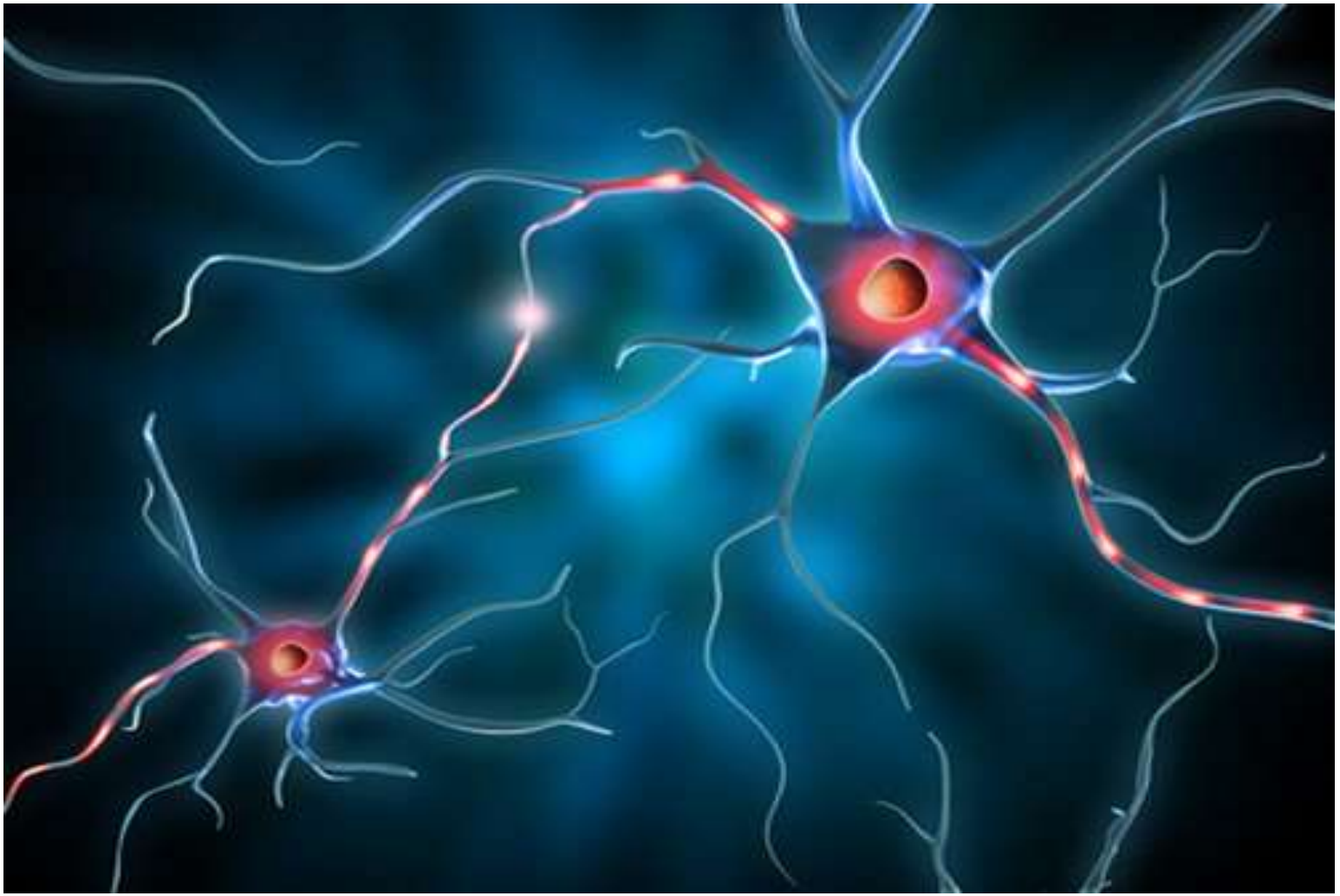
Baca : Anatomi, Histologi dan Fisiologi Sistem Saraf

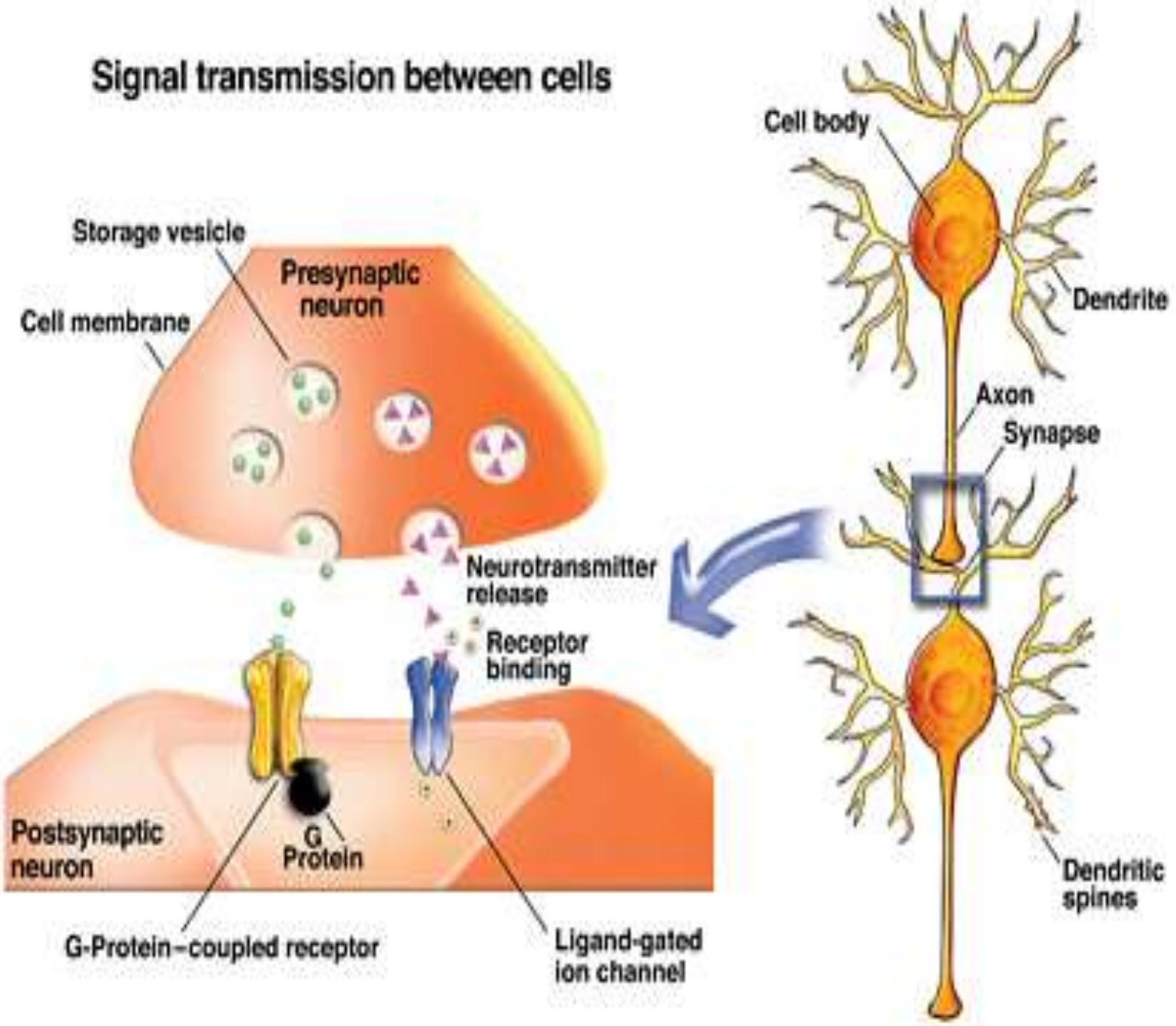
STRUKTUR OTAK



- 15 – 33 milyar neuron
- saling terhubung melalui synaps
- bagaimana cara mereka berkomunikasi?

BAGAIMANA NEURON BERKOMUNIKASI?




Signal transmission between cells
Storage vesicle
Presynaptic neuron
Cell membrane
Neurotransmitter release
Receptor binding
Postsynaptic neuron
G Protein
G-Protein–coupled receptor
Ligand-gated ion channel
Cell body
Dendrite
Axon
Synapse
Dendritic spines

- Mekanisme penghantaran

  impuls pada saraf tidak sesederhana rangkaian kabel-kabel berarus, namun berupa sekumpulan saraf-saraf halus yang teratur rapi (yang termyelinasi pada vertebrata) yang melibatkan transportasi ionik transmembran sebagai pemicu gelombang depolarisasi.
- Gelombang depolarisasi inilah yang berperan seperti layaknya arus listrik untuk memicu kontraksi otot

SYARAT-SYARAT NEUROTRANSMITER

1. Disintesis di neuron presinaps
2. Terdapat di axon terminal neuron presinaps
3. Apabila ada stimulus, maka molekul tersebut akan dilepaskan ke sinaps
4. Ada reseptor post-sinaps atau zat kimia lain yang dapat mengikat molekul tersebut
5. Memiliki mekanisme inaktivasi , yaitu untuk menghilangkan atau mendegradasi molekul tersebut dari sinaps

KLASIFIKASI

- Biogenic Amines:
  - Acetylcholine
  - Monoamine:
    - Catecholamine: Dopamine, Norepinephrine, Epinephrine
    - Serotonin
- Amino Acids : Glutamate, GABA, Glycine
- Neuropeptides:
  - Substance P
  - Opioid neuropeptid: endorphin, enkephaline
- Nitric Oxides (Gas)

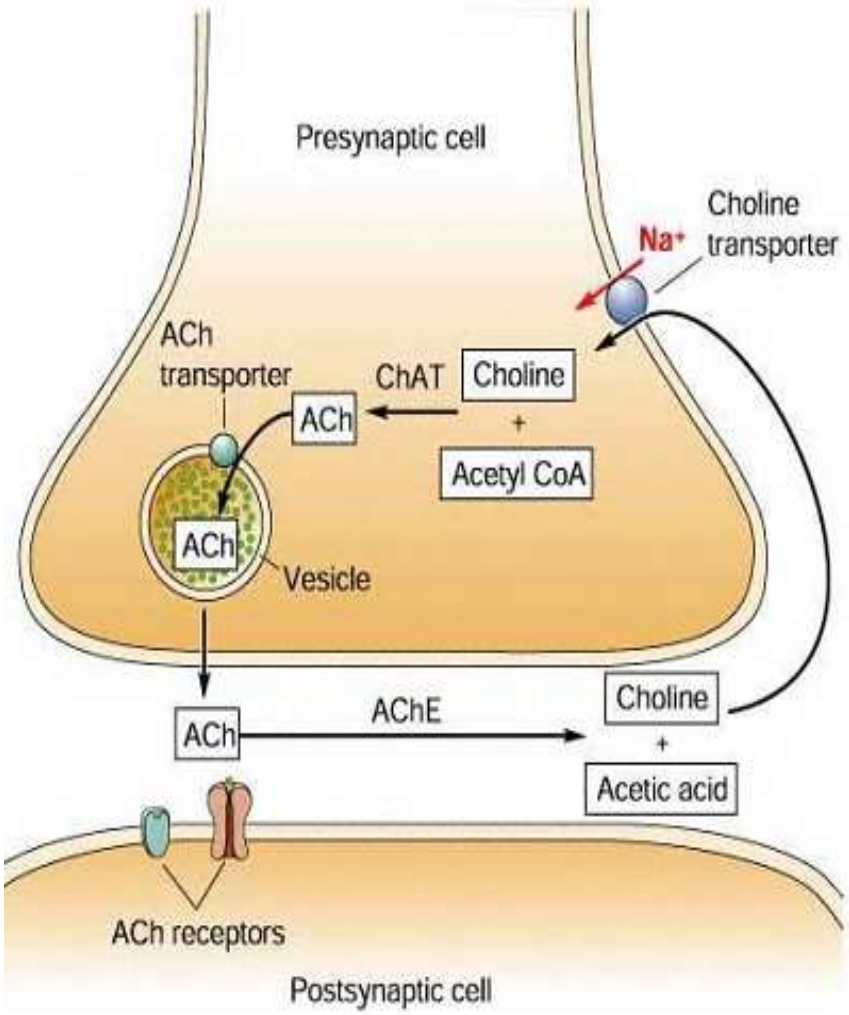
ACETYLCHOLINE

Sintesis

- Prekursor :
  - Choline
  - Acetyl CoA
- Enzyme : Choline acetyltransferase (ChAT)
- Vesicular Ach transporter

Degradasi

- Enzyme: Acetylcholine esterase
- Uptake: Choline transporter



ACETYLCHOLINE

Diproduksi di:

A. Saraf Perifer

- Saraf Motorik → kontraksi otot skelet
- Saraf Simpatis : pre-ganglionic neuron
- Saraf Parasimpatis : pre dan post-ganglionic neuron

B. Saraf Pusat:

- Otak → memori (daya Ingat) dan
- Defisiensi ACh berhubungan dengan kejadian Alzheimer

Toxin Botulinus yang dihasilkan oleh *Clostridium botulinum* dapat menghambat pelepasan Ach

RESEPTOR

- **Nicotinic (nAChR)**
  - Terdapat di seluruh neuromuscular junction (NMJ), ganglion saraf otonom, saraf pusat (sedikit)
  - Dapat diaktivasi oleh nikotin dan asetilkolin.
  - Diblok oleh curare dan hexamethonium
  - Kerusakan nAChR pd NMJ oleh antibodi → Myastenia Gravis

- **Muscarinic (mAChR)**
  - Terdapat di saraf pusat dan post-ganglion saraf parasimpatis
  - Distimulus oleh muskarin dan asetilkolin
  - Diblok oleh atropin

KASUS

Seorang petani mengalami keracunan pestisida yang ditandai dengan kejang-kejang seluruh tubuh.

Mengapa bisa terjadi kejang?

Organophosphate/ pestisida menghambat kerja enzym Acetylcholin esterase

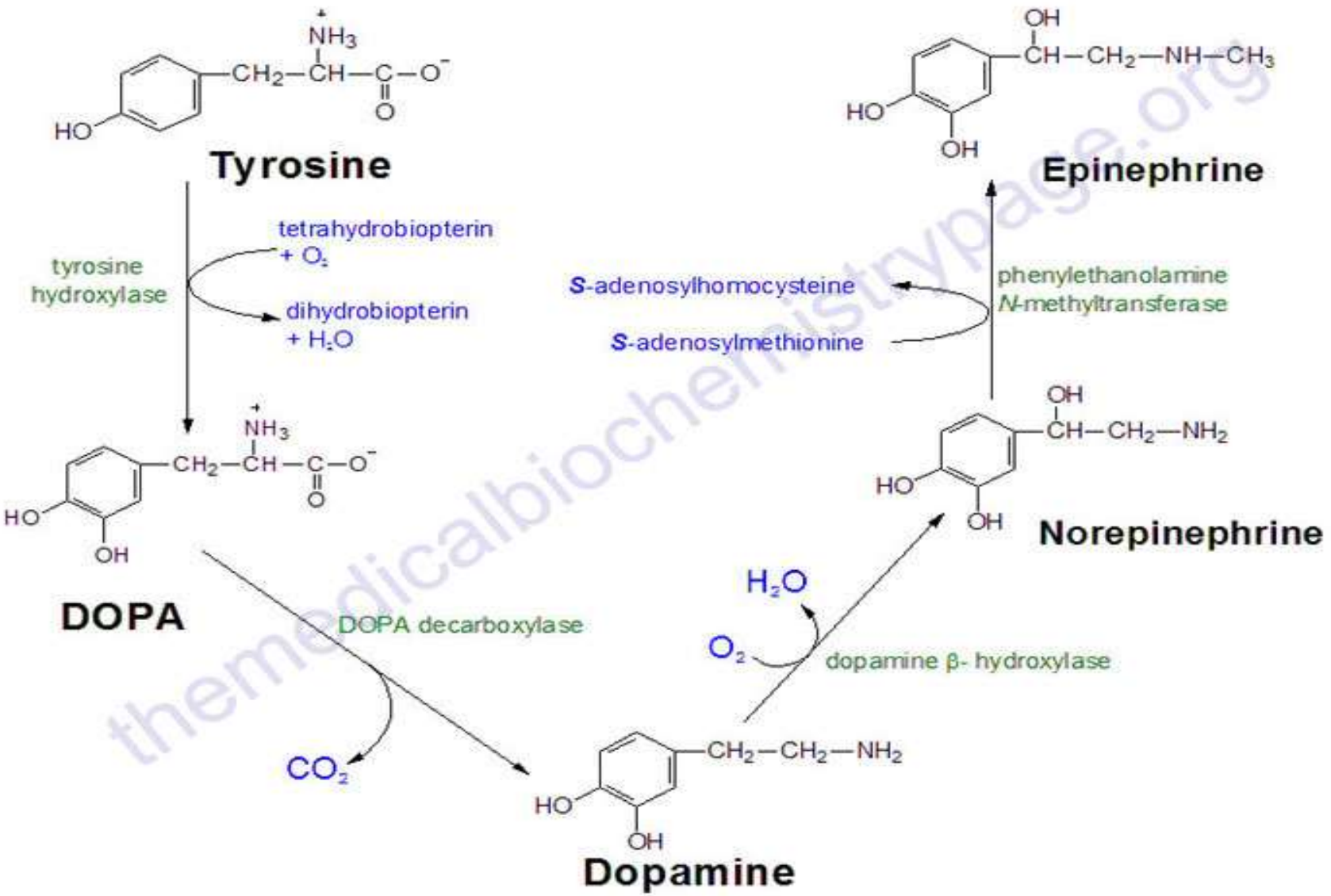
CATECHOLAMINE

- Dopamine
- Norepinephrine
- Epinephrine

- Jalur sintesis dan struktur yang sama
- Vesicular transporter dan reuptake transporter sama
- Jalur degradasi sama

- Precursor: asam amino Tyrosine yang banyak terdapat pada daging, kacang, telur dan keju.
- Memerlukan enzym Tyrosin Hydroxylase. Aktifitas enzym Tyrosin Hydroxylase memerlukan Tetrahydrobiopterin sebagai cofaktor.

SINTESIS



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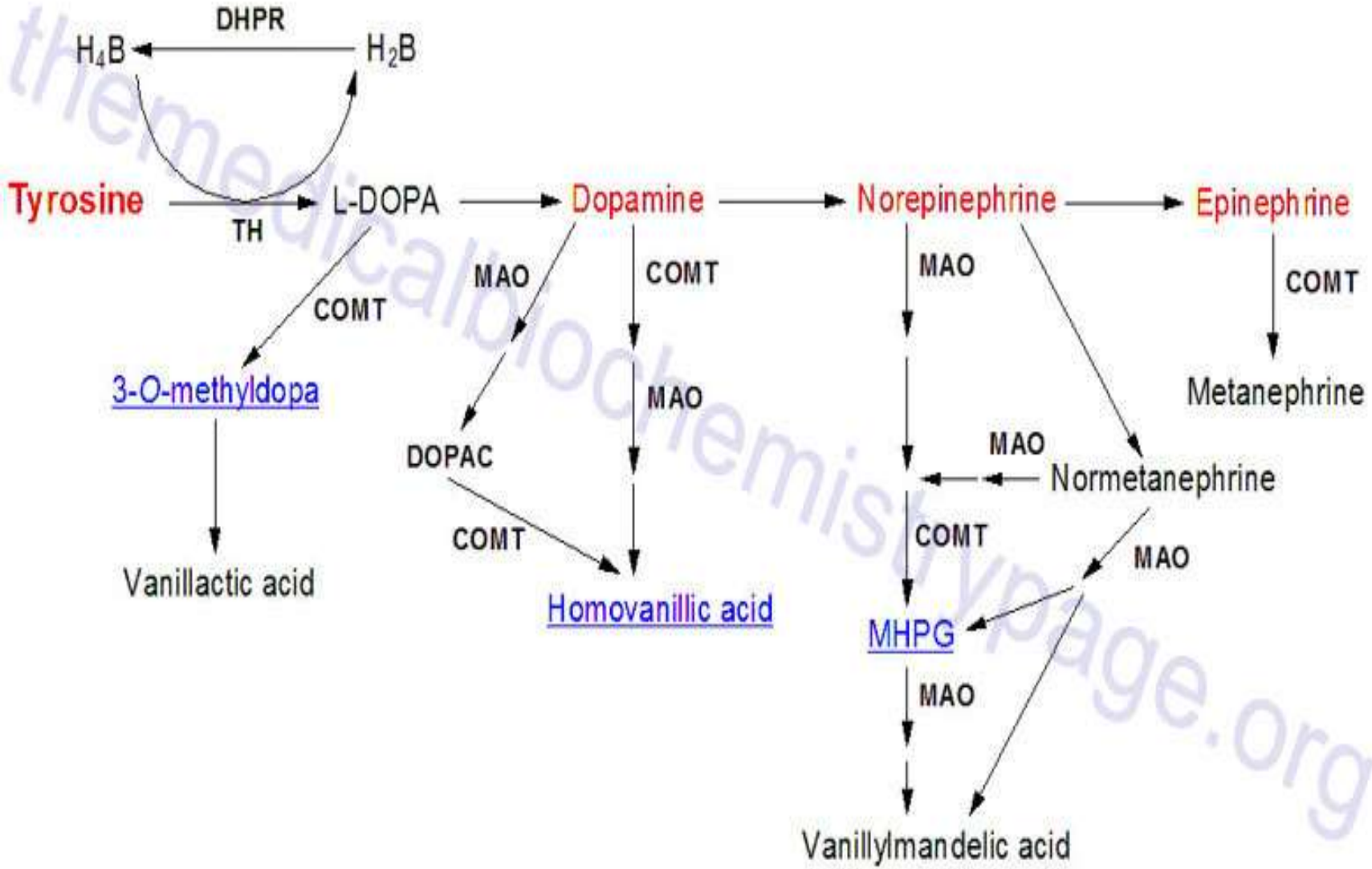
METABOLISME CATECHOLAMINE



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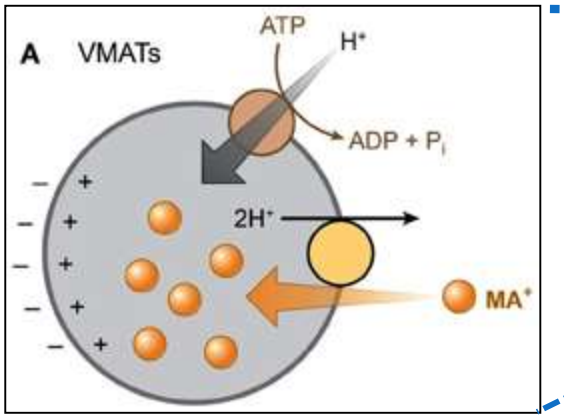
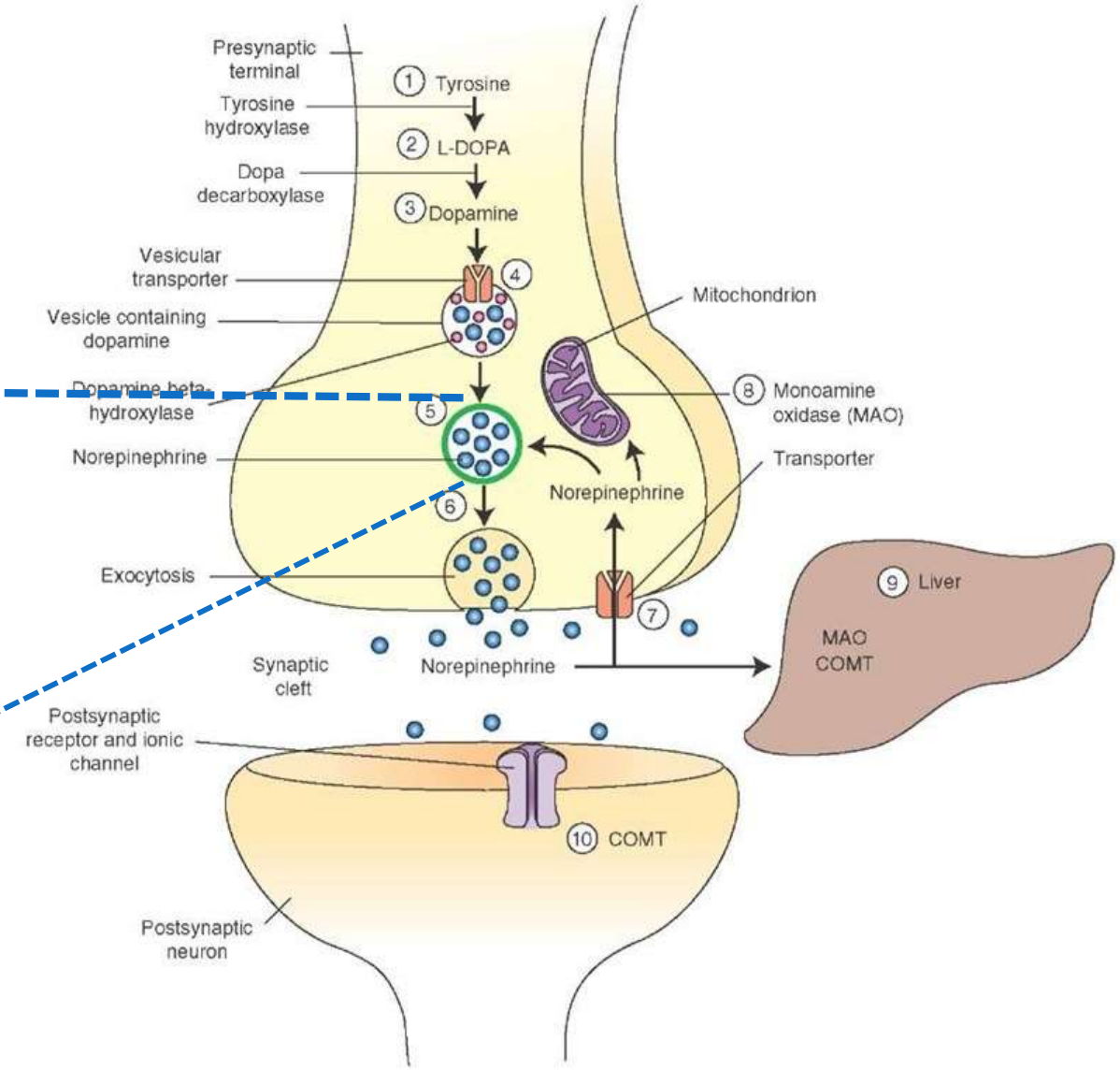
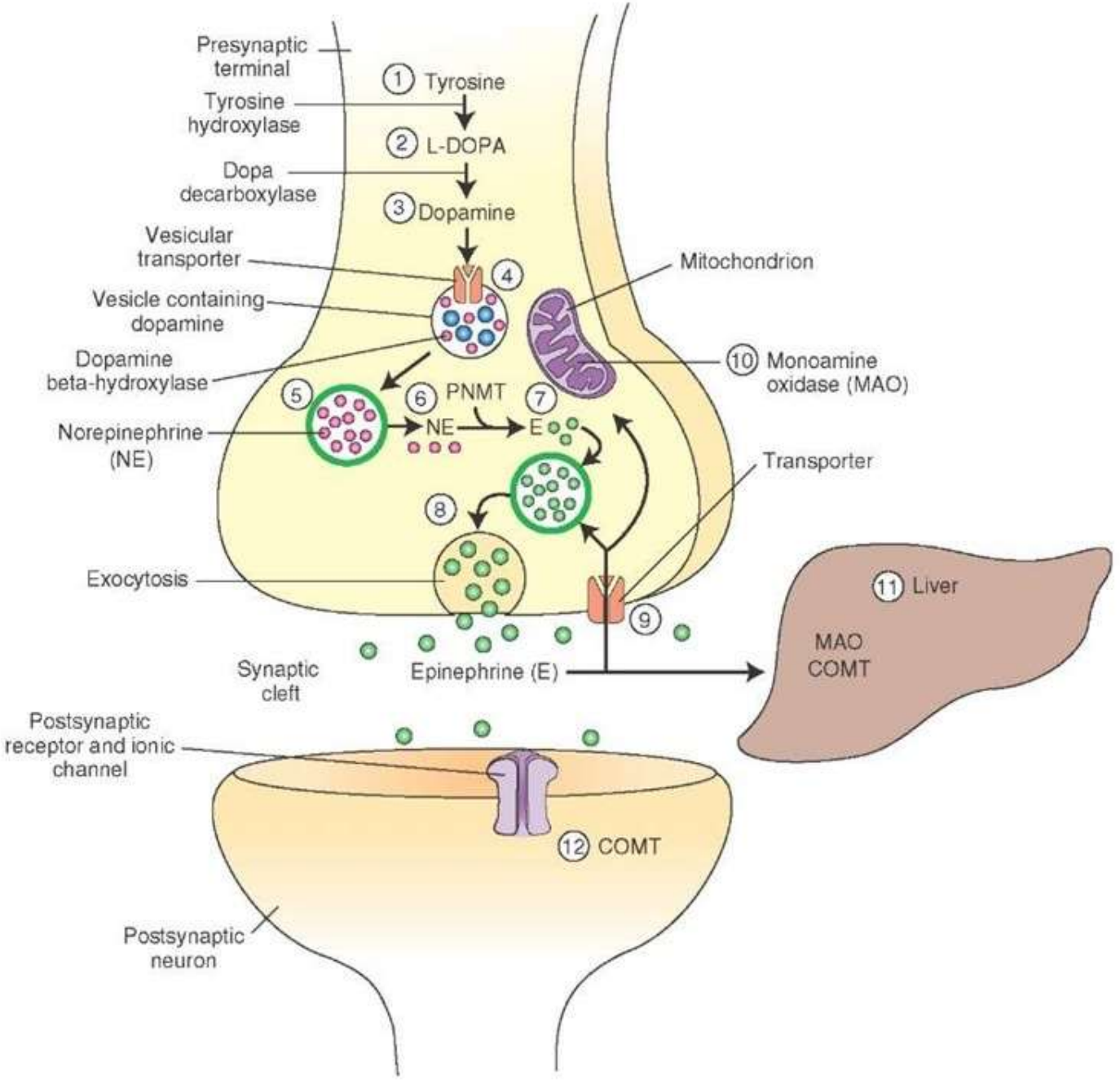
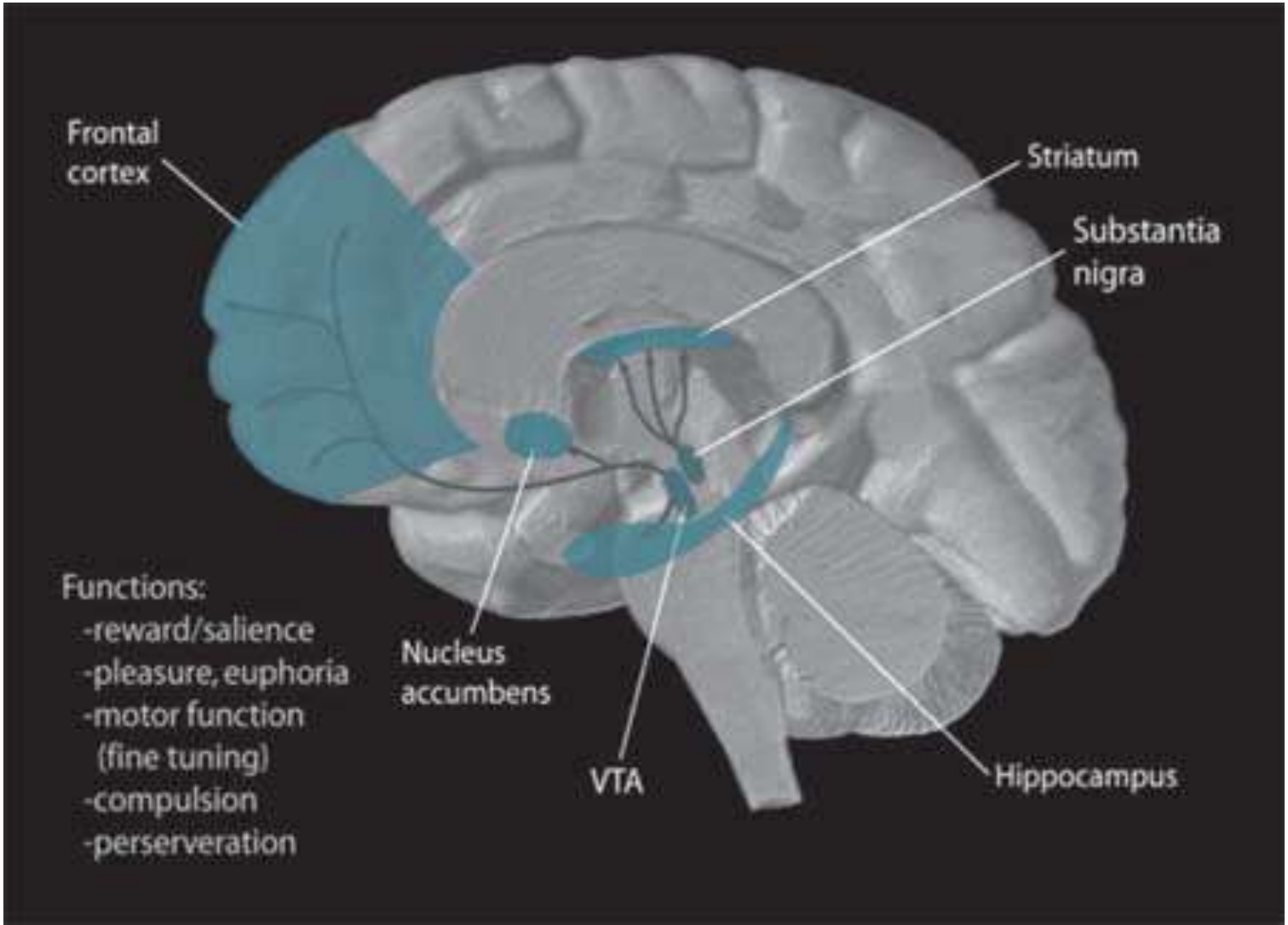
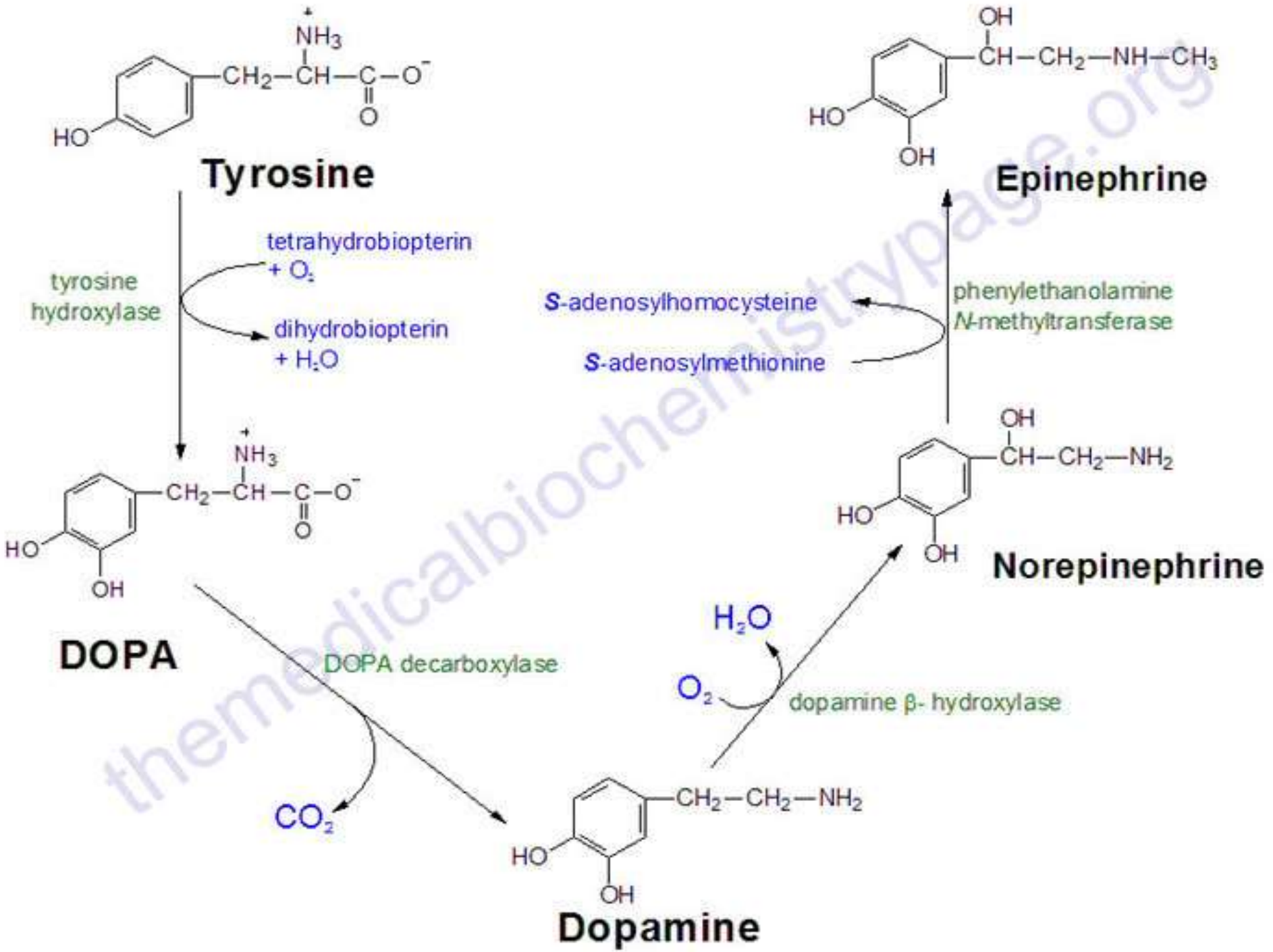

A VMATs
ATP
H+
ADP + Pi
2H+
MA+


Presynaptic terminal
1 Tyrosine
Tyrosine hydroxylase
2 L-DOPA
Dopa decarboxylase
3 Dopamine
Vesicular transporter
4
Vesicle containing dopamine
Mitochondrion
Dopamine beta-hydroxylase
5
8 Monoamine oxidase (MAO)
Norepinephrine
Transporter
Norepinephrine
6
Exocytosis
9 Liver
MAO
COMT
7
Synaptic cleft
Norepinephrine
Postsynaptic receptor and ionic channel
10 COMT
Postsynaptic neuron


Presynaptic terminal
Tyrosine hydroxylase
Dopa decarboxylase
Vesicular transporter
Vesicle containing dopamine
Dopamine beta-hydroxylase
Norepinephrine (NE)
Exocytosis
Synaptic cleft
Postsynaptic receptor and ionic channel
Postsynaptic neuron
1 Tyrosine
2 L-DOPA
3 Dopamine
4
5
6 PNMT
7
NE
E
8
9
Epinephrine (E)
10 Monoamine oxidase (MAO)
Mitochondrion
Transporter
11 Liver
MAO
COMT
12 COMT

DOPAMINE (DA)


Frontal cortex
Striatum
Substantia nigra
Functions:
-reward/salience
-pleasure, euphoria
-motor function (fine tuning)
-compulsion
-perserveration
Nucleus accumbens
VTA
Hippocampus



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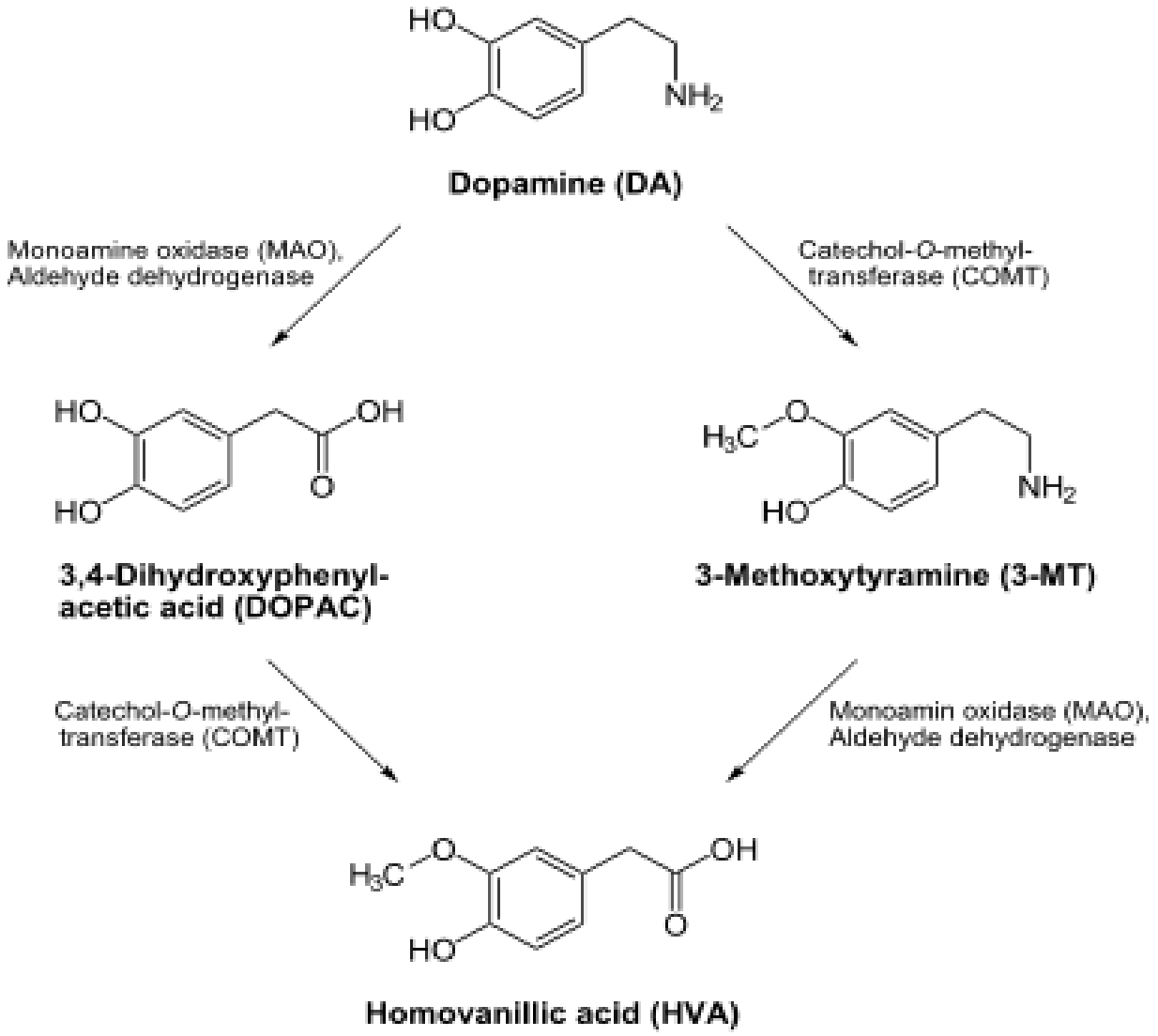
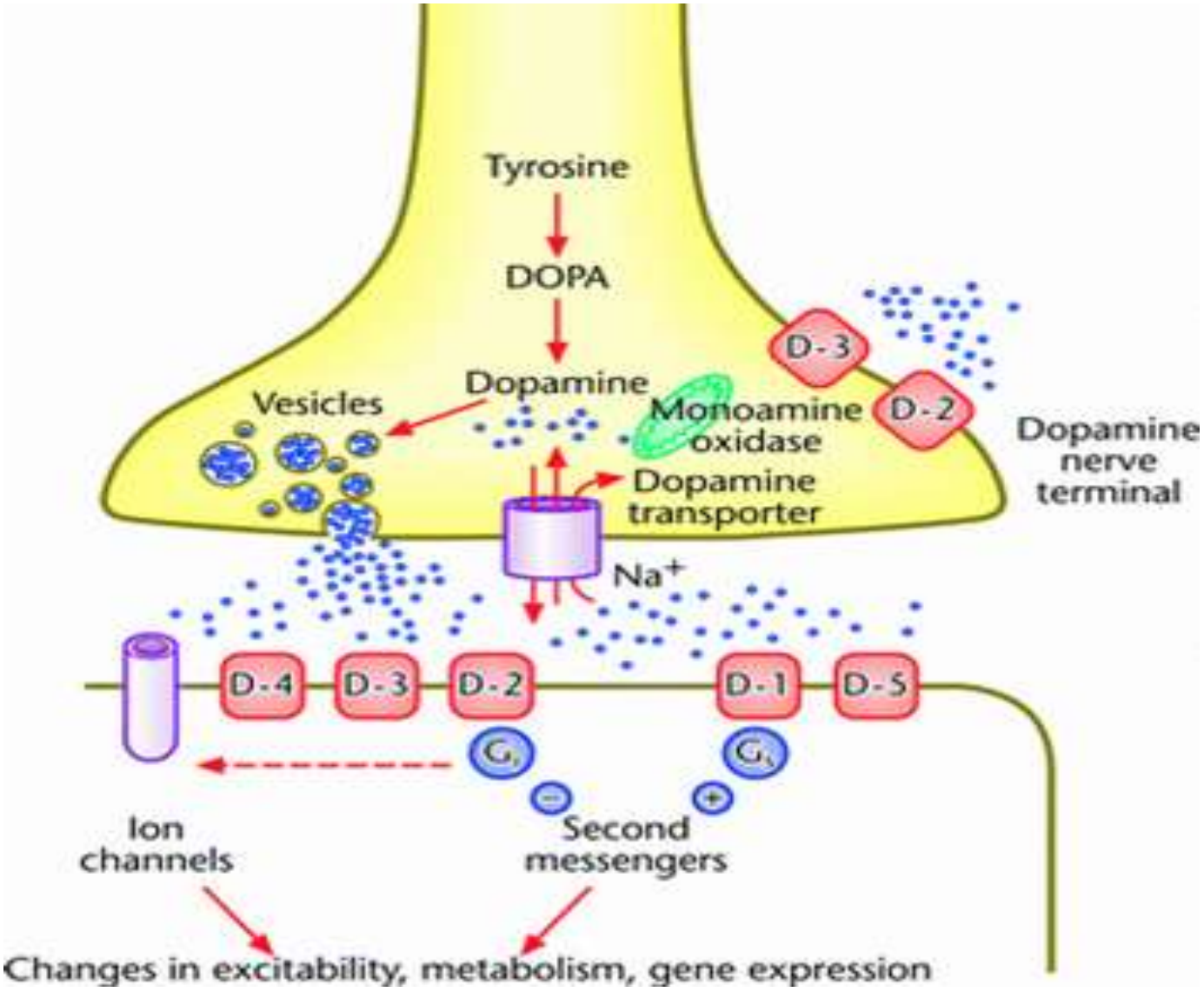
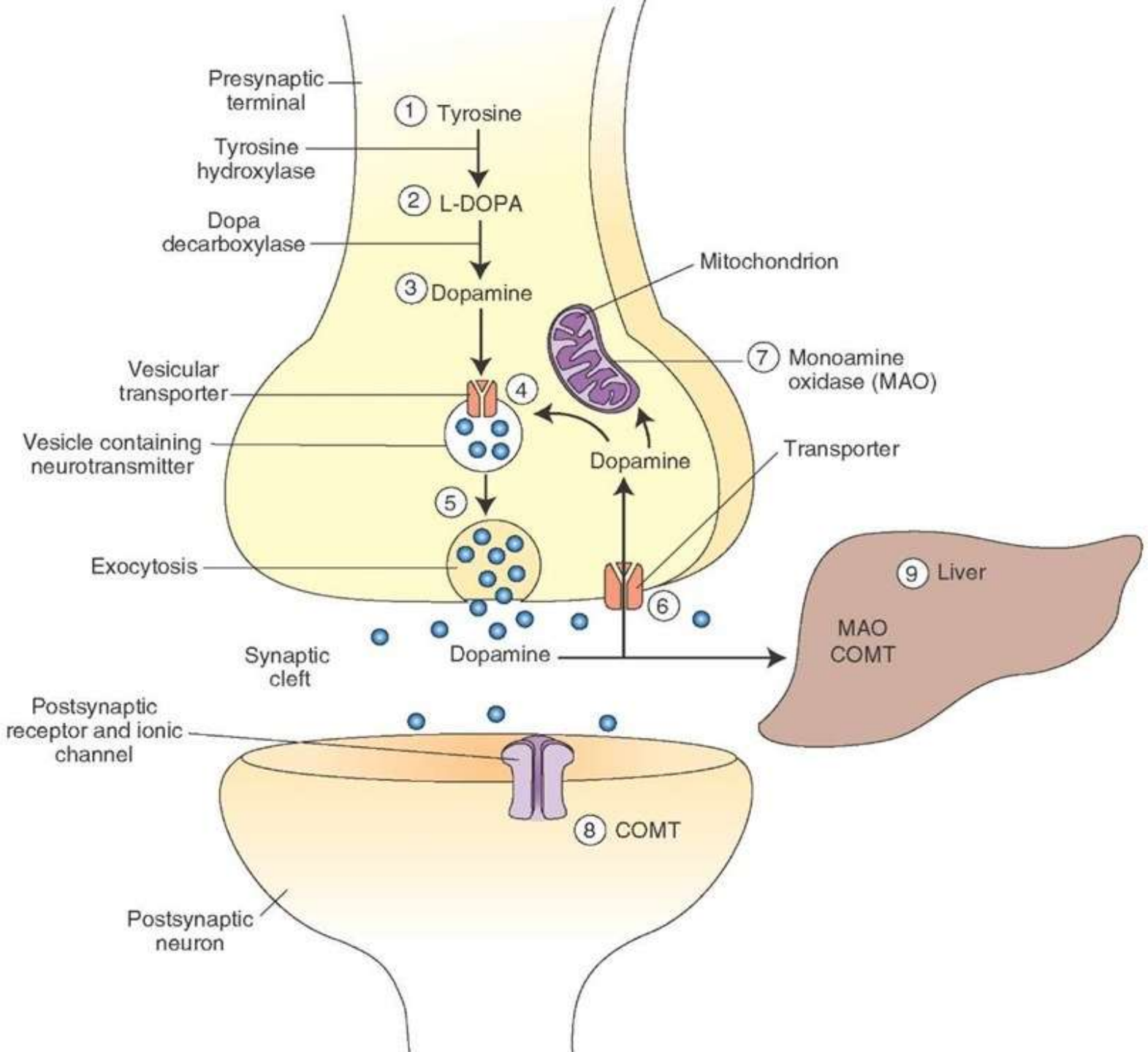
DEGRADASI


HO
HO
NH2
Dopamine (DA)
Monoamine oxidase (MAO),
Aldehyde dehydrogenase
Catechol-O-methyl-
transferase (COMT)
HO
HO
OH
O
3,4-Dihydroxyphenyl-
acetic acid (DOPAC)
H3C
O
HO
NH2
3-Methoxytyramine (3-MT)
Catechol-O-methyl-
transferase (COMT)
Monoamin oxidase (MAO),
Aldehyde dehydrogenase
H3C
O
HO
OH
O
Homovanillic acid (HVA)

SINTESIS, PELEPASAN DAN DEGRADASI




Presynaptic terminal
1 Tyrosine
Tyrosine hydroxylase
2 L-DOPA
Dopa decarboxylase
3 Dopamine
Mitochondrion
7 Monoamine oxidase (MAO)
Vesicular transporter
4
Vesicle containing neurotransmitter
Dopamine
Transporter
5
Exocytosis
9 Liver
MAO
COMT
6
Synaptic cleft
Dopamine
Postsynaptic receptor and ionic channel
8 COMT
Postsynaptic neuron

FUNGSI

- Perilaku dan kognitif
- Motivasi
- Tidur
- Mood
- *Working* memori
- Pemusatan perhatian
- belajar
- Mengontrol gerakan motorik

JALUR DOPAMINERGIK SENTRAL

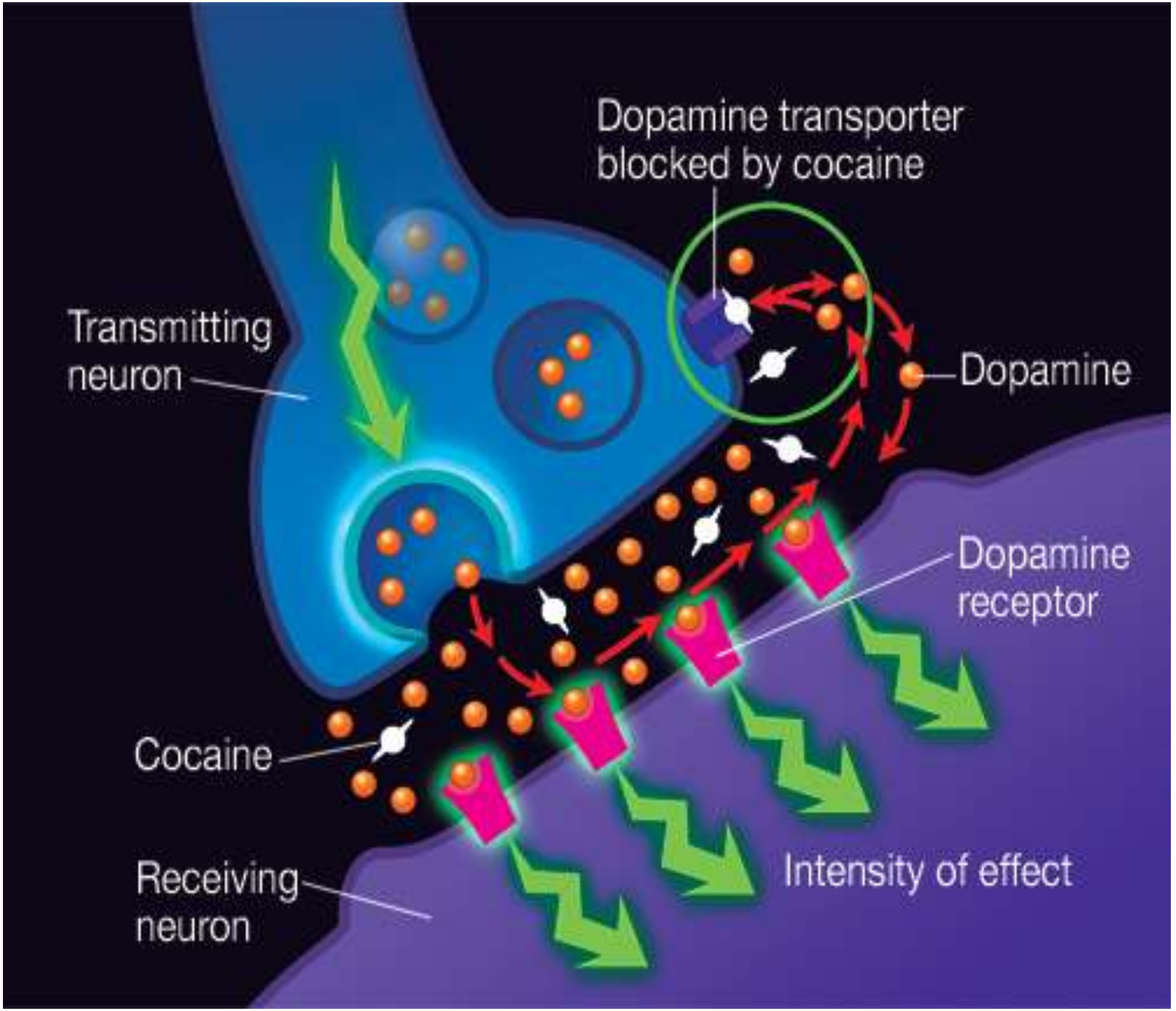
- Ada 4 jalur:
  1. Nigrostriatal
  2. Mesolimbik
  3. Mesocortical
  4. Tuberohypophysial

JALUR NIGROSTRIATAL

- DA pada jalur ini terlibat dalam inisiasi/ pengaturan gerak
- Reseptor D1/D2 berada di striatum
- Reseptor D1 memfasilitasi jalur langsung excitatorik
- Reseptor D2 memfasilitasi jalur langsung inhibitorik
- Menurunnya jumlah neuron dopaminergic di jalur nigrostriatal → Parkinson's disease

JALUR MESOLIMBIK & MESOCORTICAL

- Jalur Mesolimbik : Ventral Tegmentum Area (VTA) – Nucleus Accumbens
- Jalur Mesocortical : VTA – prefrontal/ orbitofrontal
- Fungsi:
  - Positive reinforcement behaviour : makan, minum, aktifitas seksual, penyalahgunaan obat-obatan
  - Cocaine dapat meningkatkan kadar dopamine di sinaps nucelus accumbens


Dopamine transporter
blocked by cocaine
Transmitting
neuron
Dopamine
Dopamine
receptor
Cocaine
Receiving
neuron
Intensity of effect

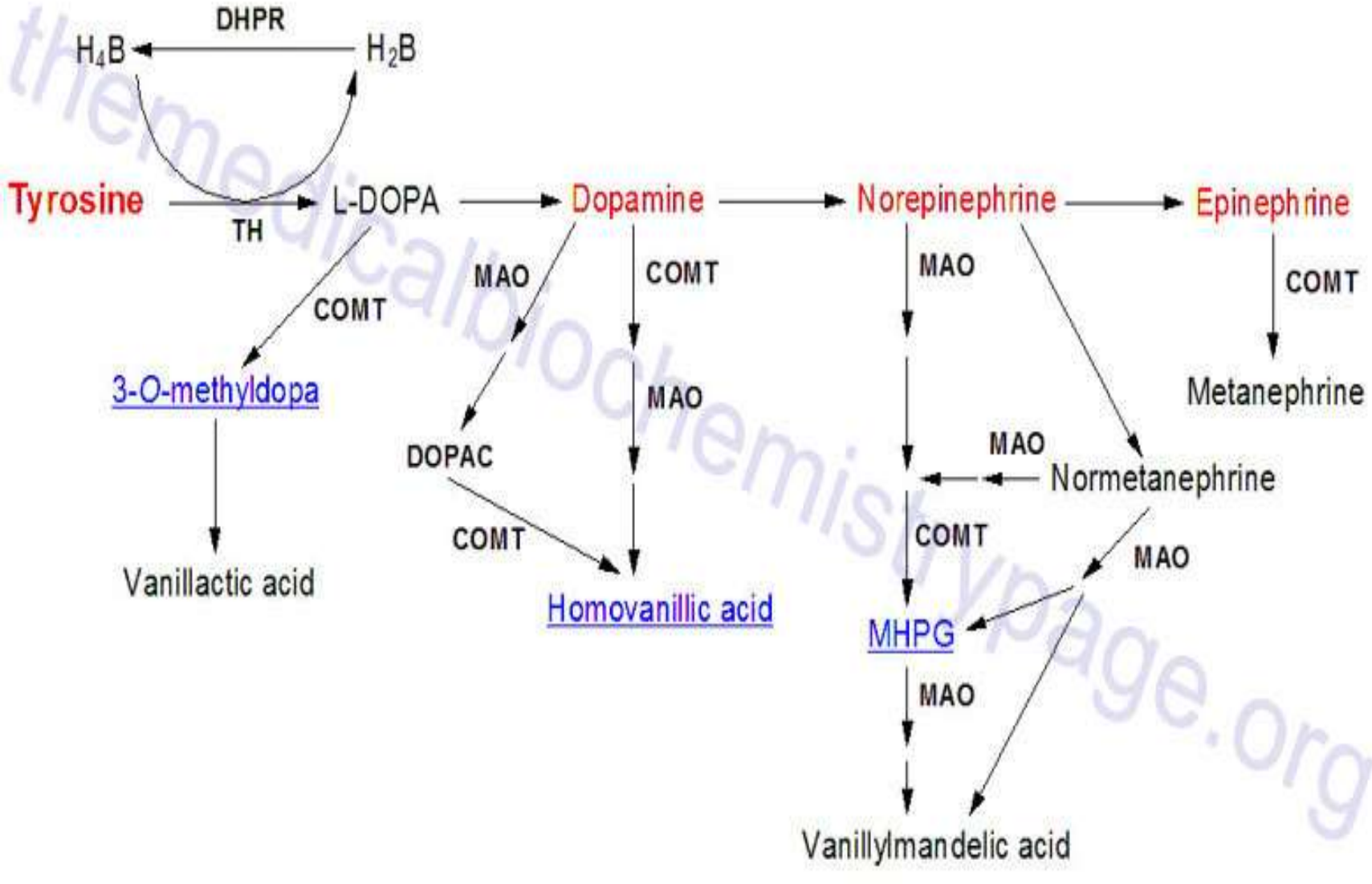
GANGGUAN KLINIS TERKAIT DENGAN DA

- Gangguan DA di daerah lobus frontal → gangguan memori/ daya ingat, perhatian dan pemecahan masalah
- Penurunan aktivitas DA → ADHD
- Peningkatan aktivitas DA di daerah jalur mesolimbik dan penurunan jumlah DA di kortek prefrontal → Schizofrenia

NOREPINEPHRINE/ EPINEPHRINE

- Disintesis di medulla adrenal dan post ganglionic saraf simpatis
- Dilepaskan saat tubuh mengalami stress → perubahan fisiologis
- Dikaitkan dengan fungsi : pengaturan mood, perhatian, emosi.
- Sedikit sekali sel saraf yang menggunakan NE/E sebagai neurotransmitter
- Inisiasi asetilkolin pada reseptor nicotinic asetilkolin post ganglionic → pelepasan NE/E
- Reseptor NE/E → reseptor adrenergik

DEGRADASI



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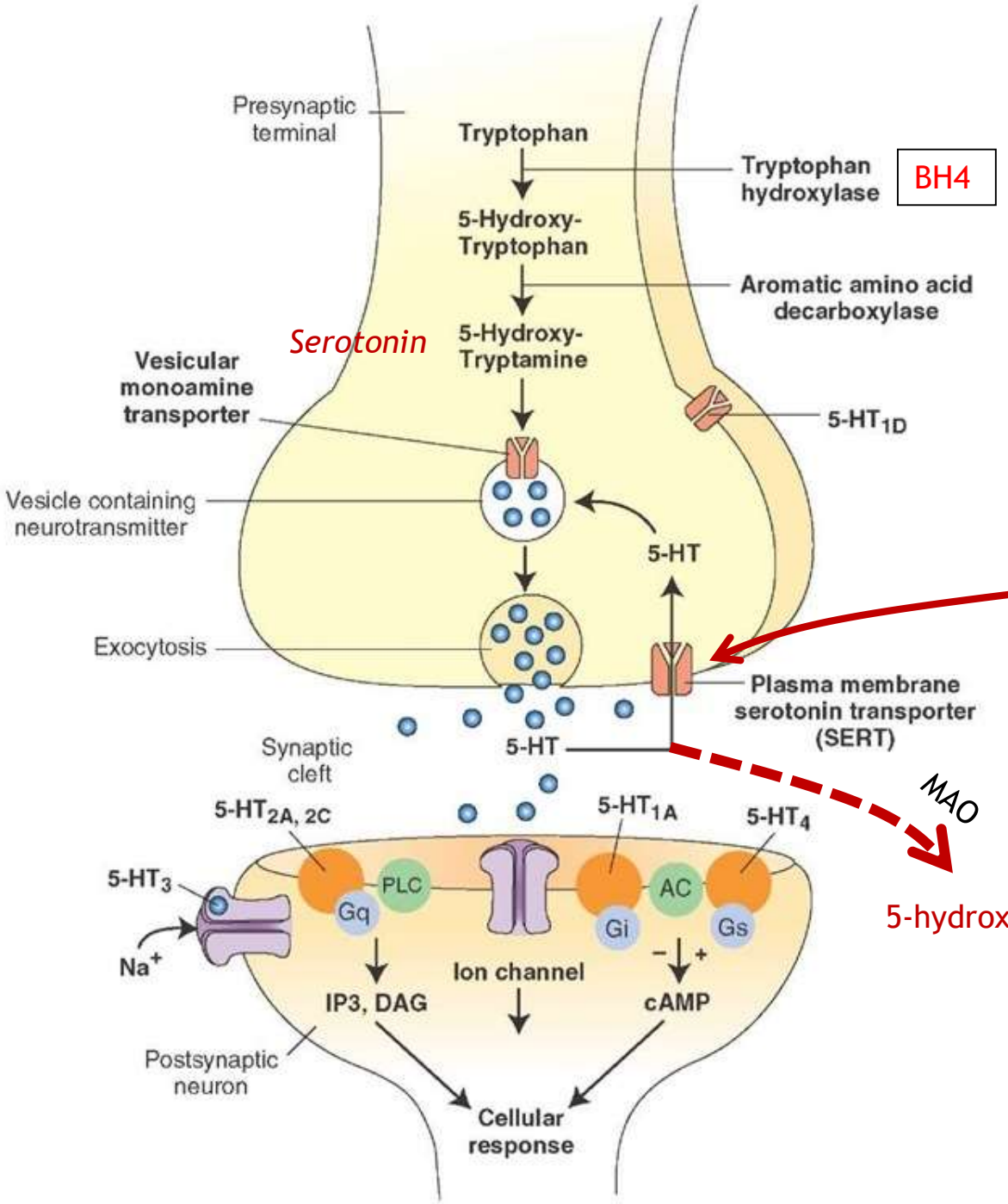
RESEPTOR

Receptor	Tissue	Response
α_1	Smooth muscle of blood vessels, iris, ureter, hairs, uterus, bladder	Contraction of smooth muscle
	Smooth muscle of gut	Relaxation of smooth muscle
	Heart muscle	Positive inotropic effect ($\beta_1 >> \alpha_1$)
	Salivary gland	Secretion
	Adipose tissue	Glycogenolysis, gluconeogenesis
	Sweat glands	Secretion
	Kidney	Na^+ reabsorbed
α_2	Adipose tissue	Inhibition of lipolysis
	Pancreas	Inhibition of insulin release
	Smooth muscle of blood vessels	Contraction
β_1	Heart muscle	Positive inotropic effect; positive chronotropic effect
	Adipose tissue	Lipolysis
	Kidney	Renin release
β_2	Liver	Glycogenolysis, gluconeogenesis
	Skeletal muscle	Glycogenolysis, lactate release
	Smooth muscle of bronchi, uterus, gut, blood vessels	Relaxation
	Pancreas	Insulin secretion
	Salivary glands	Thickened secretions

SEROTONIN

Efek dari serotonin

- Menurunkan nafsu makan
- Relaksasi/ menenangkan
- Memudahkan tidur
- Mengurangi rasa nyeri

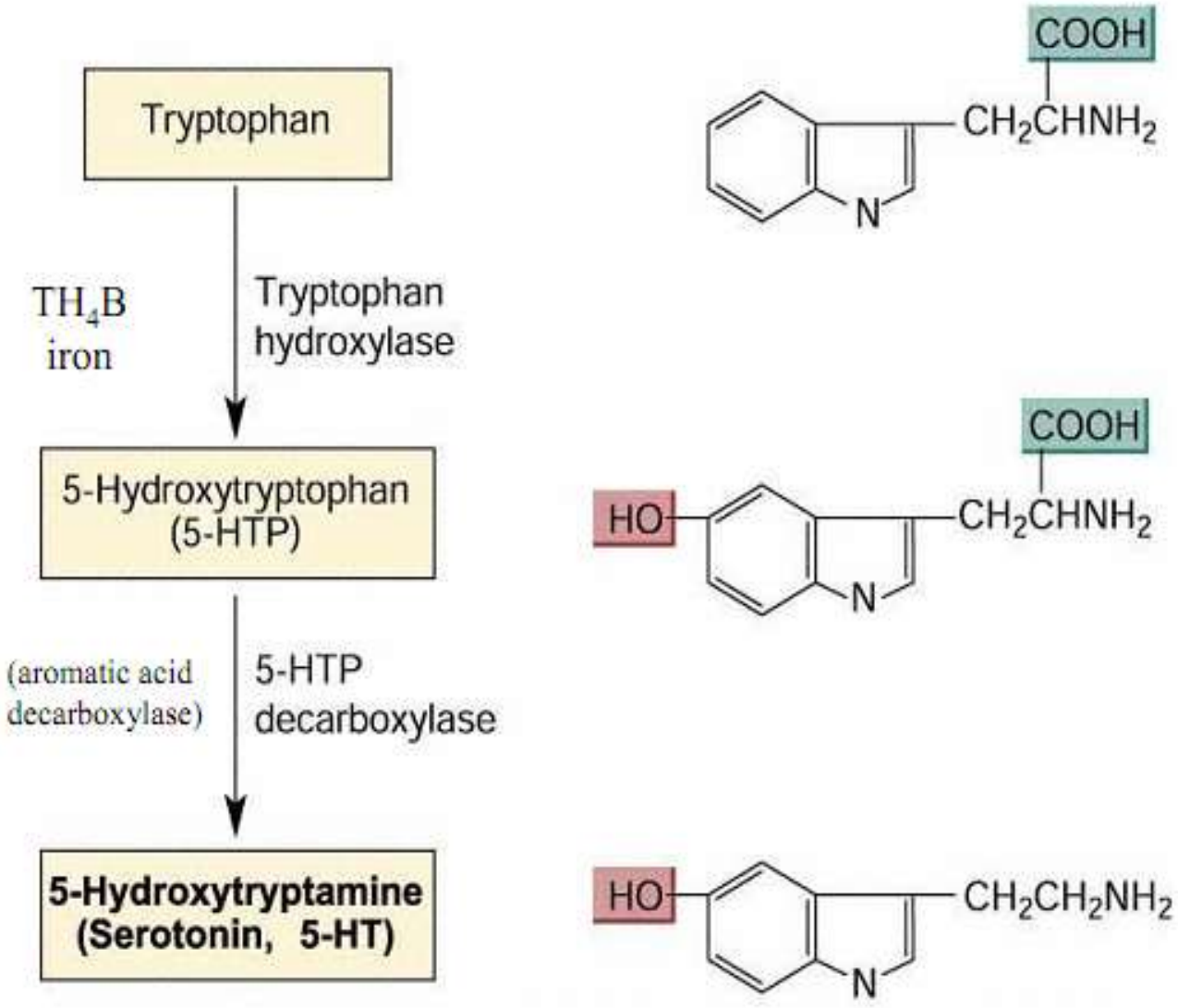


Antidepressants , called selective serotonin re-uptake inhibitors (SSRIs), like Prozac® inhibit the reuptake process resulting in prolonged serotonin presence in the synaptic cleft.

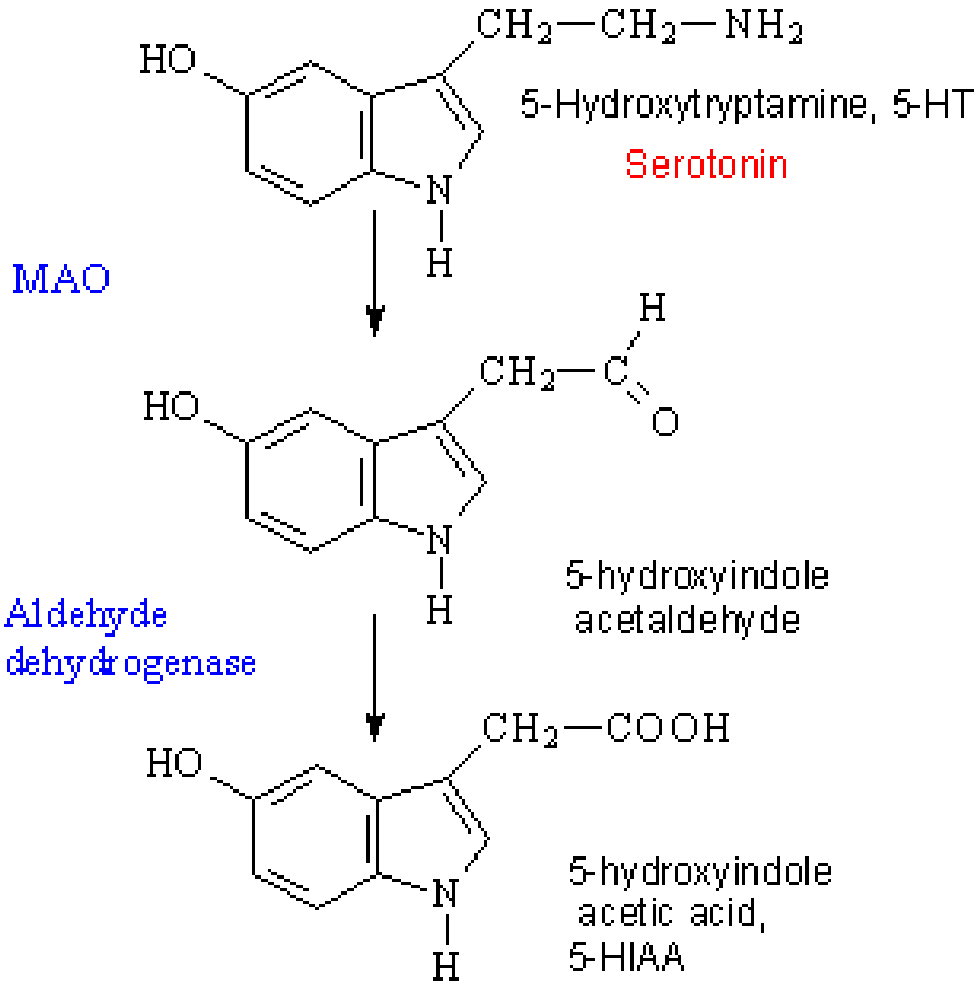
5-hydroxyindoleacetic acid

urine

Serotonin (5-HT) synthesis



DEGRADATION



FUNGSI

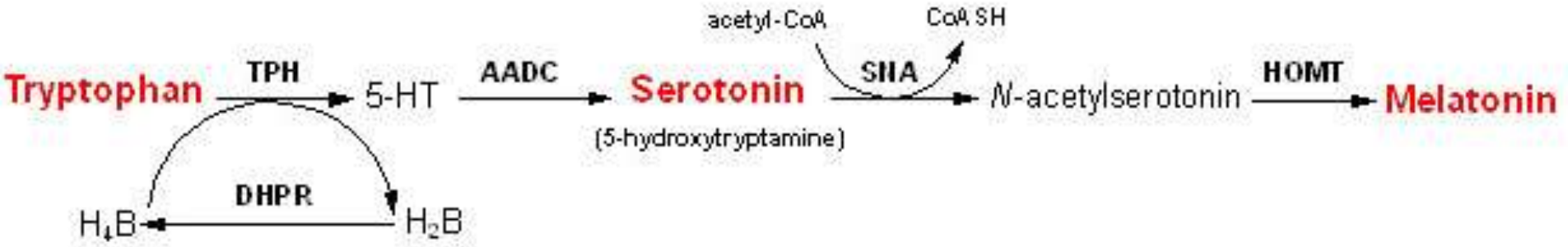
Receptor Sub-Type	Sites of Expression	Functions
$5HT_{1A}$	vasculature, CNS	aggression, anxiety, blood pressure (vasoconstriction), appetite, memory, mood, cardiovascular tone, heart rate, respiration, pupillary dilation, nociception (pain sensation), sexual behavior, erectile function, emesis (vomiting), thermoregulation, sleep, addictive behaviors
$5HT_{1B}$	vasculature, CNS	locomotion, aggression, anxiety, blood pressure (vasoconstriction), memory, mood, learning, sexual behavior, erectile function, addictive behaviors

Receptor Sub-Type	Sites of Expression	Functions
$5HT_{1D}$	vasculature, CNS	blood pressure (vasoconstriction), locomotion, anxiety
$5HT_{1F}$	CNS	involved in migraine headaches
$5HT_{2A}$	gastrointestinal tract, smooth muscles, vasculature, CNS, PNS, platelets	anxiety, blood pressure (vasoconstriction), thermoregulation, appetite, learning, memory, mood, cognitive abilities, sexual behavior, sleep, addictive behaviors
$5HT_{2B}$	gastrointestinal tract, smooth muscles, vasculature, CNS, PNS, platelets	gastrointestinal, motility, blood pressure (vasoconstriction), appetite, anxiety, sleep

Receptor Sub-Type	Sites of Expression	Functions
$5HT_{2C}$	gastrointestinal tract, smooth muscles, vasculature, CNS, PNS, platelets	anxiety, locomotion, gastrointestinal motility, blood pressure (vasoconstriction), appetite, mood, sexual behavior, erectile function, thermoregulation, sleep, addictive behaviors
$5HT_3$	gastrointestinal tract, CNS, PNS	anxiety, gastrointestinal motility, emesis (vomiting), learning, memory, addictive behaviors
$5HT_4$	gastrointestinal tract, CNS, PNS	respiration, appetite, gastrointestinal motility, learning, memory, mood, anxiety
$5HT_{5A}$	CNS	locomotion, sleep
$5HT_6$	CNS	cognitive abilities, learning, memory, anxiety, mood
$5HT_7$	gastrointestinal tract, vasculature, CNS	blood pressure (vasoconstriction), respiration, thermoregulation, sleep, memory, mood, anxiety

MELATONIN

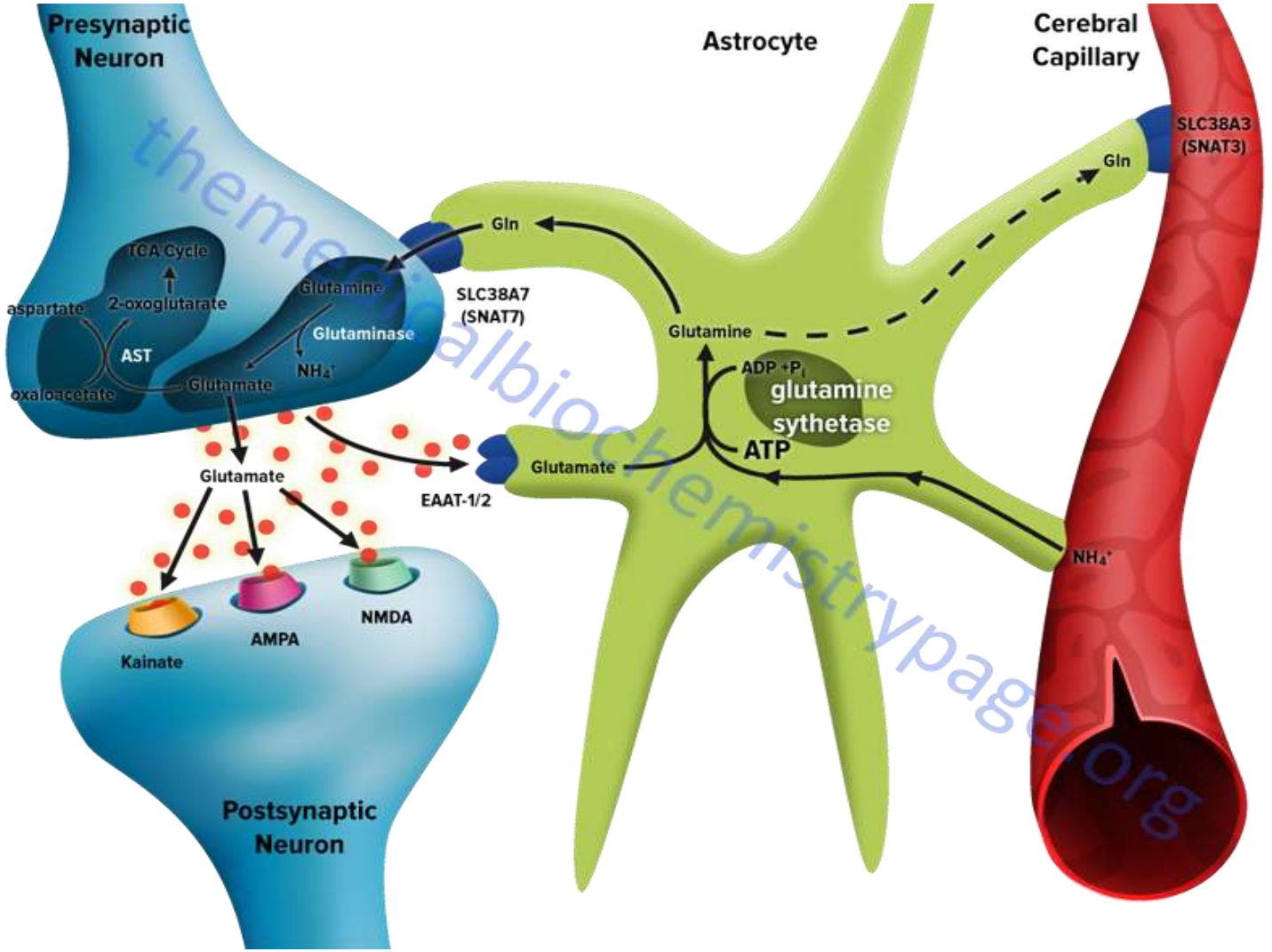
- Serotonin synthesized in the pineal gland serves as a precursor for the synthesis of melatonin, which is a neurohormone involved in regulating
  - sleep patterns
  - Seasonal and circadian (daily) rythyms
  - Dark-light cycle

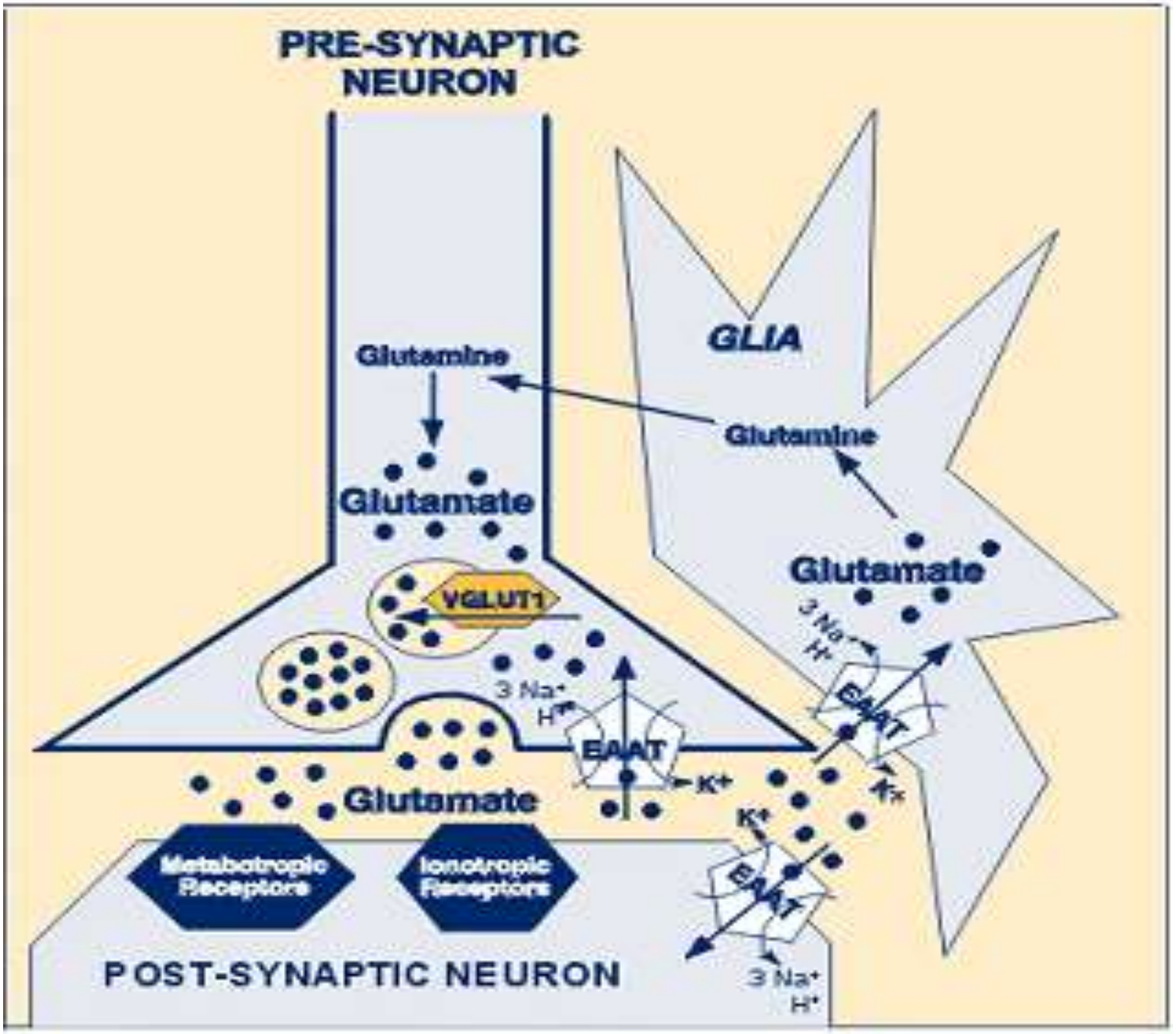


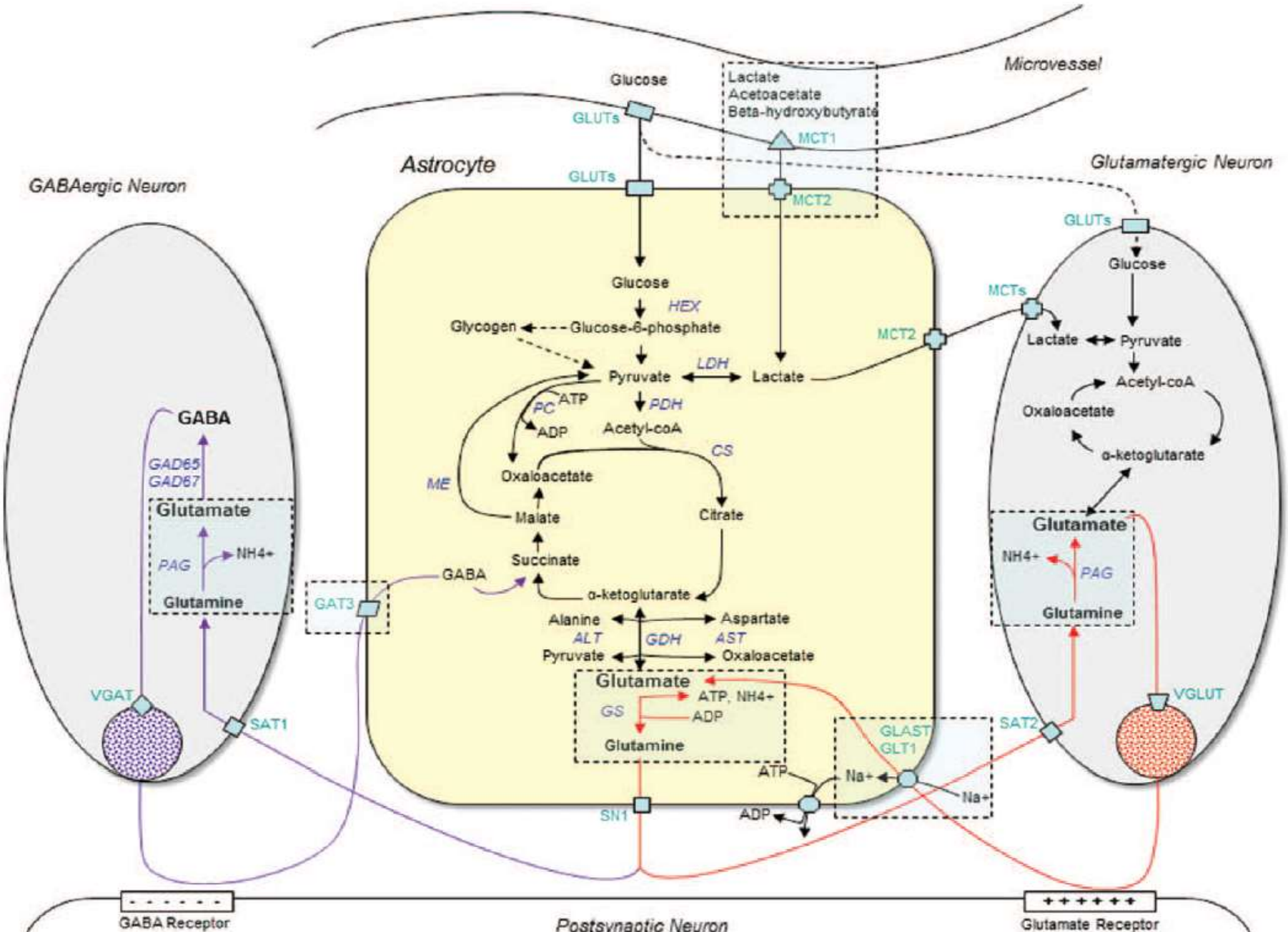
GLUTAMAT

- Neurotransmiter **excitatory**
- Disintesis :
  - Alpha-ketoglutarat dengan bantuan glutamat dehydrogenase (GDH)
  - glutamine dengan bantuan enzim glutaminase/ phosphat activated glutaminase (PAG)
- Mekanisme pengakhiran kerja glutamat pada synaps → dihilangkan:
  1. Uptake oleh neuron post sinap
  2. Re-uptake oleh neuron pre sinaps
  3. Uptake oleh astrosit melalui Excitatory Amino Acid Transporter (EAAT)

MEKANISME PELEPASAN DAN PENGAKHIRAN KERJA GLUTAMAT

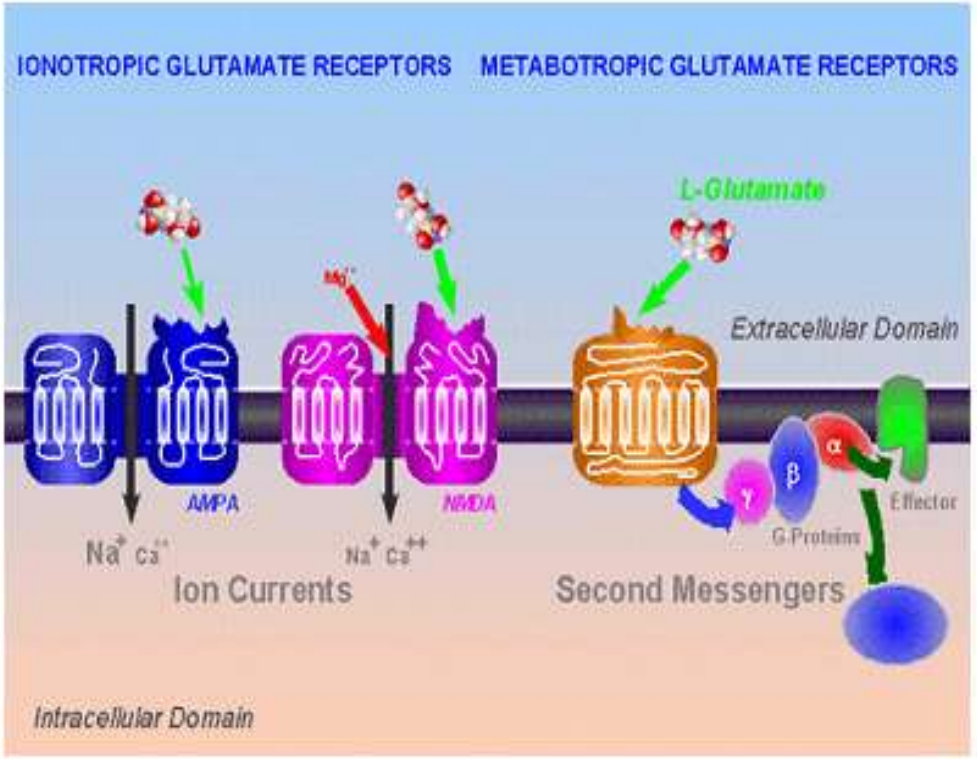



PRE-SYNAPTIC NEURON
GLIA
Glutamine
Glutamine
Glutamate
Glutamate
VGLUT1
3 Na+ H+
EAAT
K+
Glutamate
Metabotropic Receptors
Ionotropic Receptors
POST-SYNAPTIC NEURON
3 Na+ H+

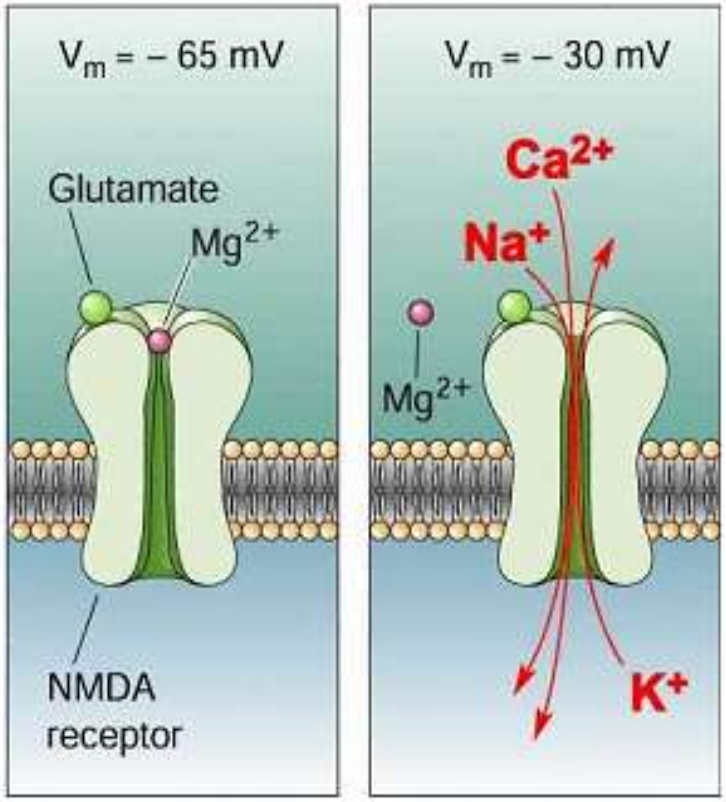

Microvessel
Glucose
GLUTs
Lactate
Acetoacetate
Beta-hydroxybutyrate
MCT1
Astrocyte
GLUTs
MCT2
GABAergic Neuron
Glutamatergic Neuron
GLUTs
Glucose
MCTs
Glucose
HEX
Glycogen
Glucose-6-phosphate
MCT2
Lactate
Pyruvate
LDH
Pyruvate
Lactate
Acetyl-coA
PC
ATP
ADP
PDH
Acetyl-coA
Oxaloacetate
CS
α-ketoglutarate
ME
Oxaloacetate
Malate
Citrate
GABA
Succinate
GAT3
α-ketoglutarate
Alanine
Aspartate
ALT
GDH
AST
Pyruvate
Oxaloacetate
GABA
GAD65
GAD67
Glutamate
PAG
NH4+
Glutamine
VGAT
SAT1
Glutamate
ATP, NH4+
GS
ADP
Glutamine
GLAST
GLT1
ATP
Na+
Na+
ADP
SN1
SAT2
Glutamate
NH4+
PAG
Glutamine
VGLUT
GABA Receptor
Postsynaptic Neuron
Glutamate Receptor

RESEPTOR

- Ionotropic
  - NMDA
  - AMPA
  - Kainate/quisqualate
- Metabotropic
  - mGluR (1-8)



NMDA RESEPTOR



(a) Glutamate

(b) Glutamate and depolarization

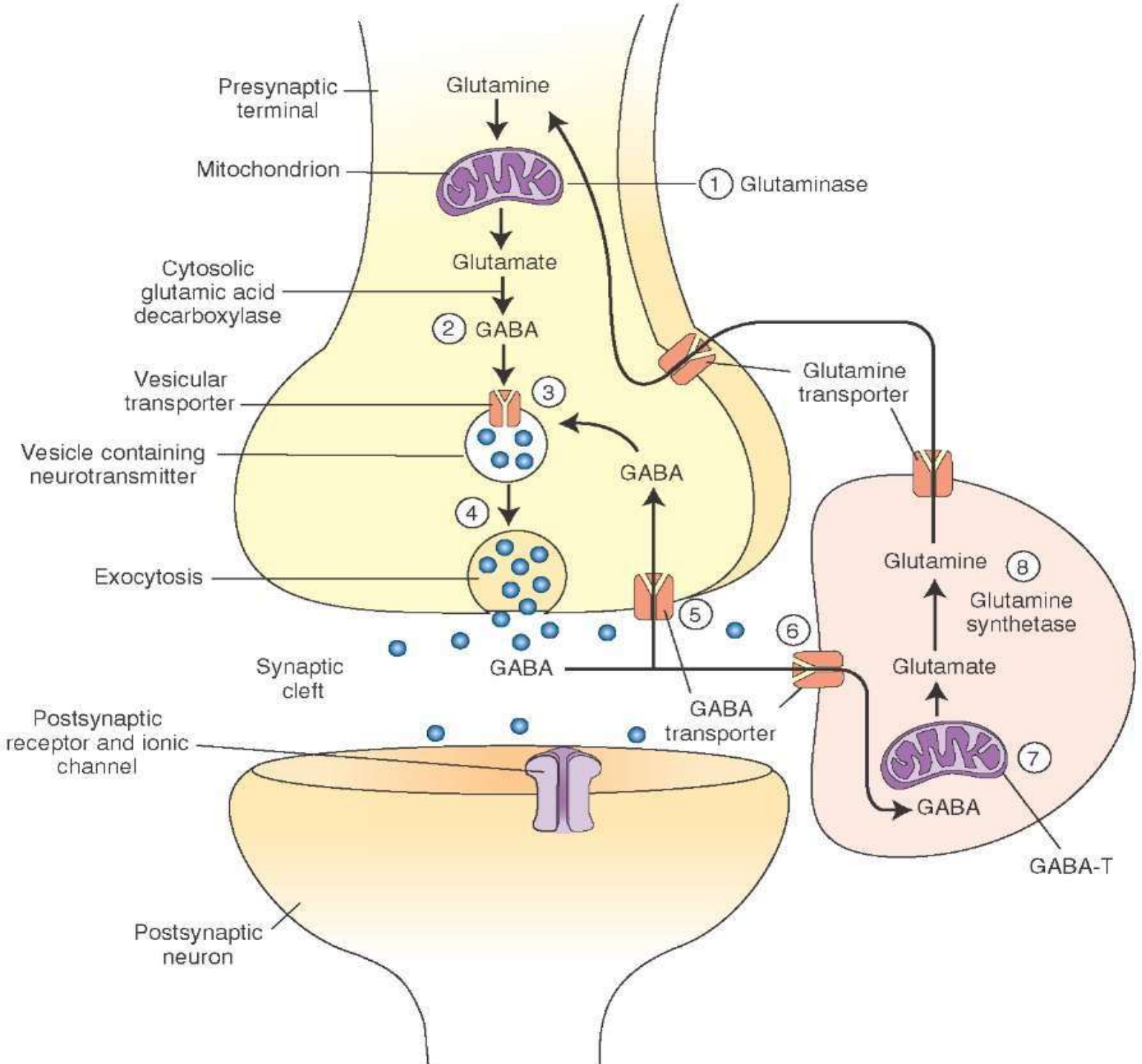
- "Ligand *and* Voltage-dependent"
  - Requires both NT *and* depolarization to open
- Blocked by Mg^{2+}
  - Depolarization displaces Mg^{2+} ions
- Channel is permeable to Na^+ *and* Ca^{2+}

PERAN SPESIFIK RESEPTOR NMDA

- Excitotoxicity
  - Kelebihan glutamat → overstimulasi NMDA reseptor → influx calsium
  - Mengaktivasi enzim protease, endonuclease, phospolipase, stimulasi NOS, produksi NO dan radikal bebas
  - Excitotoxicity terjadi pada kondisi neurodegeneratif, hipoksemia, stroke.
- Sensitisasi pusat nyeri neuropatik
- Inisiasi dan perambatan kejang
- Long Term Potentiation

GABA (GAMMA AMINO BUTIRATE)

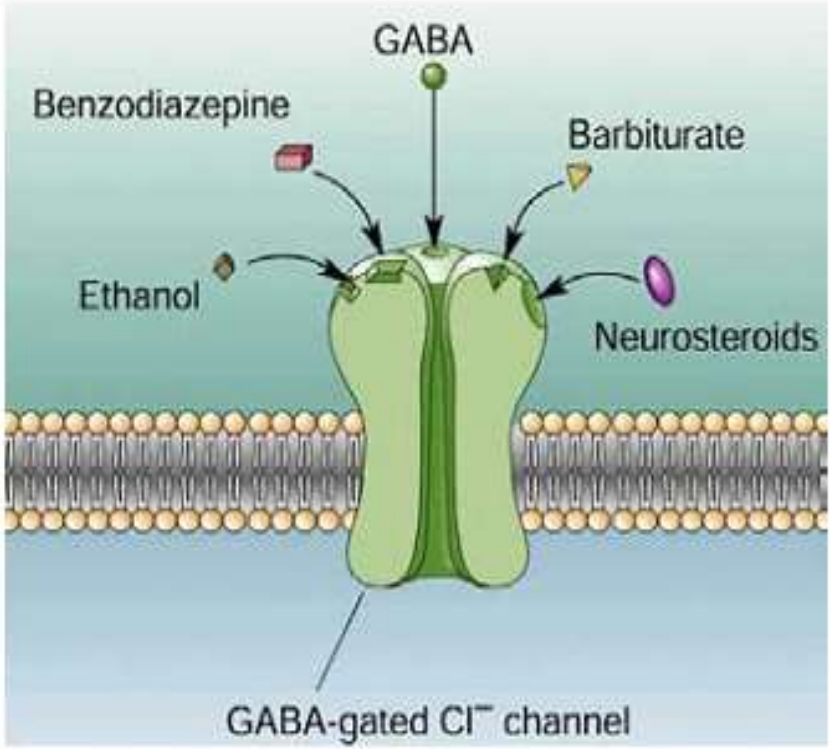
- Merupakan neurotransmitter inhibitorik utama di sistem saraf pusat
  - Ditemukan di seluruh regio otak
  - Terutama di interneuron
  - Neurotransmitter inhibitorik utama di medulla spinalis adalah glycine
- Disintesis dari Glutamat yang dikatalisis oleh enzim Glutamic acid decarboxylase (GAD)
- Degradasi oleh GABA transaminase (GABA-T) menjadi succinate dan masuk ke dalam siklus Krebs


Presynaptic terminal
Glutamine
Mitochondrion
1 Glutaminase
Glutamate
Cytosolic glutamic acid decarboxylase
2 GABA
Vesicular transporter
3
Vesicle containing neurotransmitter
GABA
4
Exocytosis
Glutamine transporter
Glutamine
8
Glutamine synthetase
Glutamate
5
6
Synaptic cleft
GABA
GABA transporter
Postsynaptic receptor and ionic channel
7
GABA
GABA-T
Postsynaptic neuron

- Aktivasi Glutamic Acid Decarboxylase (GAD) membutuhkan pyridoxal phospate (PLP) sebagai cofactor.
- PLP disintesis dari vitamin-vitamin B6 (pyridoxine, pyridoxal dan pyridoxamine) dengan bantuan pyridoxal kinase.
- Aktivasi pyridoxal kinase memerlukan Zinc sebagai cofactor.
- Defisiensi Zinc atau defect pada pyridoxal kinase dapat mencetuskan terjadinya kejang.

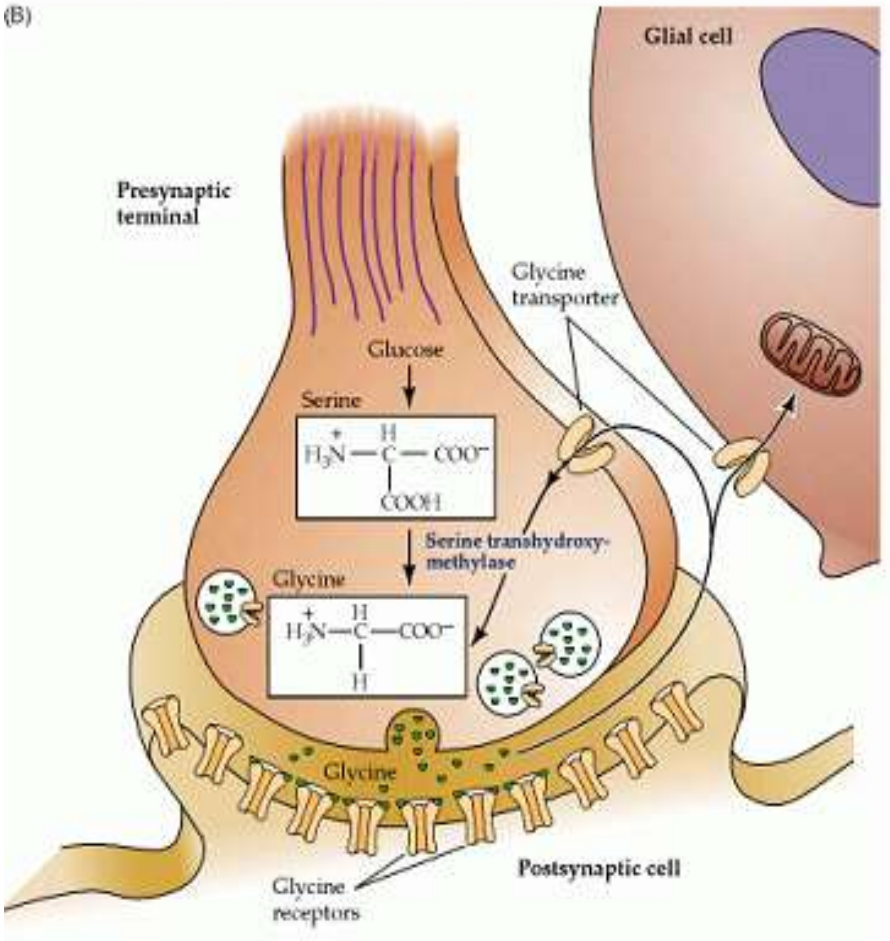
GABA RECEPTORS

- $GABA_A$
  - Ionotropic
  - Chloride channel
  - Activation causes hyperpolarization
  - Other agonists: BZDs, barbiturates, EtOH
- $GABA_B$
  - Metabotropic
  - Leads to increased efflux of K^+ and hyperpolarization
  - Also leads to decreased presynaptic Ca^{2+} influx
  - Agonist: baclofen, ?gabapentin



$GABA_A$

GLYCINE


(B)
Glial cell
Presynaptic terminal
Glycine transporter
Glucose
Serine
Serine transhydroxy-methylase
Glycine
Glycine
Postsynaptic cell
Glycine receptors

GLYCINE

- Neurotransmiter inhibitorik dominan di nukleus sub thalamic, globus pallidus dan medula spinalis
- Disintesis dari asam amino serine dengan bantuan enzym serine hydroxylmethyltransferase
- Sisa glycine di sinaps diambil oleh GLYT (Glycine Transporter)
- Reseptor:
  - Alfa dan Beta
  - Reseptor ionotropic
  - Channel Chlorida
  - Hiperpolasisasi
  - Dihambat oleh Sthrycnine

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