

PRINSIP DASAR PSIKOFARMAKOTERAPI

Fathiyah Safithri

Lab Farmakologi

FK-UMM

Frontal Cortex

**Planning, Strategizing, Logic,
Judgment**

Corpus Callosum

**Connects Hemispheres
Creativity and Problem
Solving**

Cerebellum

**Coordinates muscles/ movement
and thinking processes**

Thalamus

**Nucleus
accumbens**

**Ventral
tegmental
area**

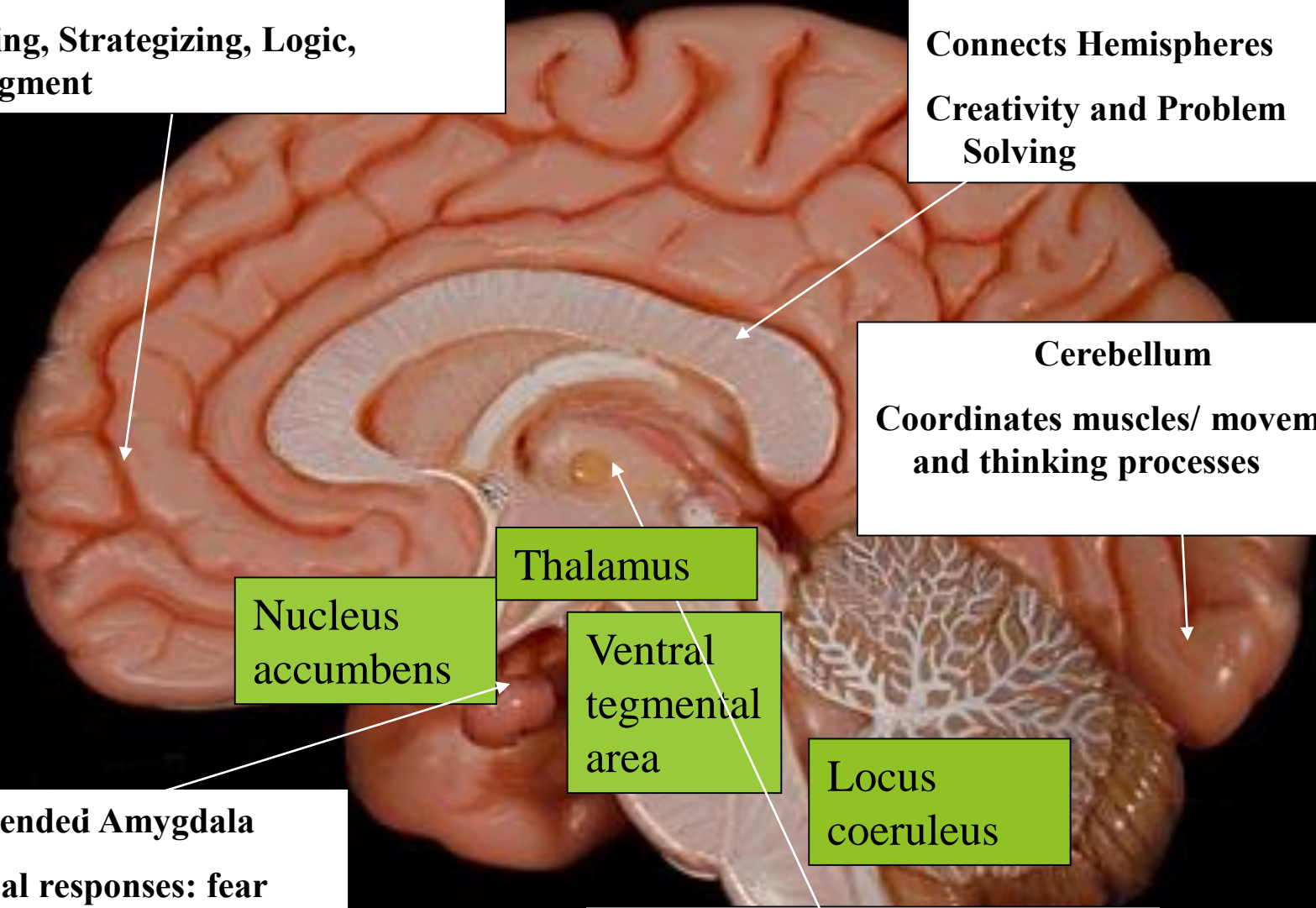
**Locus
coeruleus**

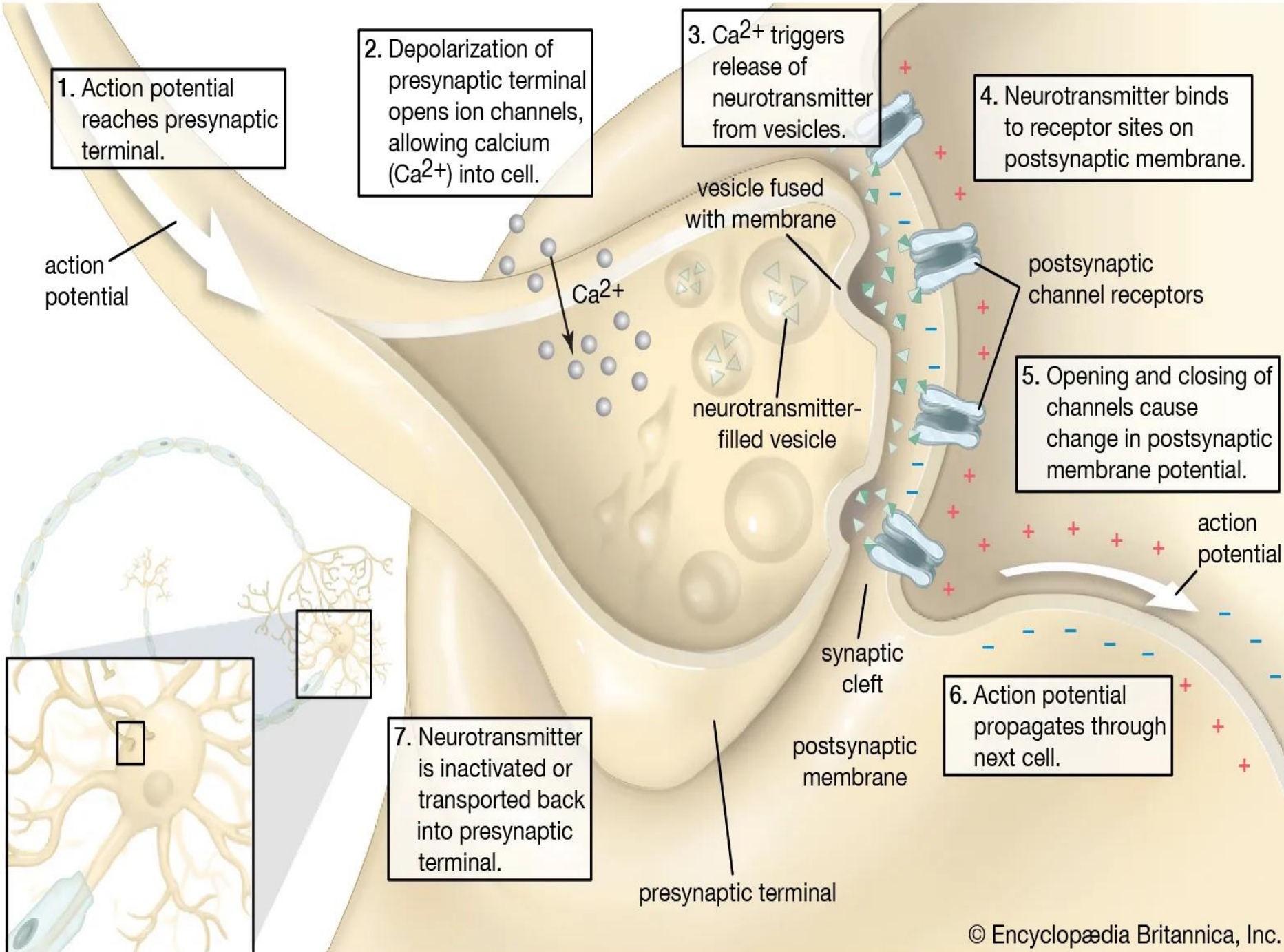
Extended Amygdala

**Emotional responses: fear
and anger**

Hippocampus

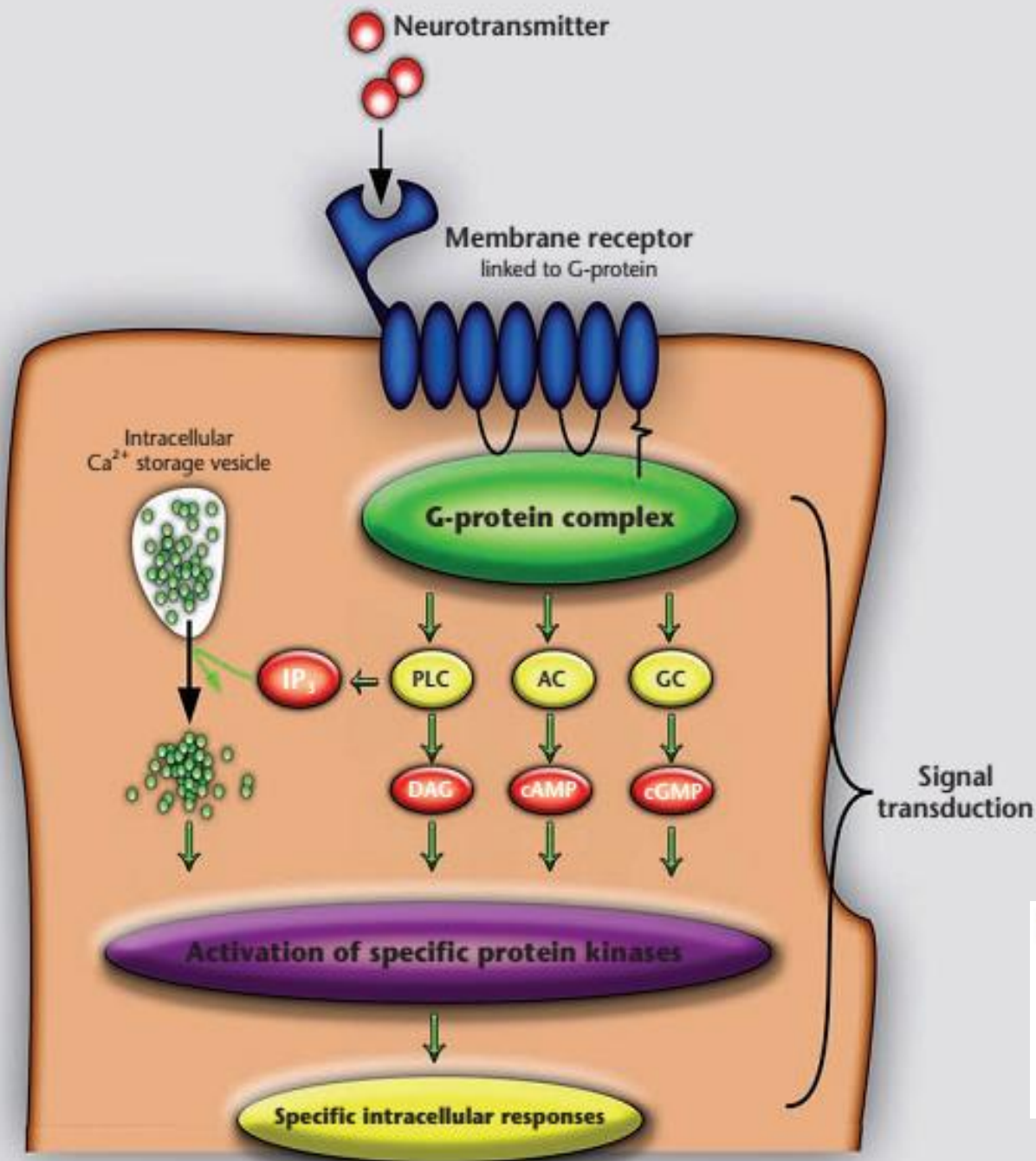
**Forms Memories
Coordinates thinking processes**





NEUROTRANSMITTER DI SSP

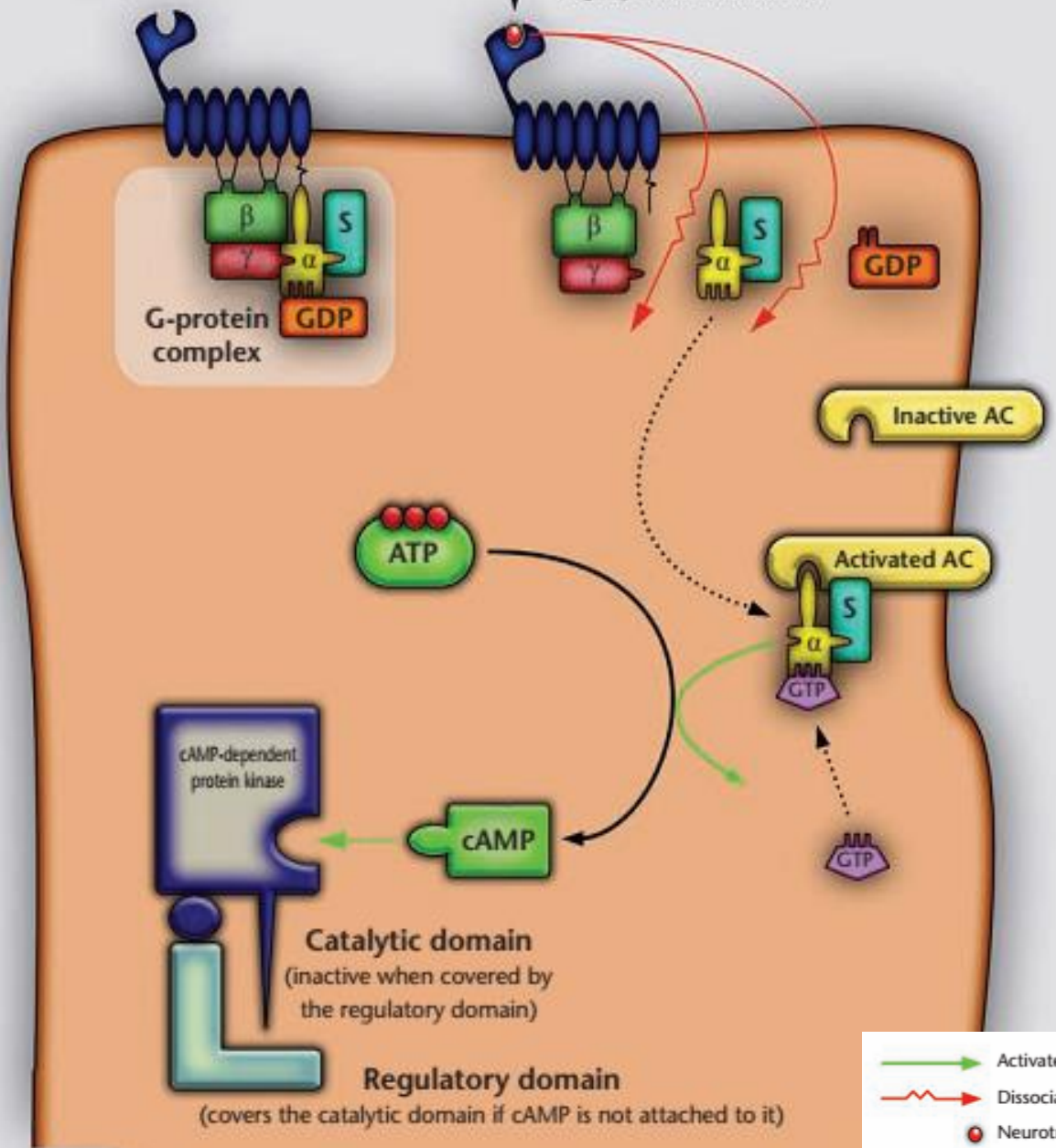
Biogenic amines	Amino acids	Peptides		Miscellaneous
Acetylcholine	Aspartate	Angiotensin	Oxycytocin	Adenosine
Dopamine	Glutamate	Bombesin	Prolactin	Adenosine triphosphate (ATP)
Histamine	Glycine	Bradykinin	Somatostatin	Nitric oxide
Norepinephrine (noradrenaline)	γ -Aminobutyric acid (GABA)	Cholecystokinin	Tachykinins	Carbon monoxide
Serotonin	Homocysteate	Endorphins	Vasoactive intestinal peptide	



	Activates/stimulates	DAG	Diacylglycerol
	Second messengers	GC	Guanylate
AC	Adenylate cyclase	IP₃	Inositol triphosphate
cAMP	Cyclic adenosine monophosphate	PLC	Phospholipase C
cGMP	Cyclic guanosine monophosphate		

Inactive membrane receptor
linked to G-protein

Activated receptor
(e.g. by neurotransmitter)



- Activates/stimulates
- - - → Dissociates
- Neurotransmitter
- α, β, γ, S Various subunits of the G-protein complex

- AC** Adenylate
- cAMP** Cyclic adenosine monophosphate
- GDP** Guanosine diphosphate
- GTP** Guanosine triphosphate

Inactive protein kinase



Active protein kinase
(cAMP attached)



cAMP-dependent protein kinase
(inactive; without cAMP attached)



Inactive (not phosphorylated) protein or transcription factor



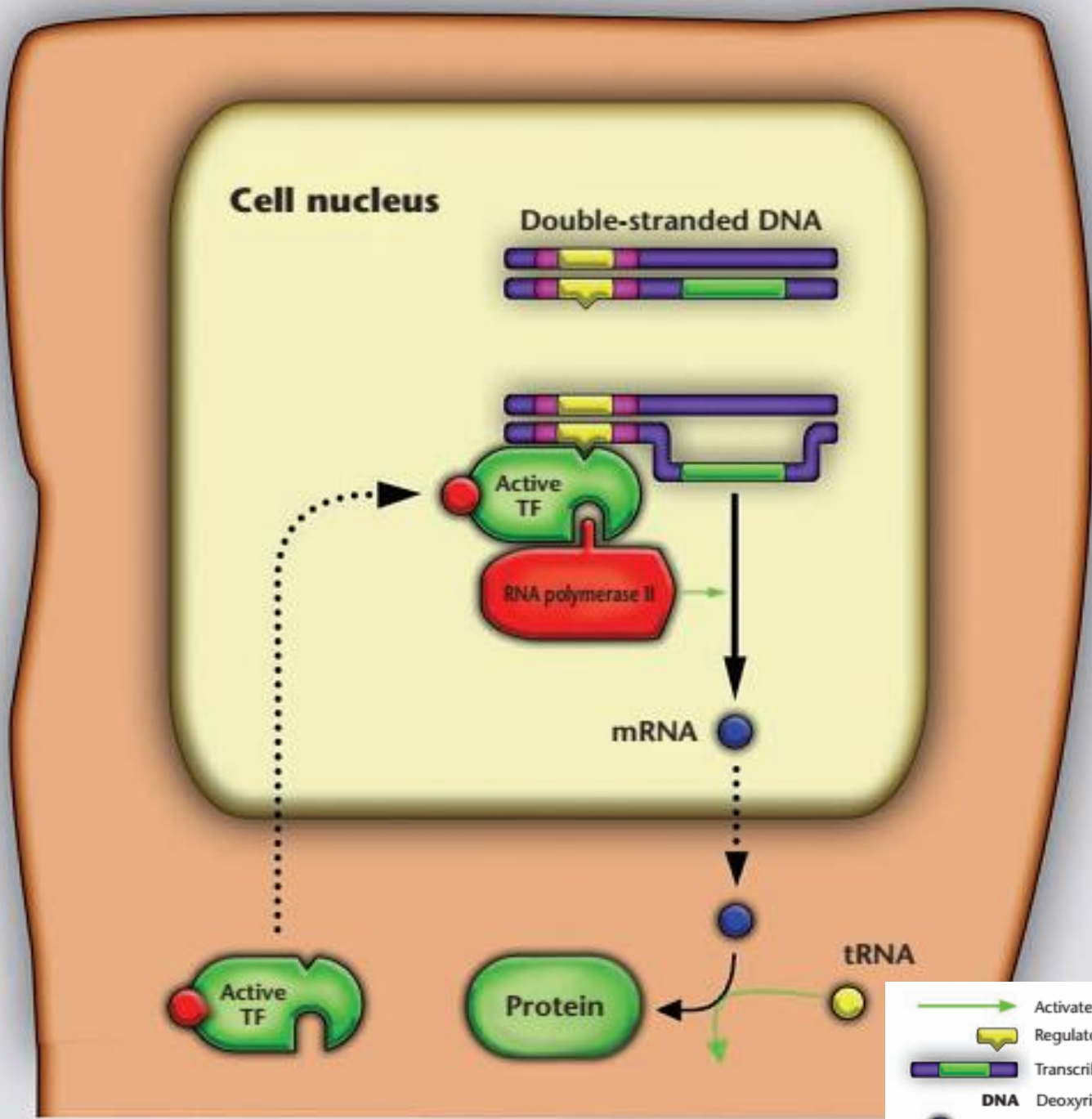
Activated (phosphorylated) protein or transcription factor (see Section 1.5)







Alters intracellular functioning
(e.g. may affect lipid/protein/glucose metabolism, cell division/differentiation, permeability/excitability of cell membrane, secretory processes, gene expression)

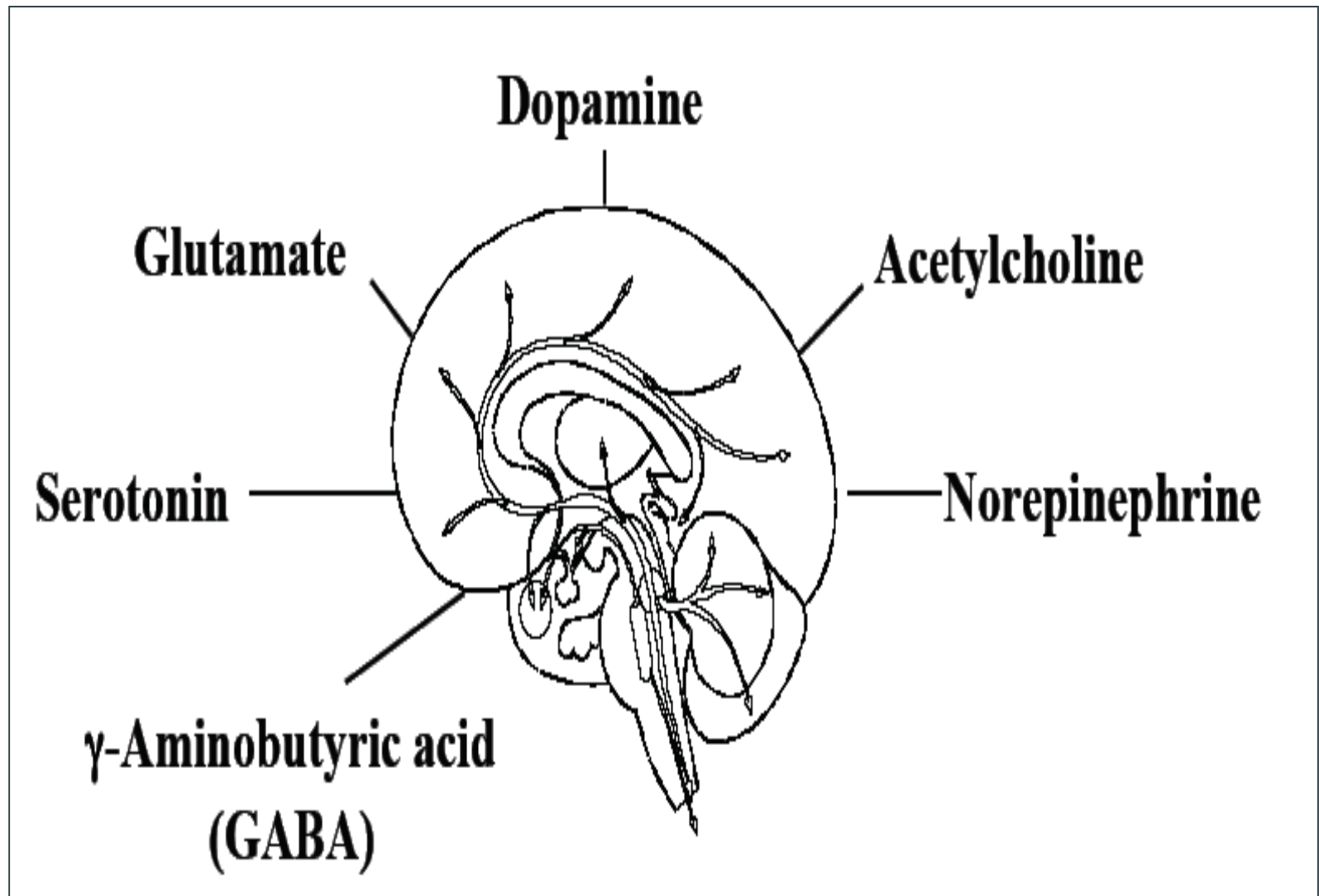


ADP Adenosine diphosphate
ATP Adenosine triphosphate
cAMP Cyclic adenosine monophosphate



-  Activates
-  Regulatory element
-  Transcribed region
- DNA** Deoxyribonucleic acid
-  **mRNA** Messenger ribonucleic acid
- RNA** Ribonucleic acid
- TF** Transcription factor
- tRNA** Transfer ribonucleic acid

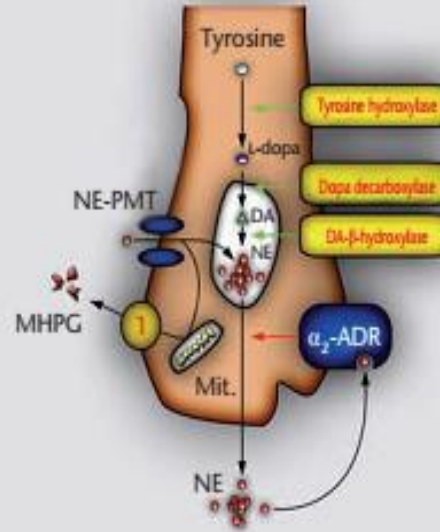
NEUROTRANSMITTER SYSTEMS IMPLICATED IN NEUROPSYCHIATRY



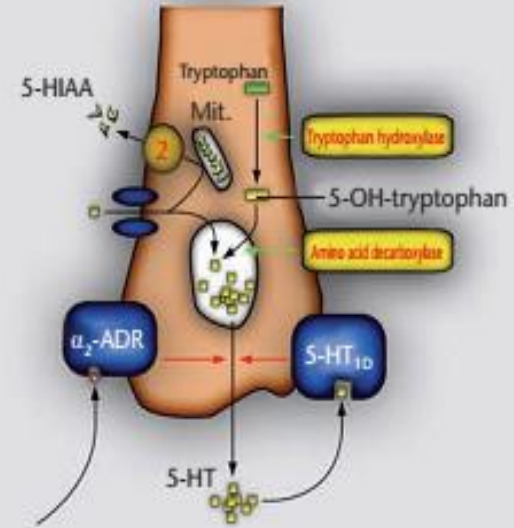
DRUG PHARMACODINAMYC

The background features abstract, overlapping geometric shapes in various shades of green, ranging from light lime to dark forest green. These shapes are primarily located on the right side of the slide, creating a modern, layered effect. The text 'DRUG PHARMACODINAMYC' is centered horizontally and rendered in a bold, green, sans-serif font.

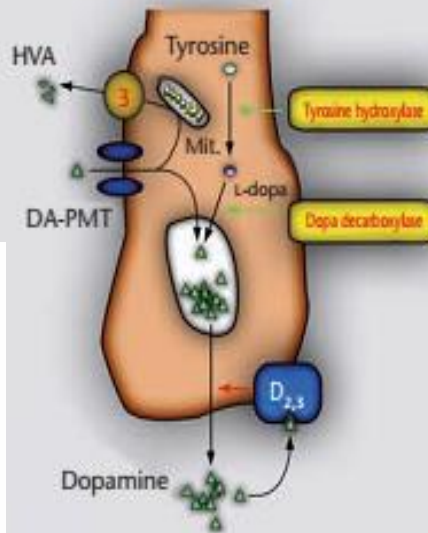
Noradrenergic nerve terminal



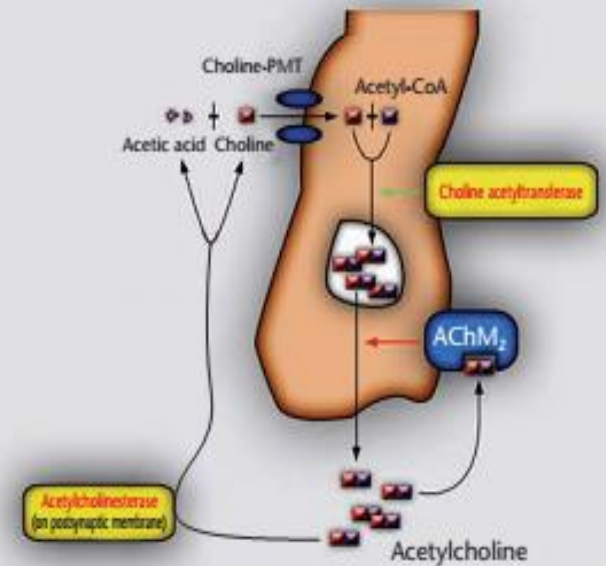
Serotonergic nerve terminal



Dopaminergic nerve terminal

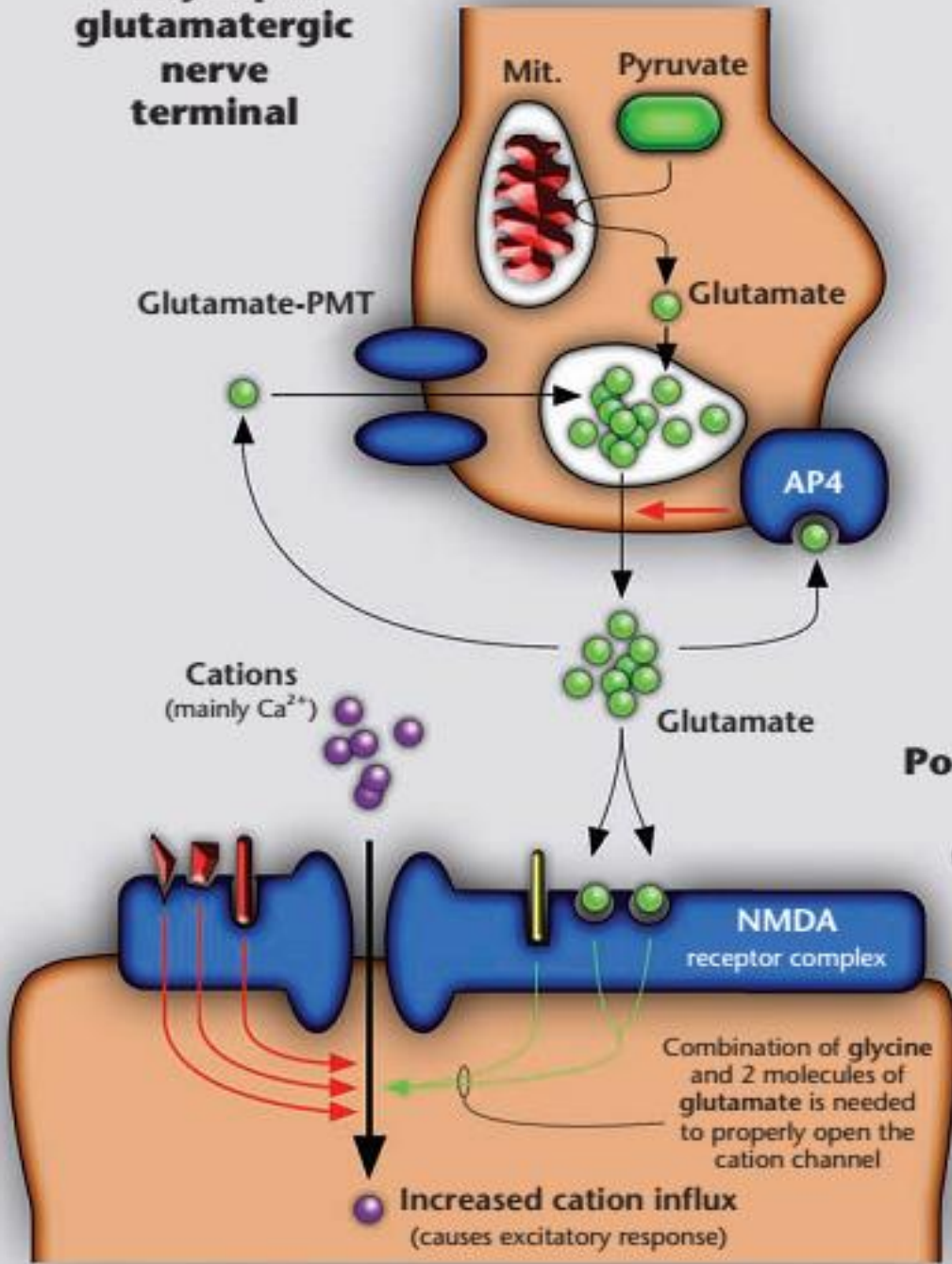


Cholinergic nerve terminal

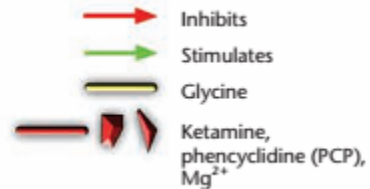


Name	1-3	Enzymes
→		Inhibits
1		MAO type A + COMT
2		MAO type A + aldehyde dehydrogenase
3		MAO type A/B + COMT
Receptor		
→		Stimulates
AChM₂		Acetylcholine muscarinic receptor subtype
D₂,₃		Dopaminergic receptor subtype
5-HIAA		5-Hydroxyindole acetic acid
5-HT		5-Hydroxytryptamine (serotonin)
Acetyl-CoA		Acetyl coenzyme A
ADR		Adrenergic
COMT		Catechol-O-methyltransferase
DA		Dopamine
HVA		Homovanillic acid
MAO		Monoamine oxidase
MHPG		3-Methoxy-4-hydroxyphenylglycol
Mit.		Mitochondria
NE		Norepinephrine (noradrenaline)
PMT		Plasma membrane transporter

Presynaptic glutamatergic nerve terminal

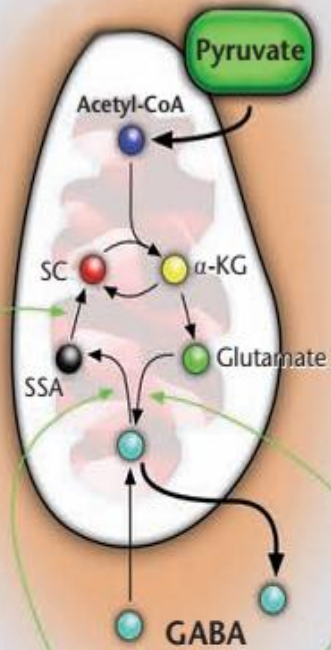


Postsynaptic nerve (any kind)



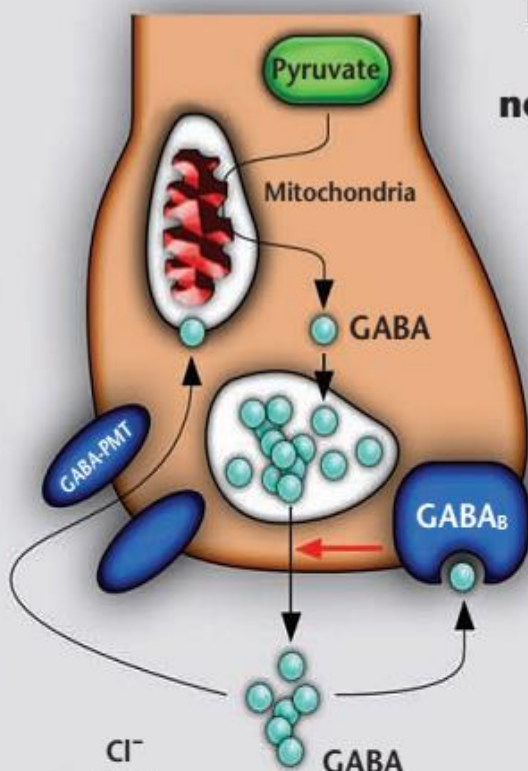
- AP4** 2-Amino-4-phosphonobutyrate (inhibitory autoreceptor)
- NMDA** N-methyl-D-aspartate
- PMT** Plasma membrane transporter
- Mit.** Mitochondria

Inside the mitochondria

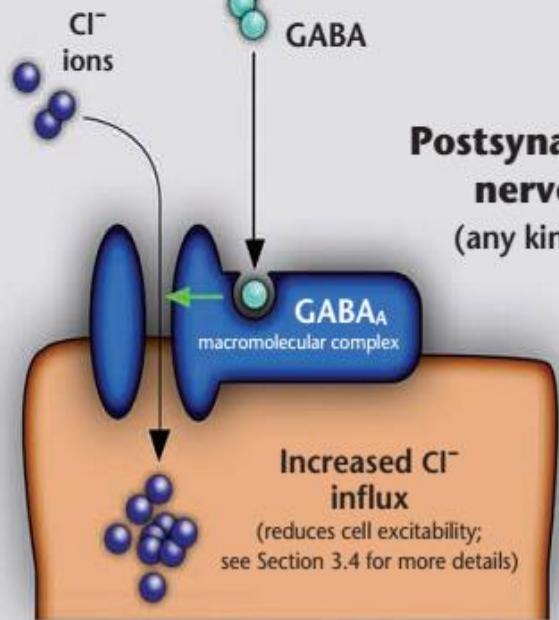


- SSAD
- GABA-T
- Glutamic acid decarboxylase

Presynaptic GABAergic nerve terminal



Postsynaptic nerve (any kind)



- | | |
|-------------------------------|-----------------------------|
| Name | Enzymes |
| | Inhibits |
| | Stimulates |
| Acetyl-CoA | Acetyl coenzyme A |
| α-KG | α -Ketoglutarate |
| GABA | γ -Aminobutyric acid |

- | | |
|---------------|--|
| GABA-T | GABA ketoglutarate transaminase (aminotransferase) |
| PMT | Plasma membrane transporter |
| SC | Succinate |
| SSA | Succinyl semialdehyde |
| SSAD | Succinyl semialdehyde dehydrogenase |

 Improved symptom (by activation of the correspondent receptor)

 Worsened symptom (by activation of the correspondent receptor)

5-HT_{1A,1D,2A,2C} Serotonergic receptor subtypes

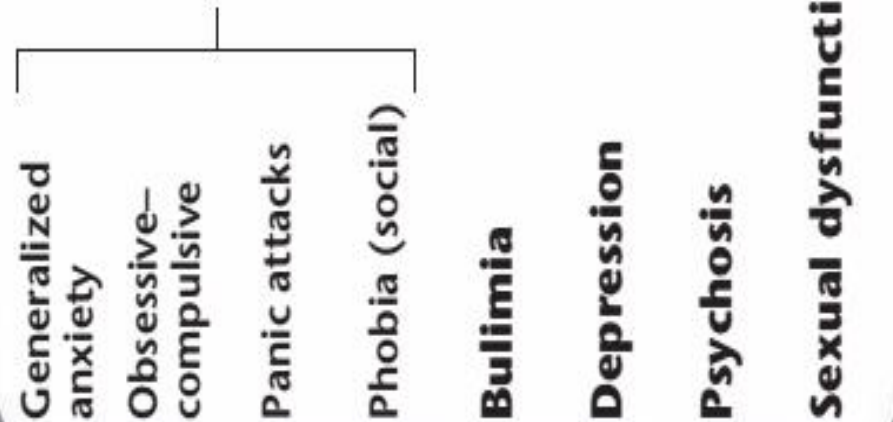
α₁-ADR Adrenergic receptor subtype

D₂ Dopaminergic receptor subtype

GABA_A γ-Aminobutyric acid receptor, type A

Psychiatric symptoms/syndromes

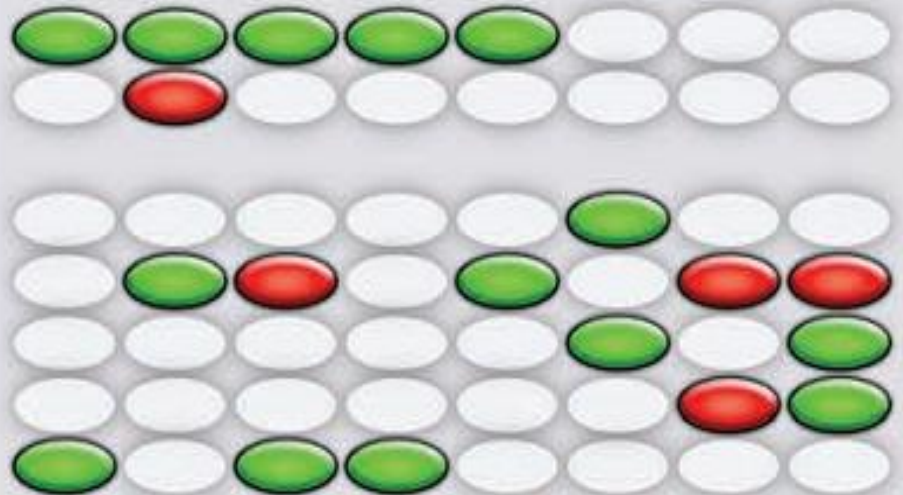
Anxiety spectrum



Stimulated receptors

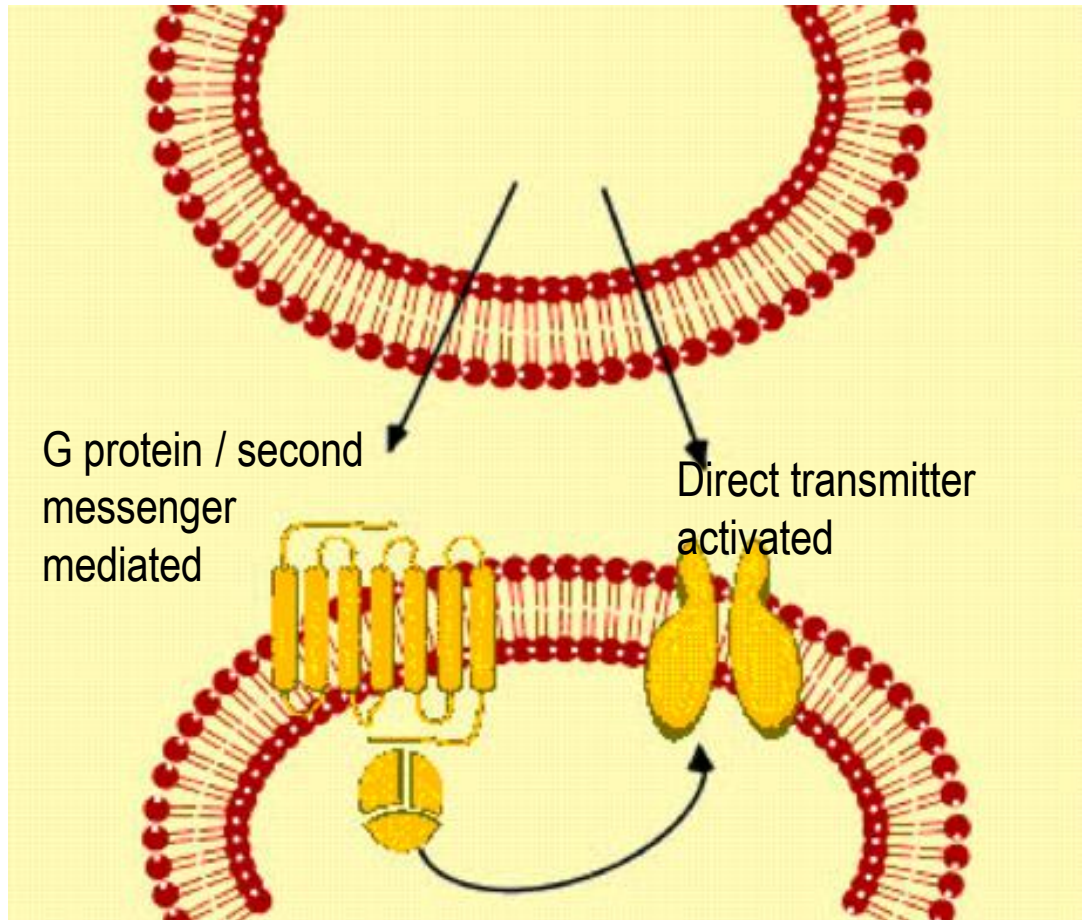
Pre-synaptic 5-HT_{1A}
5-HT_{1D}

Post-synaptic 5-HT_{1A}
5-HT_{2A/2C}
α₁-ADR
D₂
GABA_A

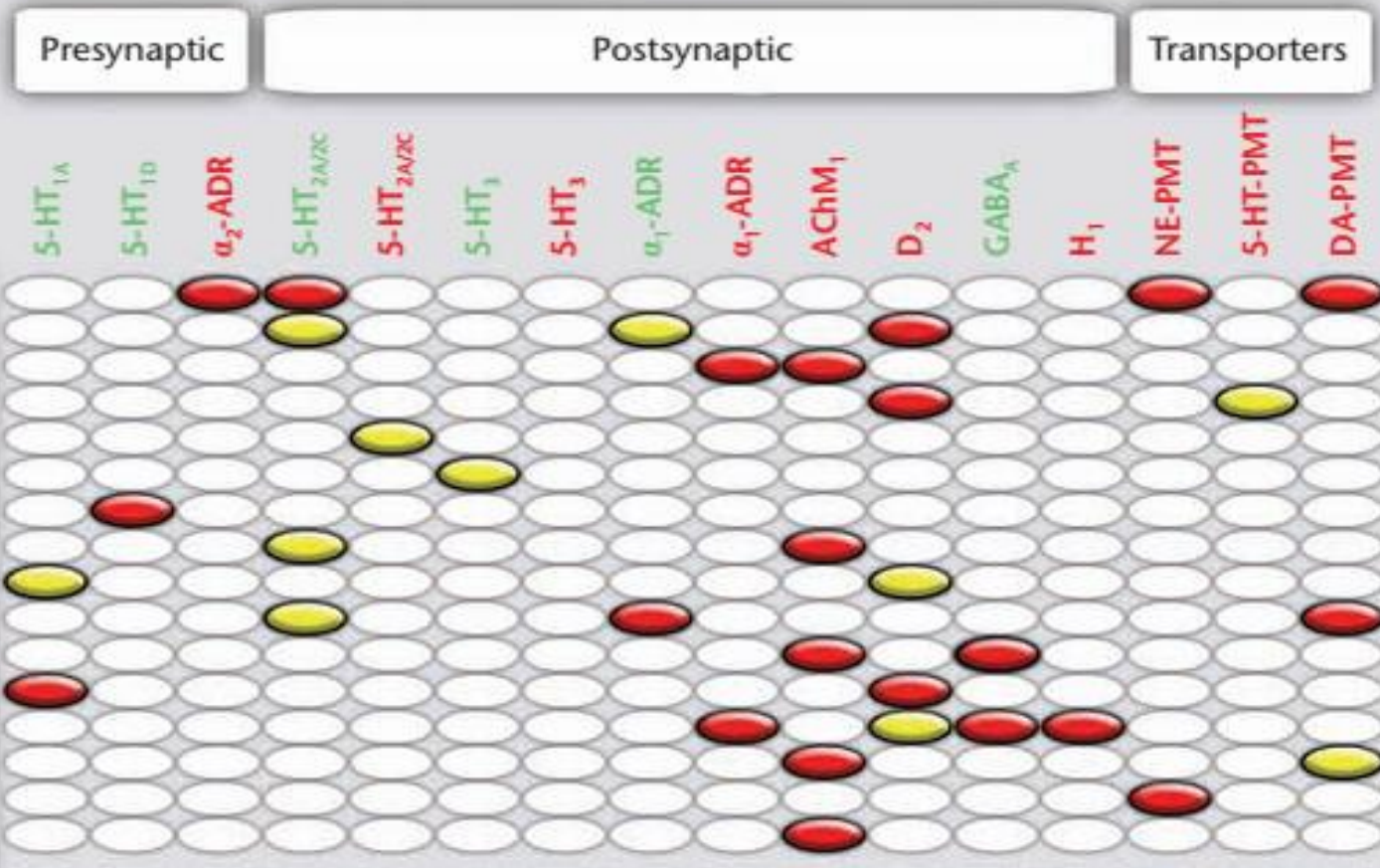


Neurotransmitter di SSP

- Transmitter : di sinap dpt bekerja pada jalur eksitasi (excitatory) atau inhibisi (inhibitory)
- Transmitter mengikat reseptor → berinteraksi langsung dg kanal ion atau dg G protein-coupled ion-channel / lewat 2nd messenger → kanal ion terbuka /tertutup





Stimulated/inhibited receptors/transporters

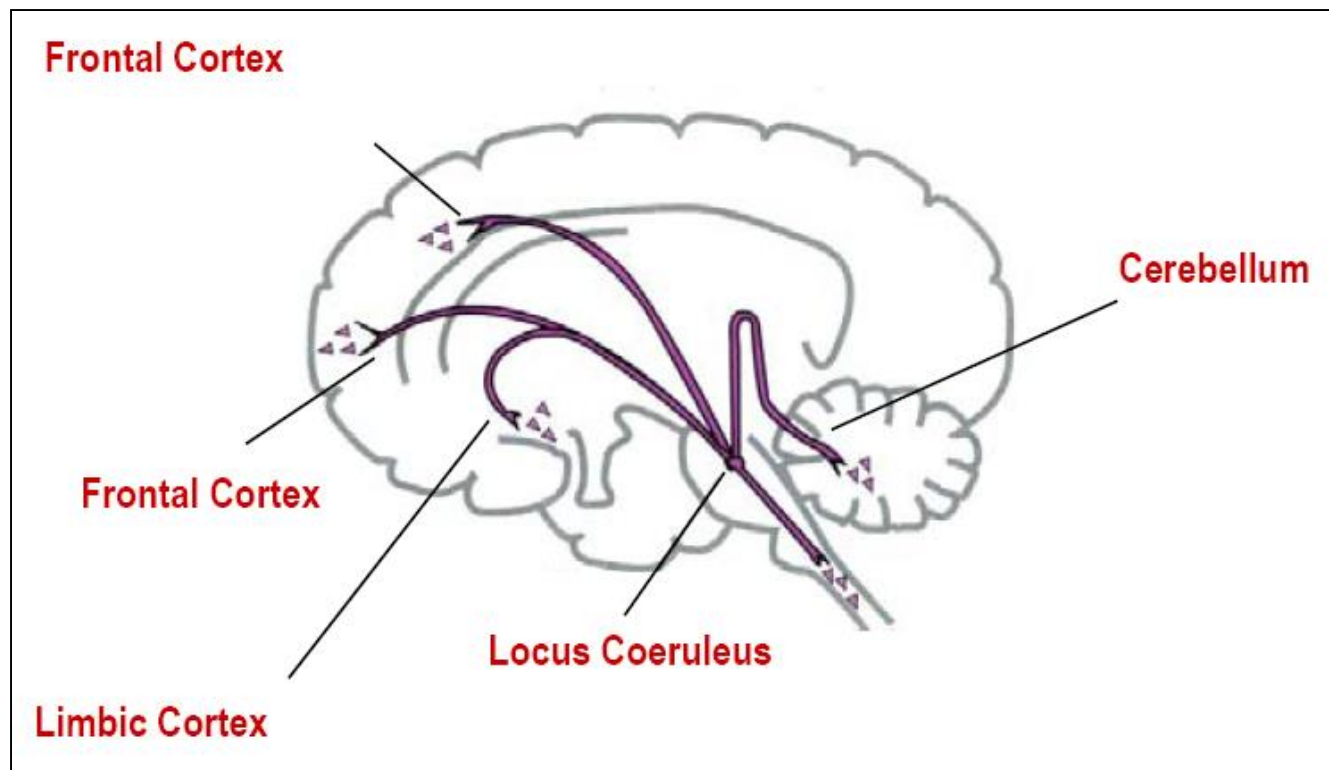


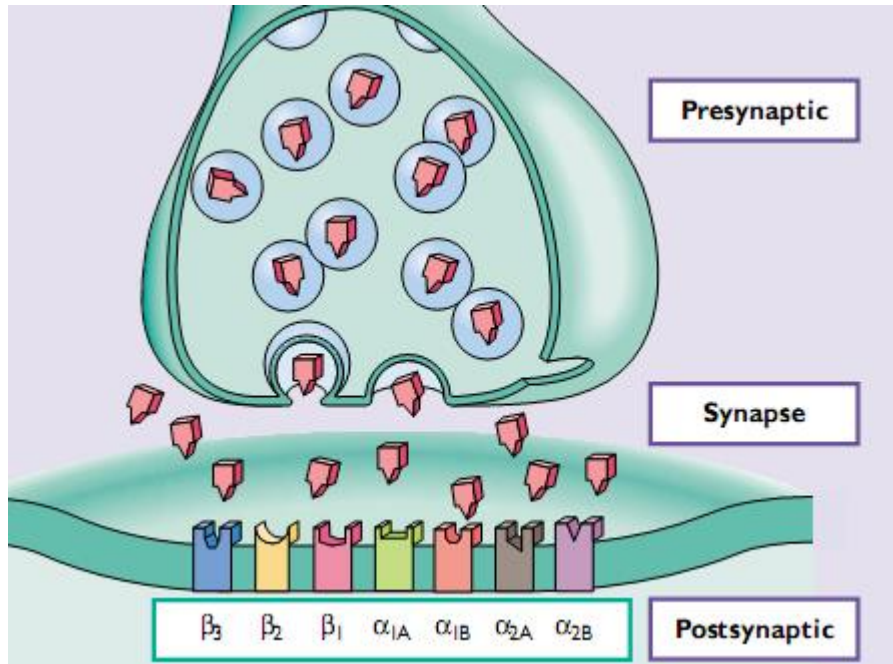
CNS

Legend

	Data fairly well established	CNS	Central nervous system
	Data not well established	CVS	Cardiovascular system
Green-colored receptor/transporter	Stimulated receptor/transporter	D₂	Dopaminergic receptor subtype
Red-colored receptor/transporter	Inhibited receptor/transporter	DA-PMT	Plasma membrane transporter for dopamine
(c)	Causes specific symptom	EPS	Extrapyramidal side-effects
(p)	Protects from specific symptom	GABA_A	γ-Aminobutyric acid receptor, type A
5-HT_{1A,1D,2A,2C,3}	Serotonergic receptor subtypes	GIT	Gastrointestinal tract
5-HT-PMT	Plasma membrane transporter for serotonin	GU	Genitourinary
α_{1,2}-ADR	Adrenergic receptor subtypes	H₁	Histaminergic receptor subtype
AChM₁	Acetylcholine muscarinic receptor, type 1	NE-PMT	Plasma membrane transporter for norepinephrine

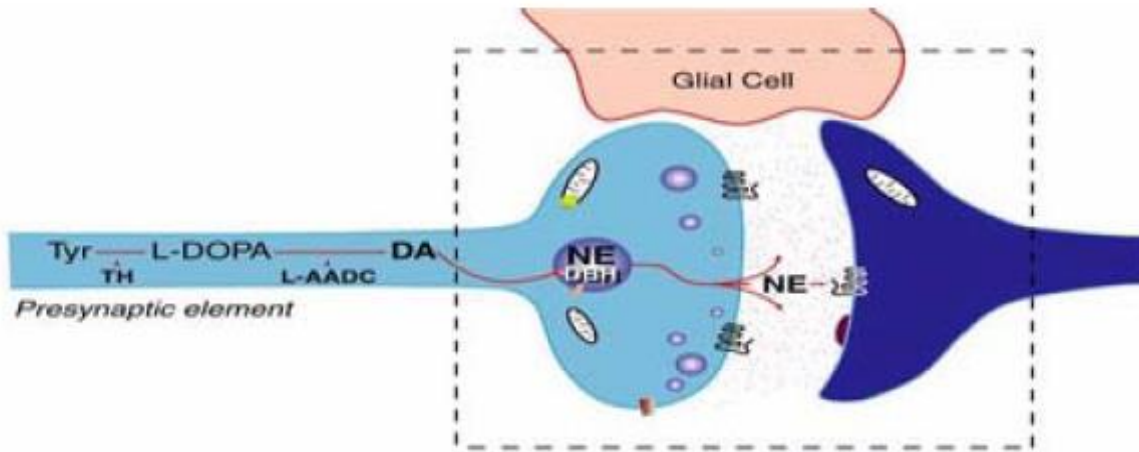
NORADRENERGIC PATHWAY





- ▶ Synthesis ; L-tyrosine converted to l-dopa by tyrosine hydroxylase, then to dopamine . Dopamine to norepinephrine (NE) by dopamine- β -hydroxylase
- ▶ Cell bodies : Locus coeruleus
- ▶ Receptors : α dan β

NORADRENERGIC (NE) SYNAPSE

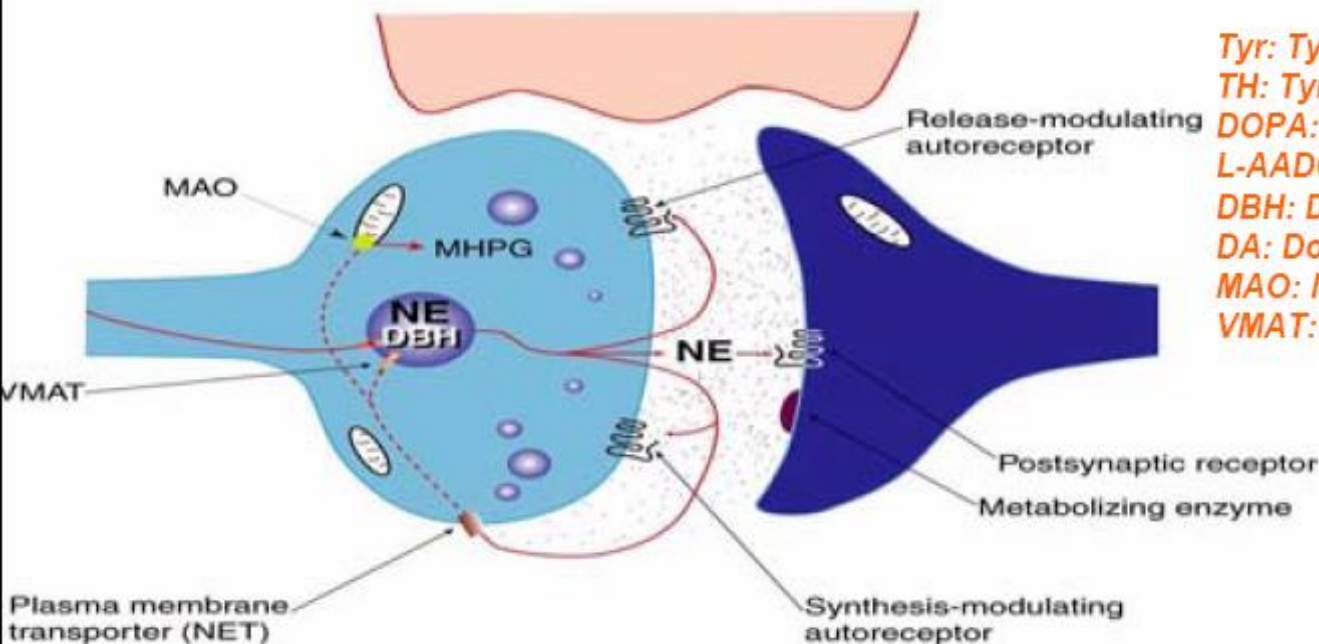


Presynaptic NE Receptors (Autoreceptors)

α_2

Postsynaptic NE Receptors (Heteroreceptors)

$\alpha_1, \alpha_2, \beta_1$



Tyr: Tyrosine

TH: Tyrosine hydroxylase

DOPA: L-Dihydroxyphenyl alanine

L-AADC: L-Aromatic amino acid decarboxylase

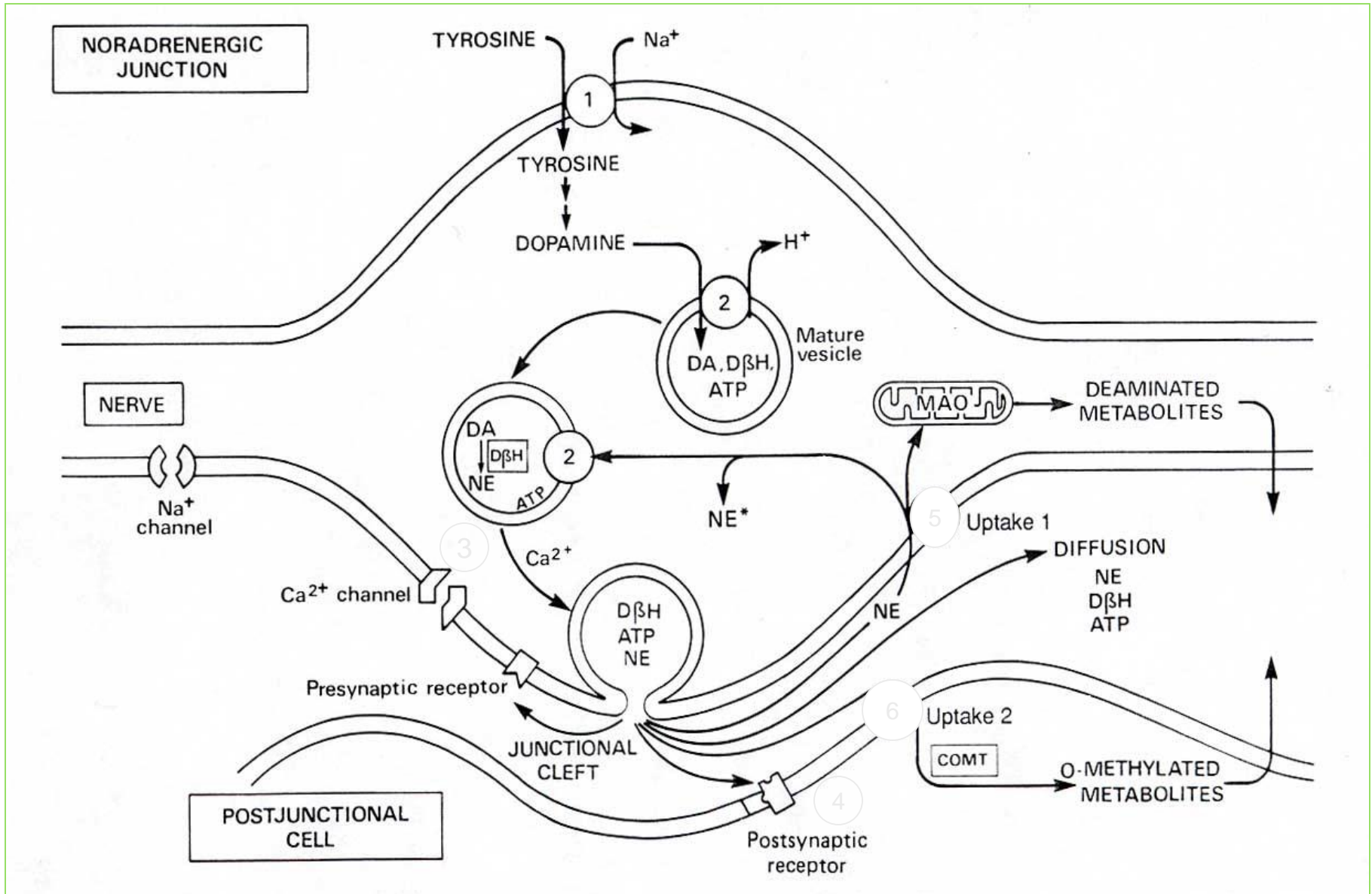
DBH: Dopamine β hydroxylase

DA: Dopamine

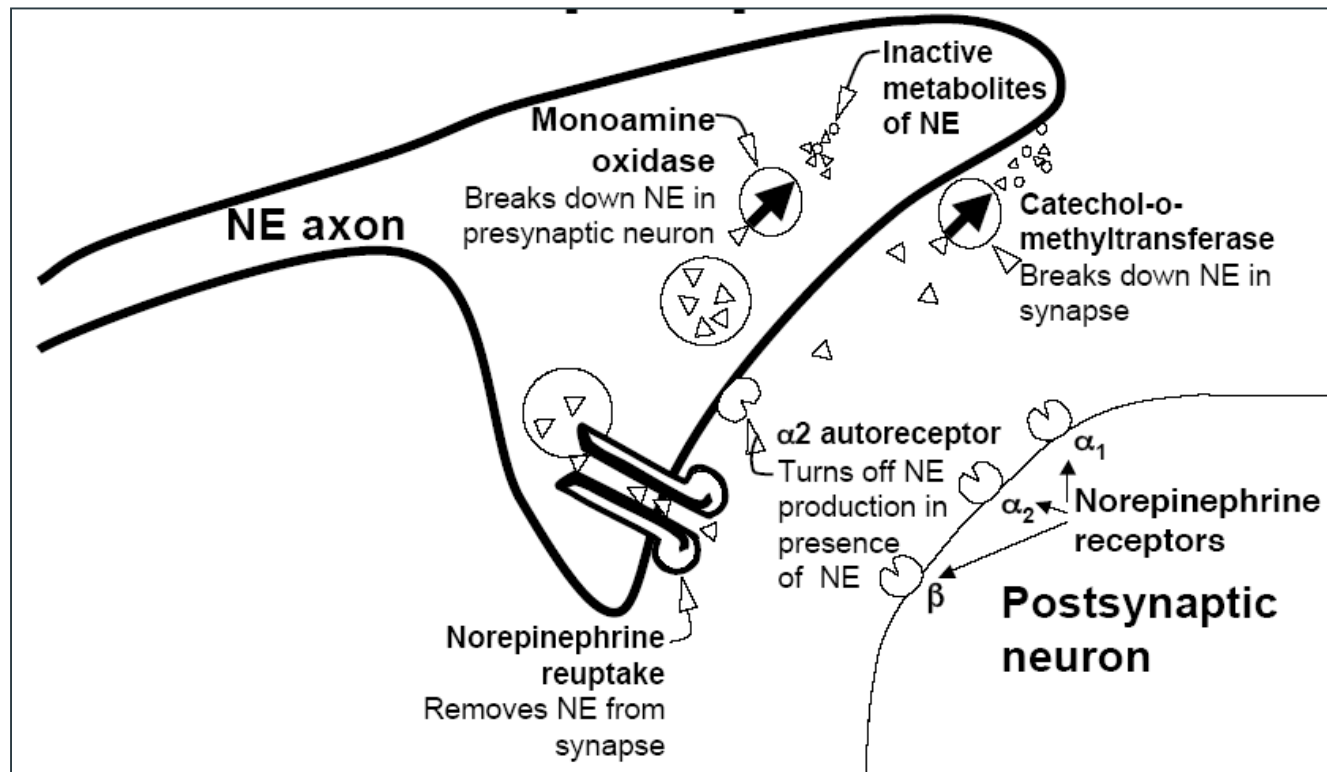
MAO: Monoamine oxidase

VMAT: Vesicular amine transporter

NEUROTRANSMISI ADRENERGIK

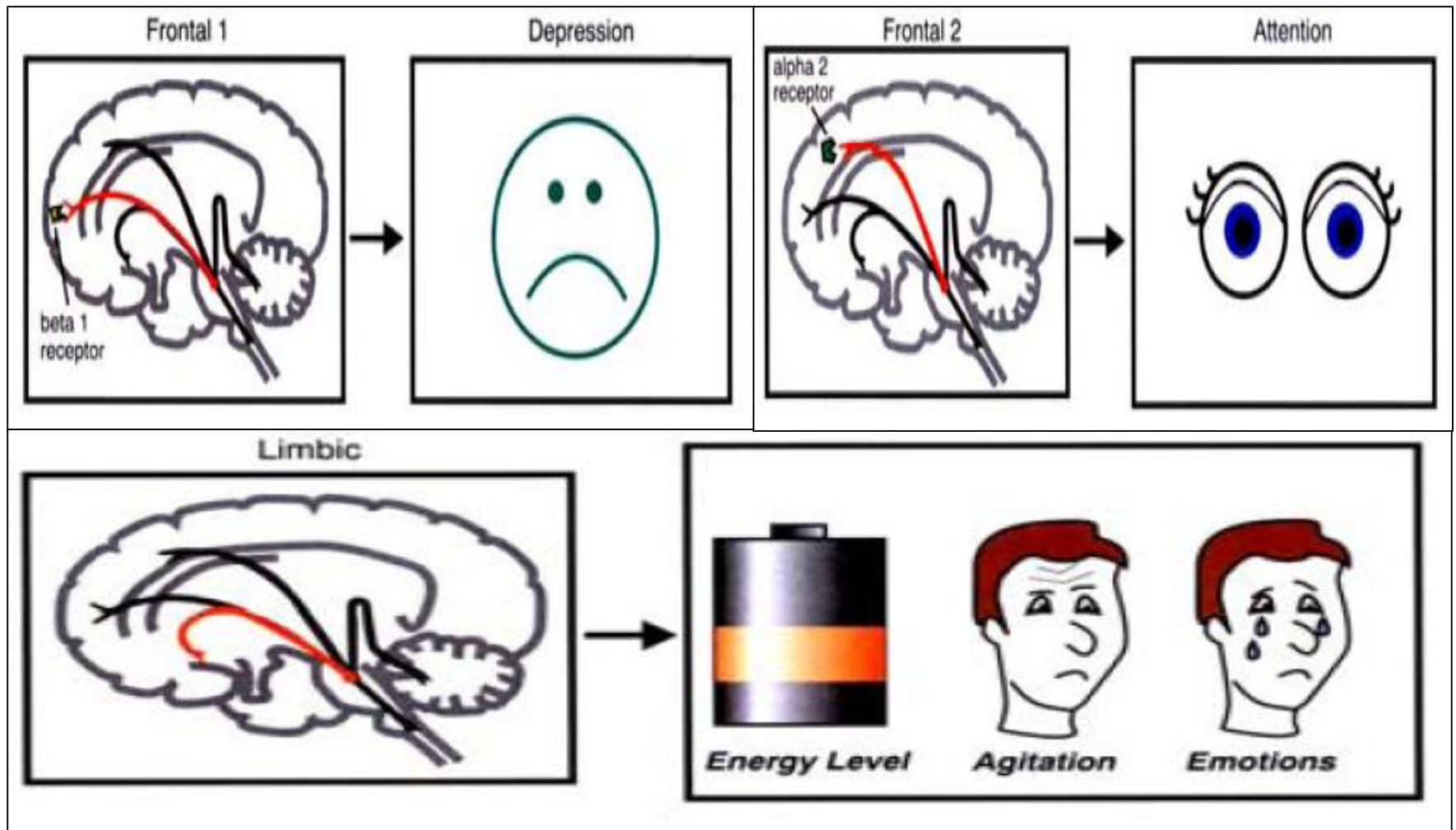


SYNAPTIC REGULATION OF NOREPINEPHRINE

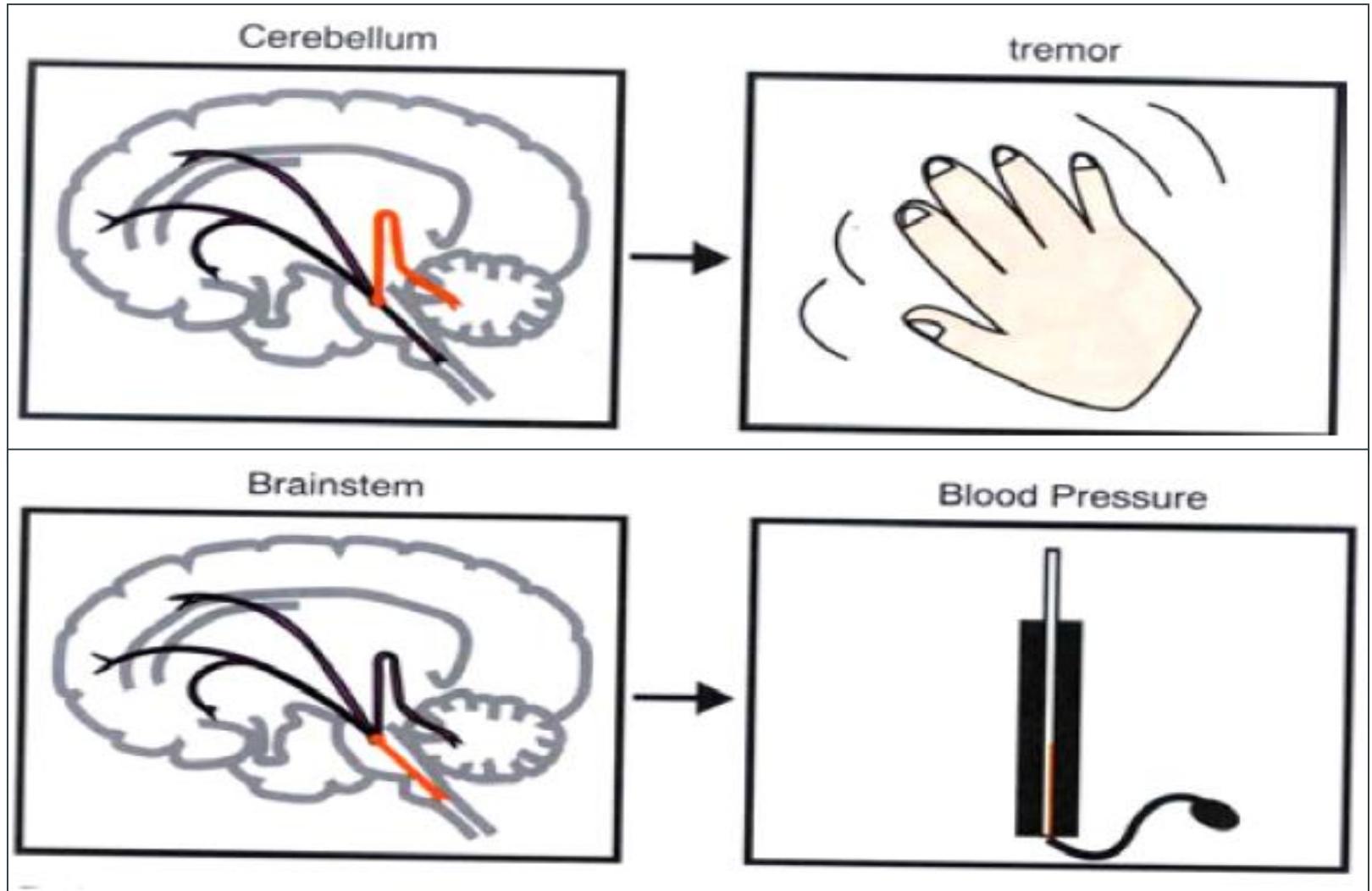


- ▶ Mediates antidepressant effects
- ▶ May augment antidepressant effects of 5-HT
- ▶ NE and 5-HT combinations enhance pain effects
- ▶ NE reuptake blockers have antidepressant effects, e.g. desipramine, reboxetine

NORADRENERGIC PATHWAY



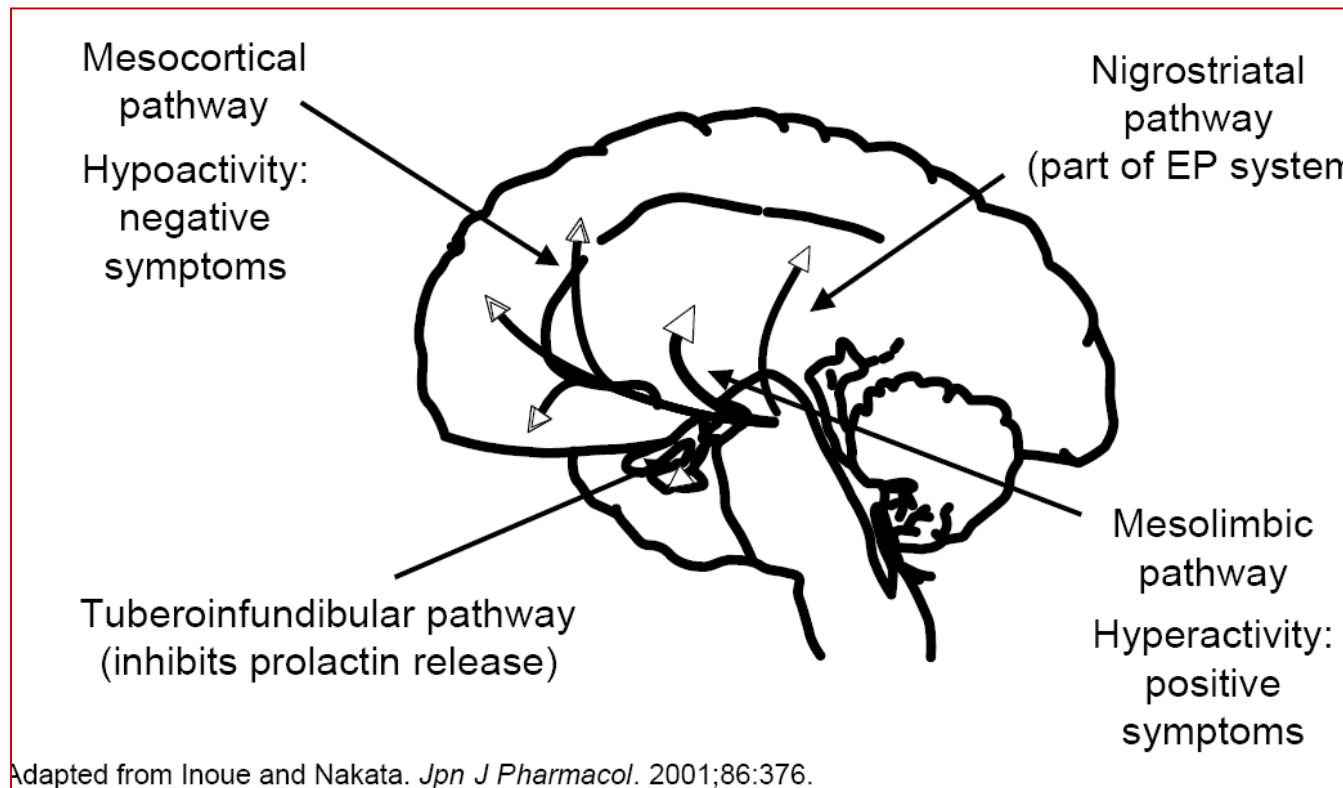
NORADRENERGIC PATHWAY



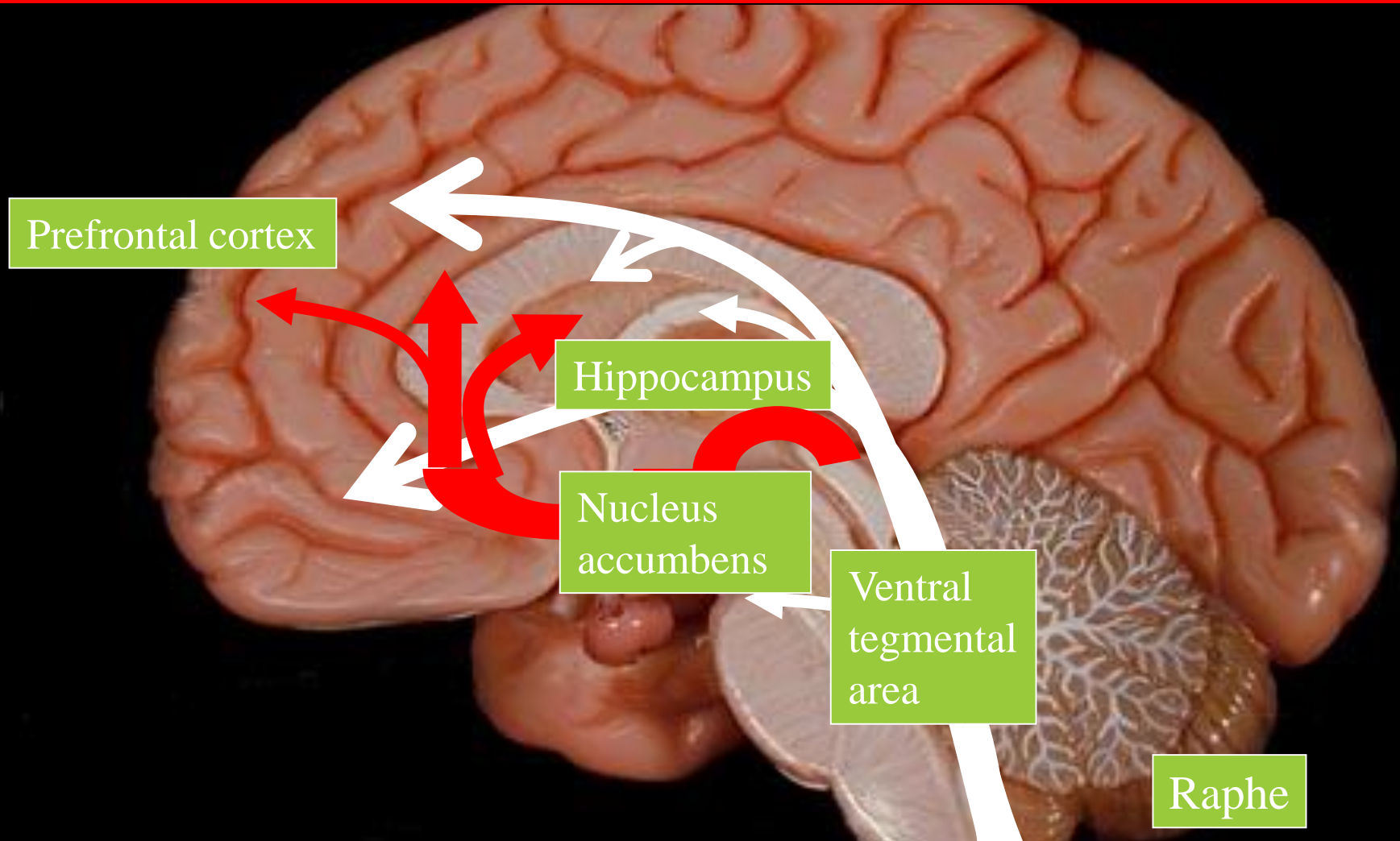
NE DEFICIENCY SYNDROME

- ▶ Impaired attention
- ▶ Problem concentrating
- ▶ Deficiencies in working memory
- ▶ Slowness of information processing
- ▶ Depressed mood
- ▶ Fatigue
- ▶ Psychomotor retardation

DOPAMINE



Dopamine Pathways: Reward, Pleasure, Euphoria, Motor Function, Decision making



Serotonin Pathways: Mood, Memory, Sleep, Cognition

- ▶ **Synthesis : L-tyrosine converted to l-dopa by tyrosine hydroxylase, then to dopamine**
- ▶ **Cell bodies : Substantia nigra, Ventral tegmental area, Hypothalamic nuclei (project to the pituitary)**
- ▶ **Receptors (two families) :
famili D1 dan D2**

DOPAMINE

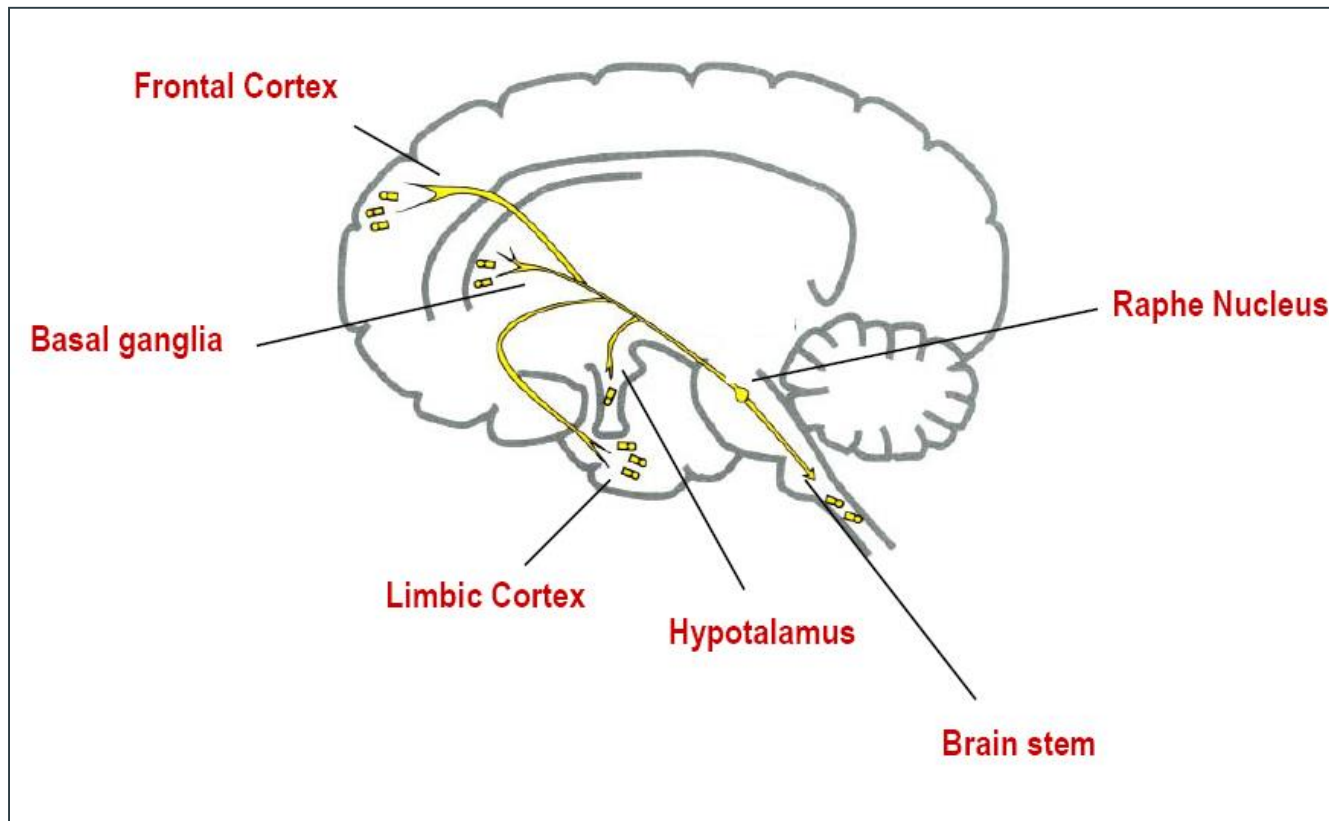
► Movement Disorder

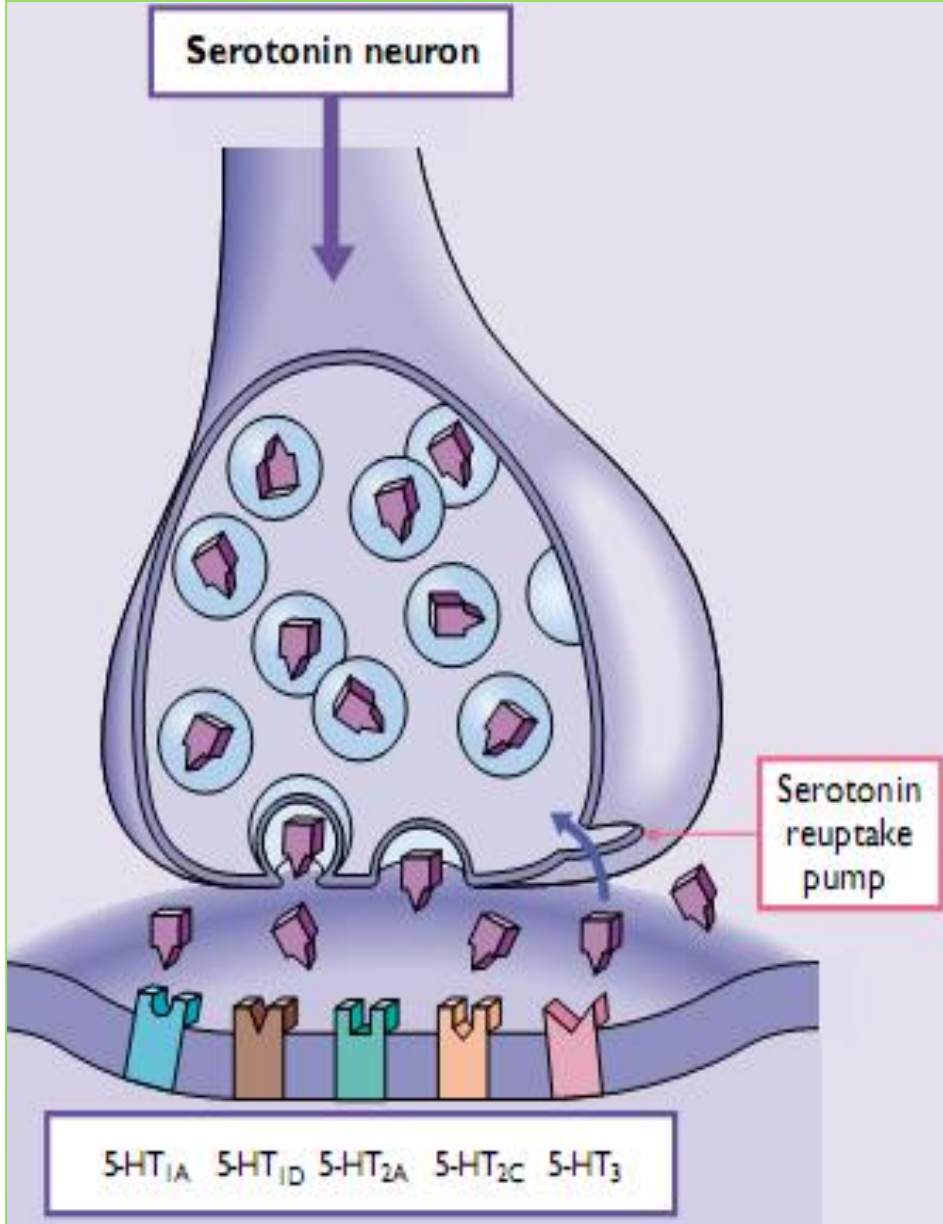
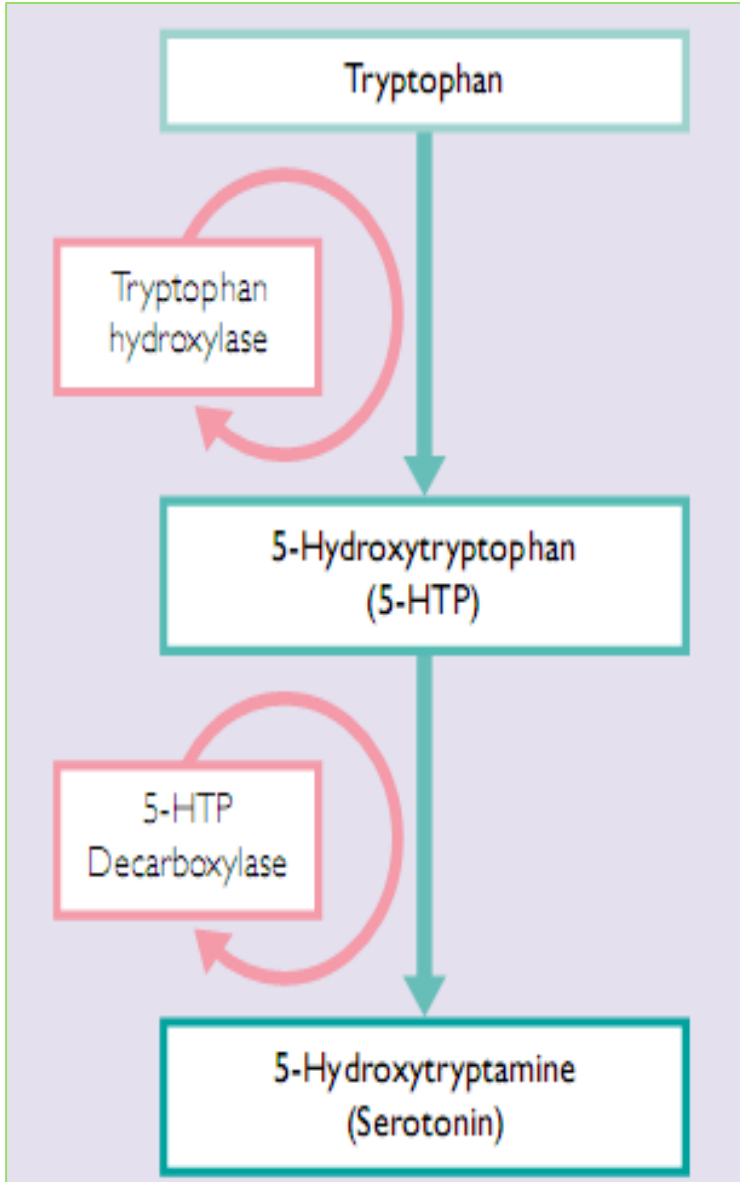
- Substantia nigra cells decline in Parkinson's
- D2 blockade causes EPS symptoms
- L-dopa reverses EPS

► Psychosis

- Amphetamine causes psychosis
- D2 receptor blockade correlated with antipsychotic potency

SEROTONIN PATHWAY





SEROTONIN PATHWAY

- Synthesis

tryptophan hydroxylase

tryptophan \longrightarrow 5 hydroxytryptophan
then decarboxylated to serotonin

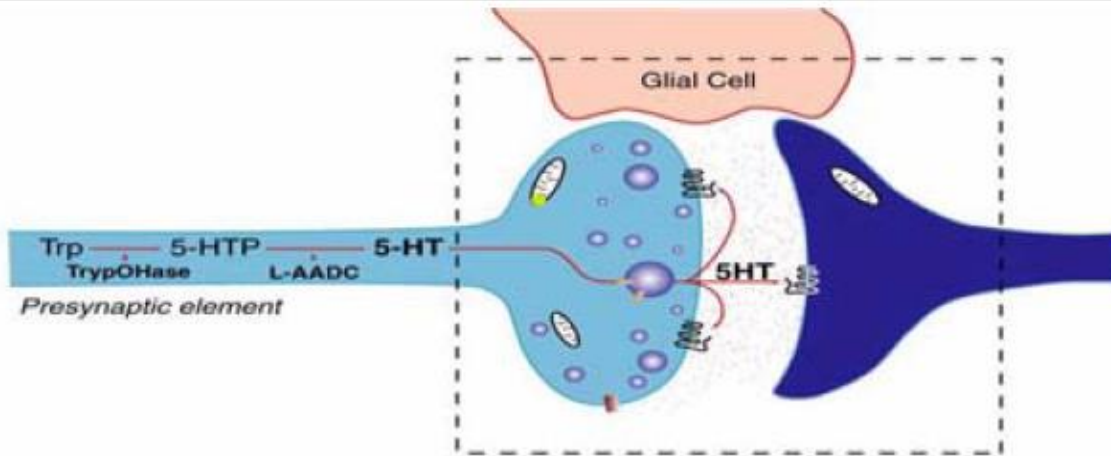
- Cell bodies

- Raphe nucleus

- Receptors

- 5-HT_{1A} principal target but 16 sub-receptors have been identified

SEROTONERGIC (5HT) SYNAPSE

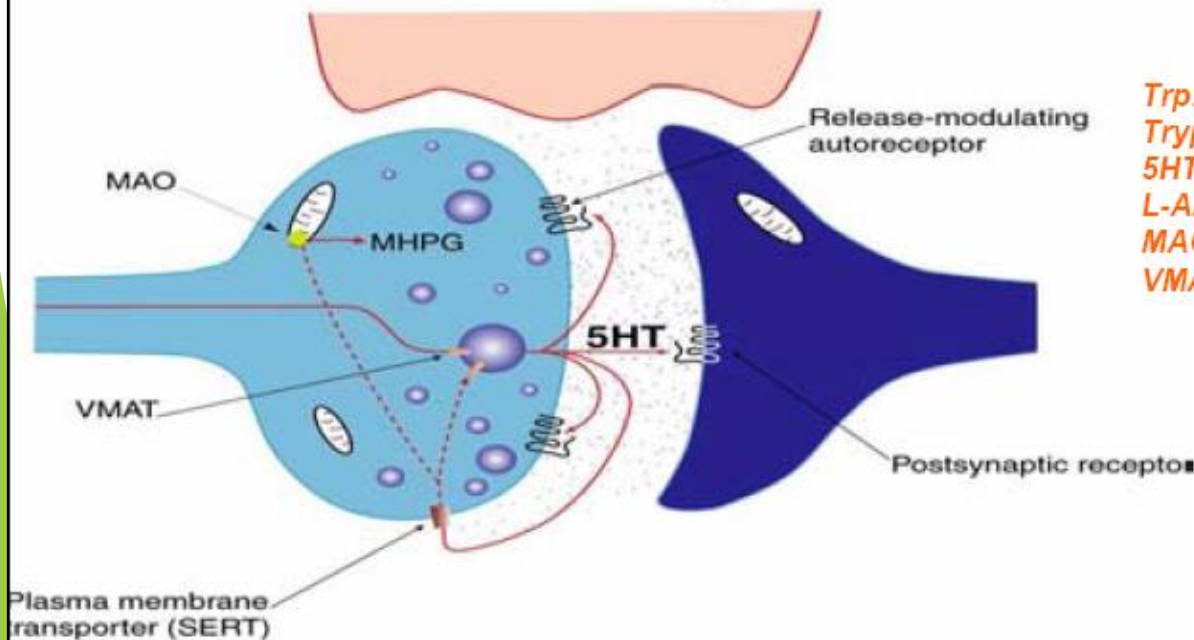


*Presynaptic 5HT Receptors
(Autoreceptors)*

5HT_{1A}, 5HT_{ID}

*Postsynaptic 5HT Receptors
(Heteroreceptors)*

5HT_{1A}, 5HT_{2A}, 5HT_{2C}, 5HT₃,
5HT_{4,6,7}



Trp: Tryptophan

TrypOHase: Tryptophan hydroxylase

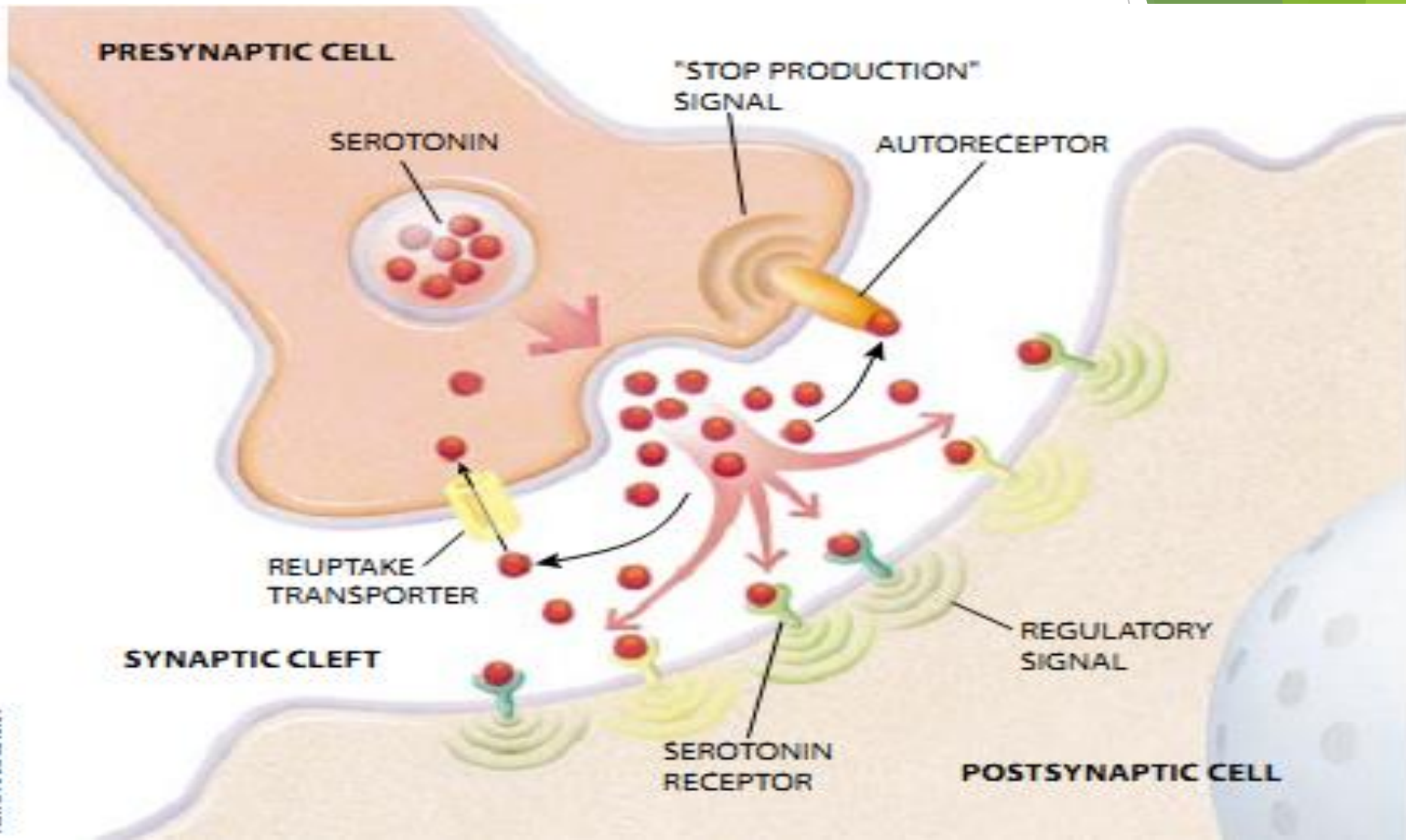
5HTP: 5-Hydroxy tryptophan

L-AADC: L-AromaticAmino acid decarboxylase

MAO: Monoamine oxidase

VMAT: Vesicular amine transporter

Neurotransmisi Serotonin

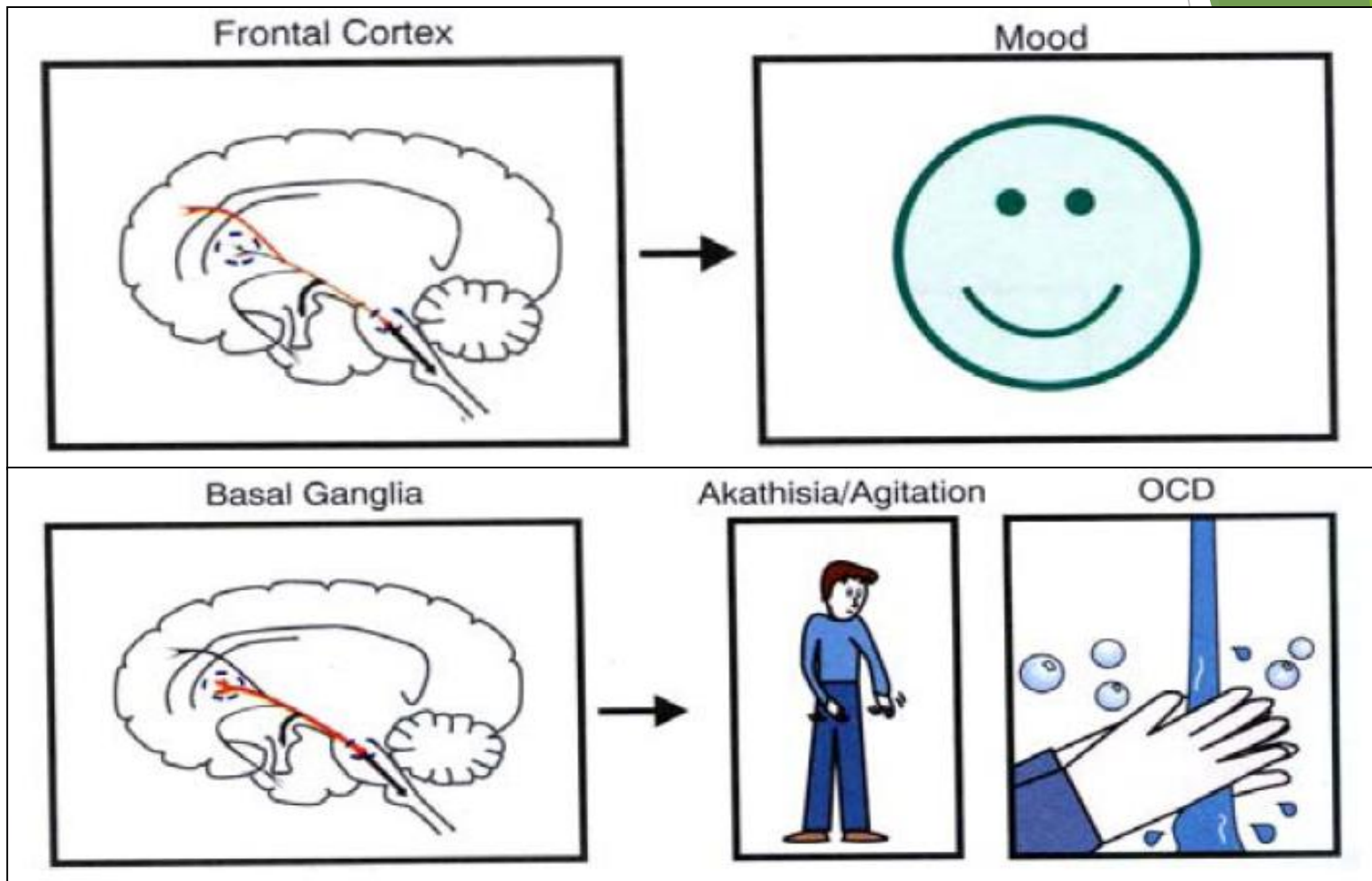


SEROTONIN

- ▶ Mediates antidepressant effects
- ▶ May have beneficial effect on reducing aggressive behavior
- ▶ Inactivated by reuptake by 5-HT transporter

- ▶ SSRIs block the 5-HT transporter

SEROTONIN PATHWAY



SEROTONIN PATHWAY

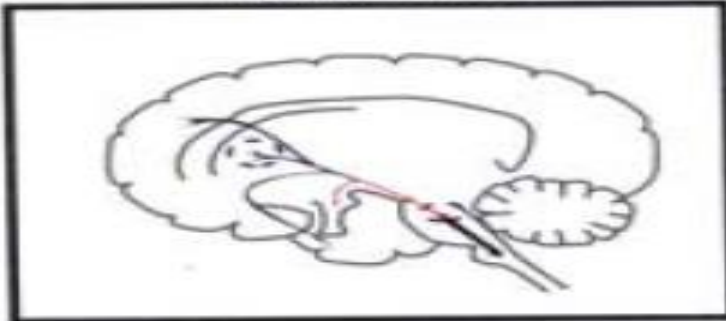
Limbic



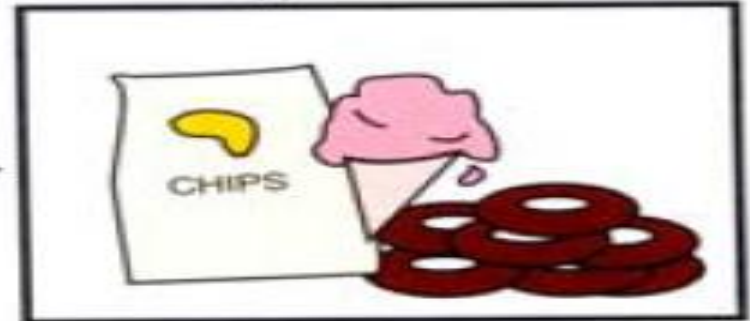
Anxiety



Hypothalamus



Appetite/bulimia



Sleep centers

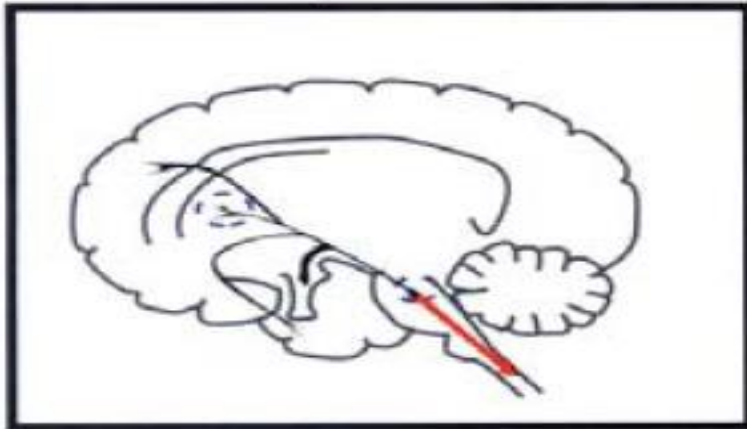


Insomnia

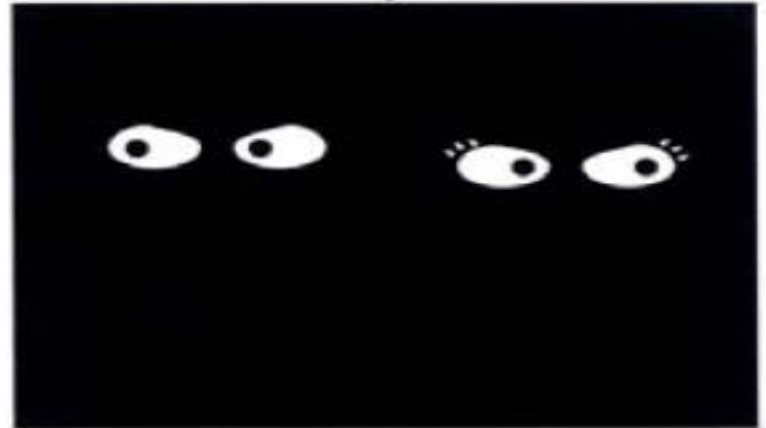


SEROTONIN PATHWAY

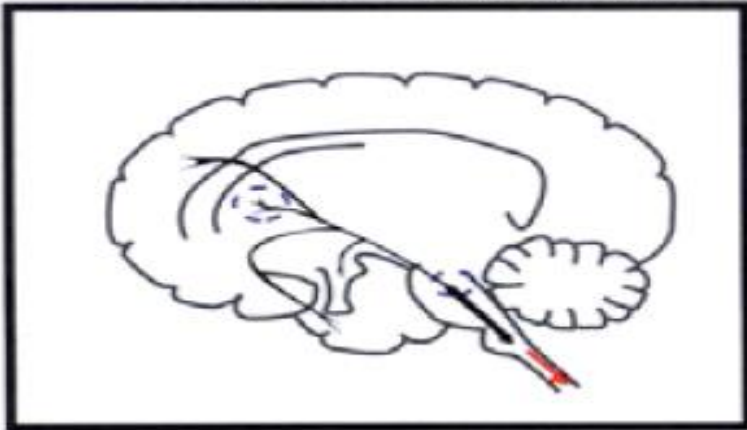
Spinal cord



Sexual dysfunction



Brainstem vomiting center



Nausea and vomiting



5HT DEFICIENCY SYNDROME

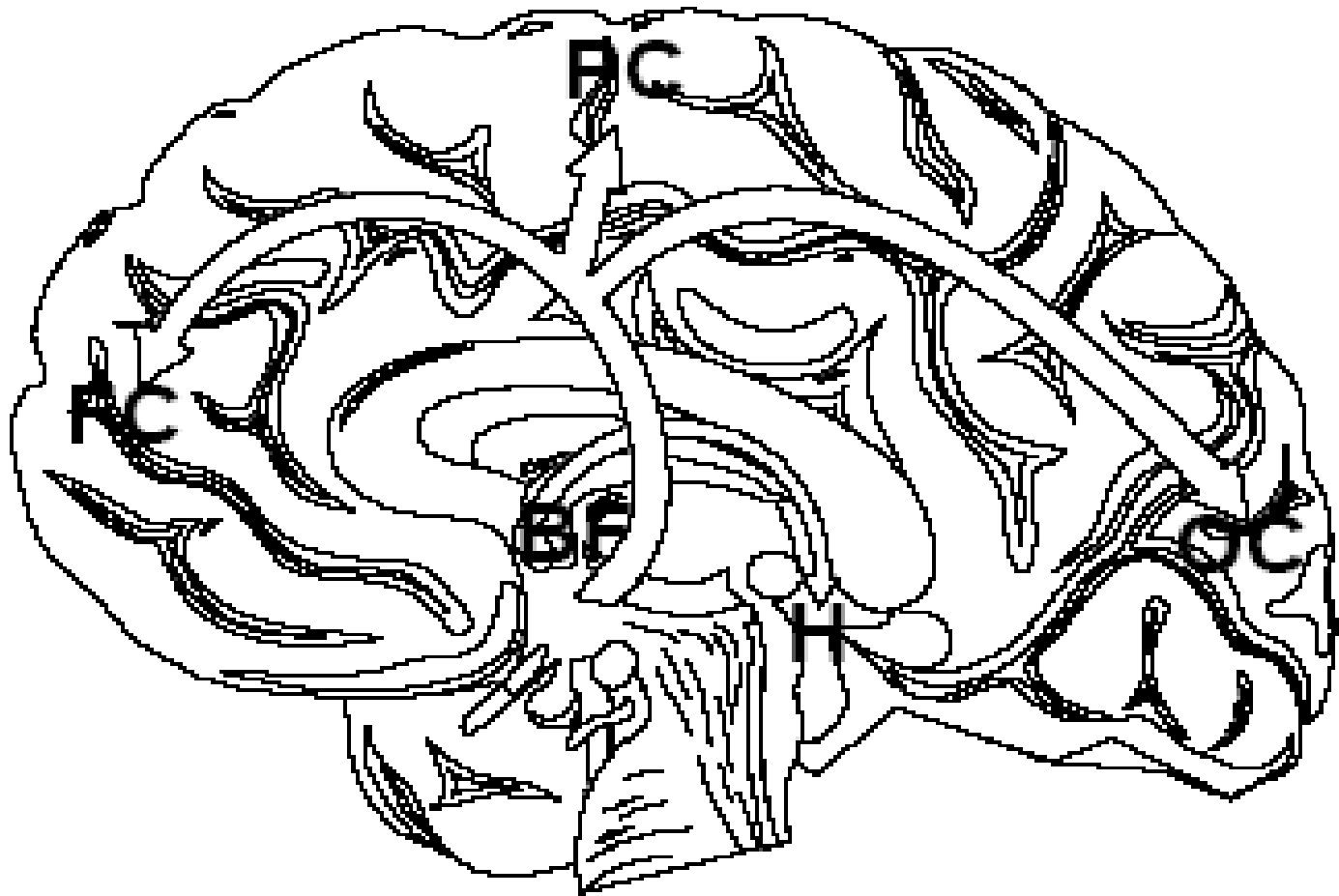
- ▶ Depressed mood
- ▶ Obsession and compulsion
- ▶ Anxiety
- ▶ Panic
- ▶ Phobia
- ▶ Food craving, bulimia

FUNCTIONS OF 5-HT RECEPTORS

1A	Anxiety Depression Sexual Behavior Appetite Aggression Pain Emesis ? Obsessions	2A	Vasoconstriction Migraine Anxiety	3	Emesis Anxiety Psychosis Migraine Reward	5	Unknown
1D	Vasoconstriction Migraine Appetite	2B	Depression Sleep Hallucinations Suicide	4	Muscle contraction gut and heart Learning Cognition Anxiety Sleep Emesis	6	Unknown
		2C	Appetite Anxiety Depression Learning Psychosis			7	Circadian rhythms

Adapted from: Dubovsky and Thomas *J Clin Psychiatry* 1995.

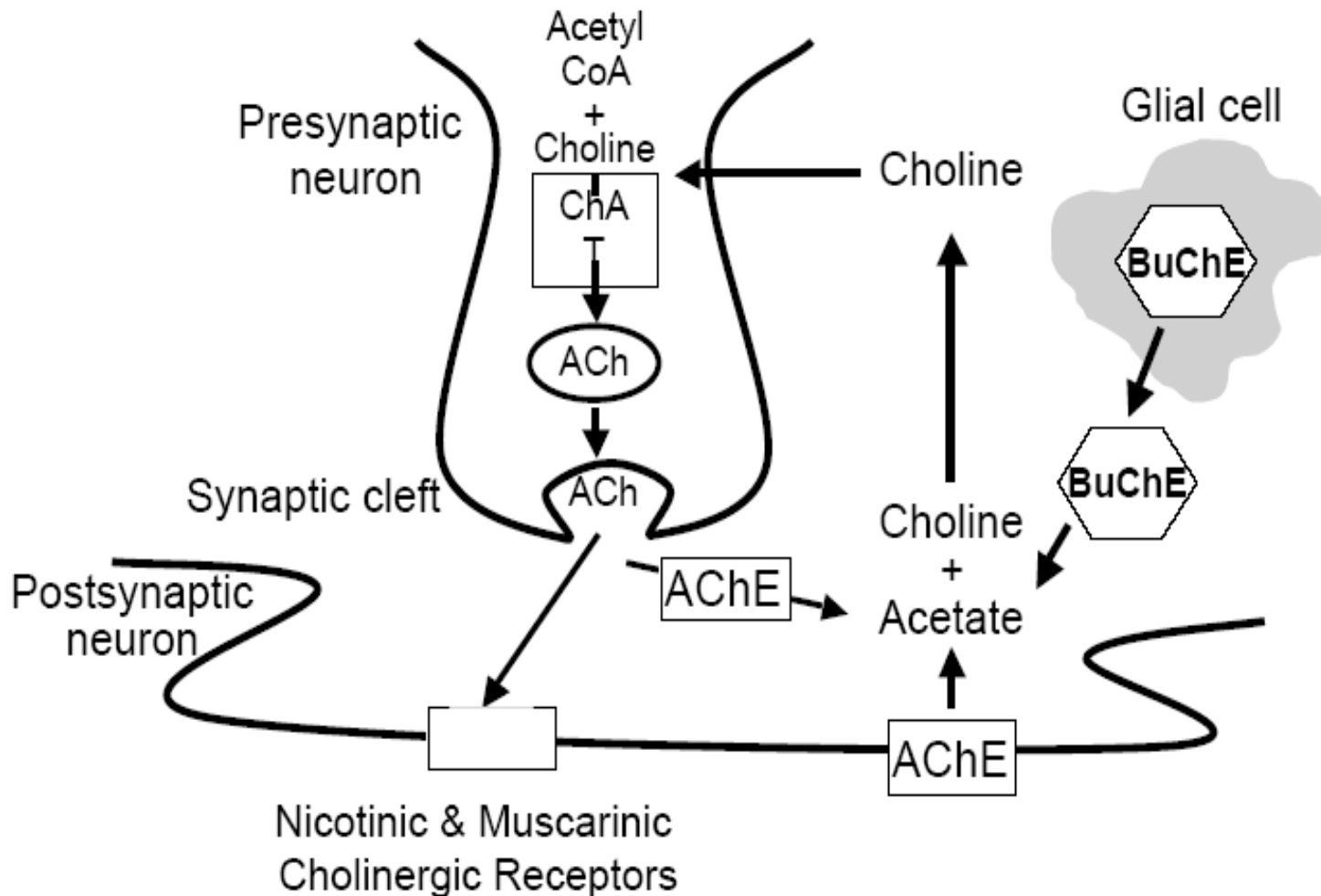
ACETYLCHOLINE PATHWAYS



ACETYLCHOLINE PATHWAYS

- ▶ Location (cell bodies) :Basic forebrain cholinergic complex, Pontomesencephalotegmental cholinergic complex
- ▶ CNS Receptors : Muscarinic (M1 -M)5 and nicotinic receptors

NORMAL CHOLINERGIC FUNCTION



ACh = acetylcholine; AChE = acetylcholinesterase; BuChE = butyrylcholinesterase; ChAT = choline acetyltransferase; CoA = coenzyme A; MR = muscarinic receptor; NR = nicotinic receptor. Adapted from Adem, 1992

- ▶ **Loss of AChE activity in the hippocampus and cerebral cortex of Alzheimer Disease (AD) patients**
- ▶ **Choline acetyltransferase reduced at autopsy in AD**
- ▶ **Blockade of central cholinergic system with scopolamine causes learning impairment in subjects without AD**

GABA

The major inhibitory neurotransmitter in the CNS

- ▶ Synthesis : GABA produced when glutamic acid is decarboxylated by glutamic acid decarboxylase
- ▶ Location (cell bodies) : Widely distributed throughout the brain
- ▶ Receptors : GABA-A and GABA-B
- ▶ Neuropharmacology : The GABA-A receptor maintains a chloride ion channel When stimulated, chloride passes into the cell resulting in hyperpolarization and decreased excitability
- ▶ Involvement in affective disorders
- ▶ Mediates effects of antianxiety drugs
- ▶ May mediate effects of anti-manic anticonvulsant drugs used for behavioral disturbance

- ▶ Benzodiazepines bind to a potentiator site on the GABA-A receptor which increases the amplitude and duration of the effects at this receptor
- ▶ Barbiturates and ethanol also potentiate the effects of GABA-A
- ▶ Valproate increases GABA synthesis and inhibits its catabolism

GLUTAMATE

- ▶ Synthesis : L-glutamate synthesized in axon terminals from glucose, α -ketoglutarate, or from glutamine
- ▶ Inactivation : Glutamate transporters on the neuron or glia
- ▶ Location (cell bodies) : Widely distributed in both local and long range circuits in the brain

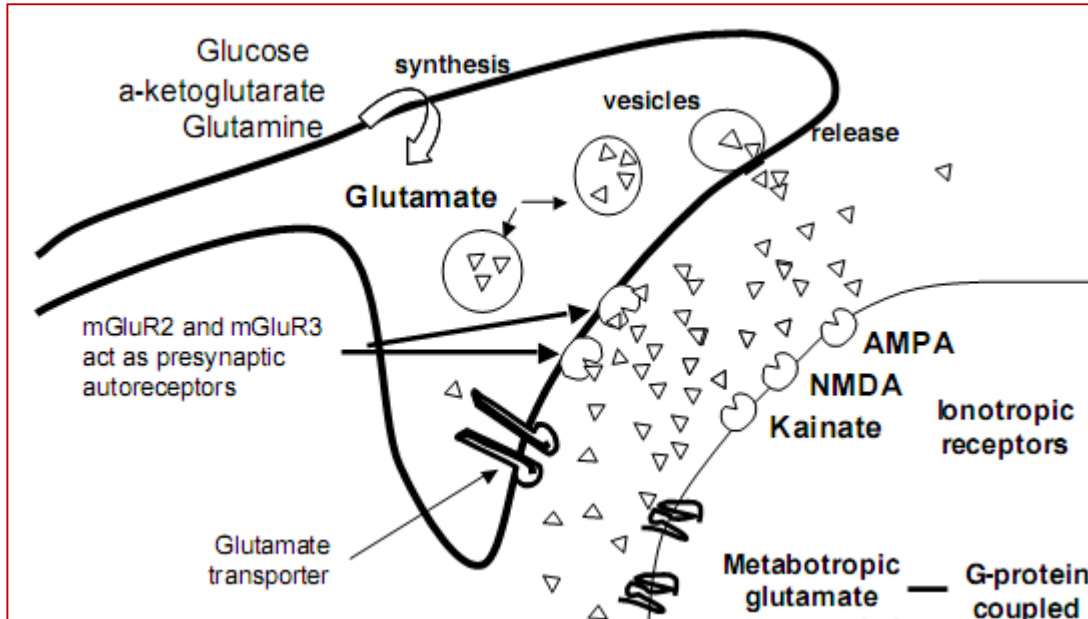
▶ Involvement in dementia : Stress related high levels of glutamate have excitotoxic effects leading to cell death

▶ CNS Receptors :

Ionotropic : NMDA (N-methyl-D-aspartate), AMPA (α -amino-3-hydroxy-5-methylisoxazolepropionic acid), $\ddot{}$ Kainate

Metabotropic : mGluR linked to Gproteins

GLUTAMATE NEUROTRANSMISSION



- ▶ Neuropharmacology
- ▶ Physiologically, glutamate plays a role in synaptic plasticity, learning and memory
- ▶ NMDA antagonists may reduce depressive symptoms
- ▶ NMDA antagonists can induce
psychotic symptoms in schizophrenia

- ▶ Anoxic injury and hypoglycemia can result in: Elevated levels of glutamate, Excessive activation of NMDA receptors, Massive Ca influx into the cell, Cell death

OBAT PSIKOTROPIK

Penggolongan Psikotropika

- ▶ Antipsikotik / neuroleptik
- ▶ Antidepresan
- ▶ Mood stabilizers
- ▶ Antidemensia
- ▶ Sedatif-hipnotik
- ▶ Antiansietas
- ▶ Stimulan

Mekanisme kerja Obat Psikotropik

- ▶ Re-uptake inhibitor
- ▶ Enzim inhibitor
- ▶ Agonis
- ▶ Parsial agonis
- ▶ Antagonis

The end...