

Neuropsychiatry is a field of scientific medicine that concerns itself with the complex relationship between human behavior and brain basis of an interaction of neurobiological and psychological–social factors

Neuropsychiatric Symptoms:

Cognitive impairment ,

Disturbance of consciousness

Neurotic complaints,

Anxiety, Mood changes ,

Psychotic States: Hallucination &

Delusion

Behavioral and Personality

changes

Neuropsychiatric disorders WHO

Stress-related disorders

- Acute stress disorder
- Adjustment disorder
- Post-traumatic stress disorder

Anxiety disorders

- Generalised anxiety
- Phobic anxiety
- Panic disorder
- Obsessive-compulsive disorder

Affective (mood) disorders

- Depressive disorder
- Mania and bipolar disorder

Schizophrenia and delusional disorders

Substance misuse disorders

- Alcohol
- Drugs

Organic disorders

- Acute, e.g. delirium
- Chronic, e.g. dementia

Disorders of adult personality and behaviour

- Personality disorder
- Factitious disorder

Eating disorders

- Anorexia nervosa
- Bulimia nervosa

Somatoform disorders

- Somatisation disorder
- Dissociative (conversion) disorder
- Pain disorder
- Hypochondriasis
- Body dysmorphic disorder
- Somatoform autonomic dysfunction

Neurasthenia

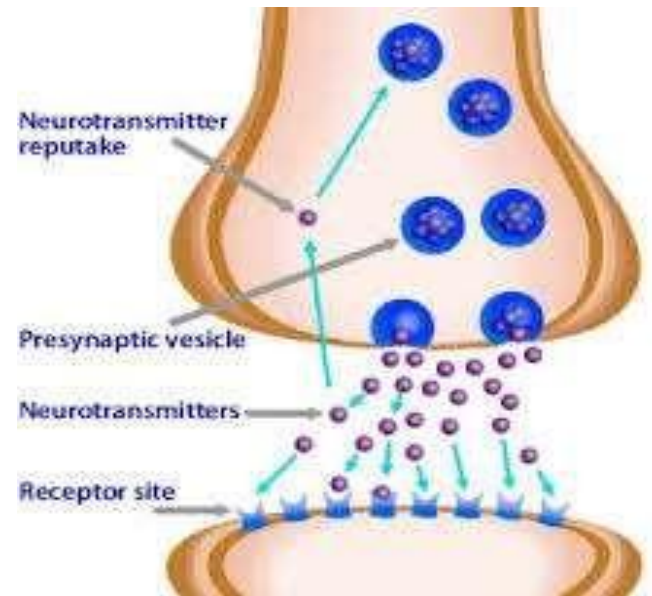
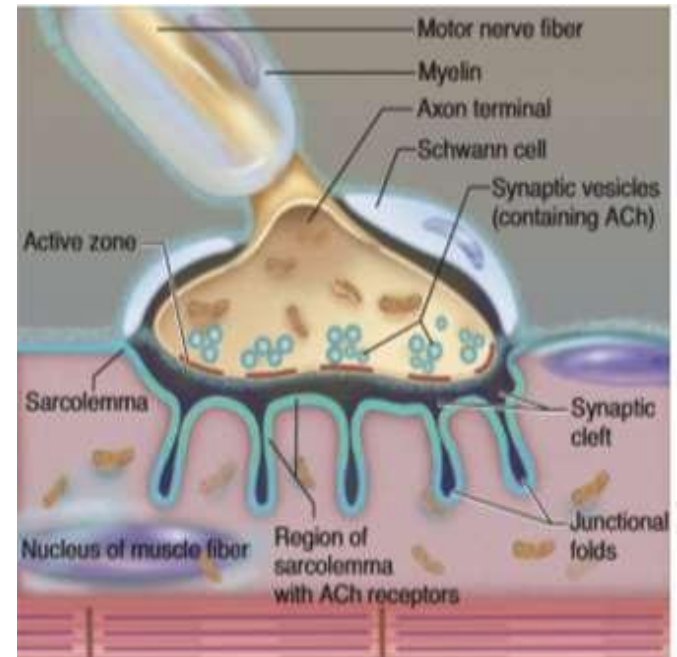
Puerperal mental disorders

Neurotransmitters

- Chemical messengers released from presynaptic nerve terminals into the synaptic cleft

❖ Criteria:

- The substance must be present within the presynaptic neuron
- The substance must be released in response to presynaptic depolarization, which must occur in a Ca^{2+} dependent manner
- Specific receptors for the substance must be present on the postsynaptic cell



Regulation of neurotransmitters is altered in a variety of psychiatric disorders

Neurotransmitters	Diseases
Acetylcholine (ACh)	Alzheimer's disease
Serotonin	Depression Migraine, Aging Attention deficit disorder (ADD) Anxiety
Dopamine	(High) Schizophrenia (Low) Parkinsonism
GABA (γ -Aminobutyrate)	Epileptic seizures
Glutamate	Migraine Stroke Autism

Role of Acetylcholine in Alzheimer's disease

- **AD is a neurodegenerative disease characterized by progressive impairment of memory and cognitive functions**
Prevalence increases with age and may be as high as 20% in individuals over 85
- **Progressive loss of neurons (cholinergic neurons) and thinning of the cortex**
- **Marked decrease in choline acetyltransferase and other markers of cholinergic function**

Alzheimer's disease (AD)

❖ Pathologic changes include:

- Mitochondrial dysfunction**
- Increased deposits of amyloid β peptide in the cerebral cortex**
- Formation of extracellular plaques and cerebral vascular lesions, and intraneuronal fibrillary tangles consisting of the tau protein**
- This interferes with synaptic signaling**

Mild Alzheimer's Disease	Moderate Alzheimer's Disease	Severe Alzheimer's Disease
▪ Memory loss starts ▪ Difficulty in finding direction ▪ Frequently asking questions ▪ One takes longer time to complete normal daily tasks ▪ Poor judgment ▪ Personality changes ▪ Diagnostic stage	▪ Damage occurs in areas of the brain that control language, reasoning, sensory processing, and conscious thought ▪ Memory loss and confusion increases ▪ Have problems recognizing family and friends ▪ Unable to learn new things and carry out tasks that involve multiple steps ▪ Hallucinations, delusions and paranoia, and may behave impulsively	▪ Plaques and tangles spread throughout the brain ▪ Brain tissue has shrunk significantly ▪ Cannot communicate and are completely dependent on others for their care ▪ Person becomes bedridden

Alzheimer's disease (AD)

- Some evidence implicates excess excitation by glutamate and abnormalities of mitochondrial function as a contributor to neuronal death

Treatment

☐ **Acetylcholinesterase inhibitors:**

For mild to moderate:

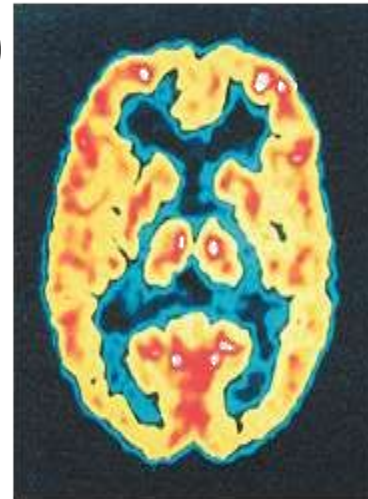
- ☐ Donepezil
- ☐ Galantamine
- ☐ Rivastigmine

For advance:

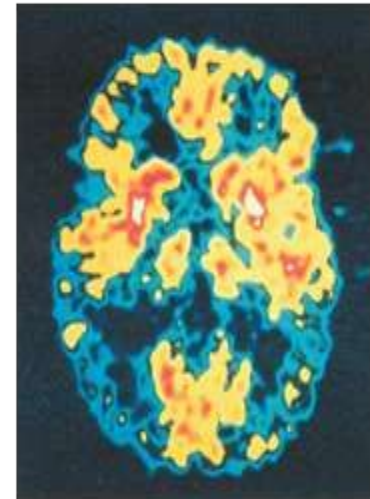
Donepezil

Diagnosis of Alzheimer's disease (AD)

- A thorough medical history
- Mental status testing
- A physical and neurological exam
- Brain imaging



NORMAL



ALZHEIMER'S

Brain scans done with Positron Emission Tomography (PET) show how Alzheimer's affects brain activity. The left image shows a normal brain, while the right is from a person with Alzheimer's. The blue and black areas in the right image indicate reduced brain activity resulting from the disease.

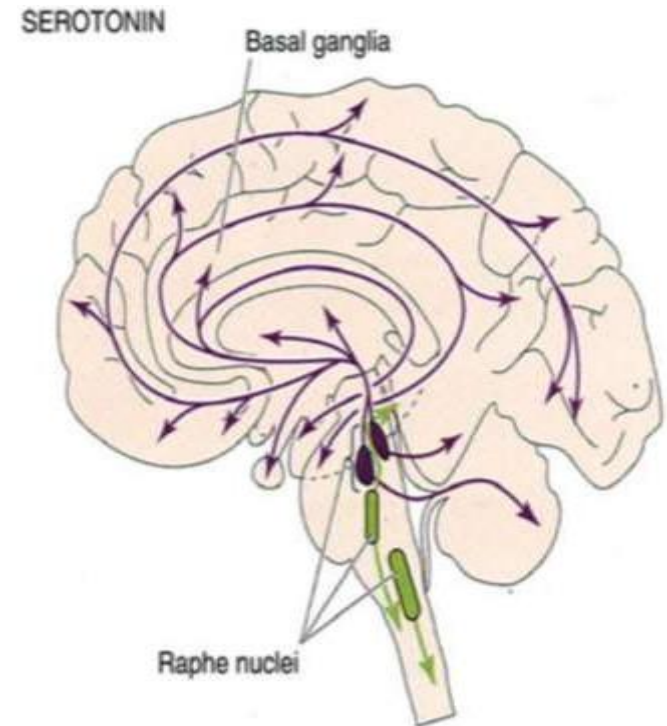
**Healthy
Brain**

**Severe
Alzheimer's**



Serotonin

- Serotonin or 5-hydroxytryptamine (5HT) is found in plant and animal tissues, venoms, and stings.
- Highest concentration is found in blood platelets and in the gastrointestinal tract, where it is found in the **enterochromaffin cells** and the **myenteric plexus**
- Smaller amounts occur in the CNS, the **raphé nuclei** of the brain stem (neurotransmitter)



Biosynthesis of Serotonin

- **Precursor:**

- Serotonin is formed in the body by hydroxylation and decarboxylation of the essential amino acid **tryptophan**
- Hydroxylation at C5 is the **rate-limiting step**
- The product, 5-hydroxytryptophan, is decarboxylated to serotonin

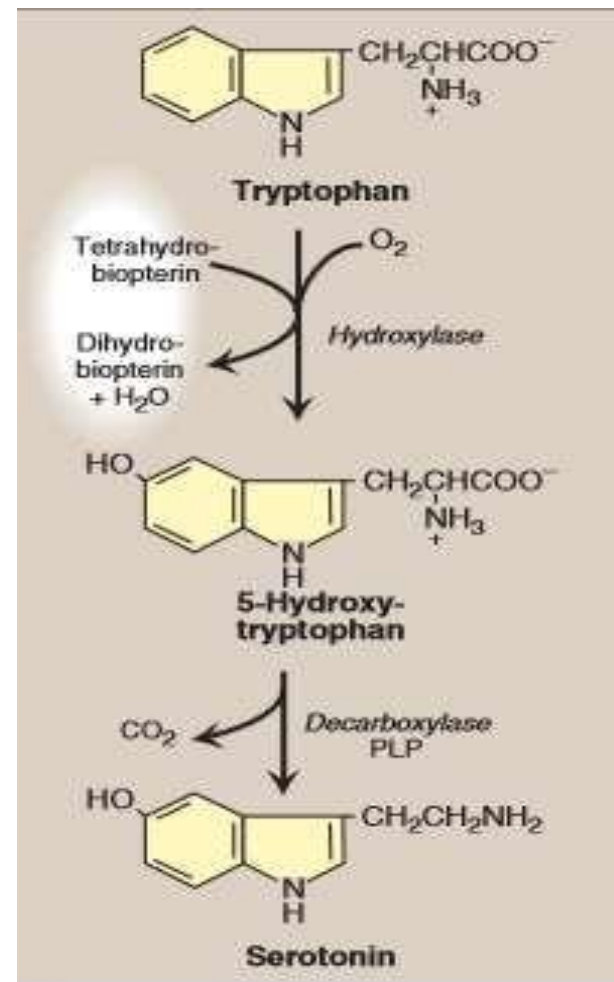
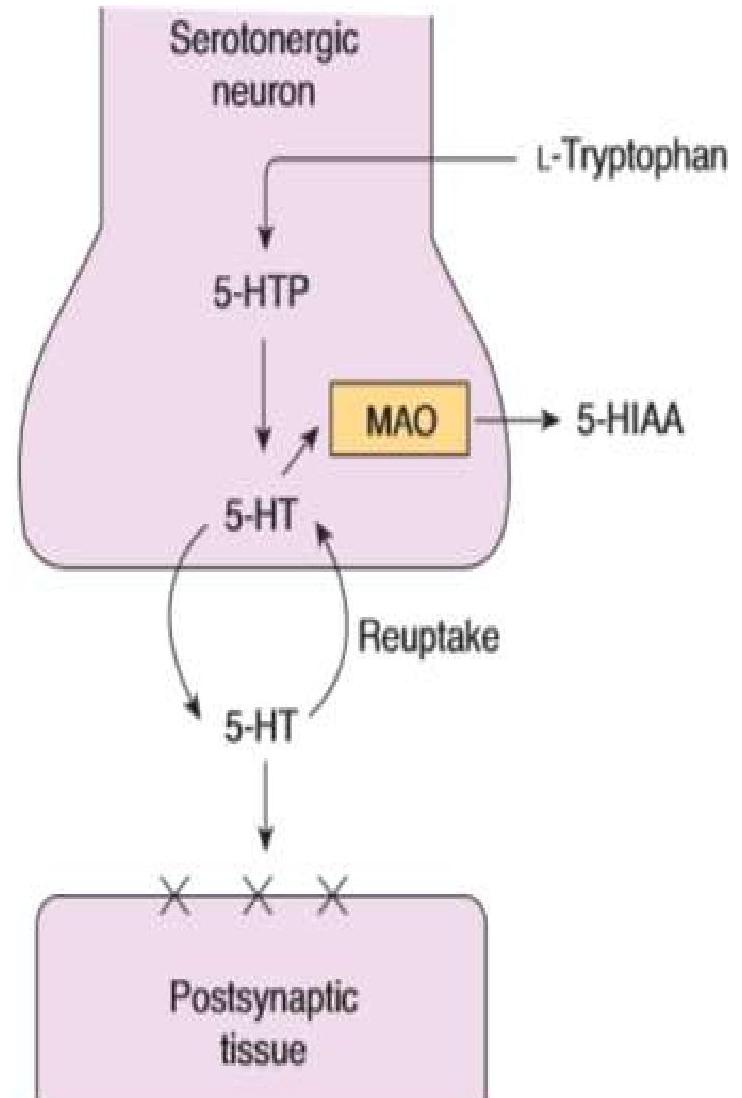


Figure 21.18

Synthesis of serotonin. PLP = pyridoxal phosphate.

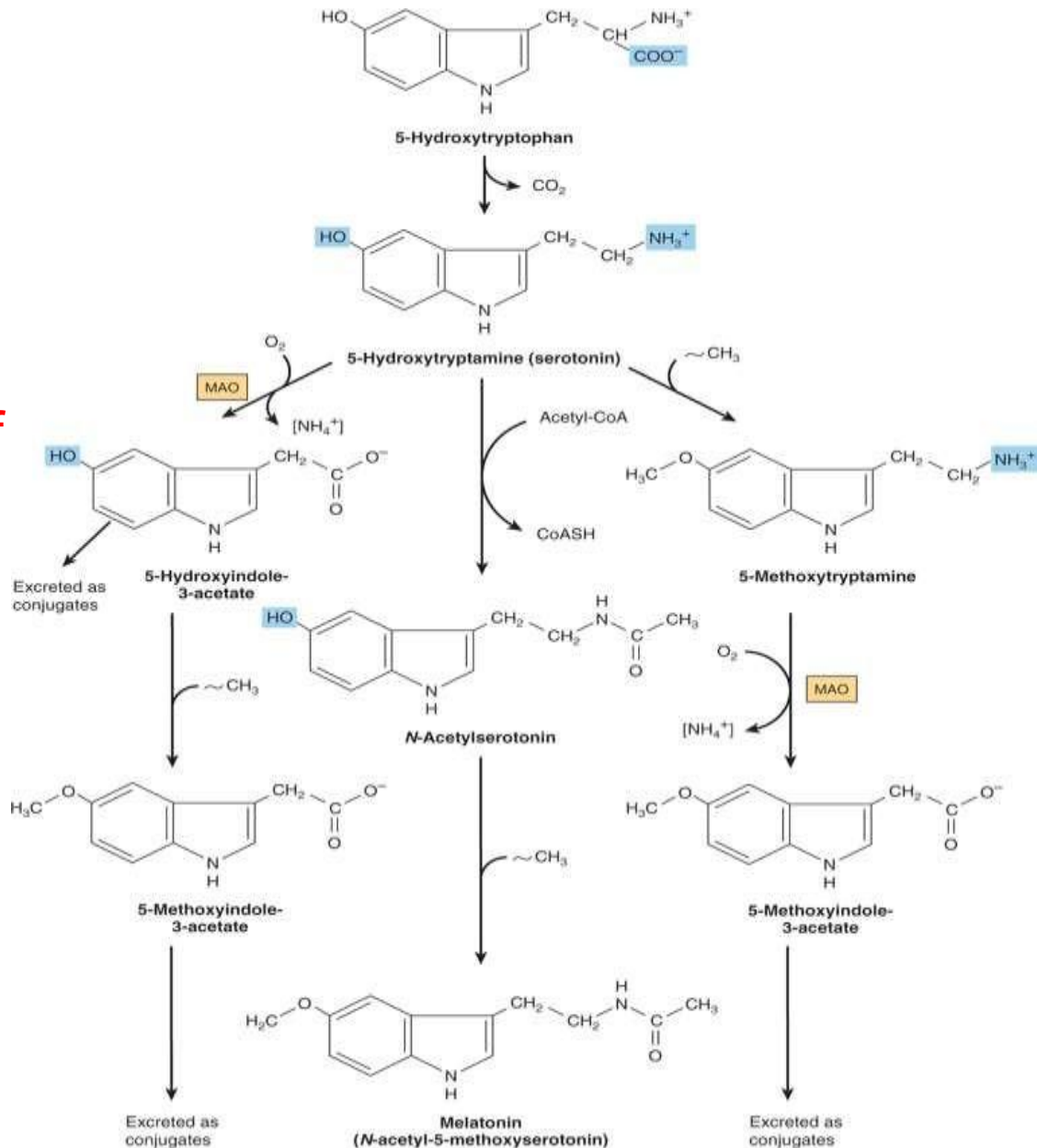
Biosynthesis of Serotonin contd...

- After release from serotonergic neurons, much of the released serotonin is recaptured by an active reuptake mechanism and inactivated by monoamine oxidase (MAO) to form 5-hydroxyindoleacetic acid (5-HIAA)
- 5-HIAA is the principal urinary metabolite of serotonin
- Urinary output of 5-HIAA is thus used as an index of the rate of serotonin metabolism in the body



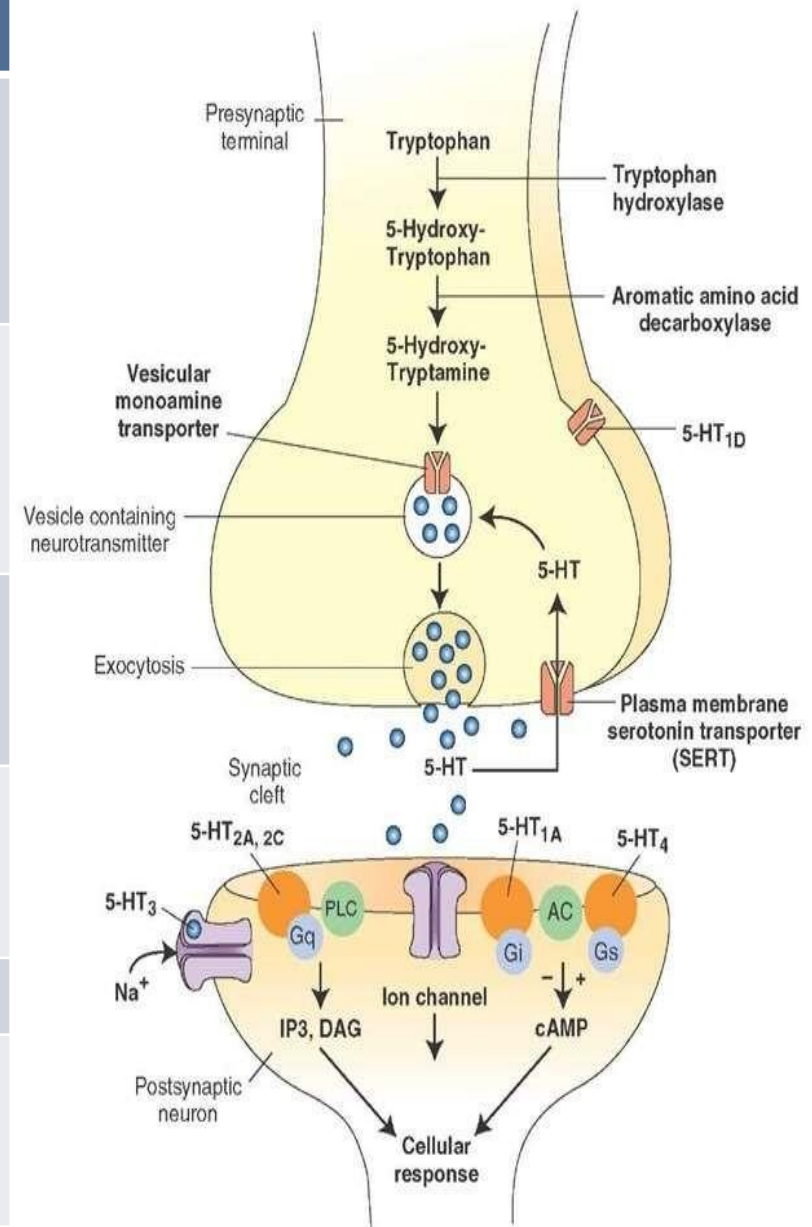
Metabolism of Serotonin

- It is degraded by MAO to form (5-HIAA)
- 5-HIAA appear in patients with **Carcinoid syndrome** (neoplasm of enterochromaffin cells)
- It is metabolized to melatonin in the pineal gland via acetylation and methylation



Serotonergic Receptors

Receptors	Location and Actions
❖ 5-HT ₁ 5-HT _{1A} , 5-HT _{1B} , 5-HT _{1D} , 5-HT _{1E} , 5-HT _{1F} , 5-HT _{1P}	Brain, Raphe nuclei
❖ 5-HT ₂ 5-HT _{2A} , 5-HT _{2B} , 5-HT _{2C}	Platelet aggregation and smooth muscle contraction
❖ 5-HT ₃	Gastrointestinal tract, area postrema; vomiting
❖ 5-HT ₄	Gastrointestinal tract; brain; secretion and peristalsis
❖ 5-HT _{5A,B}	Brain;
❖ 5-HT _{6,7}	Brain; 5-HT ₆ high affinity for antidepressant drugs



Role of Serotonin in Neuropsychiatric Diseases

- ❖ Serotonin has multiple physiologic roles, including pain perception, regulation of sleep, appetite, temperature, blood pressure, vomiting, cognitive functions, and mood (causes a feeling of well-being)
- ❖ In addition to these, it has been found to be involved in conditions such as:
 - **Depression**
 - **Anxiety**
 - **Aging**
 - **Attention deficit disorder (ADD)**
 - **Migraine**



Depression

- Most common of the major psychiatric disorders that has a lifetime prevalence of about 5-8% in population
 - i. Major depressive disorder (MDD)
 - ii. Manic depression or bipolar disorder
- ❖ MDD is characterized by:

10.8 Symptoms of depressive disorders	
Psychological	
• Depressed mood • Reduced self-esteem • Pessimism • Guilt	• Loss of interest • Loss of enjoyment (anhedonia) • Suicidal thinking
Somatic	
• Reduced appetite • Weight change • Disturbed sleep • Fatigue	• Loss of libido • Bowel disturbance • Motor retardation (slowing of activity)



- Coronary artery disease, diabetes, and stroke

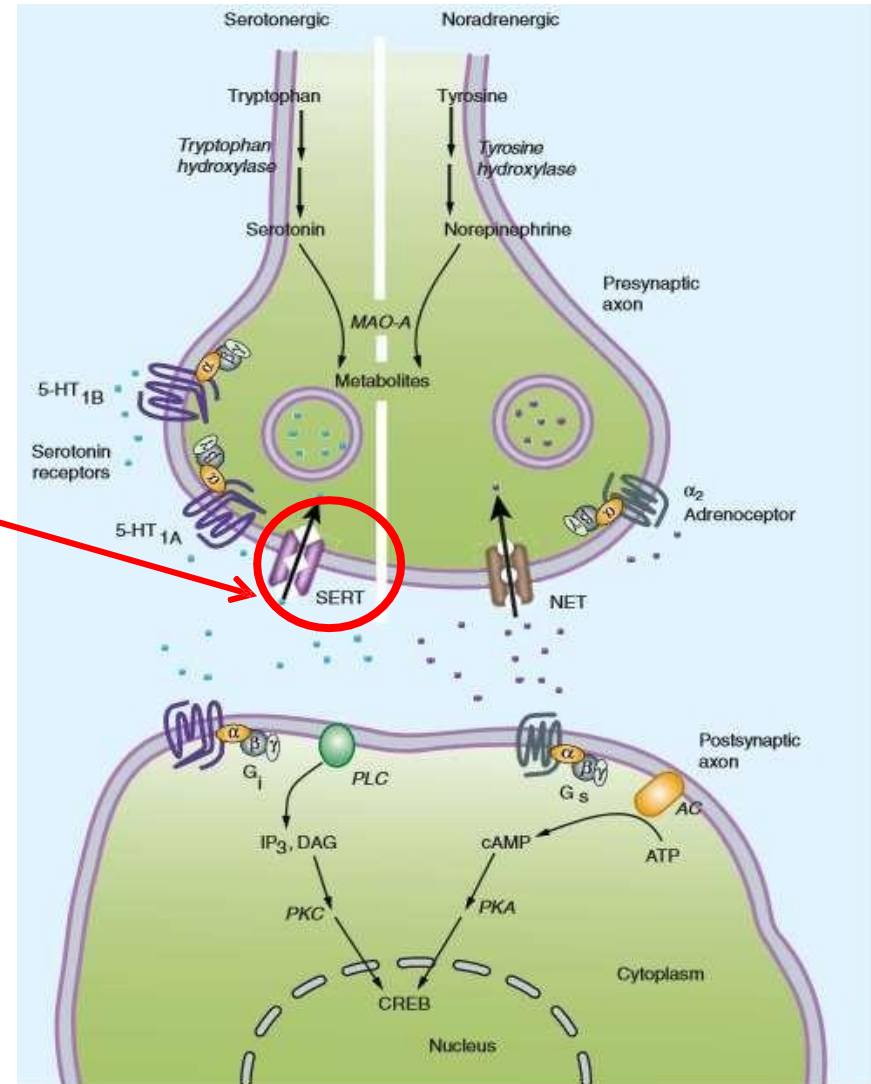
Role of Serotonin in Mood and Behavior

- A significant correlation exists between behavior and brain serotonin content
- **Examples:**
 - Lysergic acid diethylamide (LSD): A serotonin agonist and a hallucinogenic agent** produces its effects by activating 5-HT₂ receptors in the brain
 - MDMA (3,4-Methylenedioxymethamphetamine) or ecstasy:**
A popular drug of abuse
It produces euphoria initially which is followed by difficulty in concentrating, depression, and, in monkeys, insomnia

Role of Serotonin in Depression

A. Monoamine hypothesis:

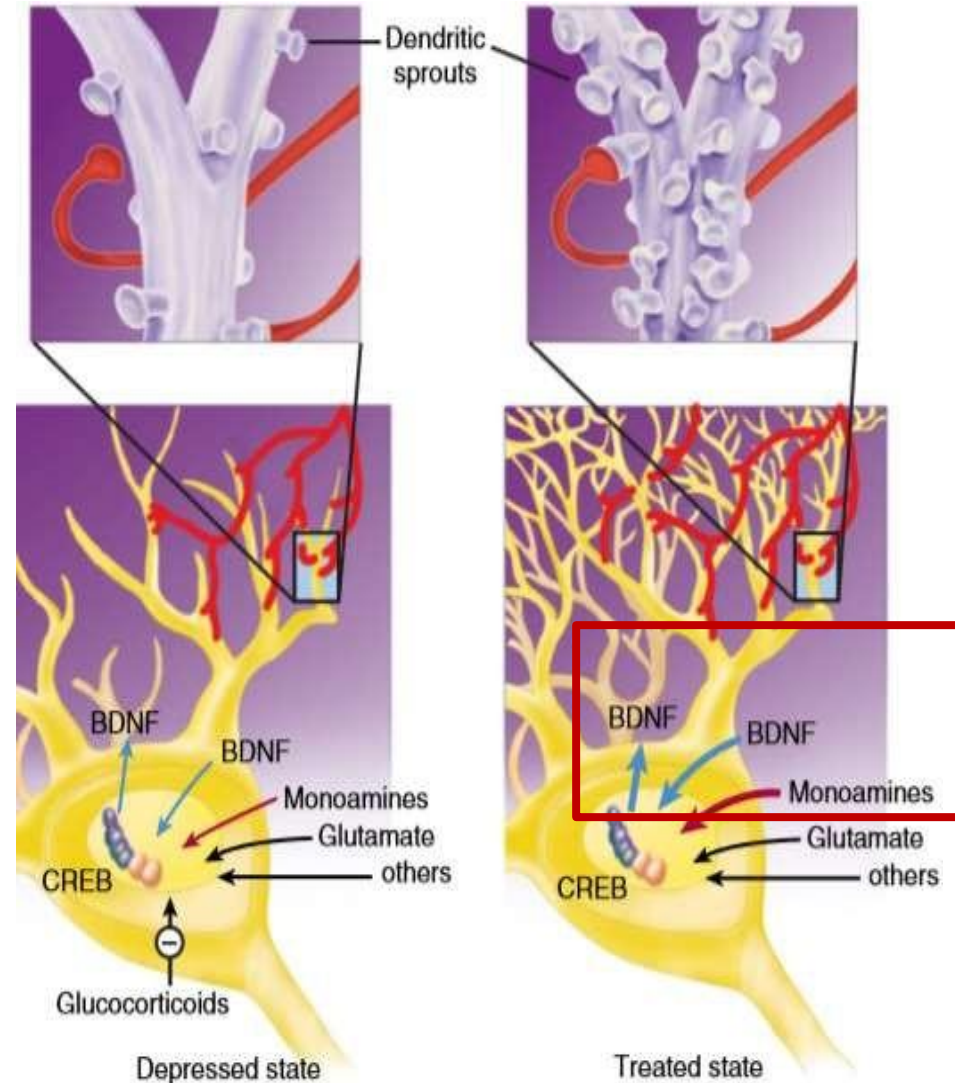
- Deficiency in the amount or function of cortical and limbic serotonin, norepinephrine (NE), and dopamine (DA)
- **SSRIs (Selective Serotonin Reuptake Inhibitors):**
Inhibition of the serotonin transporter (SERT)
Fluoxetine, Sertraline, Citalopram



Depression

B. Neurotrophic hypothesis:

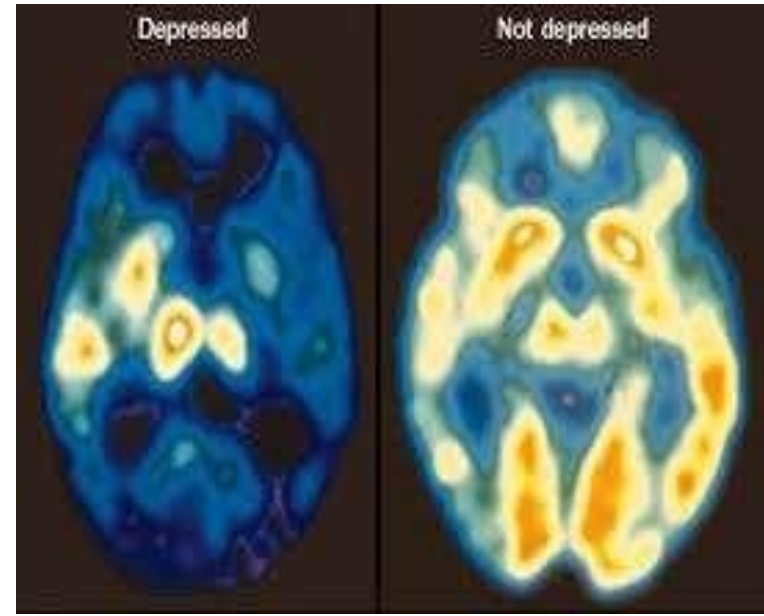
- BDNF (Brain-derived neurotrophic factor)
- Nerve growth factor that influences neuronal growth is lost in depression
- Antidepressant therapy has been found to increase neurogenesis and synaptic connectivity



Clinical Diagnosis of Depression

- i. **Structural imaging** studies in major depression is associated with a 5–10% loss of volume in the hippocampus of brain
- ii. **Biological markers of depression are:**
 - a. CSF level of 5-HIAA is low
 - b. 24hr urinary collection of 5-HIAA
 - c. Hypocholesterolemia
 - d. Low blood folate levels
 - e. Decreased 5-HT_{1A} receptor expression
 - f. Decreased BDNF in serum

Reference range: < or =210 mcg/24 hrs



However, depressive disorders are heterogeneous and diagnosed on the basis of a patient's symptoms, not on the basis of a laboratory test

Treatments for depression

- **Anti-depressants**

- i. Selective Serotonin Re-uptake Inhibitors (SSRIs)
Citalopram, Escitalopram, Fluoxetine, Sertraline
- ii. Serotonin/Norepinephrine Re-uptake inhibitors
Duloxetine, Venlafaxine
- iii. Atypical Antidepressants- Bupropion, Mirtazapine, Trazodone
- iv. Tricyclic antidepressants- Amitriptyline, Doxepin, Amoxapine
- v. Monoamine oxidase inhibitors- Phenelzine, Selegiline

- **Psychotherapy**

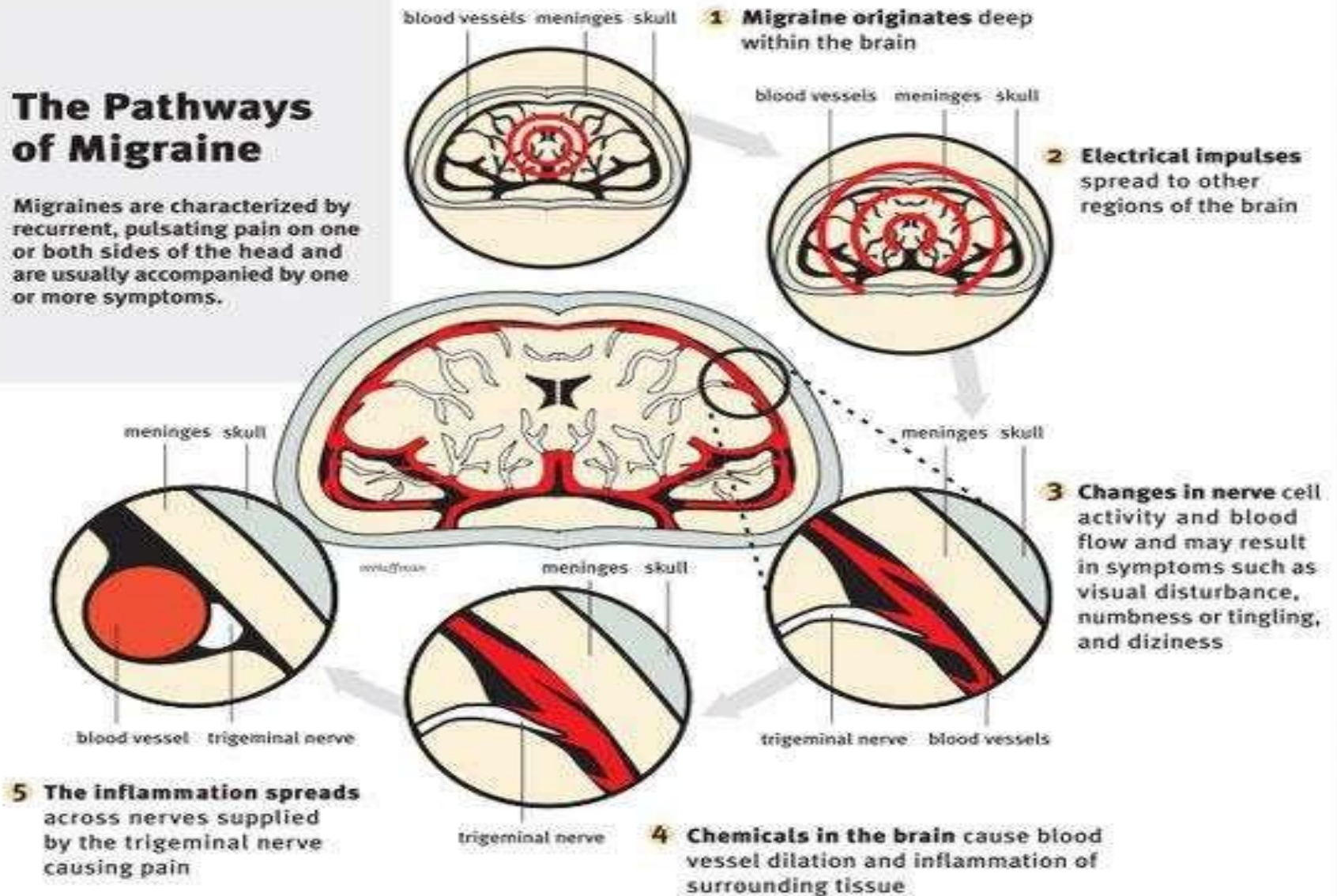
- **Electroconvulsive therapy:**
for life threatening depression



Migraine

The Pathways of Migraine

Migraines are characterized by recurrent, pulsating pain on one or both sides of the head and are usually accompanied by one or more symptoms.



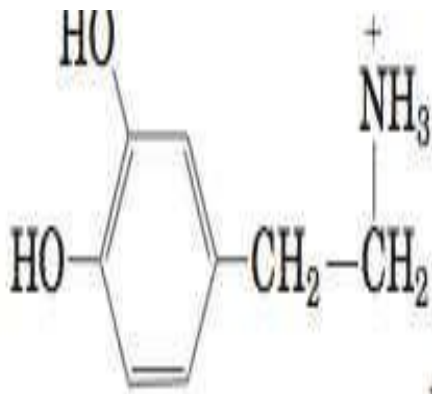
Role of Serotonin in Migraine

- Levels of serotonin in a person's system may rise and suddenly fall prior to migraine
- **Low levels of serotonin are linked to both migraines and depression**
- 5-HT concentrations in blood has been found to increase during the prodromal (aura) phase and subsequently, decrease to subnormal levels in the headache phase

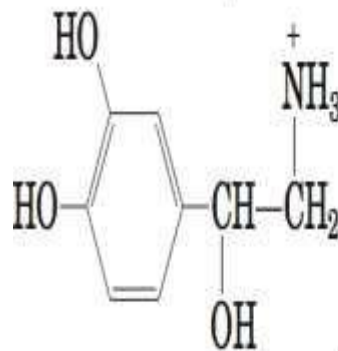


CATECHOLAMINES

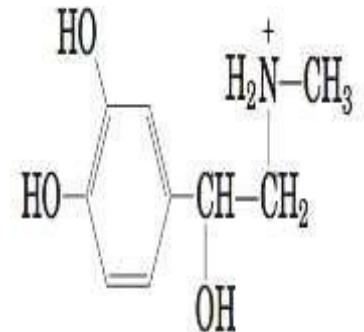
- Catecholamines are substances that have a catechol nucleus, a 3,4-dihydroxylated benzene ring
- Catecholamines transmitter are dopamine, norepinephrine, and epinephrine



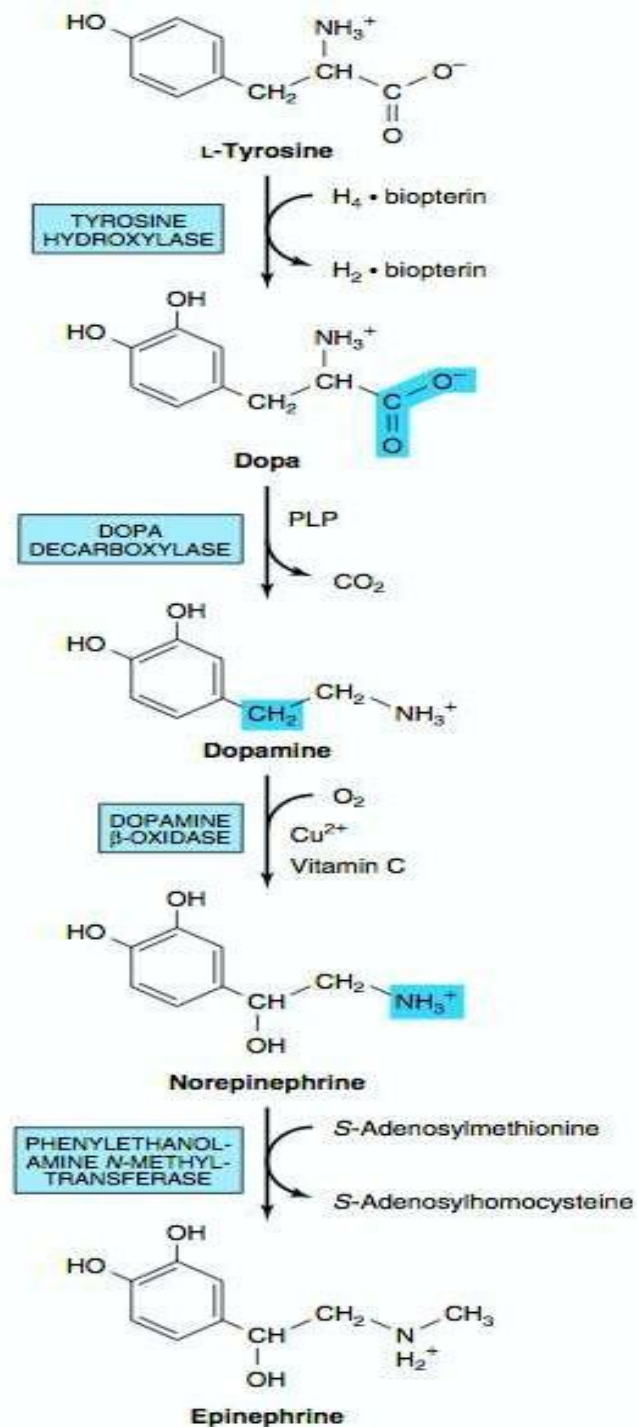
Dopamine



Norepinephrine

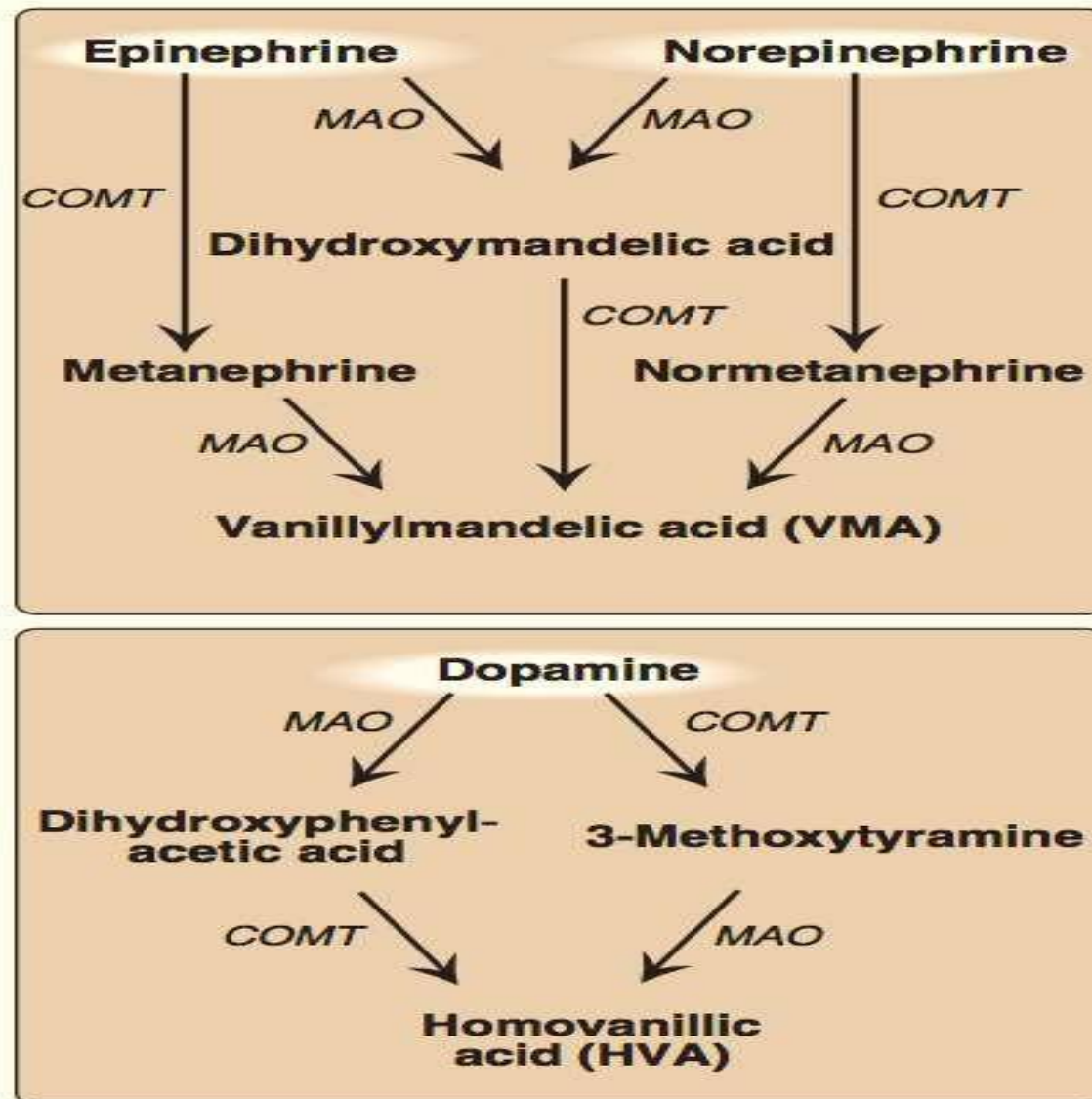


Epinephrine



- **tyrosine hydroxylase** is rate-limiting for catecholamine biosynthesis
- functions as an oxidoreductase, with **tetrahydropteridine** as a cofactor
- tyrosine hydroxylase is regulated by feedback inhibition
- **dopa decarboxylase** requires **pyridoxal phosphate**
- Compounds that resemble L-dopa, such as α -methyldopa, are competitive inhibitors
- **dopamine hydroxylase (dbh)** uses ascorbate as an electron donor, copper at the active site, and fumarate as modulator
- Synthesis of **PNMT**(phenylethanolamine-*n*-methyltransferase) is induced by

Degradation of catecholamines



Catecholamines

Norepinephrine

- stimulatory processes
- elevated levels → ANXIETY, MOOD DAMPENING
- Low levels → LOW ENERGY ability and sleep cycle problems

epinephrine

- elevated → attention deficit disorder with hyperactivity (ADDH)
- Depleted level → Long term STRESS or INSOMNIA

Diagnostic use

Ref. Range:

Younger than 1 year: < 27 mg/g creatinine

Age 1-2 years: < 18 mg/g creatinine

Age 2-4 years: < 13 mg/g creatinine

Age 5-9 years: < 8.5 mg/g creatinine

Age 10-14 years: < 7 mg/g creatinine

The reference range in persons aged 15 years and older is
2-7 mg/24 hours

Conditions associated with elevations in urinary
VMA include the following: stress and anxiety

Mechanism of action of dopamine

- Action depend upon type of receptor with which it interacts
- Central effects of dopamine

Receptor subfamily	location	action
D1 and D2	Substantia nigra and striatum	Motor control
D1 and D2	Limbic cortex and associated structure	Information processing
D2	Anterior pituitary	Inhibits prolactin release

Dopamine receptors

Are G protein coupled receptors and are grouped into two families:

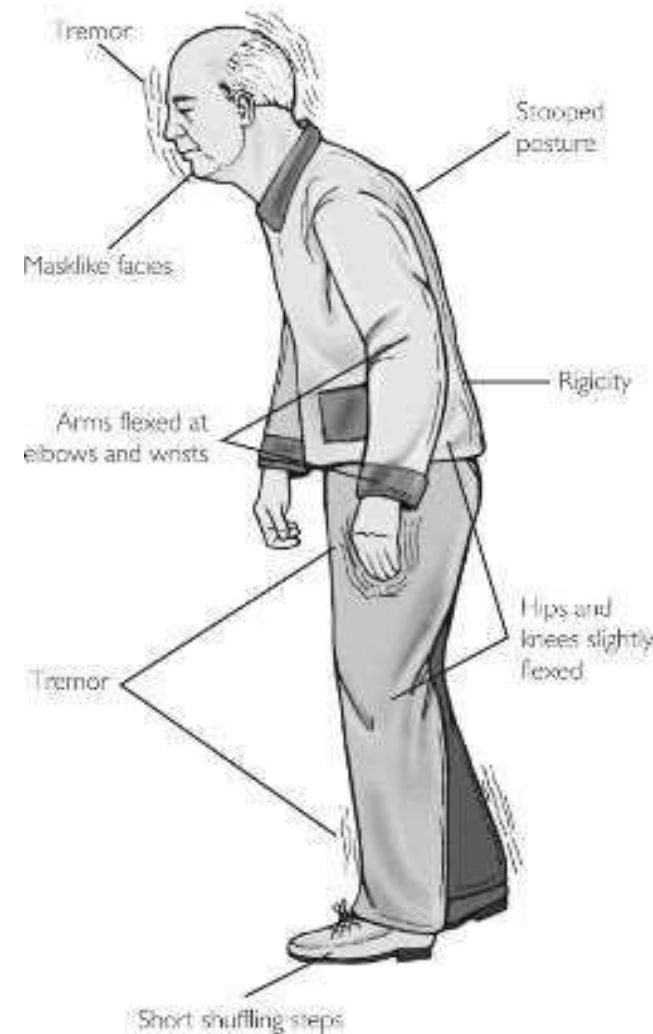
RECEPTOR	NATURE	MECHANISM
D1 like(D1,D5)	Excitatory	act by increasing cAMP formation and PIP2 hydrolysis thereby mobilizing intracellular Ca^{2+} and activating protein kinase C through IP3 and DAG
D2 like(D2,D3,D4)	Inhibitory	act by inhibiting adenylyl cyclase/opening K channels/depressing voltage sensitive Ca^{2+} channels

Manifestation of dopamine level

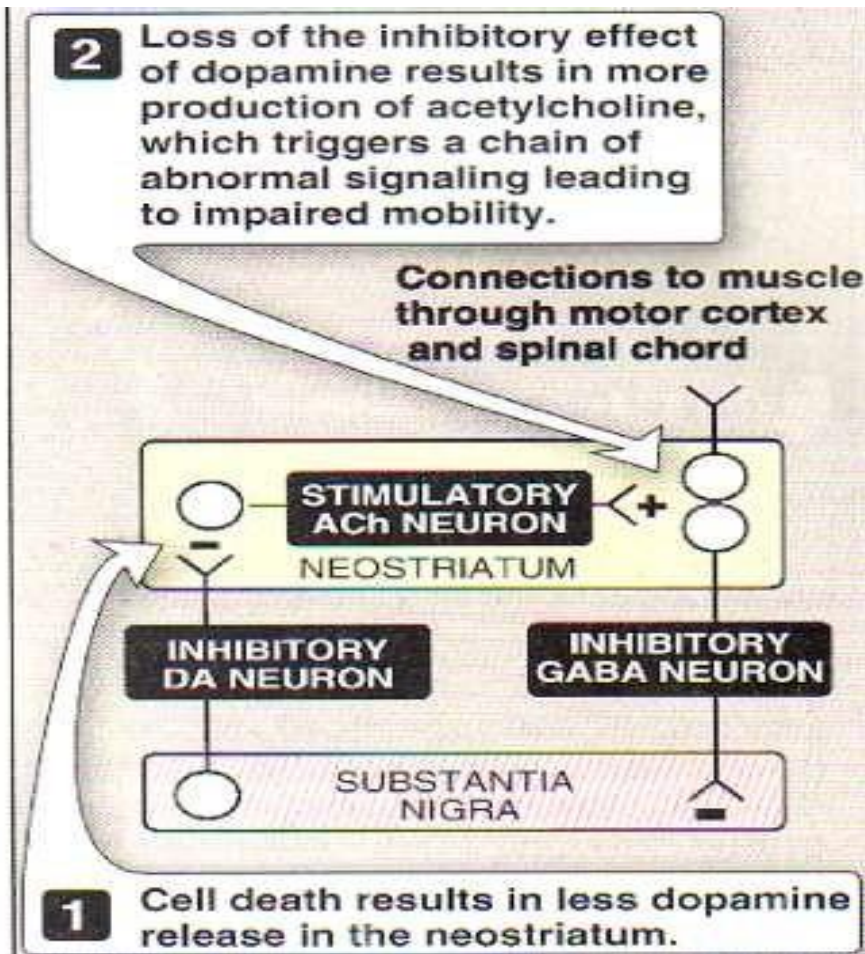
- Increased level of dopamine → schizophrenia
- Decreased level of dopamine → Parkinsonism
- Plasma reference ranges :
 - Supine adults - < 10 ng/ml
 - Ambulatory adults - < 20 ng/mL
 - Age 3-15 years - < 60 pg/mL

Parkinsonism

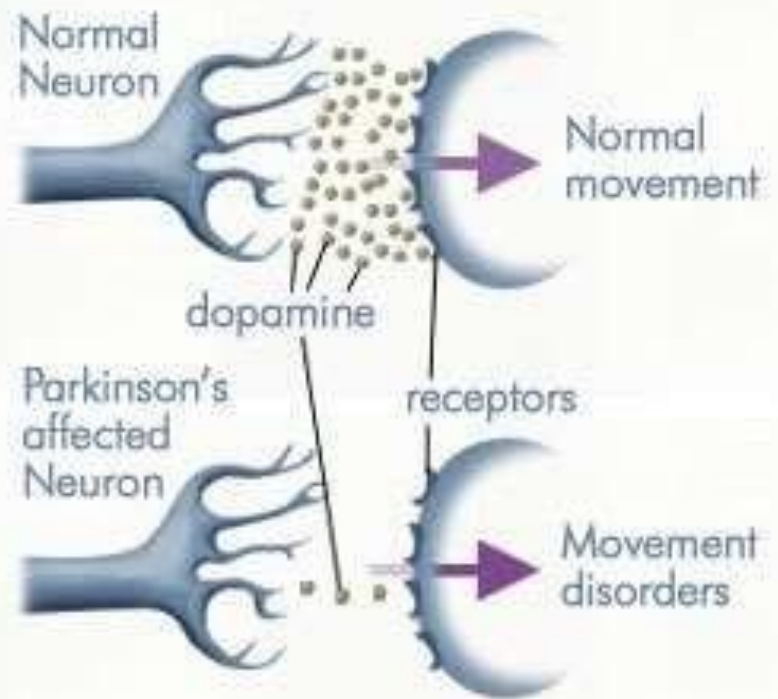
- **Parkinsonism is a neurodegenerative disorder characterized by rigidity, tremor and hypokinesia with secondary manifestations like defective posture and gait, mask-like face and sialorrhoea; dementia may accompany**
- **Dopaminergic neurons and dopamine receptors are steadily lost with age in the basal ganglia**
- **Predisposing factor:** aging (free radicals), environmental toxins, neurotoxin (MPTP), genetic factors



Parkinsonism



Dopamine levels in a normal and a Parkinson's affected neuron.



Treatment

- Medications
- Diet
- Exercise, physical and speech therapy
- Surgery
 - Cryothalamotomy
 - Pallidotomy
 - Deep brain stimulation

Schizophrenia

- **Defective dopamine transmission-
relative excess of central
dopaminergic activity**
- An increase in dopamine function in mesolimbic system and a decreased function in the mesocortical dopamine system



Positive symptoms

**Hallucinations ,
delusions, and racing
thoughts**

Negative symptoms

Apathy, difficulty
dealing with novel
situations, and little
spontaneity or
motivation



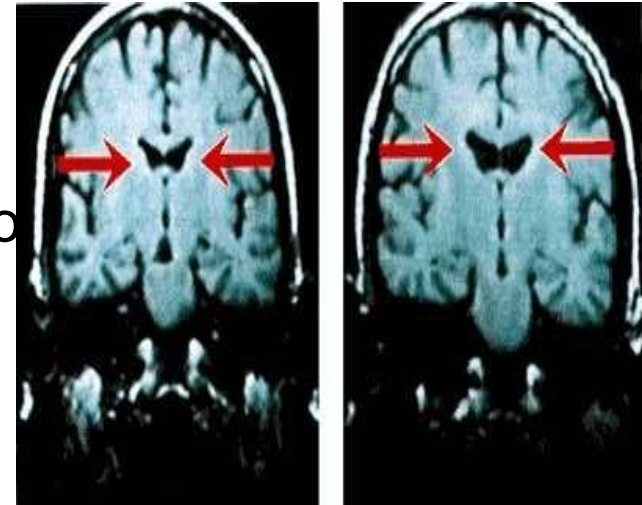
Schizophrenia

- Prominent anatomical changes in the brain

Enlarged lateral ventricle

Enlarged third ventricle

Widening of sulci , reflecting a reduction of cortical tissue, especially in the frontal lobe



- Risk for schizophrenia

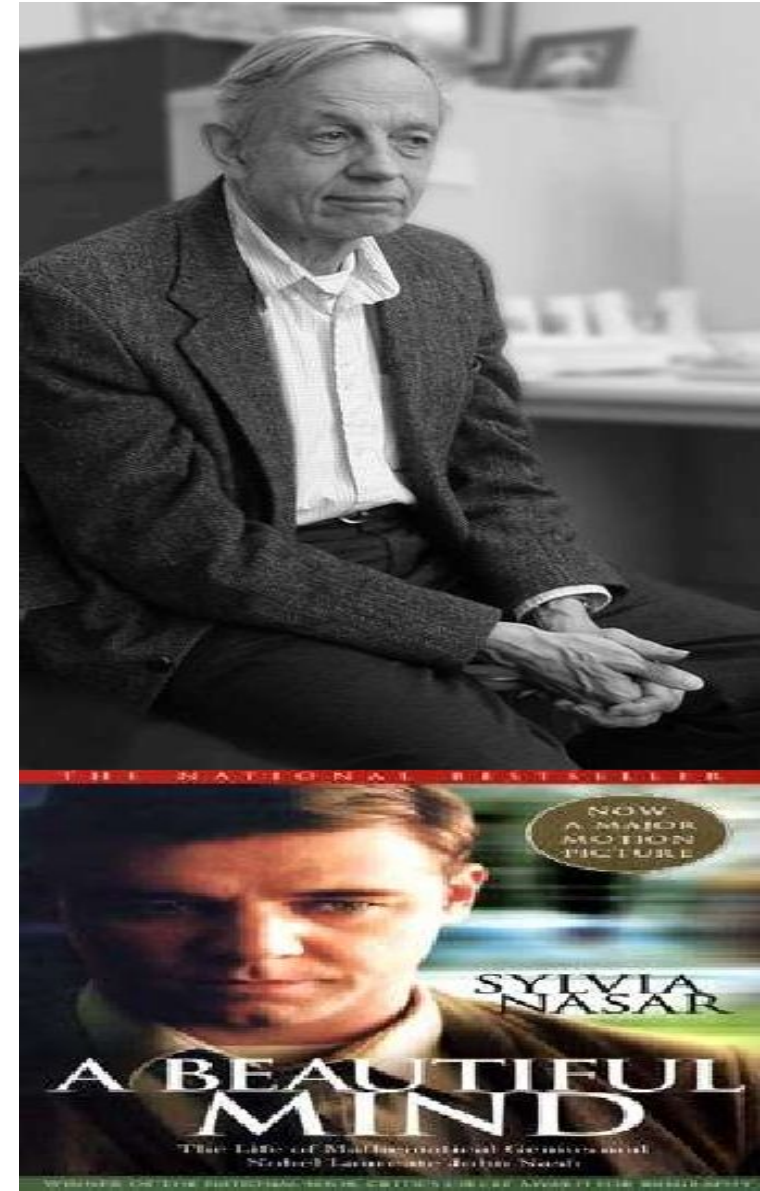
monozygotic twins--- 30-50%schizophrenia

Dizygotic twins ---15%schizophrenia

(men show the first signs of schizophrenia in their mid 20s and women show the first signs in their late 20s)

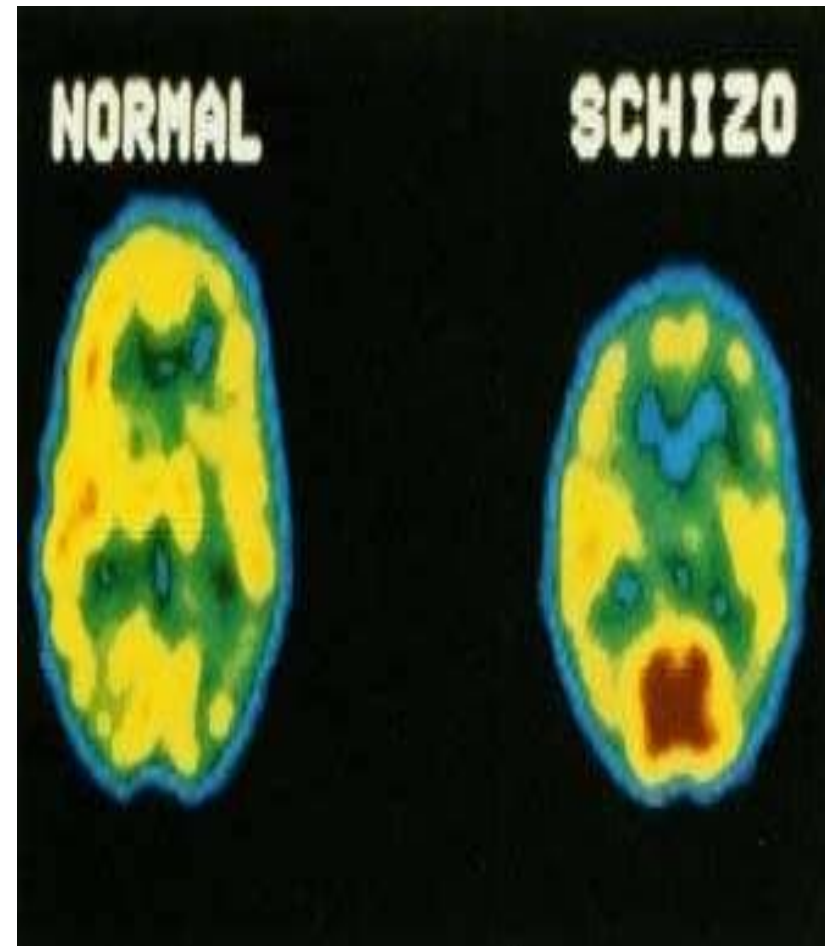
Predisposing factors

- Brain abnormalities
- Prenatal (Problems in pregnancy such as malnutrition or being exposed to a virus)
- Genetic factors
- Socio –economic theories
- Environmental
- Chemical & Biological
- 55% genes and 45% environment factors



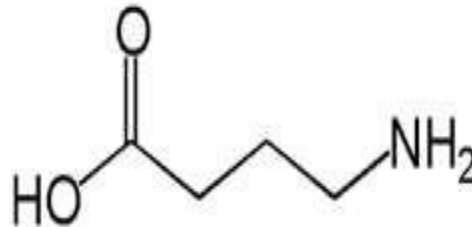
PET SCANS

- Radioactively labelled a chemical L-Dopa
- administered to patients with schizophrenia and with no diagnosis
- L-Dopa taken up quicker with schizophrenic patients
- Suggests they were producing more DA than the control group



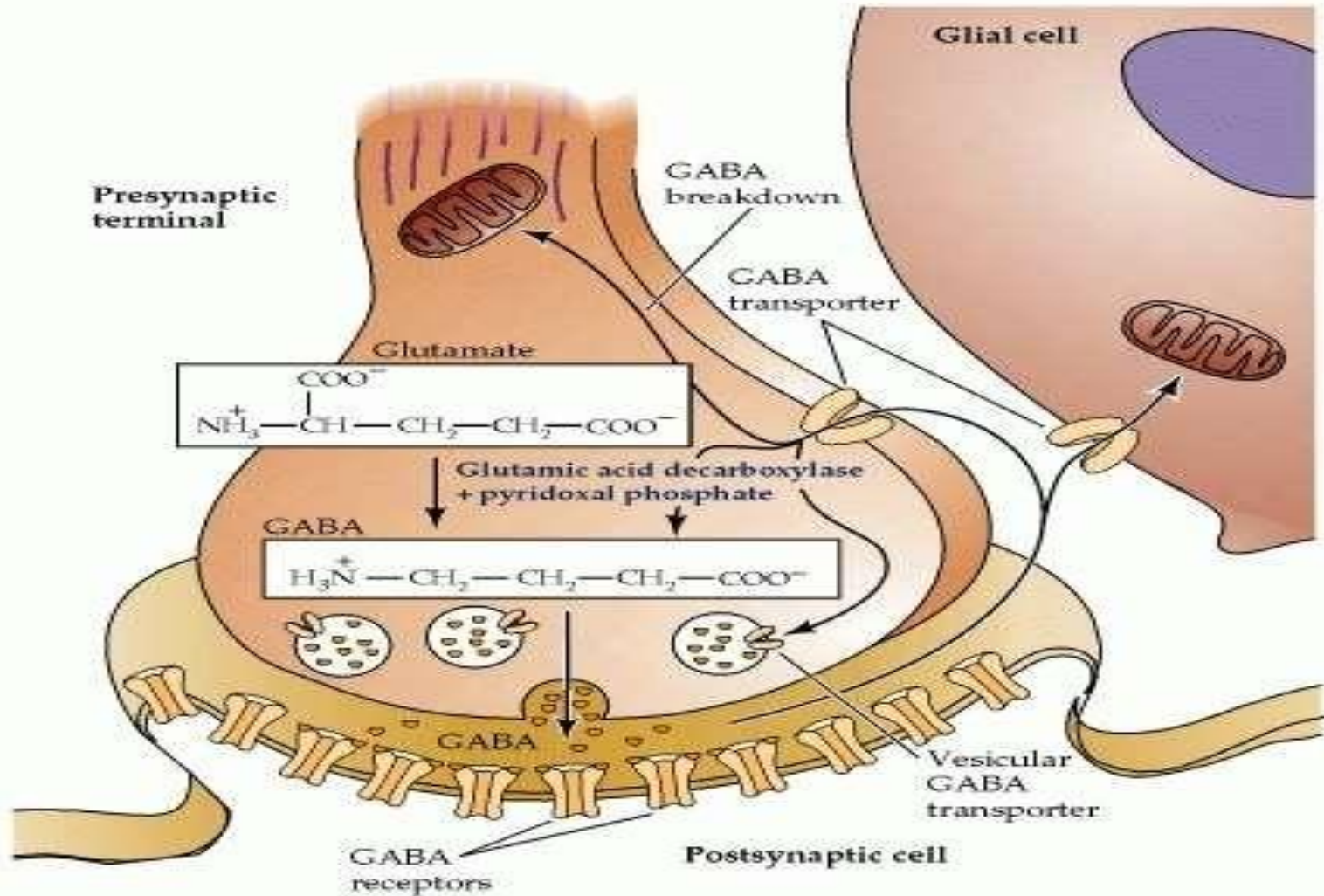
Gamma amino butyric acid (GABA)

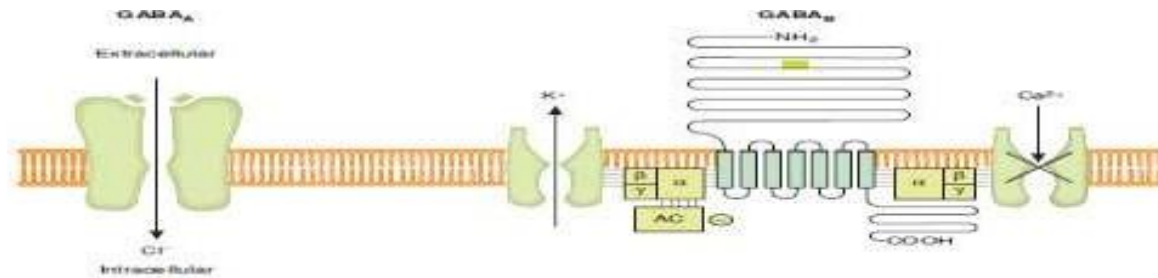
- Principle inhibitory mediator in brain
- Maintains inhibitory tone that counterbalances neuronal excitation
- Location : cerebellum, cerebral cortex, neurons mediating post synaptic inhibition, retina



GABA as neurotransmitter

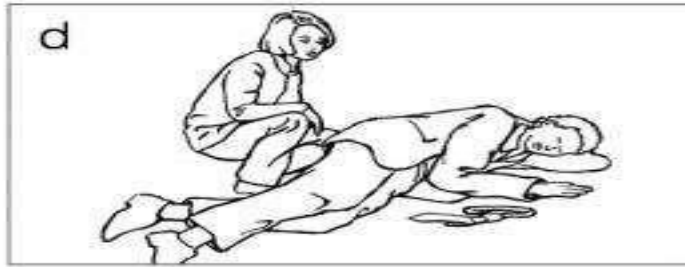
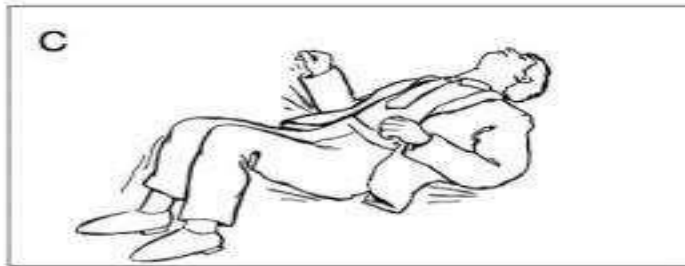
(A)





GABA receptors	location	Comments
GABA-A	CNS	•Chloride ion channel •Hyperpolarize the neuron by increasing chloride conductance •Have rapid inhibitory effect
GABA-B	CNS	•Metabotropic, G-protein coupled receptor •Increases potassium conductance hyperpolarize the neuron •inhibit adenylyl cyclase and inhibit ca²⁺ entry
GABA-C	Predominantly in retina	Chloride ion channel

Epileptic seizure



- Chronic disorder of the brain characterized by recurrent seizures accompanied by involuntary movement with loss of consciousness and control of bowel or bladder function
- Partial or generalized type
- Abnormal excessive or synchronous neuronal activity in the brain

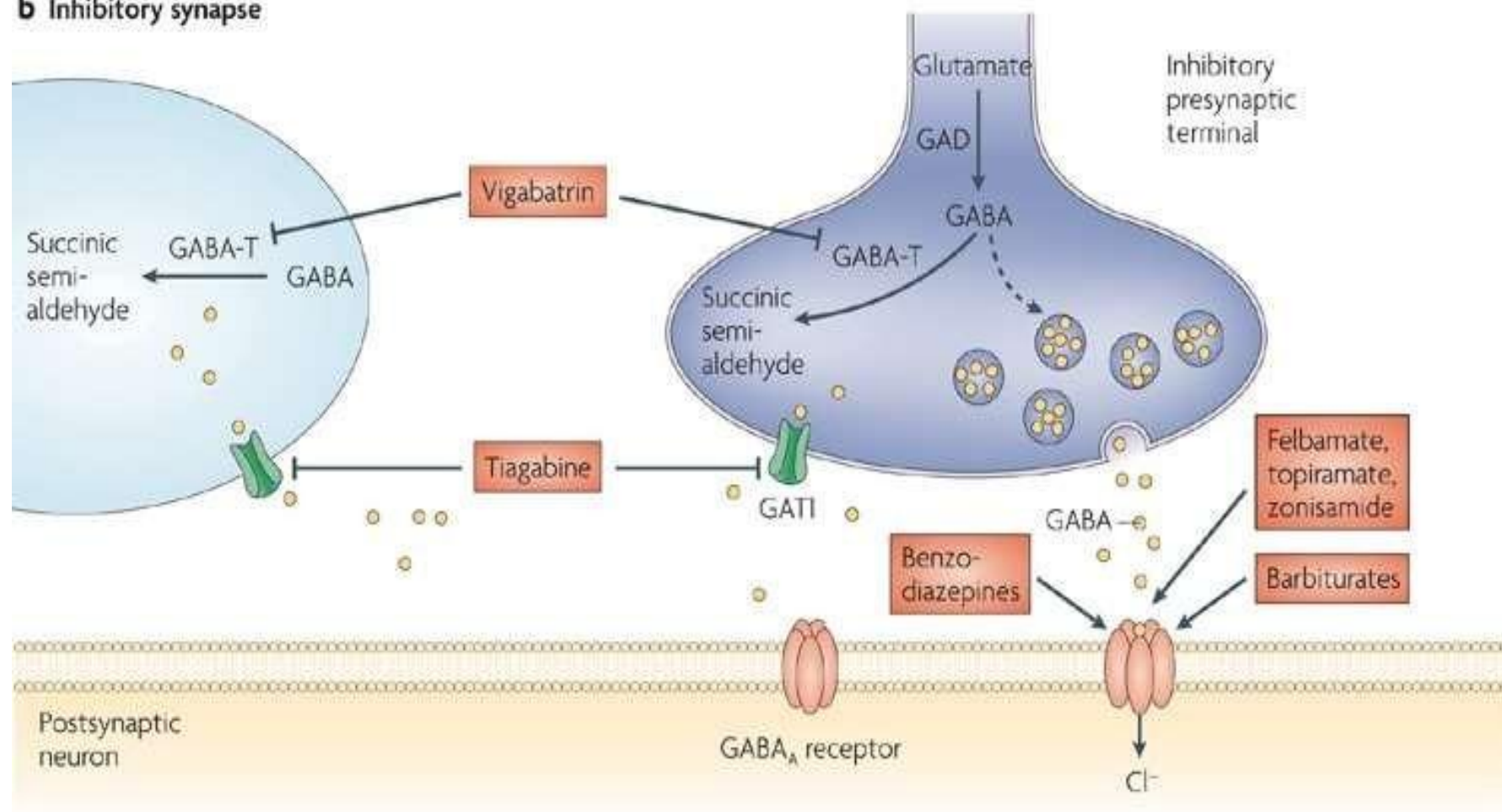
Role of GABA in epileptic seizure

- Abnormal GABAergic function have been observed in genetic and acquired animal models of epilepsy
 - Reductions in
 - GABA-mediated inhibition
 - Activity of glutamate decarboxylase
 - Binding to GABA_A and benzodiazepine sites
 - GABA in CSF and brain tissue
 - Epileptic mice have shown to have increased number of GABA immunoreactive autoantibodies (IgG)
- Normal serum level of GABA :0.2-0.8 $\mu\text{mol/ml}$

Biochemical tests for epilepsy

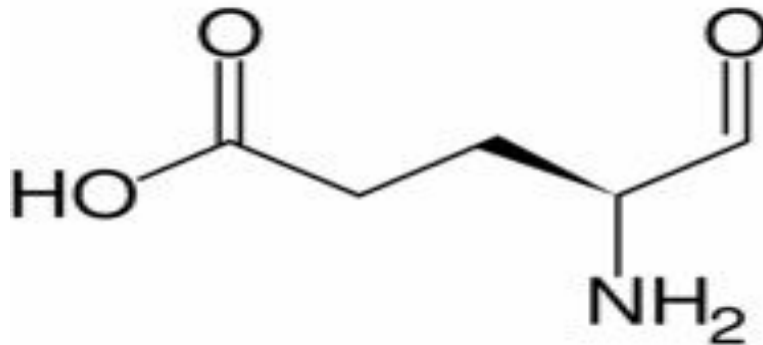
Investigations	Condition being tested for	Clinical epilepsy presentation
Succinic semialdehyde	Pyridoxine dependent epilepsy	Neonatal seizures , refractory epilepsy in childhood
ceruloplasmin	Epilepsy, mental regression	Epilepsy with learning disability
calcium	Hypocalcaemia, hypoparathyroidism	Neonatal seizure
creatinine	Creatinine deficiency syndrome	Epilepsy with learning disability
Glucose	hypoglycaemia	Epilepsy with learning disability
Uric acid	Disorder of purine metabolism	Refractory epilepsy

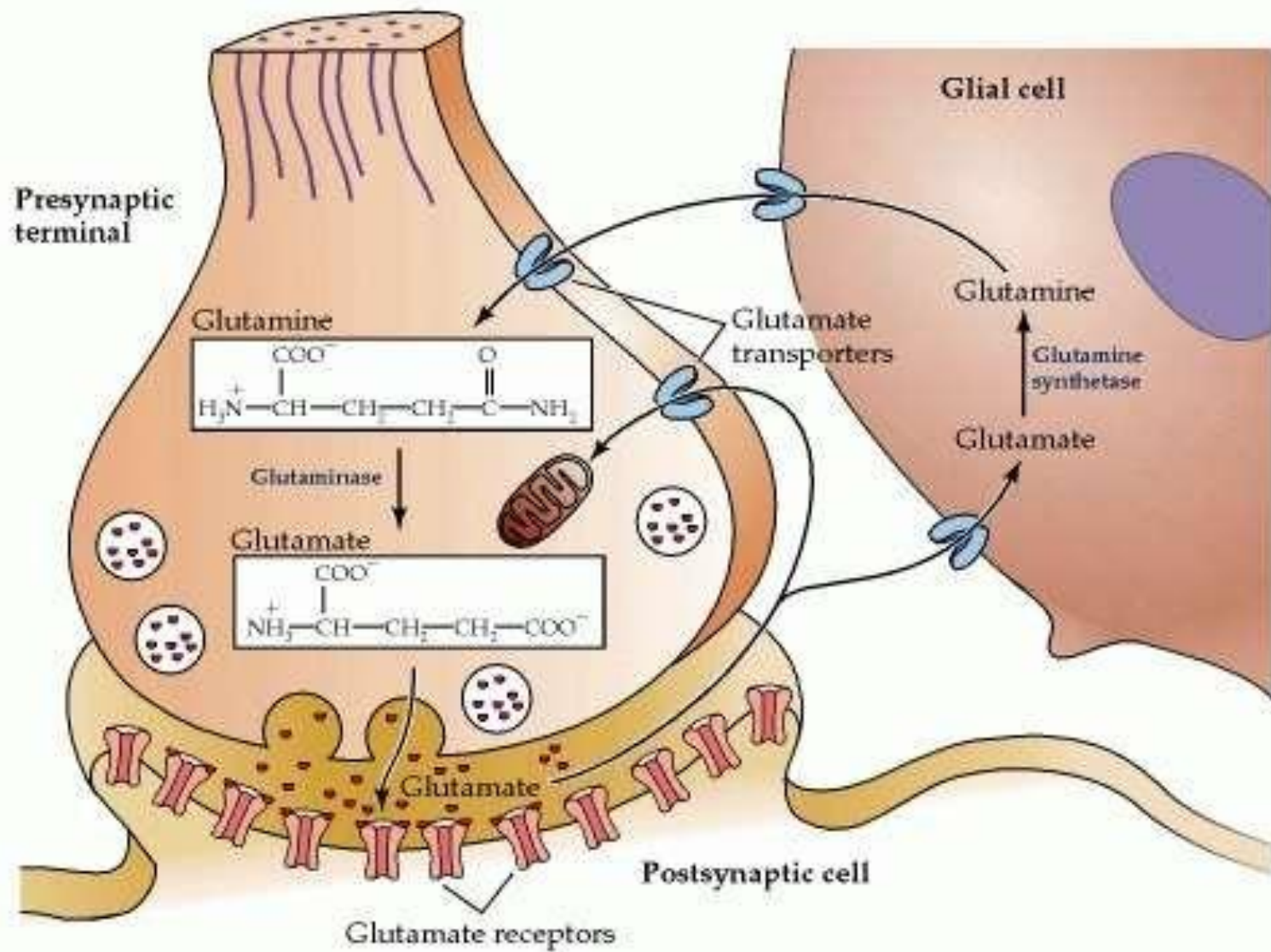
b Inhibitory synapse



Glutamate

- Major Excitatory amino acid (75 %)
- Nonessential amino acid that cannot cross blood brain barrier
- Location: cerebral cortex, brain stem





Glutamate receptors

Receptors	Type	Comments
Metabotropic	Serpentine G-protein coupled receptor	Increases intracellular IP3 and DAG Decreases intracellular CAMP
Ionotropic	Ligand gated ion channels	•Kainate receptor permits Na⁺ influx and K⁺ efflux •AMPA receptor (2 types): one permit Na⁺ influx and other also passage Ca²⁺ •NMDA receptor: permits passage relatively large amount of Ca²⁺

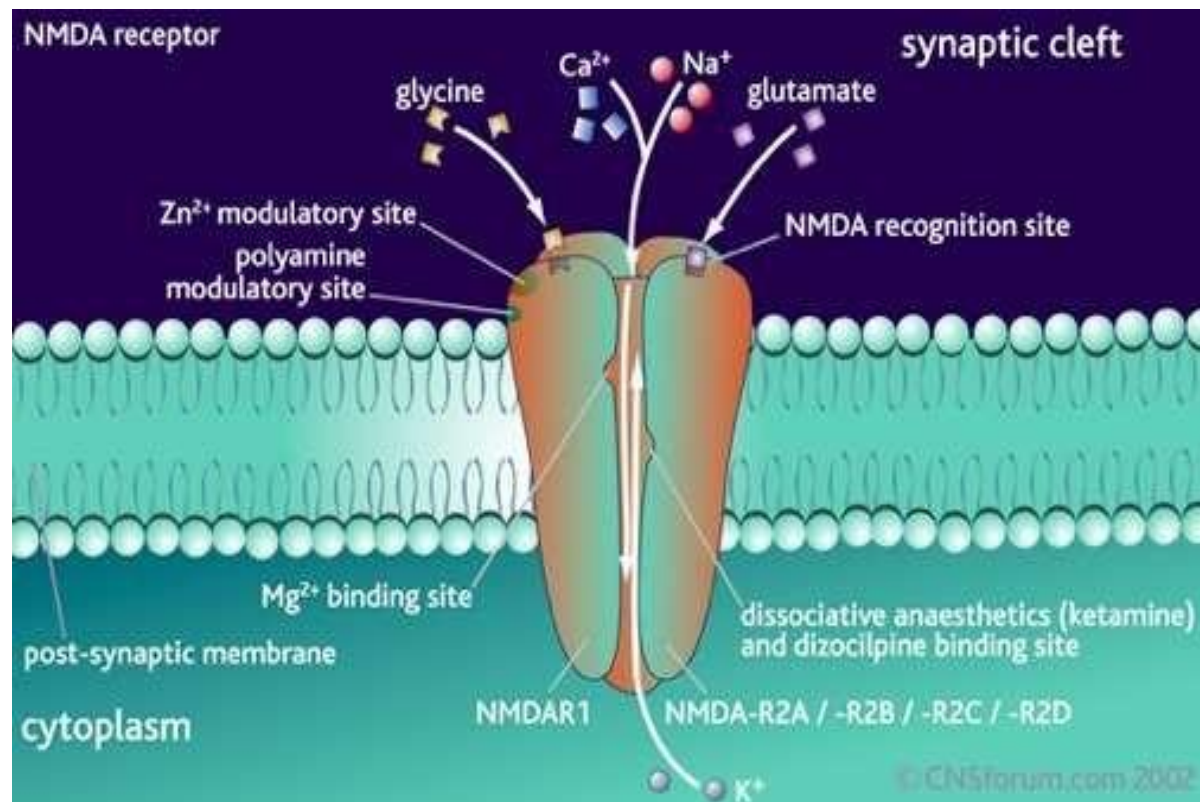


Migraine

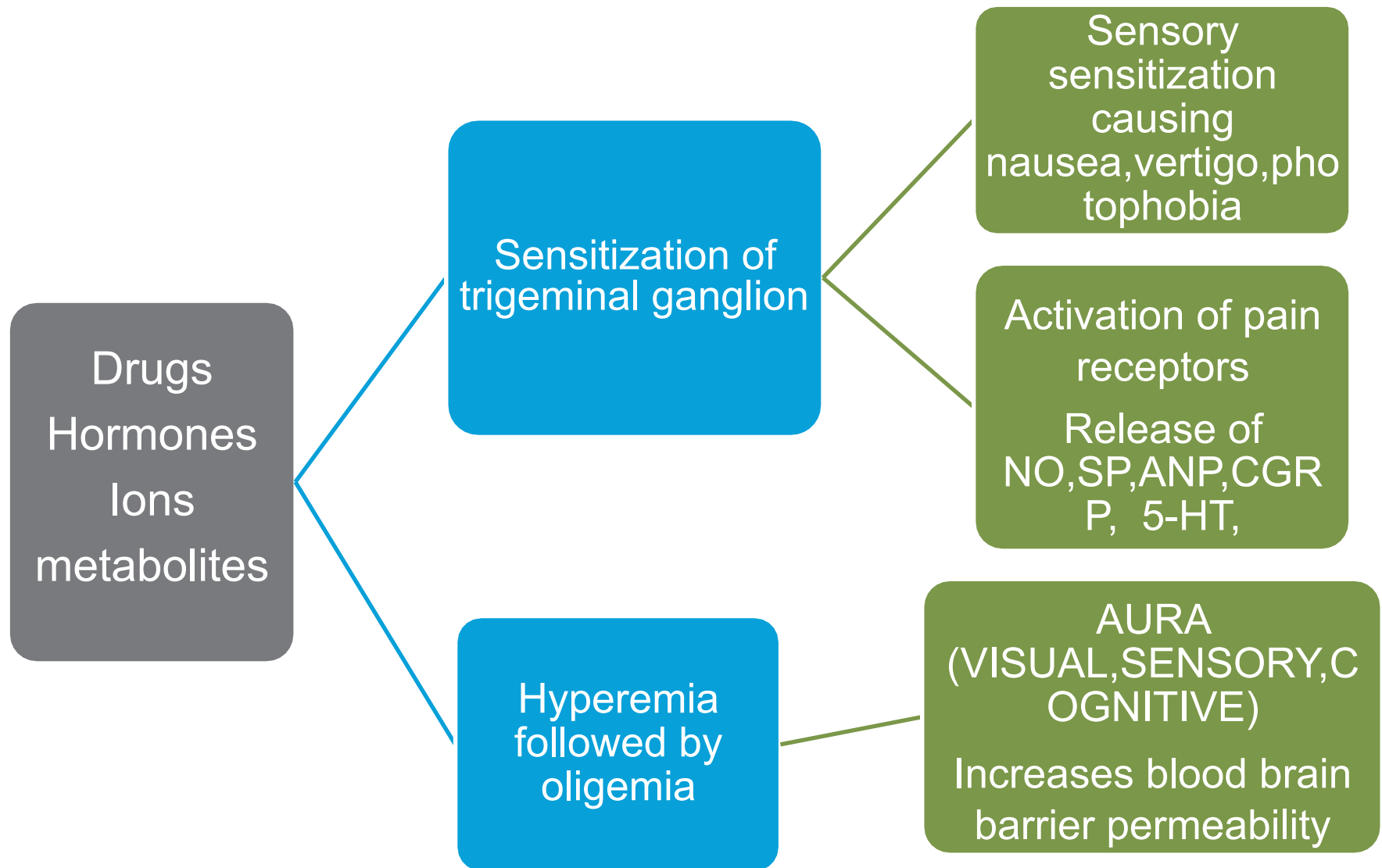
- Recurrent throbbing headache that typically affects one side of the head and is often accompanied by nausea and disturbed vision
- Migraine pain-relay centers: trigeminal ganglion and thalamus contain glutamate-positive neurons
- Neuronal hyper excitability due to decreased voltage dependent Mg^{2+} channel excitotoxic neural death and oligoemia causing migranous infarction

NMDA receptor

- Glycine facilitates its functioning by binding to it and is required for its response to glutamate
- Binding of glutamate opens channel but at normal membrane potential, it is blocked by Mg^{2+} ion



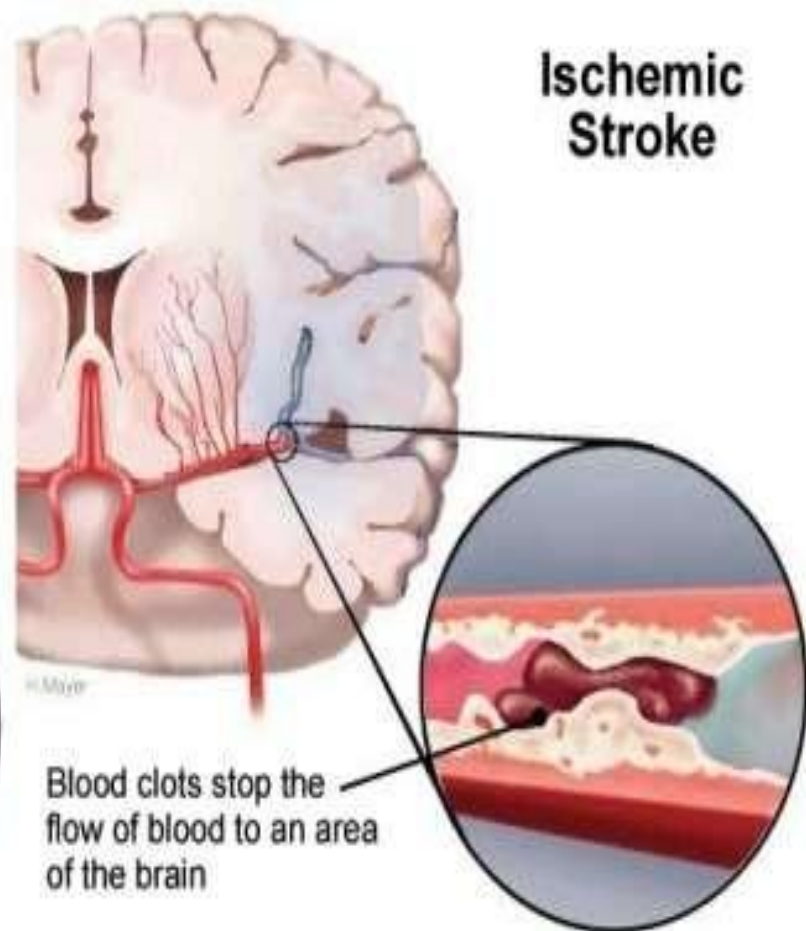
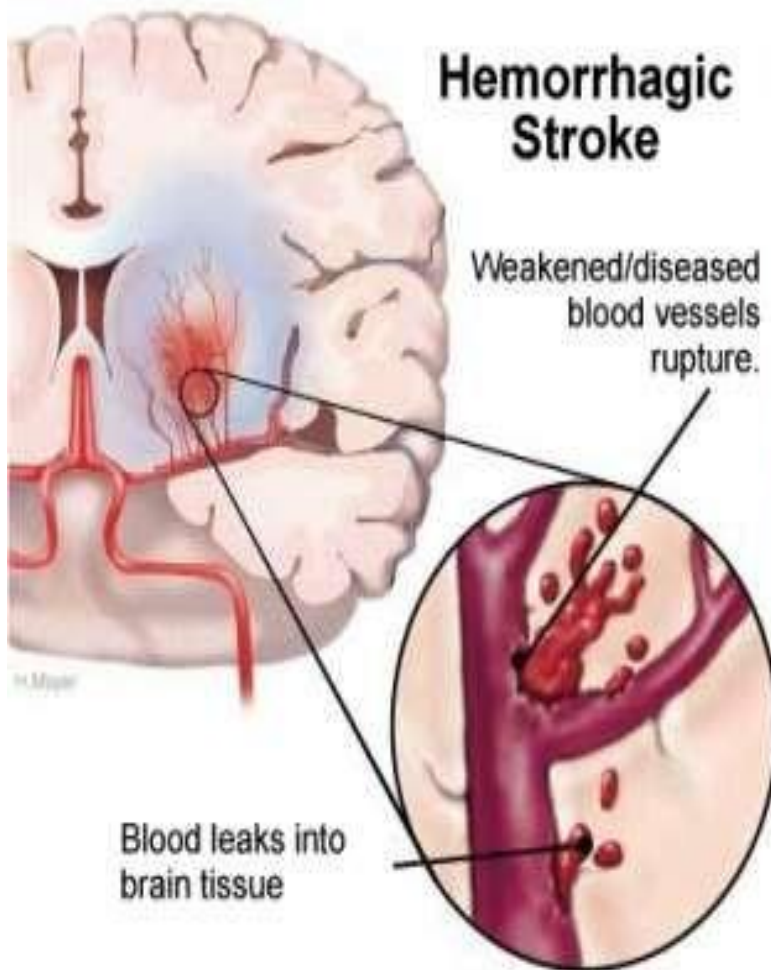
Pathophysiology of migraine



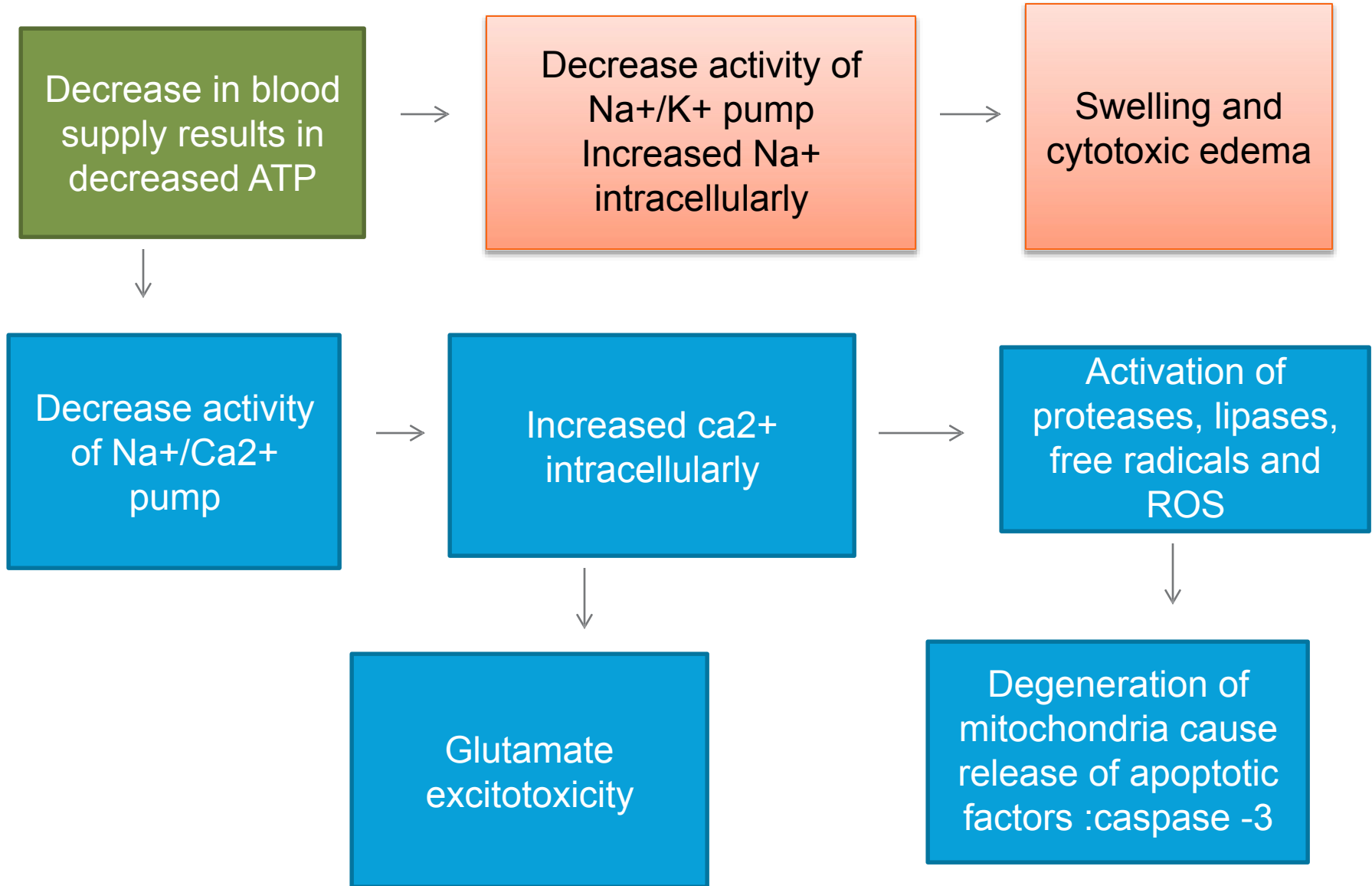
Stroke



- According to WHO “Stroke is the medical emergency caused by the interruption of the blood supply to the brain, usually because a blood vessel bursts or is blocked by a clot
- This cuts off the supply of oxygen and nutrients, causing damage to the brain tissue
- Glutamate excitotoxicity



Glutamate excitotoxicity



Blood biochemical tests for stroke

- Antiphospholipid antibodies (APL), Anticardiolipin antibodies (ACL)
- **Coagulation tests**: Prothrombin time, Partial thromboplastin time, International normalized ratio
- **Coagulation factors**: Antithrombin III, Protein C, Protein S; Factor VIII
- **Cardiac enzymes**: Troponin, Creatine kinase (CPK, CK), LDH isoenzymes
- Erythrocyte sedimentation rate (ESR), Hemoglobin electrophoresis

Biochemical markers associated with stroke

Markers of neuronal injury

Creatinine phosphokinase ñ brain band (CK-BB)

Neuron specific enolase (NSE)

Markers of glial activation

Glial fibrillary acidic protein (GFAP)

S100 β

Inflammatory mediators

Interleukin-1 (IL-1)

Interleukin-6 (IL-6)

Interleukin-8 (IL-8)

Interleukin-1 receptor antagonist (IL-1ra)

Tumor necrosis factor- α (TNF- α)

Matrix metalloproteinase-9 (MMP-9)

Monocyte chemoattractant protein-1 (MCP-1)

Endothelial leukocyte adhesion molecule-1 (ELAM-1)

Vascular cell adhesion molecule (VCAM-1)

Markers of thrombosis

D-dimer

Fibrinogen

Thrombinñantithrombin III

von Willebrand factor (vWF)

Growth factors

Platelet-derived growth factor (PDGF)

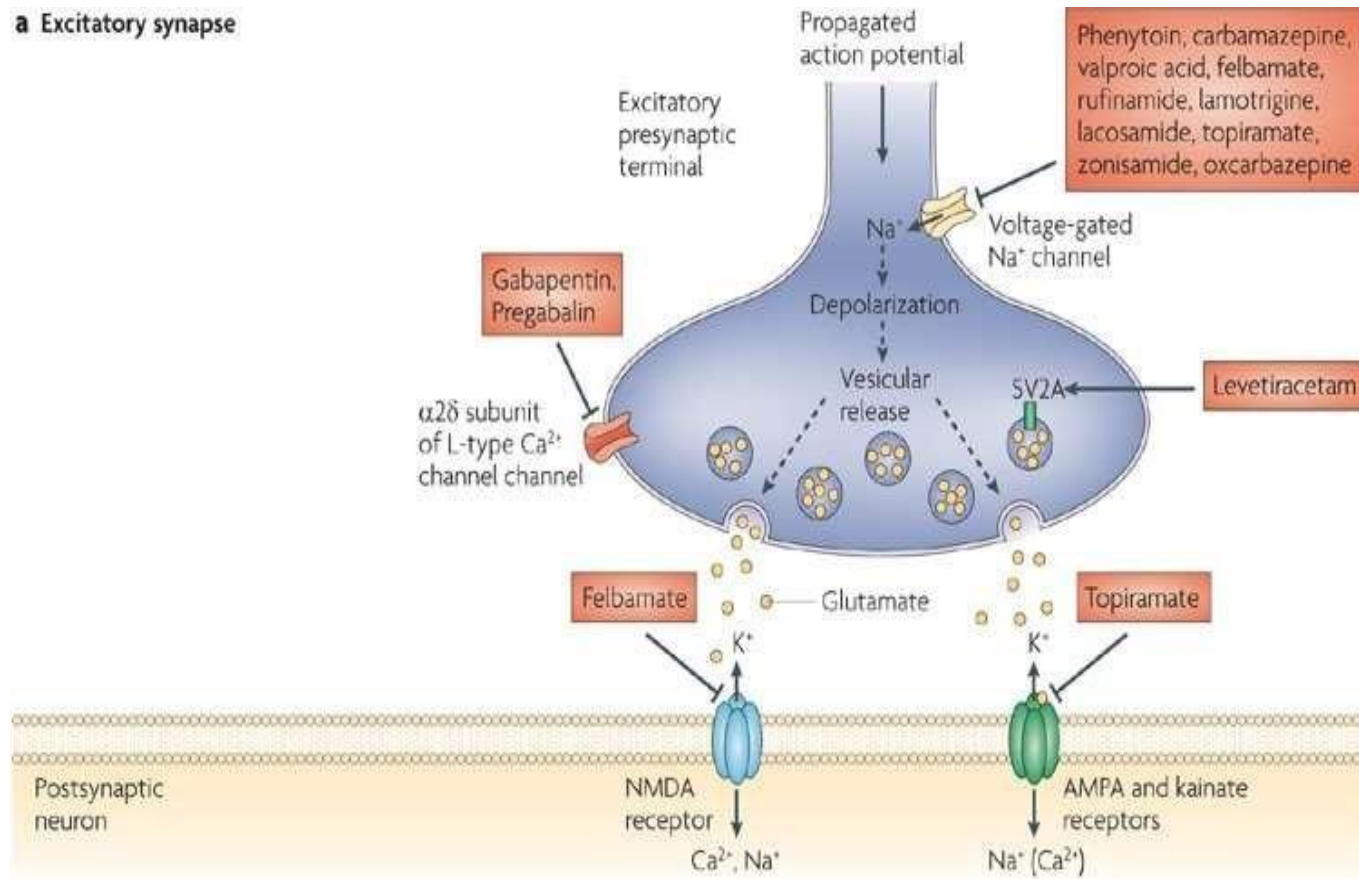
Transforming growth factor- β (TGF- β)

Vascular endothelial growth factor (VEGF)

Marker of apoptosis

Caspase-3

a Excitatory synapse





Bipolar disorder

- Extreme mood swings that include emotional highs (mania or hypomania) and lows (depression)
- Glutamate, GABA and dopamine is found to be significantly increased during the manic phase of bipolar disorder, and returns to normal levels once the phase is over

Autism

- A mental condition, present from early childhood, characterized by great difficulty in communicating and forming relationships with other people and in using language and abstract concept
- Role of group I metabotropic glutamate receptors in the pathogenesis of fragile X syndrome :the most common identified genetic cause of autism
- FMR1 gene encode for FMRP
: responsible for synapse



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