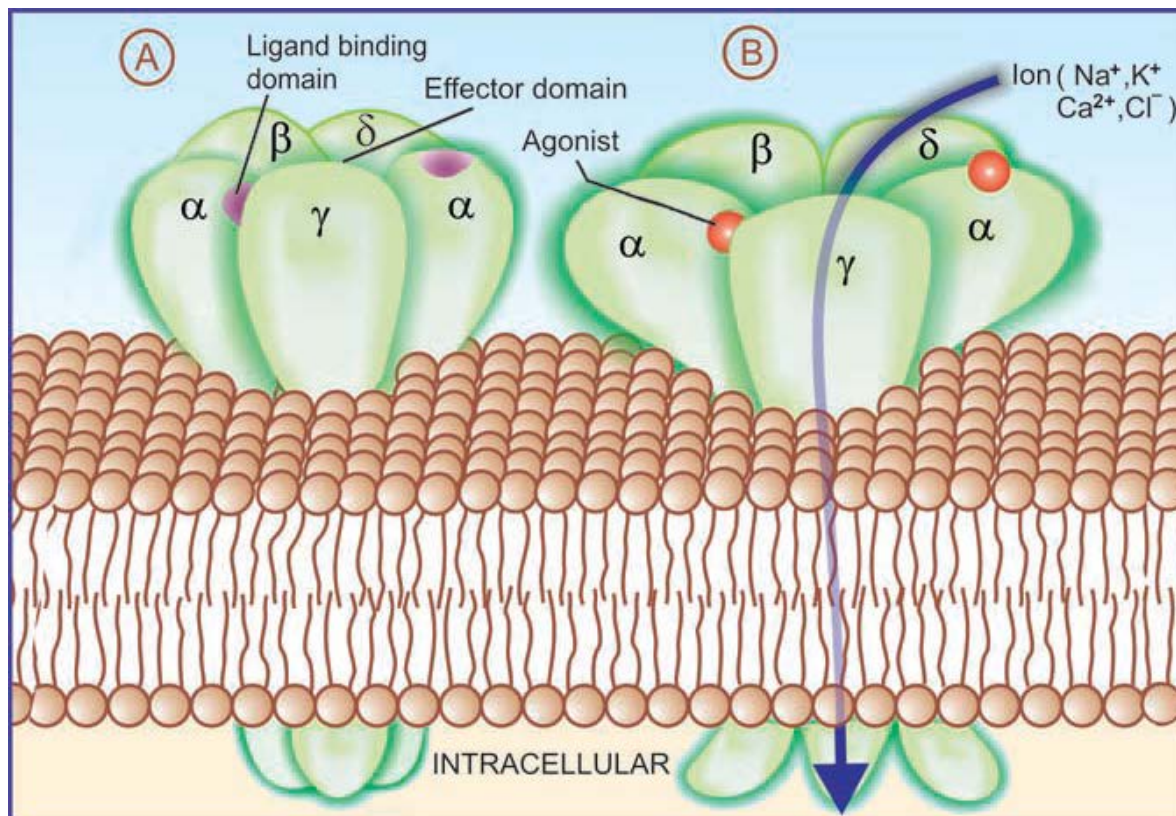


Pharmacology



(Adopted from KD Tripathi Book)

SUBJECT	Pharmacology-I
PROGRAMME/COURSE	Pharmacy/B. Pharmacy
SEMESTER	Fourth
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Disclaimer: The presented matter is compilation of books and various online materials available on the topic with modification and simplification. The content is presented here for student's easy accessibility as online study material and not for commercial purpose.

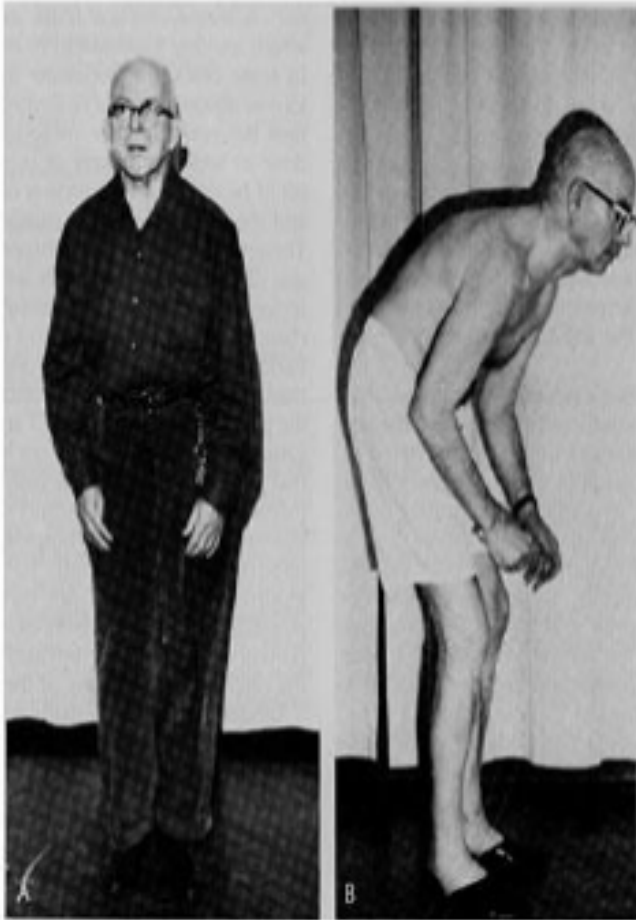
**Antiparkinsonian Drugs
or
Drugs for Parkinson's Disease**

Parkinsonism

- Parkinsonism is a progressive neurodegenerative or neurological disorder of muscle movement as a clinical syndrome consisting of 4 cardinal features:
 - 1) resting tremor (which usually disappears during voluntary movement)
 - 2) muscular rigidity
 - 3) bradykinesia (slowness of movement) and, in extreme cases, a loss of physical movement (akinesia)
 - 4) impairment of postural balance leading to disturbances of gait and falling
 - 5) The secondary manifestations are mask-like face, difficulty in speech, slowing of mental process and dementia.

PD - Signs

Parkinson's Disease



Pathological Basis

- **The main Pathological feature of Parkinson's disease is the loss of the dopaminergic nigrostriatal pathway**
- **Dopaminergic neurons in the substantia nigra that normally inhibit the output of GABAergic cells in the striatum are lost**
- **80% of the Dopamine producing cells must be lost before symptoms begin to show**

Etiology

- Nerve fibers from cerebral cortex and thalamus **secrete acetylcholine** in the **neostriatum** causing **excitatory effects** that initiate and regulate gross intentional movements of the body.
- In Parkinson's disease, **due to deficiency of dopamine in striatum**, an **imbalance between dopaminergic (inhibitory) and cholinergic (excitatory) system** occurs, leading to excessive excitatory actions of cholinergic neurons on striatal GABAergic neurons.

Treatment Strategies

- Drug therapy is aimed at **restoring the balance between the dopaminergic and cholinergic components,**
- which is achieved by:
 - **Increasing the central dopaminergic activity**
 - OR
 - **Decreasing the central cholinergic activity**
 - OR
 - BOTH

Classification

I. *Drugs affecting brain dopaminergic system*

(a) *Dopamine precursor* : Levodopa (l-dopa)

(b) *Peripheral decarboxylase inhibitors* :

Carbidopa, Benserazide.

(c) *Dopaminergic agonists*: Bromocriptine,
Ropinirole, Pramipexole

(d) *MAO-B inhibitor*: Selegiline, Rasagiline

(e) *COMT inhibitors*: Entacapone, Tolcapone

(f) *Glutamate (NMDA receptor) antagonist*
(*Dopamine facilitator*): Amantadine.

Classification

II. *Drugs affecting brain cholinergic system*

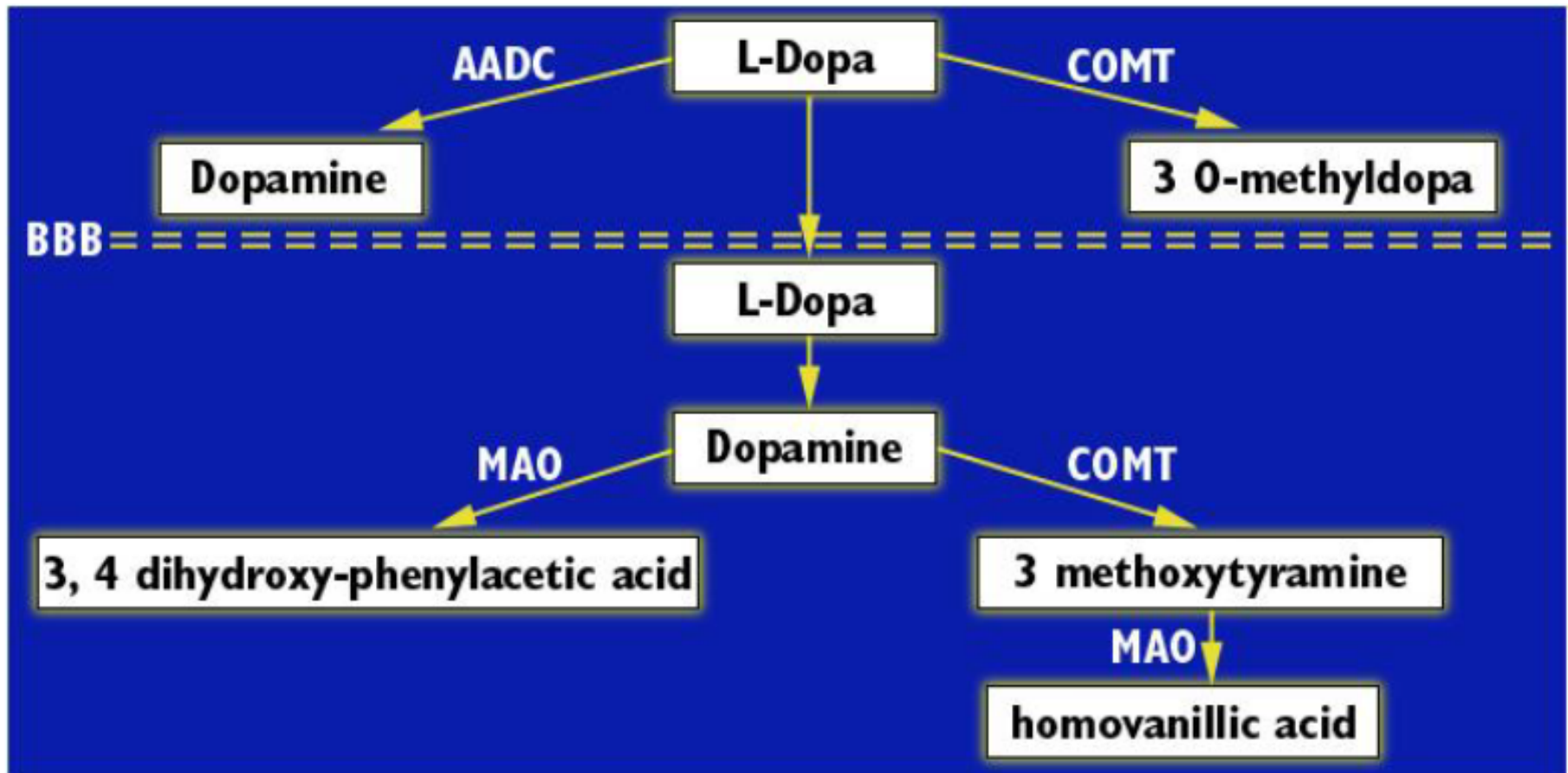
(a) *Central anticholinergics*: Trihexyphenidyl (Benzhexol), Procyclidine, Biperiden.

(b) *Antihistaminics* : Orphenadrine, Promethazine.

Levodopa

- Dopamine itself does not cross the blood-brain barrier and therefore has no CNS effects.
- However, levodopa, as an **amino acid**, is transported into the brain by amino acid transport systems, where it is **converted to dopamine by the enzyme L-aromatic amino acid decarboxylase**, which is stored and released as a transmitter.
- The effect of levodopa may be due to an increased release of dopamine from surviving dopaminergic neurones **the effectiveness of levodopa decreases as the disease advances.**

Diagram of LD Metabolism



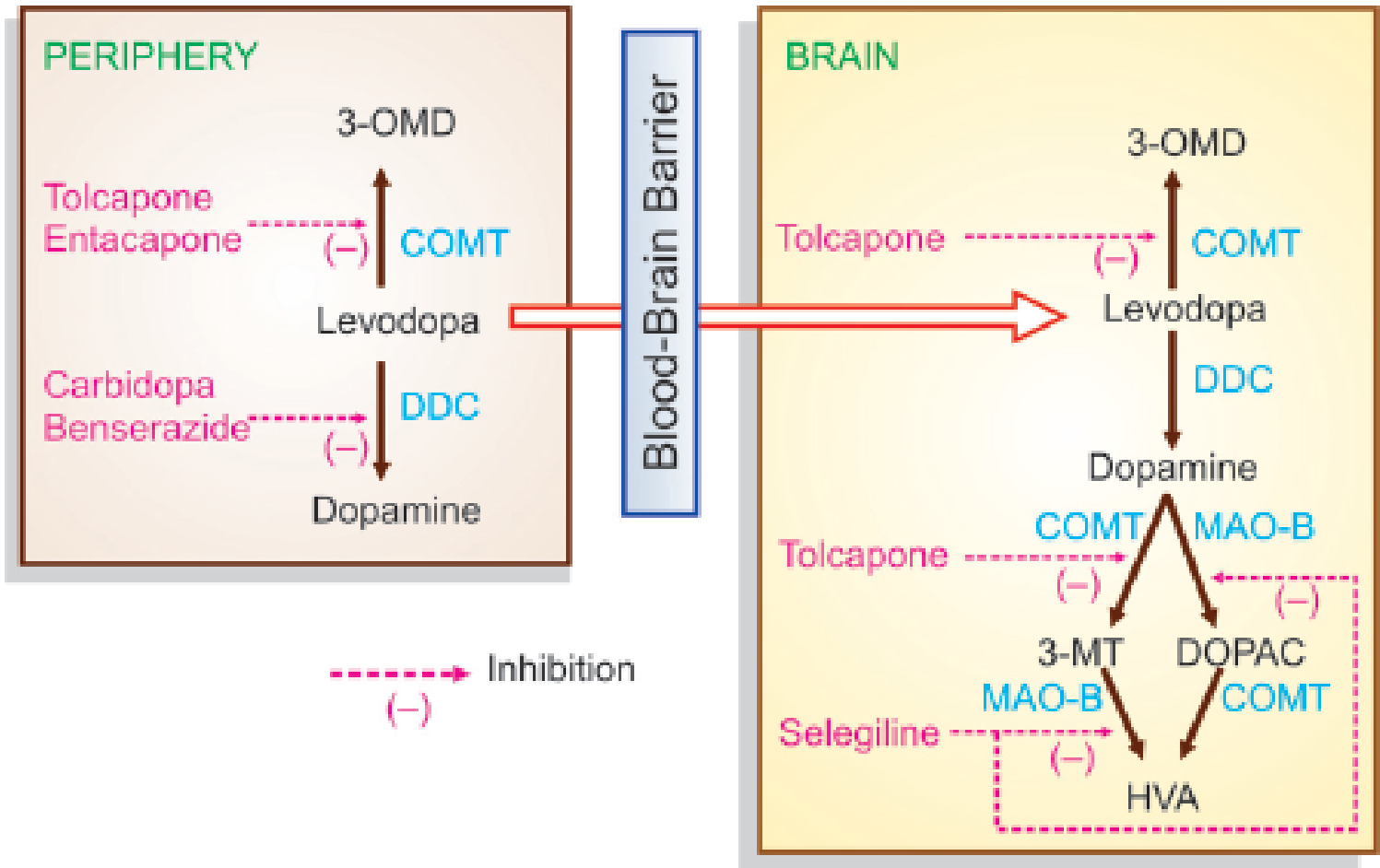


Fig. 31.2: Metabolic pathways of levodopa in the periphery and the brain.

3-OMD—3-O-methyldopa; COMT—Catechol-O-methyl transferase; MAO—monoamine oxidase; 3-MT—3-methoxytyramine; DOPAC—3,4 dihydroxy phenylacetic acid; HVA—Homovanillic acid (3-methoxy-4-hydroxy phenylacetic acid), DDC—Dopa decarboxylase

Pharmacokinetics

- Levodopa, when given without a decarboxylase inhibitor, about 70% of the dose is metabolized in the gut wall and liver, 27-29% goes to peripheral tissues to exert adverse effects and only 1-3% enters the brain.
- When levodopa is administered with Carbidopa, about 10% of the dose reaches the brain.

Levodopa

- In practice, levodopa is administered in combination with a peripherally acting inhibitor of aromatic L-amino acid decarboxylase, such as ***carbidopa, that do not penetrate into the CNS.***
- Inhibition of peripheral decarboxylase markedly increases the fraction of administered levodopa that crosses the blood-brain barrier and reduces the incidence of peripheral side effects.

Levodopa - MOA

- D1 like (D1, D3, D5) – Excitatory
- D2 like (D2, D4) – Inhibitory

- Levodopa act on D1 and D2 receptor and activate it – Smoothening muscle movement and reducing muscle tone

Pharmacological Actions

- **CNS**

- Levodopa produces marked symptomatic improvement in Parkinsonian patients.

- Hypokinesia and rigidity resolve first, later tremor as well. Secondary symptoms of posture, gait, facial expression & mood are gradually normalized.

- Produces **'general alerting response'** - progresses to excitement—frank psychosis

- Embarrassingly disproportionate increase in sexual activity

Pharmacological Actions

- **CVS**

- tachycardia by acting on β adrenergic receptors.
- Postural hypotension
- Excess DA and NA formed in the brain decrease sympathetic outflow; also DA formed in autonomic ganglia can impede ganglionic transmission.

Pharmacological Actions

- **CTZ**

- DA acts as an excitatory transmitter.

- The DA formed peripherally gains access to the CTZ without hindrance—elicits nausea and vomiting.

- Tolerance develops gradually to this action.

Pharmacological Actions

- **Endocrine**

- DA acts on pituitary mammatropes to inhibit prolactin release and on somatotropes to increase GH release.

Adverse effects

- Nausea and Vomiting
- Postural hypotension
- *Cardiac arrhythmias*
- *Exacerbation of angina*
- *Alteration in taste sensation*
- *Abnormal movements (dyskinesias)*
- *Behavioural alterations*
- *Fluctuation in motor functions*

**COGNITION ENHANCERS
(Cerebroactive drugs)**

or

Drugs for Alzheimer's disease

Introduction

- These are a heterogenous group of drugs developed for use in dementia and other cerebral disorders.

Alzheimer's disease

- A progressive neurodegenerative disorder which affects older I'D & is the most common cause of dementia.
- Atrophy of cortical & subcortical areas is associated with deposition of β -amyloid protein in the form of extracellular senile (amyloid) plaques & formation of intracellular neurofibrillary tangles.
- These abnormal proteins accumulate mostly due to reduced clearance, but in some cases, due to overproduction, and cause neuronal damage.
- There is marked cholinergic deficiency in the brain, though other NT systems, glutamate & neuropeptide, are also affected.

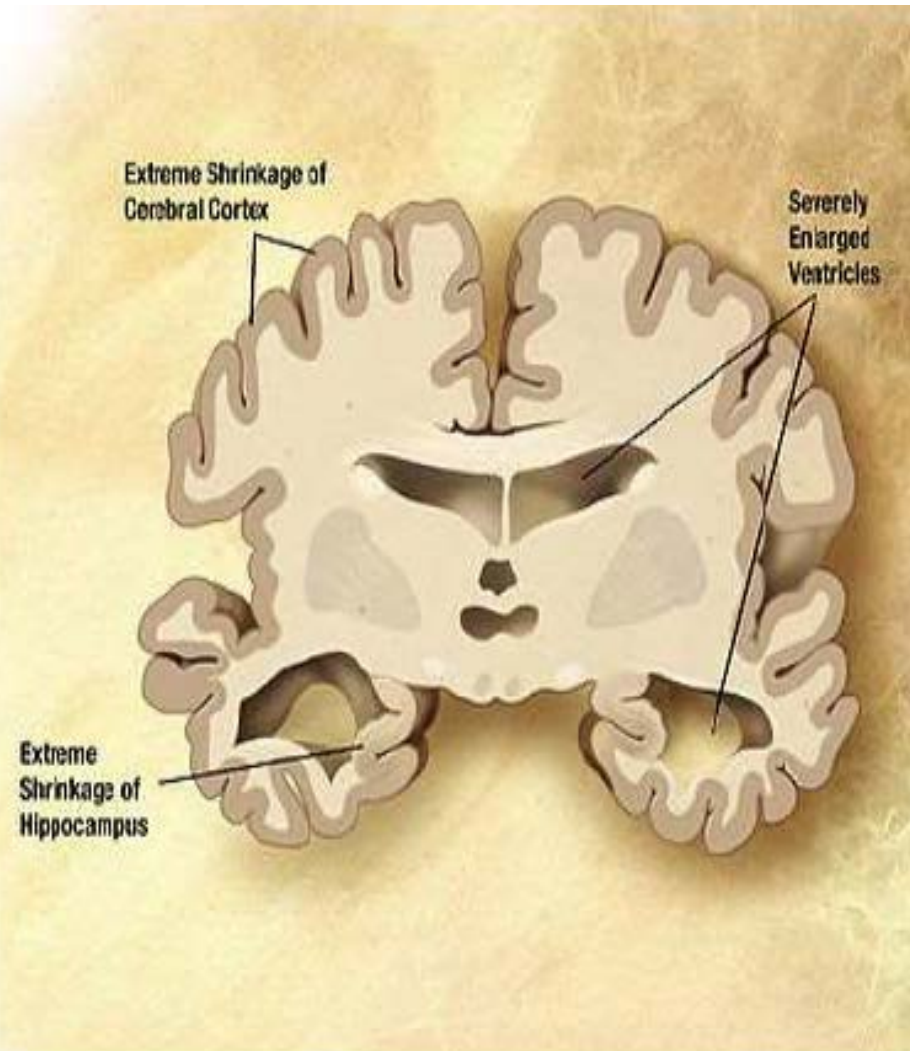
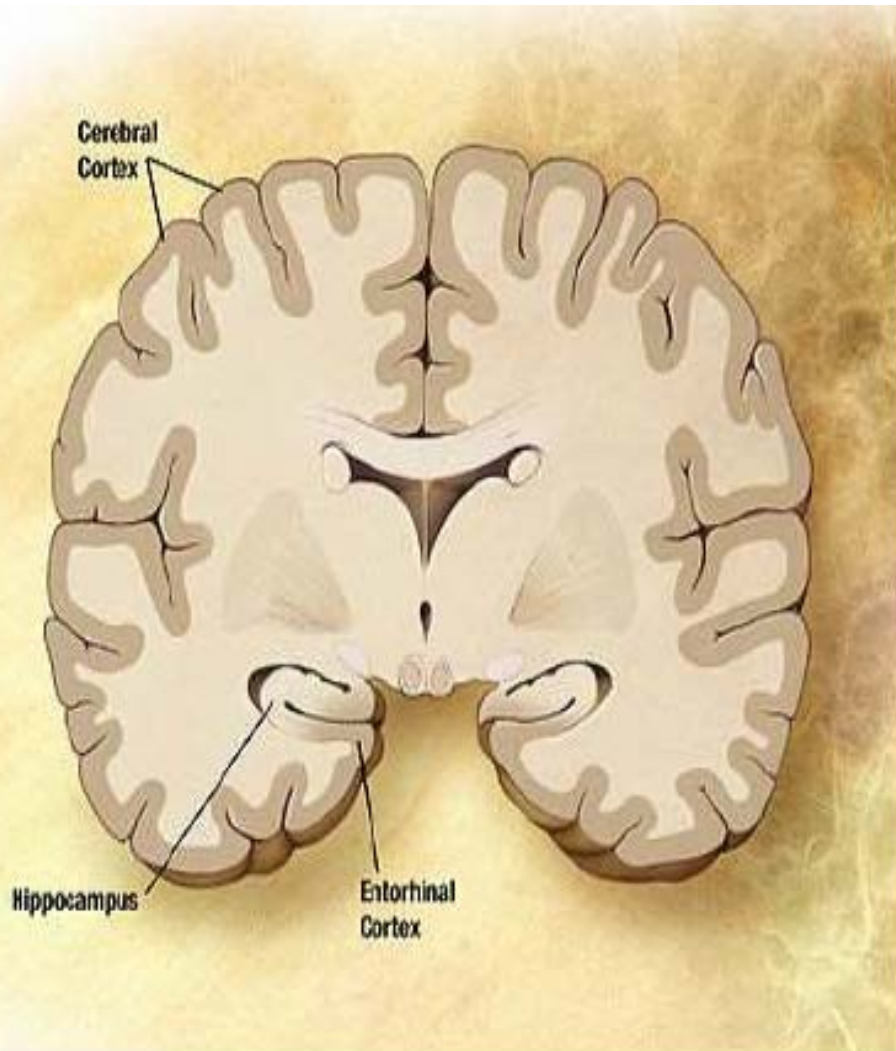
Symptoms of AD

- Gradually worsening difficulty in remembering new information
- Confusion, disorganized thinking, impaired judgment, trouble expressing themselves
- Disorientation to time, space & location

Pathological Feature

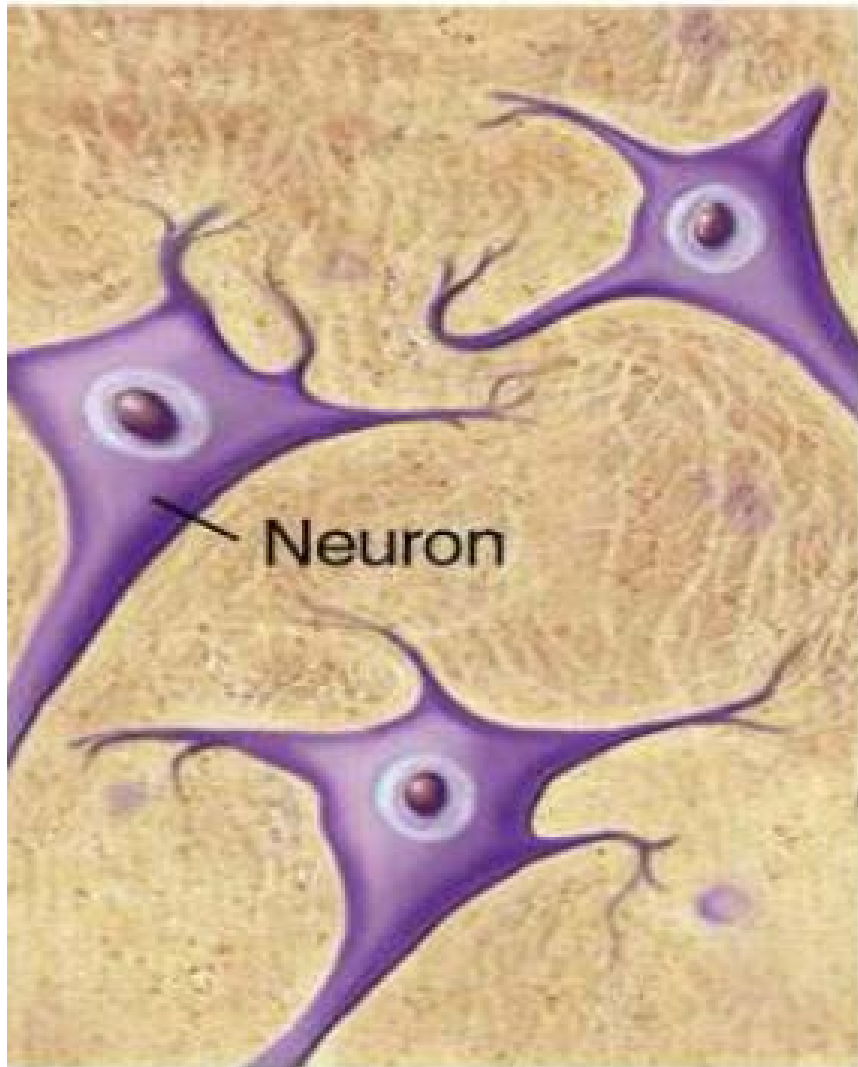
- Brain shrinkage & localised loss of neurons, mainly in the hippocampus & basal forebrain
- Loss of cholinergic neurons in the hippocampus & frontal cortex
- Diffuse atrophy of cerebral cortex & enlargement of ventricular system

Gross appearance

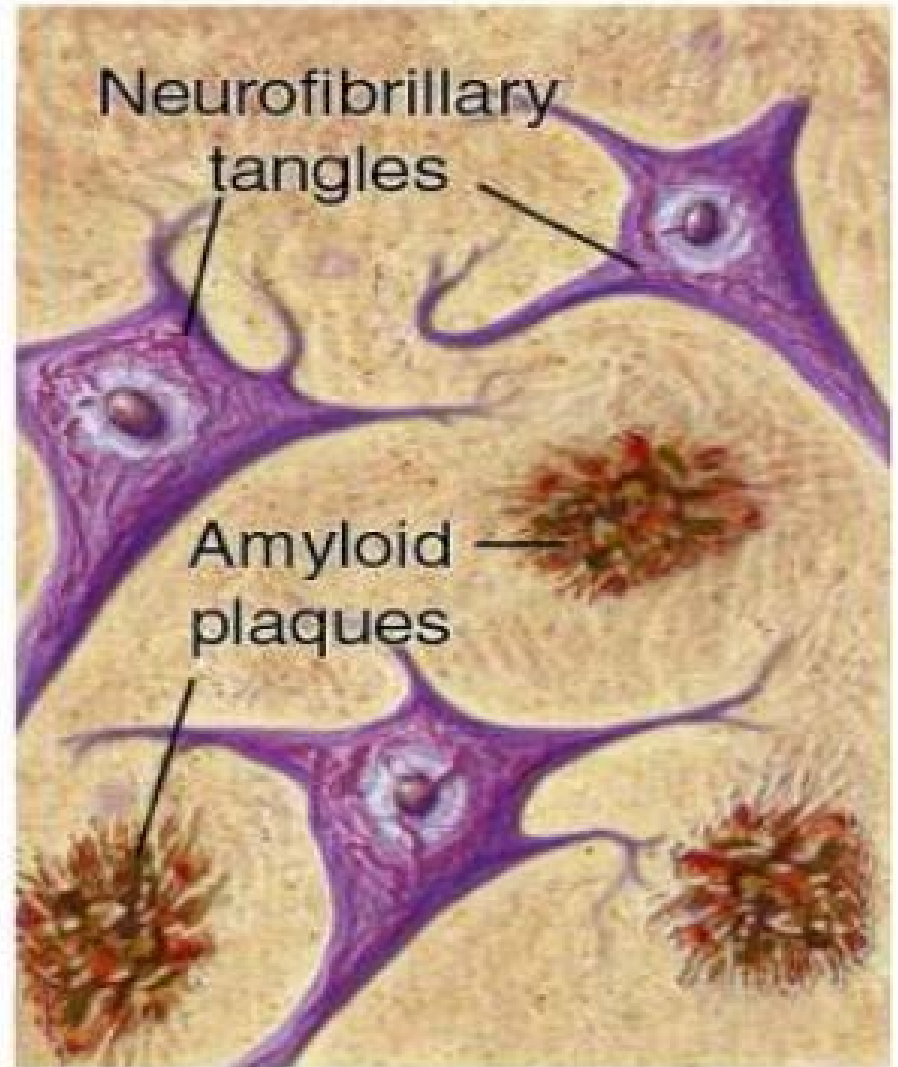


Microscopic feature

Normal



Alzheimer's



Etiology

- Marked reduction of Ach in hippocampus and cortex
- Atrophy of cortical & subcortical areas is associated with **deposition of β -amyloid protein** in the **form of extracellular senile (amyloid) plaques** & **formation of intracellular neurofibrillary tangles**

Treatment Strategies

1. Increasing global/regional cerebral blood flow (CBF) – vasodilator action
2. Direct support of neuronal metabolism.
3. Enhancement of neurotransmission.
4. Improvement of discrete cerebral functions, e.g. memory.

Classification

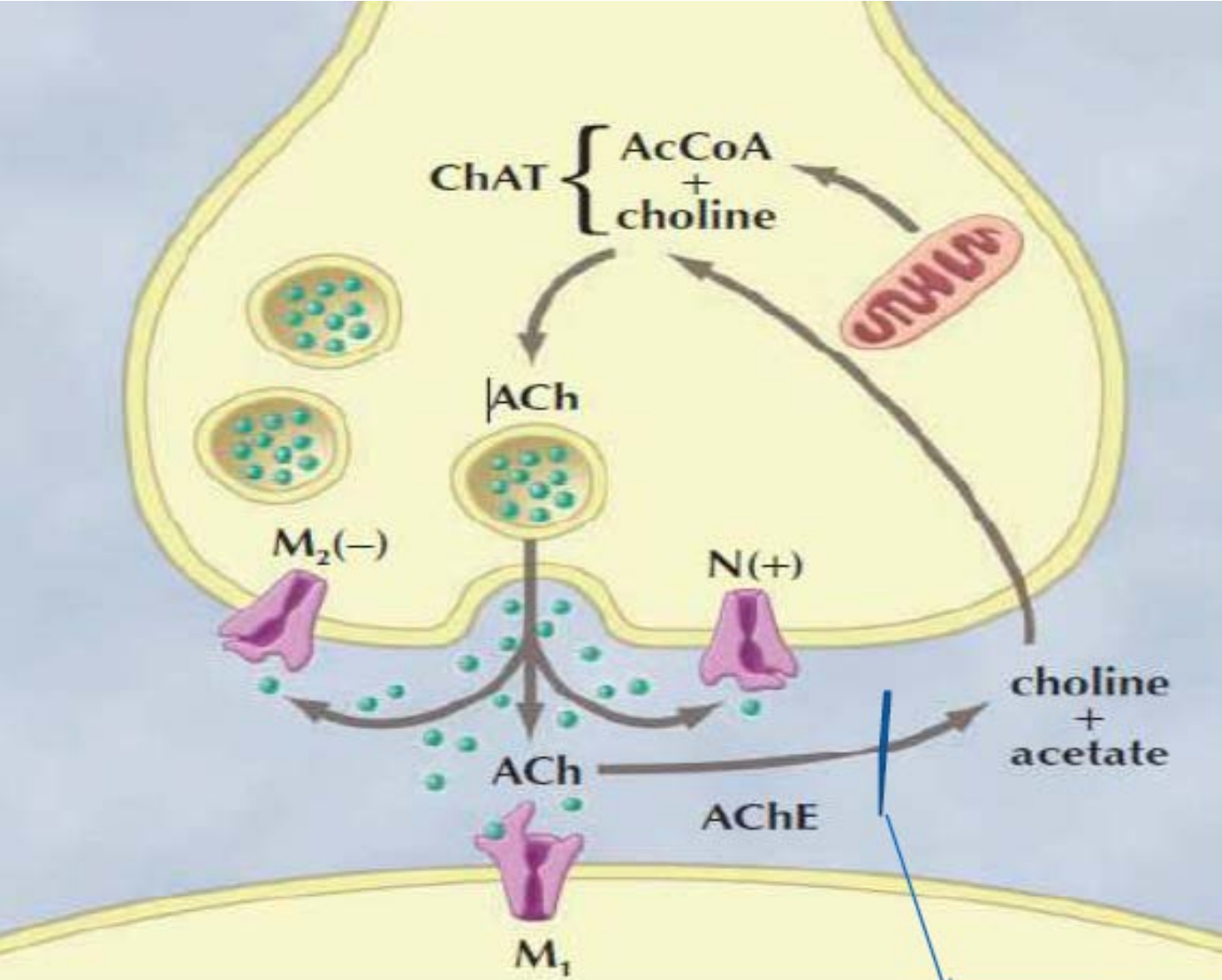
1. Acetylcholinesterase inhibitors (AChEIs) or Cholinergic activators::

Tacrine, Donepezil, Galantamine,
Rivastigmine & Huperzine A

2. Non-competitive N-methyl-D-aspartate (NMDA) receptor antagonist:

Memantine, Dimebolin

Acetylcholinesterase Inhibitors



AChEI

Mechanism of action

- The AChEIs act by **preventing the enzymatic degradation of the neurotransmitter acetylcholine (ACh)** resulting in **increased Ach concentrations in the synaptic cleft & enhanced cholinergic transmission**
- AChEIs may be divided into 3 groups: Noncovalent or “reversible” inhibitors, carbamoylating inhibitors & organophosphorus compounds

Tacrine

- 1st AChEI approved by FDA for treatment of AD was Tacrine which is a reversible inhibitor & no longer used now due to hepatotoxicity
- Major side effects: GI symptoms (Nausea, Diarrhea, Cramps), altered sleep, bradycardia & muscle cramps
- Caution when using in people with cardiac conduction conditions such as symptomatic bradycardia, or with a history of falls or syncope

Rivastigmine

- Reversible Carbamate Inhibitor
- Rivastigmine tartrate: Oral: approved for mild & moderate AD only
- It has a recently FDA-approved Transdermal patch that has been shown to eliminate GI side effects
- Rivastigmine can be safely given to patients not tolerating or not responding to donepezil

Table 1 Summary of FDA-approved medications for AD

	Donepezil	Galantamine	Rivastigmine	Memantine
Dose	5 mg/d for 30 days, then 10 mg/d.	4 mg bid for 30 d, then 16 mg bid, then 24 mg bid.	1.5 mg bid for 14 d, then 3 mg bid for 14 d, then 4.5 mg bid for 14 d, then 6 mg bid.	5 mg/d for 7 d, then 5 mg bid for 7 d, then 10 mg in AM 5 mg QHS for 7 d, then 10 mg bid.
Mechanism of action	Acetyl cholinesterase inhibitor	Acetyl cholinesterase inhibitor, also modulates nicotinic receptors	Acetyl cholinesterase and butyl cholinesterase inhibitor	N-methyl-D-aspartate receptor modulator
Indication	Mild, moderate, severe AD	Mild-moderate AD	Mild-moderate AD	Moderate-severe AD
Absorption affected by food	No	Yes	Yes	No
Protein binding	96%	0%–20%	40%	45%
Common side effects	Nausea, vomiting, diarrhea	Nausea, vomiting	Nausea, vomiting, weight loss, anorexia	Hallucination, confusion, dizziness, headache
Serum half life	70–80 hrs.	5–7 hrs.	2 hrs.	45 hrs.
Metabolism	CYP2D6, CYP3A4	CYP2D6, CYP3A4	Nonhepatic	Nonhepatic
Other concerns	Few drug-drug interaction	Renal impairment increases serum level, paroxetine/ketoconazole increases serum level	Renal impairment increases serum level	Alkalinization of urine to pH of 8 lessens clearance

Narcotics or Opioid Analgesics or Opioid Agonists

Introduction

- ***Algesia (pain)*** is an ill-defined, unpleasant bodily sensation, usually evoked by an external or internal noxious stimulus.
- ***Analgesic*** A drug that selectively relieves pain by acting in the CNS or on peripheral pain mechanisms, without significantly altering consciousness.
- Analgesics are divided into two groups, *viz.*
 - A. Opioid/narcotic/morphine-like analgesics.**
 - B. Nonopioid/non-narcotic/aspirin-like/antipyretic or antiinflammatory analgesics**

Opioid Analgesics

- **Opium** A dark brown, resinous material obtained from poppy (*Papaver somniferum*) capsule.
- It contains two types of alkaloids.
- **Phenanthrene derivatives**
 - Morphine (10% in opium)
 - Codeine (0.5% in opium)
 - Thebaine (0.2% in opium), (Nonanalgesic)
- **Benzoisoquinoline derivatives**
 - Papaverine (1%)
 - Noscapine (6%) Nonanalgesic

Classification

- 1. Natural opium alkaloids:** Morphine, Codeine
- 2. Semisynthetic opiates:** Diacetylmorphine (Heroin), Pholcodeine, Ethylmorphine
- 3. Synthetic opioids:** Pethidine (Meperidine), Fentanyl, Methadone, Dextropropoxyphene, Tramadol.

Classification

OPIOID ANTAGONISTS

1. Agonist-antagonists (κ analgesics)

Nalorphine, Pentazocine, Butorphanol

2. Partial/weak μ agonist + κ antagonist

Buprenorphine

3. Pure antagonists

Naloxone, Naltrexone, Nalmefene

Opioid Receptors

TABLE 34.1 Actions ascribed to different types of opioid receptors

μ (<i>mu</i>)	κ (<i>kappa</i>)	δ (<i>delta</i>)
Analgesia (supraspinal μ_1 + spinal μ_2)	Analgesia (spinal κ_1) (supraspinal- κ_2)	Analgesia (spinal + affective component of supraspinal)
Respiratory depression (μ_2)	Respiratory depression (lower ceiling)	Respiratory depression
Sedation	Dysphoria, psychotomimetic	Affective behaviour
Euphoria	Miosis (lower ceiling)	Reinforcing actions
Miosis	Sedation	Reduced g.i. motility
Muscular rigidity	Physical dependence (nalorphine type)	Proconvulsant
Reduced g.i. motility (μ_2)	Reduced g.i. motility	
Physical dependence (morphine type)		

Endogenous ligands

- 1. μ** – Endomorphins 1 & 2 (ago.), β -funaltrexamine (anta.)
- 2. κ** – Dynorphin (Ago.), Norbinaltorphimine (anta.)
- 3. δ** - leu/met enkephalins (Ago.), Naltrindole (anta.)

Opioid Analgesics

TABLE 34.2

Nature of interaction of opioid ligands with the three major types of opioid receptors, along with equivalent analgesic doses

<i>Ligand</i>	μ (<i>mu</i>)	κ (<i>kappa</i>)	δ (<i>delta</i>)	<i>Analgesic* dose (mg)</i>
1. Morphine	Ago. (St)	Ago. (W)	Ago. (W)	10
2. Nalorphine	Anta. (St)	Ago. (M)	—	—
3. Pentazocine	P.Ago., Anta. (W)	Ago. (M)	—	30–60
4. Butorphanol	P.Ago (W)	Ago. (St)	—	1–3
5. Buprenorphine	P.Ago	Anta. (M)	—	0.3–0.4
6. Naloxone	Anta. (St)	Anta. (M)	Anta. (W)	—
7. Naltrexone	Anta. (St)	Anta. (St)	Anta. (W)	—
8. Met/Leu enkephalin	Ago. (M)	—	Ago. (St)	—
9. β -Endorphin	Ago. (St)	—	Ago. (St)	—
10. Dynorphin A, B	Ago. (W)	Ago. (St)	Ago. (W)	—

* Equivalent single parenteral analgesic dose.

Ago—Agonist; Anta.—Antagonist

P. Ago—Partial agonist: have lower efficacy, though affinity (potency) may be high.

St—Strong action; M—Moderate action; W—Weak action (low affinity).

Mechanism of action

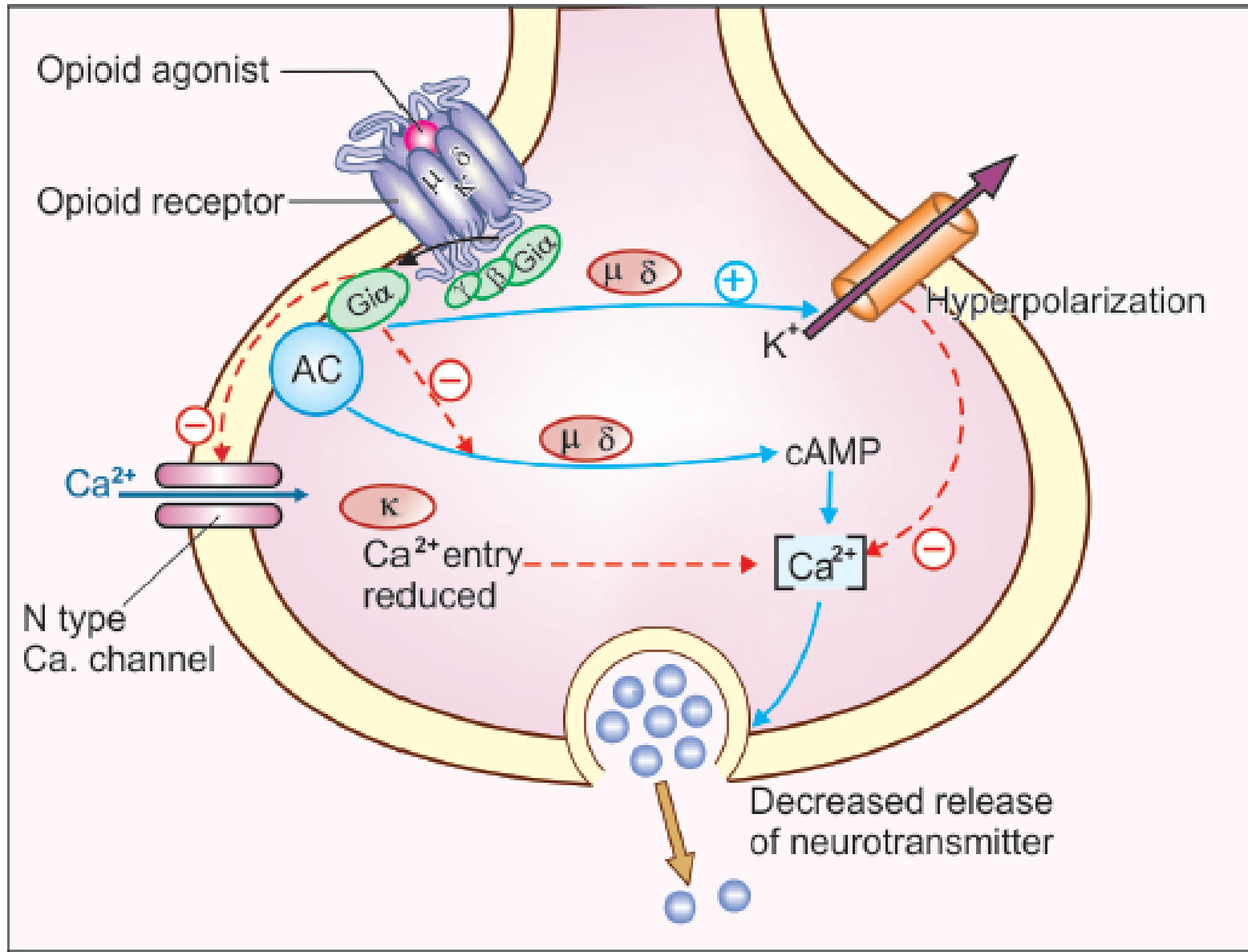


Fig. 34.1: Opioid receptor transducer mechanisms
AC-Adenylyl cyclase; Gi-coupling protein; cAMP-Cyclic AMP

Morphine – Pharmacological Actions

1. CNS

Morphine has site specific **depressant and stimulant actions in the CNS** by interacting primarily with the μ opioid receptor

The depressant actions are:

- (a) Analgesia
- (b) Sedation
- (c) Mood & subjective effects – Calming effect, Euphoria
- (d) Respiratory centre – depresses respiratory centre
- (e) Cough centre – depressed
- (f) Temperature regulating centre – depressed;
hypothermia
- (g) Vasomotor centre – depressed - fall in BP

Morphine – Pharmacological Actions

1. CNS - stimulant actions are:

- (a) CTZ - Nausea and vomiting occur as side effects
- (b) Edinger Westphal nucleus of III nerve - stimulated producing miosis
- (c) Vagal centre - stimulated → bradycardia is the usual response to morphine.
- (d) Certain cortical areas and hippocampal cells are stimulated - Muscular rigidity and immobility

Morphine – Pharmacological Actions

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Morphine – Pharmacological Actions

2. Neuro-endocrine

- **Hypothalamic activation** by afferent collaterals is dampened.
- Hypothalamic influence on pituitary is reduced.
- As a result **FSH, LH, ACTH levels are lowered**, while **prolactin and GH levels are raised**
- Increase release of ADH - reduce urine volume.

Morphine – Pharmacological Actions

3. CVS

Morphine causes vasodilatation due to:

(a) histamine release.

(b) depression of vasomotor centre.

(c) direct action decreasing tone of blood Vessels

- Decrease BP

Morphine – Pharmacological Actions

4. GIT

Morphine exerts marked effect on g.i. motility as well as on fluid dynamics across g.i. mucosa.

Constipation is a prominent feature of morphine action.

5. ANS

Morphine causes mild hyperglycaemia due to central sympathetic stimulation. It has weak anticholinesterase action.

Morphine – Pharmacological Actions

5. Other smooth muscles

(a) Biliary tract - cause biliary colic.

(b) Urinary bladder - Tone of both detrusor and sphincter muscle is increased → urinary urgency and difficulty in micturition.

(c) Uterus - slightly prolong labour.

(d) Bronchi - Morphine releases histamine - bronchoconstriction.