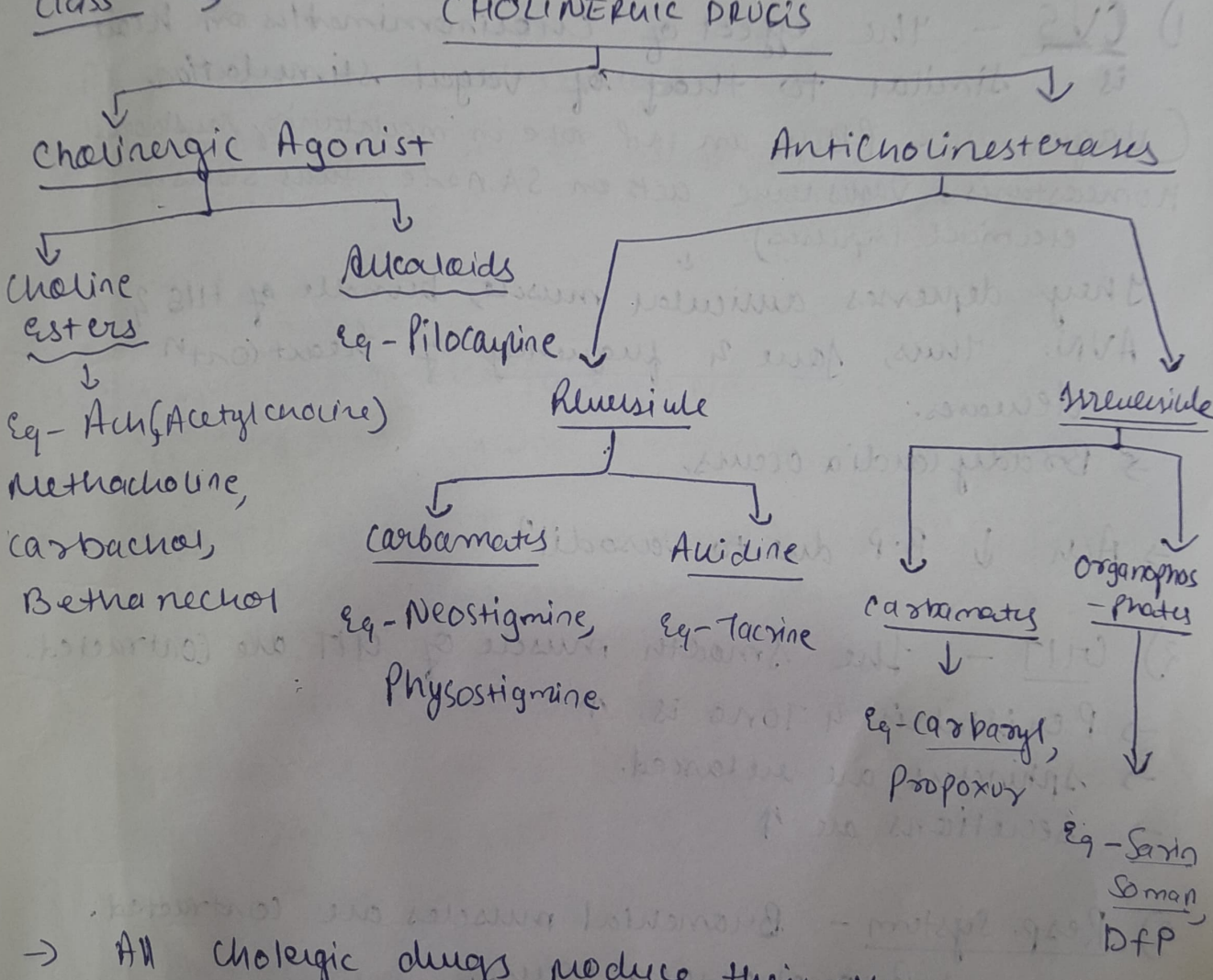
GITU

PARASYMPATHOMIMETICS (CHOLINERGICS)

→ Drugs that produce the action similar to that of parasympathetic stimulation. i.e. the drug which mimics the parasym. stimu^{n}.

Also Cled → cholinomimetic, ~~Parasympathomimetic~~ cholinergic drug.

Class^{n} →



→ All cholegic drugs produce their effects thru 2 types of receptors.

1) MUSCARINIC RECEPTORS - The actions are similar to those of Muscarine (an alkaloid).

Organs affected → Heart, Arterials, Salivary gland, eyes, stomach, uterus, B. Spleen, Skin.

2) NICOTINIC RECEPTORS - Effects are similar to those produced by Nicotine (obtained from tobacco).
Present in → Autonomic ganglia & Skeletal Muscles.

cholinergic
PHARMACOLOGICAL ACTION :-
↑ ~~↓~~ Vasodilation

1) CVS - The effect of cholinomimetics on heart is similar to that of Vagal stimulation.
(Vagus nerve plays an IMP role in maintaining physiological homeostasis - Vagus nerve acts on SA node, thus slows down electrical impulses)
They depresses auricular muscle, bundle of HIS & AVN. Thus, force & frequency of heart contⁿ decreases.
→ Bradycardia occurs.
→ Ach ↓ B.P due to vasodilⁿ

2) GIT - The smooth muscle of GIT are contracted.
→ Peristalsis & Tone is ↑
→ Sphincters are relaxed.
→ Secretions are ↑

3) Resp. System - Bronchial muscles are contracted.
→ Bronchospasm occurs.
Hence, cholinergic drugs are contraindicated in ASTHAMATIC condⁿ.

4) Urinary Bladder - They produce micturition.

5) Skeletal muscle - These drugs contract S.M. thru nicotinic effect.

6) CNS - Ach IV does not penetrat BBB, however direct inj. to brain produce behavioral & neurological effect. & can cause depression.

PHARMACOKINETICS :-

Ach is rapidly hydrolysed. So, Its ineffective orally.

Metabolism - In cholinergic Nerve terminals.

- Physostigmine is an alkaloid, so, can be absorbed orally.
- Organophosphates can be absorbed orally & can cross BBB Adr - Diarrhea, Abd. pain, cramps, N, V

THERAPEUTIC USE:-

1) They activate the Parasym. N.S by mimicking the effects of Ach.

2) Paralytic Ileus - Bethanechol & carbachol is used in this condn. They are specific for contracting smooth muscles. (Dsacondn in which muscles of intestine don't allow food to pass, resulting in blocking intestine)

3) Myasthenia Gravis - It is a disease in which there is rapid destruction of Ach occurs.
Hence, Anticholinesterases are useful in this condn as it ↑ the conc^n of Ach.

- Neostigmine is commonly used as,
  1) It X cross BBB
  2) It has selective action on skeletal muscles.

4) Cobra bite - C.B has curare like neurotoxin.
Atropine + Neostigmine can prevent respiratory paralysis.

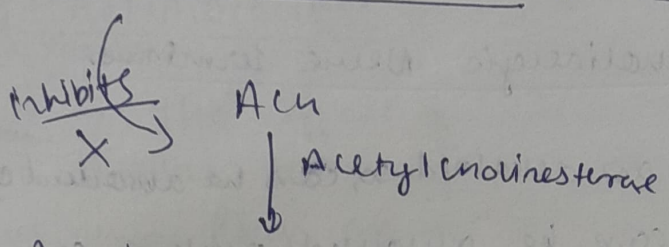
5) Atropine poisoning - Physostigmine is used, as it can cross BBB.

b) GLAUCOMA – These are used as Miotics. (Miotics are drugs that causes constⁿ of pupil)

Miotics increase the tone of ciliary muscles.

⇒ Pilocarpine & Physostigmine are commonly used here.

ANTICHOLINESTERASES or Acetylcholinesterase inhibitors



→ Anticholinesterases inhibits the enzyme cholinesterase & thereby ↑ the conc^{n} of ACh at the action site & produces parasympathomimetic action.

(Class^{n} → Previously written).

Use – Physostigmine is used in glaucoma & Atropine poisoning.
- Neostigmine is used in Myasthenia gravis.
- Organophosphates are useful in toxicology point of view.

→
* Organophos. compounds ~~poison~~ or Insecticides poisoning may occur due to ~~accidental~~ accidental consumption, suicide, or if person is occupationaly involved in spraying insectisides.

The signs of poisoning are:-

1) Muscarinic Effect - Miosis of eye, Bronchospasm Bradycardia, Hypotension, tightness in chest, Involuntary defecation & urination.

2) NICOTINIC effect - fatigue & weakness of muscles, involuntary twitchys.

3) CNS - Ataxia, slurred speech, coma, convulsion.

⇒ Atropine is an Antidote (2-4mg IV. total 8mg)
Besides, Antidote therapy, one has given O_2 inhalation & anticonvulsant agents.

PARASYMPATHOLYTICS (Anti-cholinergics)

- These agents inhibits or block the action of cholinergic agents at post-ganglionic nerve ending of Parasympathetic nerve.

Also called as - Parasympathetic blockers, Antimuscarinic agents, cholinergic blocking agents, Spasmolytics,

Class →

- Natural Alkaloids → Atropine, Hyoscine
- Semi-Synthetic derivatives → Homatropine, Atropine methonitrate, Ipratropium bromide, Tiotropium bromide
- Synthetics compounds
  - Antispasmatic/Antisynthetic → Dicyclomine, Pirenzepine
  - Mydriatics → Cyclopentolate
  - Anti-Park-insonism → Trihexyl-Phenidyl, Biperidin
  - Vasicoselective → Flavoxate

Adv. of Parasympathomimetic → Nausea, vomitting, fainting, dyspnoea,

These drugs are contraindicated in - Asthma, peptic ulcer, hypothyroidism, hypotension

Pharmacological Action

1) CNS – Atropine has overall CNS stimulant action.

→ Atropine stimulants many medulla brain centres vagal, Respiratory, Vasomotor.

⇒ By blocking cholinergic overactivity in Basal ganglia, It suppresses tremor in Parkinsonism.

→ At Higher doses, It causes hallucinations, delirium, depression & coma.

2) CVS – ~~Due to Atropine~~ the most prominent effect of Atropine is TACHYCARDIA.

~~[redacted]~~

- On repeated adm. of Atropine causes fall in B.P. which is due to depression of Vasomotor centres.

3) R.S. – Atropine causes Bronchodilⁿ & inhibits the ~~Secⁿ of Nose, Mouth, bronchi~~ nasal secn.

BC2 of these effects Atropine is used as Pre-anaesthetic agents in patient with Asthma & COPD.

4) GIT – Atropine ↓ tone, Peristalsis of GIT. All the secretion are decreased.

5) Eye – Atropine causes dilⁿ of pupil (Mydriasis). It antagonize miotic effect of parasympathomimetic drugs.

6) ADH – Atropine releases ADH (Anti-diuretic hormone) & thereby decreases diuresis. Sweat secn is also decreased. & thus Body temp ↑.

7) It relaxes uterus muscles, gall bladder etc. thus also used as Spasmolytics.

KINETICS – Orally abs. As well as by parenteral adm^{n}

Metabolism ~~Metabo~~ Liver

Excretion – Urine

Therapeutic use:-

1) Spasmolytic Agent – It relaxes smooth muscles.

2) Pre-anesthetic medication – Atropine ↓ various sec^{n}. & relaxes smooth muscles & retains urine & these effects makes it suitable for pre-anesthetic medication.

3) Organophosphorous Insecticide poisoning – Atropine is used as a Antidote for ☺.

4) Asthma – It causes Bronchodil^{n} & blocks the nasal & bronchi sec^{n}. Eg – Ipratropium bromide which is used now-a-days for Asthma treatment.

5) Parkinsonism, Motion Sickness

6) Eye – Atropine can be used to produce Mydriasis for examination of Retina.

7) Peptic ulcer – Atropine was previously used to treat P.U. Eg – Ranitidine, cimetidine. but it has certain disadvantages.

Adr: – 1) Tachycardia
2) Fever
3) constipation
4) Blurred vision
5) ↓ diuresis & sweat sec^{n}.

SYMPATHOMIMETICS (Adrenergics)

- Are the drugs that produce action similar to Sympathetic Nerve stimulation.

Class'n (Lodd)

- **Bronchodilators**
  - Salbutamol
  - Adrenaline
  - Isoprenaline
  - Terbutaline
  - Salmeterol
  - Formeterol
- **CNS Stimulant**
  - Ephedrine
  - Amphetamine
- **Nasal decongestants**
  - Neosynephrine
  - Oxymetazoline
- **Pressor agents**
  - NorAdr.
  - Dopamine
- **Cardiac Stimulant**
  - Adr.
  - Dobutamine
  - Isoprenaline

or

Class'n (Ketaniya)

1) **Directly acting** - Eg- Adrenaline, Noradrenaline, Isoprenaline, Salbutamol

2) **Indirectly acting** - Amphetamine, Tyramine

3) **Mixed** - Ephedrine, Dopamine

Pharmacological Action:-

1) **Heart** - heart consist of **β_1-adenoreceptors**

So, All Sympathomimetic drugs with β-adenoreceptor activity

↓

↑ H.R

&

also ↑ force of contn

- Contn of Blood vessel → ↑ B.P.

2) Respiratory system - lungs consist of β_2 - receptors.

Adr. & Isoprenaline cause Bronchorelaxation by acting on β_2 - receptors.

3) Uterus - Adrenaline when act on α Receptors - Uterus contn.

Adr. when act on β receptor - Uterus Relaxn

But, during Pregnancy, Adr. overall causes Relaxn

4) GIT - Produce relxn of smooth muscle

this causes ↓ in peristalsis

↓

which may cause constipation.

5) Eye - Mydriasis

6) CNS - Catecholamines (adr, non-adr; Isoprenaline) x cross BBB. so, no such effect on CNS.

If catecholamines are given IV & Non-catecholamines given orally, then it can cause restlessness, Nausea, vomiting!

Therapeutic use :- 1) Adr. & Isoprenaline causes Bronchi dilⁿ & are used in Asthma.

2) In ~~allergy & anaphylactic shock~~, Adr. is used as a bronchodilator.

3) Relaxes uterus during pregnancy.

4) Noradr. & adr. prolong the action of local anesthetics.

5) As a Nasal decongestants, which are used in Nasal drops eg. Oxymetazoline

SYMPATHOLYTICS

These drugs antagonize the action of sympathomimetic drugs.

Also cled - Symp. blocking drugs, Adrenergic blocking drugs or Adrenolytics.

(Class.) 1) α - BLOCKER

- Non-selective
  - ~~Phenoxybenzamine~~,
  - ~~Ergotamine~~
  1) Haloalkyl amines - Phenoxybenzamine
  2) Imidazolines - Tolazoline
  3) Ergot alkaloids - ~~Ergotamine~~
- Selective
  - α1
    - Prazosin
    - Terazosin
    - Tamsulosin
  - α2
    - Yohimbine

*

=) Pharmacological Actions :-

1) B.P. - All α - adrenergic blocker causes significant fall in B.P.
2) Eye - Causes Miosis
3) Nasal - Causes Nasal stuffness
4) GIT - ↑ in intestinal motility
   ↓
   can cause loose motion
5) Tone of smooth muscle of prostate is reduced
   ↓
   Urine flow in patient with Hypertrophy is improved.

   Eg - Tamsulosin

Therapeutic use -

1) Used to treat HTN
2) Tamsulosin improves the urine flow in patients with Prostate hypertrophy.
3) Prazosin ↓LDL & ↑HDL.
4) Ergot alkaloids are used to treat migraines.

β - Adrenergic Blockers

- Selective β_1
  - Metoprolol
  - Atenolol
  - Bisoprolol
  - Nebivolol.
- Non-selective ($\beta_1 + \beta_2$)
  - Sotalol
  - Pindolol
  - Timolol
  - ~~Bro~~

Generation wise

- 1st generation (older / non-selective)
  - Timolol
  - Sotalol
  - Propranolol
- 2nd (β1-selective / cardioselective)
  - Metoprolol
  - Atenolol
  - Bisoprolol
- 3rd (Ca channel blocker)
  - Labetalol
  - Carvedilol

→ Pharmacological effect

1) Heart - ↓ H.R, ↓ force of cont^{n}.
It also ↓ O_2 consumption of heart.

2) B.P. - It reduces B.P.
- It blocks noradr. release & Renin release from JG cells

3) Respiratory - β_2 - Blockers causes
↓
Bronchoconstriction
- ~~BT~~ - Specific β_1 receptor are prescribed for patient with Asthma + HTN.
eg - Bisoprolol

~~3) CNS - 3) Glaucoma - timolol~~

4) Propranolol reduces Blood sugar.
↓ glycogenolysis & lipolysis.

5) Eye - ~~Intra~~ ↓ Intraocular pressure
eg - Timolol is commanly used drug in Glaucoma.

6) CNS - It Produce Sedation & Anticonvulsant action.
- Effective in Schizophrenia.

- Therapeutic uses :-

1) HTN - Commonly used drug for treating HTN. as it ~~reduces~~ reduces B.P.

2) Glaucoma
3) Schizophrenia
4) Anxiety
5) used in Angina pectoris & M.I., as it ↓ the O2 demand of heart.

6) ~~CHF~~ used in CHF
7) cardiac dysrhythmias
8) Tremors.

NEUROMUSCULAR BLOCKERS

- These are the agents that reduce the unwanted spasm of Skeletal Muscle.

Also c/as → S.M. relaxants or Myoneural blocking agent.

- Their main site of action is → Motor End Plate of Skeletal / on voluntary muscles.

- Blocks cholinergic transmission btw^n - Motor Nerve Ending & Nicotinic receptor.

NOA ~~Skeletal~~ Skeletal Muscles are supplied with cholinergic Nerves

↓

Their releases Ach, which causes depolarisation (cont^n)

↓

N.M. blocks this cholinergic transmission at Motor End Plate

↓

↓

Ach is hydrolysed by an enzyme, cholinesterase

↓

& thus Muscle Relaxes

Class

Neuromuscular blockers

↓

Centrally Acting

→ Benzodiazepine - Diazepam

→ GABA mimetic - Baclofen

→ Antiparkinson's drugs - L-Dopa

→ ~~Others~~ Adrenergic antagonists - Methocarbamol

↓

Peripherally Acting

↓

Non-Depolarising blockers (competitive)

- d-Tubocurarine
- Pipecuronium
- Pancuronium

} long acting

- Rapacuronium → Intermediate acting

- Mivacurium → Short acting

Non-depolarising Blockers (~~competitive~~)

↓

→ Succinyl Choline

Csoxa - methonium

→ Decameth - ni

⇒ In non-dep, the drugs compete with Ach to bind to the site.

& as a result, the action produced by Ach will be blocked

⇒ Dep, → They bind to the site of Ach. & works similar to that of Ach.

↓

depolarisation.

1) Non-depolarising Blockers (competitive)

Eg- d-Tubocurarine / Gallamine

- Shows antagonist effect.
- They compete with Ach for binding site

→ They act on Nicotinic Receptors & compete with Ach

MOA

↓

Prevent binding of Ach

↓

~~Prevent depol~~ No influx of Na^+

↓

Prevent depolarisation

↓

Muscle relaxes

Pharmacological Action -

1) Skeletal Muscle - Ach produces muscle cont^n by acting on motor end plate.

d-Tubocurarine competes with Ach & prevents & block the action of Ach.

↓

& this causes → Muscle to Relax.

(But, this action can be reversed by anticholinesterase)

→ It relaxes Muscle of - 1) face
2) limbs
3) Eye
4) Neck

2) Respiration - D-tubocurarine causes release of histamine which may cause Bronchospasm

3) B.P. - d-tubocurarine causes release of histamine, which dilates Blood vessels so, B.P may ↓

Therapeutic use -

1) It relaxes all Skeletal Muscle
2) Used with Anesthesia during abd. surgery. lesser amt. of Anesthesia is required, when d-tubocurarine is given.
3) Relaxes muscles of limbs, face, eye.
4) treatment of muscle spasm.

(2) DEPOLARISING BLOCKERS →

Eg- Succinyl choline (Suxamethonium).

- It is a depolarising Neuromuscular blocker. that Structurally resembles Ach.

MOA →

Succinyl choline binds to receptor
↓
causes persistant Muscle cell depolarisation
↓
This makes muscle cells, resistant to any further stimulation of Ach.
↓
Desensitization of channels
↓

↓

gradual Repolarization

↓

Muscle Relaxes

via I.M.

→ It has shorter duration of actions

→ It does not cause release of histamine, hence, do not cause hypotension or bronchospasm

→ It is used adjuvant to anaesthetic agent, during short surgical processes.

PARKINSONISM.

- It is a CNS disorder characterized by rigidity, tremors.
- Nerve cell damage in the brain causes Dopamine levels to drop in parkinsonism.

Drugs Class

1) Dopamine precursor - Levodopa
2) Peripheral decarboxylase inhibitor - Carbidopa
3) Dopaminergic Agonist - Bromocriptine
4) MAO-B inhibitor - selegiline
5) COMT-inhibitor - Tolcapone, Entacapone
6) Dopamine Facilator - Amantadine

LEVODOPA

This compound is inactive (prodrug), however it is taken up by adrenergic neurons.

Levodopa
↓ decarboxylated by DOPA-decarboxylase
Dopamine
↓

It gives relief in ~~Psoriasis~~ Parkinsonism,

Dopamine, peripherally is converted to Noradr. to produce no. of side effects

P-C 1) On-off Effect - LD. There is a rapid fluctuation where rigidity & tremors appears & may worsen for few mins to few hrs. & then improves again.

2) CVS - as Dopamine converts to Noradr. peripherally, so, there is ↑ in HR & ↑ BP.

3) CNS - It improves akinesia & tremors.

PK - L-D. is orally absorbed
t1/2 is - 1-3 hrs.
About 95-1% of LD is metabolized peripherally & only 1% crosses BBB.

Adr - N, V, Anorexia, changes in BP, HR, arrhythmia.

Comp^n of L-Dopa & Carbidopa

3-Omethyldopa
COMT ✗ COMT-inhibitor

Brain in DOPAC ← MAO-B ✗ MAO-B inhibitor — L-Dopa → Dopamine

BBB

crosses BBB

L-Dopa

Blood

Peripherally)

L-Dopa
↓ COMT (gets converted to)
3-O-methyldopa

Dopamine ✗ Pass BBB
So we give a Prodrug, L-Dopa

But, L-Dopa

So, to prevent this we give Carbidopa.

Explanation- ⊖ Dopamine do not cross BBB.

So, L-dopa a prodrug of dopamine (Prodrug defination is explained in General pharmacology).

↓

L-Dopa cross BBB.

But, Peripherally L-DOPA converts to

↓

Dopamine which cannot cross BBB.

So, ~~this~~ This can be prevented by CARBIDOPA

L-DOPA

↓ X carbidopa.

DOPamine

Also, peripherally L-DOPA gets converted to

↓

~~3-MAO-B~~ COMT.

3-O-Methyldopa

This can be prevented by COMT-inhibitors

Eg- Tolcapone

So, L-dopa crosses BBB.

but in brain it gets converted to

X by COMT-i → 3-O Methyldopa

X by MAO-B inhib → DOPAC

so, Carbidopa prevents the peripheral conversion of L-dopa to dopamine.

Advantages of this combination-

1) The dose of L-Dopa can be reduced by 75%.
2) S.E. can be prevented
3) faster improvement
4) ↑ in t1/2 of L-dopa
5) ↑ in bioavaibility of L-dopa
6) Tolerance is delayed.

L-dopa alone → 100% — ~~70~~ 70·1. → 27·1. → 3% in Brain

70·1. ↓ metabolism in GIT

27·1. ↓ Peripheral tissues

L-dopa + Carbidopa 100% → 40·1. → 50·1. → 10·1. in Brain

40·1. ↓ Metn in GIT

50·1. ↓ peripheral tissues

Adr. — N, V, dizziness, fainting.