
بسم الله الرحمن الرحيم

Anticholinergic drugs;

Cholinergic antagonists,

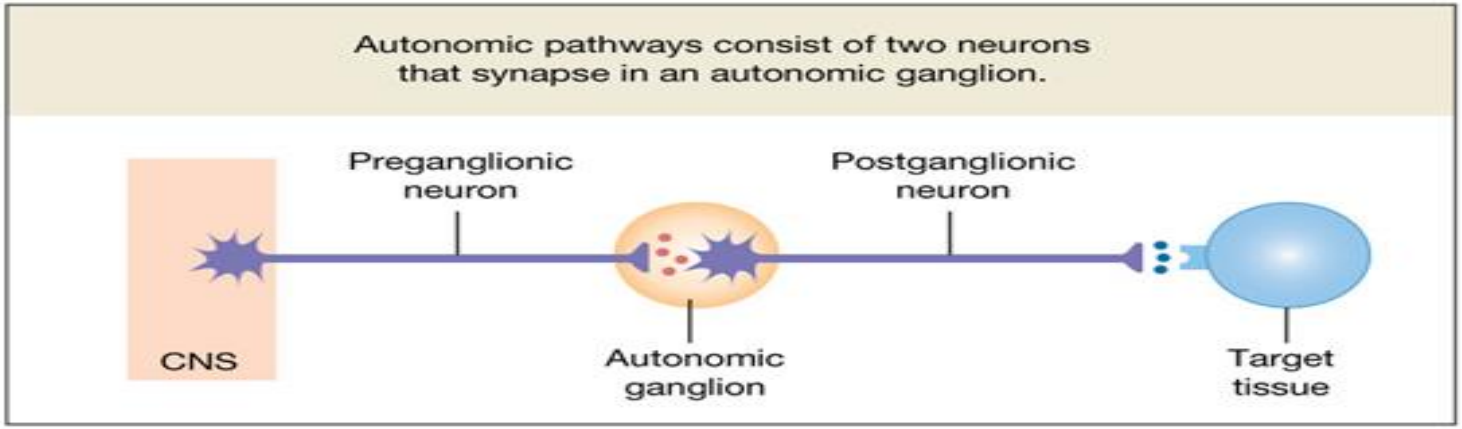
Cholinergic blockers,

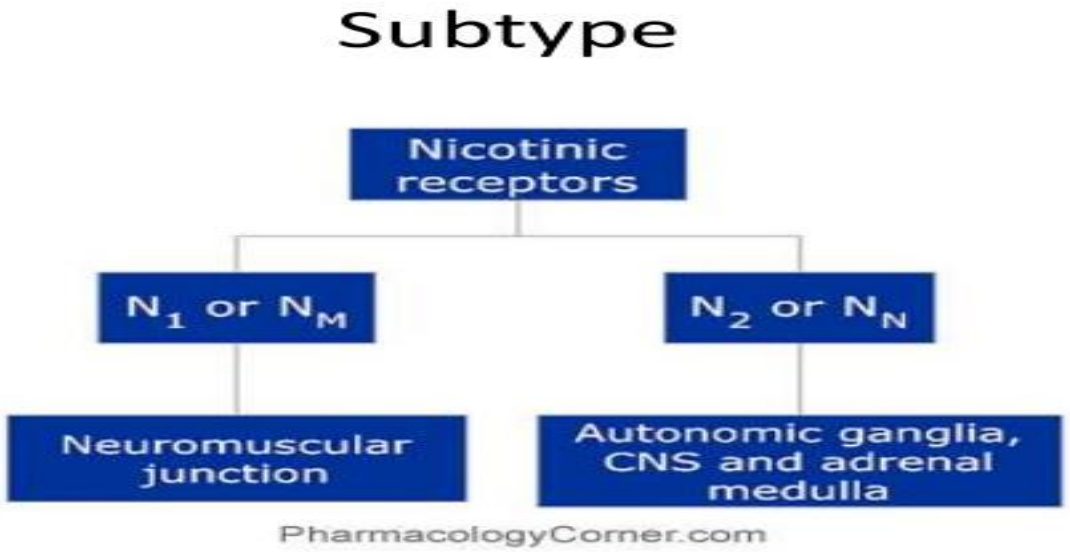
Cholinergic receptor blocking drugs,

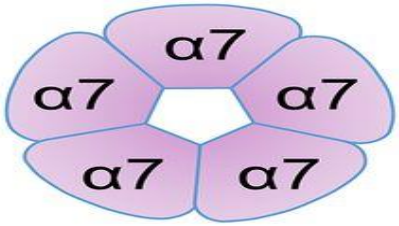
By

Dr. Muhammad Sarwar

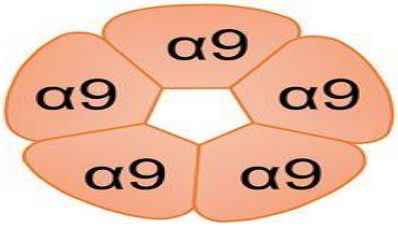
Ganglion blocking drugs;







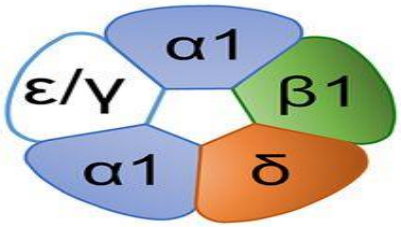
α7



α9

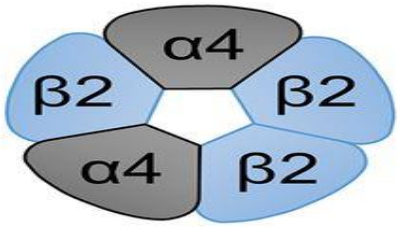
Homomeric nAChRs

N_M



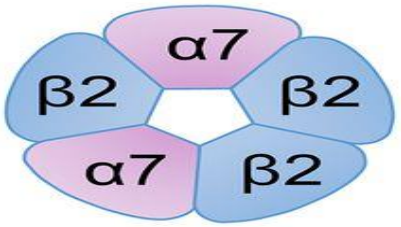
αβε(γ)δ

N_N



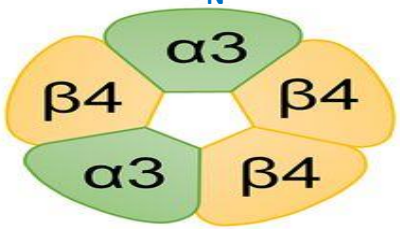
α4β2

N_N



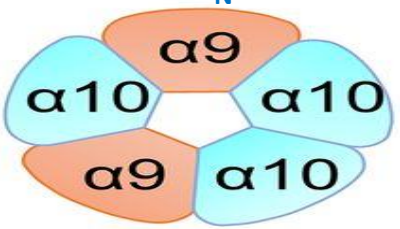
α7β2

N_N



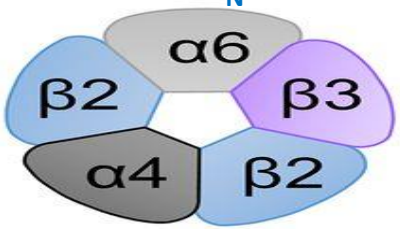
α3β4

N_N



α9α10

N_N



α4α6β2β3

Heteromeric nAChRs

Nicotinic receptors;

N_M

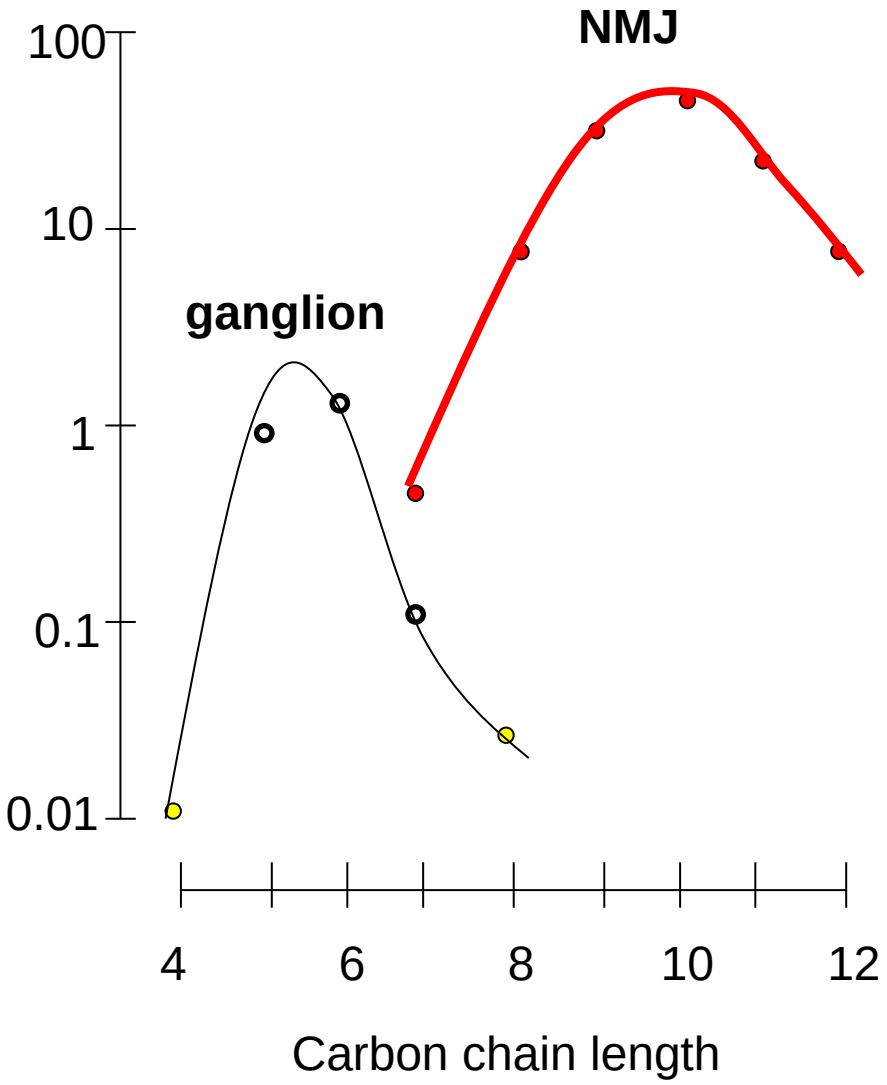
- **Neuromuscular junction;**
- **Pentamer: 5 subunits.**
- **4 distinct subunits (α_1)2, β_1, γ, δ)**
- One molecule of Ach binds Per **α subunit** to open channel for Na+.
- Selective **antagonist** at NM junction **--- tubocurarine.**

N_N

- **Autonomic ganglia, adrenal medulla, CNS;**
- **Pentamer: 5 subunits.**
- **2 distinct subunits (α,ß),** (α_3)2 and β_4)3
- **α chains contain the Ach binding sites - binding of Ach → opening of ion channel (Na+ in, K+out)**
- Selective **antagonist at AN ganglia --- trimethaphan.**

Antinicotinic drugs' Selectivity;

- Most of these drugs have a **carbon backbone.**
- **↑ carbon length,** changes effects**.**
- **C6 = selectively** bind at **ganglia.**
- **C10 = selectively** bind at **NMJ.**



Antinicotinics;

- **Ganglion Blockers;**
  - **Trimethaphan** - **Hexamethonium**
  - **Mecamylamine** - **Pempidine**
  - **Pentolinium**
- **Neuromuscular Blockers;**
- i) **Competitive Blockers --- non- depolarizing;**
  - **Tubocurarine** . **Pancuronium** . **Atracurium**
  - **Gallamine** . **Vecuronium**
- ii) **Noncompetitive Blocker (depolarizing);**

  Succinylcholine (suxamethonium)

Ganglion blocking drugs;

- Block the action of **Acetylcholine** at the **Nicotinic receptors** of **Both parasympathetic and sympathetic autonomic ganglia.**

Ganglion blockage can occur by several mechanisms;

- **By interference with ACh. release;**

  e.g., Botulinum toxin and hemicholinium.

- **By prolonging depolarization;**

  e.g., Nicotine can block ganglia after initial stimulus (Depolarizing block).

- **By interference with postsynaptic action of acetylcholine;**

  e.g., Ganglion blocking drugs act by blocking neuronal nicotinic receptors. (Non depolarizing).

GANGLION BLOCKERS;

- **The drugs which block the entire autonomic outflow.**

Classification;

A) Competitive Blockers;

- **Quaternary ammonium compounds;**
  - Hexamethonium (C6)
  - Pentamethonium (C5)
  - Pentolinium
- **Secondary amines** -- Mecamylamine
- **Tertiary amines** -- Pempidine
- **Sulphonium compounds** --- Trimetaphan

B) Depolarizing Ganglionic Blocking Agents;

- **Nicotine; (Large dose)**
- **Anticholinesterases (Large dose).**

➢ **Depolarizing blocking agents** are actually ganglionic stimulants. Thus, **for nicotine**,

- **small doses** give an action similar to that of the natural neuroeffector ACh.
- **Larger amounts** of nicotine, however, bring about a **ganglionic block** characterized initially by depolarization, followed by a typical competitive antagonism.

Pharmacokinetics;

- All ganglion-blocking drugs are **synthetic amines.**
  - **Tetraethylammonium (TEA),** the **first to be recognized** as having this action.
  - **Hexamethonium ("C6")** was developed and was introduced clinically as the **first drug effective for management of hypertension.**
    - **Decamethonium, the"C10"** analog of hexamethonium, is a depolarizing neuromuscular blocking agent.
  - **Mecamylamine**, a secondary amine, was developed to improve absorption from the GIT because the quaternary amines were poorly absorbed.
  - **Trimethaphan,** a short--acting ganglion blocker, is inactive orally and is given by **intravenous infusion.**

Pharmacodynamics;

Mechanism of Action;

Ganglion blockers, like neuromuscular blockers, are subject to both **depolarizing (agonist)** and **non depolarizing (agonist) block.**

- **Depolarizing block; Nicotine** itself and even **acetylcholine** (if amplified with a cholinesterase inhibitor) can produce depolarizing ganglion block.
- **Non--depolarizing block;** Drugs now used as ganglion blockers are classified as **non--depolarizing competitive antagonists**.

However, **hexamethonium** actually produces most of its blockade by occupying sites in or on the nicotinic ion channel, not by occupying the cholinoceptor itself. In contrast, **trimethaphan** appears to block the nicotinic receptor, not the channel pore. Blockade can be surmounted by increasing the concentration of acetylcholine.

Ph. Actions; Predominant autonomic nervous system on effector sites;

Site	Predominant ANS Tone	Effect of Ganglion blockade
Arterioles	Sympathetic	vasodilation, hypotension.
Veins	Sympathetic	vasodilation, ↓venous return, ↓Cardiac output, pooling of blood, postural hypotension, syncope.
Heart	Parasympathetic	Tachycardia.
Iris	Parasympathetic	mydriasis (dilation)
Ciliary muscle.	Parasympathetic	Cycloplegia (loss of accommodation)
GIT	Parasympathetic	↓tone, ↓motility, constipation.
Urinary tract	Parasympathetic	urinary retention.
Male sexual function	Parasympathetic + Sympathetic	Inhibition of erection } Impotency Inhibition of ejaculation }
Salivary glands	Parasympathetic	xerostomia (dry mouth)
Sweat glands	Sympathetic	Anhidrosis (low sweating).

Are Ganglion blockers selective in their action?

TRUE OR FALSE.

- Ganglion blockers cause
  - –Complex & unpredictable responses.
  - –Selective actions cannot be achieved.
  - – A broad range of undesirable effects.

Clinical Uses;

- **Are Ganglionic blocking drugs widely used because of their fewer side effects?**

True or False.

➢ **Their use is now obsolete.**

EXCEPT;

- **Trimethaphan;**

  Hypertensive emergencies

- **Emergency lowering of BP when other agents cannot be used or not available.**
  - **— Dissecting aortic aneurysm.**
  - **Intraoperative BP reduction.**

    (Controlled hypotension) (to reduce bleeding in operative field especially in neurosurgical procedures).
- In the management of **autonomic hyperreflexia** following injury to the upper spinal cord.
  - **Dose;**

    I/V Bolus (50 mg) followed by infusion.

    When infusion is stopped BP rises within 10 minutes.

Adverse Effects;

- **Blurred vision --** moderate mydriasis and cycloplegia.
- **Constipation.**
- **Urinary hesitancy.**
- **Sexual dysfunction --- Impaired erection.**

  Impaired ejaculation.
- **Dry mouth, dry skin and dry eyes (grittiness).**
- Glands -- ↓ in salivation, lacrimation, sweating and gastric secretion.
- **Severe orthostatic hypotension.**
- **CNS adverse effects;**
- **Quarternary amines (Hexamethonium, Pentamethonium , Pentolinium & Trimethaphan) are devoid of central effects.**
- **Mecamylamine (secondary amine) enters the CNS ---------- sedation, tremors, choreiform movements.**

Drug Interaction;

Potentiation of ganglion blocking drugs;

- –Halothane, chloroform, ether, barbiturates,
- –TCA,
- –MAO inhibitors,
- –Local anesthetics, Hyoscine,
- –Non-depolarizing muscle relaxants,
- –Propranolol, Procainamide, quinidine, hydralazine.

- **Can autonomic drugs act in presence of ganglion blockage?** **Yes or No**
  - –Because the effector cell receptors (muscarinic, alpha, beta) are not blocked.


Thank You