Cholinergic receptors and their functions $ clinical application

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HISTORY :

In 1936 Henry Dale and Otto Loewi shared the Nobel prize for their pioneering research on chemical neurotransmission and in particular for the discovery and the functional characterization of the first identified neurotransmitter, acetylcholine

The history of this neurotransmitter dated back to the crucial experiments performed by Dale, who identified acetylcholine as responsible of a strong vasodepressor effect

Loewi who demonstrated chemical neurotransmission in the frog vagus nerve-heart preparation
This 15-year long story found a first conclusion
with the demonstration that acetylcholine was actually present in mammalian organs

Since then, the history of acetyl-choline in neuroscience has been one of great advancement of our knowledge in many functions of the nervous system as well as in very harmful neuropathologies

Cholinoceptors

Two classes of receptors for Ach are recognized muscarinic and nicotinic ;

The muscarinic receptor is a G protein coupled receptor, while The Nicotinic receptor is a ligand gated cation channel.

Table 7.1: Sites of cholinergic transmission and type of receptor involved

Site	*Type of receptor*	*Selective agonist*	*Selective antagonist*
1. *a.* All postganglionic parasymp. *b.* Few postganglionic symp. (sweat glands, some blood vessels)	Muscarinic	Muscarine	Atropine
2. *a.* Ganglia (both symp. and parasymp). *b.* Adrenal medulla	Nicotinic (N_N)	DMPP*	Hexamethonium
3. Skeletal muscles	Nicotinic (N_M)	PTMA**	Curare
4. CNS (cortex, basal ganglia, spinal cord and other sites)	Muscarinic	Muscarine/ Oxotremorine	Atropine
	Nicotinic	Carbachol	Curare

* DMPP—Dimethyl phenyl piperazinium
** PTMA—Phenyl trimethyl ammonium

Muscarinic receptors

Characteristics	M_1 (neuronal)	M_2 (cardiac)	M_3 (glandular)
1. Location	Neural: Ganglia (autonomic and enteric), gastric paracrine cells, CNS (cortex and hippocampus)	Cardiac: SA node, AV node, atrium, ventricle; neural: presynaptic terminals	Exocrine glands, smooth muscles, vascular endothelium
2. Function	Gastric acid secretion, GI motility, CNS excitation	SA node: ↓ rate of impulse generation. AV node: ↓ velocity of conduction ↓ contractility: vagal bradycardia	↑ exocrine secretions, smooth muscle contraction[1]
3. Mechanism[2]	↑ IP_3, ↑ DAG, ↑ cytoplasmic Ca^{++}, depolarisation	Inhibition of adenylate cyclase (↓ cAMP) and opening of K^+ channels. Inhibits neuronal Ca^{++} channels (presynaptic inhibition of ACh release)	Same as for M_1 receptors
4. Agonists	M_1NA-343*, oxotremorine	Methacholine	Bethanechol
5. Antagonists	Pirenzepine* Telenzepine*	AF-Dx 116* Tripitramine*	4-DAMP Tolterodine Darifenacin*

Nicotinic Receptors :

Characteristics	Muscle type (N_m)	Neuronal type (N_n)	In CNS
1. Location	At skeletal neuromuscular junction (NMJ); Postsynaptic	At all autonomic ganglia and at adrenal medulla; Postsynaptic	At sensory nerve terminals and in other parts of brain but mostly located presynaptically
2. Function	Contraction of skeletal muscle	Transmission of impulse through autonomic ganglia and firing of postganglionic neuron, and secretion of NE & E from adrenal medulla	Presynaptic facilitation of the release of dopamine and glutamate
3. Mechanism	Ligand gated ion channel family of receptors - opening of cation (Na^+) channel (end plate depolarisation)	Same as for N_n receptors	—
4. Agonists	ACh, Succinyl choline, PTMA*, Nicotine	Nicotine, DMPP* Epibatidine*	—
5. Antagonists	d-Tubocurarine α-Bungarotoxin*	Hexamethonium Trimethaphan*	—

Table 11.1 Classification of Parasympathomimetic Drugs

PARASYMPATHOMIMETICS

DIRECTLY ACTING

1. **Acetylcholine (prototype)**
2. **Synthetic Choline Esters**
   - i) Methacholine
   - ii) Carbachol
   - iii) Bethanechol
3. **Natural Alkaloids**
   - i) Muscarine
   - ii) Nicotine
   - iii) Pilocarpine
   - iv) Arecoline
4. **Miscellaneous**
   - i) Tremorine
   - ii) Oxotremorine
   - iii) Cevimeline

INDIRECTLY ACTING (anticholinesterases)

REVERSIBLE*

1. **Natural Alkaloids**
   Physostigmine
2. **Quaternary Compounds**
   - i) Edrophonium
   - ii) Neostigmine
   - iii) Pyridostigmine
   - iv) Ambenonium
   - v) Demecarium
   - vi) Rivastigmine

IRREVERSIBLE**

1. **Organophosphates**
   - i) Isoflurophate (DFP)
   - ii) Ecothiophate
   - iii) Paraoxon
   - iv) Parathion
   - v) Malathion
   - vi) Diazinon
2. **Carbamates**
   Propoxur

* These drugs have short to intermediate duration of action.
** These drugs usually have a longer duration of action.

Cholinergic agonists

Class of drug	Drug name	Receptors	Pharamacological approach	ADR
Choline esters	Ach		Not used	
Cholin esters	bethanechol	Mainly muscarinic-bladder & GIT (M3) -devoid of nicotinic effects	-Post operative/post partum non obstructive urinary retention & neurogenic bladder. -GIT atony	Overdosage-CNS stimulation,miosis ,spasm of accommodation for distance vision,bronchoconstriction,abd.cramps , sweating
Alkaloid	Pilocarpine	Dominant M3 recptors Mild action at ganglia(Nn)	-glaucoma. -prevent/break the adhesion of iris with lens or cornea -sialagogue-xerostomia	Above n for systemic-pul.oedema

CHOLINERGIC AGONISTS

Class of drug	Drug name	Receptors	Pharamacological approach	ADR
Alkaloid	muscarine	Muscarinic receptors	Not used	Mushroom poisioning
Alkaloid	arecoline		No therapeutic use Tried in demenia to enhance cognitive function.	

CHOLINERGIC AGONISTS

Class of drug	Drug name	Receptors	Pharamacological approach	ADR
Anticholinesterases(reversible)	**Physostigmine**	Mainly muscarinic(M1 toM3)	- (opthal) glaucoma. -prevent/break the adhesion of iris with lens or cornea -Belladona posionng	More potent than pilocarpine-highly lipid soluble and toxic hence rarely used
Anticholinesterases(reversible)	**Neostigmine**	Mainly at Nm (S.M)& direct agonistic action NMJ	Myasthenia gravis, . Postoperative paralytic ileus/ urinary retention. Postoperative decurarization. Cobra Bite	Hypotension , bronchospasm

CHOLINERGIC AGONISTS

Class of drug	Drug name	Receptors	Pharamacological approach
Anticholinesterases(reversible)	**Edrophonium**	Mainly at Nm & possess direct agonistic action at nicotinic receptor of NMJ	- In the diagnosis of myasthenia gravis - Short duration of action-not used
Anticholinesterases(reversible)	**Demecarium**	Mainly M3	Long acting miotic-Glaucoma

Irreversible cholinesterase

Organophosphorus compounds.

T. Uses :

In the eye : for glaucoma

Echothiophate : 0.06% ↓ 1 0 T for 1 – 3 weeks.

ADR : Ciliary spasm, headache, blurred vision.

ORGANOPHOSPHORUS (OP) COMPOUND POISOING

Symptoms : Muscaninic effects

Nicotinic effects

CNS effects.

Muscaninic effects :-

salivation,sweating,nausea,vomiting,abdominal cramps

Nicotinic effects :-

Fasiculations of sk.muscles leading to paralysis

CNS effects :-

Restlessnes , tremor , convulsions , ataxia , resp.arrest

Treatment of acute OP Poisoning

1. Termination of exposure
2. Airway
3. Supportive measures.
4. Specific antidotes

   A.. **Atropine**

   B. **Cholinesterase reactivaters : Oximes**

- Pralidoxime (2 – PAM) : 500 mg / 20 ml
- Diacetylmono-oxime (DAM) : Crosses BBB
- Obidoxime

ADR : Oximes : local irritation, drowsiness, blurred vision, diplopia, tachycardia, hypotension,

High doses of Oximes—NM blockade.

Nerve gases

- Tabun (GA) - Gerhard Schrader – discovered 1936
- Sarin (GB) – Gerhard Schrader – discovered 1937
- 30,000 tons of tabun produced 1942-45
- Soman (GD) – Richard Kuhn – discovered 1944

- Classes :

there are two main classes

1. G series
2. V series

- G series named because of first developed by german

  eg: Tabun , Sarin, Soman

- V series

  eg : VX, VG

These are mainly used as chemical warfare agents during II world war

- UN resolution 687 (april 1991)

  As chemical weapons they are classified as weapons of mass destruction by UN
- Chemical weapons convention (1993)

  their reproduction and stockpiling were outlawed
- Chemical weapons convention officially took effect on april 29 1997

Antimuscarinic agents

These are the drugs which blocks the actions of Ach especially mediated through muscarinic receptor.

Table 11.4 Classification of Muscarinic Receptor Antagonists.

ANTIMUSCARINIC DRUGS*			
Natural alkaloids	Semisynthetic derivatives	Synthetic derivatives	
ATROPINE (dl-hyoscyamine)	HOMATROPINE and its salts	EUCATROPINE	PROPANTHELINE
	ATROPINE methionitrate	CYCLOPENTOLATE	DROTAVERINE
	HYOSCINE methylbromide	TROPICAMIDE	OXYPHENONIUM
	BENZTROPINE	DICYCLOMINE	GLYCOPYRROLATE
	IPRATROPIUM bromide	FLAVOXATE	CLIDINIUM
	TIOTROPIUM bromide	OXYBUTININ	TOLTERODINE
		PIRENZEPINE	PIPENZOLATE
		TELENZEPINE	VALETHAMATE
SCOPOLAMINE (l-hyoscine)		TRIHEXYPHENIDYL	
		PROCYCLIDINE	

Miscellaneous group of drugs possessing significant antimuscarinic effects are: Antihistamines (DIPHENHYDRAMINE, PROMETHAZINE, ORPHENADRINE); phenothiazine group of antipsychotics (CHLORPROMAZINE, THIORIDAZINE); butyrophenone group of antipsychotics (HALOPERIDOL); tricyclic antidepressants (AMITRIPTYLINE, IMIPRAMINE)

Atropine

HISTORY :

- Atropine extracts from the Egyptian henbane were used by Cleopatra in the last century B.C. to dilate her pupils, in the hope that she would appear more alluring.
- In the Renaissance, women used the juice of the berries of *Atropa belladonna* to enlarge the pupils of their eyes, for cosmetic reasons. This practice resumed briefly in the late nineteenth- and early twentieth-century in Paris.

- The mydriatic effects of atropine were studied among others by the German chemist Friedlieb Ferdinand Runge (1795–1867).
- In 1831, the German pharmacist Heinrich F.G. Mein (1799-1864)[58] succeeded in preparing atropine in pure crystalline form.[59]

  The substance was first synthesized by German chemist Richard Willstätter in 1901

EYES (M3 receptor blockade) --mydriatic

Mydriatic,prevent adhesion between iris and ant.surface of lens,iritis,iridocyclitis

CVS

In heart, M_2 receptor is blocked by atropine in S.A node and A.V node leads to tachycardia.

It also blocks muscarinic autoreceptors on vagal nerve endings augmenting ach release, this leads to

Predominant bradycardia and finally tachycardia.

CNS

At low doses atropine do not cross BBB.

At higher doses it produce CNS stimulant action.

Hyoscine produce CNS depressant effect even at low doses.

Atropine stimulates many medullary centers – vagal, respiratory, vasomotor.

It depresses vestibular excitation and has antimotion sickness property.

It suppresses the tremor and rigidity of parkinsonism by blocking the cholinergic over activity in basal ganglia.

In high doses cause cortical excitation, restlessness, disorientation, hallucinations and delirium followed by respiratory depression and coma

Smooth muscle

All visceral smooth muscles are relaxed by atropine (M_3 blocked).

The tone & contraction of stomach and intestine are reduced; the passage of chyme is slowed – constipation may occur, spasm may be relieved.

Atropine causes bronchodilatation and reduces air way resistance, specially in COPD and asthma patients.

It has a relaxant action on ureter and urinary bladder;

Urinary retention may occur in older males with BPH.

relaxation of biliary tract and uterus is minimal.

Glands

Atropine decreases sweat, salivary, tracheobronchial and lacrimal secretion (M_3 blockade).

Skin & eye become dry, talking and swallowing may be difficult.

It also decreases G.I secretions like pepsin, mucous, HCl etc

Local anesthetic → Atropine has a mild anesthetic action on the cornea.

Therapeutic use

I. As antisecretory

1. *Pre anesthetic medication*

   when irritant general anesthetics (ether) are used, prior administration of anticholinergics (atropine, hyoscine, glycopyrrolate) are imperative to check increased salivary and tracheobronchial secretions.

2. *Peptic ulcer*

   atropine drugs decrease gastric secretion and afford symptomatic relief in peptic ulcer (but it is not using nowadays due to their side effects as well as the entry of H2 – blockers).

3. *To check excessive sweating or salivation*. E.g.:- parkinsonism.

II. As antispasmodic

1. Intestinal and renal colic, abdominal cramps.

2. Nervous and drug (reserpine, guanethidine) induced diarrhea, functional diarrhea.

3. Spastic constipation, irritable colon.

4. Pylorospasm, gastric hyper motility, gastritis, nervous dyspepsia.

5. To relieve urinary frequency and urgency, enuresis in children

III. Bronchial asthma, asthmatic bronchitis, COPD

These drugs are less effective than adrenergic drugs.

Ipratropium bromide is used in COPD. It has additive bronchodilator action with adrenergic drugs and theophylline.

IV. As mydriatic & cycloplegic

1. *Diagnostic* :- for testing error of refraction, both mydriasis and cycloplegia are needed. Tropicamide is used widely.

   To facilitate fundoscopy only mydriasis is needed.

2. *Therapeutic* :- atropine is used in the treatment of iritis, iridocyclitis, choroiditis, keratitis and corneal ulcer.

ANTICHOLINERGIC DRUGS

NAME OF DRUG	CLASS	receptors	Pharmacological approach
Atropine	alkaloid	Nonselective competative antagonist all muscaranic receptors in CNS and periphery	OP poisonong Pre anaesthetic mydriatic
Hyosine	alkaloid	unknown mechanism in CNS	Motion sickness
homatropine	semisynthetic	Competative antagonism to all M receptors	mydriasis
Ipratropiumbromide	semisynthetic	Competative,nonselective antagonist at M1 to M3 receptors	Bronchial asthama
cyclopentolate	synthetic	competative antagonism at all M receptors	Mydriasis Iritis uveitis

NAME OF DRUG	CLASS	receptors	Pharmacological approach
propantheline	synthetic	Selectevely blocks M1 receptors	Peptic ulcer Gastritis
Oxyphonium	synthetic	Selectevely blocks M1 receptors	Peptic ulcer Gastrointestinal hypermotility
clidinium	synthetic	Selectevely blocks M1,M3	Nervous dyspepsia Gastritis Irritable bowel syndrome Peptic ulcer
Isopropamide	synthetic	Selectevely blocks M1,M3	Nervous dyspepsia Irritable bowel Gastrointestinal problems
glycopyrrolate	synthetic	Selectevely blocks M3 receptors	Pre anaesthetic medication and during anaesthesia

NAME OF DRUG	CLASS	Receptors	pharmacological approach
Oxybutynin	Vasicoselective	slight M3 – selective muscaranic antagonist	Neurogenic bladder, spina bifida,and nocturnal enuresis.
Tolterodine	Vasicoselective	greater selectivity for M3 receptors	Over active bladder
Trihexphenidyl	Antiparkinsonian	Antagonist at M receptors in basal ganglia	symptomatic treatment of Parkinsons disease
Procyclidine	Antiparkinsonian	Antagonist at M receptors in basal ganglia	Parkinsons disease
Biperiden	Antiparkinsonian	Antagonist at M receptors in basal ganglia	Parkinsons disease

Drugs that block nicotinic receptors

1. Neuro muscular blockers
2. Ganglion blockers

Peripherally acting muscle relaxants (or) Neuromuscular blocking agents.

A. Non depolarizing (competitive) blockers

i. Long acting : d-Tubocurarine, Pancuronium, Doxacurium, Pipecuronium.

ii. Intermediate acting : Vecuronium, Atracurium,Cisatracurium, Rocuroniun, Rapacuronium.

iii. Short acting : Mivacuranium.

B. Depolarizing blockers

Succinylcholine (SCh, Suxamethonium), Decamethonium

Table 27–1. Some properties of neuromuscular blocking drugs.

Drug	Elimination	Clearance (mL/kg/min)	Approximate Duration of Action (minutes)	Approximate Potency Relative to Tubocurarine
Isoquinoline derivatives				
Atracurium	Spontaneous[1]	6.6	20–35	1.5
Cisatracurium	Mostly spontaneous	5–6	25–44	1.5
Doxacurium	Kidney	2.7	> 35	6
Metocurine	Kidney (40%)	1.2	> 35	4
Mivacurium	Plasma ChE[2]	70–95	10–20	4
Tubocurarine	Kidney (40%)	2.3–2.4	> 35	1
Steroid derivatives				
Pancuronium	Kidney (80%)	1.7–1.8	> 35	6
Pipecuronium	Kidney (60%) and liver	2.5–3.0	> 35	6
Rocuronium	Liver (75–90%) and kidney	2.9	20–35	0.8
Vecuronium	Liver (75–90%) and kidney	3–5.3	20–35	6
Depolarizing agent				
Succinylcholine	Plasma ChE[2] (100%)	>100	< 8	0.4

[1]Nonenzymatic and enzymatic hydrolysis of ester bonds.
[2]Butyrylcholinesterase (pseudocholinesterase).

Uses of SMR

- 1. In conjunction with GA
- 2. Painful muscle conditions
- 3. Spastic neurological conditions

Ganglion blockers

Tetraethyl ammonium
Hexamethonium
Trimethaphan
Mecamylamine

Table 11–5 Usual Predominance of Sympathetic or Parasympathetic Tone at Various Effector Sites, and Consequences of

SITE	PREDOMINANT TONE	EFFECT OF GANGLIONIC BLOCKADE
Arterioles	Sympathetic (adrenergic)	Vasodilation; increased peripheral blood flow; hypotension
Veins	Sympathetic (adrenergic)	Dilation: peripheral pooling of blood; decreased venous return; decreased cardiac output
Heart	Parasympathetic (cholinergic)	Tachycardia
Iris	Parasympathetic (cholinergic)	Mydriasis
Ciliary muscle	Parasympathetic (cholinergic)	Cycloplegia—focus to far vision
Gastrointestinal tract	Parasympathetic (cholinergic)	Reduced tone and motility; constipation; decreased gastric and pancreatic secretions
Urinary bladder	Parasympathetic (cholinergic)	Urinary retention
Salivary glands	Parasympathetic (cholinergic)	Xerostomia
Sweat glands	Sympathetic (cholinergic)	Anhidrosis
Genital tract	Sympathetic and parasympathetic	Decreased stimulation

Uses of Ganglion blockers

1. To produce controlled hypotension – during surgery

2. Acute hypertensive crisis
3. Chronic severe HTN

} Not used now a days

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