CHOLINERGIC AGONISTS AND ANTAGONISTS

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Types of Acetylcholine receptor agonists

1. **Direct acting Ach receptor agonists**

- **These bind and activate Ach receptors**

i. Choline esters

a) Acetylcholine

b) Bethanechol — Synthetic Ach analogues

c) Carbachol

ii. Plant alkaloids

a) Muscarine

b) Nicotine

c) Pilocarpine

iii. Other synthetic agonists

- These act by augmenting the Ach signal transduction

a) Cevimeline

b) Varenicline

2. Indirect acting Ach receptor agonists

2.1 Drugs that inhibit cholinesterase

- These inhibit cholinesterase thus leading to inhibition of Ach metabolism which subsequently increases Ach synaptic concentration

i. Reversible cholinesterase inhibitor

a) Donepezil
b) Edrophonium
c) Neostigmine
d) Physostigmine
e) Pyridostigmine

ii. Quasi – reversible cholinesterase inhibitors

a) Ecothiophate
b) Malathion
c) Pralidoxine

3. Type 5 - phosphodiesterase inhibitors

- Sildenafil (Viagra)
- Tadalafi (Cialis)
- Vardenafil (Levitra)

Direct acting acetylcholine receptor agonists

General properties

- These are positively charged quaternary ammonium compounds that are poorly absorbed from the gut and are not distributed to the CNS
- Acetylcholine and Carbachol activate both muscarinic and nicotinic receptors while bethanechol only activates muscarinic receptors
- Because of lack of specificity for muscarinic subtypes, the muscarinic agonists cause a wide range of effects on many organ systems

Effects of Muscarinic receptor agonists on organs and systems

Ocular effects

- Muscarinic receptor agonists increase lacrimal gland secretion and stimulate contraction of the iris sphincter muscle and the ciliary muscle
- Contraction of the iris sphincter muscle leads to pupillary constriction (Miosis)
- Contraction of ciliary muscle enables accommodation of the lens to focus on close objects

Respiratory tract effects

- Stimulation of muscarinic receptors increase bronchial muscle contraction
- Also increases secretion of mucus in the entire respiratory tract
- The bronchial muscle contraction leads to bronchoconstriction and thus muscarinic receptor agonists should be avoided in asthma and other obstructive lung disease

Cardiac effects

- Muscarinic receptor agonists decrease impulse formation in the sino atrial node by reducing the rate of diastolic depolarization

- This consequently leads to slowed heart rate

- Additionally, they slow conduction of the cardiac action potential through the AV node and thus leading to an increased PR interval (Time between the beginning of the p wave and to the beginning of the QRS complex) on the Electrocardiogram (ECG)

Vascular effects

- Acetylcholine typically causes vasodilation though vasoconstriction may occur under some conditions
- The vasodilative effect is mediated by M_3 receptors located in vascular endothelial cells
- This is accomplished by muscarinic activation of the nitric oxide synthetase which subsequently leads to formation of nitric oxide (NO)
- NO is a gas that diffuses into vascular smooth muscle cells and activate guanylyl cyclase to increase the formation of cyclic guosine monophosphate (cGMP)
- Increased cGMP leads to vascular smooth muscle relaxation and vasodilation

Gastrointestinal and urinary tract effect

- When muscarinic receptor agonists are taken , they stimulate salivation, gastric and other secretion in the GIT
- Through stimulation of enteric nervous system located in the gut wall, they increase the contraction of smooth muscles (except sphincters) This eventually leads to increased GIT motility
- Where as the muscarinic receptor agonists stimulate the bladder detrusor muscle, they relax the internal sphincter which leads to promotion of micturition
- Higher doses of these agonists can produce excessive salivation and cause diarrhea, intestinal cramps and urinary incontinence
- This is referred to as **"All faucets turned on"** syndrome

Choline esters
Acetylcholine

Chemistry and pharmacokinetics

- It is known to be a choline ester of acetic acid
- It is rapidly hydrolyzed by cholinesterase and has an extreme short half life

Effects and Indications

- Acetylcholine has limited clinical application because of limited absorption, short duration of action and lack of specificity for muscarinic or nicotinic receptors
- Ophthalmic acetylcholine is available for use during cataract surgery where it produces miosis after removal of the lens
- Can be useful in other ophthalmic surgeries where rapid or complete miosis is desired
- Topical administration is not effective as it is hydrolyzed by corneal cholinesterase before it can penetrate to the iris and ciliary muscle
- In most cases vasodilative effect of Ach is more than vasoconstrictive effect but an intracoronary injection causes a localized vasoconstrictive response in patients with vasospastic angina and is thus used to help establish the diagnosis of vasospastic angina

Bethanechol and Carbachol

Chemistry and pharmacokinetics

- These are called choline esters of carbamic acid and are known to be resistant to hydrolysis by cholinesterase

- Their duration of action is relatively short,lasting for several hours after ocular or systemic administration

Effects and indications

Bethanechol

- selectively activates muscarinic receptors and has been used to stimulate bladder or GIT muscle without significantly affecting heart rate or blood pressure

- Postoperatively or postpartumly, it is given to increase muscle tone in patients with non-obstructive neurogenic urinary retention after receiving anaesthesia during childbirth or other surgery

- Therapeutic doses of bethanechol given orally or subcutaneously has little effect on BP but should not be given through I.V as it can cause hypotension and bradycardia

Carbachol

Effects and indications

- It is available as a solution that is instilled intraocularly to produce miosis during ophthalmic surgery
- Surgical procedures where it is used are cataract surgery and iridectomy
- It is no longer being used in treating open angle glaucoma as it has been replaced by agents with fewer side effects

Plant Alkaloids

Muscarine and Nicotine

Source and effects

- Muscarine is found in mushrooms of the genera inocybe and clitocybe
- Consumption of these poisonous mushrooms can cause diarrhea, sweating, salivation and lacrimation
- Amanita muscaria is known to be the original source of muscarine
- Nicotine is derived from nicotiana plants and is contained in cigarettes and other tobacco plants

Indications

- Muscarine has no medical use
- Nicotine is available in chewing gums, transdermal patches and other products meant for use in smoking

Pilocarpine

- It is a second line drug for treatment of chronic angle glaucoma in which it lowers intraocular pressure by increasing the outflow of aqueous humour
- Also used in acute closed angle glaucoma, a medical emergency where blindness may occur if intraocular pressure is not lowered in good time
- Decreased night vision is the main side effects of ocular administration of pilocapine caused by miosis and difficult in focusing on distant objects as the lens is accommodated for close objects
- Pilocarpine is administered orally for treatment of xerostemia (dry mouth)
- To avoid side effects, low doses are needed because of its high sensitivity of the salivary glands to muscarinic stimulation

Other direct acting acetylcholine agonist

Cevimeline

- This is a synthetic and is administered orally to treat dry mouth in patients who have had radiation therapy for head or neck cancer

- Also used in Sjogren syndrome (Dry mouth, dry eyes and arthritis)

Adverse effect

- Increased sweating, nausea and visual disturbance caused by drug induced miosis

- As with other Ach agonists, cevimeline should be used cautiously in patients with asthma and cardiac arrythmias

Varenicline

- This is a partial agonist at the nicotinic receptor subtype in the brain that mediates the reinforcing effect of nicotine in smokers

Indication

- The drug is used for smoking cessation and has been found to reduce both the craving and the withdrawal effects caused by nicotine

Indirect acting Acetylcholine receptor agonists

- One group of indirect acting agonists function by inhibiting cholinesterase

- The other group inhibits type 5-phosphodiesterase and potentiates the vasodilative effects of cGMP

Drugs that inhibit cholinesterase

- Cholinesterase inhibitors prevent the breakdown of acetylcholine at all cholinergic synapses and thus increases the Ach concentration at cholinergic synapses

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- The Shorter acting drugs are called reversible agonists while longer acting ones are called quasi reversible cholinesterase inhibitor

Reversible cholinesterase inhibitors

Edrophonium

Chemistry and pharmacokinetics

- Edrophonium is a positive alcohol that reversibly binds a negatively charged site on cholinesterase

- Its reversible binding and rapid renal excretion are responsible for its short duration of action (about 10mins)

Indications

- Useful in intial diagnosis of myasthenia and in distinguishing between myathenia crisis and cholinergic crisis in myasthenia patients being treated with pyridostigmine

- **Myasthenia gravis** is an autoimmune disease in which antibodies are directed against nicotinic receptors thereby impairing neuromuscular transmission causing severe fatigue. It mostly affects muscles of the face, throat and neck

Myasthenia crisis cholinergic crises

- Myasthenia gravis patients may experience muscle weakness from either under-treatment or over treatment with a cholinesterase inhibitor

- In the untreated conditions or in patients not receiving adequate doses of the drug, muscle weakness is caused by acetylcholine deficiency and is called **Myasthenia crisis**

- In this situation, a test dose of edrophonium will increase acetylcholine levels and muscle strength

- Patients who are over-treated with cholisterase inhibitors may experience muscle weakness caused by excessive acetylcholine at the neuromuscular junction and this condition is called **cholinergic crisis**

Neostigmine, Physostigmine and Pyridostigmine

Chemistry and pharmacokinetics

- Physostigmine is a plant alkaloid that is well absorbed from the gut and penetrates the blood brain barrier
- Pyridostigmine and neostigmine are synthetic drugs that exist as positively charged at physiologic pH and hence they are less absorbed and do not cross the blood brain barrier

Indications

- Long term Use in myasthenia gravis where they improve muscle tone and reduces eyelid and facial ptosis
- Neostigmine, pyridostigmine and edrophonium are routinely used during surgery to reverse effects of curariform drugs when muscle relaxation is no longer required
- Physostigmine is used in the treatment of glaucoma though other drugs are used today
- As a parenteral preparation, physostigmine is used as an antidote to counteract seizure caused by atropine overdose

Quasi reversible cholinesterase inhibitors

- Most of these are organophosphate compounds and only few have been used therapeutically like ecothiophate, isoflurophate, malathion
- Most of them are used as pestcides while some like soman and sarin were developed as chemical warfare agents
- Most of organophosphates are highly lipid soluble and are effectively absorbed from all sites in the body including the skin, mucus membranes, eyes and the gut
- They augment cholinergic neurotransmission at both the central and peripheral cholinergic synapses
- Systemic exposure to organophosphates will produce all effects of muscarinic activation such as salivation, lacrimation, miosis, accommodative spasms, bronchoconstriction, intestinal cramps, and urinary incontinence

Type 5 phosphodiesterase inhibitors

- These drugs potentiate the vasodilative effect of acetylcholine released from parasympathetic neurons in the pelvic plexus

- Sildenafil commonly marketed as Viagra used in management of erectile dysfunction was the first to be developed while others are tadalafil and vardenafil

Mechanism

- Penile erection occurs when acetylcholine stimulates M_3 receptors in vascular endothelial cells leading to increased nitric oxide which diffuses into the vascular smooth muscle cells in the corpus carvenosum, where it activates guanylyl cyclase where it increase cGMP leading to muscle relaxation and vasodilation

- Sildenafil and the related drugs inhibit the breakdown of cGMP by type 5 phosphodiesterase (5-PDE) leading to elevated levels of cGMP and increased smooth muscle relaxation which then results in increased blood flow into the penis and the eventual erection

Indications for 5-PDE inhibitors

- In addition to its efficacy in treating erectile dysfunction, tadalafil has been shown to significantly improve urinary symptoms of benign prostatic hypertrophy (BPH) including urge to urinate, difficulty in starting micturition, weak urine flow, frequent urination during the night

- Tadalafil and sildenafil are approved for pulmonary arterial hypertension

Adverse effects and interactions

- Adverse effects of 5-PDE inhibitors are usually mild and transient but include headache, nasal congestion, dyspepsia, myalgia, back pain and visual disturbances

- These drugs should not be used by patients who take nitroglycerine or other organic nitrates as they also increase cGMP formation and can lead to profound hypotension which can cause death

ACETYLCHOLINE RECEPTOR ANTAGONISTS

Classification

1. Muscarinic receptor antagonists

- Atropine
- Hyoscyamine
- Scopolamine

Belladona (Beautiful lady - Italian) alkaloid derived from sollanneous plants like Atropa belladonna, datura stramonium, hyoscyamus niger

2. Semisynthetic and synthetic Muscarinic receptor antagonists

- Dicyclomine
- Glycopyrrolate
- Ipratropium
- Oxybutinin
- Tropicamide

3. Nicotinic receptor antagonists

i. Neuromuscular blocking agents

a). Non depolarizing neuromuscular blocking agents

- Rocuronium
- Cisatracurium
- Pancuronium

b). Depolarizing neuromuscular blocking agents

- Succinylcholine (Suxamethonium)

Atropine and scopolamine

Chemistry and pharmacokinetics

- These are non ionized tertiary amines that are well absorbed from the gut and are readily distributed to the CNS

- After systemic administration, they are excreted in the urine with half life of about 2 hours while when administered topically i.e. ocularly they have a longer lasting effects as they bind to pigments in the iris that release the drug slowly

Indications

1. In ocular conditions

- atropine and related drugs are used to produce mydriasis and facilitate ophthalmoscopic examination of the peripheral retina

- Because of the ability to reduce muscle spasms and pain, muscarinic receptor blockers are also used in treatment of iritis and cyclitis (inflammation of the iris and ciliary muscle respectively) associated with infection or trauma

2. Cardiac conditions

- Atropine is used to treat sinus bradycardia in cases where the slow sinus rhythm reduces the cardiac output and blood pressure and produce sympathetic symptoms of hypotension or ischaemia which usually occurs after myocardial infarction

3. Respiratory conditions

- Atropine and other muscarinic receptor blockers are used to reduce salivary and respiratory secretions and thereby preventing airway obstruction in patients receiving general anesthetics

- This role has been taken by glycopyrrolate which is often used for this purpose today

- Previously atropine was used for treatment of asthma and obstructive lung disease because of its bronchodilating effects but this has been overtaken by ipratropium bromide

4. GIT and Urinary tract indication

- Atropine and related drugs are used to relieve intestinal spasms and pain associated with GIT disorders
- Also used to relieve urinary bladder spasms in persons overactive bladder

5. CNS indications

- Transdermal formulation of scopolamine is used to prevent motion sickness

6. Other indications

- Atropine and glycopyrrolate are used to prevent muscarinic side effects when cholinesterase inhibitors are used in patients with myasthenia gravis

7. Hyoscyamine

- As an isomer of racemic atropine, hyoscyamine is a natural form of alkaloids that occurs in plants
- Formulations of hyocyamine like hyoscine butyl bromide (Buscopan) for oral or sublingual administration are used for intestinal spasms

8. Ipratropium and Tiotropium

- These are derivatives of atropine and are administered by inhalation to patients with obstructive lung disease
- Because these drugs are not well absorbed from the lungs into the systemic circulation they produce few adverse effects
- This does not impair the ciliary clearance of secretions from the airways like atropine
- This make them particularly useful in treating patients with asthma, emphysema and chronic bronchitis

9. Oxybutynin, Solifenacin, Dicyclomine

- Dicyclomine is a synthetic amine used to relax intestinal smooth muscle and thereby relieve bowel symptoms such as intestinal cramping

- Oxybutynin, Solifenacin and related drugs are used to reduce the four major symptoms of overactive bladder which are daytime urinary frequency, nocturia (frequent urination at night), urgency and incontinency

10. Tropicamide

- A synthetic drug that was developed for topical ocular administration as a mydriatic (Pupillary dilator)

- Also given before ophthalmoscopic examination of the peripheral retina

11. Pirenzepine

- A muscarinic receptor antagonist that is selective for M_1 receptors was developed to reduce vagally stimulated gastric secretion in patients with peptic ulcers

- It blocks M_1 receptors on paracrine cells and inhibits the release of histamine, a potent gastric acid stimulant

Nicotinic receptor antagonists

Neuromuscular blocking agents

- Also referred to as paralytics or muscular relaxants which bind to the muscle type of nicotinic acetylcholine receptor and inhibit neurotransmission at skeletal neural muscular junction

- Divided into two classes;

i. Non depolarizing blockers – competitive antagonists at the neuromuscular junction

ii. Depolarizing agents - cause persistent depolarization of the motor end plate

- These neuromuscular blocking agents are extremely dangerous because they can cause complete respiratory failure in patients lacking external ventilator support

Non depolarizing neuromuscular agents

- These are also referred to as curariform drugs which include pancuronium, atracurium, rocuronium, vecuronium, cisatracurium
- Tubocurarine the original drug was extracted from plants used by native South Americans as arrow poisons for hunting wild game
- Curare is the other name for the arrow poison
- These drugs are not absorbed from the gut and do not cross the blood brain barrier and hence they do not cause poisoning when meat containing these agents is ingested

Mechanism and effects of non-depolarizing neuromuscular blockers

- Curariform drugs act as competitive antagonists of acetycholine at nicotinic receptors in the skeletal muscle leading to muscle relaxing effects

- After administration, the curariform drugs first papralyses the small and rapidly moving muscles of the eyes and face, then paralyses the larger muscles of the limbs and trunk and finally paralyses the intercostal muscles and the diaphragm causing ceasure of respiration

- This sequency is good in that it enables relaxation of abdominal muscles for surgical procedures without causing apnea

- Respiratory function should however be closely monitored in patients receiving a neuromuscular blocking agents

Indications of neuromuscular blockers

- Primarily used to induce muscle relaxation during surgery to enable surgical manipulation
- Used sometimes as adjuncts to electroconvulsive therapy to prevent injuries that might be caused by involuntary muscle contractions
- Facilitation of intubation of the respiratory tract so as to enable ventilation and endoscopic procedures

Selection of neuromuscular blockers

- The selection of non-depolarizing agent for a particular clinical application is dependent on

I. Duration of action where atracurium, cisatracurium, rocuronium, veruconium having an estimated duration of action of 30 – 60 mins

II. Drug induced changes in blood pressure and heart rate

- At higher doses, atracurium causes histamine release while the intermediate acting ones have minimal effects on the cardiovascular and respiratory function

- When longer duration of action is required doxacurium or pancuronium are preferred for selection

- Tubocurarine is no longer used clinically because it is associated with higher incidences of histamine release and adverse effects

Depolarizing neuromuscular blocking agent

- Succinylcholine is the only clinically useful depolarizing agent today
- It binds to nicotinic receptors and causes persistent depolarization as it is is not hydrolyzed by cholinesterase as is acetylcholine and there is no known antidote for it
- When compared to curariforms, succinylcholine has a short duration of action, 5 – 10 minutes due it hydrolysis by plasma cholinesterase while the sequency of paralysis is the same
- Administration of succinylcholine produces transient muscle contractions called **fasciculations** which are quickly followed by a sustained muscle paralysis

Indications for succinylcholine (Suxamethonium)

- Muscle relaxation before and during surgery
- Facilitation of intubation
- Because of its duration of action succinylcholine offers the best chance for resumption of spontaneous breathing if endotracheal intubation fails and hence it is the preferred neuromuscular blocker for adults with emergency airway situations
- Patients with **Atypical cholinesterase**, an inherited disorder cannot metabolize succinylcholine at normal rate and are susceptible to prolonged neuromuscular paralysis and hence non emergent patients should be screened before being given the drug
- Succinylcholine causes hyperkalemia sufficient to cause cardiac arrest especially in patients with unhealed skeletal muscle injury like third degree burns

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