Cholinergic Agonists & Antagonists

• **Course:**
  Integrated Therapeutics I

• **Professor:**
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• **Material covered on:**
  Exam #1

• **Reading:**
  Katzung 12\textsuperscript{ed} Chapter 7, 8, 9, 10
CHOLINERGIC AGONISTS

• Autonomic pharmacology terminology and definitions
• Drugs activating cholinergic receptors
• Drugs inhibiting cholinesterase (anticholinesterase drugs)
• Clinical use of drugs activating cholinergic receptors
• Autonomic drugs
  • *mimic* or *prevent the* effects of
    • sympathetic and parasympathetic neurons
  • by *activating* or *blocking*
    • *adrenergic* & *cholinergic* transmission

• Cholinergic drugs
  • Cholinergic agonists, or Cholinomimetics
    • (muscarinic or nicotinic)
  • Cholinergic antagonists, or Cholinolytics
    • (muscarinic or nicotinic)
    • *Anti-cholinergic drugs*; *Anti-muscarinic* & *Anti-nicotinic drugs*
KEEP CALM & ACTIVATE THE PARASYMPATHETIC NERVOUS SYSTEM
Good idea for the most part EXCEPT:

Digestion and urination are stimulated by the Parasympathetic and slowed by the Sympathetic branches of the Autonomic Nervous System.
Good idea for the most part EXCEPT:

Digestion and urination are stimulated by the Parasympathetic and slowed by the Sympathetic branches of the Autonomic Nervous System.

So why do we micturate when scared?
Parasympathetic

Brain activity decrease
Metabolic rate decrease
Stimulates flow of saliva
Slows heartbeat
Constricts bronchi
Stimulates peristalsis and secretion
Stimulates release of bile
Contracts bladder
Stimulates sexual arousal, erection of genital

Sympathetic

Brain activity increase
Metabolic rate increase
Dilates pupil
Inhibits flow of saliva
Accelerates heartbeat
Dilates bronchi
Inhibits peristalsis and secretion
Conversion of glycogen to glucose
Secretion of adrenaline and noradrenaline
Inhibits bladder contraction
Stimulates orgasm, ejaculation

Ganglion
Medulla oblongata
Vagus nerve
Solar plexus
Chain of sympathetic ganglia

http://setmarburg.wikiangels.com/our-approach-of-the-treatment/
REMEMBER THIS SLIDE???
AUTONOMIC DRUGS TERMINOLOGY

Cholinergic drugs

- Parasympathetic: Cardiac and smooth muscle, gland cells, nerve terminals
- Sympathetic: Sweat glands

- Sympathetic: Cardiac and smooth muscle, gland cells, nerve terminals
- Sympathetic: Renal vascular smooth muscle
- Somatic: Skeletal muscle

Adrenergic drugs
• Parasympathetic drugs
  • modulate function of parasympathetic nervous system
    – Parasympathetic Agonists, or Parasympathomimetic drugs
      • mimic or promote effects of acetylcholine (ACh) at muscarinic receptors in parasympathetic NS
    – Parasympathetic antagonists, or Parasympatholytic drugs
      • prevent effects of ACh at muscarinic receptors in parasympathetic NS
      • Act (bind) at muscarinic cholinergic receptors
This image demonstrates the sympathetic chains running down the back of the chest cavity over the heads of the ribs. The arrows indicate the typical levels at which we cut the sympathetic chain for palmar and axillary hyperhidrosis.

AUTONOMIC DRUGS TERMINOLOGY

Cholinergic drugs

Parasympathetic drugs

- Cardiac and smooth muscle, gland cells, nerve terminals
- Sweat glands

Adrenergic drugs

- Cardiac and smooth muscle, gland cells, nerve terminals
- Renal vascular smooth muscle
- Skeletal muscle

Medulla
Spinal cord
Voluntary motor nerve
Adrenal medulla
Epi, NE
ACh
Parasympathetic
Sympathetic
ACh
Sympathetic
ACh
Sympathetic
ACh
Sympathetic
ACh
Sympathetic
ACh
Sympathetic
ACh
AUTONOMIC DRUGS TERMINOLOGY

• Sympathetic drugs
  – modulate function of sympathetic nervous system
  – Usually act (bind) at adrenergic receptors – adrenergic drugs
  – Adrenergic Agonists:
    • mimic or promote effects of
      – NE/E/Dopamine (DA) at – adrenergic receptors in sympathetic NS
    • Also called: Sympathomimetic drugs, Adrenomimetics
  – Adrenergic Antagonists:
    • prevent effects of
      – NE/E/DA at adrenergic receptors in sympathetic NS
    • Also called: Sympatholytic drugs, Adrenolytics, Anti-adrenergic drugs or Adrenoblockers
      – antagonists at α- or β-adrenoceptors
AUTONOMIC DRUGS TERMINOLOGY

Cholinergic drugs

Parasympathetic
Cardiac and smooth muscle, gland cells, nerve terminals

Sympathetic
Sweat glands

Sympathetic drugs

Sympathetic
Cardiac and smooth muscle, gland cells, nerve terminals

Sympathetic
Renal vascular smooth muscle

Somatic
Skeletal muscle

Adrenergic drugs

Voluntary motor nerve

Adrenal medulla

Epi, NE

Spinal cord

Medulla
AUTONOMIC DRUGS TERMINOLOGY

• Direct-acting drugs
  – produce their effects via
    • *direct interaction* with adrenergic or cholinergic receptors
  – E.g., Cholinergic/adrenergic receptor agonists
  – Cholinergic/adrenergic receptor antagonists

• Indirect-acting drugs
  – produce their effects by
    – *increasing or reducing* concentration of
      • *norepinephrine or acetylcholine* at target receptors
  – Act by *altering neurotransmitter concentrations* at target sites
TARGETS FOR DIRECT AND INDIRECT DRUGS

Pre-Synaptic Neuron

Synapse

Post-Synaptic Neuron

Action Potential

Ca^{2+}

Synthesis

Vesicular Release

Vesicular Storage

Inhibitory Autoreceptors

Enzymatic Degradation

Reuptake

Cellular Effect

Post-synaptic Receptors

Targets for INDIRECT-Acting Autonomic Drugs

Targets for DIRECT-Acting Autonomic Drugs
DIRECT AND INDIRECT DRUGS

• Steps in autonomic transmission – effects of direct and indirect drugs

• Indirect drugs
  – Action potential propagation
  – Transmitter synthesis
  – Transmitter storage
  – Transmitter release
  – Transmitter uptake after release
  – Enzymatic inactivation of the transmitter

• Direct drugs
  – Direct receptor activation or blockade
CHOLINERGIC AGONISTS

• Autonomic pharmacology terminology and definitions
• **Drugs activating cholinergic receptors**
• Drugs inhibiting cholinesterase (anticholinesterase drugs)
• Clinical use of drugs activating cholinergic receptors
CHOLINERGIC NEUROTRANSMISSION

Pre-Synaptic Neuron

Choline Acetyltransferase

Acetyl-CoA

ChAT

Choline

Synapse

ACh

Nicotinic Receptors

Muscarinic Receptors

Post-Synaptic Site

Acetylcholinesterase

ACh = acetylcholine
TYPES OF CHOLINERGIC AGONISTS

- Direct-acting drugs
  - Muscarinic and nicotinic agonists
    - Acetylcholine
    - Carbachol
  - Muscarinic agonists
    - Bethanechol
    - Methacholine
    - Cevimeline
    - Pilocarpine
  - Nicotinic agonists
    - Varenicline
    - Nicotine

- Indirect-acting drugs
CHOLINERGIC AGONISTS: COMMON SITES OF ACTION

Pre-Synaptic Neuron

Synapse

Post-Synaptic Site

Muscarinic and Nicotinic Receptor Agonists

DIRECT ACTING

Nicotinic Receptors

Muscarinic Receptors

ACETYLCHOLINESTERASE

Cholinesterase Inhibitors

INDIRECT ACTING

ACh = acetylcholine
CHOLINE ESTERS vs. ALKALOIDS: PHARMACOKINETIC DIFFERENCES

Choline esters – *quaternary amines*

- Methacholine
- Carbachol
- Bethanechol

• *Pharmacokinetics*
  - Poorly absorbed from the site of administration
  - Poorly distributed into CNS
  - Hydrolyzed in GI tract
CHOLINE ESTERS: STRUCTURE

Acetylcholine chloride

Methacholine chloride

Bethanechol chloride

Carbachol chloride
**Uses:**

Choline esters are rarely if ever used.

- **Ach:** Not used

- **Methacholine:** Rarely used to terminate parosysmal supraventricular tachycardia.

- **Bethanecol:** Used in post operative / post partum nonobstructive urinary retention, neurogenic bladder atony, congenital Megacolon.
  - **Dose:** 5mg SC repeated after 15 to 30 min if necessary

- **Carbachol:** Used as topical drug in chronic therapy of narrow angle glaucoma.

- **Pilocarpine**
  - Used only in the eye as 0.5 - 4% drops in open angle glaucoma.
  - Other uses - to counteract Mydriatics to prevent or break adhesion of iris with lens.

Muscarine & Arccoline: has no therapeutic use.
CHOLINE ESTERS vs. ALKALOIDS: PHARMACOKINETIC DIFFERENCES

Alkaloids – tertiary amines
  – Pilocarpine
  – Nicotine

• Pharmacokinetics
  – Well absorbed from sites of administration
  – Nicotine is well absorbed through skin
  – Penetrate into CNS
  – Excreted by kidneys – acidification of urine accelerates clearance
# ALKALOIDS

## Cholinergic Agents

<table>
<thead>
<tr>
<th>Alkaloids</th>
<th>Synthetic Agents</th>
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<tbody>
<tr>
<td>Nicotine</td>
<td>Dimethylphenylpiperazinium-</td>
</tr>
<tr>
<td></td>
<td>(DMPP)</td>
</tr>
<tr>
<td>Lobeline</td>
<td>Oxotremorine</td>
</tr>
<tr>
<td>Arecoline</td>
<td>Methacholine</td>
</tr>
<tr>
<td>Muscarine</td>
<td>Bethanechol</td>
</tr>
<tr>
<td>Pilocarpine</td>
<td>Carbachol</td>
</tr>
<tr>
<td></td>
<td>Cevimeline</td>
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</tbody>
</table>
LOCATION OF M AND N RECEPTORS

• Muscarinic receptors (M)
  – Target organs
    • innervated by postganglionic parasympathetic neurons
  – Some tissues
    • innervated by postganglionic sympathetic neurons (sweat glands)
  – Some tissues
    • not innervated (parasym. directly)
      – endothelial cells - dilating blood vessels (act by NO)
  – Neurons in CNS
    • Brain & spinal cord
LOCATION OF M AND N RECEPTORS

- **Nicotinic receptors (N)**
  - All parasympathetic ganglia
  - All sympathetic ganglia
  - Adrenal medulla
  - Motor end plates of skeletal muscle fibers
  - Neurons in CNS (Brain [loaded] and spinal cord)
EFFECTS OF ACTIVATION OF PARASYMPATHETIC NERVOUS SYSTEM

- **EYES**: Constricts pupil: miosis
- **SALIVARY GLANDS**: Increased salivation
- **HEART**: Decreases heart rate; Slows conduction through AV node
- **LUNGS**: Contraction of bronchial smooth muscle; Increased secretion
- **GI TRACT**: Increased motility (contracts smooth muscle, relaxes sphincters); Increased secretions
- **BLADDER**: Contraction (urination)
- **VASCULAR SMOOTH MUSCLE**: NO EFFECT
EYE:
Constricts pupil: miosis

SALIVARY GLANDS:
Increased salivation

HEART:
Decreases heart rate
Slows conduction through AV node

LUNGS:
Contraction of bronchial smooth muscle;
Increased secretion

GI TRACT:
Increased motility (contracts smooth muscle, relaxes sphincters)
Increased secretions

BLADDER:
Contraction (urination)

VASCULAR SMOOTH MUSCLE:
Muscarinic receptors but no direct parasympathetic innervation

SWEAT GLANDS:
Sweating (sympathetic effect)
Pupil constricts as circular muscles of iris contract (parasympathetic)

Bright light

Normal light

Pupil

Anterior views

Pupil dilates as radial muscles of iris contract (sympathetic)

Dim light
VASODILATION BY MUSCARINIC AGONISTS

- M₃ receptors on endothelial cells
- IP₃/DAG pathway
- Increased Ca^{++} in endothelial cells stimulates nitric oxide synthase (NOS)
- **Nitric oxide (NO)** diffuses to smooth muscle cells and causes relaxation
- Direct **stimulation** of M₃ receptors on *smooth muscle* causes contraction
ORGAN SYSTEM EFFECTS OF NICOTINIC AGONISTS

*Effects of stimulation of nicotinic receptors*

- **CNS**
  - *Mild, alerting action*
  - *At increased concentration,* tremor, stimulation of respiratory center, convulsions, coma may be induced

- **Neuromuscular junction**
  - *Activation of muscle contraction*
  - Depending on the concentration, responses may vary from *disorganized twitching* to a *strong contraction* of entire muscle
  - Muscle *paralysis* may follow
Effects of stimulation of nicotinic receptors

- Peripheral nervous system –
  - *simultaneous activation* of both
    - sympathetic & parasympathetic ns
  - Effects on: **Cardiovascular** system
    - effects are primarily sympathomimetic - *agonist*
      - *(severe hypertension, tachycardia)*
  - Effects on: **GI and urinary tracts**
    - effects are largely *parasympathomimetic* - *agonist*
TOXICITY OF
DIRECT CHOLINERGIC AGONISTS

• Muscarinic agonists
  – Drug overdose, some types of mushroom poisoning
    • Symptoms: activation of parasympathetic system
  – Treated with muscarinic antagonists (Atropine)

• Nicotinic agonists – Nicotine
  – Acute toxicity
    • Fatal dose = 40 mg = 1 drop = 2 cigarettes
  – CNS stimulation
    • convulsion, coma, respiratory depression
  – Skeletal muscle end plate depolarization
    • may lead to depolarization blockade and respiratory paralysis
  – Cardiovascular system
    • Hypertension, Arrhythmias
TOXICITY OF DIRECT CHOLINERGIC AGONISTS

• *Chronic toxicity* of nicotine
  (associated mostly with tobacco smoking)
  – 1979 Surgeon General Report:
  – "cigarette smoking is clearly the largest single preventable cause of illness and premature death in the United States"
    • (on the fricking *Earth!!*)
  – *Addictive power* of tobacco smoking is directly related to their nicotine content
  – Nicotine contributes to:
    • Vascular disease and hypertension
    • Sudden coronary death and arrhythmias
    • Peptic ulcer
    • Calcium loss in bone
CHOLINERGIC AGONISTS

- Autonomic pharmacology terminology and definitions
- Drugs activating cholinergic receptors
- Drugs inhibiting cholinesterase
  - (anticholinesterase drugs)
- Clinical use of drugs activating cholinergic receptors
TYPES OF CHOLINESTERASE INHIBITORS

- Direct-acting drugs
- Indirect-acting drugs (inhibitors of cholinesterase)
  - *Quaternary alcohols*
    - Edrophonium
  - *Carbamic acid esters*
    - Physostigmine
    - Pyridostigmine
    - Neostigmine
  - *Organophosphates*
    - Echothiophate
MECHANISM OF ACTION

• **Inhibition of cholinesterase**
  • leading to accumulation of **ACh in cholinergic synapses**

• **Reversible**
  • **Edrophonium**
    • reversible electrostatic bond at active center of enzyme preventing the access of ACh – *no covalent bond*

• **Physostigmine, Neostigmine**
  • form covalent bond at active center of the enzyme that is *hydrolyzed within 30 min to 6 h*

• **Irreversible**
  • **Organophosphates**
    • form **very stable covalent bond** within active center that takes hundreds of hours to hydrolyze
ABSORPTION & DISTRIBUTION

• Quaternary amines (Edrophonium, Neostigmine)
  – Poor GI absorption
  – Poor CNS penetration
  – Need much higher dose to induce effects

• Tertiary amines (Physostigmine)
  – Good absorption from all sites – especially effective for ophthalmic uses
  – Good penetration into CNS
  – More toxic
ORGAN SYSTEM EFFECTS OF CHOLINESTERASE INHIBITORS

• CNS
  – Low dose – increased alertness
  – High dose – convulsions

• Cardiovascular system
  – Both sympathetic and parasympathetic systems are activated

• Eye, respiratory, gastrointestinal, and urinary systems
  – Similar to effects of direct cholinergic agonists - cholinomimetics

• Neuromuscular junction
  – Prolong and intensify action of ACh –
    • increased strength of skeletal muscle contraction
  – Higher doses may cause muscle twitching and paralysis
CHOLINERGIC AGONISTS

- Autonomic pharmacology terminology and definitions
- Drugs activating cholinergic receptors
- Drugs inhibiting cholinesterase (anticholinesterase drugs)
- Clinical use of drug activating cholinergic receptors
CLINICAL PHARMACOLOGY OF CHOLINERGIC AGONISTS

- Glaucoma
- GI and urinary disorders
- Xerostomia - dry mouth or dry mouth syndrome
- Myasthenia gravis – muscle relaxation (eye lids)
- Intoxication with anti-muscarinic compounds
- Alzheimer disease
- Nicotine addiction
GLAUCOMA

• Increased intraocular pressure
  – can lead to damage of optic nerve
• Cholinergic agonists (parasympathomimetics)
  – not first line drugs but are still used
• Contraction of sphincter muscle & ciliary muscle
  – facilitates outflow of aqueous humor into canal of Schlemm
  – drains anterior chamber – decreases intraocular pressure
• Pilocarpine - drops, most common drug used of this type
• Carbachol - drops
• Echothiophate - longer acting
  – reserved when not able control with other drugs
• Physostigmine - also used
Conditions with **depressed smooth muscle function** 
**w/o obstruction**

- **Atony or paralysis of GI tract**
  - Postoperative ileus (atony or paralysis of stomach or bowel following surgery)
  - Congenital megacolon - no (or partial) large intestine innervation (Hirschsprung's disease (HD))
  - Reflux esophagitis – to increase tone of lower esophageal sphincter

- **Urinary retention** (*need ACh for urination*)
  - Post-surgery retention
  - Postpartum
  - Spinal cord injury
  - Neurogenic bladder (diseases associated with depressed neural regulation of the bladder)

- **Drugs most widely used**: Bethanechol, Neostigmine
Bethanechol is an agonist specific for muscarinic receptors; it can be used to enact micturition or defecation (defecation in adynamic ileus patients).
XEROSTOMIA

- Dry mouth associated with reduced salivation
- Pilocarpine
  - following head/neck radiation treatment/surgery or Sjogren’s syndrome
    - *autoimmune disorder* in which the glands that produce tears & saliva are destroyed
- Cevimeline
  - treatment of dry mouth associated with Sjogren’s syndrome
MYASTHENIA GRAVIS

- **Autoimmune disease** affecting **neuromuscular junction**
  - **degradation of nicotinic receptors** (nAChR) by **auto- antibodies**
- **Symptoms**
  - Weakness, easy fatigue
  - **Facial & eye muscles** usually affected first
- **Treatment**
  - **Immune suppression**
  - Treatment with **inhibitors of cholinesterase**
    - Pyridostigmine, Ambenonium, Neostigmine
TOXICITY OF CHOLINESTERASE INHIBITORS

INDIRECT-ACTING CHOLINERGIC AGONISTS = NON-SELECTIVE ACTIVATION OF CHOLINERGIC RECEPTORS

AUTONOMIC EFFECTS

• Nicotinic receptors on autonomic ganglia = effects on sympathetic AND parasympathetic ns
  • Decreased heart-rate and blood pressure

• Muscarinic receptors on target organs
  • Ocular effects: miosis; impaired vision
  • Respiratory effects: bronchospasm; increased secretions
  • Sweating; salivation
  • Nausea/vomiting
  • Diarrhea/cramps
  • Urination

CNS EFFECTS

• Nicotinic receptors and muscarinic receptors
  • Anxiety, confusion
  • Tremors, seizures
  • Coma
  • Depression of respiratory centers

MOTOR EFFECTS

• Nicotinic receptors on skeletal muscle
  • Muscle twitching followed by weakness and paralysis
  • Respiratory failure

ANTICHOLINESTERASE OVERDOSE:

• Usually occurs as an insecticide poisoning with irreversible agents (organophosphates)
• Respiratory effects = lethal
• Usual route of exposure = lungs or skin; ocular and respiratory symptoms first to emerge (followed by CNS effects)
• Treatment:
  Artificial respiration
  Atropine
  Enzyme reactivation using (Pralidoxime)

Contact 50, Slide 37
CLINICAL PHARMACOLOGY OF CHOLINERGIC AGONISTS

- Glaucoma
- GI and urinary disorders
- Xerostomia
- Myasthenia gravis
- Intoxication with antimuscarinic compounds
- Alzheimer disease
- Nicotine addiction
Myasthenia gravis. The edrophonium (Tensilon) test can be used to confirm the diagnosis. Facial weakness is provoked by repeated facial movements (11.130). Edrophonium chloride, a short-acting anticholinesterase, is then given by slow intravenous injection. In myasthenia gravis the facial weakness is rapidly relieved by this test (11.131). Objective testing of muscular power elsewhere in the body will reveal similar responses. This test should be always undertaken in hospital where there are resuscitation facilities and with a drawn up syringe of atropine present.

http://www.hakeem-sy.com/main/node/15498
Signs and Symptoms of Myasthenia Gravis

Although myasthenia gravis may affect any voluntary muscle, muscles that control eye and eyelid movement, facial expression, and swallowing are most frequently affected. The onset of the disorder may be sudden. Symptoms often are not immediately recognized as myasthenia gravis.

- Drooping of one or both eyelids (ptosis)
- Blurred or double vision (diplopia) due to weakness of the muscles that control eye movements
- Unstable or waddling gait
- Weakness in arms, hands, fingers, legs, and neck
- Change in facial expression
- Difficulty in swallowing and shortness of breath
- Impaired speech (dysarthria)
- Shortness of breath

From *Immunity: The Immune Response in Infectious and Inflammatory Disease* by DeFranco, Locksley and Robertson

Normal

Myasthenia gravis

TO BE DISTINGUISHED FROM BELL’S PALSY


http://besthealth.bmj.com/x/topic/392830/what-is-it.html
ANTI-MUSCARINIC DRUG INTOXICATION

• Causes of toxicity
  – Ingestion of plants containing anti-muscarinic alkaloids (Jimson weed, Atropa belladonna)
  – Atropine – competitive M<sub>r</sub> antagonist
  – Tricyclic antidepressants
  – First generation of antihistamines
  – All above drugs are competitive antagonists at M-receptors

• Drugs of choice – anticholinesterase inhibitors
  – Induce accumulation of ACh
    • competes with Atropine & other antimuscarinic drugs
  – Physostigmine – enters CNS – accumulates ACh
    • Only used when patient
      – develops very high temperature or
      – Very rapid supraventricular tachycardia
NEOSTIGMINE

Uses – similar to physostigmine

Neostigmine is more effective for the treatment and diagnosis of myasthenia gravis

Improves diplopia, ptosis, general muscular weakness, other features of myasthenia gravis
• Alzheimer’s disease
  – Impairment of memory & cognitive function
  – Early degeneration of cholinergic neurons in brain
  – Acetylcholinesterase inhibitors
    • used to improve the function of cholinergic neurons and to boost the level of ACh in the brain
  – Drugs used:
    • Tacrine, Donepezil, Rivastigmine, Galantamine
  – Efficacy is modest
    • Tacrine causes severe adverse effects: hepatic toxicity with jaundice, vomiting, nausea
Cholinergic neurons and networks in the rodent CNS. bas, nucleus basalis; BLA, basolateral amygdala; DR, dorsal raphe; EC, entorhinal cortex; hdb, horizontal diagonal band nucleus; icj, islands of Cajella; IPN, interpeduncular nucleus; LC, locus ceruleus; ldt, laterodorsal tegmental nucleus; LH, lateral hypothalamus; ms, medial septal nucleus; PPN, pedunculopontine nucleus; si, substantia innominata; SN, substantia nigra; vdb, vertical diagonal band nucleus. Reprinted from Woolf and Butcher, Cholinergic systems mediate action from movement to higher consciousness, 2011, with permission from Elsevier.

http://www.nature.com/articles/npjparkd20161
Distribution of Muscarinic Receptors

\[ M_1: \text{Brain (cortex, hippocampus); salivary glands; sympathetic ganglia} \]
\[ M_2: \text{Heart; hindbrain; smooth muscle} \]
\[ M_3: \text{Smooth muscle; salivary glands; brain} \]
\[ M_4: \text{Brain (forebrain, striatum)} \]
\[ M_5: \text{Brain (substantia nigra); eye} \]
CENTRAL NERVOUS SYSTEM CONDITIONS

• **Nicotine addiction**
  – Associated with tobacco smoking
  – **Nicotine**
    • used for replacement of nicotine contained in tobacco smoke – for smoking cessation
  – **Varenicline**
    • centrally active direct nicotinic agonist – used for smoking cessation
## Direct acting Cholinomimetics, NICOTINIC

<table>
<thead>
<tr>
<th>DRUG</th>
<th>CLINICAL USE</th>
<th>TOXICITIES</th>
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</thead>
<tbody>
<tr>
<td>NICOTINE (full Nn agonist)</td>
<td>Smoking cessation</td>
<td>Generalized ganglionic stimulation: hypertension, tachycardia, nausea, vomiting, diarrhea&lt;br&gt;MAJOR overdose: convulsions, paralysis, coma</td>
</tr>
<tr>
<td>VARENICLINE (partial Nn agonist)</td>
<td>Smoking cessation</td>
<td>HPN, sweating, sensory disturbance, diarrhea, polyuria, menstrual disturbance</td>
</tr>
<tr>
<td>SUCCINYLCHOLINE (selective Nm agonist)</td>
<td>Neuromuscular Relaxation</td>
<td>Initial Muscle spasms and postoperative pain</td>
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</table>
**Succinylcholine chloride** is indicated as an adjunct to general anesthesia, to facilitate tracheal intubation, and to provide skeletal muscle relaxation during surgery or mechanical ventilation.

Which of the following are direct acting muscarinic agonists?

a. Bethanechol and Varenicline
b. Bethanechol and Pilocarpine
c. Methacholine and Acetylcholine
d. B & C
e. None of the above
Which of the following are direct acting muscarinic agonists?

a. Bethanechol and Varenicline
b. Bethanechol and Pilocarpine
c. Methacholine and Acetylcholine
d. B & C
e. None of the above
Varenicline is a________.

A. Nicotine receptor agonist  
B. Nicotine receptor antagonist
Varenicline is a_________.

A. Nicotine receptor agonist
B. Nicotine receptor antagonist