Autonomic Pharmacology

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Nervous System

Organization of the nervous system
Nervous System

Peripheral Nervous System (PNS)

Central Nervous System (CNS)

Organization of the nervous system
Organization of the nervous system
Organization of the nervous system

- Nervous System
  - Peripheral Nervous System (PNS)
    - Efferent Division
    - Somatic System
  - Central Nervous System (CNS)
    - Afferent Division

Sensory input → Integration → Motor output
Organization of the nervous system

Nervous System

Peripheral Nervous System (PNS)
- Efferent Division
  - Autonomic System (ANS)
  - Somatic System

Central Nervous System (CNS)
- Afferent Division

Autonomic System (ANS)
- Constricts pupil
- Stimulates tear glands
- Strong stimulation of salivary flow
- Inhibits heart, dilates arterioles
- Constricts bronchi
- Stimulates stomach motility and secretion, stimulates pancreas
- Stimulates intestinal motility
- Contracts bladder

Somatic System
- Stimulates erection
- Stimulates ejaculation
- Dilates pupil
- No effect on tear glands
- Weak stimulation of salivary flow
- Accelerates heart, constricts arterioles
- Dilates bronchi
- Inhibits stomach motility and secretion, inhibits pancreas and adrenals
- Inhibits intestinal motility
- Relaxes bladder
Organization of the nervous system

Peripheral Nervous System (PNS)
- Efferent Division
  - Autonomic System (ANS)
    - Parasympathetic
    - Sympathetic
      (Enteric)
  - Somatic System
- Afferent Division

Central Nervous System (CNS)
- Efferent Division
- Afferent Division

Parasympathetic Division
- Constricts pupil
- Stimulates tear glands
- Strong stimulation of salivary flow
- Inhibits heart, dilates arterioles
- Constricts bronchi
- Stimulates stomach motility and secretion, stimulates pancreas
- Stimulates intestinal motility
- Contracts bladder

Sympathetic Division
- Dilates pupil
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- Weak stimulation of salivary flow
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- Inhibits stomach motility and secretion, inhibits pancreas and adrenals
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- Stimulates erection
- Stimulates ejaculation
- Relaxes bladder

Organization of the nervous system
The Enteric Nervous System (+SNS/PSNS)
Drugs that produce their primary therapeutic effect by mimicking or altering the functions of autonomic nervous system are called autonomic drugs.
The Neuron

The neuron is the basic unit of the nervous system that permits integration of information and transmits this info to other cells

1) The **dendrites** receive info from other neurons (or sensory endings)

2) The **cell body** integrates the dendritic input and determines whether an axon potential is fired

3) The **axon** is the cable that transmits the action potential

4) The **synaptic terminal** is where the action potential is converted into neurotransmitter release that is sensed by the postsynaptic cell
The Synapse: Part I

- The synapse converts the electrical signals of action potentials into the chemical signals of neurotransmitter (NT) release.
- NTs are packaged at high concentration in synaptic vesicles via transporters.
- Action potential depolarization of the terminal activates voltage-dependent $\text{Ca}^{++}$ channels, causing an influx of $\text{Ca}^{++}$. 
The Synapse: Part II

- **Ca**\(^{++}\) influx interacts with synaptic vesicle proteins called SNAREs to promote fusion between these proteins in the synaptic vesicles and the plasma membrane, fusing the two membranes.

- Release of NT activates postsynaptic and presynaptic ion channels and GPCRs.
**Neurotransmitters**

**Receptors**

![Diagram of neurotransmitters and receptors]

- Brain stem or spinal cord
  - Pre-ganglionic neuron
  - Ganglionic transmitter
  - Post-ganglionic neuron
  - Neuroeffector transmitter
  - Effector organ
  - Efferent neurons of ANS
"Rest and digest" stimuli

Parasympathetic output (discrete)

Sympathetic and parasympathetic actions often oppose each other

"Fight or flight" stimuli

Sympathetic output (diffuse)
The release of noradrenaline has the following effects:

- stimulates heartbeat
- raises blood pressure
- dilates the pupils
- dilates the trachea and bronchi
- stimulates the conversion of liver glycogen into glucose
- shunts blood away from the skin and viscera to the skeletal muscles, brain, and heart
- inhibits peristalsis in the gastrointestinal (GI) tract
- inhibits contraction of the bladder and rectum
Parasympathetic stimulation causes:

- slowing down of the heartbeat
- lowering of blood pressure
- constriction of the pupils
- increased blood flow to the skin and viscera
- peristalsis of the GI tract
Neurotransmitters

Brain stem or spinal cord

Pre-ganglionic neuron

Ganglionic transmitter

Post-ganglionic neuron

Neuroeffector transmitter

Effector organ

Efferent neurons of ANS

drugs
Neurotransmitters
- Synthesis
- Storage
- Release
- Inactivation

Receptors
- Activation

Brain stem or spinal cord

Pre-ganglionic neuron

Ganglionic transmitter

Post-ganglionic neuron

Neuroeffector transmitter

Effector organ

Efferent neurons of ANS
Drug actions and classification

1. Mechanisms of drug actions

1.1 Direct actions on the receptors

- Agonists
- Antagonists

1.2 Indirect actions via affecting transmitters

- Synthesis
- Transport and storage
- Release
- Inactivation

1.3 Mimetics and antagonists

(1) Mimetics
- direct-acting: receptor agonists
- indirect-acting: increasing amounts and/or effects of transmitters

(2) Antagonists
- direct-acting: receptor antagonists
- indirect-acting: decreasing amounts and/or effects of transmitters
Cholinergic Pharmacology
Adrenergic Pharmacology
1. Choline Uptake

2. ACh Synthesis

Choline acetyltransferase (ChAT)
Choline + AcCoA → ACh
ChAT

3. ACh Storage

4. ACh Release

5. ACh Effects
   a) Postsynaptic
   b) Presynaptic

6. ACh Metabolism

Acetylcholinesterase (AChE)

ACh → Choline + Acetate
AChE
Acetylcholine Release
by exocytosis

Regulation

- by autoreceptors
  ACh acting on presynaptic M₂-cholinergic receptors

- by heteroreceptors
  NE acting on presynaptic α₂-adrenergic receptors

- by metabolism (extraneuronal)
**Cholinesterases**

Acetylcholinesterase is located at cholinergic synapses and in erythrocytes (*does not hydrolyze succinylcholine*)

Pseudocholinesterase (*synonyms: plasmacholinesterase or butyrylcholinesterase*) occurs mainly in plasma, liver and in glia (*hydrolyzes succinylcholine*)
Ganglionic Neurotransmission

N = Nicotinic AChR
M = Muscarinic AChR
EPSP = Excitatory Postsynaptic Potential
IPSP = Inhibitory Postsynaptic Potential
Cholinergic Receptors
(cholinoceptors, acetylcholine receptors)

- **Muscarnic receptors (M receptors)**
  - $M_{1,3,5}$; $M_{2,4}$
  - G-protein Coupled
  - End Organs

- **Nicotinic receptors (N receptors)**
  - $N_{N_1}$ (N$_1$) receptors; $N_{M_2}$ (N$_2$) receptors
  - Ligand-gated Ion Channels
  - NMJ & Ganglia
**M receptors**: G-protein Coupled

**Muscarinic Receptor Signaling Pathways**

- **Smooth Muscle contraction**
  - Stimulation of phospholipase C
  - Protein kinase C
  - Diacylglycerol
  - Inhibition of adenyl cyclase
  - cAMP decrease
  - Regulation of K⁺ channels
  - Heart rate decrease

- **Heart rate decrease**
  - cAMP decrease
  - Regulation of K⁺ channels
M receptors: end organs and effect of activation

• **Depression of the heart** (heart rate, conduction)

• **Contraction of smooth muscles** (sensitive: GI tract, bronchial, urinary bladder; insensitive: uterine, blood vascular) Mostly smooth muscle contraction - heart being the main exception

• **Exocrine glands** (sensitive: sweat, tears, salivary; insensitive: GI tract);

• **Eye** (contraction of sphincter muscle of iris: miosis; contraction of ciliary muscle: contraction for near vision)

• CNS
Cholinergic Vasodilation

- The response of an isolated blood vessel to ACh depends on whether the endothelium is intact (unrubbed) or missing.
- When the endothelium is present, ACh causes smooth muscle relaxation by stimulating the production of nitric oxide (NO) in the endothelium.
- In the absence of the endothelium, a small amount of vasoconstriction is observed.
**N receptors : subtypes and location**

- $N_N$ receptors (N$_1$ receptors)
- Sympathetic and parasympathetic ganglia
- Adrenal medulla

- $N_M$ receptors (N$_2$ receptors)
- The Neuromuscular Junction (NMJ)
  (Contraction of skeletal muscles)
**N receptors**: **Ligand-gated Ion Channels**

- At the NMJ, *N receptors* Pentameric with four types of subunits, two α subunits bind ACh for ligand gating

- All other nAChRs, including those at the peripheral ganglia, have 2 α’s and 3 β’s
The Neuromuscular Junction (NMJ)
Myasthenia Gravis

- This means “serious disorder the NMJ”
- This is an autoimmune disease
- Antibodies against the $\alpha$ subunit of the nAChR
- The ability of ACh to activate the nAChRs is blocked by the antibodies
- As for many autoimmune diseases, stress can make the symptoms worse
- Treatment is to potentiate cholinergic signaling and to remove the antibodies (blood dialysis)
1 Cholinomimetics

(1) Direct-acting drugs: Cholinoreceptor agonists

- M, N receptor agonists: acetylcholine
- M receptor agonists: pilocarpine
- N receptor agonists: nicotine

(2) Indirect-acting drugs: Cholinesterase inhibitors (Anticholinesterases)

- Reversible: neostigmine
- Irreversible: organophosphates
Cholinomimetics: Direct-acting drugs

ACh Derivatives

- ACETYLCHOLINE
  - 胆碱乙酰化物
- METHACHOLINE
  - 甲酰胆碱

AChE Resistant

- CARBACHOL
  - 卡巴胆碱
- BETHANECHOL
  - 氯贝胆碱

Bond cleaved by AChE

- $(\text{CH}_3)_3\text{NCH}_2\text{CH}_2\text{OCCH}_3$
  - 乙酰甲胆碱
- $(\text{CH}_3)_3\text{NCH}_2\text{CHO\text{CCH}_3}$
  - 乙酰胆碱
**Bethanechol** is most commonly used, particularly post-op for the treatment of paralytic ileus and urinary retention.
Natural Muscarinic Agonists

(Most to least nicotinic)

• Muscarine (毒蕈碱): *amanita muscaria* (mushroom)
• Pilocarpine (毛果芸香碱): *pilocarpus* (S. Amer. shrub)
• Arecoline (槟榔碱): *areca* or *betal nuts* (India, E. Indies)
“Food” Poisoning

- Poisoning causes muscarinic overstimulation
  - salivation, lacrimation, visual disturbances;
  - abdominal colic and diarrhea
  - bronchospasm and bradycardia
  - hypotension; shock
- Treatment is with atropine

Amanita muscaria => muscarine  Atropa belladonna => atropine
Muscarinic Agonists: Parasympathetic Effects & Therapeutic Uses

Pilocarpine

(1) Eyes

• Miosis: contraction of sphincter muscle of iris
• Lowing intraocular pressure: enlarging angle of anterior chamber, increasing drainage of aqueous humor
• Spasm of accommodation: contraction of ciliary muscle, contraction for near vision

• Ophthalmological uses
  Glaucoma: narrow (closed)- or wide (open)-angles
  it is the drug of choice in the emergency lowering of intraocular pressure
  Iritis: miotics/mydriatics
Atropine:
-_paralysis of accommodation
- mydriasis
- far sight

Pilocarpine:
- spasm of accommodation
- miosis
- near sight

Diagram labels:
- Ciliary muscle (contraction)
- Anterior chamber
- Iris
- Zonule
- Canal of Schlemm
- Posterior chamber
- Lens
Circulation of Aqueous humor

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Glaucoma

• Disease of the aging eye - increased intraocular pressure, degeneration of the optic head, and restricted visual field typify primary open-angle glaucoma.

• Obstruction of the aqueous drainage leads to elevated intraocular pressure (IOP), and may result in glaucomatous damage to the optic nerve.
Glaucoma

- Glaucoma management involves lowering IOP by
  - Decreasing aqueous production by the ciliary body
  - Increasing aqueous outflow through the trabecular meshwork and uveal outflow paths
Pilocarpine Increase Aqueous Humor Outflow

- **pilocarpine**: parasympathomimetics increase aqueous outflow by contraction of the ciliary muscle to increase tone and alignment of the trabecular network.
Muscarinic Agents: Parasympathetic Effects & Therapeutic Uses

Pilocarpine

• Promoting secretion of exocrine glands, especially in sweat, salivary and tear glands
  
  • Systemic use

  Antidote for atropine poisoning
**N receptor agonists:**

**Nicotine**

- actions at ganglia, NMJ, brain

Actions are complex and frequently unpredictable, because of the variety of neuroeffector sites and because nicotine both stimulates and desensitizes effectors. Nicotine typically will affect the

**Periphery:** $\uparrow$HR, $\uparrow$BP, $\uparrow$GI tone & motility

*and also*

**CNS:** stimulation, tremors,$\uparrow$ respiration, emetic effects

The addictive power of cigarettes is directly related to their nicotine content.
**Drugs classification**

1. **Cholinomimetics** (*Parasympathomimetics*)
   
   (1) **Direct-acting drugs:** Cholinoceptor agonists
   
   - **M, N receptor agonists:** acetylcholine
   - **M receptor agonists:** pilocarpine
   - **N receptor agonists:** nicotine

   (2) **Indirect-acting drugs:** Cholinesterase inhibitors (Anticholinesterases)
   
   - Reversible: neostigmine
   - Irreversible: organophosphates
Drug classification

1 Cholinomimetics

(1) Direct-acting drugs: Cholinoceptor agonists
- M, N receptor agonists: acetylcholine
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Cholinergic antagonists: Cholinesterase reactivators
- pralidoxime iodide
Cholinomimetics-
Indirect Agents: AChE Inhibitors
Acetylcholinesterase (AChE) Activity
Cholinomimetics - Indirect Agents: AChE Inhibitors

A. Edrophonium 依酚氯铵 (reversible, competitive)

B. Carbamates 氨甲酰类 (slowly reversible)

C. Organophosphates 有机磷类 (irreversible)

These agents are reversible and are used medically (glaucoma or MG)

These agents are irreversible and are used as pesticides or for glaucoma
Acetylcholinesterase Inhibitors: Reversible

Edrophonium 依酚氯铵

Rapidly absorbed;  
A short duration of action (5-15min);  
Competitive (reversible)

Used in diagnosis of myasthenia gravis.

Excess drug may provoke a cholinergic crisis, Atropine is the antidote.
Acetylcholinesterase Inhibitors: Carbamates

Inhibitory Effects are slowly reversible

Representative Drugs
neostigmine 新斯的明
(quaternary amine)
physiostigmine 毒扁豆碱
(tertiary amine)
pyridostigmine 吡斯的明
(quaternary amine)

quaternary amines effective in periphery only
tertiary amines effective in periphery and CNS
(fat-soluble)
Acetylcholinesterase Inhibitors: Carbamates
neostigmine (quaternary amine)

- **Pharmacological effects**
  - $AChE(-), ACh\ \text{release} \uparrow, \text{stimulating } N_M R$
  - stronger effect on skeletal muscles
  - effective on GI tract and urinary bladder
  - more polar and can not enter CNS
  - relatively ineffective on CVS, glands, eye

- **Clinical uses**
  - **Myasthenia gravis:** symptomatic treatment, overdose: cholinergic crisis
  - **Paralytic ileus and bladder:** post operative abdominal distension and urinary retention
  - **Paroxysmal supraventricular tachycardia** (阵发性室上速)
  - **Antidote for tubocurarine and related drug poisoning**
Acetylcholinesterase Inhibitors: Carbamates

neostigmine (quaternary amine)

- **Adverse effects**
  - **Cholinergic effects**: muscarinic and nicotinic effects, treated with atropine (muscarinic)
  - **Contraindications**: mechanical ileus, urinary obstruction, bronchial asthma, poisoning of depolarizing skeletal muscle relaxants (e.g. succinylcholine)
Acetylcholinesterase Inhibitors: Irreversible

These agents are used as pesticides or for glaucoma.
Acetylcholinesterase Inhibitors: Organophosphates

Effects of Organophosphates are irreversible (covalent bond formation)

Pralidoxime (碘解磷定) can restore AChE activity if administered soon after toxin exposure.

- Conjugating with organophosphate by oxime group;
- Conjugating with free organophosphates
Acetylcholinesterase Inhibitors: Organophosphates

(1) Toxic symptoms

- Acute intoxication
  - Muscarinic symptoms: eye, exocrine glands, respiration, GI tract, urinary tract, CVS
  - Nicotinic symptoms: $N_N$: elevation of BP, increase of HR; $N_2$: tremor of skeletal muscles
  - CNS symptoms: excitation, convulsion(抽搐); depression (advanced phase)

- Chronic intoxication
  - usually occupational poisoning
  - plasma ChE activity ↓
  - weakness, restlessness, anxiety, tremor, miosis, ......
Acetylcholinesterase Inhibitors: Organophosphates

(2) Detoxication

- Elimination of poison; Supportive therapy
- Antidotes
  - Atropine – antagonizing muscarinic effects; early, larger dose, and repeated use
  - Cholinesterase reactivators – reactivation of phosphated AChE; moderate-severe patients, early use (More effective on tremor), combined with atropine
    - Pyraloxime methiodide (氯解磷定): saver than PAM
    - Pralidoxime chloride (PAM)
    - Obidoxime chloride (双复磷): two active oxime groups
Why isn’t this ACHEI pesticide neurotoxic to humans?

Insects and mammals metabolize the ‘prodrug’ differently

**Insects - P450 metabolism**: P-S bond converted to P-O bond: now, the molecule, **malaoxon**, is an active organophosphate inhibitor

**Mammals – esterase activity**: hydrolyzes the molecule into inactive metabolites
Summary: ACHEI Applications

Pharmacological Actions: Increases ACh concentrations at cholinergic synapses, thereby increasing cholinergic activity.

- glaucoma (e.g. physostigmine, Echothiophate)
- myasthenia gravis (e.g. Edrophonium, neostigmine, pyridostigmine)
- reverse neuromuscular blockade from competitive antagonists (neostigmine)
- Alzheimer’s disease (tacrine & donepezil)
- chemical warfare agents
- insecticides
2 Cholinergic antagonists

(1) Cholinoceptor antagonists

• M cholinoceptor antagonists
  – atropine (Antimuscarinic drugs)

• N cholinoceptor antagonists
  – $N_N$ cholinoceptor antagonists: mecamylamine
    (Ganglionic Blocking drugs, rarely used)
  – $N_M$ cholinoceptor antagonists: succinylcholine
    (Neuromuscular Blocking drugs)

• Botulinum Toxin (blocks ACh release)
Muscarinic Antagonists
(Antimuscarinic drugs)

Tertiary amines

Quaternary amines

Atropine 阿托品

Methyl-atropine

Scopolamine 东莨菪碱

Ipratropium

Tiotropium
Atropine

1. Pharmacological effects
(1) Eye

- **intraocular pressure** ↑

  - Ciliary muscle (relaxation)
  - Canal of Schlemm
  - zonule
  - posterior chamber
  - Anterior chamber
  - lens

- **paralysis of accommodation**

- **mydriasis**

  - far sight

  - atropine

- **spasm of accommodation**

  - near sight

  - pilocarpine
Atropine

1. Pharmacological effects

(2) Antispasmodic action on smooth muscle

- sensitive: GI, urinary bladder (spasmodic state)
- relatively insensitive: bile duct, urinary tract, bronchial tract
- insensitive: uterus

(3) Inhibition of exocrine gland secretion

- salivary, sweat glands
- tear, respiratory tract glands
- relatively ineffective: GI tract
1. **Pharmacological effects**

(4) **Cardiovascular System: dose dependent**

- Lower therapeutic doses: HR ↓ (bradycardia); Blood vessels and blood pressure: no effect
- Moderate to high therapeutic doses / high vagal tone: HR ↑ (tachycardia); A-V conduction ↑
- Larger doses: cutaneous vasodilatation

(5) **CNS stimulation**

- sedation, memory loss, psychosis (high dose)
Atropine

2. Clinical uses

(1) Ophthalmology
• Measurement of the refractive errors (验光): children
• Acute iritis or iridocyclitis: mydriatics/miotics (to prevent synechiae/adhesion)

(2) Antispasmodic agent
• GI, biliary or renal colic, enuresis (遗尿)

(3) Inhibiting exocrine gland secretion
• Preanesthetic medication

(4) Bradyarrhythmia
• sinus or nodal bradycardia, A-V block

(5) Antidote for organophosphate poisoning
Atropine

3. Adverse effects

(1) Side effects  dry mouth, blurred vision, “sandy eyes”

(2) Toxicity  Lethal dose: 80~130 mg (adult), 10 mg (child)
  - Low: xerostomia (dry mouth); anhidrosis (dry skin), tachycardia
  - Moderate: above plus mydriasis, cycloplegia; difficulty on speaking, swallowing & urinating; and hot, red, dry skin
  - High: above plus ataxia, hallucinations & delirium; coma (i.e. CNS symptoms)

(3) Detoxication
  - Symptomatic treatment: e.g. diazepam.
  - Physostigmine or pilocarpine

(4) Contraindications
  - glaucoma, prostataux, fever
Scopolamine

• **Actions and clinical uses**
  
  – Peripheral effects are similar to atropine; but has stronger central effects (depression)
  
  – Pre-anesthetic medication, prevention of motion sickness, Parkinson’s disease
others

- **Propantheline** (普鲁本辛):
  - poor absorption (po) and BBB penetration
  - *antispasmodic* effects in GI, treatment of peptic ulcer disease

- **Tropicamide** (托吡卡胺): *mydriatics, cycloplegic* (睫状肌麻痹)
  - shorter duration (1/4 day)
  - Examination of eyes

- **Ipratropium** (异丙托溴胺): *asthma*

- **Benztropine**: *Parkinson’s disease*
Nicotinic receptor antagonists
$N_N$ receptor antagonists
(Ganglionic Blocking drugs)

- Acting on sympathetic and parasympathetic ganglionic cells; reducing blood pressure by inhibiting sympathetic ganglia (have been abandoned for clinical use, due to their lack of selectivity)

- Short-acting; tachyphylaxis

- Used for treatment of hypertension
  - Trimethaphan (樟磺咪芬)
  - Mecamylamine (美卡拉明)
Two classes:

**Non-depolarizing**: drugs act as competitive antagonists

**Depolarizing**: succinylcholine (琥珀胆碱)

*Note: Belong to Skeletal Muscle Relaxants. It is important to realize that muscle relaxation does not ensure unconsciousness, amnesia, or analgesia.*
**N\textsubscript{M} receptor antagonists**

( Neuromuscular Blocking drugs )

1. **Depolarizing neuromuscular blockers** *(Non-competitive)*
   - *(depolarizing skeletal muscle relaxants)*
     - act as acetylcholine (ACh) receptor agonists
       - the depolarized membranes remain depolarized and unresponsive to subsequent impulses (ie, they are in a state of depolarizing block).
     - not metabolized by AChE
       - they diffuse away from the neuromuscular junction and are hydrolyzed in the plasma and liver by pseudocholinesterase (nonspecific cholinesterase, plasma cholinesterase, or butyrylcholinesterase) and elimination by kidney
Succinylcholine, Scoline

Succinylcholine is the only depolarizing agent used clinically ($t_{1/2} = 2-4$ min).

Properties of actions:
- initially transient fasciculations
- anti-AChE potentiates their effects
- tachyphylaxis after repeated uses
- no ganglion-blocking effects at therapeutic doses
- the drugs are highly polar, poor bioavailability; i.v.
- as quaternary compounds...do not enter CNS
Succinylcholine, Scoline

• **Main pharmacological effects**

  – Transient excitation (fasciculations), and then inhibition (relaxation)

  – Relax **Skeletal Muscles** in neck, limbs > face, tongue, throat; less effective on breath muscles at therapeutic doses
Succinylcholine, *Scoline*

- **Clinical uses**
  - An adjuvant in anesthesia or operation
  - Intubation of trachea, esophagus, etc.
  - Prevention of trauma during electroshock therapy

- **Contraindicated** in awake patients, should use under anesthesia
Succinylcholine, Scoline

- **Adverse effects**

  1. **Apnea (respiratory paralysis)**
     - overdose or hypersensitive patients;
     - neostigmine potentiates the toxic effects

  2. **Fasciculations** (肌束震顫)
     - muscular pain after operation
     (because of transient fasciculations)
Succinylcholine, Scoline

(3) Elevation of $K^+$ in plasma
- contraindicated in patients with a tendency of hyperkalemia (burn injury, massive trauma, neurological disorders)

(4) Malignant hyperthermia
- genetic abnormality

(5) Others
- rise in intraocular pressure (glaucoma);
- histamine release
Genetic Variation: Effects on Duration of Action of Succinylcholine

- The duration of action is prolonged by high doses or by abnormal metabolism. The latter may result from hypothermia, low pseudocholinesterase levels, or a genetically aberrant enzyme. (hypothermia decreases the rate of hydrolysis)

- Low pseudocholinesterase levels generally produce only modest prolongation of succinylcholine's actions (2–20 min).

- One in 50 patients has one normal and one abnormal (atypical) pseudocholinesterase gene, resulting in a slightly prolonged block (20–30 min).

- Even fewer (1 in 3000) patients have two abnormal genes (homozygous atypical) that produce an enzyme with little or no affinity for succinylcholine and have a very long blockade (e.g., 4–8 h) following administration of succinylcholine.

- Scoline Apnea: mechanical ventilation
• Of the recognized abnormal pseudochocholinesterase genes, the dibucaine-resistant (variant) gene, which displays 1/100 of normal affinity for succinylcholine, is the most common.
• Therefore, adequacy of pseudochocholinesterase can be determined in the laboratory quantitatively in units per liter (a minor factor) and qualitatively by dibucaine number.
• "Dibucaine number" test identifies patients with abnormal plasma cholinesterase
  – Dibucaine is an amide local anesthetic that inhibits wild type plasma cholinesterase by 80%; however, it inhibits atypical enzyme by only 20%.
  – The percentage of inhibition of pseudochocholinesterase activity is termed the dibucaine number. The dibucaine number is proportional to pseudochocholinesterase function and independent of the amount of enzyme
    • If dibucaine number equals 80: normal cholinesterase
    • If dibucaine number equals 20: homozygous for atypical cholinesterase
Drug interactions

- Thiopental (硫喷妥)

- ChE inhibitors:
  - AChE inhibitors, cyclophosphamide, procaine, etc.

- Some antibiotics:
  - kanamycin, polymyxins, etc. (synergism in neuromuscular blocking)
2. **Nondepolarizing neuromuscular blockers**
   
   (Competitive)

   • *(nondepolarizing skeletal muscle relaxants)*

   **Tubocurarine** (筒箭毒碱)

   Reversibly bind to the nicotinic receptor at the neuromuscular junction (competitive antagonists)

   *(note: curare rarely used)*
**Tubocurarine**

**Effects:** competitive blockade of $N_M$ receptors

**Uses:** adjuvant treatment of anesthesia or operations

**Adverse effects:**
- **Respiratory paralysis:** can be reversed by neostigmine
- **Enhancing histamine release:** BP ↓, hypotension, bronchoconstriction, salivary secretion
- **Blocking ganglion:** BP ↓

**Contraindications:** myasthenia gravis, bronchial asthma, shock, child (< 10 y)

**Drug interactions**
- Similar to these of scoline
Other nondepolarizing neuromuscular blockers

- **Benzylisoquinolines**
  - Benzylisoquinolines
  - Atracurium
  - Doxacurium
  - Mivacurium

- **Ammonio steroids**
  - Pancuronium
  - Vecuronium
  - Pipecuronium
  - Rocuronium

It is important to realize that neuromuscular junction blocking agents produce paralysis, not anesthesia.

In other words, muscle relaxation does not ensure unconsciousness, amnesia, or analgesia.

*Note: currently used NMJ blockers differ in time of onset and clinical duration: pancuronium > atracurium > rocuronium*
**Botulinum Toxin**

- Skeletal Muscle Relaxants
- blocks ACh release from cholinergic terminals
- selective for ACh terminals
- irreversible; Botox acts as a protease that cleaves specific proteins involved in exocytosis. . .results in flaccid paralysis in muscles;
(can also be used for excessive sweating, tension/migraine)
Acts by cleaving SNARE proteins → inhibits ACh release
Amazing Details on Botulinum Toxin

. . How does it do it. . . ?

- an anaerobic bacillus, clostridium botulinum can multiply in preserved food

- it synthesizes a protein that can be absorbed (pinocytosis or transport?) from the GI tract to reach the systemic circulation

- penetrates tissues to reach cholinergic nerve terminals

- then, it is uptaken (pinocytosis) and internalized in vesicles whose lumen becomes acidified

- the low pH of the vesicles splits the inactive molecule into 2 active enzymes that have proteolysis functions
Botulinum Toxin Applications

- **Strabismus** (lack of parallelism of eyes, 斜视), blepharospasm (eyelid spasm), dystonia (abnormal tonicity, 肌张力障碍).
- **Excessive sweating**
- **Cosmetic procedures** ("frown lines" or "crow’s feet")

Note: effects can last for ~3-6 months.
Cholinergic Pharmacology

Adrenergic Pharmacology
**Parasympathetic NS**

**EYE**
Contraction of iris sphincter muscle (pupil dilates)
Contraction of ciliary muscle (lens accommodates for near vision)
**Lacrimal gland**
Stimulates tears
**Salivary gland**
Copious, water secretion
**Trachea and bronchioles**
Constricts, increase secretion
**Heart**
rate ↓ contractility ↓
**Gastrointestinal**
Muscle motility & tone ↑
**Ureters and bladder**
Contraction of detrusor
Relaxation of trigone & sphincter
**Genitalia-male**
Stimulates erection

---

**Sympathetic NS**

**EYE**
contraction of iris radial muscle (pupil dilates)
contraction of ciliary muscle (lens accommodates for near vision)
**Salivary gland**
copious, water secretion
**Trachea and bronchioles**
dilates
**Heart**
rack ↑ contractility ↑
**Blood vessels**
dilatation (Skeletal muscle)
constriction (skin, mucus, membranes & splanchnic area)
**Gastrointestinal**
muscle motility & tone ↓
contraction of sphincters
**Ureters and bladder**
relaxes detrusor
**Genitalia-female**
Relaxation of uterus
Neurotransmitters
• Synthesis
• Storage
• Release
• Inactivation

Receptors
• Activation

Drug actions and classification
Noradrenergic Nerve: Synthesis, storage and release of NE

Tyrosine
  ↓ tyrosine hydroxylase (TH)
L-DOPA
  ↓ DOPA decarboxylase
dopamine (DA)
  ↓ dopamine beta-hydroxylase (DBH)
norepinephrine (NE)

• Uptake neurotransmitter transporters
  – uptake 1: neuronal uptake
  – uptake 2: non-neuronal uptake

• Enzymatic degradation
  – monoamine oxidase (MAO)
  – catechol-O-methyltransferase (COMT)
Regulation of NE Synthesis and Turnover

Tyrosine hydroxylase (TH) activity is rate limiting

TH activity inhibited by NE product

TH activity modulated by presynaptic autoreceptors
- alpha$_2$ receptors can reduce NE release
- beta$_2$ receptors can increase NE release

Presynaptic heteroreceptors can modulate NE release
- ACh can reduce NE release

TH activity increases or decreases to maintain steady-state levels of norepinephrine.

The above processes contribute to regulation of steady-state NE levels (rate of synthesis = rate of output)
Norepinephrine and Epinephrine Synthesis in the Adrenal Medulla

- NE is stored in vesicles
- DBH is located in vesicles
- PNMT is located in the cytosol.
- EPI is stored in vesicles
- **EPI (~80%)** and NE (~20%) released into blood

- These hormones bind adrenergic receptors on target cells, inducing the same effects as direct sympathetic nervous stimulation.

**EPI disposition**: metabolism by COMT, MAO, sulfation, uptake into NE terminals
NE Metabolism
- takes place within the same cells where the amines are synthesized, and in liver
- Extraneuronal O-methylation of norepinephrine and epinephrine to metanephrines represent minor pathways of metabolism.

\[
\text{MHPG: was used as an index of CNS NE turnover but generated mostly from periphery}
\]
\[
\text{VMA: sometimes used as an index of NE turnover}
\]
\[
\text{Sulfate conjugates also prevalent}
\]
Norepinephrine (NE) release

- Receptor binding (reversible)
- Receptor activation
- Signal transduction
- Response

Adrenergic Receptors/Adrenoceptors

- α
  - α₁
  - α₂
- β
  - β₁
  - (β₂, β₃)

G-Protein Coupled Receptors

Low affinity for binding NE
Adrenergic Receptor Subtypes & G-Protein Coupled Mechanisms

\( \alpha_1 \) Adrenergic Receptors:
G protein termed \( G_q \) phospholipase C activation, \( IP_3 \)
→ mechanism: mobilizes and increases intracellular free calcium
→ effects: primarily smooth muscle contraction

\( \alpha_2 \) Adrenergic Receptors:
Inhibition of adenylyl cyclase through \( G_i \) proteins
→ mechanism: decreases intracellular cAMP levels
→ effects: decreased protein phosphorylation, decreased cellular function

\( \beta \) Adrenergic Receptors:
Activation of adenylyl cyclase through \( G_s \) proteins
→ mechanism: increases intracellular cAMP levels
→ effects: phosphorylation of intracellular proteins → smooth muscle relaxation, cardiac muscle contraction
The SNS Plays a Very Important Role in the Regulation of the Cardiovascular System, which, except for the Heart, is not Innervated by the PSNS
SNS Regulation of Cardiac Function

- The SNS innervates the entire heart while the PSNS only innervates the S-A and A-V nodes.
- Neural modulation of heart rate occurs in part through enhancement (NE via $\beta_1$ ARs) or reduction (ACh via M$_2$R) of pacemaker activity, which is directly stimulated by elevated cAMP levels.
- The SNS via $\beta_1$ ARs also increases the force of contraction. Both heart rate and contractile force contribute to cardiac output.
The SNS Enhances Smooth Muscle Contraction Primarily by $\alpha_1$ ARs, and Reduces Contraction Primarily by $\beta_2$ ARs.
SNS Regulation of Blood Pressure

- Acute loss of SNS function lowers blood pressure
- Chronic loss of SNS function greatly increases blood pressure variability
Four Major Activators of the Adrenergic System

1- Hypoglycemia
2- Hypothermia
3- Hypoxia
4- Hypotension
• Hypoxia - response is mainly cardiovascular: $\beta_1$ receptors via SNS NE increase heart rate & contractility, resulting in greater cardiac output; $\beta_2$ receptors via adrenal Epi vasodilate blood vessels in muscle, increasing oxygen delivery, and mediate bronchodilation to facilitate oxygen intake.

• Hypoglycemia - response is mainly metabolic (next slides), but $\beta_2$ vasodilation in muscle increases glucose (as well as oxygen) delivery.
Response to Hypoglycemia (insulin injection)

The release of E (and to a lesser extent NE) by the adrenal is in direct response to falling blood glucose levels.
Glycogenolysis (糖原分解)

- The brain and muscle must have glucose
- The main sites of glycogenolysis are the liver and muscle
- Glycogen is broken down by glycogen phosphorylase
- This enzyme is activated by both PKA and PKC through stimulation of $\beta_2$ and $\alpha_1$ adrenergic receptors, respectively
Gluconeogenesis (糖异生)

- The liver and kidney are the key sites
- Substrates: lactate (from muscle) and glycerol (from fat)
- Several enzymes in the pathway are activated by PKC through $\alpha_1$ stimulation
- Both glycogenolysis & gluconeogenesis are indirectly stimulated by facilitating release of glucagon ($\beta_2$) & inhibiting release of insulin ($\alpha_2$)

Lipolysis (脂解作用)

- Lipases are stimulated by $\beta$ (esp. $\beta_3$) receptors
Energy Mobilization by Epinephrine

- Glucose
- Lactate
- Ketones
- Free Fatty Acids

(+)
GLYCOGENOLYSIS

(+)
GLUCONEOGENESIS

(+)
KETOGENESIS

LIVER

(-)
INSULIN
(+)
GLUCAGON

MUSCLE

(+)
GLYCOGENOLYSIS

ADIPOSE TISSUE

PANCREAS
Response to Hypothermia:
1 - Piloerection
2 - Peripheral vasoconstriction
3 - Thermogenesis
   - Brown fat
      a) activation
      b) proliferation
Peripheral Vasoconstriction

- To reduce heat loss, vasoconstriction occurs peripherally
- Lower temperatures increase the affinity of the $\alpha_2$ receptors, which are located on the peripheral vasculature, for NE & E
- This leads to constriction of the peripheral vasculature
## Other SNS Functions

<table>
<thead>
<tr>
<th>Eye</th>
<th>Effect</th>
<th>Mediator</th>
<th>Mechanism</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Dilation of pupils</td>
<td>Radial muscle of iris</td>
<td>$\alpha_1$ contraction</td>
</tr>
<tr>
<td>Lung</td>
<td>Dilation of the airway</td>
<td>Bronchial smooth muscle</td>
<td>$\beta_2$ relaxation</td>
</tr>
<tr>
<td>Skin</td>
<td>Raised hair (piloerection)</td>
<td>Piloerector muscle</td>
<td>$\alpha_1$ contraction</td>
</tr>
<tr>
<td>Spleen</td>
<td>↑ circulating blood cells</td>
<td>Splenic capsule</td>
<td>$\alpha_1$ contraction</td>
</tr>
<tr>
<td>Gut</td>
<td>Digestion</td>
<td>Smooth muscle &amp; Secretion</td>
<td>$\beta_2$ relaxation $\alpha_2$ inhibition</td>
</tr>
<tr>
<td>Vas Deferens</td>
<td>Ejaculation</td>
<td>Smooth muscle of vas</td>
<td>$\alpha_1$ contraction</td>
</tr>
</tbody>
</table>
Summary:
Adrenoceptors (adrenergic receptors)

\(\alpha\) receptors

- \(\alpha_1\) receptors:
  (vasoconstriction: increased peripheral resistance, BP \(\uparrow\); contraction of radial muscle of iris: mydriasis)

- \(\alpha_2\) receptors:
  (CNS, presynaptic membranes of adrenergic nerves: vasodilatation, inhibition of NE release; inhibition of insulin release)
Summary:
Adrenoceptors (adrenergic receptors)

\( \beta \) receptors

- \( \beta_1 \) receptors (contractility ↑, automaticity ↑, conduction ↑, oxygen-consumption ↑, cardiac output ↑: heart stimulation; increased lipolysis)

- \( \beta_2 \) receptors (relaxation of bronchial smooth muscles: bronchodilation; slight vasodilation; increased muscle and liver glycogenolysis; increased release of glucagon)

- \( \beta_3 \) receptors (lipolysis, thermogenesis)
Drug actions and classification

1. Mechanisms of drug actions

1.1 Direct actions on the receptors

- Agonists
- Antagonists

1.2 Indirect actions via affecting transmitters

- Synthesis (L-dopa)
- Transport and storage (imipramine, reserpine)
- Release (ephedrine, amphetamine)
- Inactivation (MAOI)

1.3 Mimetics and antagonists

(1) Mimetics

- direct-acting: receptor agonists
- indirect-acting: increasing amounts and/or effects of transmitters

(2) Antagonists

- direct-acting: receptor antagonists
- indirect-acting: decreasing amounts and/or effects of transmitters
Structure-activity relationship of catecholamines and related compounds
**Sympathomimetic amines**

- **Catecholamine**
  - High potency in activating $\alpha$ or $\beta$ receptors
  - Rapid inactivation by COMT and by MAO
  - Poor penetration into the CNS

- **Non-catecholamine**
  - Indirect-acting by causing the release of stored catecholamine.
  - Not inactivated by COMT; some are poor substrate for MAO (orally active, a prolonged duration of action)
  - Greater access to the CNS
The mode of action of sympathomimetic drugs

- **Direct mode**
  - e.g. Norepinephrine
  - epinephrine
  - isoproterenol

- **Indirect mode**
  - Enhances release of stored catecholamines
    - e.g. amphetamine
  - Inhibition of reuptake of released catecholamines
    - e.g. cocaine
  - Inhibition of MAO
    - e.g. pargyline

- **Mixed mode**
  - e.g. ephedrine
Adrenoceptors

A. α Adrenoceptors

<table>
<thead>
<tr>
<th></th>
<th>Epinephrine</th>
<th>Norepinephrine</th>
<th>Isoproterenol</th>
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</thead>
<tbody>
<tr>
<td>α Receptor</td>
<td><img src="image1" alt="Diagram" /></td>
<td><img src="image2" alt="Diagram" /></td>
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<tr>
<td>High affinity</td>
<td><img src="image7" alt="Diagram" /></td>
<td><img src="image8" alt="Diagram" /></td>
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B. β Adrenoceptors

<table>
<thead>
<tr>
<th></th>
<th>Epinephrine</th>
<th>Isoproterenol</th>
<th>Norepinephrine</th>
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<tbody>
<tr>
<td>β Receptor</td>
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<td><img src="image11" alt="Diagram" /></td>
<td><img src="image12" alt="Diagram" /></td>
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<td><img src="image14" alt="Diagram" /></td>
<td><img src="image15" alt="Diagram" /></td>
</tr>
<tr>
<td>High affinity</td>
<td><img src="image16" alt="Diagram" /></td>
<td><img src="image17" alt="Diagram" /></td>
<td><img src="image18" alt="Diagram" /></td>
</tr>
</tbody>
</table>

Low affinity
Drug actions and classification

Adrenoceptor agonists

(1) $\alpha$, $\beta$ receptor agonists
- epinephrine (adrenaline), dopamine, ephedrine

(2) $\alpha$ receptor agonists
- $\alpha_1 \alpha_2$ receptor agonists: norepinephrine
- $\alpha_1$ receptor agonists: phenylephrine
- $\alpha_2$ receptor agonists: clonidine

(3) $\beta$ receptor agonists:
- $\beta_1 \beta_2$ receptor agonists: isoproterenol
- $\beta_1$ receptor agonists: dobutamine
- $\beta_2$ receptor agonists: salbutenol
Pharmacological effects

α₁, α₂, β₁, β₂ receptor agonists

(1) Cardiac effects

• β₁: contractility ↑ (positive inotropic),
  HR ↑ (positive chronotropic),
  cardiac output ↑,
  oxygen consumption ↑,
  inducing arrhythmia

(2) Vascular effects

• α₁: vasoconstriction (skin, mucous, viscera),
  especially at larger doses
• β₂: vasodilatation of skeletal muscles
  and coronary vessels
Concentration-dependent response in vascular smooth muscle to epinephrine

Predominant Effects

low [EPI] $\beta_2 > \alpha$

high [EPI] $\alpha > \beta_2$
Epinephrine, Adrenaline

(3) Blood pressure
• Systolic BP ↑, Diastolic BP ↓ (slight)

(4) Respiratory
• $\beta_2$: dilatation of bronchial smooth muscles (Bronchodilatation)
• $\alpha_1$: reducing congestion and edema of bronchial mucosa

(5) Metabolic effects
• blood glucose ↑ (hyperglycemia);
  free fatty acids ↑ (lipolysis)
Effects of catecholamines (therapeutic doses)

Predominant Effects:
- **NE**: $\alpha$ & $\beta_1$ effects
- **EPI**: $\beta_1$, $\beta_2$ then at higher concentrations $\alpha$ effects predominate
- **ISO**: $\beta_1$ and $\beta_2$
Epinephrine, Adrenaline

Clinical uses

Systematic uses:
- Cardiac arrest
- Anaphylactic shock
- Acute bronchial asthma

Topical uses:
- Adjuvant of local anesthesia
- Bleeding
Epinephrine, Adrenaline

**Adverse effects**

(1) **Cardiac arrhythmias**

(2) **Hemorrhage** (cerebral or subarachnoid):
   - reason: a marked elevation of BP

(3) **Central excitation**: anxiety, headache...

(4) **Contraindications**: heart diseases, hypertension, coronary arterial disease, arteriosclerosis, hyperthyroidism
Dopamine (多巴胺):

DIRECT

Pharmacological effects:
α, β receptor, dopaminergic receptor agonists

(1) Cardiac effects: β1 receptor, weak
(2) Vascular effects:
  DA receptor: vasodilatation of renal and mesenteric arteries, blood flow ↑(small doses);
  α1 receptor: vasoconstriction of skin, mesenteric vessels (larger doses)

(3) Renal effects: renal vasodilatation; natriuretic effects
Dopamine

Clinical uses
(1) Shock
• cardiac and septic shock
(2) Acute renal failure
• combined with furosemide

Adverse effects – short-lived
• tachycardia, arrhythmia, reduction in urine flow (renal vasoconstriction)
**Ephedrine** (麻黄碱): **MIXED**

- Promoting release of NE, weak agonist effects on $\alpha_1$, $\alpha_2$, $\beta_1$, $\beta_2$ receptors

**Properties:**
- chemically stable, orally effective;
- less potent but longer action duration;
- central stimulating: alertness $\uparrow$, fatigue $\downarrow$, prevents sleep (adverse effects);
- Tachyphylaxis (快速耐受).
Ephedrine

Clinical uses

(1) Prevention of hypotension: anesthetics
(2) Nasal decongestion: nasal drop
(3) Bronchial asthma: mild, chronic cases
(4) Relieving allergic disorders: urticaria (风疹), angioneurotic edema
Norepinephrine, Noradrenaline
(去甲肾上腺素): DIRECT

**Pharmacological effect**

$\alpha_1$, $\alpha_2$ receptor agonists

(1) **Vascular effects:**

- $\alpha_1$: vasoconstriction (skin, renal, brain, hepatic, mesenteric, etc.), blood flow ↓
- $\alpha_2$: inhibiting NE release
Actions of norepinephrine on post-synaptic ($\alpha_1$) and pre-synaptic ($\alpha_2$) receptors
Norepinephrine, Noradrenaline

(2) Blood pressure:
- Systolic BP ↑, Diastolic BP ↑ (especially at larger doses)

(3) Cardiac effects:
- weak direct stimulation ($\beta_1$); inhibition via reflex (in vivo)
- Net result: little cardiac stimulates
Effects of catecholamines (therapeutic doses)

Predominant Effects:
- **NE**: $\alpha$ & $\beta_1$ effects
- **EPI**: $\beta_1$, $\beta_2$ then at higher concentrations $\alpha$ effects predominate
- **ISO**: $\beta_1$ and $\beta_2$
**Clinical uses** *(limited therapeutic value)*

(1) **Shock**
- used in early phase of some types of shock:
  small doses and shorter duration
  *(dopamine is better; replaced by Metaraminol)*

(2) **Hypotension due to drug poisoning**
- especially for **chlorpromazine** *(氯丙嗪)*

(3) **Hemorrhage in upper alimentary tract**
- orally given after dilution
Adverse effects

(1) Ischemia and necrosis at the site of iv administration relieved by filtrating the area with phentolamine (α receptor antagonist)

(2) Acute renal failure avoiding larger doses and longer duration; monitoring urinary volume

(3) Contraindication hypertension, arteriosclerosis, heart diseases, severe urinary volume ↓, microcirculation disorders
\( \alpha_1 \) receptor agonists

**Methoxamine** 甲氧明：DIRECT>INDIRECT

**Phenylephrine** 去氧肾上腺素：DIRECT>INDIRECT

- Induces reflex bradycardia, used in hypotension, paroxysmal supraventricular tachycardia;

- **Phenylephrine**: Mydriasis, pupillary dilator muscles, no or less effect on intraocular pressure, short-acting (for several hours); act as a nasal decongestant
Clonidine

- **Clonidine**: DIRECT
  - **Uses**: antihypertensive drug; can be administered as transdermal patch (permits continuous administration)
  - **Mechanism of action**:
  - $\alpha_2$ - adrenergic partial agonist; actions predominantly in CNS
  - lowers blood pressure by inhibiting sympathetic vasomotor tone
  - **Adverse effects**: (iv administration may result in transient increase in blood pressure (activation of post-synaptic receptors); dry mouth, sedation

**$\alpha_2$ receptor agonists**
Isoproterenol, Isoprenaline

**Pharmacological effects:**

- **β₁, β₂ receptor agonists**

1. **Cardiac effects** ($β₁$ receptor)

2. **Vascular effects and blood pressure**
   - $β₂$ receptor: dilatation of skeletal muscles and coronary vessels;
     - $SP \uparrow$, $DP \leftrightarrow$ or $\downarrow$, pulse pressure $\uparrow$

3. **Bronchodilatation** ($β₂$ receptor)

4. **Metabolism**
   - Promoting effects as epinephrine
Effects of catecholamines (therapeutic doses)

Predominant Effects:
- **NE**: $\alpha$ & $\beta_1$ effects
- **EPI**: $\beta_1$, $\beta_2$ then at higher concentrations $\alpha$ effects predominate
- **ISO**: $\beta_1$ and $\beta_2$
Isoproterenol, Isoprenaline

Clinical uses

(1) Cardiac arrest / A-V block: in emergencies
(2) Shock / Bronchial asthma: replaced by other sympathomimetics

Adverse effects

(1) Heart stimulation, arrhythmia
(2) Contraindications: coronary heart disease, myocarditis, hyperthyroidism...
\( \beta_1 \) receptor agonists

*Dobutamine* (多巴酚丁胺): DIRECT

- **Heart failure** (after cardiac surgery or congestive HF or acute myocardial infarction; short-term treatment)

- **Cardiac stimulation**
**β₂ receptor agonists**

*Terbutaline* (特布他林): DIRECT

- **Uses:** Bronchial asthma
  
  dilation of bronchial smooth muscle; β₂ > β₁ agonist (partially selective): preferential activation of pulmonary β₂ receptors by inhalation.

  Use: Premature Labor (with ritodrine).

- **Adverse effects:**
  
  headache, cardiac stimulation and skeletal muscle fine tremor (β₂ receptors on presynaptic motor terminals; their activation enhances ACh release).
# INDIRECT-acting drugs (summary)

<table>
<thead>
<tr>
<th>Process</th>
<th>Compound</th>
<th>Site</th>
<th>Effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>Synthesis</td>
<td>α-Methyl-tyrosine</td>
<td>tyrosine hydroxylase</td>
<td>Depletes terminal NE</td>
</tr>
<tr>
<td>Storage</td>
<td>Reserpine</td>
<td>vesicular transporter</td>
<td>Depletes terminal NE</td>
</tr>
<tr>
<td>Release</td>
<td>tyramine</td>
<td>neuronal transporter</td>
<td>Increases synaptic NE</td>
</tr>
<tr>
<td>Neuronal reuptake</td>
<td>Cocaine</td>
<td>neuronal transporter</td>
<td>Increases synaptic NE</td>
</tr>
<tr>
<td>Neuronal reuptake and release</td>
<td>amphetamines</td>
<td>neuronal transporter</td>
<td>Increases synaptic NE</td>
</tr>
<tr>
<td>Metabolism</td>
<td>Pargyline (MAO-A and B inhibitor)</td>
<td>monoamine oxidase</td>
<td>Increases synaptic NE</td>
</tr>
<tr>
<td></td>
<td>Deprenyl (MAO B) inhibitor</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Adrenergic Receptor Antagonists

antagonists of NE at either $\alpha$ or $\beta$ receptors.

- **competitive antagonists** *(reversible)*, blocking endogenous norepinephrine
- **irreversible** antagonists

Antagonist characteristics:
- receptor occupancy *(binding affinity)*
- no receptor activation *(no efficacy)*

- nonselective and selective drugs available for both the $\alpha$ or $\beta$ receptors.
Drug actions and classification

Adrenoceptor antagonists

(1) $\alpha$ receptor antagonists

- $\alpha_1 \alpha_2$ receptor antagonists:
  - short-acting: phentolamine (酚妥拉明)
  - long-acting: phenoxybenzamine (酚苄明)

- $\alpha_1$ receptor antagonists: prazosin (哌唑嗪)

- $\alpha_2$ receptor antagonists: yohimbine (育亨宾)
Drug actions and classification

Adrenoceptor antagonists

(2) \(\beta\) receptor antagonists
- \(\beta_1\beta_2\) receptor antagonists: propranolol (普萘洛尔)
- \(\beta_1\) receptor antagonists: atenolol (阿替洛尔)
- \(\beta_2\) receptor antagonists: butoxamine (布他沙明)

(3) \(\alpha, \beta\) receptor antagonists
- labetalol (拉贝洛尔)
**α-Adrenergic blockers** have no effect on the actions of *isoproterenol*, which is a pure β agonist.

<table>
<thead>
<tr>
<th>Catecholamine</th>
<th>Untreated control</th>
<th>Pre-treatment with an α blocker</th>
<th>Pre-treatment with a β blocker</th>
</tr>
</thead>
<tbody>
<tr>
<td>Isoproterenol</td>
<td>200</td>
<td></td>
<td>200</td>
</tr>
<tr>
<td>mm Hg</td>
<td>0</td>
<td></td>
<td>0</td>
</tr>
<tr>
<td>Epinephrine</td>
<td>200</td>
<td></td>
<td>200</td>
</tr>
<tr>
<td></td>
<td>0</td>
<td></td>
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</tr>
<tr>
<td>Norepinephrine</td>
<td>200</td>
<td></td>
<td>200</td>
</tr>
<tr>
<td></td>
<td>0</td>
<td></td>
<td>0</td>
</tr>
</tbody>
</table>

**α-Adrenergic blockers** reverse the vasoconstrictive action of epinephrine.
Epinephrine reversal

\(\alpha\) antagonist epinephrine

BP

Epinephrine reversal

(adrenaline reversal)
Phentolamine (酚妥拉明)

- competitive, nonselective ($\alpha_1$, $\alpha_2$ receptor antagonists)

**Pharmacological effects**

1. **Vasodilatation**
   - Blocking $\alpha_1$ receptor: vasodilation in both arteriolar resistance vessels and veins

2. **Cardiac Stimulation**
   - Reflex; blocking $\alpha_2$ receptor $\sim$ NE release $\uparrow$

3. **Cholinergic and histamine-like effects**
   - Contraction of GI smooth muscles,
   - Gastric acid secretion $\uparrow$
Phentolamine

Clinical uses

(1) • Hypertension from pheochromocytoma (short term use).
• pre- and post-operation of pheochromocytoma
• Diagnostic test for pheochromocytoma

(2) Peripheral vascular diseases
• Acrocyanosis, Raynaud’s disease

(3) Local vasoconstrictor extravasation

Major Adverse effects – postural hypotension, reflex tachycardia, arrhythmia, angina pectoris, GI reactions
**Pheochromocytoma** is a rare catecholamine-secreting tumor derived from chromaffin cells of the adrenal medulla that produces excess epinephrine.

- Hypertension & Crises
- Elevated Metabolic Rate
  - heat intolerance
  - excessive sweating
  - weight loss
- Temporarily manage with
  - adrenergic antagonists ($\alpha_1$ & $\pm \beta$)
Pheochromocytoma
**Phenoxybenzamine** (酚苄明)

- Irreversible, nonselective (\(\alpha_1\) and \(\alpha_2\) antagonists)
- Long-acting
- Similar to phentolamine in actions and clinical uses
\( \alpha_1 \) receptor antagonists

- prazosin
  treatment for hypertension

\( \alpha_2 \) receptor antagonists

- yohimbine
  for research use only
β receptor antagonists

ADME

• First-pass elimination,
  low bioavailability: propranolol

• Hepatic metabolism and renal excretion,
  hepatic and renal functions alter the effects of the drugs and result in large individual variation

• So, dose individualization is necessary.
Effects of an $\beta$ AR Antagonist


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β receptor antagonists

Pharmacological effects

(1) β receptor blockade

A. Cardiovascular effects:

- **Depressing heart:** reduction in HR, A-V conduction, automaticity, cardiac output, oxygen consumption
- **Hypotension:** peripheral blood flow ↓, hypotensive effects in hypertensive patients
\[ \beta \text{ receptor antagonists} \]

(1) \( \beta \) receptor blockade

B. Bronchial smooth muscles
- induces bronchial smooth muscle contraction in asthmatic patients

C. Metabolism
- lipolysis \( \downarrow \), glycogenolysis \( \downarrow \), potentiating insulin effects \( \sim \) hypoglycemia

D. Renin secretion
- decreasing secretion of renin
β receptor antagonists

(2) Intrinsic sympathomimetic effects
• Partial agonists: e.g. pindolol, acebutolol

(3) Membrane-stabilizing effects
• Larger doses of some drugs: quinidine-like effects, Na⁺ channel block

(4) Others
• Lowering intraocular pressure;
• Inhibiting platelet aggregation
**β receptor antagonists**

**Clinical uses**

1. **Arrhythmia**: supraventricular, sympathetic activity ↑
2. **Hypertension**
3. **Angina pectoris and myocardial infarction**
4. **Chronic heart failure**
5. **Others**: hyperthyroidism, migraine headache, glaucoma (timolol) ...
**β receptor antagonists**

**Adverse effects**

1. **Heart depression:** contraindicated in heart failure, severe A-V block, sinus bradycardia
2. **Worsening of asthma:** contraindicated in bronchial asthmatic patients
3. **Withdrawal syndrome:** up-regulation of the receptors
4. **Worsening of peripheral vascular constriction**
5. **Others:** central depression, hypoglycemia, etc.
Propranolol （普萘洛尔）

- $\beta_1$, $\beta_2$ receptor blocking
- no intrinsic activity
- first-elimination after oral administration, individual variation of bioavailability

Timolol （噻吗洛尔）

- For treatment of glaucoma (wide-angle)
Atenolol  （阿替洛尔）
Metoprolol  （美托洛尔）

- \( \beta_1 \) receptor antagonists, no intrinsic activity.
- Atenolol: longer t\(_{1/2} \), once daily
- Usually used for treatment of hypertension
α, β receptor antagonists

Labetalol （拉贝洛尔）

- α, β receptor blocking, β > α
- usually used for treatment of hypertension
## summary

<table>
<thead>
<tr>
<th>Agonist</th>
<th>Receptor specificity</th>
<th>Therapeutic uses</th>
<th>Adverse effects/ contraindications</th>
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<tbody>
<tr>
<td>epinephrine</td>
<td>α1,α2 β1,β2</td>
<td>• Acute asthma,</td>
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<td></td>
<td></td>
<td>• anaphylactic shock,</td>
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<td></td>
<td></td>
<td>• in local anesthetics</td>
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<td></td>
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<td>• to increase duration of action</td>
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<tr>
<td>norepinephrine</td>
<td>α1,α2 (β1)</td>
<td>• shock</td>
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<tr>
<td>isoproterenol</td>
<td>β1,β2</td>
<td>• Asthma</td>
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<td></td>
<td></td>
<td>• As cardiac stimulant</td>
<td></td>
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<tr>
<td>dopamine</td>
<td>Dopaminergic α, β</td>
<td>• Shock</td>
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<tr>
<td></td>
<td></td>
<td>• Congestive heart failure</td>
<td></td>
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<tr>
<td>dobutamine</td>
<td>β1</td>
<td>• Heart failure</td>
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<tr>
<td>Ephedrine</td>
<td>α, β CNS</td>
<td>• asthma</td>
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<td></td>
<td></td>
<td>• as a nasal decongestant</td>
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<tr>
<td>Metaraminol</td>
<td>α</td>
<td>• Shock</td>
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<tr>
<td></td>
<td></td>
<td>• hypotension</td>
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<tr>
<td>Phenylephrine</td>
<td>α1</td>
<td>• supraventricular tachycardia</td>
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<td>• glaucoma</td>
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<td>• as a nasal decongestant</td>
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<tr>
<td>Methoxamien</td>
<td>α1</td>
<td>• supraventricular tachycardia</td>
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<tr>
<td>Clonidine</td>
<td>α2</td>
<td>• hypertension</td>
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<tr>
<td>Salbutemol</td>
<td>β2</td>
<td>• Asthma</td>
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<td>Terbutaline</td>
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<td>• Premature labor</td>
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<td>Ritodrine</td>
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<td>Albuterol</td>
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<tr>
<td>Phentolamine Phenoxybenzamine</td>
<td>α1, α2</td>
<td>• pheochromocytoma</td>
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<td></td>
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<td>• Peripheral vascular diseases</td>
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<td>• Local vasoconstrictor extravasation</td>
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<tr>
<td>prazosin</td>
<td>α1</td>
<td>• hypertension</td>
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</tr>
<tr>
<td>propranolol</td>
<td>β1, β2</td>
<td>• Hypertension</td>
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<td>• Glaucoma</td>
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<td>• Migraine</td>
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<td>• Hyperthyroidism</td>
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<td>• Angina pectoris</td>
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<td>• Myocardial infarction</td>
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<td>timolol</td>
<td>β1, β2</td>
<td>• Glaucoma</td>
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<td>• hypertension</td>
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<td>Atenolol Metoprolol</td>
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Therapeutic Uses of $\alpha_1 \ (\pm \beta)$ AR Agonists

1. Hypotension
- To preserve adequate blood perfusion to heart, brain or kidneys in cases of hemorrhage, overdose of antihypertensive drugs or spinal cord injuries.

- Short duration of treatment: NE, phenylephrine, methoxamine, ephedrine ($\alpha_1$ AR agonists).

2. Shock
- Inadequate perfusion to tissues as a consequence of hypovolemia, cardiac failure, or altered vascular resistance.

- Usually associated with hypotension.

- Use of $\alpha_1$-adrenergic agonists to increase peripheral vascular resistance, and $\beta_1$-adrenergic agonists to improve cardiac function.

3. Cardiogenic Shock
- Massive myocardial infarction.

- Stimulation of cardiac $\beta_1$-adrenergic receptors is needed: isoproterenol, norepinephrine, epinephrine, dobutamine, dopamine.
Therapeutic Uses of $\alpha_1$ (±$\beta$) AR Agonists

4. Local Vascular Effects
-Reduction of regional blood flow in surgery (nose, throat, larynx) to improve visualization by limiting hemorrhage.

-Epinephrine retards the absorption of local anesthetics and increases the duration of anesthesia (vasoconstrictor effect of epinephrine)

5. Nasal Decongestion
- $\alpha_1$-Adrenergic agonists are used as nasal decongestants.

-These drugs decrease the volume of the nasal mucosa and therefore reduce the resistance to airflow.

-Oxymetazoline, phenylephrine and ephedrine are commonly used.

6. Allergic Reactions
-Epinephrine (s.c.) is used in acute hypersensitivity reactions.

-Activation of $\beta$-adrenergic receptors on mast cells suppresses the release of histamine and leukotrienes.
1. Asthma

-Asthma is a condition of overreactive airways. Asthma attacks can make it very difficult to breath because of excess bronchoconstriction.

- $\beta_2$ AR agonists such as albuterol, metaproterenol and terbutaline are used.

-The drugs are administered by inhalation and are absorbed slowly, limiting their systemic side effects, and $\beta_2$ selectivity reduces cardiac stimulation.

2. Premature Labor

-When labor occurs prematurely (before 37 weeks), it is a risk to the fetus.

- $\beta_2$ AR agonists relax the smooth muscle of the uterus and help prevent premature delivery. The goal is to reach at least 37 weeks when the fetal lungs have matured.
1. Pheochromocytoma

2. Hypertension

-While not commonly used anymore, $\alpha_1$ blockers can be used to treat hypertension.

-Somewhat more common is the use of $\beta$ blockers. These work centrally (the most important effect – the mechanism is not completely understood) and peripherally (decrease heart rate some).

3. Heart Failure

-After a myocardial infarction, the SNS will be activated to increase the cardiac output from the remaining good heart tissue. This is good in the short-term, but long-term changes lead to cardiac hypertrophy and failure.

-Ironically, $\beta$ blockers reduce the incidence of sudden death from heart failure.
Other Important Catecholamine Drugs

- TH Inhibitor – α-methyl-ρ-tyrosine
- DBH Inhibitors – (no good selective ones)
- VMAT Inhibitors – reserpine & amphetamine
- False Transmitters – tyramine &
  \[ \alpha\text{-methyl-DOPA} \rightarrow \alpha\text{-methyl-NE} \]
- MAO Inhibitors – pargyline (nonselective), chlorgyline (MAOA), deprenyl (MAOB)
- NET Inhibitors – desipramine, reboxetine
- Neurotoxin – 6-hydroxydopamine, DSP-4