AUTONOMIC PHARMACOLOGY

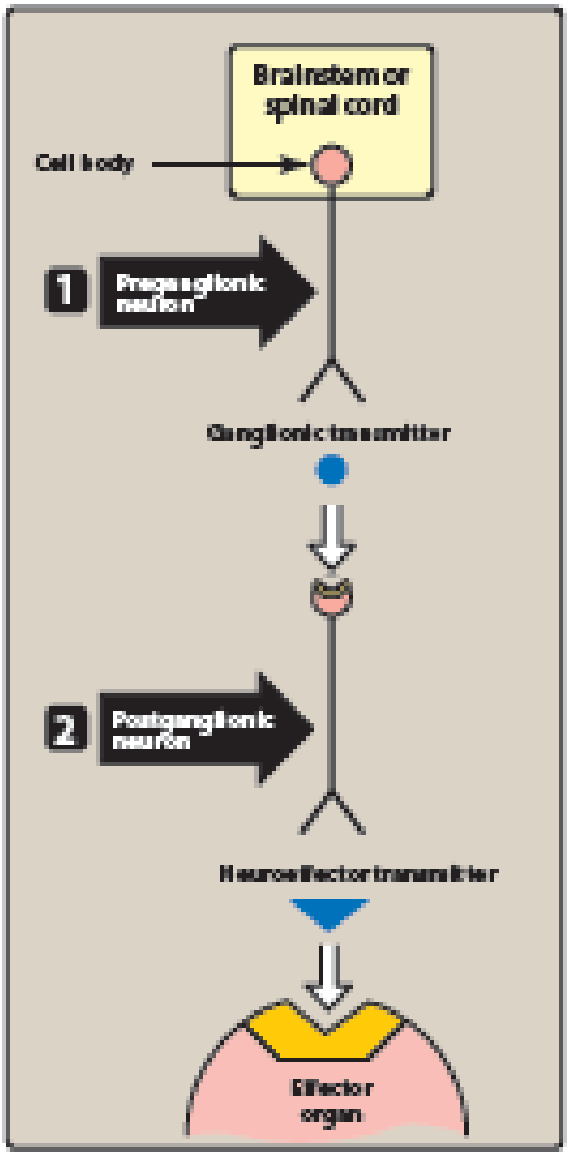
Introduction

The autonomic nervous system (ANS) regulates visceral functions that occur without conscious control. All visceral organs are innervated by ANS except skeletal muscles, being under the control of the somatic nervous system.

The ANS originates from CNS (brain and spinal cord). There are two divisions of the ANS, based on the type of efferent nerves: **Sympathetic** and **Parasympathetic.**

ANS

- Other names: Visceral, involuntary nervous system
- Composed of efferent neurons that innervate smooth muscle of effector organs:
  - Viscera
  - Cardiac muscle
  - Vasculature
  - Exocrine glands
- Controls digestion, cardiac output, blood flow, glandular secretions

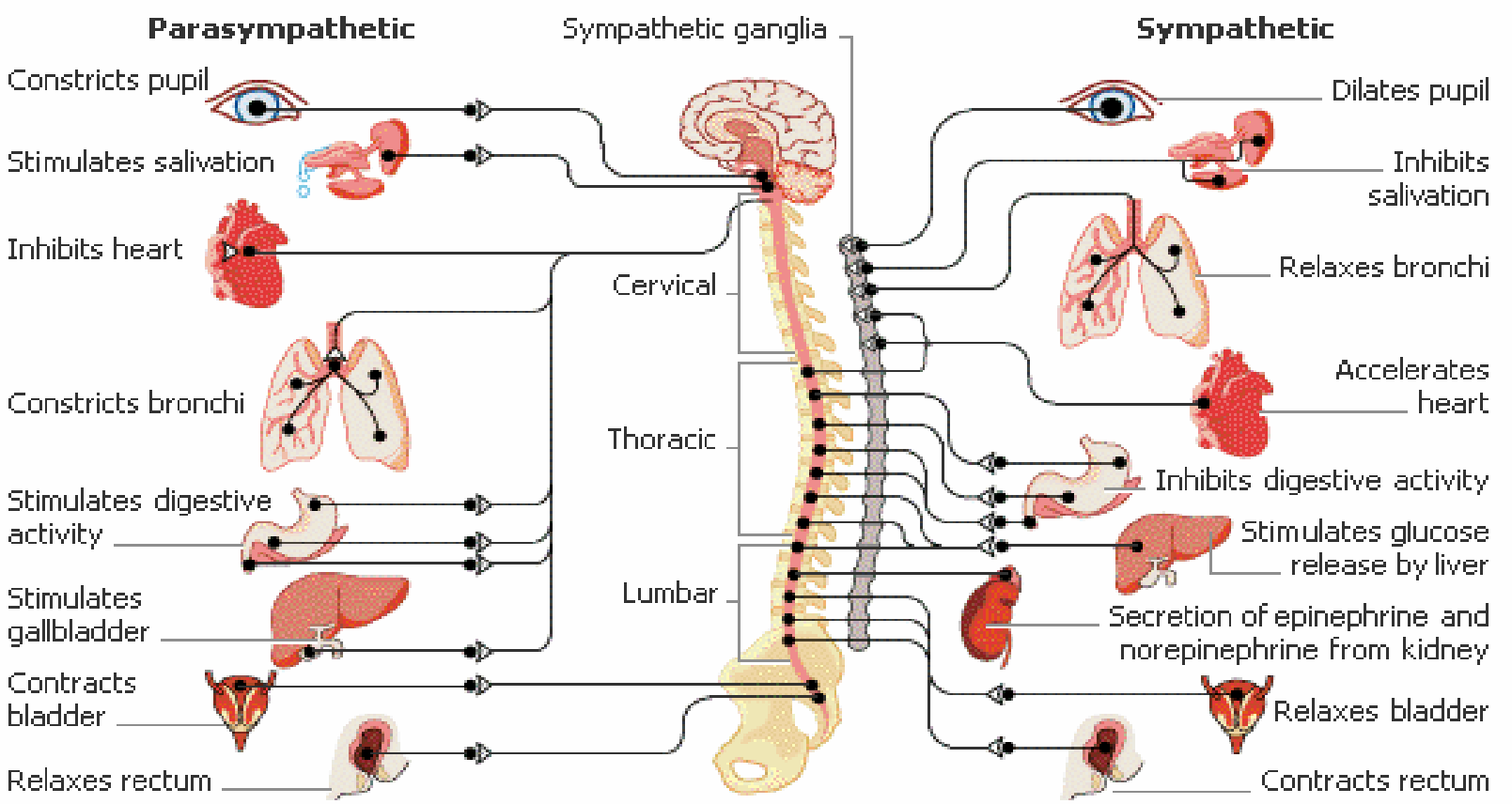


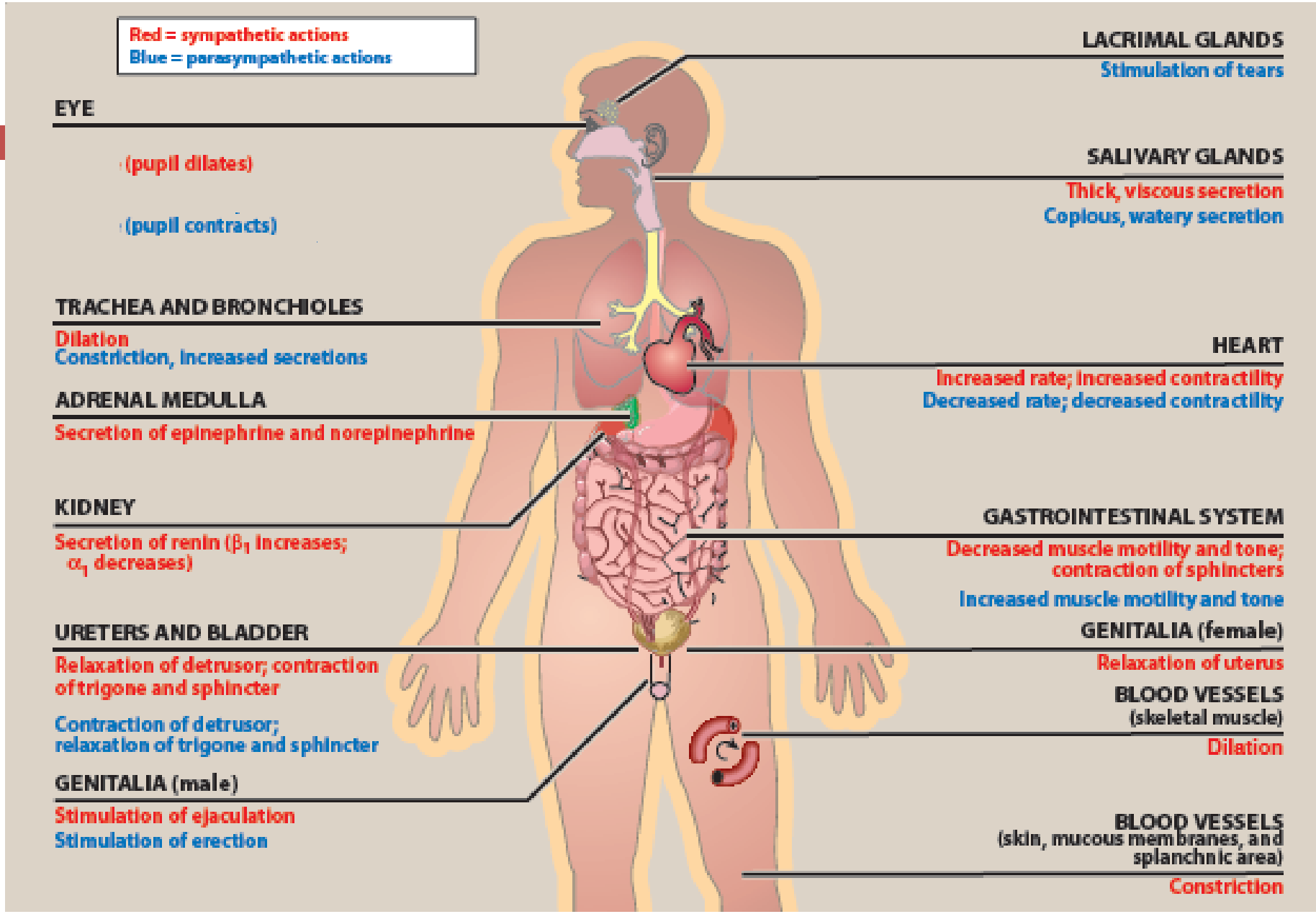
Sympathetic and Parasympathetic Divisions of ANS

Anatomically,

The sympathetic fibers originate from the first thoracic to the second or third lumbar segments of the spinal cord

The parasympathetic fibers originate from the midbrain, medulla oblongata, and the sacral part of the spinal cord.





Sympathetic nervous system

- Sympathetic nervous system:
  - Functions: adjusting response to stressful situations:
    - Fear
    - Trauma
    - Hypoglycemia
    - Cold
    - Exercise

Sympathetic nervous system

- Sympathetic stimulation:
  - Increases heart rate and blood pressure
  - Mobilizes energy stores of the body
  - Increases blood flow to skeletal muscles and heart
  - Reduces blood flow to skin and internal organs
  - Dilates pupil and bronchioles
  - Affects GI motility, bladder functions and sexual organs

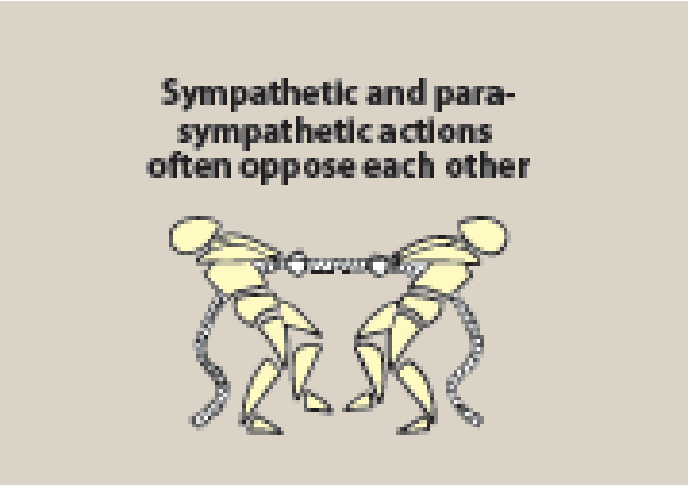
Sympathetic nervous system

- "Fight or flight" response: Changes in the body during emergencies.

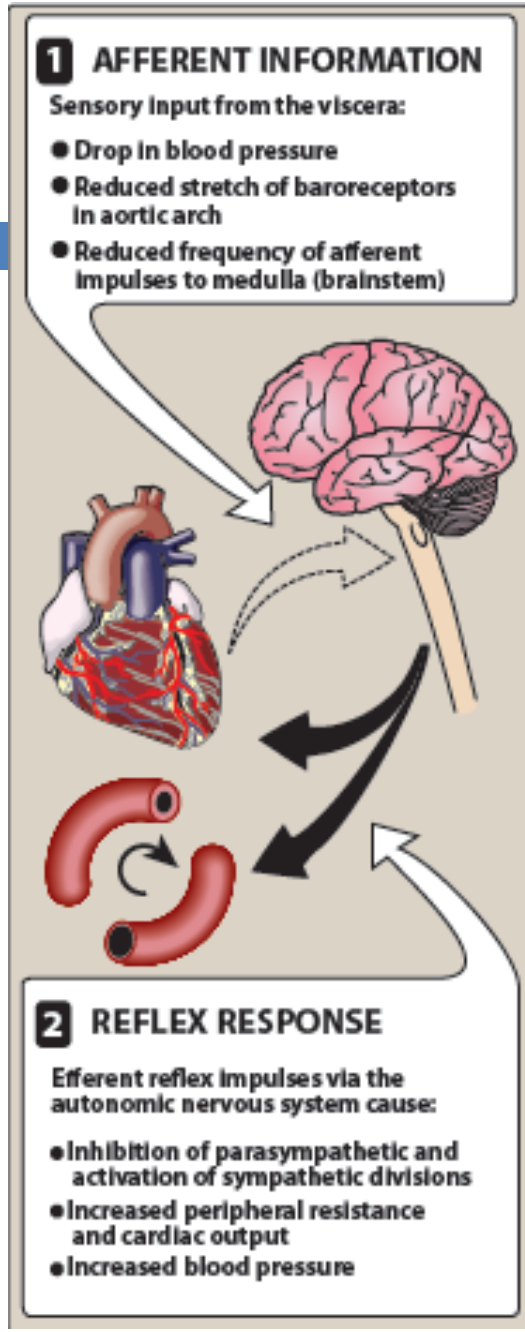
- Caused by:
  - Direct sympathetic activation of effector organs
  - Stimulation of the adrenal medulla to release epinephrine and norepinephrine

Parasympathetic nervous system

- Functions:
  - Maintaining homeostasis within the body
  - Maintains essential body functions like digestion and elimination of wastes
- "Rest and digest" situations



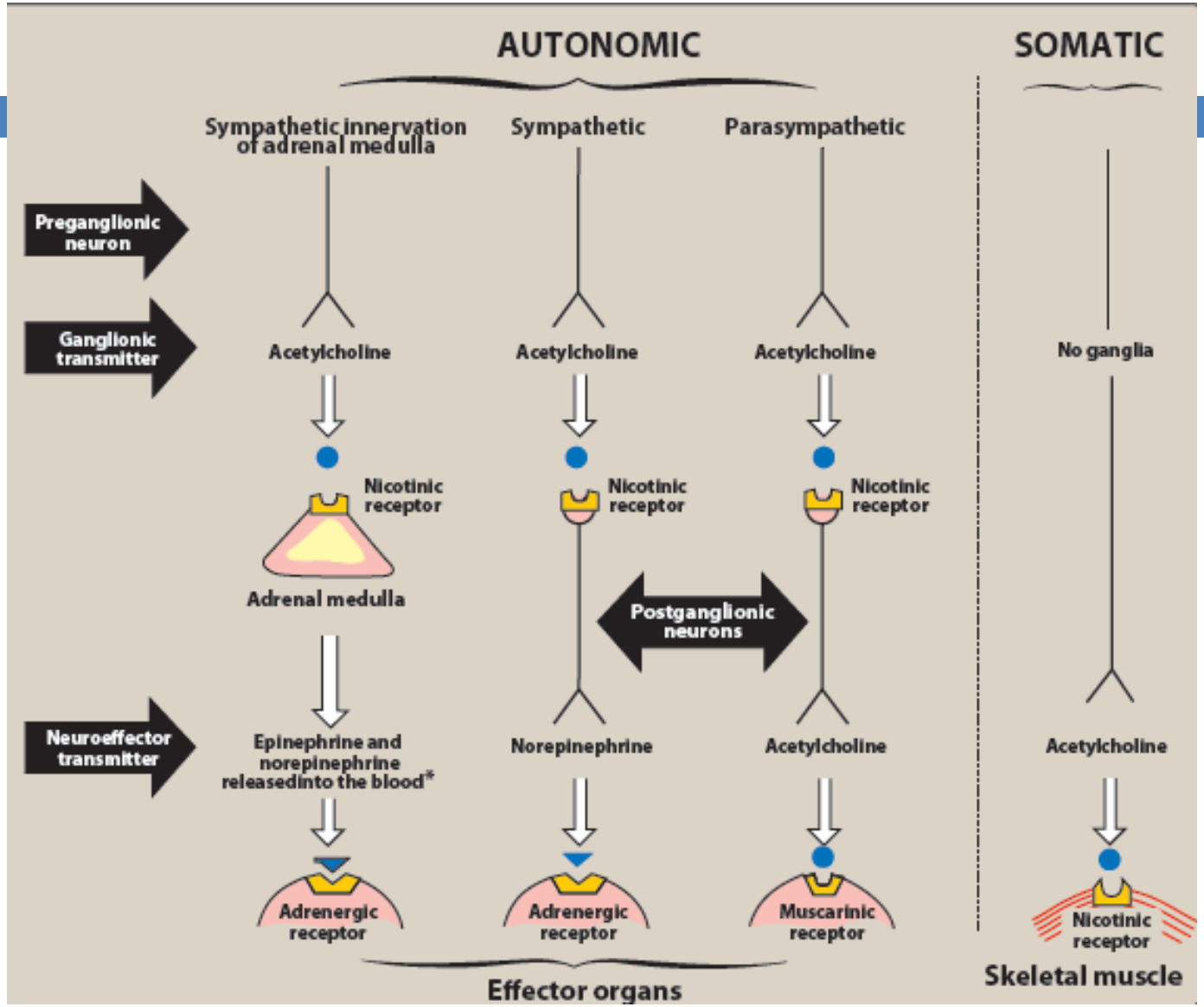
- CNS control over autonomic functions involves reflex responses without consciousness
- Stimuli causing strong feelings like rage, fear can modify ANS activities
- Most organs receive dual innervation by both systems



Types of Neurotransmitters

- Acetylcholine (ACh) → Cholinergic neurons
  - Transmission of nerve impulse across ganglia in sympathetic and parasympathetic systems
  - From postganglionic nerves to the effector organs in the parasympathetic system

- Norepinephrine (NE) and epinephrine → Adrenergic neurons
  - Transmission of nerve from postganglionic nerves to the effector organs in the sympathetic system



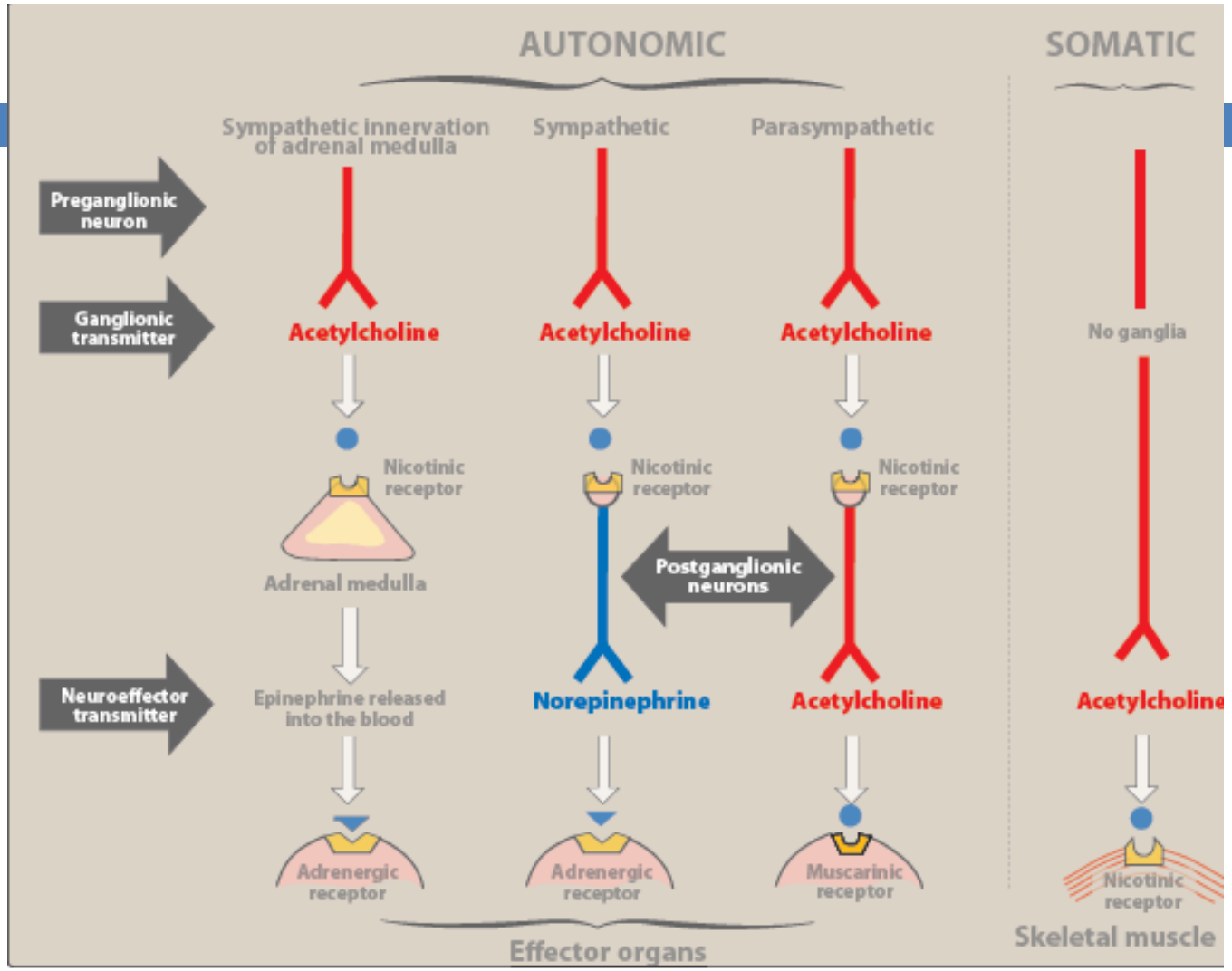


Figure 3.9
Cholinergic (red) and adrenergeric (blue) neurons found within the autonomic and somatic nervous systems.

Autonomic Receptors

ACh's effects are mediated through two subtypes of receptors: muscarinic (M) and nicotinic (N) receptors.

M receptors are present in the neuro-effector junction of the parasympathetic division.

N receptors are present in the autonomic ganglia of both sympathetic and parasympathetic divisions of the ANS and in the neuro-muscular junction.

NE and epinephrine's effects are mediated by two receptor subtypes: α and β.

α receptors are either α_1 or α_2.

α_1 receptors are present in the arteriolar smooth muscles. Activation leads to vasoconstriction.

α_2 receptors are found pre-ganglionically and in the CNS. Activation leads to decrease in the sympathetic flow from CNS.

β receptors are either β_1 or β_2.

β_1 receptors are found in the heart and kidney. Activation leads to increased H.R., force of contraction, and release of renin from kidney.

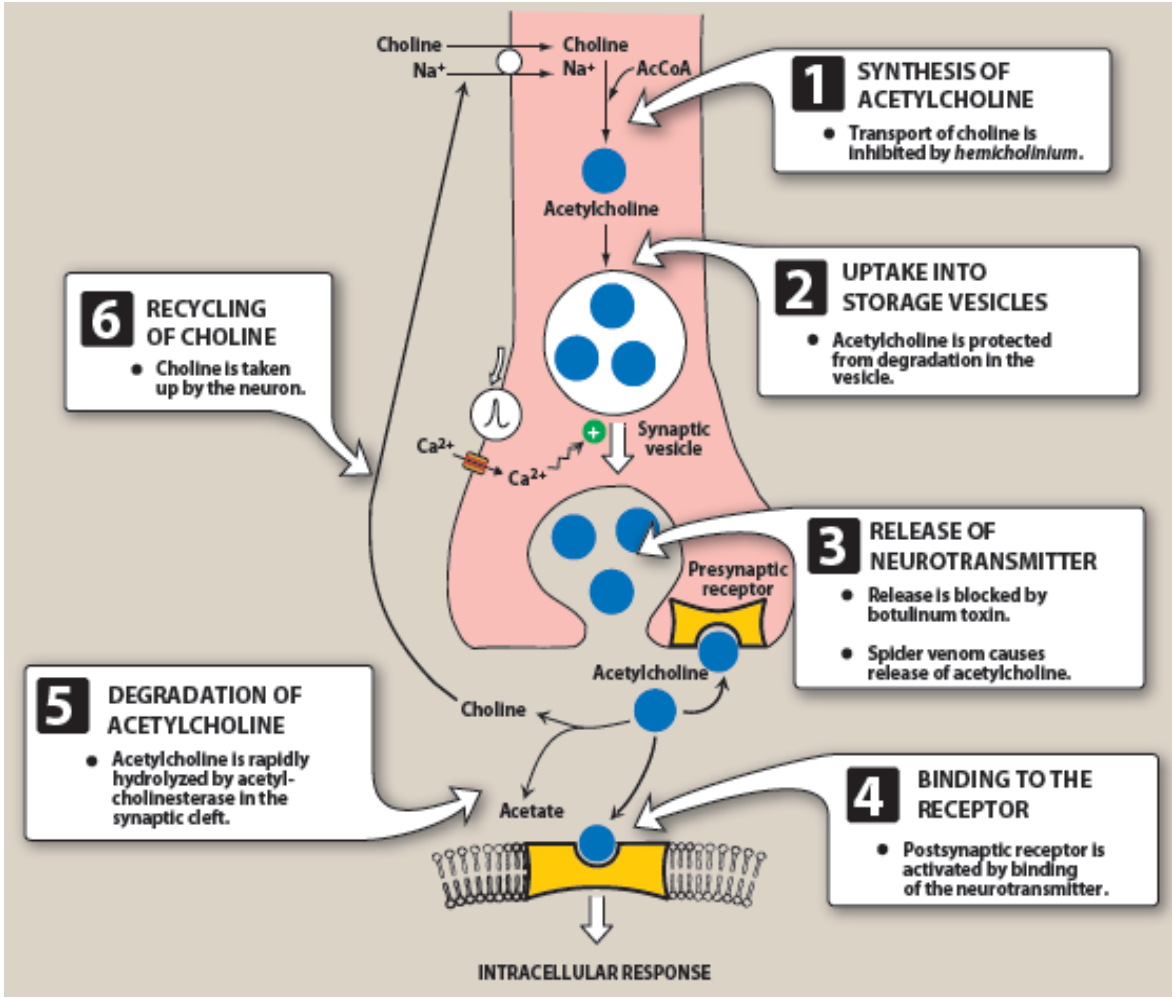
β_2 receptors are found in smooth muscles of blood vessels and bronchi. Activation leads to vasodilation and bronchodilation.

- Autonomic drugs: Drugs that produce their therapeutic effects by mimicking or altering the function of the autonomic nervous system (ANS)
  - Stimulating portions of the ANS
  - Blocking the actions of the autonomic nerves

- Divided based on the type of neuron involved in their mechanism of action
  - Cholinergic drugs: act on receptors activated by acetylcholine (ACh)
  - Adrenergic drugs: act on receptors stimulated by norepinephrine (NE) or epinephrine

Neurotransmission in the cholinergic neuron

1. Synthesis of ACh
2. Storage of ACh in vesicles
3. Release of ACh
4. Binding of ACh to the receptor
5. Degradation of ACh
6. Recycling of choline and acetate



Parasympathomimetics or Cholinergic agonists mimic the effects of parasympathetic nerve stimulation

Direct acting Cholinergic agonists

- Bind directly to cholinergic receptors
  - Acetylcholine
    - Rapidly inactivated by cholinesterase
      - ↓↓ Heart rate and cardiac output
      - ↓↓ Blood pressure
      - ↑↑ Salivary secretion and intestinal motility
      - Urinary expulsion
      - Miosis
    - No therapeutic use
  - Pilocarpine (stimulate muscaranic receptors)
    - Used to treat Glaucoma

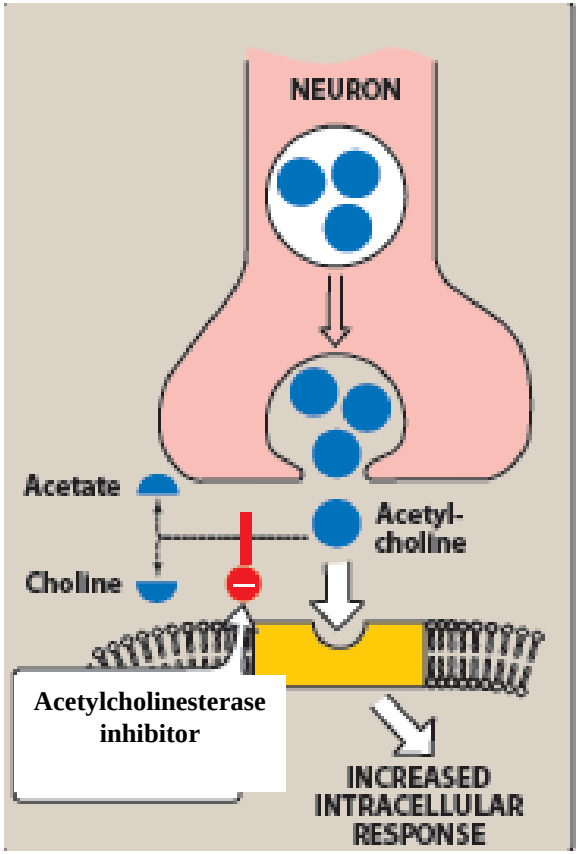
Cholinergic agonists Adverse effects

- Salivation
- Diaphoresis
- Nausea
- GI hyperactivity
- Diarrhea
- Miosis
- Urinary urgency

Indirect acting cholinergic agonists
Acetylcholinesterase inhibitors

- AChE is the enzyme that cleaves ACh to acetate and choline

- AChE inhibitors provide a cholinergic action by prolonging the time ACh is available at the cholinergic nerve endings



AChE inhibitors

- Edrophonium
  - Prototype short acting AChE inhibitor
- Physostigmine
  - Increases intestinal and bladder motility
  - Topically in the eye, produces miosis and lowering of intraocular pressure
  - Used to treat glaucoma
- Neostigmine
  - Used to stimulate the bladder and GI.

AChE inhibitors

- Myasthenia gravis: chronic autoimmune neuromuscular disease characterized by weakness of the skeletal muscles
  - Treatment
    - Neostigmine
    - Pyridostigmine

AChE inhibitors

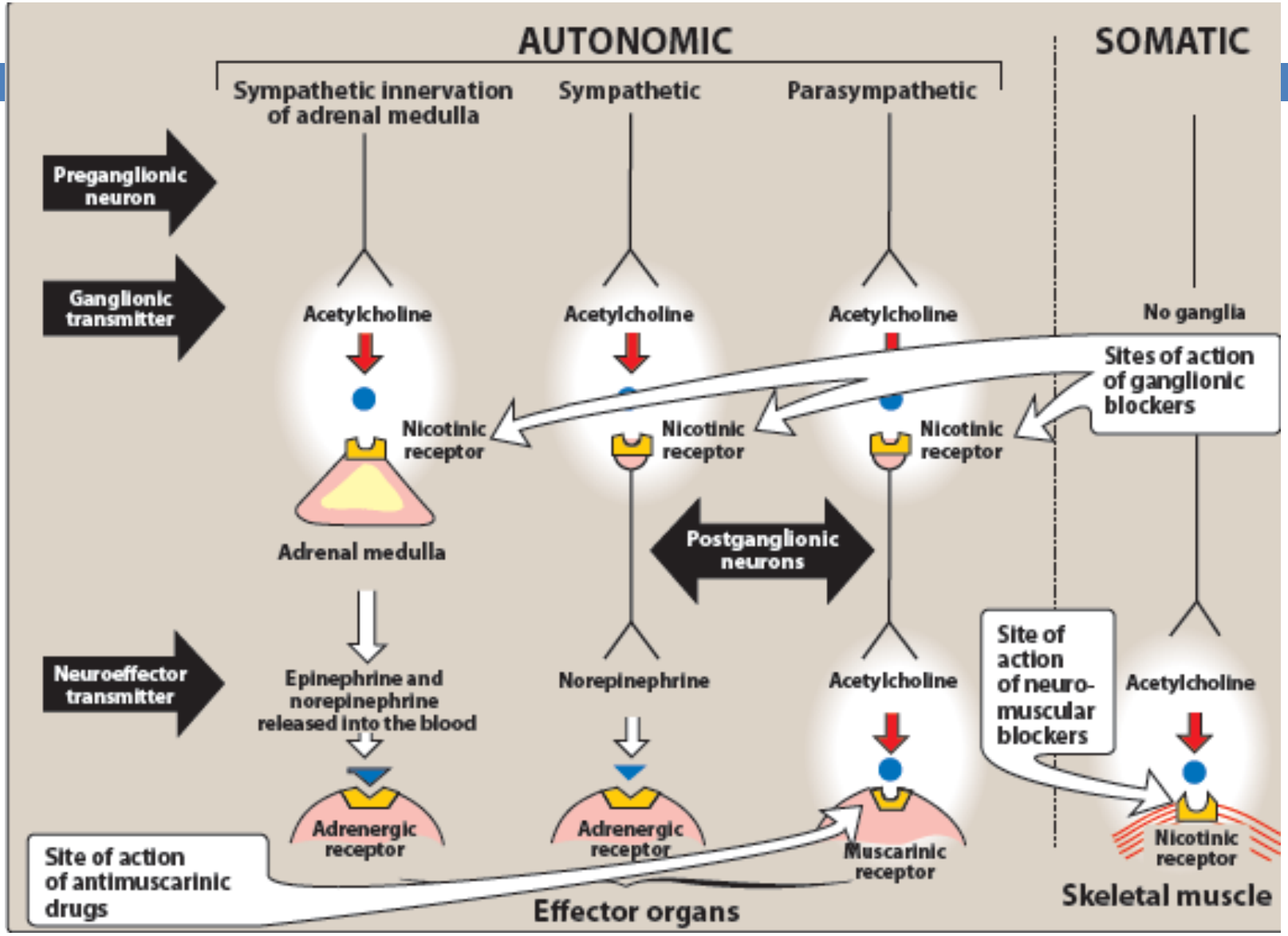
- Alzheimer's disease: Progressive memory loss with a decline in cholinergic neurons in the central nervous system
  - Treatment: AChE inhibitors
    - Tacrine (less used because of hepatotoxicity)
    - Donepezil
    - Rivastigmine
    - Galantamine

AChE inhibitors

- Organophosphate compounds
  - Irreversible inhibitors of AChE
  - Long-lasting increase in ACh
  - Many are extremely toxic and were developed by military as nerve agents
  - Some are insecticide
  - Cause paralysis of skeletal muscles including breathing difficulties and convulsions
  - Echothiophate
    - Ophthalmic solution for chronic treatment of glaucoma

Cholinergic antagonists

- Parasympatholytics or cholinergic antagonists or anticholinergic drugs.
- Drugs that bind to cholinergic receptors but they do not trigger the usual response
- Divided into 3 groups
  - Antimuscaranic agents
  - Ganglionic blockers
  - Neuromuscular blockers



Antimuscaranic agents

- Block muscaranic receptors
- Atropine
- Scopolamine
- Ipratropium
- Benztropine
- Trihexyphenedil

Atropine

- Mechanism: Binds to muscaranic receptors and prevents ACh from binding
- Effects:
  - Eye: Mydriatic
  - GI: Antispasmodic
  - Urinary retention
- Uses
    - Mydriatic agent.
    - Antispasmodic
    - Antidote for cholinergic agonists
    - Antisecretory prior to surgery

Atropine

- Side effects
  - Blurred vision
  - Tachycardia
  - Urinary retention
  - Constipation

Antimuscaranic agents

- Scopolamine: used for motion sickness
  - Side effects: similar to atropine
- Ipratropium: Inhaled bronchodilator
- Benztropine and tryhexyphenidyl: used for Parkinson's disease which is characterized by imbalance between ACh and dopamine in the brain

Ganglionic blockers

- Act on the nicotinic receptors of both sympathetic and parasympathetic ganglia
- No therapeutic application
- Nicotine
- Nicotine patches

Neuromuscular blockers

- Block cholinergic transmission between motor nerve endings and the nicotinic receptors on skeletal muscles
- Structural analogs of acetylcholine
- Used to relax skeletal muscles in anesthesia during surgery
- Also used in facilitating tracheal intubation

Nondepolarizing competitive neuromuscular blockers

- Curare and tubocurare
- No longer used for anesthesia
- Mechanism: bind to nicotinic receptors at the neuromuscular junction and prevent ACh binding
- Antidote: Neostigmine, Pyridostigmine

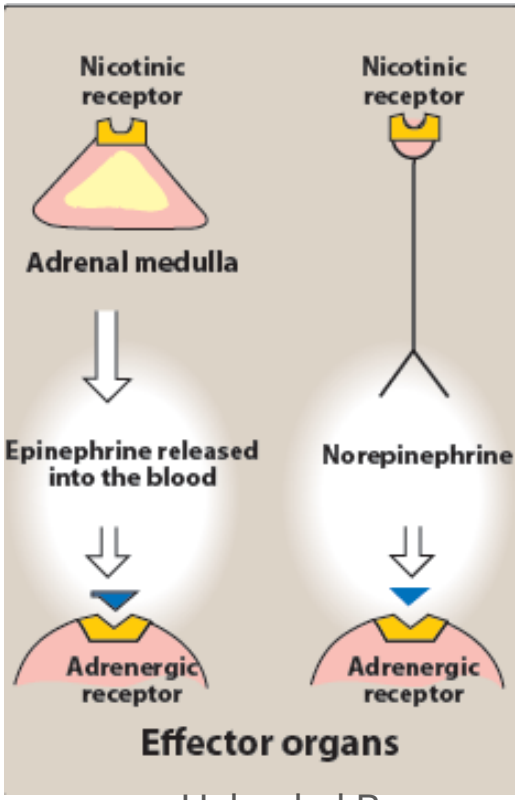
  (Cholinergic agonists)

Depolarizing neuromuscular blockers

- Succinyl choline
  - Attaches to nicotinic receptors and acts like ACh to depolarize the junction
  - Unlike ACh, they remain attached to the receptor providing constant stimulation of the receptor
  - Constant binding makes the receptor unresponsive to further impulse causing flaccid paralysis
  - Respiratory muscles paralyze last
  - Used for endotracheal intubation or electroconvulsive shock treatment
  - Adverse effects: Apnea

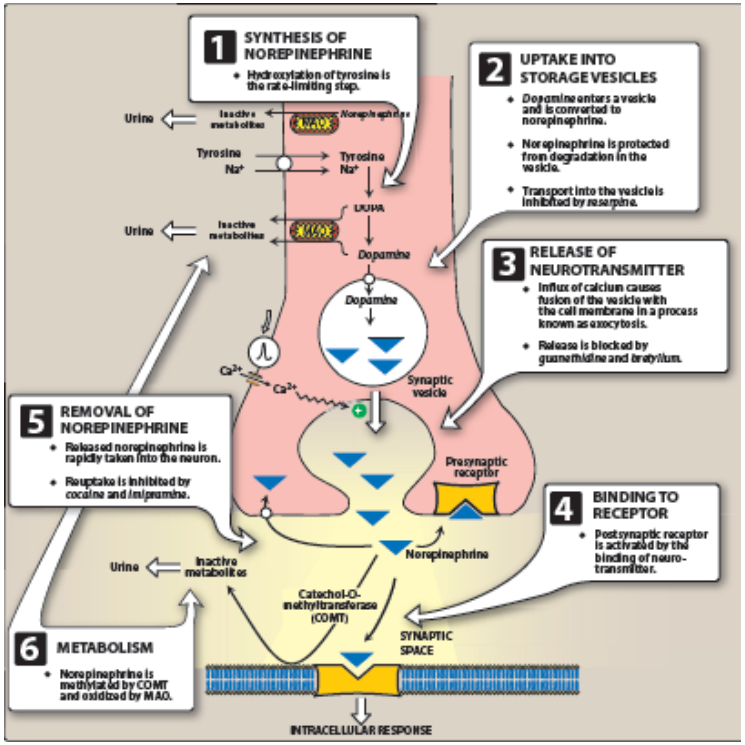
Adrenergic agonists

- Adrenrgic agonists; sympathomimetics: drugs that activate adrenoceptors



Adrenergic neurons

1. Synthesis of norepinephrine
2. Storage of NE in vesicles
3. Release of NE
4. Binding to receptors
5. Removal of NE
6. Metabolism by the enzymes Catechol O-methyltransferase (COMT) and monoamine oxidase (MAO)



Sympathomimetic Agents

These drugs exert their effects via direct stimulation of the adrenergic receptors (α_1, α_2, β_1, β_2) leading to a wide-range of pharmacological effects

Endogenous sympathomimetic drugs include:

- Epinephrine (adrenaline)
- Norepinephrine (noradrenaline)
- Dopamine

Adrenoceptors

- α_1
  - Present on postsynaptic membranes of effector organs
  - Constriction of smooth muscle, vasoconstriction, increased blood pressure, total peripheral resistance
- α_2
  - Located on presynaptic nerve endings
  - Stimulated α_2 cause feedback inhibition of NE release
- β_1 (Heart, Kidney)
  - Tachycardia, Increased myocardial contractility, Renin release
- β_2 (Bronchi, blood vessels, uterus)
  - Bronchodilation, Vasodilation, Relax uterine smooth muscles

Direct acting adrenergic agonists

- Epinephrine
- Norepinephrine
- Isoprotrenol
- Dopamine
- Albuterol
- Terbutaline

Direct acting adrenergic agonists

- Epinephrine
  - Strengthens the contractility of myocardium (β1)

    (positive inotrpic effect)
  - Increases cardiac output (β1)
  - Promotes renin release, increase blood pressure (β1)
  - Constriction of arterioles (α1)
  - Dilation of vessels going to liver and skeletal muscles (β2)
  - Bronchodilation (β2)
  - Hyperglycemia (β2)

Epinephrine

- Therapeutic uses
  - Bronchospasm, emergency for acute asthma
  - Anaphylactic shock
  - Anesthetics, to increase the duration of local anesthesia (vasoconstriction)
- Pharmacokinetics
  - Rapidly metabolized by COMT and MAO
  - Administered IV for emergencies
  - Can be administered IM or SC but not oral
- Adverse effects: cardiac arrhythmia, CNS effects: anxiety, tremor

Norepinephrine (NE)

- Acts mostly on α receptors
- Effects
  - Vasoconstriction
  - Increase total peripheral resistance
  - Increase blood pressure
- Therapeutic uses
  - Shock, NE increases blood pressure
- Administered IV
- Adverse effects: similar to epinephrine

Isoprotrenol

- β1 and β2 agonist, nonselective, rarely used
- Increase heart rate and force of contraction, increasing cardiac output
- Used to stimulate the heart in emergencies (cardiac arrest)
- Adverse effects: similar to epinephrine

Dopamine

- Activates α and β receptors
- Increases heart rate and force of contraction
- Used for
  - Shock treatment
  - Hypotension
  - Severe congestive heart failure
- Adverse effects
  - Hypertension
  - Arrhythmia

Direct acting adrenergic agonists

- Albuterol and terbutaline
  - β2 agonists
  - Used as bronchodilators, administered by a metered dose inhaler
  - Terbutaline is used as uterine relaxant to suppress premature labor

Indirect acting adrenergic agonists

- Inhibit reuptake of norepinephrine
- Amphetamine
  - CNS stimulant

Adverse effects of adrenergic agonists

Arrhythmias

Headache

Hyperactivity

Insomnia

Nausea

Tremors

Adrenergic antagonists, sympatholytics: bind to adrenoceptors but do not trigger the usual receptor mediated effects. Prevent the activation of receptors by epinephrine and norepinephrine.

α-Adrenergic blockers

- Affect blood pressure
- Phentolamine: used for pheochromocytoma (adrenal medulla tumor)
- Prazocin: used for hypertension and benign prostatic hyperplasia
- Adverse effects
  - Tachycardia

β-Adrenergic blockers

- Uses
  - Hypertension
  - Angina
  - Cardiac arrhythmias
  - Myocardial infarction
  - Congestive heart failure

Propranolol

- Non selective β antagonist (blocks β1 and β2)
- Reduces cardiac output and heart rate
- Reduces blood pressure
- Bronchoconstriction (β2)
- Uses
  - Hypertension
  - Migraine
  - Angina
  - Myocardial infarction
- Adverse effects
  - Bronchoconstriction
  - Arrhythmia

Adrenergic antagonists

- Timolol
  - Blocks β1 and β2 adrenoceptors
  - Used topically for decreasing intraocular pressure in glaucoma
- Atenolol, metoprolol
  - Selective β1 antagonists
  - No bronchoconstriction side effects (no β2 effects)
  - Lowers blood pressure
  - Uses: hypertension with impaired pulmonary function
- Labetalol and carvedilol
  - Block α1 and β receptors, reducing blood pressure
  - Used for hypertension

Drugs affecting neurotransmitter uptake

- Cocaine
  - Highly addictive and abused
  - Blocks reuptake of norepinephrine, serotonin and dopamine into presynaptic neurons