Autonomic Pharmacology

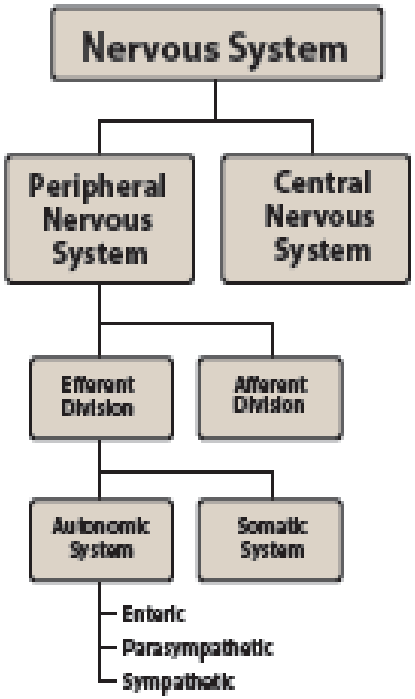
Autonomic nervous system (ANS)

- ANS along with the endocrine system coordinate the regulation and integration of bodily functions

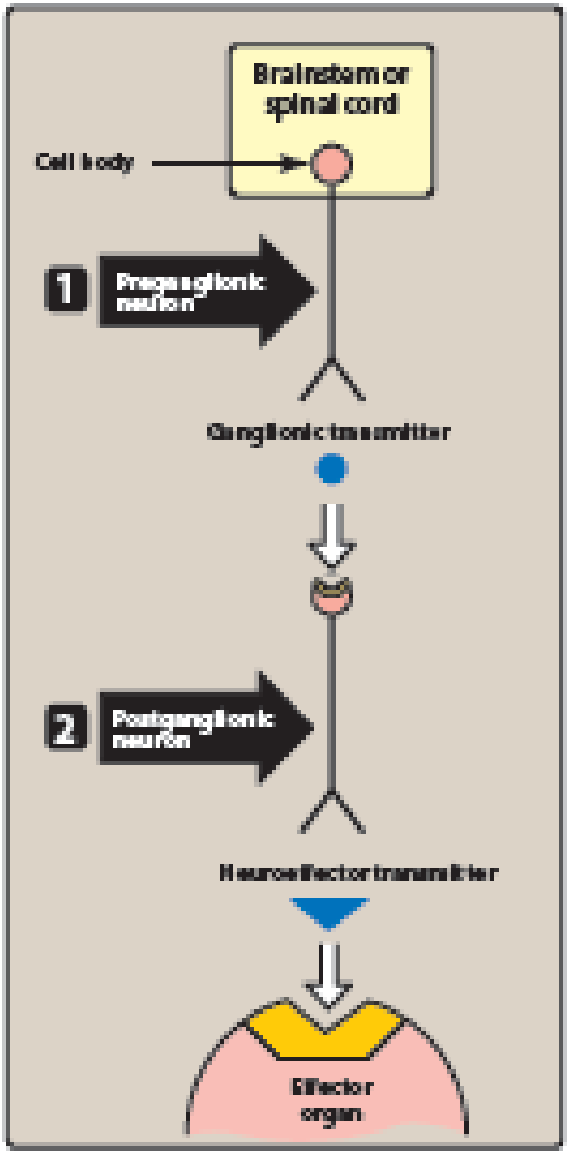
- Autonomic drugs: Drugs that produce their therapeutic effects by mimicking or altering the functions of the ANS

ANS

- Visceral, vegetative, involuntary nervous system
- Regulates everyday requirements of vital bodily functions without the conscious participation of the mind
- Composed of efferent neurons innervating smooth muscles of viscera, cardiac muscle, vasculature and exocrine glands
- ANS controls digestion, cardiac output, blood flow and glandular secretions



- Efferent neurons: carry nerve impulses from the CNS to effector organs
  - Sympathetic neurons
  - Parasympathetic neurons
  - Enteric neurons: fibers that innervate GIT, pancreas and gall bladder



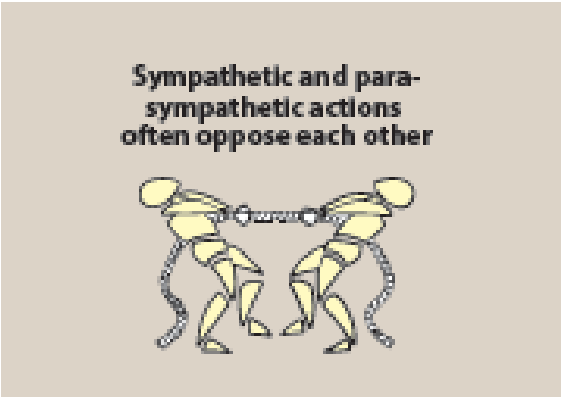
ANS

- Sympathetic nervous system: adjusts response to stressful situations like fear, trauma, hypoglycemia, cold and exercise
  - Fight or Flight response

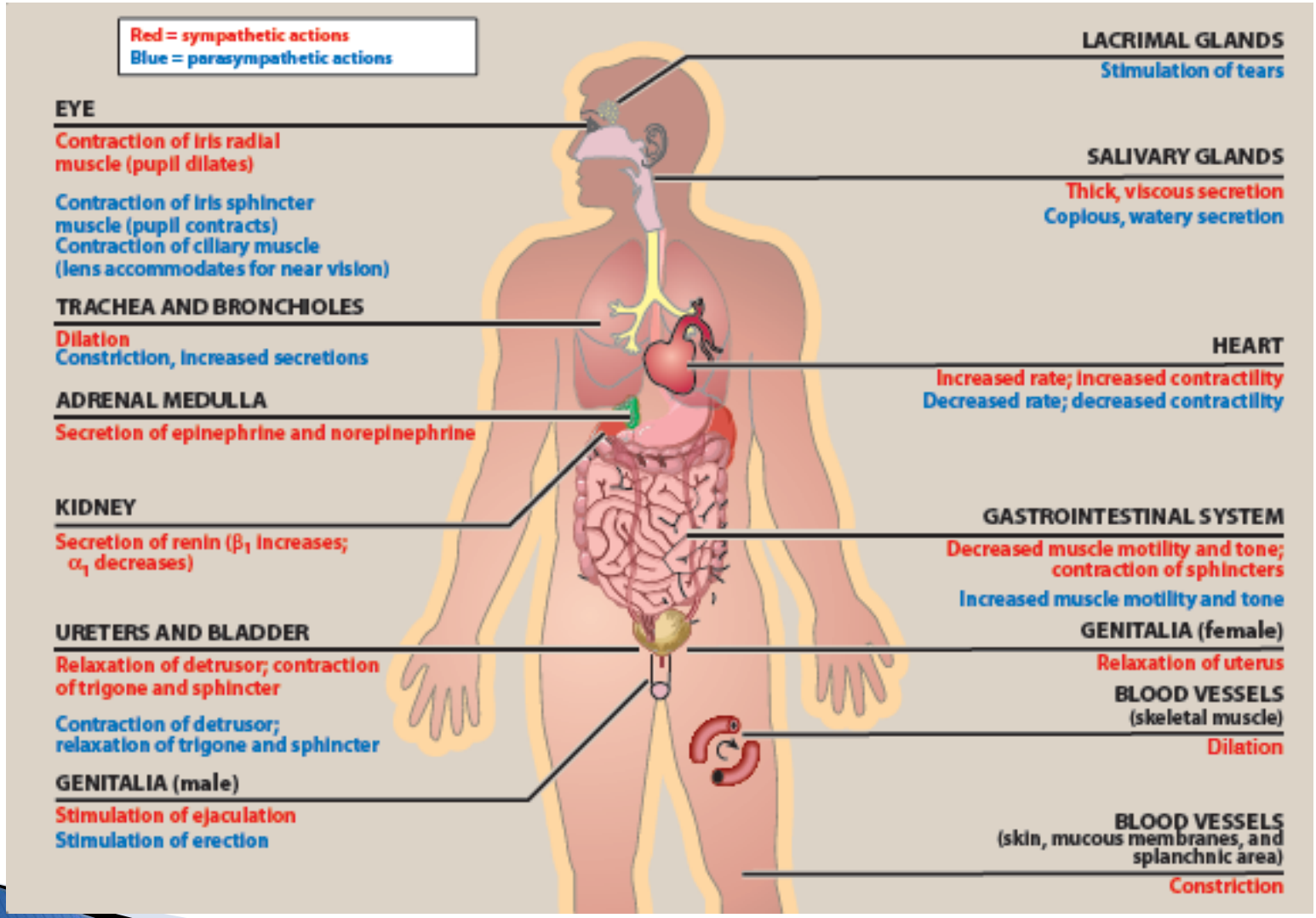
    (changes in the body during emergencies)
    - Sympathetic activation of effector organs
    - Stimulation of adrenal medulla to release epinephrine and norepinephrine
  - ↑Heart rate, ↑blood pressure, mobilize energy stores

ANS

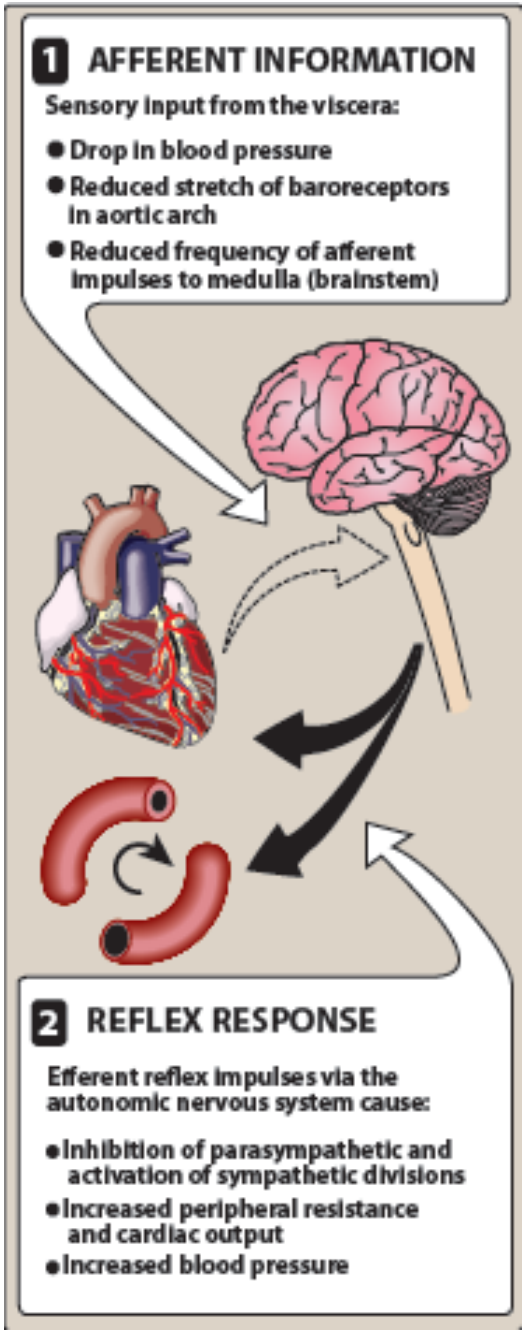
- Parasympathetic nervous system:
  - Maintaining homeostasis in the body
  - Maintain essential body functions like digestion, elimination of waste
  - Oppose and balance the actions of sympathetic nervous system
  - Rest or digest situations



ANS



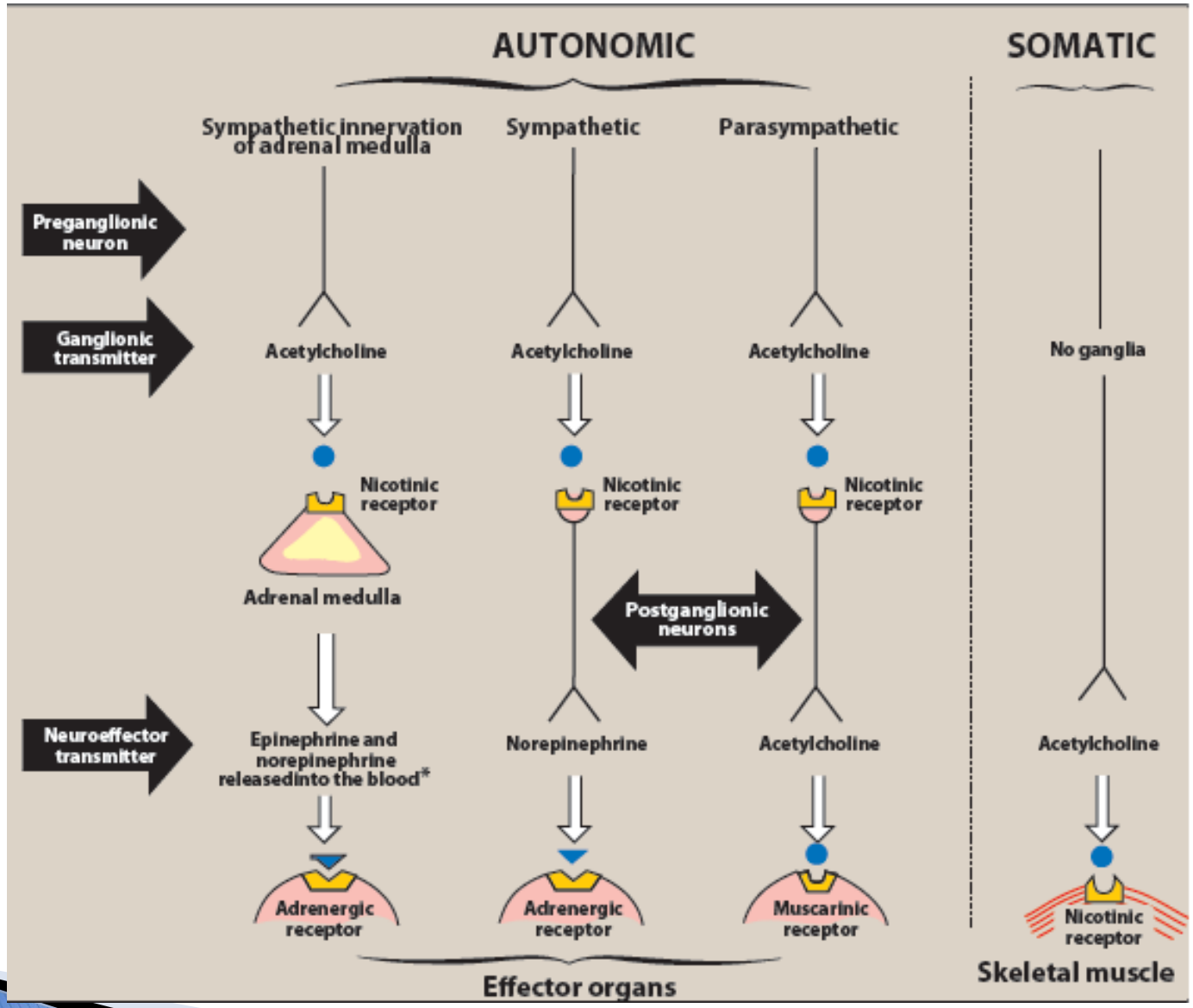
- CNS control over autonomic functions involves reflex responses without consciousness
- Stimuli causing strong feelings like rage, fear can modify ANS activities
- Most organs receive dual innervation by both systems



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 impulse from postganglionic nerves to the effector organs in the sympathetic system



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 increase 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

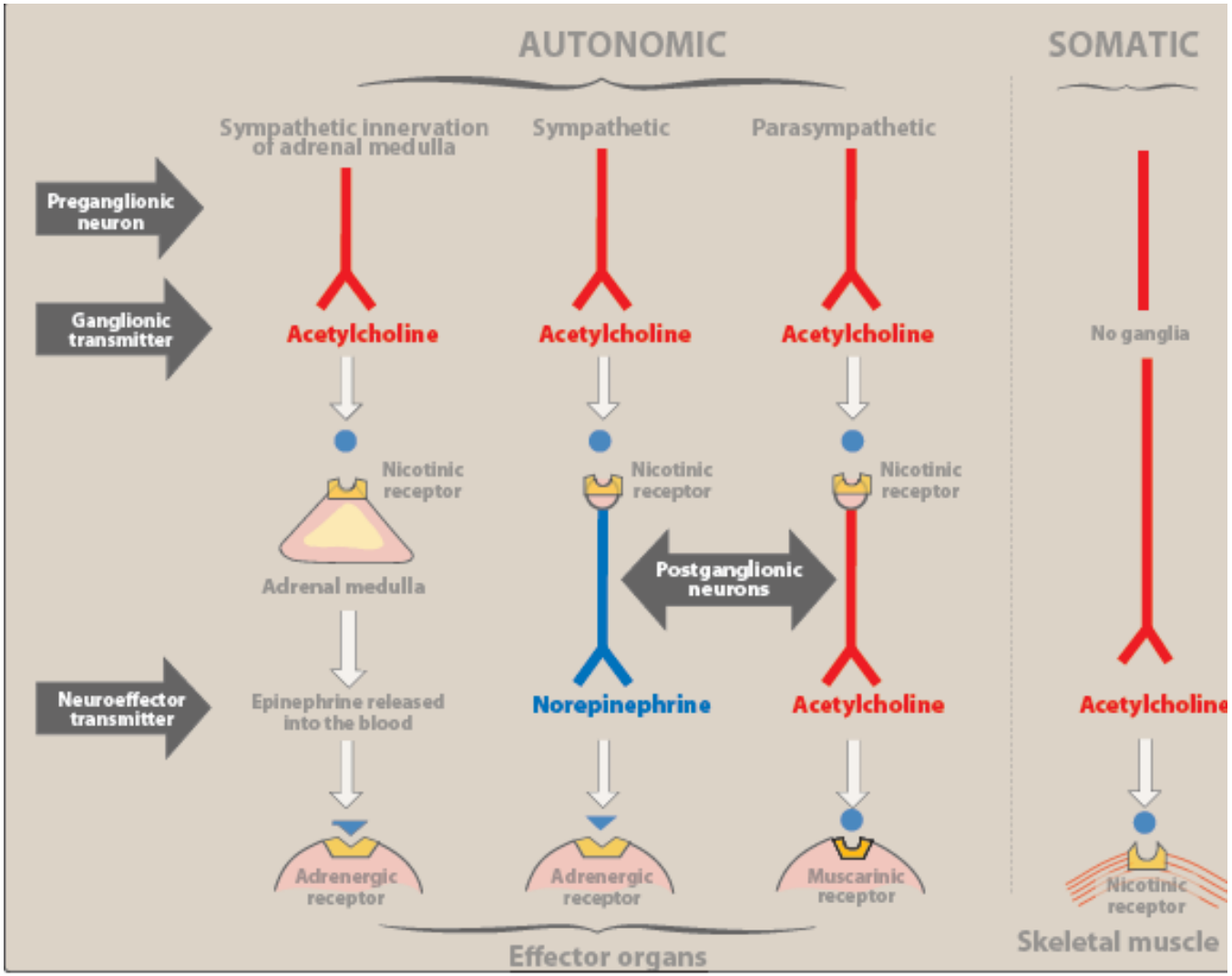


Figure 3.9
Cholinergic (red) and adrenergeric (blue) neurons found within the autonomic and somatic nervous systems.

Autonomic drugs

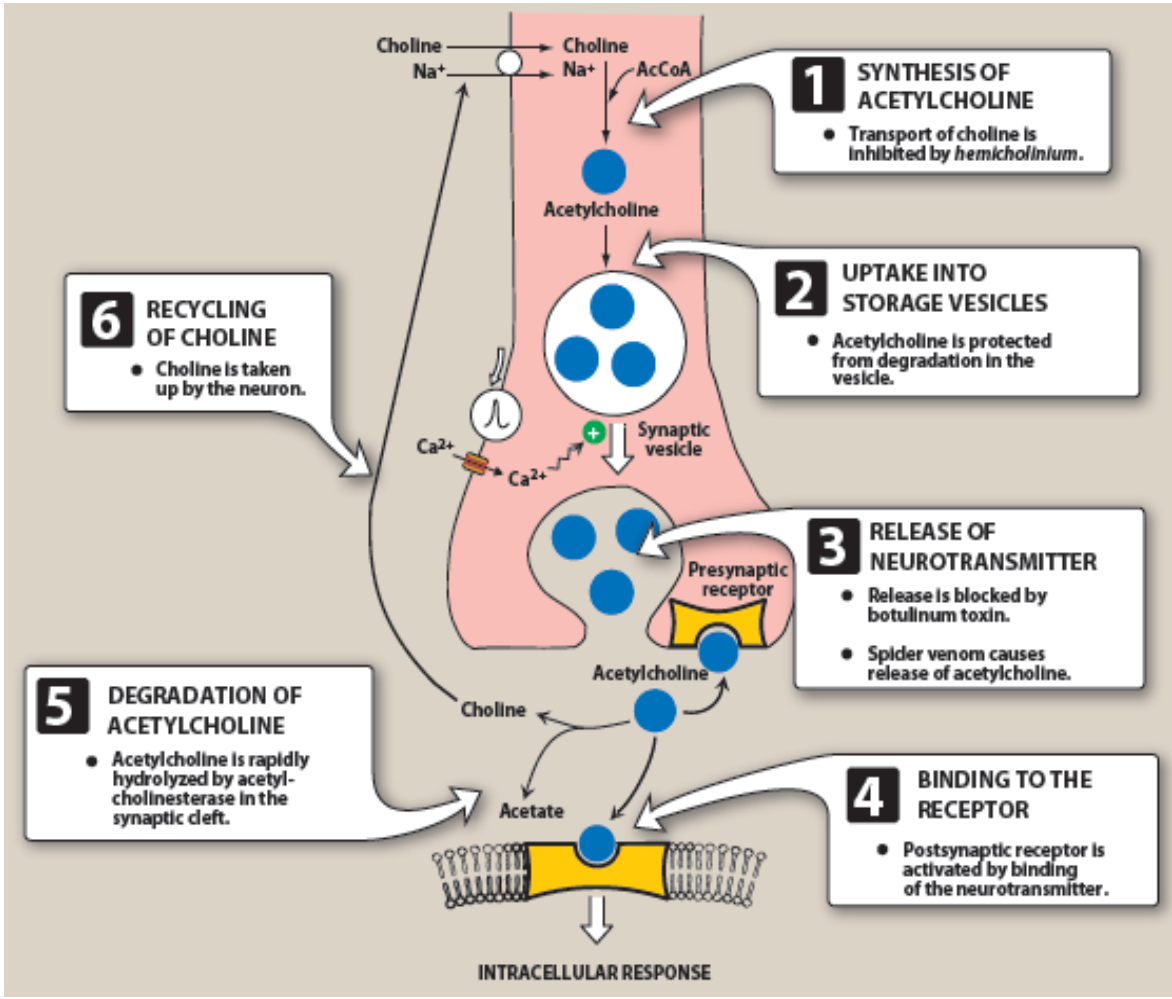
- Cholinergic agonists
- Cholinergic antagonists
- Adrenergic agonists
- Adrenergic antagonists

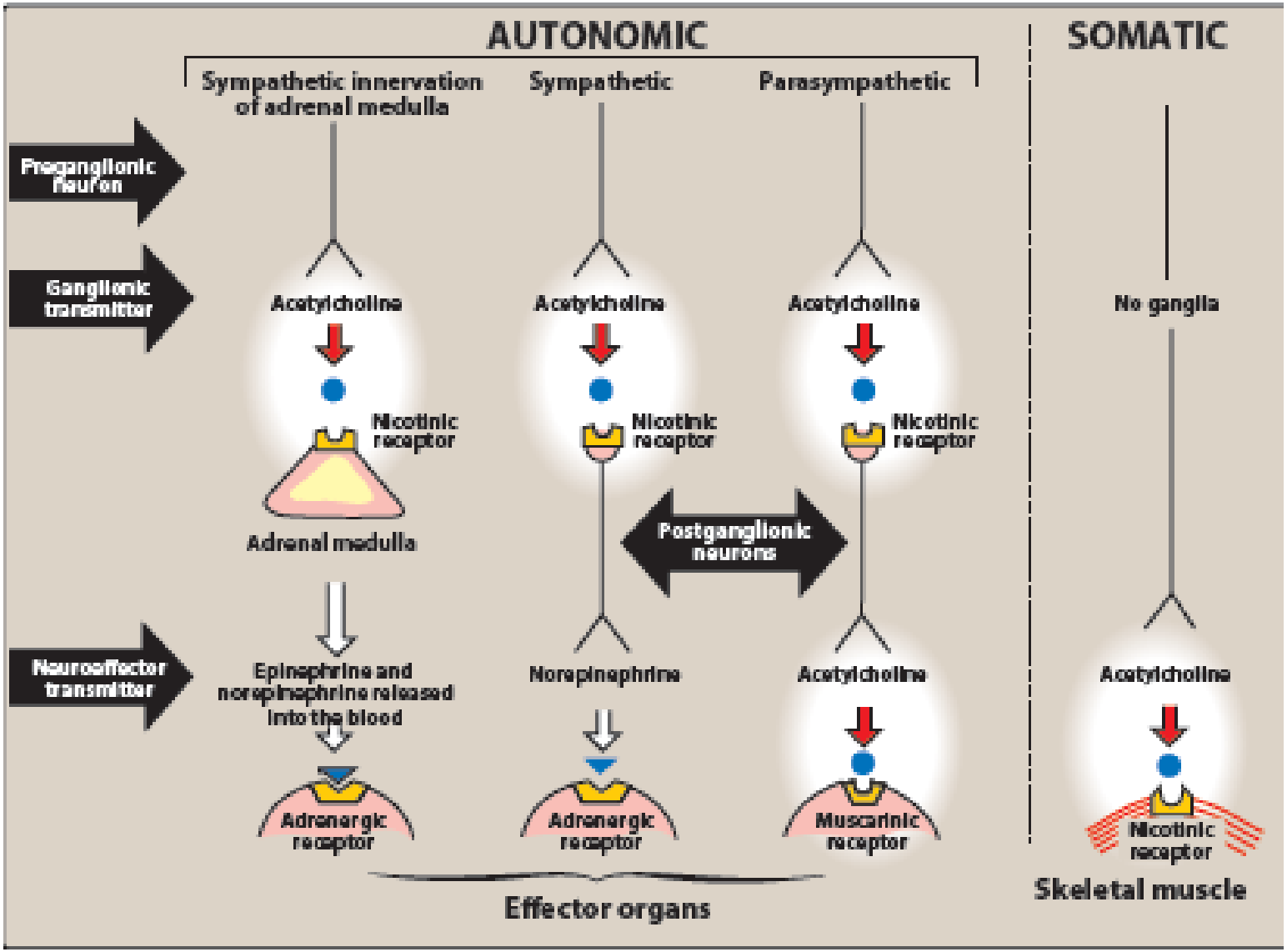
- Autonomic drugs: Drugs that produce their therapeutic effects by mimicking or altering the function of the ANS
  - Stimulating portions of the ANS
  - Blocking the action of the autonomic nerves

- 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 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





Cholinergic receptors (Cholinoceptors)

1. Muscaranic receptors
   - G-protein coupled receptors
   - 5 subclasses
     - M_1, M_2, M_3, M_4, M_5
   - Location, all 5 subtypes were found on neurons

     M_1 on gastric parietal cells

     M2 on cardiac cells and smooth muscle

     M_3 on bladder, exocrine glands and smooth muscle

Parasympathomimetics or Cholinergic agonists mimic the effects of parasympathetic nerve stimulation

Direct acting Cholinergic agonists

- Bind directly to cholinergic receptors and mimic the effects of ACh
  - Acetylcholine
    - Rapidly inactivated by cholinesterase
      - ↓↓ Heart rate and cardiac output
      - ↓↓ Blood pressure
      - ↑↑ Salivary secretion and intestinal motility
      - Urinary expulsion
      - Miosis
    - No therapeutic use
      - Due to multiplicity of its action leading to diffuse effects
      - Rapid inactivation by cholinesterase

Acetylcholine

1. Decrease heart rate and cardiac output
   - Mimic the effect of vagal stimulation
   - Negative chronotropic effect
   - Decreases stroke volume by reducing the rate of firing at the SA node
2. Decrease blood pressure
   - By causing vasodilation
   - ACh activates M_3 receptors on the endothelial lining of the smooth muscles in blood vessels
   - This causes the release of nitric oxide (NO) which relaxes smooth muscles in the blood vessels by inhibition of phosphodiesterase-3

Direct acting cholinergic agonists

- Bethanechol
  - Muscaranic agonist
  - Poor substrate for choliesterase
  - Increase intestinal motility
  - Stimulates detruser muscle of the bladder while relaxing the trigone and sphinctor muscles causing urine expulsion
  - Uses
    - To stimulate atonic bladder postpartum or postoperative
  - Adverse effects
    - Sweating, salivation, decreased blood pressure, nausea, abdominal pain, diarrhea and bronchospasm

Direct acting cholinergic agonists

- Carbachol
  - Muscaranic and nicotinic agonist
  - Poor substrate for cholinesterase
  - Profound effects on cardiovascular and GI systems

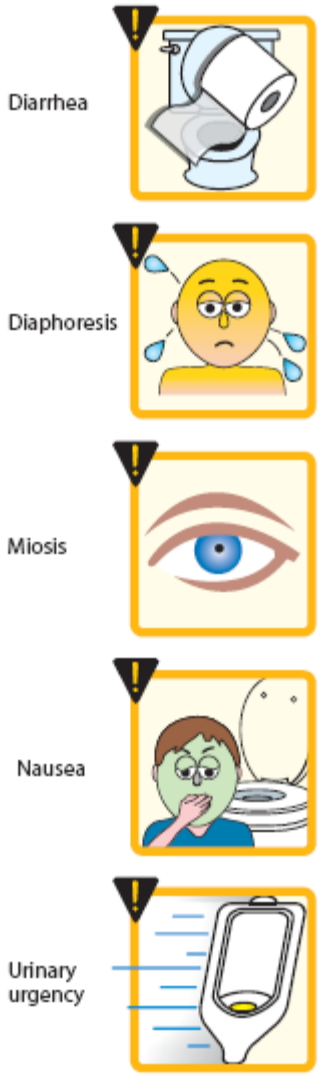
  first stimulating and then depressing (ganglion stimulation)
  - Can cause release of epinephrine from adrenal medulla due to its nicotinic action
  - Use: rarely used except in the eye as a miotic agent to treat glaucoma causing pupillary contraction and decreased intraocular pressure (IOP)
  - Ophthalmic preperation has no or little systemic effects

Direct acting cholinergic agonists

- Pilocarpine
  - Muscaranic agonist
  - Stable to hydrolysis by cholinesterase
  - Ophthalmic preparation is used to treat Glaucoma causing contraction of ciliary muscles and miosis
  - Used for emergency lowering of intraocular pressure
  - Oral pilocarpine is used for Sjören's syndrome
- Adverse effects
  - Can cross the BBB and cause CNS disturbance
  - Salivation and sweating (diaphoresis)

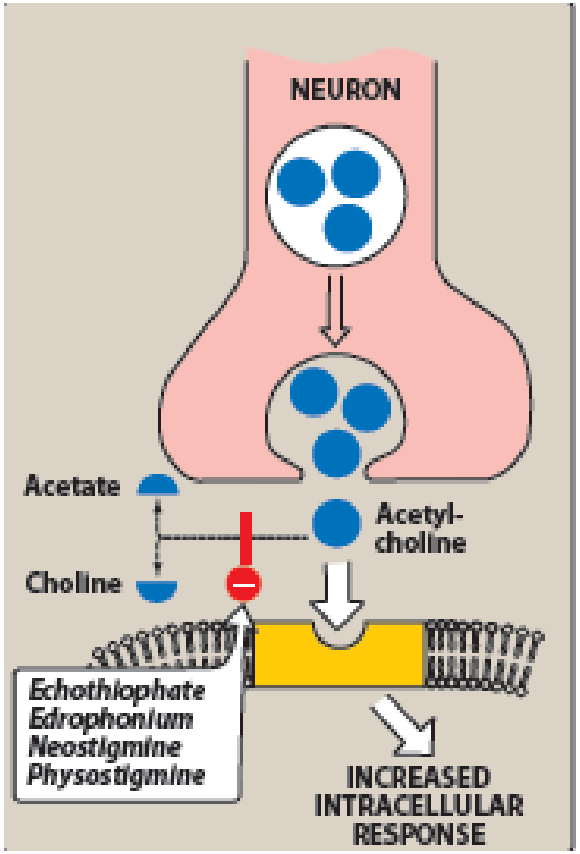
Cholinergic agonists Adverse effects

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



Indirect acting cholinergic agonists Acetylcholinesterase inhibitors

- AChE inhibitors provide a cholinergic action by prolonging the time ACh is available at the cholinergic nerve endings
- Act on muscaranic, nicotinic receptors and NMJ



Acetylcholinesterase inhibitor

AChE inhibitors

- Edrophonium
  - Prototype short acting AChE inhibitor
  - Binds reversibly to the active site of AChE preventing ACh hydrolysis
  - Used in diagnosis of myasthenia gravis
  - IV injection rapidly increases muscle strength in myasthenia gravis
  - Use is limited due to the risk of cholinergic crisis

AChE inhibitors

- Physostigmine
  - Reversibly inactivates AChE
  - Stimulates muscaranic and nicotinic sites of ANS and NMJ
  - Increases intestinal and bladder motility, used in the case of atony in either organs
  - Used to treat glaucoma (Topically in the eye)
  - Used for treatment of overdose of anticholinergic drugs

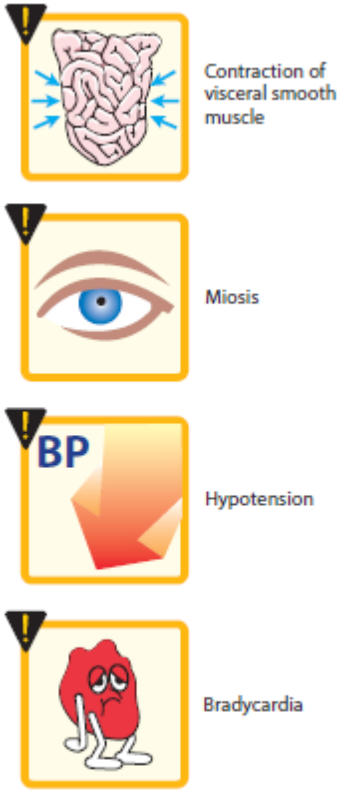


Figure 4.9
Some actions of *physostigmine*.

AChE inhibitors

- Physostigmine
  - Adverse effects (rarely seen at therapeutic doses)
    - Can cross BBB and lead to convulsions at high doses
    - Bradycardia and reduced cardiac output
    - Paralysis of skeletal muscle due to overaccumulation of ACh at NMJ

AChE inhibitors

- Neostigmine
  - Reversibly inhibits AChE
  - Does not enter the CNS
  - Used to stimulate the bladder and GI
  - Used to treat myasthenia gravis
  - Antidote for neuromuscular blocking agents
  - Adverse effects

    (Generalized cholinergic stimulation)

    Salivation, flushing, decreased blood pressure, nausea, abdominal pain, diarrhea and bronchospasm.

AChE inhibitors

- Myasthenia gravis: chronic autoimmune neuromuscular disease characterized by weakness of the skeletal muscles
- Treatment (AChE inhibitors)
  - Neostigmine
  - Pyridostigmine
  - Ambenonium
  - Adverse effects: similar to neostigmine

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
    - Adverse effects: mainly GI disturbances
    - Only delay the progression of the disease, can not stop the disease.

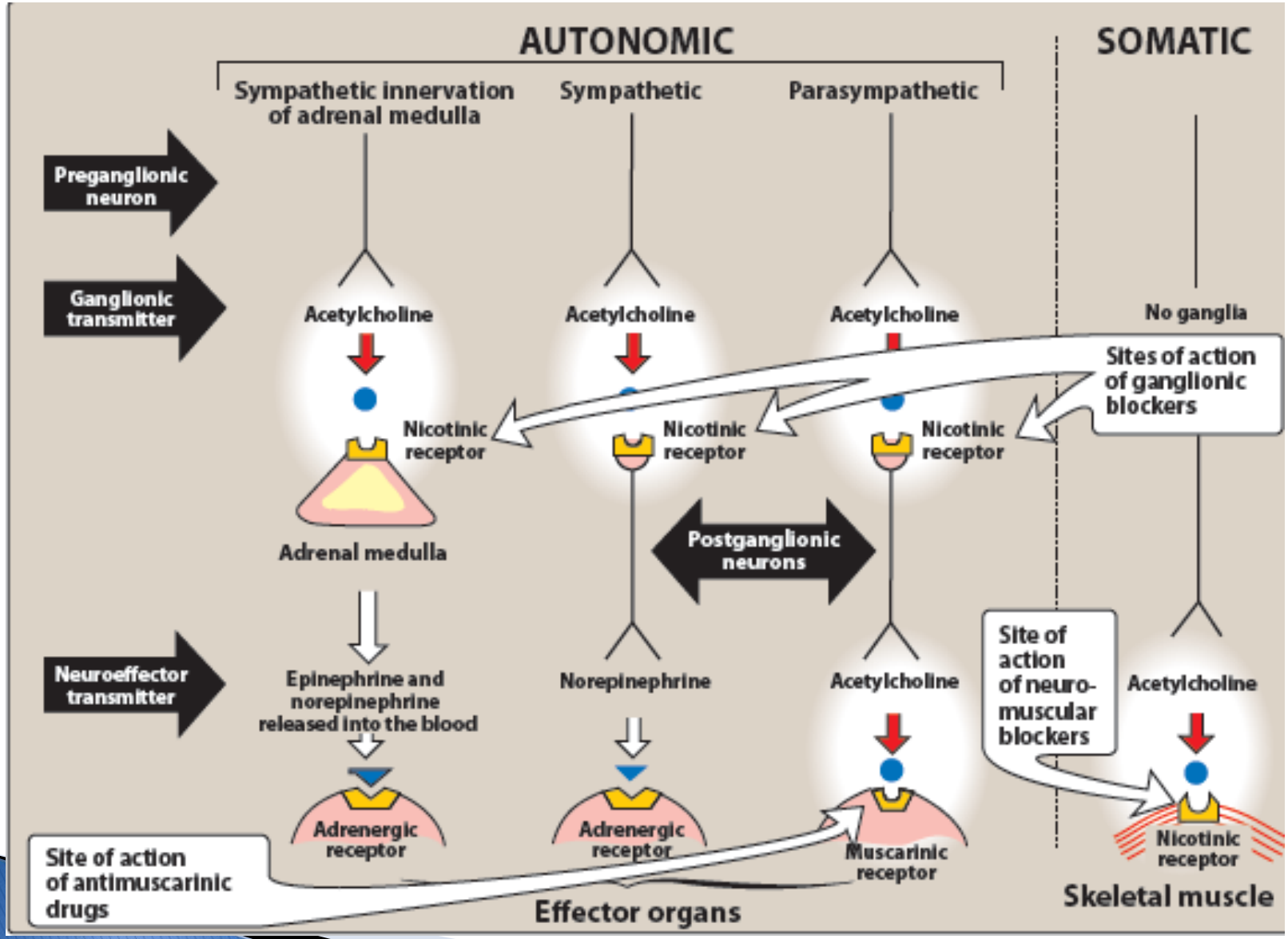
AChE inhibitors

- 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

- Treatment of toxicity caused by organophosphate insecticides (AChE inhibitors)
  - Pralidoxime reactivates inhibited AChE, but it can not cross the BBB, can not reverse CNS toxicity
    (Pralidoxime is a weak AChE inhibitor)
  - Atropine (antimuscaranic) to reverse muscaranic side effects
  - Diazepam for persistent convulsions
  - Artificial respiration

Cholinergic antagonists

- Parasympatholytics, cholinergic blockers, cholinergic antagonists, 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 and trihexyphenedil
  - Oxybutynin and tolterodine

Atropine

- Belladonna alkaloid
- Mechanism: Binds to muscaranic receptors competitively and prevents ACh from binding
- Effects:
  - Eye: Mydriatic
  - GI: Antispasmodic, reduces activity of GI, reduces saliva secretion
  - Urinary retention

Atropine

- Uses
  - Mydriatic agent (ophthalmic preparation) for eye examination, causes cycloplegia
  - Antispasmodic
  - Antidote for cholinergic agonists like in AChE inhibitors toxicity such as some insecticides
  - Antisecretory to block secretions prior to surgery

Atropine

- Side effects (dose dependent)
  - Dry mouth
  - Blurred vision
  - Tachycardia
  - Urinary retention
  - Constipation
  - CNS effects (restlessness, confusion, hallucinations, delirium)
  - Collapse of respiratory and circulatory systems
  - Death
- Low dose AChE inhibitors like physostigmine can be used for atropine toxicity

Antimuscaranic agents

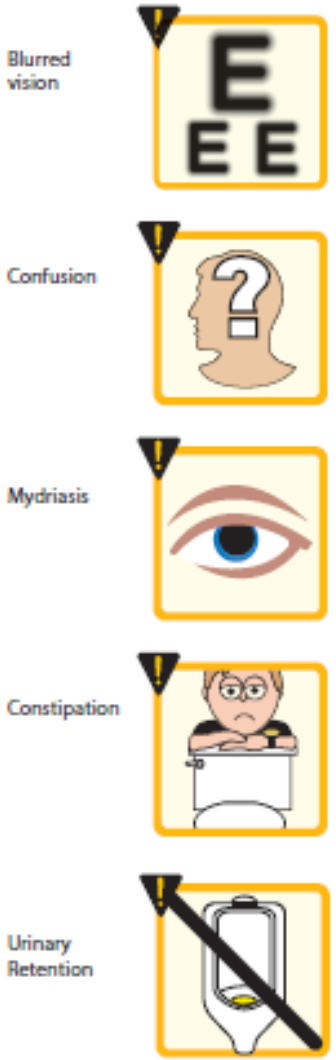
- Scopolamine
  - Used for motion sickness
  - Causes sedation
  - Adjunct drug in anesthetic procedures
  - Side effects: similar to atropine

- Ipratropium and tiotropium: Inhaled bronchodilators
  - Used for maintenance of bronchospasm associated with chronic obstructive pulmonary disease (COPD), chronic bronchitis, and emphysema

Antimuscaranic agents

- Tropicamide and cyclopentolate
  - Ophthalmic solutions for mydriasis and cycloplegia
- Benztropine and tryhexyphenidyl
  - Centrally acting antimuscaranic agents
  - Used for Parkinson's disease which is characterized by imbalance between ACh and dopamine in the brain
- Oxybutynin and tolterodine
  - Block muscaranic receptors in the bladder, increasing bladder capacity and reduces frequency of bladder contraction
  - Used for overactive urinary bladder disease
  - Side effects: dry mouth, constipation and blurred vision
  - Oxybutynin transdermal patch shows reduced mouth dryness than with oral preparations

Adverse effects of antimuscarinic agents

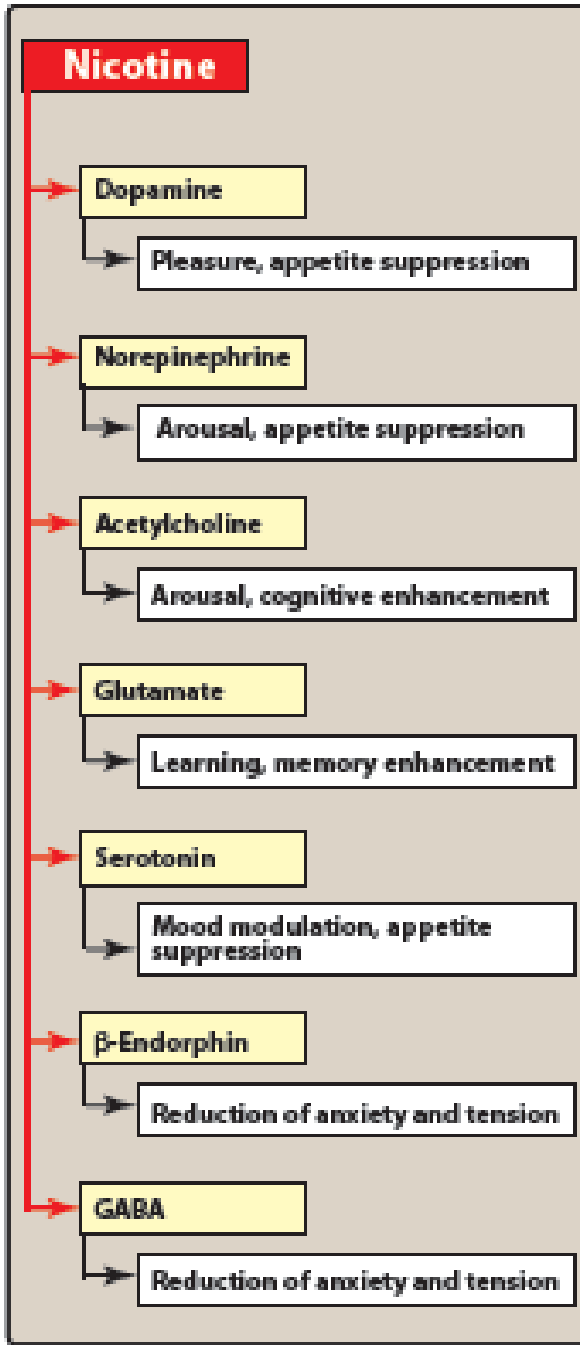


Ganglionic blockers

- Act on the nicotinic receptors of both sympathetic and parasympathetic ganglia
- No therapeutic application, they do not show specificity for sympathetic or parasympathetic ganglia
- Nicotine

Nicotine

- A poison with many undesired actions
- No therapeutic benefit
- Affects both sympathetic and parasympathetic ganglia resulting in complex effects
- Increases release of neurotransmitters
- Overall effects, increased heart rate and blood pressure
- Nicotine patches



Neuromuscular blockers

- Block cholinergic transmission between motor nerve endings and the nicotinic receptors on skeletal muscles
- Structural analogs of acetylcholine
- Used during surgery for complete muscle relaxation , so that less anesthetic is required to produce muscle relaxation and patients and recover quickly after surgery
- Also used in facilitating tracheal intubation

Nondepolarizing competetive neuromuscular blockers

- Curare and tubocurare
- No longer used for anesthesia
- Newer agents: Atracurium, cisatracurium
- Mechanism:
  - Bind to nicotinic receptors at the neuromuscular junction and prevent Ach binding
  - Prevent the depolarization of the muscle cell membrane and inhibit muscular contraction
- Antidote: Neostigmine, pyridostigmine (Cholinergic agonists, cholinesterase inhibitors)

Nondepolarizing competetive neuromuscular blockers

- Actions
  - Small rapidly contracting muscles of the face and eye are paralyzed first followed by fingers
  - Limbs, neck and trunk muscles are paralyzed afterwards
  - Lastly the diaphragm muscles are paralyzed
  - Recovery occurs in a reverse manner (diaphragm first)
- Therapeutic uses: adjuvant in anesthesia to relax skeletal muscles, to facilitate intubation

Depolarizing neuromuscular blockers

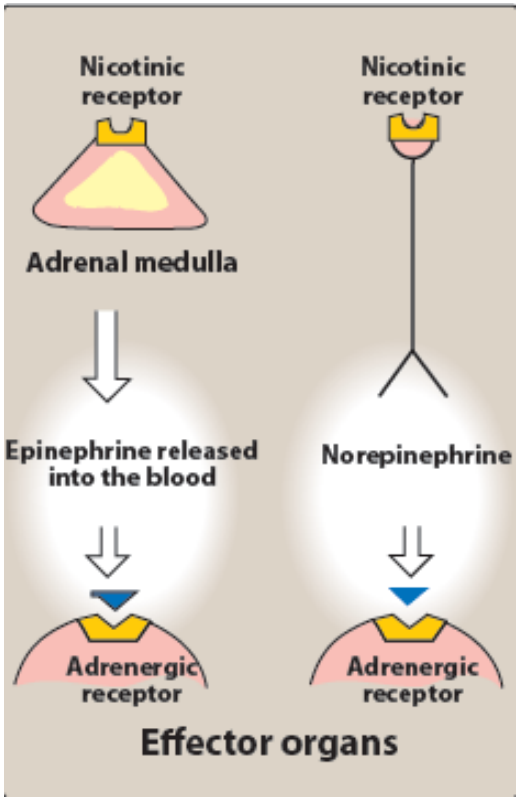
- Depolarize the plasma membrane of the muscle fiber, similar to ACh
- More resistant to degradation by AChE
- Remain attached to the receptor for a longer time causing constant stimulation of the receptor
- Continuous binding makes the receptor unable to transmit further impulses causing flaccid paralysis

Depolarizing neuromuscular blockers

- Succinyl choline
  - Attaches to nicotinic receptors and act like ACh to depolarize the junction
  - Remains attached to the receptor providing constant stimulation of the receptor, hence causing flaccid paralysis
  - Respiratory muscles paralyze last
  - Used for endotracheal intubation or electroconvulsive shock treatment
  - Adverse effects:
    - Hyperthermia when administered with halothane as anesthetic
    - Apnea

Adrenergic agonists

- Adrenrgic agonists; sympathomimetics: drugs that activate adrenoceptors
  (Receptors stimulated by norepinephrine or epinephrine)

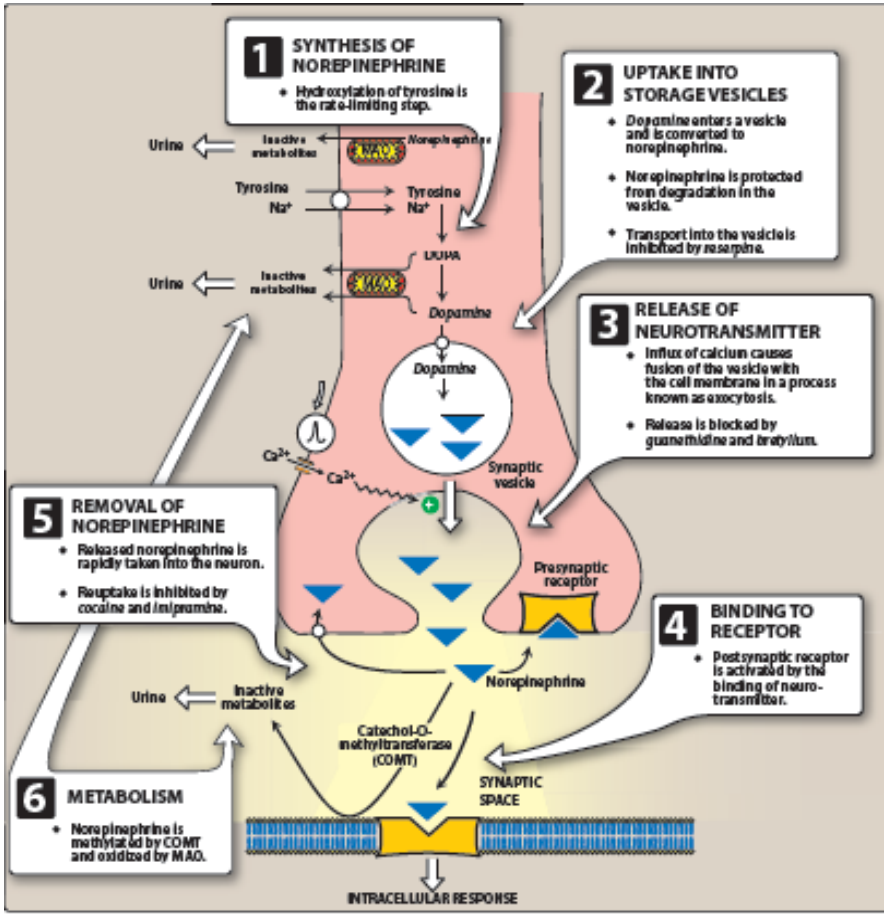


Adrenergic neurons

- Adrenergic neurons release NE as the primary neurotransmitter
- Adrenal medulla NE is converted to epinephrine, they are both stored and released upon stimulation
- Found in the CNS and sympathetic nervous system
- Adrenergic receptors located presynaptically on the neuron or postsynaptically on the effector organ are the sites of action of adrenergic drugs

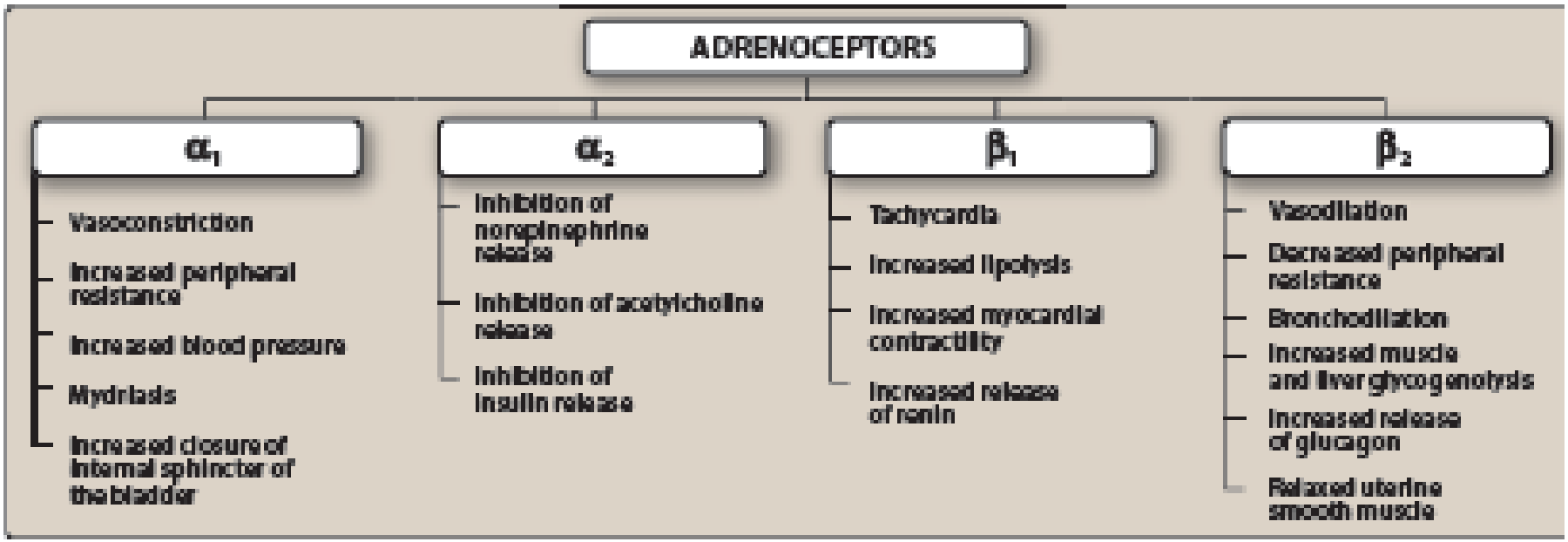
Neurotransmission at adrenergic neurons

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 COMT and MAO



Adrenoceptors

- α_1
  - Present on postsynaptic membranes of effector organs
  - Constriction of smooth muscle, vasoconstriction, increased blood pressure, total peripheral resistance
  - Subdivided to α_{1A}, α_{1B}, α_{1C}, and α_{1D}
- α_2
  - Located on presynaptic nerve endings
  - Stimulated α_2 cause feedback inhibition of NE release
  - Subdivided to α_{2A}, α_{2B} and α_{2C}
- β_1 (Heart, Kidney)
  - Tachycardia, Increased myocardial contractility, Renin release
- β_2 (Bronchi, blood vessels, uterus)
  - Vasodilation, Bronchodilation, Relax uterine smooth muscles
- β_3



- Desensetization of adrenoceptors: Reduction in the responsiveness of these receptors due to prolonged exposure to catecholamines
- Mechanisms for desentization
  - Sequestration of the receptors, so they are not available for binding
  - Downregulation of receptors by destruction or decreased synthesis
  - Inability to couple to G protein

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, norepinephrine, dopamine

- Catecholamines: Sympathomimetic amines

(NE, epinephrine, dopamine and isoprotrenol)

Highly potent in stimulating adrenergic receptors

Rapidly inactivated by COMT and MAO

Poor CNS penetration

- Non catecholamine adrenergic agonists have longer duration of action

Direct acting adrenergic agonists

- Epinephrine
- Norepinephrine
- Isoprotrenol
- Dopamine
- Dobutamine
- Oxymetazoline
- Phenylphrine
- Clonidine
- Metaprotrenol
- Albuterol (salbutamol) and terbutaline
- Salmeterol and formoterol

Direct acting adrenergic agonists

- Epinephrine
  - Commonly used in therapy
  - Strengthens the contractility of myocardium (β1) (positive inotrpic effect)
  - Increases the rate of contraction (β1)
  - Increase cardiac output (β1)
  - Promotes renin release, increase blood pressure (β1 on kidney)
  - Constriction of arterioles (α_1)
  - Dilation of vessels going to liver and skeletal muscles (β2)
  - Bronchodilation (β2)
  - Hyperglycemia (β2 in liver)

Epinephrine

- Therapeutic uses
  - Bronchospasm, emergency for acute asthma
  - Anaphylactic shock
  - Cardiac arrest
  - 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

- Acts mostly on α receptors
- Effects
  - Vasoconstriction (α1 effect)
  - Increase total peripheral resistance
  - Increase blood pressure
  - Reflex bradycardia due to stimulation of baroreceptor
- Therapeutic uses
  - Shock, NE increases peripheral resistance and 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 (

(AV block or cardiac arrest)

- Adverse effects: similar to epinephrine

Dopamine

- Activates α and β receptors
- A neurotransmitter that occurs naturally in the CNS and adrenal medulla
- Increases heart rate and force of contraction

(positive chronotropic and inotropic effects)

- Rapidly metabolized by MAO and COMT
- Used for
  - Shock treatment
  - Hypotension
  - Severe congestive heart failure
- Adverse effects
  - Hypertension
  - Arrhythmia

Direct acting adrenergic agonists

- Dobutamine
  - β1 agonist
  - Increases cardiac rate and output
  - Uses:
    - Increase cardiac output in acute congestive hear failure
    - For inotropic support after cardiac surgery
  - Adverse effects:
    - Similar to epinephrine

Direct acting adrenergic agonists

- Oxymetazoline
  - Stimulates α_1 and α_2 receptors
  - Used locally in the eye or nose as a vasoconstrictor
  - Mechanism: Directly stimulates α receptors on blood vessels in nasal mucosa and conjunctiva to reduce blood flow and decrease congestion
  - Found in many OTC short-term nasal decongestants
  - Found in ophthalmic solution for relief of eye redness
  - Rebound congestion and tolerance can occur with long term use

Direct acting adrenergic agonists

- Phenylphrine
  - Stimulates α_1 receptors
  - Vasoconstrictor
  - Used in ophthalmic solutions for mydriasis
  - Used as nasal decongestant
  - Can be used to raise blood pressure and to terminate episodes of supraventricular tachycardia

Direct acting adrenergic agonists

- Clonidine
  - α_2 agonist
  - Used in essential hypertension to lower blood pressure
  - Acts centrally to inhibit sympathetic activity and outflow to periphery
  - Side effects
    - Lethargy
    - Sedation
  - Abrupt discontinuation leads to rebound hypertension

Direct acting adrenergic agonists

- Albuterol (salbutamol) and terbutaline
  - β2 agonists
  - Used as bronchodilators, administered by MDI
  - Terbutaline is used as uterine relaxant to suppress premature labor (off label use)
  - Side effects:
    - Tremor
    - Restlessness

- Salmeterol and formoterol
  - β2 agonists
  - Long acting bronchodilators, administered by MDI

Indirect acting adrenergic agonists

- Inhibit reuptake of norepinephrine or cause norepinephrine release from presynaptic terminal
- Amphetamine
  - CNS stimulant
  - Can increase blood pressure by stimulation of α_1 and β_1 receptors
  - Used in hyperactivity of children, narcolepsy
- Cocaine:
  - Inhibits reuptake of norepinephrine
  - CNS stimulant

- Cocaine
  - Highly addictive
  - Blocks reuptake of epinephrine, serotonin and dopamine into presynaptic terminals
  - Prolongs the peripheral and central actions of these neurotransmitters
  - Dopaminergic effects in the brain's pleasure system (limbic system) produce the euphoria associated with cocaine

Adverse effects of adrenergic agonists

Arrhythmias

Headache

Hyperactivity

Insomnia

Nausea

Tremors

Mixed action adrenergic agonists

- Induce the release of norepinephrine from presynaptic terminals and activate adrenergic receptors on the postsynaptic membrane
- Ephedrine and pseudoephedrine
  - Release stored NE from nerve endings and directly stimulate α and β receptors
- Pseudoephedrine is used orally to treat nasal and sinus congestion

Adrenergic antagonists

Adrenergic blockers, sympatholytics: bind to adrenoceptors but do not trigger the usual receptor-mediated intracellular effects.

These drugs bind to receptors reversibly or irreversibly and prevent the activation of receptors by epinephrine and norepinephrine

α-Adrenergic blockers

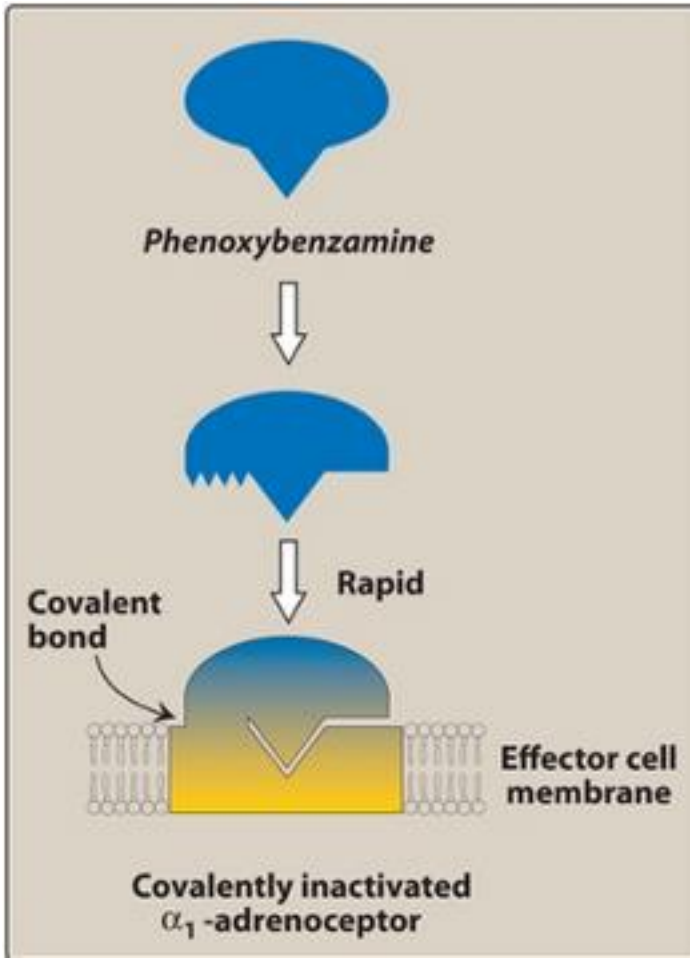
- Affect blood pressure
- Blocking α-receptors reduces the sympathetic tone of the blood vessels decreasing the peripheral vascular resistance
- Lowered blood pressure induces reflex tachycardia

α-Blockers

- Alfuzosin
- Doxazosin
- Phenoxybenzamine
- Phentolamine
- Prazosin
- Tamsulosin
- Terazosin
- Yohimbine

Phenoxybenzamine

- Nonselective, binds to α_1 and α_2
- The block is irreversible and noncompetetive, to overcome the block, the body has to synthesize adrenoceptors (requires a day or longer)



Phenoxybenzamine

- Actions
  - Prevents vasoconstriction of peripheral blood vessels by endogenous cathecholamines
  - Reflex tachycardia occurs
  - α_2 receptors are also blocked causing increased cardiac output
  - Phenoxybenzamine use for hypertension was discontinued because it was unsuccessful in maintaining lower blood pressure due to blockade of α_2 and α_1 receptors

Phenoxybenzamine

- Uses:
  - Treatment of pheochromocytoma
  - Used for Raynaud's disease and frostbite

- Adverse effects
  - Postural hypotension
  - Nasal stuffiness
  - Nausea and vomiting

Phentolamine

- Competitively blocks α_1 and α_2 receptors
- Causes reflex tachycardia
- Used for pheochromocytoma
- Adverse effects
  - Postural hypotension
  - Arrhythmia

Prazosin, terazosin, doxazosin, tamsulosin and alfuzosin

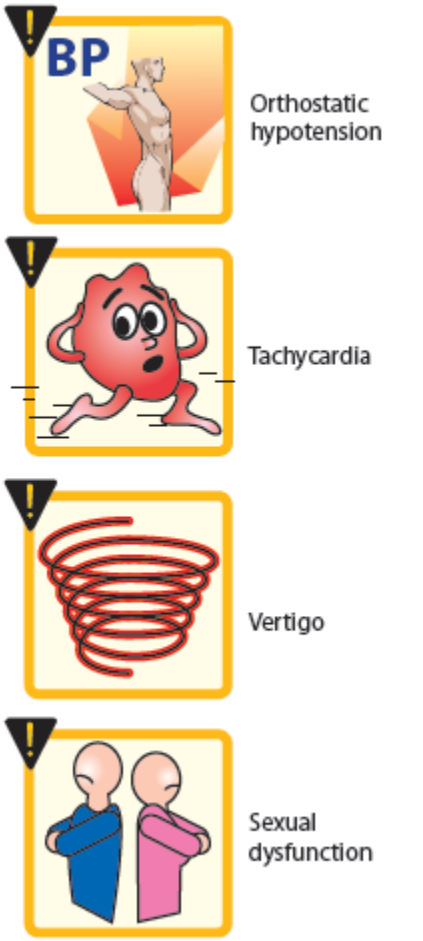
- Selective competitive blockers of α_1 receptors
- Prazosin, terazosin and doxazosin are useful for treating hypertension
- Tamsulosin and alfuzosin are indicated for BPH
- Effects
  - Decrease peripheral vascular resistance by causing relaxation of arterial and venous smooth muscle
  - Cause minimal change in cardiac output
  - Can cause first dose syncope (fainting)
    - First dose administered should be adjusted to 1/3 the regular dose, or given at bedtime

Prazosin, terazosin, doxazosin, tamsulosin and alfuzosin

- Uses:
  - Congestive heart failure
  - Prazosin, terazosin and doxazosin are useful for treating hypertension due to blockade of α_1 receptors
  - Tamsulosin (selectivity for α_1 on prostate) and alfuzosin are indicated for BPH because the blockade of α-receptors decreases the smooth muscle tone of the bladder neck and prostate and improves urine flow

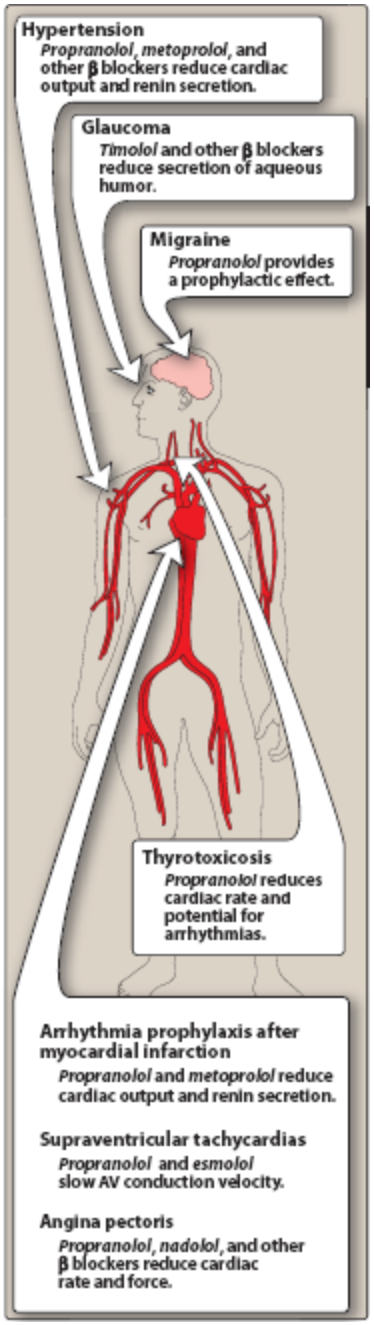
Prazosin, terazosin, doxazosin, tamsulosin and alfuzosin

- Adverse effects
  - Dizziness
  - Lack of energy
  - Orthostatic hypotension
  - Tachycardia
  - Inhibition of ejaculation due to blockade of α-receptors in the ejaculatory ducts



β-Adrenergic blockers

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



Propranolol

- Non selective β antagonist
- Reduces cardiac output and heart rate
- Reduces blood pressure
- Causes bronchoconstriction
- Uses
  - Hypertension
  - Hyperthyroidism
  - Migraine
  - Angina
  - Myocardial infarction
- Adverse effects
  - Bronchoconstriction
  - Arrhythmia

Timolol and Nadolol

- Non selective β-antagonists
- More potent than propranolol
- Nadolol has a very long duration of action
- Timolol is used topically for glaucoma

Acebutolol, atenolol, metoprolol, bisoprolol, esmolol

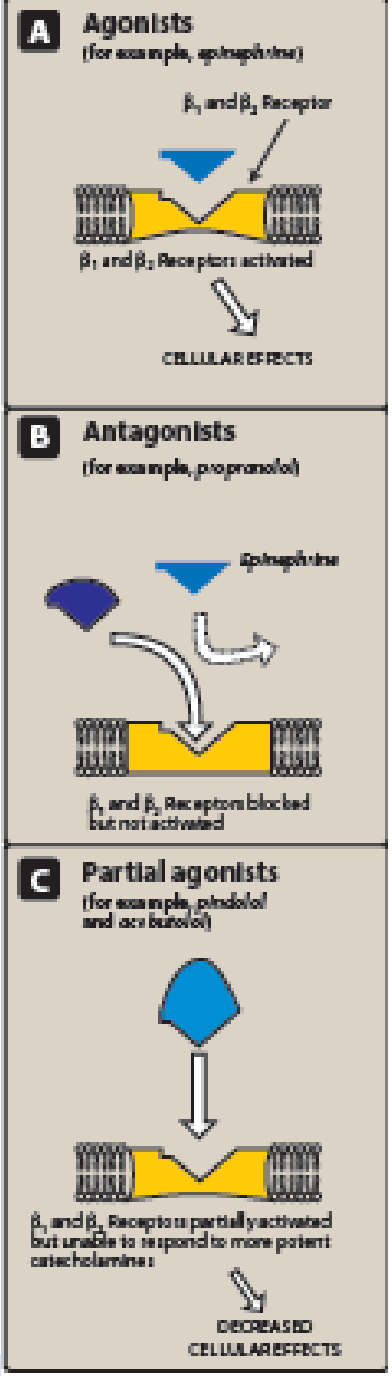
- Selective β1 antagonists
- Cardioselective (at low doses)
- No β2 antagonism (no bronchoconstriction)
- Little effect on peripheral resistance
- Therapeutic use
  - Hypertension
  - Angina

Acebutolol and pindolol

- Antagonists with partial agonist activity
- Have intrinsic sympathomimetic activity
- Acebutolol is β1 selective antagonist
- Pindolol is non selective β-blocker
- Used for hypertensive patients with moderate bradycardia because they cause less heart rate decrease

Labetalol and carvedilol

- Antagonists of both α and β
  - Block α_1 receptors causing peripheral vasodilation and reducing blood pressure
- Used for hypertension
- Labetalol can be used in pregnancy-induced hypertension
- Intravenous labetalol can be used for hypertensive emergencies
- Adverse effects:
  - Orthostatic hypotension



Adverse Effects of β-blockers:

- In patients with AV conduction defects, β_1 blockers may cause life-threatening bradyarrhythmias
- Abrupt discontinuation of long-term β_1 blockers use in angina can exacerbate angina and may increase risk of sudden heart attack
- β_2 receptor blockade can worsen bronchoconstriction in asthmatic populations
  - β_1-selective blockers or non-selective β blockers with partial β_2 agonism produce less bronchoconstriction than non-selective β blockers

Drugs affecting neurotransmitter release or reuptake

- Reserpine
  - Blocks the transport of the biogenic amines norepinephrine, dopamine and serotonin from the cytoplasm into storage vesicles in adrenergic nerves
  - Causes depletion of biogenic amines
  - Impairs sympathetic function
  - Long duration of action
- Guanethidine
  - Blocks the release of stored norepinephrine
  - Causes orthostatic hypotension