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
- ANS regulates everyday requirements of vital bodily functions without the conscious participation of the mind
- ANS is 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

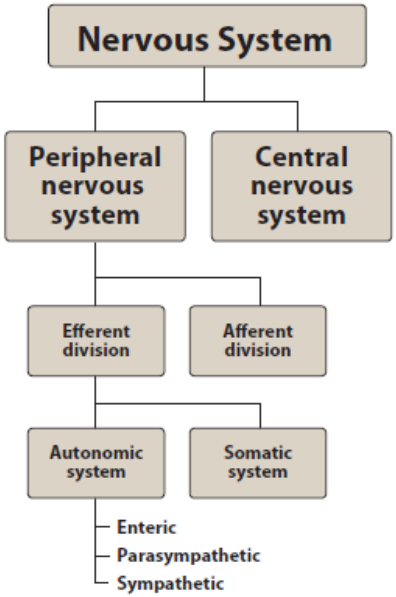
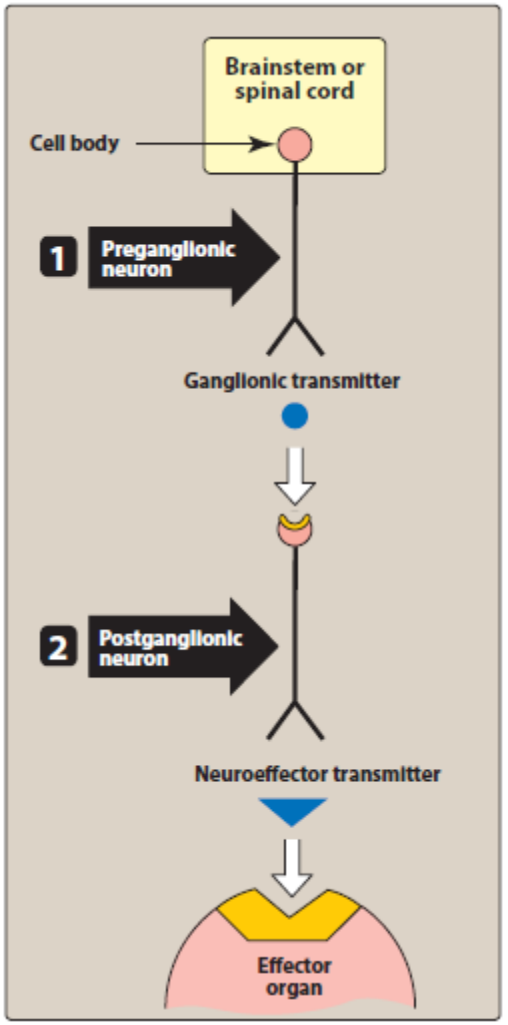


Figure 3.1
Organization of the nervous system.

- 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



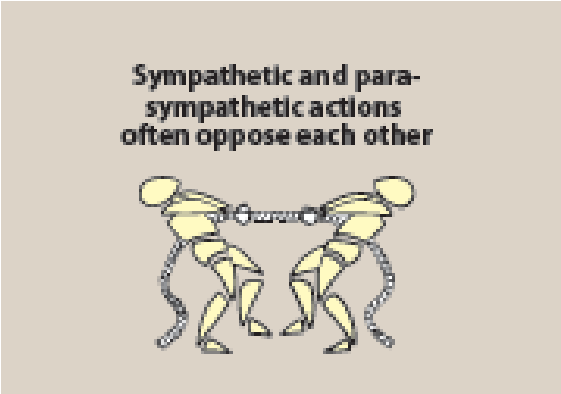
ANS

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

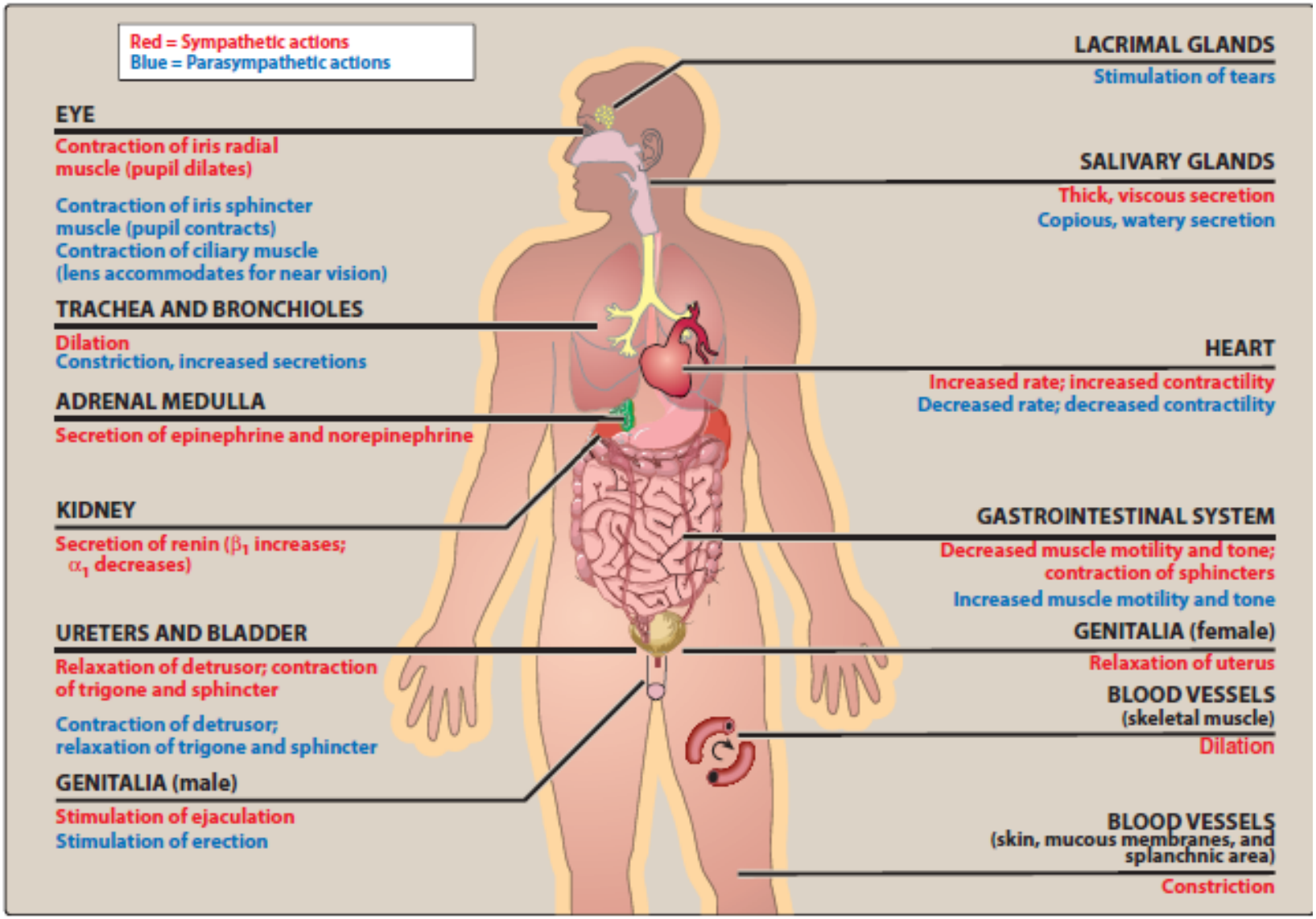
    (changes in the body during emergencies)
    - Sympathetic activation of effector organs
    - Stimulation of adrenal medulla to release Epinephrine and norepinephrine
  - ↑Heart rate, ↑blood pressure, mobilize energy stores

ANS

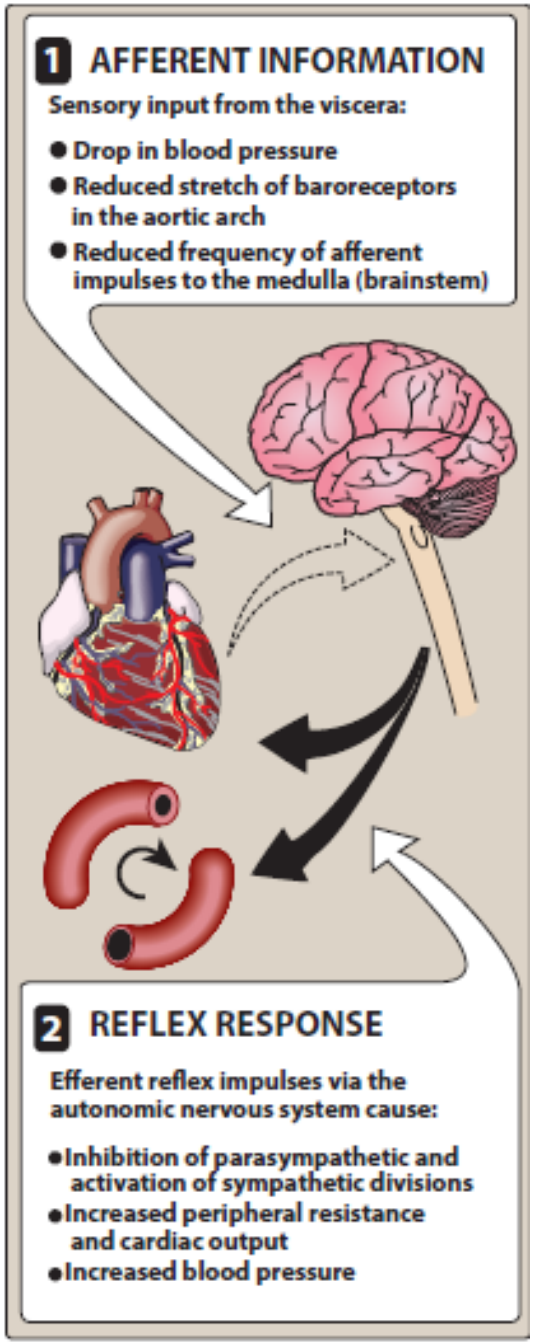
- Parasympathetic nervous system:
  - Maintaining homeostasis in the body
  - Maintain essential body functions like digestion, elimination of waste
  - Oppose and balance the actions of sympathetic nervous system
  - Rest or digest situations



ANS


Red = Sympathetic actions
Blue = Parasympathetic actions
EYE
Contraction of iris radial muscle (pupil dilates)
Contraction of iris sphincter muscle (pupil contracts)
Contraction of ciliary muscle (lens accommodates for near vision)
TRACHEA AND BRONCHIOLES
Dilation
Constriction, increased secretions
ADRENAL MEDULLA
Secretion of epinephrine and norepinephrine
KIDNEY
Secretion of renin (β_1 increases; α_1 decreases)
URETERS AND BLADDER
Relaxation of detrusor; contraction of trigone and sphincter
Contraction of detrusor; relaxation of trigone and sphincter
GENITALIA (male)
Stimulation of ejaculation
Stimulation of erection
LACRIMAL GLANDS
Stimulation of tears
SALIVARY GLANDS
Thick, viscous secretion
Copious, watery secretion
HEART
Increased rate; increased contractility
Decreased rate; decreased contractility
GASTROINTESTINAL SYSTEM
Decreased muscle motility and tone; contraction of sphincters
Increased muscle motility and tone
GENITALIA (female)
Relaxation of uterus
BLOOD VESSELS (skeletal muscle)
Dilation
BLOOD VESSELS (skin, mucous membranes, and splanchnic area)
Constriction

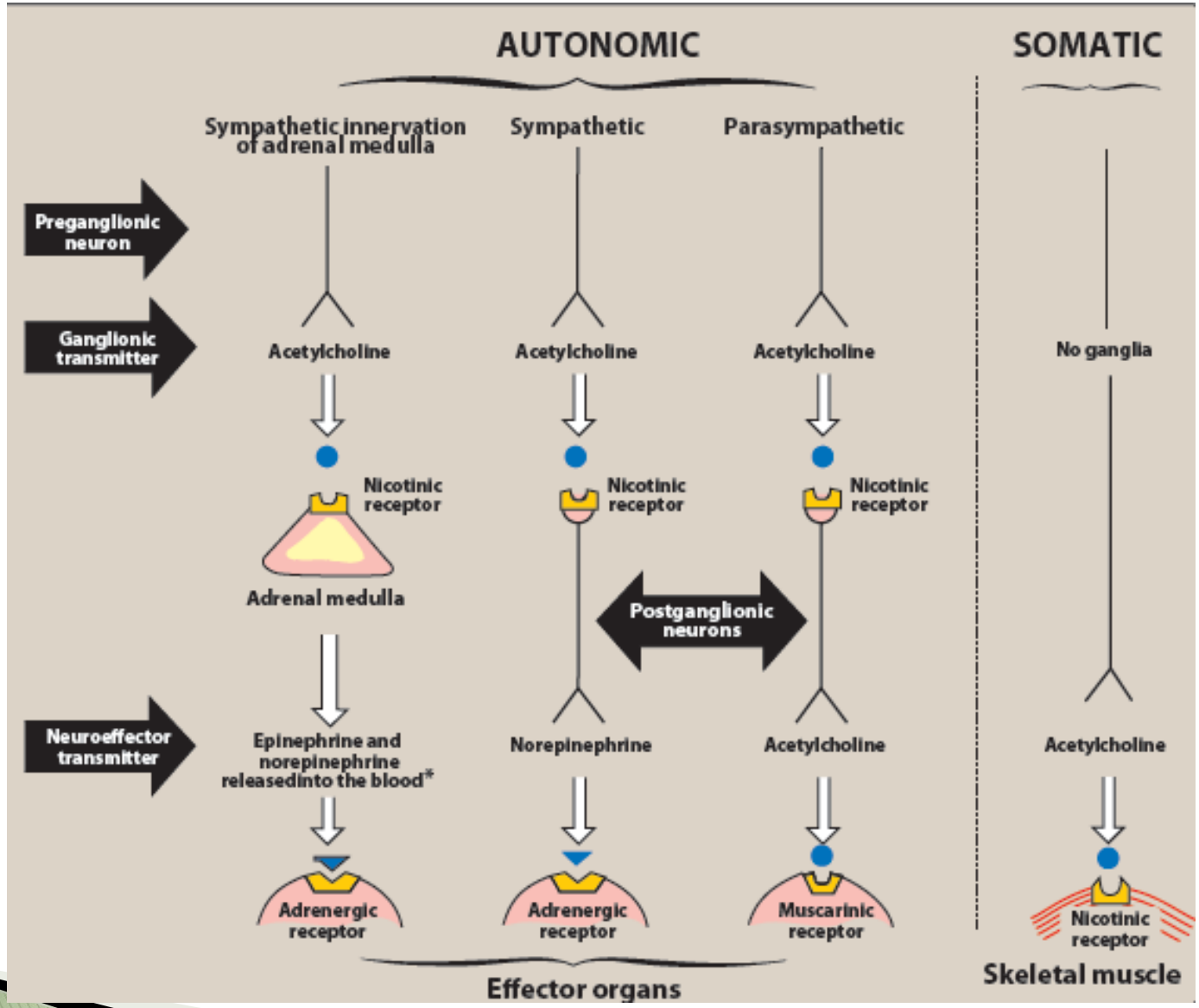
- CNS control over autonomic functions involves reflex responses without consciousness
- Stimuli causing strong feelings like rage, fear can modify ANS activities
- Most organs receive dual innervation by both systems



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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Neuroeffector transmitter
Epinephrine and norepinephrine releasedinto the blood*
Norepinephrine
Acetylcholine
Acetylcholine
Adrenergic receptor
Adrenergic receptor
Muscarinic receptor
Nicotinic receptor
Effector organs
Skeletal muscle

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

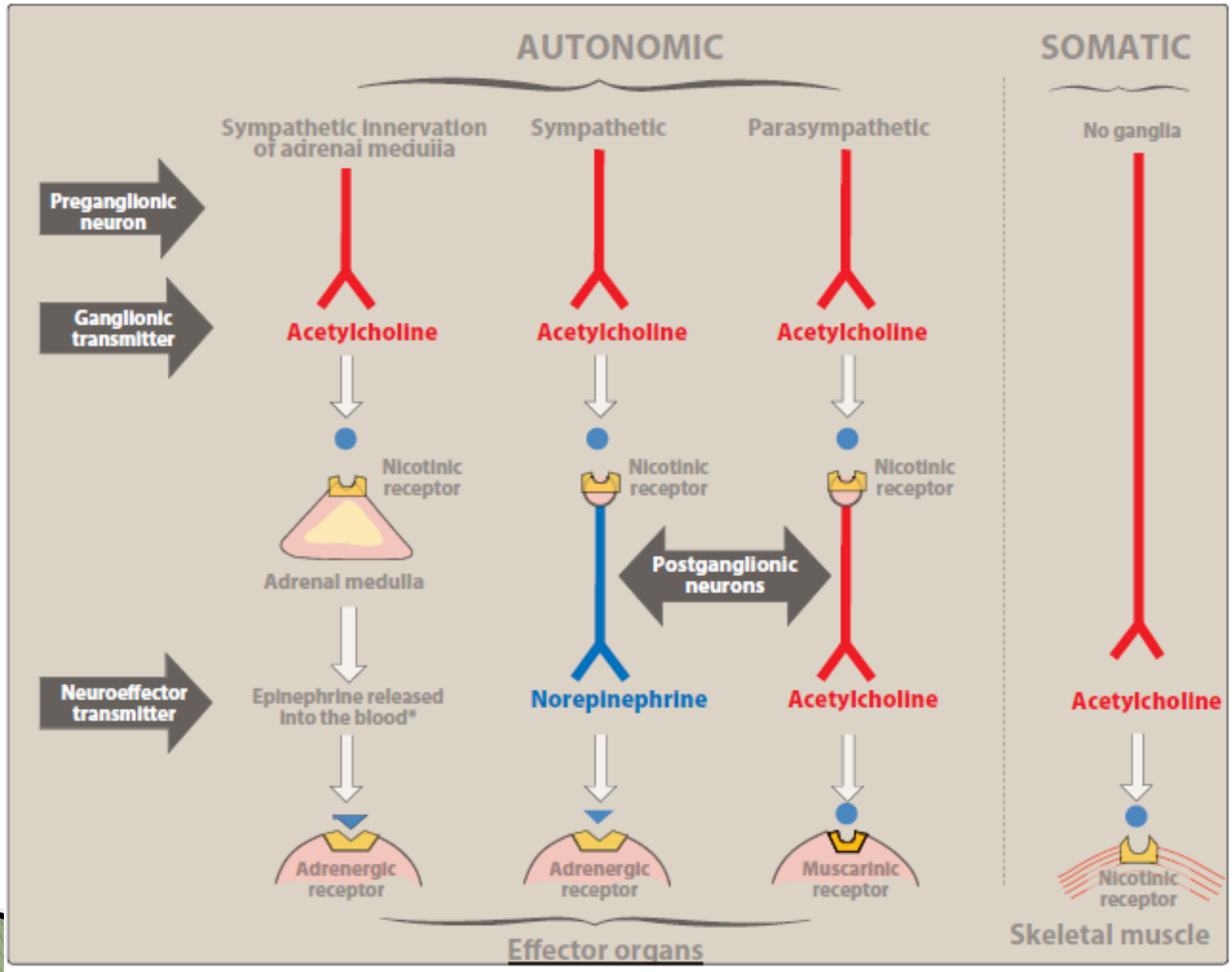
α_1 receptors are present in the arteriolar smooth muscles, Activation leads to vasoconstriction.

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.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Autonomic drugs

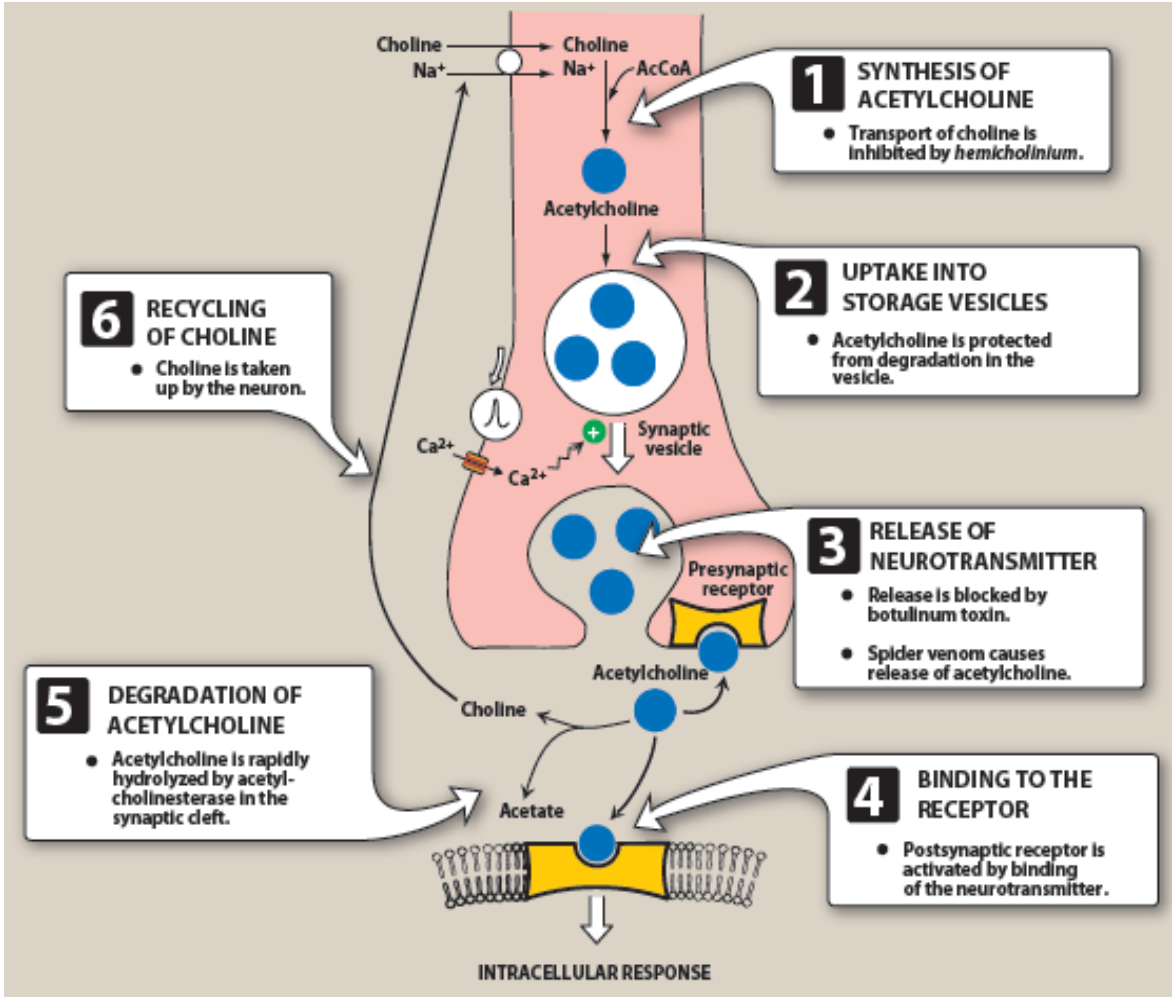
- Cholinergic agonists
- Cholinergic antagonists
- Adrenergic agonists
- Adrenergic antagonists

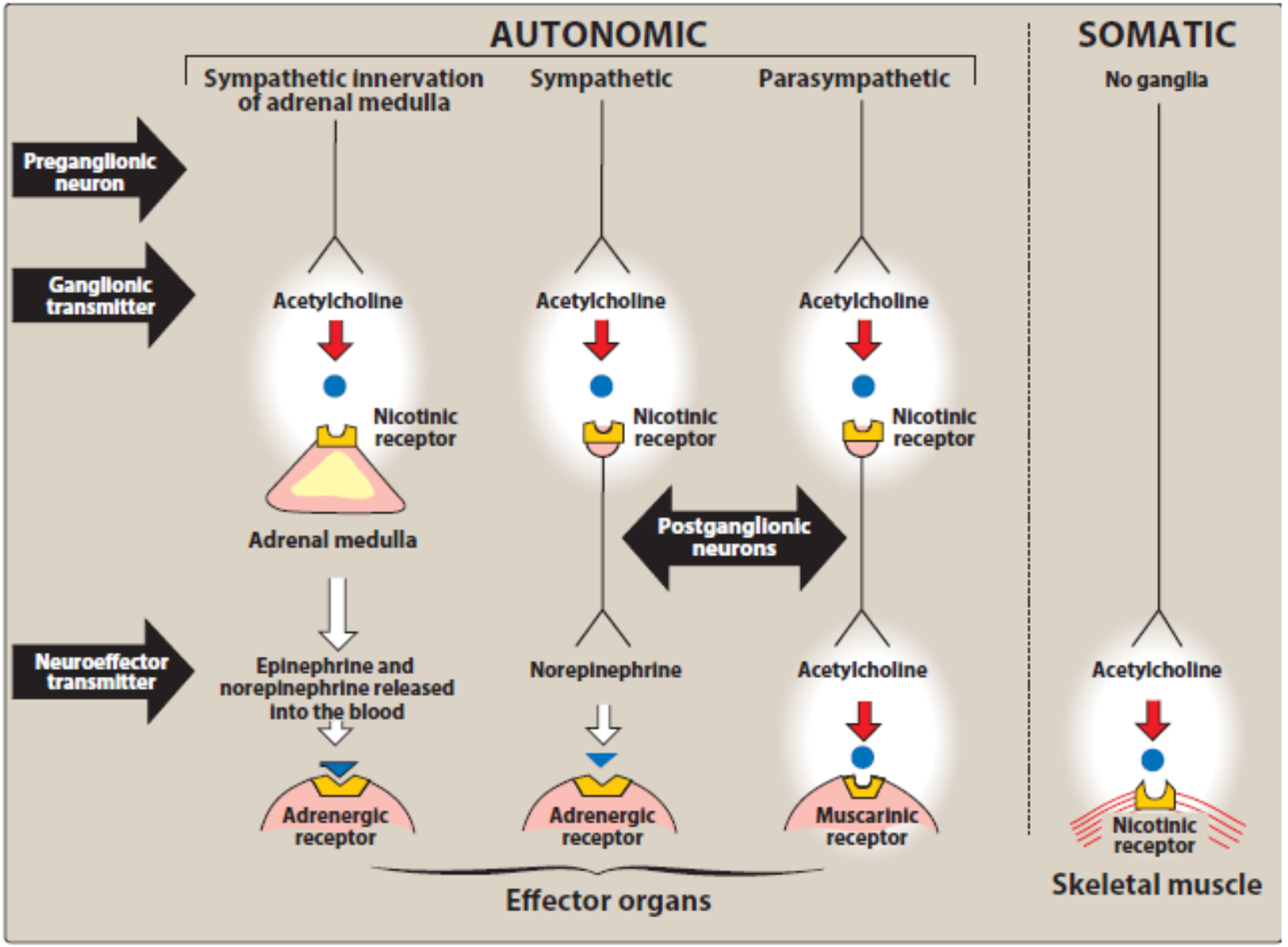
- Autonomic drugs: Drugs that produce their therapeutic effects by mimicking or altering the function of the autonomic nervous system (ANS)
  - Stimulating portions of the ANS
  - Blocking the action of the autonomic nerves

- 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

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Cholinergic receptors (Cholinoceptors)

1. Muscarinic 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
     M3 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 (decrease in heart rate)
   - Decreases stroke volume by reducing the rate of firing at the sinoatrial (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
  - Muscarinic agonist
  - Poor substrate for choliesterase
  - Increase intestinal motility
  - Stimulates the 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
  - Muscarinic and nicotinic agonist
  - Poor substrate for cholinesterase
  - Profound effects on cardiovascular and GI systems

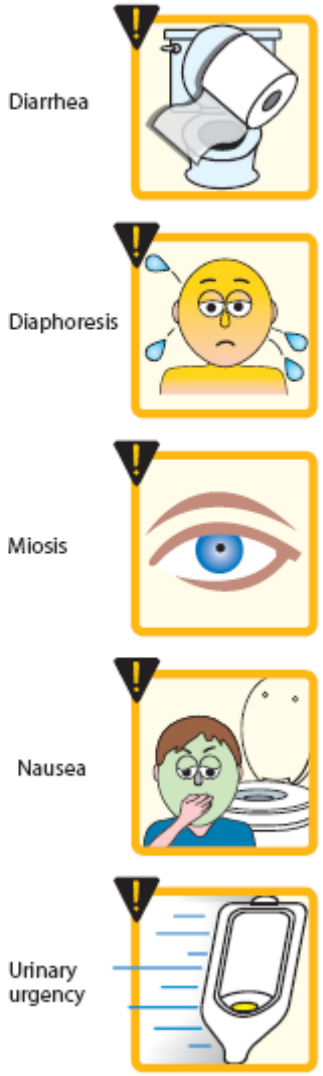
  first stimulating and then depressing (ganglion stimulation)
  - Can cause release of epinephrine from adrenal medulla due to its nicotinic action
  - Use: rarely used except in the eye as a miotic agent to treat glaucoma causing pupillary contraction and decreased intraocular pressure (IOP)
  - Opthalmic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

Direct acting cholinergic agonists

- Pilocarpine
  - Muscarinic agonist
  - Stable to hydrolysis by cholinesterase
  - Opthalmic 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 (dry mouth and lack of tears)
- Adverse effects
  - Can cross the BBB and cause CNS disturbance
  - Salivation and sweating (diaphoresis)

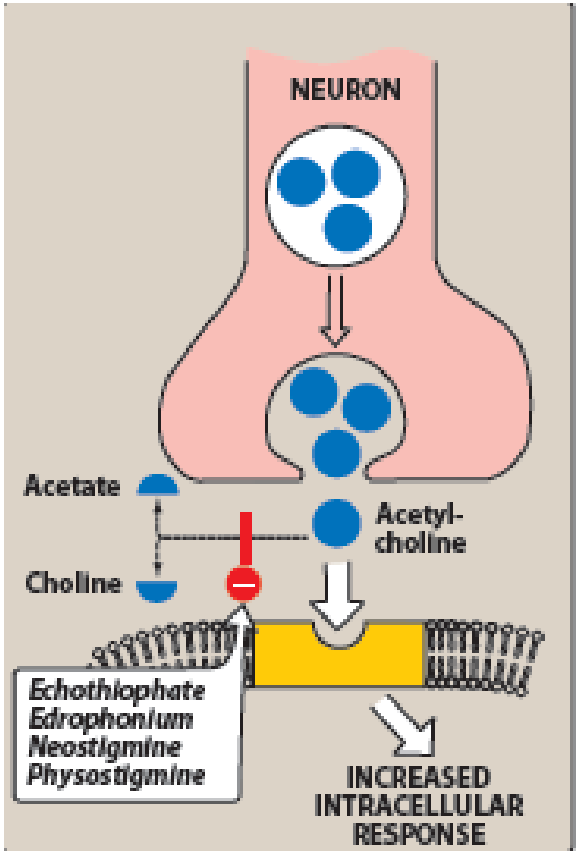
Cholinergic agonists Adverse effects

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



Indirect acting cholinergic agonists Acetylcholinesterase inhibitors

- AChE is the enzyme that cleaves ACh to acetate and choline, terminating its action
- AChE inhibitors provide a cholinergic action by prolonging the time ACh is available at the cholinergic nerve endings
- Act on muscarinic, nicotinic receptors and NMJ



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 (autoimmune disease caused by antibodies causing degradation of nicotinic receptors on NMJs)
  - 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 potentiating cholinergic activity in the body
  - Stimulates muscarinic and nicotinic sites of ANS and NMJ
  - Increases intestinal and bladder motility, used in the case of atony in either organs
  - Topically in the eye, produces miosis and lowering of intraocular pressure
  - Used to treat glaucoma
  - Used for treatment of overdose of anticholinergic drugs

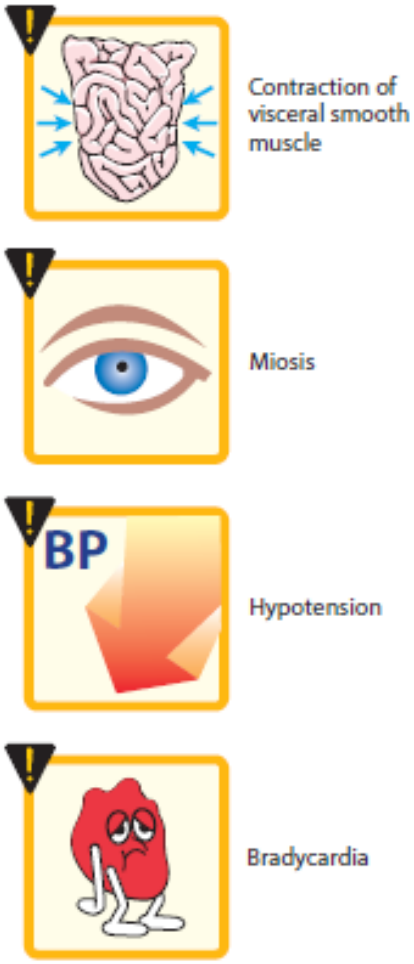


Figure 4.9
Some actions of *physostigmine*.

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.

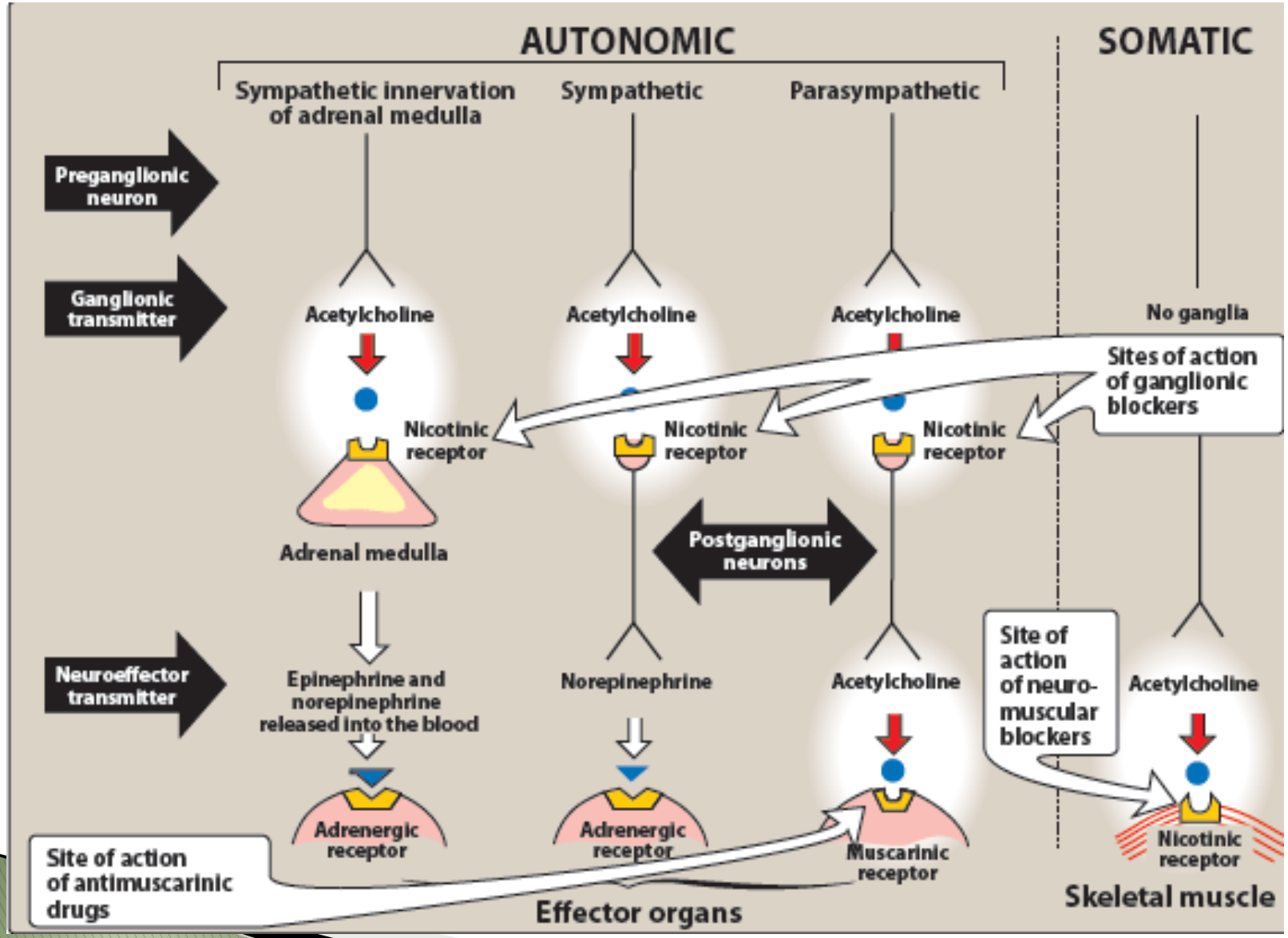
AChE inhibitors

- Organophosphate compounds
  - Irreversible inhibitors of AChE
  - Long-lasting increase in ACh
  - Many are extremely toxic and were developed by military as nerve agents (e.g. sarin)
  - Some are insecticide (e.g. parathion, malathion)
  - 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 (antimuscarinic) to reverse muscarinic 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
  - Antimuscarinic agents
  - Ganglionic blockers
  - Neuromuscular blockers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Site of action of antimuscarinic drugs
Effector organs
Skeletal muscle

Antimuscarinic agents

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

Atropine

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

Atropine

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

- 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

Antimuscarinic agents

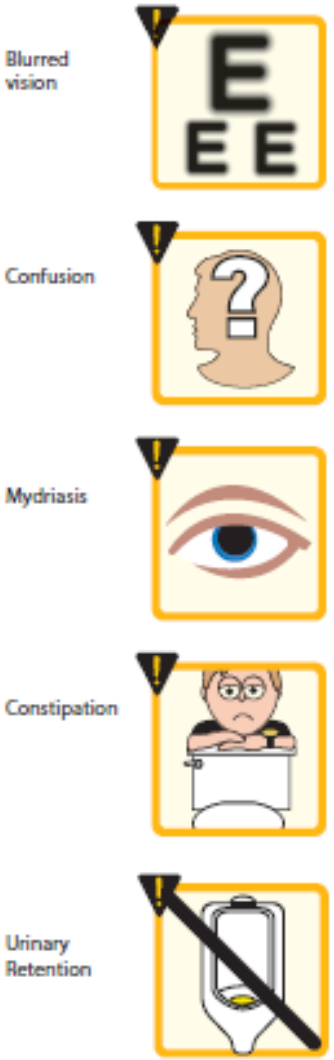
- Scopolamine
  - Used for motion sickness
  - Causes sedation
  - Adjunct drug in anesthetic procedures
  - Side effects: similar to atropine

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

Antimuscarinic agents

- Tropicamide and cyclopentolate
  - Opthalmic solutions for mydriasis and cycloplegia
  - Have largely replaced atropine due to the prolonged mydriasis observed with atropine
- Benztropine and tryhexyphenidyl
  - Centrally acting antimuscarinic agents
  - Used for Parkinson's disease which is characterized by imbalance between ACh and dopamine in the brain
- Oxybutynin and tolterodine
  - Block muscarinic 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

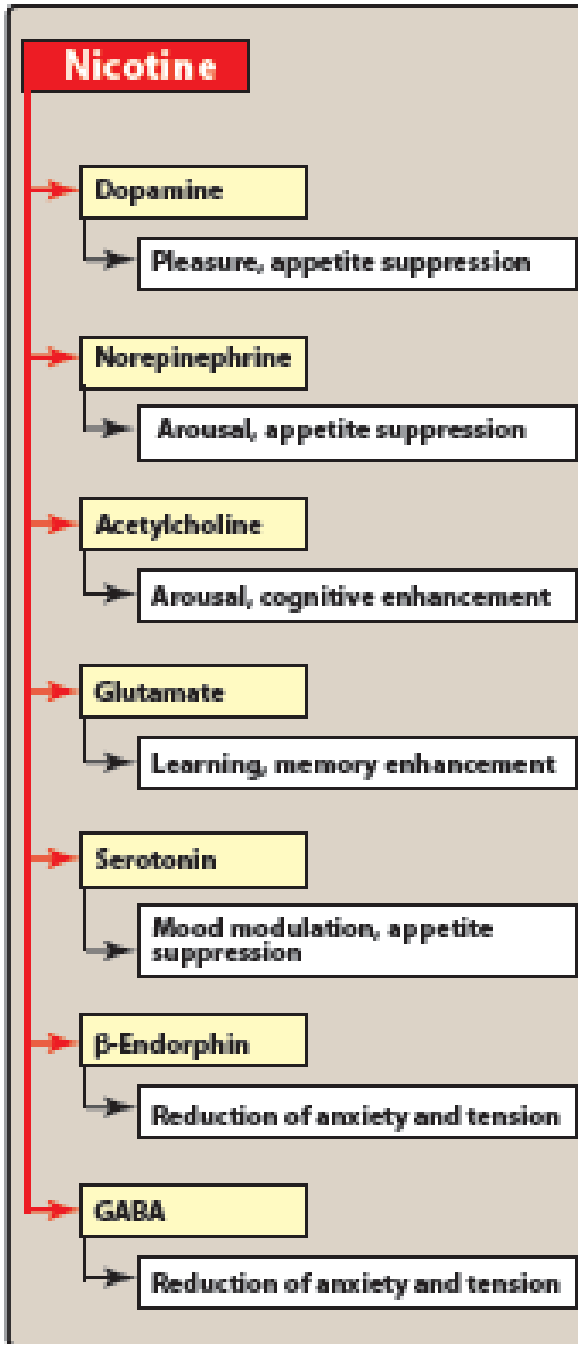


Ganglionic blockers

- 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 (high doses of anesthesia can produce respiratory paralysis and cardiac depression)
- Also used in facilitating tracheal intubation

Nondepolarizing competetive neuromuscular blockers

- Curare and tubocurare
  - No longer used for anesthesia
- Newer agents: Atracurium, cisatracurium, pancuronium, rocuronium, vecuronium
- 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 with the 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