AUTONOMIC PHARMACOLOGY - OVERVIEW

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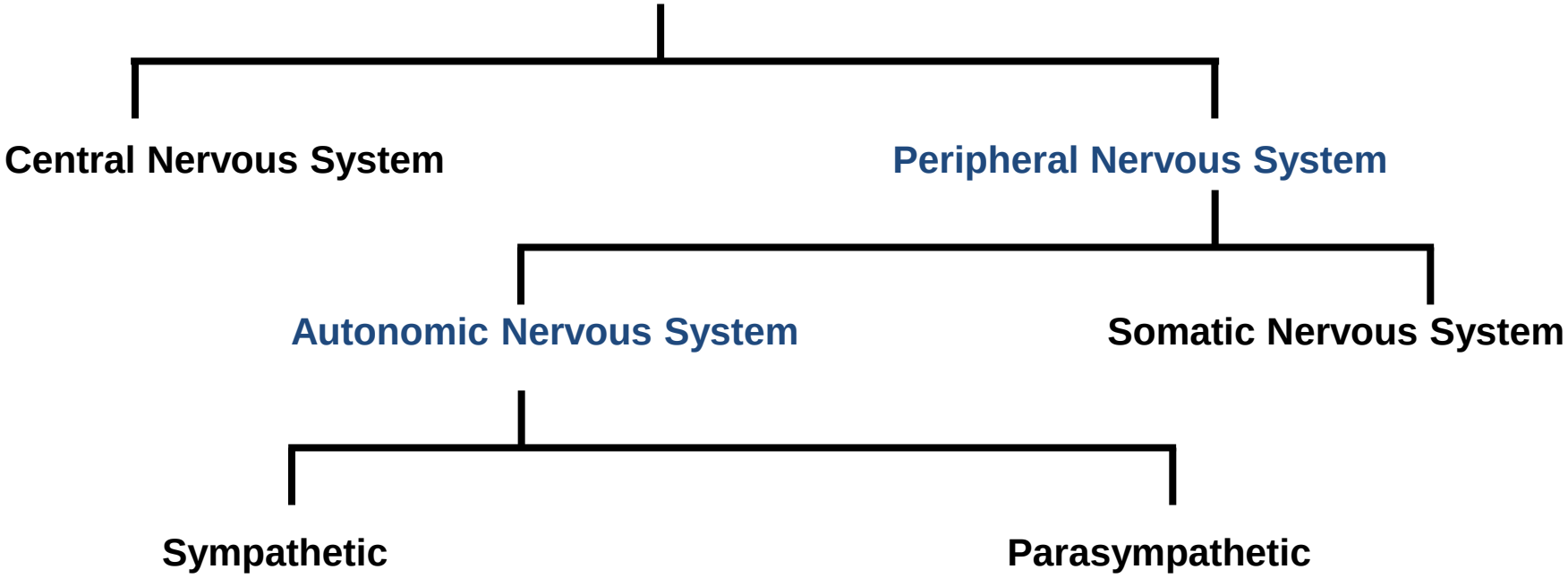
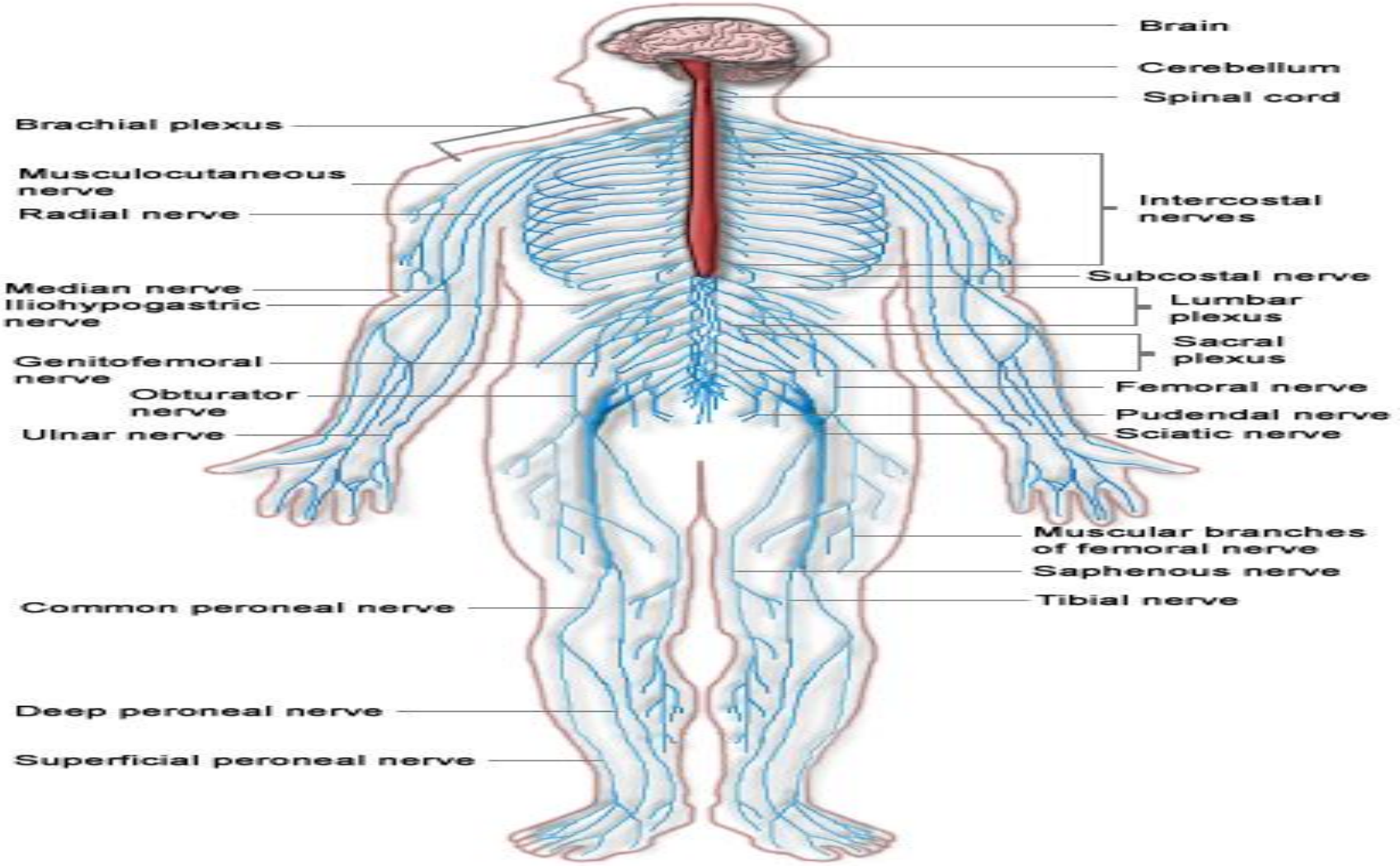
Organization of The Nervous System



Nervous System



Key definitions

Neurotransmitter

A chemical that transmits signals from one neuron to another or from a neuron to an effector cell

Synapse

A junctional connection between two neurons, across which a signal can pass

Pre-synaptic neuron

Where a neurotransmitter is synthesized, stored and released upon cell activation

Post-synaptic neuron or effector cell

Where neurotransmitter is detected and its action translated into cellular activities

Autonomic Nervous System

The autonomic nervous system is the subdivision of the peripheral nervous system that regulates body activities that are generally not under conscious control:

- Involuntary
- Functions to maintain homeostasis

Central control of the autonomic nervous system comes mostly from the hypothalamus, with some input from the limbic system and the reticular activating system

Divisions of the autonomic nervous system

- Parasympathetic division
- Sympathetic division

Anatomical distribution of the autonomic nervous system

Parasympathetic neurons

Originate in the midbrain, medulla oblongata and sacral spinal cord

Sympathetic neurons

Originate from the thoracic and lumbar portions of the spinal cord

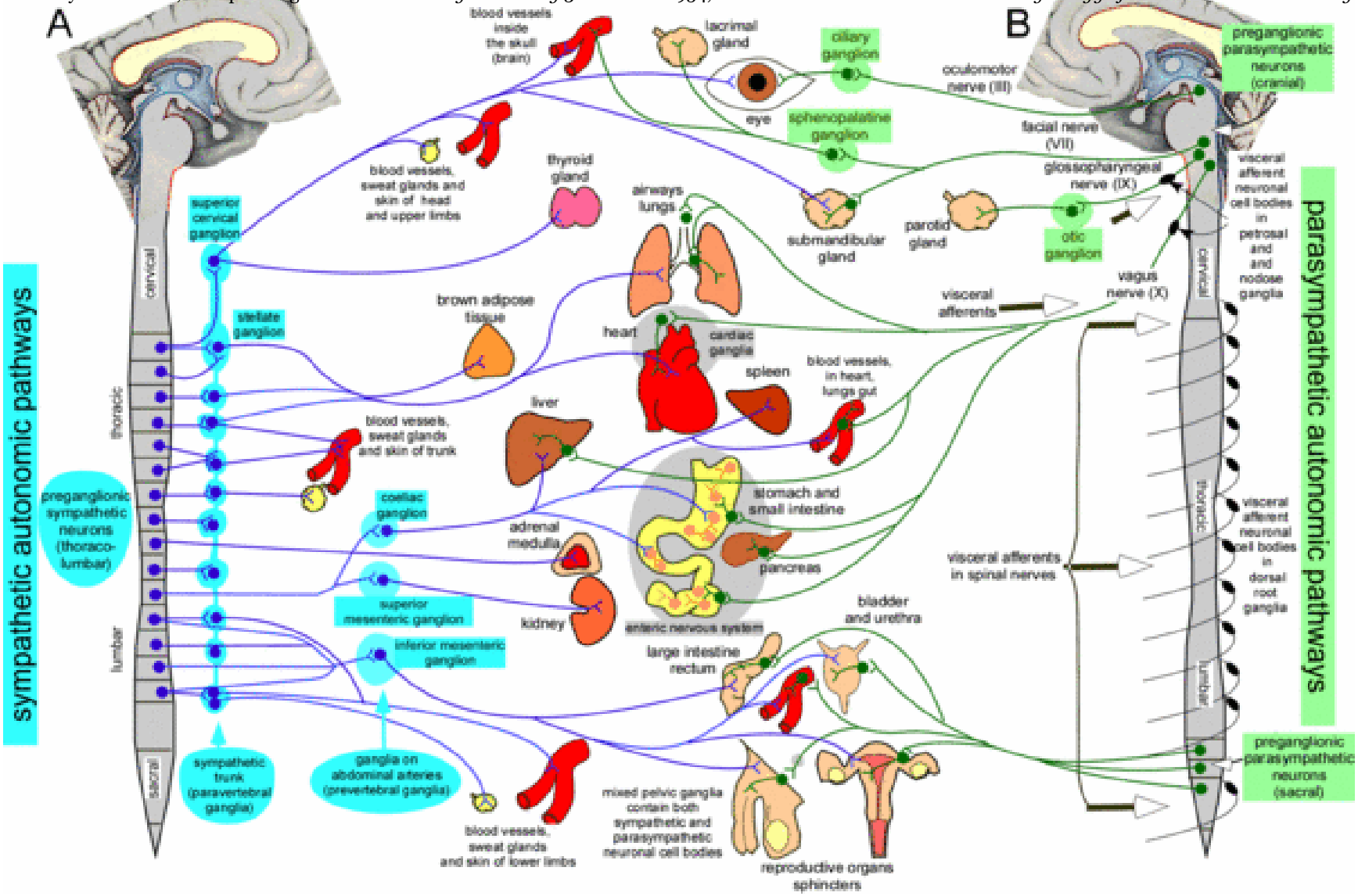
Autonomic system consists of chains of two motor neurons:

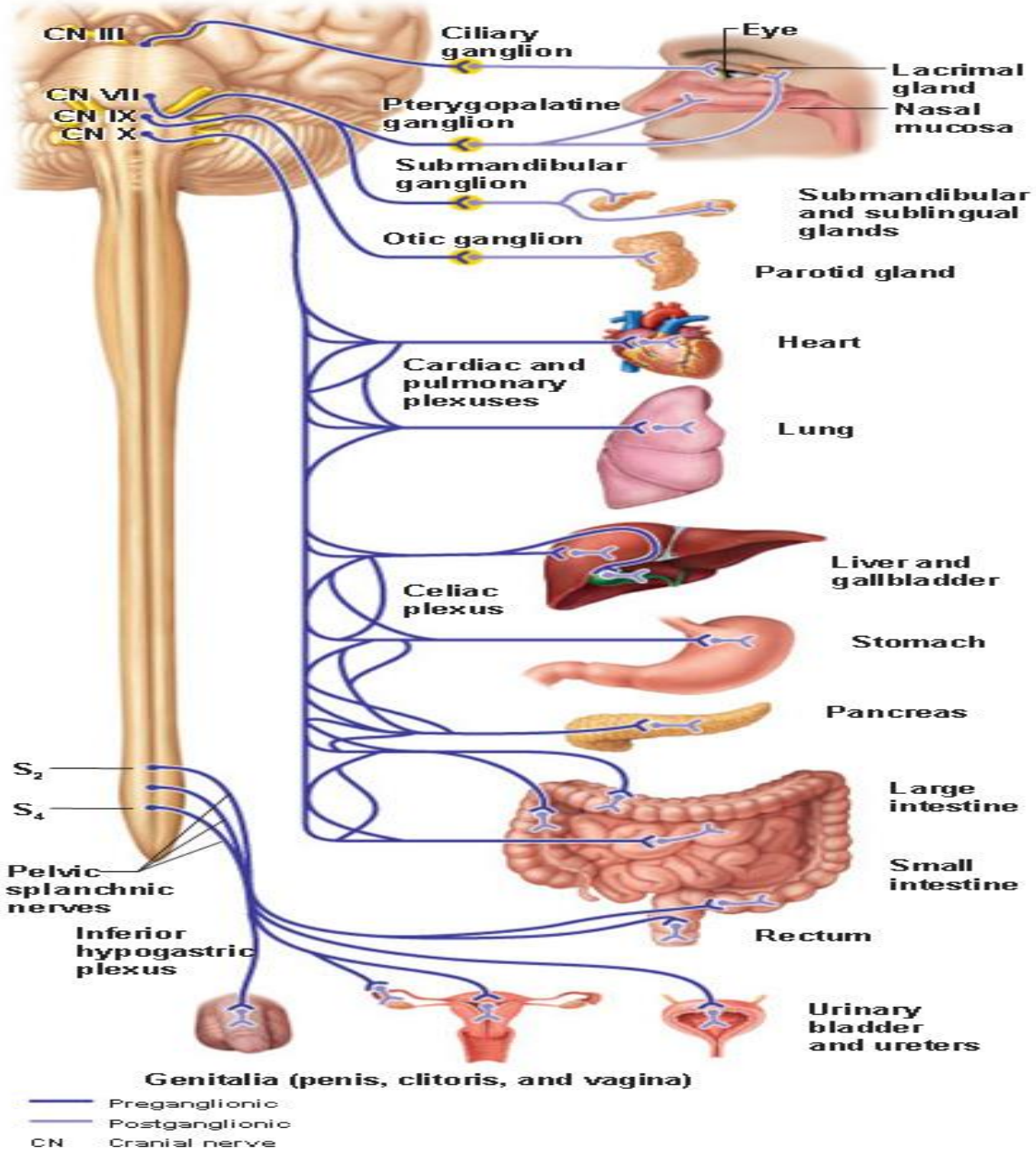
1st: Preganglionic neuron (in brain or spinal cord)

2nd: Postganglionic neuron (cell body in ganglion outside CNS)

- Axon of 1st (preganglionic) neuron leaves CNS to synapse with the 2nd (postganglionic) neuron
- Axon of 2nd (postganglionic) neuron extends to the organ it serves

Figure drawn by the authors, incorporating material from *Gray's Anatomy* 31st Edition 1954, and from Cannon and Rosenblueth *Physiology of the Autonomic Nervous System*, 193




CN III
CN VII
CN IX
CN X
Ciliary ganglion
Pterygopalatine ganglion
Submandibular ganglion
Otic ganglion
Eye
Lacrimal gland
Nasal mucosa
Submandibular and sublingual glands
Parotid gland
Heart
Cardiac and pulmonary plexuses
Lung
Liver and gallbladder
Celiac plexus
Stomach
Pancreas
Large intestine
Small intestine
Rectum
S_2
S_4
Pelvic splanchnic nerves
Inferior hypogastric plexus
Urinary bladder and ureters
Genitalia (penis, clitoris, and vagina)
Preganglionic
Postganglionic
CN Cranial nerve

Neurotransmitters in the autonomic nervous system [ANS]

- The principal neurotransmitters in the ANS are acetylcholine and noradrenaline
- All preganglionic neurons and parasympathetic postganglionic neurons use acetylcholine as neurotransmitter
- Acetylcholine is the neurotransmitter at all autonomic ganglia, neuromuscular junctions and parasympathetic tissue synapses
- Most postganglionic sympathetic neurons use norepinephrine (noradrenaline) as the neurotransmitter

There are exceptions:

<u>Sweat glands</u>

Innervation of the thermoregulatory sweat glands is anatomically sympathetic, but the postganglionic neurons release acetylcholine as the neurotransmitter

Neurotransmitters in the autonomic nervous system …. cont'd

Exceptions ….. cont'd

Kidneys

- Postganglionic neurons to the smooth muscle of the renal vasculature release dopamine

Adrenal gland

- Preganglionic neurons synapse directly on the adrenal gland, release acetylcholine, and activate nicotinic receptors in the adrenal gland medulla
- The adrenal glands release epinephrine (adrenaline) into systemic circulation

Neurotransmission in the parasympathetic nervous system

- The principal neurotransmitter in the parasympathetic nervous system is acetylcholine
- There are two types of acetylcholine receptors: nicotinic (N) and muscarinic (M)
- Neurotransmission in the ganglia is achieved by preganglionic fibers releasing acetylcholine into the synaptic space, which activates nicotinic receptors on postganglionic nerve dendrites
- Depolarization of postganglionic cholinergic nerves results in the release of their stored acetylcholine within the innervated tissue. The acetylcholine activates muscarinic receptors on effector cells to produce biological effects
- There are 5 sub-types of muscarinic receptors: M1, M2, M3, M4 and M5
- The release of acetylcholine is regulated by acetylcholine acting on presynaptic M2 receptors – activation of these receptors inhibits release of acetylcholine

Acetylcholine (Ach)

- Ach is synthesized in nerve terminals by the cytoplasmic enzyme choline acetyltransferase which catalyses the transfer of an acetate group from acetyl coenzyme A to choline that has been transported into cholinergic neurons by a sodium dependent membrane carrier
- The synthesized Ach is transported from the cytoplasm to storage vesicles
- Ach is released from the vesicles by nerve action potentials through calcium-dependent exocytosis. Release can be blocked by botulinum toxin.
- The effect of ACh on postsynaptic tissue is terminated by rapid action of acetylcholinesterase (AChE) that metabolizes ACh to acetate and choline. The liberated choline is taken into the presynaptic nerve terminal.
- Ach is not administered for therapeutic purposes because it is hydrolysed almost instantly by butyrylcholinesterase in plasma (pseudocholinesterase, plasma cholinesterase)

Functions of the parasympathetic nervous system

- Eye: constriction of the pupil (meiosis) and accommodation
- Lacrimation
- Salivation
- Slowing of the heart (bradycardia)
- Decrease in blood pressure
- Production of bronchial secretions
- Production of digestive juices from stomach, pancreas and gallbladder
- Increased gastrointestinal tract tone and peristalsis
- Sphincter relaxation
- Urination and defecation
- Penile erection

Parasympathetic nervous system

Effector Organ	Receptor Subtype	Response to Cholinergic Stimulation
Eye:		
Sphincter muscle, iris	M_3	Contract to cause meiosis
Ciliary muscle	M_3	Contract for near vision
Heart:		
Sinoatrial node	M_2	Decrease rate of depolarization
Atria	M_2	Decrease contractility
Atrioventricular node	M_2	Decrease rate of depolarization
Arteries, arterioles:		
Endothelial cells	M_1, M_3	Vasodilation (predominant) – mediated by nitric oxide
Smooth muscle cells	M_1, M_3	Vasocontriction by direct action on smooth muscle

Parasympathetic nervous system …. cont'd

Effector Organ	Receptor Subtype	Response to Cholinergic Stimulation
Respiratory:		
Tracheal, bronchial smooth muscle	M_1, M_3	Constriction
Bronchial glands	M_2, M_3	Increased mucous secretion
Gastrointestinal tract:	M_2, M_3	Increased contractility, motility & secretions
Urinary Bladder:		
Detrusor muscle	M_2, M_3	Contraction
Trigone & sphincter muscle	M_2, M_3	Relaxation
Salivary glands:	M_2, M_3	Increased watery secretion
Erectile tissue:	M_2, M_3	Vasodilation of cavernosa of penis and clitoris, increased blood pooling

Parasympathetic nervous system …. cont'd

Cholinergic Receptor subtype	Receptor distribution	Signal transduction activated
Muscarinic, M_1	CNS neurons, smooth muscle	Phosphoinositol-coupled, excitatory, increase smooth muscle contraction
Muscarinic, M_2	Cardiac conduction system, myocardium	K^+-channel activators, inhibit adenylyl cyclase
	Presynaptic nerve endings	K^+-channel activators, inhibit adenylyl cyclase, decrease neurotransmission
Muscarinic, M_3	Exocrine glands, smooth muscle	Phosphoinositol-coupled, increase smooth muscle contraction.
Muscarinic, M_4	Uncertain	Inhibit adenylyl cyclase
Muscarinic, M_5	Uncertain	Activate phosphoinositol metabolism

Neurotransmission in the sympathetic nervous system

- Preganglionic neurons (synapse with postganglionic neurons in the ganglia) release acetylcholine as the primary neurotransmitter
- Postganglionic neurons release norepinephrine as the primary neurotransmitter

Synthesis of catecholamines (dopamine, norepinephrine and epinephrine)

In presynaptic nerves, tyrosine is hydroxylated by tyrosine hydroxylase to form dihydroxyphenylalanine (dopa). Dopa is then decarboxylated by dopa decarboxylase to form dopamine. Dopamine is then transported into vesicles (this step is blocked by the drug reserpine), where it is hydroxylated to form norepinephrine. In certain areas of the brain and in the adrenal medulla, norepinephrine is methylated to epinephrine.

Norepinephrine storage and release

Norepinephrine is stored in the vesicle with ATP and neuropeptide Y (co-transmitters)

Norepinephrine is released into the synaptic cleft by exocytosis (a calcium-dependent process) when the nerve terminal is depolarized. The released norepinephrine interacts with specific adrenergic receptors (adrenoceptors) to produce tissue/organ response:

- Postsynaptic - response
- Presynaptic - modulation of further neurotransmitter release

Norepinephrine release can be blocked by such drugs as bretylium and guanethidine

Norepinephrine and epinephrine release

- Norepinephrine also exists in a non-vesicular cytoplasmic pool that is released by indirectly acting sympathomimetic amines (e.g. tyramine, amphetamine, ephedrine) by a process that is not calcium-dependent.
- Norepinephrine and some epinephrine are released from adrenergic nerve endings in the brain
- In the periphery, epinephrine is the major catecholamine released from the adrenal medulla into the general circulation, where it functions as a hormone

Termination of norepinephrine action

- The action of norepinephrine is terminated primarily by active transport into the cytoplasm of the pre-synaptic neurone (uptake 1) – this process can be inhibited by cocaine and tricyclic antidepressants such as amitriptyline. Norepinephrine is then transported by a second carrier system into storage vesicles (a process also blocked by reserpine)
- Norepinephrine is also taken into post-synaptic tissue (uptake 2)
- In the cytoplasm of pre-synaptic nerve cells, synaptic cleft and in post-synaptic tissues, norepinephrine is metabolized by monoamine oxidase (MAO) or catechol-O-methyltransferase (COMT) to inactive intermediates and finally to homovanillic acid (HVA) and methoxyhydroxy mandelic acid (VMA)

Regulation of adrenergic neurotransmitter release

Pre-synaptic receptors on sympathetic nerve terminals influence the release of norepinephrine:

- α_2-adrenergic and muscarinic M1/M2 receptors decrease norepinephrine release
- AT_1-angiotensin and nicotinic receptors increase norepinephrine release

Sympathetic nervous system

Effector Organ	Receptor Subtype	Response to Adrenergic stimuli
Eye:		
Pupillary dilator muscle	α_1	Contracts to cause mydriasis
Ciliary muscle	β_2	Relaxes to allow for far vision
Heart:		
Sinoatrial node	β_1, β_2	Increased rate of depolarization (increased heart rate - positive chronotropy)
Atrioventricular node	β_1	Increased conduction rate
Atria, ventricles	β_1	Increased contractility (positive inotropy)
Arteries, arterioles:		
Arterial smooth muscle cells in most vascular beds	α_1, α_2	Contraction (vasoconstriction)
Arteries/arterioles in skeletal muscle and brain	β_2	Relaxation (vasodilatation)
Respiratory tract:		
Tracheal, bronchial smooth muscle	β_2	Relaxation
Bronchial glands	α, β_2	Decreased mucous secretion

Sympathetic nervous system

Effector Organ	Receptor Subtype	Response to Adrenergic stimulation
Gastrointestinal tract:		
Smooth muscle wall	β_2	Relaxation, decreased motility
Sphincters	α_1	Contraction, decreased transit time
Urinary Bladder:		
Detrusor muscle	β_2	Relaxation, decreases voiding
Trigone & sphincter muscle	α_1	Contraction, decreases voiding
Metabolic function:		
Liver	α_1, β_2	Glycogenolysis
Fat cells	β_3	Increased lipolysis
Kidneys	β_1	Renin release
Sexual organs:	α_1	Ejaculation, orgasm
Adrenal Medulla:	N_N	Epinephrine release

Sympathetic nervous system …. cont'd

Adrenergic receptors and their effector systems

Adrenergic receptor	G-protein coupling	Signal transduction processes
β_1	G_s	Activate adenylate cyclase; open calcium channels
β_2	G_s	Activate adenylate cyclase; increase OR decrease intracellular calcium levels
β_3	G_s	Activate adenylate cyclase; activate fatty acid lipase
α_1	G_q	Activate PLC, PLD, PLA_2; increase intracellular calcium levels
α_2	$G_{i,o}$	Decrease adenylate cyclase; open K^+ channels; (reduced intracellular calcium) Activate PLC, PLA_2 (increased intracellular calcium)

Role of the sympathetic nervous system

Helps the body cope with external stimuli and functions during stress (triggers the flight or fight response)

Functions of the sympathetic nervous system

- Increased heart rate (tachycardia)
- Vasoconstriction of skin and viscera
- Vasodilatation in skeletal muscle
- Sweating
- Bronchodilatation
- Dilation of the pupil (mydriasis)
- Inhibition of production of digestive juices
- Inhibition of peristalsis
- Relaxation of the uterus

Integration of autonomic function

Generally the parasympathetic system causes discrete changes in organ function and usually associated with “rest and digest”:

- Increased salivary secretion
- Increased GI motility
- Increased urination, defecation
- Increased bronchial constriction, secretions
- Decreased heart rate
- Pupillary constriction, decreased visual accommodation
- Increased sexual arousal

Parasympathetic activity does not usually cause generalized organ system activation unless:

- Acetylcholine metabolism is significantly inhibited (nerve gas, insecticides)
- Exposure to muscarinic agonists (muscarine from mushrooms)

Integration of autonomic function …. cont'd

- Sympathetic nervous system is designed to provide more wide-spread activation of organ systems during severe stress
- This is assured by interconnections between sympathetic ganglia in the chain ganglia that allow almost simultaneous activation of multiple nerve bundles supplying different organs

Sympathetic activation prepares the organism to flee from or fight a potential threat:

- Pupils dilate, lens flatten for far-vision
- Heart rate, force increased
- Vasoconstriction
- Blood shunted from viscera to skeletal muscle
- Increased respiration rate
- Glucose release by liver
- Kidney blood flow and water loss decreased
- GI and bladder function decreased
- Skin blood flow decreased, pilo-erection

How do drugs influence the autonomic nervous system?

- Mimic or block the effects of the two primary neurotransmitters, acetylcholine and norepinephrine/epinephrine
- Drugs that mimic neurotransmitters are referred to as "*receptor agonists*": these drugs activate receptors
- Drugs that block neurotransmitters are referred to as "*receptor antagonists*": these drugs block the endogenous neurotransmitters from activating receptors

Classification of drugs affecting the autonomic nervous system

Parasympathetic nervous system

- Mimic acetylcholine = cholinergic = muscarinic agonists = parasympathomimetic
- Block acetylcholine = anticholinergic = anti-muscarinic = muscarinic antagonist = parasympatholytic

Sympathetic nervous system

- Mimic norepinephrine/epinephrine = adrenergic = adrenergic agonist = sympathomimetic
- Block norepinephrine/epinephrine = anti-adrenergic = adrenergic antagonist = sympatholytic

THE END