Autonomic nervous system (Lec1)

-Anything in red is not required.

-linked to emotions, behaviors, and immune system.

-To meet with the metabolic and thermoregulatory demand, the ANS adjusts blood flow, cardiac output and is integrated with the central respiratory network.

-Linked to neuroendocrinal physiology.

-Carries out its function without requiring consciousness (sometimes referred to as involuntary NS).

-Its Ultimate responsibility is to ensure physiological integrity of (cells, tissues and organs) and to maintain homeostasis despite external and internal perturbations.

-Some autonomic functions rely both on the autonomic (involuntary) and somatic (voluntary) nervous system, Ex: GI tract and urinary tract.

-Many drugs, toxins function by altering neurotransmission within the ANS (adrenergic/cholinergic) or by exerting a downstream action on autonomic or non-autonomic effector organ.

-Some drugs can have specific autonomic target organ (drugs for erectile dysfunction).

-Some natural products (mainly plants) mimic the action of neurotransmitters (Ex: muscarine/ pilocarpine/ atropine or hyoscine).

The three major divisions of ANS:

1-The enteric nervous system:

-Intrinsic to the wall of the GI tract, works with sympathetic and parasympathetic to control digestion, it influences the function of nearly all organs and controls all innervated organs and tissues except skeletal muscles.

2-The sympathetic nervous system (fight or flight):

-The word -**adrenergic**- mostly refers to sympathetic neurotransmission.

-Sympathetic and parasympathetic divisions of the ANS are anatomically and functionally distinct, they can function **antagonistically, synergistically, or independently.**

-Some autonomic organs are innervated by **both**, and they function as **physiological antagonists** (heart, bronchi, stomach and urinary bladder).

-Some autonomic organs are innervated by **both**, and they function **synergistically** to control the function (iris muscles in the eye and sexual organs).

-Some autonomic organs are innervated **only** by sympathetic (blood vessels, brown adipose tissue and pineal gland).

-Sympathetic NS is activated during intense emotions (fear, rage and pain), all elements of the sympathetic NS work in unison (**all-or-non response**), and its major rule was to allow individuals to respond to danger and threat.

-Survival might be **possible** without sympathetic NS, but the ability to adapt to environmental stressors is severely compromised.

-β-adrenoceptor agonists are used for treatment of asthma.

-β-adrenoceptor antagonists are used for treatment of (cardiovascular disorders, glaucoma, essential tremor and anxiety disorders).

3-The parasympathetic nervous system (rest and digest):

-The word -**cholinergic**- mostly refers to parasympathetic neurotransmission.

- Some autonomic organs are innervated **only** by parasympathetic (ciliary muscles and nasopharyngeal glands).

-Without an intact parasympathetic NS survival is **problematic** as you lose the ability to eliminate wastes and toxins from your body.

-Toxins like nerve gas interfere with cholinergic transmission at the neuromuscular junction and at the autonomic effector organ.

-Its role is to conserve energy, promote digestion and getting rid of waste.

α-motor neurons and γ-motor neurons

-α-motor neurons = contraction of the extrafusal fibers of the muscles.

-γ-motor neurons = sensory within the intrafusal fibers of the muscles.

-They are co-activated and work in synchrony to mediate skeletal muscle contraction, allow gross fine motor control to maintain posture and balance (Ex: locomotion, eye movement, vocalization and swallowing).

Adrenergic drugs (Lec 2+3)

-Anything in red is not required.

-Neurotransmitters: chemical mediators released by the neurons to transmit the signals through the synapse.

-Sympathomimetic: a drug that **activates sympathetic** NS.

-Parasympathomimetic: a drug that **activates parasympathetic** NS.

-Sympatholytic: a drug that **decreases or blocks sympathetic** response.

-Parasympatholytic: a drug that **decreases or blocks parasympathetic** response.

-Adrenaline (ADR) = epinephrine

-Noradrenaline (NA)= norepinephrine

Synthesis and metabolism of catecholamines:

-Phenylalanine→ Tyrosine→ Dopa→ Dopamine→ Noradrenaline (all adrenergic neurons) → Adrenaline (only adrenal medullary cells)

-NA leaking into the cytoplasm and axonal transport from the vesicles is attacked by **MOA** (monoamine oxidase).

-NA in the circulation is attached by **COMT** (catechol-o-methyl transferase) expressed in the liver and other tissues.

Sympathomimetics

-Direct: act directly as agonists for the adrenoceptors (ADR, NA, Isoprenaline)

-Indirect: act on adrenergic neuron to release NA (amphetamine)

-Mixed action: act directly as well as indirectly (dopamine)

Adrenergic receptors

α→ α1/α2

β→β1/β2/β3

(potency/antagonist/effector pathway are not required)

-The action of CAs depends on the predominant receptor type present in each tissue.

Adrenaline = has an effect on α1/α2/β1/β2

Noradrenaline = has an effect on α1/α2/β1

Isoprenaline = has an effect on β1/β2 **(no α action)**

Required effects of the autonomic nervous system: heart, blood vessels and lung airways.

-Here are the only required functions of adrenergic receptors (blue is not required), this table is not from the slides, but I thought it would be better to study it first.

A1	A2	B1	B2
-Vasoconstriction of most blood vessels. - Relaxation of GIT and urinary bladder wall.	-It is mainly found in presynaptic nerve endings where it decreases the release of NA. -Limited vasoconstriction. -Relaxation of GIT and urinary bladder wall.	-Found in the heart; ↑ all cardiac properties.	-Vasodilation in skeletal muscles, the liver and coronaries -Bronchodilation. -Relaxation of uterus.

Therapeutic classifications

1.Pressor agents (increase blood pressure): NA/DA

2.Cardiac stimulants: ADR/ ISO

3.Bronchodilation (mainly through β2 action): ISO/ drugs ending with terol (Salme**terol**/Formo**terol**)

4.Nasal decongestants: drugs ending with ine (Phenylephr**ine**, Naphazol**ine**, Pseudoephedr**ine**)

5.CNS stimulants: drugs ending with amine (Amphet**amine**, Methamphet**amine**)

6.Uterine relaxant vasodilators (used in the cases of premature labor)

Heart

-Predominantly β1, ADR increases the automaticity of SA and NA node, increasing cardiac contraction, output and oxygen consumption.

-When BP rises, the vagal nerve stimulates reflex bradycardia (slowing down of the heart).

Blood vessels

-α1/2 stimulate vasoconstriction in cutaneous, mucous membranes and renal beds (beds= blood vessels).

-β2 stimulates vasodilation in skeletal muscles, the liver and coronaries.

-sympathetic NS has no prominent effect on cerebral vessels.

Lungs

-β2 stimulates bronchodilation by the action of ADR and ISO but **not NA,** ADR can also directly stimulate the respiratory center.

-β2 stimulant drugs are used in reversible airway obstruction and bronchial asthma.

Selective β2 agonists

-They cause Bronchodilation, vasodilation, uterine relaxation without significant cardiac stimulation.

-Ex: Salbutamol has 10 times more affinity for β2 than β1.

-They can be used in bronchial asthma and delay premature labor, most important side effect is muscle tremor.

-The doctor mentioned a lot of things here that aren't directly written in the slides (blue color), so you have the option to not read them if you want.

Long-acting prodrugs: those are drugs that are usually given orally for prolongated effect.

Short-acting drugs: those are drugs used for a short-lasting effect, ex: drugs used for acute asthmatic attack, they are usually given in the form of sprays.

Administration

-CAs are orally inactive (degraded by **COMT**)

-ADR is administered systematically (S.C or I.M injection), 0.2-0.5mg dose. Lasts 0.5-2hs.

Contraindication

-Hypertensive, hyperthyroid and angina patients, and patients receiving β blockers (marked rise in BP).

-shouldn't be used **dentally** as a local vasodilator added to local anesthetics.

-Certain anesthetics sensitize the heart to the arrhythmic action of ADR.

Adrenoblockers (antagonists)

1.α blockers

-General effects: ↓peripheral resistance ↓venousreturn ↓cardiac output, pooling of blood.

-Only inhibit α receptors (no β effect).

Nonequilibrium: cannot be reversed by large concentrations of ADR, forms stable covalent bond at α sites.

Equilibrium: nonselective and competitive (can be reversed by large concentrations of ADR), examples:

1-Hydrogenated ergot alkaloids:

-**Natural** ergot alkaloids are partial agonists for serotonergic and dopaminergic receptors and weak α blockers, they produce long-lasting vasoconstriction (due to serotonergic receptors activity). Ex: **Ergo**tamine and **Ergo**toxine, used in treating migraine.

-**Hydrogenated** ergot alkaloids have increased α blocking activity, they reduce vasoconstriction, used in symptoms of mental decline in elderly and as a cognition enhancers.

Ex: Di**hydroergot**amine and Di**hydroergot**oxine

2-Nonselective α1-blockers (non-selective here means that it has no tissue specificity):

-A lot of α blockers end with sin.

-Phentolamine: short acting, used in pheochromocytoma, hypertension and cheese reaction.

-Prazo**sin**: highly selective α1 blocker, anti-hypertensive, used in benign hypertrophy (BHP), patients receiving it shouldn't stand up after being supine (dental chair).

-Terazo**sin** and doxazo**sin**: longer half-life, suitable for daily dosing in BHP.

-Tamsulo**sin**: relatively uroselective (uro means it affects the urinary tract, α1A subtype), no effect on BP and HR, relive urinary symptoms of BHP, given as modified release capsule (once daily).

3- Nonselective α2-blockers:

-Yohimbine: alkaloid from west African plant, short DOA, no clinical use.

Side effects

-Palpitations/ postural hypotension/ nasal blockage/ loose motions/ fluid retention/ inhibition of ejaculation and impotence.

2.β blockers

-usually end with lol.

-Nonselective (β1 and β2): with intrinsic sympathomimetic activity (can be partial agonists for other types of β receptors), without intrinsic sympathomimetic activity (pure blocker for all types of β receptors) or with additional α blocking activity.

-**Cardioselective** (β1): Metopro**lol**

-First generation: old/nonselective

- Second generation: β1/selective

-third generation: additional α blocking

Therapeutic uses

1.hypertension: mild anti-hypertensives/first choice because of good patient acceptability and cardioprotective.

2.Angina pectoris: taken regularly to decrease the frequency of attacks and increase tolerance.

3.Cardiac arrhythmias: suppress adrenergically mediated tachycardias during anesthesia.

4.migrane: chronic prophylaxis. Propranolol

5.Anxity: used in PTSD, phobias and stage fright. Propranolol

6.Thyrptoxicosis: rapidly controls symptoms without affecting thyroid status, used pre-operatively while waiting response of anti-thyroid drugs. Propranolol

Propranolol drug interaction

-ADR/Iso (decreases the effect of the blocking)/ Ergot alkaloids (they lead to vasoconstriction)/ Lidocaine (and anything ending with caine) / Salbutamol/ clonidine/ NSAID.

Parasympathetic system (Lec4+5)

Anything in red is not required

Anything in blue is extra information

-The main neurotransmitter in parasympathetic is Ach, but it can also have sympathetic and even somatic effects.

Synthesis and metabolism

ATP+ Acetate+ CoA→ Acetyl CoA

Acetyl CoA+ Choline→ Acetylcholine (by the action of Choline acetylase)

-It has an ester group in its structure.

-To stop its effect after the stimulation is over, it is attacked by Cholinesterase and recycled.

Cholinoceptors

There are two classes of cholinoceptors:

1.Muscarinic: stimulated by muscarine and blocked by atropine (selective), found in the heart, blood vessels, eye, glands (GI/respiratory/urinary and sweat glands) and CNS.

-Dilation of all blood vessels (indirectly by synthesis of EDRF, not by innervation), but a few receive cholinergic innervation (skin of face and neck).

-smooth muscle contraction in organs, increased secretion from glands, bronchoconstriction, miosis (contraction of iris muscles) and contraction of ciliary muscle which reduces intraocular tension (helpful in glaucoma patients).

-There are 5 subtypes, but only 3 have clinical uses:

M1: gastric secretion and vagal stimulation which causes relaxation of lower esophageal sphincter.

M2: Cardiac, mediates bradycardia through vagus nerve.

M3: Visceral (GIT) smooth muscle contraction and glandular secretions.

2.Nicotinic: no therapeutic uses.

Nm: skeletal muscles, mediate contraction (somatic NS).

Nn: all ganglionic cells on ANS (sympathetic and parasympathetic), adrenal medulla, spinal cord and brain, high dose of Ach can stimulate both ganglia of sympathetic and parasympathetic leading to tachycardia and high BP.

Parasympathomimetic

1.Direct: mimic Ach, bind directly on the receptor.

-**Alkaloids** (natural sources):

Muscarine: poisonous mushrooms, muscarinic function (no nicotinic function), not therapeutic, **Atropine** is an antidote.

Pilocarpine: muscarinic action, increased sweating and salivation, when applied to the eye causes miosis (lasting 4-8h), used in glaucoma.

Arecoline: betel nut, muscarinic and nicotinic function, CNS effect.

-**Choline esters**: Acetyl**chol**ine/Metha**chol**ine/Carbo**chol**/Bethane**chol**

2.indirect: inhibit cholinesterase, protecting Ach from hydrolysis thus increasing its concentration (anticholinesterases).

-More intense actions than direct stimulators.

They are esters of carbamic acid (can be reversible or irreversible) or derivatives of phosphoric acid (irreversible, like organophosphates).

-organophosphates are easily absorbed from all sites of the skin and lungs.

-irreversible anticholinesterases are generally found in Insecticides and nerve gases.

Therapeutic uses of anticholinesterases

1.Glucoma: optic nerve damage associated with raised intraocular pressure, miotics like pilocarpine (which is a direct stimulator) and physostigmine are used to: lower intraocular pressure, reverse mydriatics after refraction testing (medical eye examination) and prevent adhesion between iris and lens (by causing miosis, miotics help to create space and prevent the adherence).

2.Cobra bites: antagonize the action of neurotoxins.

3.Belladonna poisoning (poising with atropine, which is an anticholinergic drug): usage of physostigmine.

4.Alzheimers disease (neurodegenerative disorder, affecting cholinergic neurons): by cerebroselective anticholinesterases, we can see some symptomatic improvement. So, we use anticholinesterases to increase the concentration of Ach.

Anticholinesterases poisoning

- Anticholinesterases are easily available (agriculture and household insecticides), accidental or suicidal poisoning are common.

Immediately, there will be local muscarinic effect at the site of exposure (skin, eye, GIT), then after a while it will be followed by complex systemic effects (muscarinic as well as nicotinic).

Anticholinergic drugs (lec6)

-Also called antagonists, Atropinic or parasympatholytic.

-**muscarinic antagonists**: they block the action of Ach in ANS and CNS through muscarinic receptors.

-**Nicotinic antagonists**: block some actions of Ach (referred to as ganglionic blockers).

-all anticholinergic drugs are competitive antagonists.

-other classes of drugs like **antidepressants** and **antihistamines** posses antimuscarinic actions.

Classification

1.natural alkaloids:

Atropine: it is the prototype drug of this class, highly selective for muscarinic receptors, stimulates many medullary centers.

-It suppresses tremor and rigidity of parkinsonism by blocking cholinergic overactivity.

-Prevent salivation during dental and oral procedures.

-Causes tachycardia due to blockage of M2 receptors on SA node, but atropine doesn't have any marked effect on BP.

-Sensitivity to different organs varies:

Saliva, sweat, bronchial secretion > eye, bronchial muscle, heart > smooth muscle of intestine, bladder > gastric glands, and smooth muscle

Hyoscine: differ from atropine by producing depressant effects at low doses (drowsiness, amnesia, fatigue), does not produce CNS effects and generally used for colics and GIT disorders (not used in Parkinson).

2.Atropine substitutes (synthetic and semisynthetic):

-Synthetic: mydriatics (for eye testing), antisecretory, antiparkinsonian**.**

-semisynthetic derivatives:

Ipr**atrop**ium bromide: inhalation in bronchial asthma and COPD, and unlike atropine it does not depress mucociliary clearance in the lungs.

Tio**trop**ium: more broncho-selective than ipratropium.

-Both can be inhaled in addition to β2 agonists in sever COPD and bronchial asthma.

-In addition, Atropine substitutes can have the following effects:

-Antiemetic properties used in motion sicknesses, antispasmodic properties to hasten dilation of the cervix during labor, mydriatic and antimuscarinic action used in parkinsonism.

Ganglionic stimulants

1.Selective nicotinic agonists: nicotine (small dose)

Nicotine: from Nicotiana tabacum (smoking or chewing tobacco), has no therapeutic uses (no useful purpose of stimulation both sympathetic and parasympathetic).

-Nicotine transdermal and chewing gums for smoking cessation.

2.Nonselective (muscarinic) agonists (all the previously mentioned adrenergic stimulators): Ach, Carba**chol**, Pilocarpine and Anticholinesterase.

Ganglionic blockers

-No clinical relevance (uses).

1.competitive blockers: quaternary ammonium and amines.

-Were used in the 1950s for hypertension and ulcers but now they have been totally replaced because they produce several side effects.

2.Persistent depolarizing blockers (cause prolongated depolarization leading to more sustained and potentially irreversible effect): Nicotine (large doses), anticholinesterases (large doses).

By Mahde Al-Sabbagh

Good luck :)