Lecture 1

Nervous system

The nervous system is divided into the central nervous system (CNS; brain and spinal cord) and peripheral nervous system (somatic and autonomic nervous systems; comprised of nerves emerging from or entering the CNS).

The somatic nervous system regulates conscious movements via efferent nerves exit from the CNS to skeletal muscles.

The autonomic nervous system regulates functions of internal organs, e.g., gastrointestinal (GI) and cardiovascular, autonomously, i.e., independent of conscious effort, and is subdivided into the parasympathetic, sympathetic and enteric nervous systems. The parasympathetic nervous system (PSNS) operates largely during relaxation (rest and digest), while the sympathetic nervous system (SNS) operates largely during stressful conditions (fight or flight). The enteric nervous system (ENS) is found within the walls of GI tract. It receives nerve impulses from the PSNS and SNS and influence from chemical mediators (e.g., serotonin, substance P) released by other types of neurons within the GI tract.

Classification of the autonomic nervous system

1. **Anatomical classification**: origin of preganglionic fibers from the brainstem or spinal cord.
   - PSNS - Cranial (brain and spinal cord) and sacral outflow.
   - SNS – Thoracic and lumbar outflow.
2. **Physiological classification**: transmitter released from the nerve terminal.
   - Cholinergic – Acetylcholine (ACh) released.
   - Adrenergic– Norepinephrine (or noradrenaline; NE) or epinephrine (or adrenaline; E) released.

Anatomy of the peripheral nervous system

The cell bodies of the preganglionic fibers of the sympathetic and parasympathetic nerves originate in the brain and spinal cord. Nerve impulses arising from the preganglionic fibers release the neurotransmitter ACh at the synaptic cleft to activate the postganglionic cells. The postganglionic cells subsequently send nerve impulses along their fibers to nerve terminals thereby causing the release another transmitter (ACh, NE, E or dopamine) to the effector organs/tissues.

All preganglionic nerves release ACh. Most postganglionic parasympathetic nerve terminals release ACh, and all postganglionic sympathetic nerve terminals release NE, or in a few cases dopamine, from the sympathetic nerve terminals. The adrenal medulla releases 85% E and 15% NE.

The somatic nerves to skeletal muscles do not have a ganglion and they release ACh at the neuromuscular junction (the synapse between the nerve terminal and the skeletal muscle).

Fate of Acetylcholine (ACh)

ACh is synthetized within the cholinergic nerve terminals and is transported into and stored in vesicles. An action potential along the nerve fiber causes Ca^{++} influx, fusion of the vesicular and cell membranes, and release of ACh (exocytosis). Released ACh can activate cholinceptors (nicotinic or muscarinic
receptors) at effector organs to elicit a response, or be rapidly destroyed by the enzyme acetylcholinesterase. There is negligible circulating ACh. ACh release is blocked by botulinum toxin.

Cholinoreceptors and directly-acting cholinoreceptor agonists

ACh released at the cholinergic nerve terminals can bind to and activate cholinergic receptors (or cholinoreceptors) which can be nicotinic or muscarinic. Nicotinic receptors are present in skeletal muscle (at the postsynaptic side of the neuromuscular junction of somatic nerves) and autonomic ganglia (parasympathetic/sympathetic), and these receptors are known as neuromuscular nicotinic receptors and ganglionic nicotinic receptors, respectively. Muscarinic receptors are present in effector organs of postganglionic parasympathetic nerves. Whereas ACh can activate both nicotinic and muscarinic receptors, nicotine (an alkaloid) activates only nicotinic receptors. The muscarinic receptor agonists muscarine (an alkaloid) and methacholine (synthetic drug) activate only muscarinic receptors.

Adrenoceptors and directly acting adrenoceptor agonists

There are two main types of adrenergic receptors (adrenoceptors) at effector organs/tissues, namely, alpha (α1 or α2)-adrenoceptors and beta (β1, β2 or β3)-adrenoceptors. Epinephrine, the transmitter released by the adrenal medulla can bind to and activate all 5 subtypes of adrenoceptors (α1, α2, β1, β2 or β3); norepinephrine, the transmitter released by the adrenergic nerve terminal, can readily activate all the above subtypes of adrenoceptors except β2. A few synthetic chemicals can selectively activate either α-adrenoceptors (phenylephrine) or β-adrenoceptors (isoproterenol).

Brief generalization of the autonomic nervous system

The SNS mediates fight or flight reactions. This is exemplified by pupil dilation to facilitate light to enter the retina, bronchodilation to ease respiration, inhibitions of GI activity and urination, increase of heart rate and cardiac contraction, and reduction of arterial flow to the skin and gut, but increase of flow to skeletal muscles. These actions are mediated via released norepinephrine and epinephrine from the postganglionic nerve terminals and/or adrenal medulla, as well as by the presence of selective adrenoceptors at certain target tissues.

The PSNS facilitates activities at rest via the release of ACh at the cholinergic nerve terminals. The firing of PSNS nerves releases ACh at the nerve terminals. Released ACh can cause pupil constriction and bronchoconstriction, facilitation of GI and urinary activities, and reduction of heart rate. The influence of the PSNS depends on the presence of PSNS nerves (release of ACh) and presence of receptors (nicotinic or muscarinic).
Lecture 2

Activities of the autonomic nervous system

ACh, released from parasympathetic nerves, can activate M receptors on the sinoatrial (SA) and atrioventricular (AV) nodes of the heart to reduce heart rate (HR), and cause contraction of bronchial smooth muscle (narrowing the airway), and increase activities of the gastrointestinal (GI) tract (increased peristalsis) and bladder (urinary urgency). Released ACh is rapidly broken down by acetylcholinesterase. Parasympathetic nerves do not directly affect vascular tone because muscarinic receptors (that exist in blood vessels) are not innervated. (Note: Muscarinic receptors are further subdivided into 5 subtypes, but this is beyond the scope of this course.)

ACh (or the muscarinic agonist methacholine), given by intravenous (i.v.) injection, can cause effects similar to those elicited by parasympathetic nerve activation, except that i.v. injected ACh and methacholine can cause vasodilatation by activating muscarinic receptors on endothelial cells of arterioles (resistance blood vessels) leading to the release of nitric oxide (NO). NO then diffuses to the smooth muscle of arterioles to cause vasodilatation (increasing vascular lumen diameter). Vasodilatation of arterioles leads to a reduction of flow resistance, increase of blood flow (and cardiac output), and reduction of blood pressure (BP).

\[ \text{Blood pressure equation: } \text{BP (mmHg)} = \text{cardiac output (ml/min) x total peripheral resistance (mmHg.min/ml)}; \]

*Note*: An acute (abrupt) reduction of BP (say, by ACh) can activate the baroreceptor reflex system thereby increasing activity of the SNS and reducing activity of the PSNS. This may cause reflex tachycardia (increased HR) to compensate for the reduction in BP.

Indirectly acting cholinoceptor agonists

Chemicals that stimulate cholinoceptors (nicotinic and muscarinic) include ACh and cholinesterase inhibitors which increase the concentration of ACh in the synaptic cleft. Clinically used cholinesterase inhibitors include: 1) neostigmine, a quaternary ammonium compound that is hydrophilic, poorly absorbed, and that does not penetrate the CNS, and 2) physostigmine, a tertiary amine which is lipophilic and is well absorbed from all sites. Both have duration of action of 1-2 hours due to eventual breakdown by cholinesterase. In contrast, Soman and sarin (chemical weapons) and Malathion (an insecticide) are “irreversible” cholinesterase inhibitors which form strong covalent bonds with cholinesterase.

Directly acting cholinoceptor agonists

This includes ACh (nicotinic and muscarinic), nicotinic receptor agonists (nicotine), and muscarinic receptor agonists muscarine (an alkaloid), methacholine and bethanechol (choline esters).

Choline esters have quaternary ammonium structure (+ charged and hydrophilic) and are poorly absorbed orally and distributed to the CNS. The have limited clinical use due to multiple sites of action (lack of selectivity). *Bethanechol* can be used to increase the tone of the GI tract and urinary bladder in conditions of GI hypotonia and urinary retention, respectively.

Cholinergic blockers

*Cholinergic blockers* can block either muscarinic (e.g., atropine and scopolamine), nicotinic ganglionic (hexamethonium) or nicotinic neuromuscular (e.g., tubocurarine; an active ingredient of curarine) receptors.

*Antimuscarinic* drugs (e.g., atropine) inhibit the actions of endogenously released ACh, and can cause tachycardia, mydriasis (pupil dilation), inhibition of accommodation of the eye, dry mouth (inhibition of
secretion), reduced GI motility and urinary retention. High doses of muscarinic receptor antagonists can cause central stimulation (excitation, hallucination).

**Ganglionic blockers** inhibit functions of both the sympathetic and parasympathetic nervous systems, and are rarely used, except for emergency management of hypertension.

**Neuromuscular blockers** are used to relax skeletal muscle in preparation for surgery.
Lecture 3:

Fate of dopamine, norepinephrine (NE) and epinephrine (E)

NE is synthesized from dopamine in the adrenergic nerve terminals, and is transported into storage vesicles. Propagation of an action potential along the nerve causes Ca^{++} influx, fusion of the vesicular and cell membranes, and release of NE and/or dopamine (exocytosis). Released dopamine can activate dopamine receptors, and released NE can activate adrenoceptors (α or β) at effector organs to elicit a response. At the adrenal medulla, NE leaves the vesicles and is made into E which reenters the vesicles. The adrenal medulla releases 85% E and 15% NE into the circulation. There are prejunctional adrenoceptors at nerve terminals that modify transmitter release: α2 (↓ NE release); β (↑ NE release).

(Within the gastrointestinal tract, prejunctional α2-adrenoceptors are present to reduce release of ACh from parasympathetic nerves that innervate intestinal smooth muscles.)

The action of released NE is primarily terminated by the Uptake-1, a Na+-dependent transporter which couples spontaneous Na+ influx to uptake of NE or DA back into the nerve terminals. NE or dopamine is subsequently taken up into storage vesicles by a vesicular monoamine transporter (which is inhibited by reserpine). Cocaine, a local anesthetic, can block Uptake-1 thereby intensifying the effects of released NE and dopamine causing increased blood pressure and central stimulation, respectively.

A few “indirectly acting” amines (amphetamine, ephedrine) can activate α and β adrenoceptors as well as causing non-exocytotic release of NE (via displacement of NE from uptake transporters). [Note: Ephedrine and pseudoephedrine are active ingredients of the plant Ephedra sinica (Ma huang) which is now banned in US and Canada.)

NE that diffuses away from the nerve terminal can be taken up by Uptake-2 into postjunctional cells of organs and into the liver, and be enzymatically destroyed there.

Adrenoceptors and directly acting adrenoceptor agonists

Phenylephrine (α1-adrenoceptor agonist) can cause mydriasis, vasoconstriction, and constriction of gastrointestinal (GI) and urinary sphincters.

Salbutamol can activate β2-adrenoceptors (bronchodilation, vasodilatation, ↑ muscle tremor, relax uterus, gluconeogenesis, glycogenolysis, ↓ GI and genitourinary (GU) activity).

Isoproterenol can activate β1 (↑ cardiac rate and contractility), β2 (see above) and β3 (lipolysis) adrenoceptors.

E can activate all subtypes of adrenoceptors: α1, α2, β1, β2 and β3.

NE can activate all adrenoceptors except β2.

Actions of sympathomimetic agents

α + β Anaphylaxis. Immediate (type I) allergic reaction involves interaction of antigen with IgE on mast cells, resulting in the release of mediators of allergy (e.g., histamine, leukotrienes) thereby causing hypotension, bronchospasm, and increased secretion in the respiratory tract. Epinephrine can be given by intramuscular injection to activate adrenoceptors: α1 (vasoconstriction to ↑ BP and ↓ secretion and edema in mucous membrane), β1 (↑ cardiac contractility) and β2 (bronchodilatation). Patients at risk of developing anaphylaxis should carry an autoinjector (EpiPen) of epinephrine.
α₁ Decongestion. Phenylephrine is given orally or by nasal drops to vasoconstrict the mucous membrane to relieve nasal congestion due to hay fever or common cold. This often leads to after-congestion (rebound hyperemia).

Local vasoconstriction. Epinephrine is added to a solution containing a local anesthetic to constrict blood vessels in the skin and mucous membrane thereby prolonging the action and reducing the required dose of the local anesthetic.

Ophthalmology. Phenylephrine is topically applied to the eye to cause mydriasis to allow view of the retina.

α₂ Antihypertensive. Clonidine or α-methyl dopa can reduce blood pressure by decreasing sympathetic outflow from the CNS and release of norepinephrine (peripheral presynaptic action).

β₁ Cardiac arrest and heart block. Epinephrine may be used to increase pacemaker activity (SA node) and conduction velocity in the AV node. (Note: electrical pacemaker is safer and more effective).

β₂ Asthma. Salbutamol can be given by inhalation to dilate the bronchioles. (Note: Glucocorticoids is primary therapy to reduce edema and bronchial hyperactivity).

Premature labor. Salbutamol can be used to relax the uterus to delay labor, but benefit of treatment is uncertain.

CNS Attention deficit hyperactivity disorder (ADHD), narcolepsy. Amphetamine may be given to increase central release of NE and dopamine in children to increase their attention span. It is also used to reduce sleepiness in patients with excessive sleepiness.

Appetite suppression. Ephedrine has been used as an anorexiant in obese patients. Drug effectiveness disappears after 6 months’ therapy.

Toxicities of adrenoceptor agonists.

α₁: High blood pressure.

α₂: Sedation, dry mouth, very high blood pressure following abrupt withdrawal of therapy.

β₁: Increased heart rate, abnormal cardiac rhythm, angina (pain due to lack of oxygen supply to the heart).

β₂: Skeletal muscle tremor.

CNS: Insomnia, severe abnormal mental states (paranoid state).
Adrenoceptor antagonists

Adrenoceptor antagonists, via binding to α- or β-adrenoceptors at target organs, inhibit the α- or β-adrenoceptor mediated effects, respectively, of endogenously released as well as exogenous administered adrenoceptor agonists, e.g., epinephrine (E), norepinephrine (NE), phenylephrine, isoproterenol and salbutamol.

α-Adrenoceptor antagonists

Examples are: 1) Phentolamine: blocks both α₁ and α₂-adrenoceptors, and 2) Prazosin: selectively blocks α₁-adrenoceptors. Prazosin is used to reduce blood pressure of hypertensive patients. Its adverse effects include nasal stuffiness (due to ↑ blood flow to the mucus membrane), orthostatic hypotension (dilatation of veins thereby reducing return of blood to the heart) and tachycardia (reflex increase in sympathetic discharge in response to a decrease in blood pressure).

β-Adrenoceptor antagonists

Examples are: 1) Propranolol: blocks β₁- and β₂-adrenoceptors, and 2) Atenolol: selectively blocks β₁-adrenoceptors.

Both propranolol and atenolol are effective antihypertensive drugs. Their mechanism of action involves blockade of β₁-adrenoceptors in the CNS to reduce sympathetic outflow and peripherally (prejunctionally) to reduce NE release.

Both drugs are cardiac protective (via reducing heart rate, cardiac work and myocardial O₂ demand).

Propranolol, via blockades of β₁-adrenoceptors (↓ sympathetic nerve activity) and β₂-adrenoceptors (to reduce tremor in skeletal muscles) is also useful for the management of acute panic symptoms and performance anxiety.

As blockade of β₁-adrenoceptors reduces heart rate and cardiac contraction, caution needs to be exercised in patients with compromised cardiac function. In addition, the use of β-blockers (especially propranolol) in asthmatic patients is risky because blockade of β₂-adrenoceptors can cause bronchoconstriction.

Antiadrenergic drugs

Adrenergic neuron blockers, via inhibiting transmitter (NE and E) release from adrenergic nerves, reduce the activity of the sympathetic nervous system but not the actions of already circulating E, NE or sympathomimetic drugs.

Clonidine and α-methyl dopa. Both drugs, via activation of central and peripheral prejunctional α₂-adrenoceptors, reduce sympathetic outflow and release.

Reserpine. Via blockade of vesicular monoamine transporter, reduces uptake of dopamine and norepinephrine into storage vesicles thereby prevents transmitter release.

Guanethidine: Blocks release of NE from adrenergic storage vesicles via inhibition of propagation of the action potential (inhibition of Na⁺ influx into cells). It acts like a local anesthetic (inhibits sensation of pain at site of application).

Ganglionic blockers

As ganglionic blockers (e.g., hexamethonium) bind to and inhibit the action nicotinic receptors at both sympathetic and parasympathetic ganglia, their influences depend on predominance of parasympathetic or sympathetic tone at a particular site. Inhibition of activity in organs with high parasympathetic tone
would increase heart rate, and would also cause mydriasis, paralysis of accommodation, urinary retention
and decreased gastrointestinal tone. Inhibition of activity in organs with predominate sympathetic tone
would cause dilatation of arterioles and veins resulting in reduced blood pressure and pooling of blood in
the lower limbs.