# INTRODUCTION TO NEUROPHARMACOLOGY

## INTRODUCTION

The Nervous System is divided into two anatomical divisions:

- The Central Nervous System (C.N.S) - the brain and spinal cord
- The Peripheral Nervous System (P.N.S) - the neurons located outside the brain and spinal cord, that is, any nerve that enters or leaves the C.N.S. The PNS is further divided into the efferent nerves that carry signals away from the brain and spinal cord to the peripheral tissues and the afferent division, whose neurons bring information from the periphery to C.N.S.
- The efferent division of the P.N.S. can be further divided into two major functional subdivisions: The Somatic and the Autonomic Nervous System.
- The Somatic efferents are involved in voluntarily controlled body functions such as contraction of skeletal muscles in locomotion or posture.
- The Autonomic Nervous System (ANS) functions involuntarily to regulate essential body functions.

### The Autonomic Nervous System (ANS)

The ANS is composed primarily of visceral motor (efferent) neurons that innervate smooth muscles of the viscera, cardiac muscles, vasculature, and the exocrine glands.

### The Autonomic Efferent Neurons

The efferent neurons of the ANS are anatomically divided into two namely:

1. Sympathetic (or thoracolumbar).
2. Parasympathetic (or Craniosacral)

Both the sympathetic and the parasympathetic neurones emerge from the brain stem or spinal cord and terminate in the motor ganglia. The function of the ganglia is that it relays information between the preganglionic neurone and the postganglionic neuron. The preganglionic fibres of the sympathetic nervous system are short. They end in ganglia adjacent to the spinal cord. *The only exception is the adrenal medulla's preganglionic fibre which is analogous to a postganglionic fibre,* because it releases epinephrine and norepinephrine directly. These neurotransmitters are released into the blood stream when stimulated by preganglionic fibers. **It is important to note that the postganglionic sympathetic fibres are long like the preganglionic fibers of the Parasympathetic Nervous System which are generally long,** while the postganglionic fibres are short. The physiologic functions of the two systems usually oppose one another to bring about a state of balance. When the balance is disrupted, drug therapy may be indicated to restore the original balance necessary for homeostasis.

**The Sympathetic (adrenergic) Nervous System Receptors**

The receptors are divided into

1. Alpha-1
2. Alpha-2
3. Beta-1
4. Beta-2
5. Dopaminergic

Generally the alpha-1 and alpha-2 are stimulatory and the beta receptors are inhibitory.

**The Parasympathetic Nervous System Receptors**

The Parasympathetic **(**cholinergic) Nervous System receptors are **nicotinic** and **muscarinic** receptors.

**Neurotransmitters:**

The primary neurotransmitters of the adrenergic sites are **norepinerphrine, epinerphrine, and dopamine.** Epinephrine stimulates the alpha and beta receptors and is a potent stimulator of the heart and a powerful dilator of the bronchioles.

Acetylcholine is the neurotransmitter at the sympathetic postganglionic fibre of the sweat glands and blood vessels. The neurotransmitter for cholinergic sites is acetylcholine. Acetylcholine combines with both nicotinic and muscarinic receptors.

Cholinergic sites are found in both the *sympathetic and parasympathetic nervous* Systems. **The nicotinic receptors are found in all the *Autonomic ganglia*, in the *Adrenal medulla* and at the neuromuscular junction of the somatic nervous system. The muscarinic receptors are found at the synapse of postganglionic fibres of the parasympathetic nervous system and at few of the sympathetic postganglionic fibres.**

**How Drugs Affect the Autonomic Nervous System**

1. Mimicking neurotransmitters
2. Interfering with neurotransmitter release
3. Interfering with the breakdown or reuptake of neurotransmitters at the synapse
4. Blocking the attachment of neurotransmitters to receptors.

**Classes of Autonomic Nervous System Agents**

Cholinergic agents are drugs that stimulate receptors sites mediated by acetylcholine. This is achieved by the drug mimicking the action of acetylcholine. This could be done in two ways:

**1)** The drug might have a direct action

**2)** The drug might have an indirect action on the receptors

The drug is said to have a direct action on the receptors when it sensitizes the receptor by mimicking acetylcholine. The drug is said to be indirectly acting when it inhibits the breakdown of acetylcholine. The cholinergic drugs (agents) are also called parasympathomimetic drugs.

**Clinical Uses**

1. Aids in diagnosis of myasthenia gravis
2. Reduce the intraocular pressure of the glaucoma
3. Stimulate GI motility
4. Treat urinary retention
5. Control vomiting
6. Act as an antidote for neuromuscular blockers.

**Examples of Direct-acting Cholinergic Agents**

1. **Carbamylcholine:-** It had been used to treat atony of the gastrointestinal tract and to stimulate uterine contraction in swine.
2. **Bethanechol (urecholine):-** Used in G.I and urinary tract atony.
3. **Pilocarpine:-** It is used to treat glaucoma by reducing the intraocular pressure.
4. **Metoclopramide:-** It is used to control vomiting.

**Direct-acting Cholinergic (Anticholinesterase) Agents**

1. **Endophonium:** Is used to diagnose myasthenia gravis.
2. **Neostigmine:** These products are used to treat urinary retention, GI atony and as antidote to neuro-muscular blocking agents.
3. **Organophophate Compounds:** These are commonly used as insecticide dips and may result in toxicity if not appropriately used.
4. **Demecarium:** This is used in the preventive management of glaucoma.

**Side effects of cholinergic drugs**

Bradycardia, hypotension, lacrimation, diarrhoea, vomiting.

**Cholinergic Blocking Agents (Anticholinergics)**

Cholinergic blocking agents are drugs that oppose the effect of acetylcholine and this group of drugs elicit their effect at the muscarinic receptors of the Parasympathetic Nervous System.

**Examples:**

1. **Atropine:** It is used as a pre-anaesthetic drug to dry secretions and prevent bradycardia. It is also used to treat organophosphate poisoning.
2. **Scopolamine:** This is used in anti diarrhea medication.
3. **Methscopolamine:** Similar to the effect of Scopolamine.
4. **Glycopyrrolate:** Is a quaternary ammonium compound with action similar to atropine, but has provides longer action than atropine and is used as a preanaesthetic agent.
5. **Aminopentamide:** Is used to control diarrhea in dogs and cats.
6. **Pralidoxime (2-PAM):** A cholinesterase reactivator used to treat organophosphate intoxication.

**Side effects:**

Drowsiness, disorientation, tachycardia, photophobia, constipation, anxiety, burning at site of injection.

**Adrenergic (Sympathomimetic Agents)**

Adrenergic agents are agents that mimick the action of epinephrine or norepinephrine**.** Adrenergic agents are classified as catecholamines or non-catecholamines and either of these categories can be classified according to the specific receptor types activated namely:

1. Alpha -1
2. Alpha -2
3. Beta -1
4. Beta -2

**Examples**

1. **Epinephrine (Adrenaline):** Used to increase heart rate and cardiac output and constriction of the blood vessels in the skin.
2. **Norepinephrine:** Stimulates alpha receptors. It influences vasopressor effect and raises the blood pressure.
3. **Isoproterenol: I**t is a beta stimulator it is used as a bronchodilator.
4. **Dopamine:** Dopamine is a precursor of epinephrine and norephinephrine. It is dose dependent and to treat shock and congestive heart failure.
5. **Ephedrine, Terbutaline**, **Albuterol:** these are beta agonists and are brochodilators.
6. **Phenylpropanolamine (prolamine):** Is used to treat urinary incontinence in dogs.

**Side effects:**

- Tachycardia, hypertension, nervousness, cardiac arrhythmias, pulmonary oedema.

**Adrenergic Blocking Agents**

Adrenergic blocking agents are used to disrupt the activity of sympathetic nervous system. The adrenergic blocking agents are classified as:

a) Alpha blockers

b) Beta blockers

c) Ganglionic blockers

**Alpha Blockers**

- Alpha blockers have limited use in veterinary medicine
- The most frequently used in veterinary medicine is **Phenoxybenzamine**

**1) Phenoxybenzamine** could be used in

a) Laminitis treatment in horses

b) Urethral obstruction in cats.

**2) Tranquilizers** (acepromazine, droperidol) - These tranquilizers act as alpha blockers and cause vasodilation.

**3) Prazosin:-** is used as an hypotensive agent.

**4) Yohimbine:-** used to treat xylazine toxicity.

**5) Atipamezole:-** this is a reversal agent of medetomidine

**Side effects of alpha receptor blockers**

- Hypotension, tachycardia, muscle tremors (phenoxybenzamine), seizures (acepromazine).

**Beta blockers**

Used to treat glaucoma, arrhythmias, and hypertrophic cardiomyopathy.

**Examples**

1. **Propranolol:-** is used to treat cardiac arrhythmia and hypertrophic cardiomyopathy.
2. **Timolol:-** is an ophthalmic preparation that is to treat glaucoma.
3. **Atenolol:-** used in a similar way to propranolol.

**Side effects of B-Blockers**

Bradycardia, hypotension, worsening heart failure, bronchoconstriction.