Systemic Pharmacology

Lecture 6: Neuropharmacology

Objectives: Upon completion of following 2 lectures, student will be able to

1. Identify important divisions of the Nervous System.
2. Compare and contrast the actions of the sympathetic and parasympathetic divisions of the autonomic nervous system.
3. Discuss the classification and naming of autonomic drugs
4. Describe the therapeutic actions, indications, pharmacokinetics, contraindications and cautions, most common adverse reactions, and important drug–drug interactions associated with drugs acting on the Autonomic NS
5. Outline the nursing considerations, including important teaching points, for patients receiving drugs acting on the Autonomic NS

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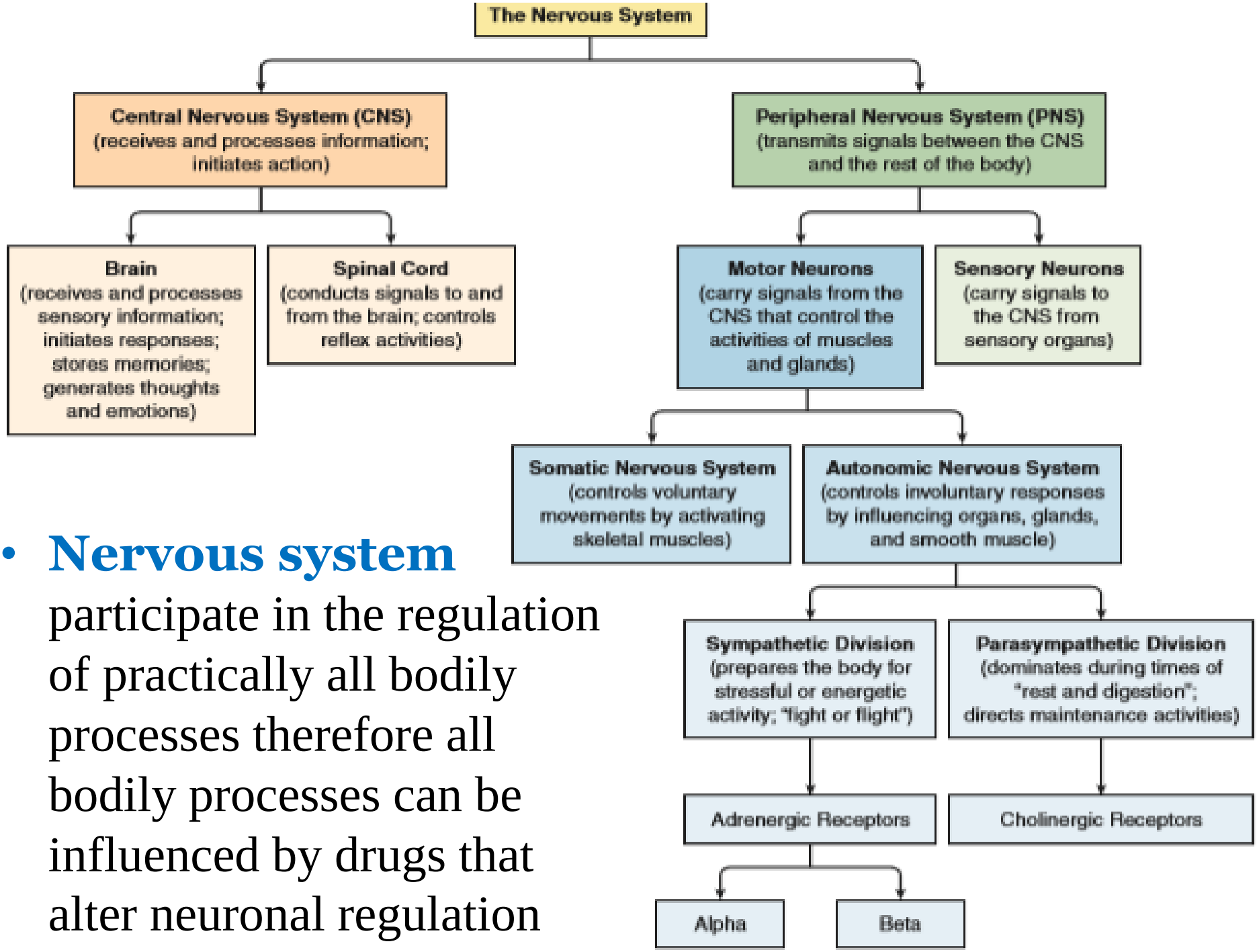


- **Nervous system** participate in the regulation of practically all bodily processes therefore all bodily processes can be influenced by drugs that alter neuronal regulation

- **Neuropharmacology** is the study of drugs that alter processes controlled by the nervous system.
- **Neuropharmacologic drugs** produce effects equivalent to those produced by excitation or suppression of neuronal activity.
- Neuropharmacologic drugs constitute a large and important family of therapeutic agents. These drugs have widespread clinical application: they used to treat conditions that range from depression to epilepsy to hypertension to asthma…..
- Neuropharmacologic drugs can be divided into two broad categories:

1) Peripheral nervous system (PNS) drugs
2) Central nervous system (CNS) drugs.

Peripheral nervous system (PNS) drugs

- To understand peripheral nervous system drugs, we must first understand the peripheral nervous system itself.
- The peripheral nervous system has two major subdivisions:
- (1) the somatic motor system and (2) the autonomic nervous system.
- Autonomic NS controls involuntary (automatic) body functions and has three principal functions: ❶ Regulation of heart, ❷Regulation of secretary gland (salivary, gastric, sweat, & bronchial gland), and ❸ Regulation of smooth muscles (muscle of bronchi, blood vessels, urogenital system, & GIT).
- The autonomic nervous system is further subdivided into the **parasympathetic nervous system** and the **sympathetic nervous system**.

Drugs acting on the Autonomic NS

❶ Drugs act on Parasympathetic NS (cholinergic system)

- **Cholinergic Drugs** (Parasympathomimetics)
- **Anticholinergic Drugs** (Parasympatholytics)

❷ Drugs act on Sympathetic NS (adrenergic system)

- **Adrenergic Drugs** (Sympathomimetics)
- **Antiadrenergic Drugs (**Sympatholytics)

- For each autonomic NS drug that you study, you should learn the identity of the receptors at which the drug acts, the normal responses to activation of those receptors, and whether the drug increases or decreases receptor activation.

Question??

- What is meant when drugs are described as cholinergic or anticholinergic?

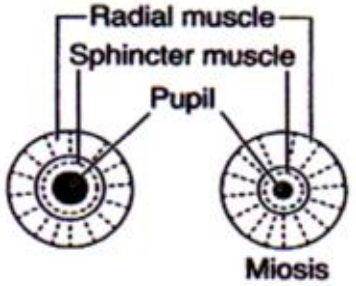
Cholinergic drugs.

(Parasympathomimetics)

- Cholinergic drugs or parasympathomimetics because their effect mimics the effect of parasympathetic nerve stimulation.
- Cholinergic drugs are drugs with acetylcholine-like effects and stimulate the cholinergic receptors {Nicotinic (N_N and N_M), and Muscarinic (M) receptors}.
- These cholinergic drugs induce the rest-and-digest response

Pharmacological effects produce by cholinergic drugs

Receptor Subtype	Location	Response to Receptor Activation
Nicotinic$_N$	All autonomic nervous system ganglia and the adrenal medulla	Stimulation of parasympathetic and sympathetic postganglionic nerves and release of epinephrine from the adrenal medulla
Nicotinic$_M$	Neuromuscular junction	Contraction of skeletal muscle
Muscarinic	All parasympathetic target organs:	
	Eye	Contraction of the ciliary muscle focuses the lens for near vision Contraction of the iris sphincter muscle causes miosis (decreased pupil diameter)
	Heart	Decreased rate
	Lung	Constriction of bronchi Promotion of secretions
	Bladder	Voiding
	GI tract	Salivation Increased gastric secretions Increased intestinal tone and motility Defecation
	Sweat glands*	Generalized sweating
	Sex organs	Erection
	Blood vessels†	Vasodilation



*Although sweating is due primarily to stimulation of muscarinic receptors by acetylcholine, the nerves that supply acetylcholine to sweat glands belong to the sympathetic nervous system rather than the parasympathetic nervous system.
†Cholinergic receptors on blood vessels are not associated with the nervous system.

- **There are two groups of cholinergic drugs:**

1. **Directly acting drugs (Muscarinic agonists):**
   bind to muscarinic receptors and increase their activity throughout the body

e.g., **Bethanechol, Methacholine, Carbachol**

Pilocarpine, Muscarine

★All of the direct-acting cholinergic drugs have longer durations of action than Ach. Because these drugs are relatively resistant to the destructive effects of the enzyme AchE.

★These agents used infrequently today because of their widespread parasympathetic activity. More-specific and less-toxic drugs are now available and preferred.

- 2. **Indirectly acting drugs** also called **Cholinesterase Inhibitors:** Drugs that increase the concentration of Ach at cholinergic receptors, usually by inhibiting acetyl-cholinesterase (AchE) enzyme, which in turn causes activation of muscarinic receptors, nicotinic receptors in ganglia and the NMJ, and cholinergic receptors in the CNS, and include the following:

a. Reversible cholinesterase Inhibitors ☆Neostigmine ☆ Physostigmine ☆ Pyridostigmine ☆Ambenonium ☆Tacrine and Donepezil ☆Edrophonium (have very brief duration of action)

b. Irreversible cholinesterase Inhibitors

- The irreversible inhibitors produce prolonged effects and are highly toxic. These drugs binding to AchE irreversibly, the binding is permanent, therefore effects persist until new molecules of enzyme can be synthesized.
- These agents used primarily as poisons (i.e., Organophosphate compounds – insecticides and nerve gases).
- The only therapeutic use of these drugs is in the treatment of glaucoma – ☆Echothiophate – only one drug available.

- **Therapeutic Uses of Cholinergic drugs**
- Therapeutic drugs that work by altering parasympathetic nervous system function are used primarily for their effects on the GIT, the bladder, and the eye. Occasionally, these drugs also used for effects on the heart and lungs.

1. Directly acting cholinergic drugs used to treat glaucoma:

- ☆Pilocarpine ☆ Carbachol

2. Direct-acting drug e.g., ☆ Bethanechol orally used (nowadays is rarely used) to treat postoperative abdominal distention due to paralytic ileus and postpartum or postoperative urinary retention due to urinary bladder atony. However, it has only a limited role in the relief of urinary retention; its use has been superseded (out of date) by catheterization.

3. The major use of reversible cholinesterase inhibitors is treatment of myasthenia gravis.

- For Diagnosis: Edrophonium (short duration of action)
- For Treatment: Neostigmine, Pyridostigmine

4. Secondary uses for reversible cholinesterase inhibitors are treatment of Alzheimer's disease, glaucoma, Parkinson's disease dementia, and poisoning by muscarinic antagonists.

- **Adverse effects**
- Cholinergic drugs have limited usefulness in medicine, partly because of the adverse reactions that may occur during administration.
  - Unless applied topically, as in the treatment of glaucoma, cholinergic drugs are not selective in action. Therefore, they may affect many organs and structures of the body, causing a variety of adverse effects.
  - **Muscarinic responses**:
  - **Neuromuscular Effects**.
  - **CNS**. Effects on the CNS vary with drug concentration.
  - Topical administration usually produces few adverse effects, but a temporary reduction of visual acuity (sharpness) and headache may occur.
  - Adverse effects unrelated to inhibition of AchE can also occur. Tacrine presents a high risk of hepatotoxicity, which limits its use.

- **Contraindications**

1. Hypersensitivity to the drugs
2. Urinary or GI tract obstruction
3. Individuals with asthma
4. Individuals with peptic ulcer disease
5. Patients with inflammatory abdominal conditions and recent bowel surgery
6. Patients with hyperthyroidism
7. Pregnant women should not take cholinergic medications. The safety of these drugs has not been established for use during pregnancy (Pregnancy Category C), lactation, or in children.

- Care should be exercised in administering pilocarpine to elderly patients because it can enter the CNS and affect memory and cognition, even when applied topically to the eye.

Cholinesterase inhibitors toxicity and management

- **Toxicity** can result from

* Ingestion of certain mushrooms
* Overdosing with direct acting cholinergic drugs or cholinesterase inhibitors.
* Organophosphate insecticides: poisoning may occur accidentally during their manufacture and use – poisoning may occur by accident ingestion of organophosphate insecticides or from attempted suicide.
* Most organophosphate cholinesterase inhibitors are highly lipid soluble. As a result, they can be absorbed directly through the skin and distributed easily to all tissues and organs.
* In addition, a number of cholinesterase inhibitors, including the nerve gases have been used in chemical warfare.

- **Nursing consideration:**

Preadministration assessment:

- ✓ Assess the patient's condition in relation to disorders for which cholinergic drugs are used.
- In patients known to have myasthenia gravis, assess for muscle weakness.
- In patients with possible urinary retention, assess for bladder distention, time and amount of previous urination, and fluid intake.
- In patients with possible paralytic ileus, assess for presence of bowel sounds, abdominal distention, and elimination pattern.
- In patients with Alzheimer's disease, assess for abilities and limitations in relation to memory, cognitive functioning, self-care activities, and pre-existing conditions that may be aggravated by a cholinergic drug.
- Identifying High-Risk Patients

- **Nursing consideration:**

✓ **Nursing diagnoses:** Determine the potential nursing diagnoses related to drug therapy and health problems that the drug might cause.

✓ **Planning**: patient goals and expected outcomes including specific interventions directed to solving or preventing the problem

✓ **Ongoing Evaluation and Interventions**

✓ Intervention with continues observation to ensuring therapeutic effects and minimizing adverse effects

✓ Monitor the patient for adverse effects or toxicity of the drugs

✓ Evaluate the effectiveness of drug therapy by confirming that the patient goals and expected outcomes have been met

- **Anticholinergic Drugs** (Parasympatholytics) and can be divided into:
  - **Antimuscarinic drugs or muscarinic antagonists**
  - **Antinicotinic drugs** and include: ganglion-blocking agents and neuromuscular-blocking agents

Anticholinergic drugs (Parasympatholytics)

- Drug that are used to block or opposes the effect of Ach at cholinergic receptors in the parasympathetic nervous system.

Antimuscarinic drugs or muscarinic antagonists

(Atropine related drugs)

- Antimuscarinic drugs, e.g., **Atropine** and **Hyoscine**, produce their effects selectively by binding with muscarinic receptors & preventing their activation by endogenous Ach or other muscarinic agonist drugs.
- ☆**Atropine:** the oldest known muscarinic blocking compounds, is natural alkaloids from the deadly night shade *Atropa belladonna* and is the best prototype drug of this group. Like all other receptor antagonists, atropine has no intrinsic activity, and can produce its effects only by blocking the activation of muscarinic receptors and prevent Ach from interacting with receptors on target effector organs.
- At therapeutic doses, atropine does not affect the nicotinic action of Ach on the autonomic ganglion or on skeletal muscle.

- Specific pharmacological effects of atropine & other antimuscarinic drugs on body tissues and organs (heart, smooth muscle, glands, and the eye) are opposite to those caused by muscarinic activation (previous table).
- **Home work:** What are the pharmacological effects of atropine?
- ☆ **Pharmacokinetics:** Atropine and other antimuscarinic drugs are readily absorbed, partially metabolized by the liver, and eliminated primarily in urine, half-life of about 4 hours. Atropine can be given orally, topically and injection.

Clinical indications

- **Preoperative use or Pre-anesthetic medication**:
- **Ophthalmology**:
- **GI Disorders:** Intestinal Hypertonicity and Hypermotility
- **Genitourinary Disorders** :
- **Respiratory Disorders:**
- **Cardiac Disorders:**
- **Used as antiemetic to prevent Motion Sickness:**
- **Parkinson's disease: e.g.,** centrally acting antimuscarinic agent **(Benztropine)**.

- **Toxicity and Poisoning:** Atropine is a specific antidote to poisoning of direct & indirect cholinergic drugs that activates muscarinic receptors.

Adverse reactions: Adverse reactions that may be seen with the administration of a cholinergic blocking drug include:

- Gastrointestinal tract – dryness of mouth caused by decreased salivation, nausea, vomiting, difficulty in swallowing, heartburn, Constipation, caused by reduced in intestinal tone and motility.
- Eyes – blurred vision (paralysis of ciliary muscle may reduced visual acuity), mydriasis, cycloplegia, increased intraocular tension, photophobia (aversion to bright light)
- CNS – headache, flushing, nervousness, drowsiness, weakness, insomnia, nasal congestion, fever.

- Urinary tract—urinary hesitancy and retention, dysuria
- Cardiovascular system – palpitations, tachycardia (especially after higher doses of atropine)
- Anhidrosis (a deficiency or absence of sweat). Since sweating is necessary for cooling, people who cannot sweat are at risk of hyperthermia.
- Asthmatic attack by causing thickening and drying of bronchial secretion
- Other – urticaria, anaphylactic shock, other skin manifestations.

- The severity of many adverse reactions is often dose dependent, that is, the larger the dose, the more intense the adverse reaction. Even in normal doses, some degree of dryness of the mouth almost always occurs.

- **Nursing consideration:**

Preadministration assessment:

✓ Assess the patient's condition in relation to disorders for which anticholinergic drugs are used.

- Assess for disorders in which anticholinergic drugs are contraindicated.
- Assess use of other drugs with anticholinergic effects (drug interactions), such as antihistamines (histamine1 receptor antagonists, antipsychotic agents, and tricyclic antidepressants) these drugs can cause excessive muscarinic blockade.
- Identifying High-Risk Patients

✓ **Nursing diagnosis**: Determine the potential nursing diagnoses related to drug therapy and health problems that the drug might cause.

✓ **Planning**: patient goals and expected outcomes including specific interventions directed to solving or preventing the problem

✓ **Ongoing Evaluation and Interventions**

✓ Intervention with continues observation to ensuring therapeutic effects and minimizing adverse effects

- **Nursing consideration:**

✓ Monitor the patients for adverse drug effects and apply measures used to minimize these adverse effects, include:

⇨⇨Dryness of mouth – decreased salivation can dry the mouth. Teach patients that dry mouth can be relieved by chewing gum, sucking on hard candy and sipping fluids.

⇨⇨ Constipation – advise patients that constipation can be reduced by increasing dietary fiber and fluids.

⇨⇨ Blurred vision – warn patients to avoid hazardous activities if vision is impaired.

⇨⇨Photophobia – muscarinic blockade prevents the pupil from constricting in response to bright light. Keep hospital room lighting low to reduce visual discomfort. Advise patients to wear sunglasses outdoors.

- ⇨⇨Urinary retention and dysuria – advise patients to voiding just prior to taking drugs. If urinary retention is severe, catheterization may be required.
- ⇨⇨Tachycardia – monitor pulse and report significant increases.
- ⇨⇨Hyperthermia: The nurse should observe patients receiving this drug during the hot summer months for signs of heat prostration (fever or hyperthermia, warm dry skin, tachycardia, flushing, mental confusion) because this drug decrease sweating & sweating is necessary for cooling. Patient should advise to avoid activities that might lead to overheating
- ✓ Evaluate the effectiveness of drug therapy by confirming that the patient goals and expected outcomes have been met