Drtugs affecting the Autonomic Nervous System(ANS)

Nervous system composed of two main divisions

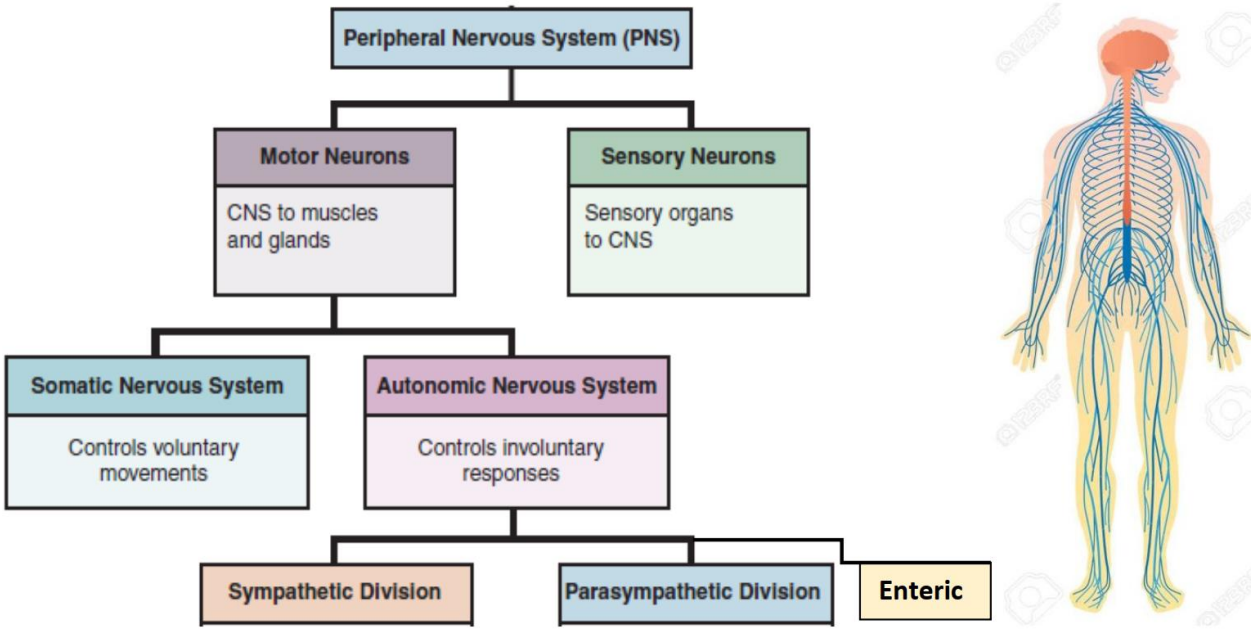
1- Central nervous system (CNS) **which consist from the brain and the spinal cord**

2- The peripheral nervous system (PNS), **which include all neurons outside the CNS (The** afferent **sensory and** efferent **motor neurons).**

The efferent motor neurons subdivided into:

(1) the *somatic motor system* **(involved in voluntary control)**

(2) the *autonomic nervous* **system (ANS) which subdivided into** *enteric*, *parasympathetic and sympathetic* **nervous system.**



The ANS innervate involuntary visceral organs as

(1) Heart .

(2) Smooth muscles of (bronchi, blood vessels, urogenital system, and GI tract and eye).

(3) Exocrine secretory glands (salivary, lachrymal, gastric , sweat, and bronchial).

⊡ Differences between somatic and autonomic transmission:

i- The autonomic nervous system regulates the functions of involuntary vital organs without conscious of the mind , while somatic nervous system regulates the voluntary function of skeletal muscles.

ii- Autonomic neurons usually carries nerve impulses from the CNS to the effector organs through two types of neurons :

1) Preganglionic mylinated neurons 2) Postganglionic non mylinated neurons.

While somatic carry impulses through single myelinated neuron to the skeletal muscle.

iii- The Autonomic possess both excitatory and inhibitory effects while somatic mediated an excitatory effect only cause contraction of skeletal muscles.

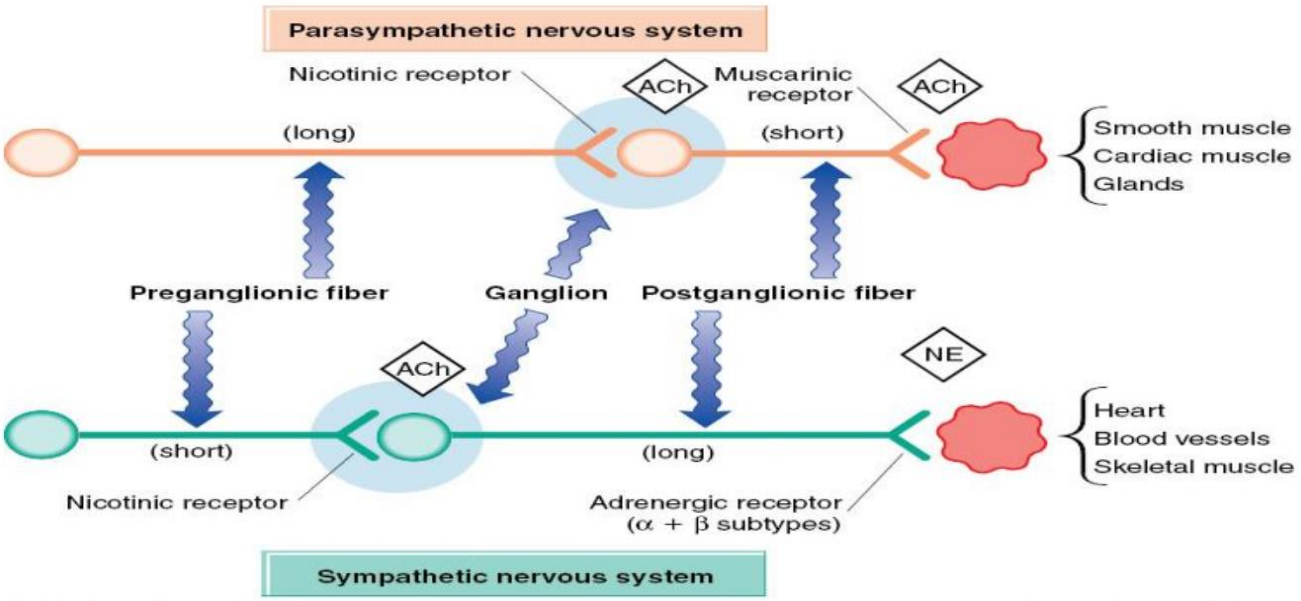


FIGURE 20-1 Parasympathetic and sympathetic nervous systems and their relationship to one another. *ACh*, Acetylcholine; *NE*, norepinephrine.

▣ Functional differences between sympathetic and parasympathetic divisions

• The sympathetic activity increased in response to *stressful situations* as *fear, anger, exercise, trauma, hypoglycemia, cold weather., producing* (Fight and Flight reaction). These situations required energy and associated with increase in heart rate , blood pressure, and increase in blood flow through coronary arteries and to skeletal muscles, providing glucose for the brain and fatty acids for muscles, as well as involve in dilation of the pupils, bronchioles and reduces GI motility and affects function of bladder.

• The parasympathetic nervous system usually function to counteract or oppose the actions of the sympathetic division, and its activity increase during rest (rest and digest response)

result in slowing of HR, increase gastric secretions, empty bladder and bowel, focus on near vision ,constrict pupil and bronchi. This system concerned primarily with *digestion of food and excretion of wastes*. In addition helps the *control of vision* and *preserve energy* .

▣ Autonomic Receptors

1- Cholinergic receptors on which Acetyl choline (Ach)

2- Adrenergic receptors on which Nor Epinephrine(NE) + Adrenaline (Epinephrine)

Also dopamine at certain level can act on adrenergic receptors

▣ Subtypes and locations of Autonomic Receptors

1- Cholinergic receptors: that mediate responses at all sites where *acetylcholine* is the transmitter, and present in two types:

i- Muscarinic receptors:

These are metabotropic (GPCRs) receptors located postsynaptically at the effector organs that supplied by the parasympathetic fibers. <u>There are five subtypes of muscarinic receptors:</u>

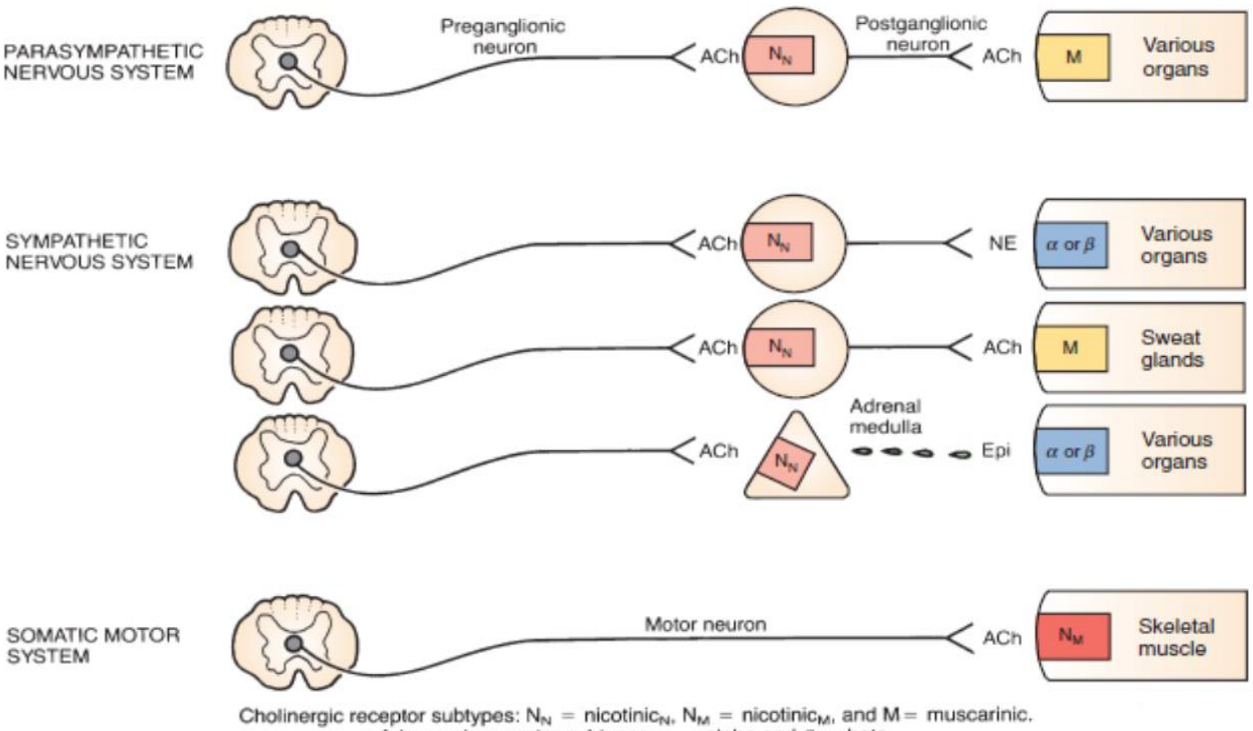
- M1 (CNS & gastric parietal cell)
- M2 (CNS, Heart)
- M3 (CNS, Smooth muscle, exocrine gland)
- M4& M5 found in CNS

ii-Nicotinic receptors :

These are ionotropic (ligand-gated ion channel) receptor, located at the adrenal medulla, autonomic ganglia (sympathetic and parasympathetic) ganglia in addition to the CNS and such receptors known as (Nn). While the muscular subtype of nicotinic receptors located at the neuromuscular junction (NMJ) known as Nm..

2- The Adrenergic receptors; mediate responses to *Norepinephrine , Epinephrine and dopamine*.

The adrenergic receptors were classified into *alpha and beta* which further subdivided into (α1,α2, and β1, 2 and 3)



Cholinergic receptor subtypes: N_N = nicotinic$_N$, N_M = nicotinic$_M$, and M = muscarinic.
Adrenergic receptor subtypes: α = alpha and β = beta.

- **Locations of cholinergic and adrenergic receptor subtypes.**

1. *Nicotinic$_N$* receptors are located on the *cell bodies of all postganglionic neurons* of the *parasympathetic* and *sympathetic* nervous systems. *Nicotinic$_N$* receptors are also located on cells of the *adrenal medulla*.
2. *Nicotinic$_M$* receptors are located on *skeletal muscle*.
3. *Muscarinic* receptors are located on *all organs* regulated by the *parasympathetic* nervous

Drugs affecting Autonomic transmission
Drugs that alter the function of ANS are used primarily for their effects on the GIT, bladder, heart, lungs and the eyes.
I- Drugs affect the Parasympathetic or cholinergic transmission
1-Drugs that enhance the cholinergic transmission known as (Parasympathomimetics, Cholinomimetics or Cholinergic Agonists)

2-Drugs that reduce or inhibit the cholinergic transmission called (Anticholinergic, cholinergic blockers or antagonists)

II- Drugs affect the adrenergic or sympathetic transmission
1- Drugs that enhance the adrenergic transmission (Sympathomimetics or adrenergic agonists)
2- Drugs that reduce or inhibit the adrenergic transmission (Antiadrenergic or adrenergic receptor blockers or antagonists) .

⊡Cholinergic Drugs
Parasympathomimetics = Cholinomimetics = Cholinergic agonists
Cholinergic drugs induce the rest-and-digest response produce Acetylcholine-like effects and stimulate the cholinergic receptors {Nicotinic (NN and NM), and Muscarinic (M) receptors}.
Clinical Ach has no therapeutic benifit as systemic drug , its used only for experimental procedures and locally present as intraocular preparation to produce miosis during ophthalmic surgery. Ach is rapidly inactivated by Ach Esterase enzyme (AchE).

⊡ Pharmacological actions of (Ach)
1- Activation of Nn nicotinic receptors
o Activation of these receptors present at autonomic ganglia will promotes ganglionic transmission at all ganglia of both sympathetic and parasympathetic. While activation of Nn receptors present in adrenal medulla to promote the release of epinephrine.
o Activation of nicotinic M (muscle) receptors causes contraction of skeletal muscle.
2- Activation of muscarinic receptors produce response relative to the organ involved ;
1- Effect on the Eye→ Contraction of muscle of the iris, resulting in miosis (reduction in pupillary diameter).
2- Urinary bladder→ increase frequency of urination by causing contraction of the detrusor muscle and relaxation of the trigone and sphincter muscles .

3- Effect on CVS;
Heart → Slowing of heart rate (negative chronotropic), slow firing of SA node and decrease conductivity and
Blood vessels : Diltation of blood vessels by indirect mechanism that may decrease the blood pressure.
4- GIT→ increase tone, motility and secretions result in abdominal cramps and increase bowel movement (defication)
5- Respiratory system→ constriction of bronchial smooth muscle and increased r secretions
6- Increase exocrine secretions ; Salivation, sweating , secretion of gastric acid ,bronchial secretions ,….

At recommended dosages, cholinergic drugs *primarily affect the muscarinic receptors,* but at *high dosages the nicotinic receptors can also be stimulated*. Most of desired effects come from *muscarinic receptor stimulation*; many of the undesirable adverse effects are due to *nicotinic receptor stimulation.*

Cholinergic Drugs
1-Cholinergic agonist (Cholinomimetics);
These drugs can stimulate the parasympathetic nervous system producing effect similar to that of endogenous Ach.
They were classified according to their *mechanism of action* into;
***1- Direct-acting* drugs bind directly to cholinergic receptors and activate them.**
***2- Indirect-acting* drugs work by inhibiting the action of acetylcholinesterase by one of two ways:**
***a-* Reversibly bind to cholinesterase for short to intermediate period of time.**
b-Irreversible binding provide prolong or permanent inhibition , in this situation the body must then generate new enzymes to override the effects of the irreversible drugs.

• Direct-Acting Cholinergic Agonists
Include drugs which can activate cholinergic receptor directly, and broadly classified into two groups:
1) Choline esters; include *synthetic esters of choline,* such as *Methacholine, carbachol* and *bethanechol*.
2) Naturally occurring alkaloids; such as *pilocarpine* (muscarinic agonist)

Pharmacological effects of cholinomimetics:

✓ **Cardiovascular effects**

➢ **Decreased heart rate , ↓Cardiac output and conductivity.**

➢ **Indirect Vasodilatation and lower the mean arterial BP**

✓ **Intestine and bladder**

➢ **Increased gastric secretions**

➢ **Increased gastrointestinal motility**

➢ **Increased urinary frequency**

✓ **Eye**

➢ **Constriction (miosis)**

➢ **Reduced intraocular pressure(IOP)**

➢ **Accommodation for near vision (contraction of ciliary muscle)**

➢ **Increase lacrimation and congestion of conjuctival blood vessels.**

✓ **Increased salivation and sweating**

✓ **Respiratory effects; Cause constriction of bronchial smooth muscle with increased of bronchial secretion.**

● **In general effects of cholinomimetics can be summarized by DUMBBELSS acronym**
[Diarrhea, Urinary incontinence , Miosis, Bradycardia, Bronchospasm , Emesis, Lacrimation, Salivation, and Sweating] .

Synthetic (Direct-acting)choline esters
All choline esters are quaternary compound, hydrophilic, poorly absorbed orally with limited penteration to CNS, and they have longer duration than Ach .
A-Methacholine; Effective on muscarinic receptor, with no nicoting action and longer duration than Ach. Its mainly used for diagnosis of bronchial asthma.
B. Carbachol: its has both muscarnic and nicotinic action , and resist the hydrolysis by AchE. Because of its nicotinic effect , it's use limited for pharmacological study and for topical application as eye drop to reduce intraocular pressure in patients with glaucoma.
C- Bethanechol: It has only muscarinic effect , stable against the effect of AchE , given orally or by injection to stimulate and increase motility of non obstructive atonic intestine or bladder .

Natural direct acting cholinomimetic drug
• **Pilocarpine;**
It a natural lipid soluble drug, absorbed orally and can penetrate the CNS at therapeutic doses. clinically used as the drug of choice for emergency lowering of intraocular pressure (IOP) of both open-angle and angle-closure glaucoma.
- Used to reverse the mydriatic effect of atropine .

- Also given orally to promote salivary or lacrimal secretions in patients with xerostomia.

Indirect-acting cholinergic agonists (Reversible):
Inhibition of AChE provide indirect cholinergic action by preventing the degradation of ACh. This results in an accumulation of ACh in the synaptic space . Therefore, these drugs can provoke a response at all cholinoceptors, including both muscarinic and nicotinic receptors of the ANS, as well as at the NMJ and even in the CNS.

Adverse effects of cholinomimetics
- Nausea –diarrhea- abdominal cramps- salivation,…
- Bradycardia , Hypotension, …..
- Diaphoresis (increase sweating) & urination
- Bronchospasm and increase secretions.
- Miosis result in visual disturbance
- Muscle weakness (Nicotinic effect)

● Contraindications (patients at risk):
- patients with hypersensitivity to the drug
- Patients with peptic ulcer disease
- Patients with recent bowel surgery or obstructive bladder or intestine
- Asthmatic patients
- Hyperthyroid or coronary artery disease
- Pregnancy (Category C) , lactating women, & children
- Parkinson's (For centrally acting cholinergic drugs)
- Acute inflammation of the eye
Interactions:
Anticholinergics (Atropine), antihistamines, and sympathomimetics may antagonize cholinergic drugs and lead to reduced response to them. While cholinomimemitic drugs have an additive effects.

Nursing Implications
A- Preadministration assessment:
1-Identify the goal of treatment to assess baseline data for patient's condition relative 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 patient memory, cognitive functioning,& self-care activities.....

2- Assess patients at risk of *allergies* , *presence of GI obstructions, asthma, peptic ulcer disease, hypertension, or coronary artery disease* .
3- Take initial vital signs (B.p, HR, Respiration,..
B- Implementation : Administration assessment
▪ Administration of drug as ordered [*Route, Dose, and frequency*] to improve therapeutic effects.
▪ e.g; Encourage patients with myasthenia advised to take medication 30 minutes before eating to help improve chewing and swallowing.
▪ For muscarnic agonists should be given 1hr before meal or 2hrs after meal to reduce gastric upset
▪ Therapeutic effects of anti-Alzheimer's drugs may not occur for up to 6 weeks
C- Evaluate therapeutic effects
o e.g; In patients with urinary retention/hypotonic bladder, urination should occur within 60 minutes of bethanechol administration
D- Monitor for adverse effects; HR, BP, Respiration and secretions.
o Patients should notify their physician if they experience side effects as muscle weakness, abdominal cramps, diarrhea or difficulty breathing
E- Management of toxicity : muscarnic symptoms of overdose DUMBBLESS
❖ Atropine is the antidote for cholinergics, and it should be available in the patient's room for immediate use if needed.