Autonomic Nervous System 4: Reflexes
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OBJECTIVES:

Please note that these objectives pertain to ANS lectures 1-4.

At the end of these lectures you should know and understand the following material:

1. The relationship between the organization of the sympathetic and parasympathetic divisions of the ANS to their overall physiological effects.
2. Anatomical and functional differences between the skeletal neuromuscular junction and autonomic neuroeffector junctions.
3. Transmitters used at ganglionic and neuroeffector junctions and highlights of the transmitter life cycle: Storage, release, biological inactivation, metabolism and de novo synthesis for acetylcholine (Ach), norepinephrine (NE) and the hormone, epinephrine (EPI).
4. Receptor types for Ach and the catecholamines, NE and EPI and their effects.
5. The mechanism of action of other transmitters/mediators including ATP, NO and peptides.
6. The organization of autonomic reflexes.
7. The overall physiological effects of the parasympathetic and sympatho-adrenal systems and the receptor types that mediate the responses.

Reading: Berne, Levy, Koeppen and Stanton: Physiology, 5th edition. 2004; Ch. 11, Pages 206-215 –Table 11-1 is too detailed. Use Table in handout.
Costanzo: Physiology, 2006 Ch. 2, Pages 45-64

Note: Please follow the version in the handout wherever discrepancies exist between the textbooks and the handout.

LECTURE IV OUTLINE

AUTONOMIC REFLEXES

Schematic autonomic reflex
Comparison with somatic reflexes

Examples of reflex control:

Pupillary light reflex
Reflex activation of adrenal medullary secretion
Reflex control of gastrointestinal function

parasympathetically mediated excitation
sympathetically mediated inhibition
circuit involving CNS, collateral ganglia and ENS:
global sympathetic inhibition (fight or flight)

circuit involving collateral ganglia and ENS:
selective sympathetic inhibition
ongoing (tonic) sympathetic inhibition

NOVEL TRANSMITTERS

PEPTIDES
ATP
NITRIC OXIDE (NO)

REFLEXES

DEFINITION OF A REFLEX

Reflexes are stereotyped responses to specific sensory inputs

Sensory input over -----> Integrative -----> Efferent limb -----> Response elicited
afferent limb                     Center                                                  by effectors

CLASSIFICATION OF REFLEXES

1. Somatic reflex: mediated over skeletal muscle
2. Autonomic reflex: expressed by the effectors controlled by the ANS

COMPARISON OF SOMATIC AND AUTONOMIC REFLEXES:

SOMATIC REFLEX: tendon knee jerk

Figure 1.

- Integrative center lies in the spinal cord restricted to a specific segment
- Monosynaptic
- Somatic motor nerve (afferent) excites skeletal muscle
- Little modulation from higher centers
ANS REFLEX

Figure 2

- Afferent limb: general visceral afferents but others used also as for somatic reflexes
- Integrative center is not well localized in the CNS; can be in spinal cord, in brain stem or not even in CNS
- Never monosynaptic
- Efferent limb includes a ganglion
- Efferent limb may produce excitation or inhibition of the effector
- Higher centers in the CNS (cognitive, emotional) exert profound influence on ANS reflexes

EXAMPLES OF ANS REFLEXES

Pupillary light reflex
Stress activation of adrenal medulla
Reflex activation of the GI tract

Parasympathetic:

Vago-vagal activation of stomach
Gastro-colic reflex

Sympathetic:

Global inhibition (stress response)
Selective inhibition: Enterogastric reflex
Tonic inhibition
PUPILLARY LIGHT REFLEX:

This is an example of a reflex to a specific stimulus (light) that produces a very discrete response that not subjected to much central modulation:

The circuitry of this reflex is well established.

Figure 3. PUPILLARY LIGHT REFLEX

LOCATION OF LESIONS WITHIN THE PATHWAY

Lesion to motor nerve of left eye:

Shine light in left eye → pupillary constriction in right eye but no response in left eye
Shine light in right eye → pupillary constriction in right eye but no response in left eye

Damage to optic nerve from left eye

Shine light in left eye → no response in either eye
Shine light in right eye → normal response in both eyes

REFLEX ACTIVATION OF THE ADRENAL MEDULLA

Reflex release of adrenal CA is normally triggered through activation of sympathetic preganglionic nerves running in the splanchnic nerve that supplies the chromaffin cells.
WHAT TYPE OF STIMULI RELEASE ADRENAL MEDULLARY CATECHOLAMINES?

Physiological stimuli for catecholamine release from the adrenal medulla are:

- psychological: emotional states (e.g. fear, anxiety, anger, "fight or flight reaction")
- metabolic: hypoglycemia (the most powerful)
- hypothermia

Pathological stimuli include:

- severe hemorrhage
- heart attack
- pain

After severe trauma, the adrenal medulla may be depleted of CA and opioid peptides (enkephalins) that are co-released with the amine.

IMPORTANT NOTE: ASTHMATIC ATTACKS DO NOT TRIGGER RELEASE OF CA FROM THE ADRENAL MEDULLA. This is surprising given that EPI produces relaxation of the airways via beta-2 receptor activation. Selective beta-2 agonists can be used to treat asthmatic attacks acutely.

ANGIOTENSIN-II

Under certain pathological conditions (e.g. severe loss of blood), the hormone, ANGIOTENSIN-II also produces CA secretion. Under these conditions, circulating levels of angiotensin-II become markedly elevated and the angiotensin-II interacts
directly with angiotensin-II receptors on the chromaffin cells of the adrenal medulla to produce CA release. You will learn about the production of angiotensin –II in the lectures on renal physiology.

REFLEX CONTROL OF GI FUNCTION

PARASYMPATHETIC CONTROL (EXCITATORY)

- **Reflex activation of the stomach**: Food within the stomach stimulates chemico and mechano receptors in the stomach wall and signals are conveyed to the CNS over GVA fibers. Reflex activation of the vagus stimulates mechanical and secretory activity in the stomach wall.
- **Reflex activation of the bowel**: The presence of food in the stomach or upper part of the intestine triggers activity in sacral parasympathetic nerves innervating the colon and produces a massive propulsive contraction. This is the gastro (stomach) colic (large intestine) reflex.

The parasympathetic coordinates digestive activity along the length of the GI tract.

ENTERIC NERVOUS SYSTEM

The ENS is an independent nervous system comprised of local sensory neurons, local interneurons and local motor neurons. Parasympathetic postganglionic nerves are just one type of motor neuron in the ENS. It extends along the entire length of the GI tract.

The ENS exerts local reflex control over many digestive processes. It mediates many stereotyped movements, e.g. peristalsis.
SYMPATHETIC CONTROL OF GI FUNCTION (INHIBITORY)

- Global inhibition (fight or flight response)
- Discrete inhibition of specific area (e.g. gastric emptying) during digestion
- Tonic inhibition of tonic parasympathetic tone

Figure 6
Sympathetic activity regulates GI function at two different levels:

- via activation over the CNS (global inhibition)
- via activation of postganglionic neurons within the collateral ganglia without any CNS involvement (discrete inhibition and tonic inhibition)

Most sympathetic inhibition of GI function is mediated presynaptically over alpha-2 hetero-receptors that lie on the terminals of postganglionic parasympathetic nerves. Inhibition of GI motility and secretory activity is therefore INDIRECT. NE released from sympathetic postganglionic neurons inhibits the release of the excitatory transmitter, Ach, thereby reducing the activation of the target tissues.

GLOBAL INHIBITION OF GI FUNCTION IN THE FIGHT OR FLIGHT RESPONSE

The afferent limb of this reflex involves cognition (recognition of a threatening situation) as well as CNS regions involved in autonomic control.

Sympathetic nerves innervating the GI tract are activated. Released NE produces

- Inhibition of the motility of GI smooth muscle and secretory activity of many glands mediated over presynaptic alpha-2 hetero receptors that lie on the terminals of the excitatory postganglionic parasympathetic nerves and inhibit release of Ach.
- Reduction of blood flow via alpha 1 receptor activation on the smooth muscle of blood vessels.
- Activation of sphincter muscles (alpha-1 receptors) to prevent food from moving from one part of the gut to another.

Adrenal medullary EPI is released into the circulation and

- produces GI smooth muscle relaxation directly via beta-2 receptors

ENTERO-GASTRIC REFLEX

- Activated after the stomach has emptied some of its contents into the duodenum.
- Inhibition of further emptying allows the acid pH of the chyme to be raised so the pancreatic proteases can work. Bicarbonate secreted by the exocrine pancreas neutralizes the acid chyme from the stomach.
- The stomach is inhibited from further emptying until the pH of the chyme in the duodenum has been raised.
This reflex involves:

- Activation by acid of LOCAL SENSORY NEURONS within the ENTERIC NERVOUS SYSTEM in the wall of the duodenum
- Activation of POSTGANGLIONIC SYMPATHETIC NEURONS in the COELIAC (COLLATERAL) GANGLION by these local sensory neurons
- Inhibition of the stomach motility (pyloric end). Inhibition is brought about by NE released from sympathetic terminals acting at PRESYNAPTIC ALPHA-2 HETERO-RECEPTORS on the terminals of the excitatory parasympathetic postganglionic nerves to reduce release of Ach.

This reflex does not involve the CNS. The efferent (motor) limb is the postganglionic sympathetic nerve.

**TONIC SYMPATHETIC INHIBITION**

Ongoing activity of the GI tract is always restrained by tonic sympathetic activity.

- This inhibition is mediated by postganglionic sympathetic nerves within the three collateral ganglia in response to activation of local sensory neurons within the enteric NS.
- The NE released from the terminal branches of the sympathetic postganglionic neurons acts on presynaptic alpha-2 hetero-receptors to inhibit release of excitatory transmitter (ACh) from local motor neurons (parasympathetic postganglionic neurons).
SELECTIVE SYMPATHETIC INHIBITION OF GI FUNCTION:

Figure 7. EXAMPLE: INHIBITION OF GASTRIC EMPTYING DURING DIGESTION OF A MEAL (ENTERO-GASTRIC REFLEX)
NOVEL TRANSMITTERS

The ANS uses other signaling molecules besides NE and Ach. This is particularly true in the case of the ENS that contains many PEPTIDERGIC NEURONS.

These novel transmitters fall into three types:

- **PEPTIDES**
- **ATP**
- **NITRIC OXIDE, (NO)**

PEPTIDE TRANSMITTERS

As noted earlier, a distinct class of dense core vesicles found in the terminals of some autonomic nerves store specific peptides. Thus, vasoactive intestinal peptide (VIP) occurs in some postganglionic parasympathetic nerves, whereas neuropeptide Y (NPY) is found in some sympathetic postganglionic nerves.
These peptides have particular characteristics:

- Release only occurs with high frequency nerve stimulation
- Exocytosis takes place at non-junctional membrane
- Effects are long lasting (mins) indicating that the biological inactivation by peptidases is slow
- VIP is found in the parasympathetic innervation to salivary gland. It is released on high frequency stimulation when it enhances the stimulatory effects of ACh on salivary secretion
- NPY occurs in sympathetic nerves supplying blood vessels. It is released in response to high frequency stimulation and augments the contractile response elicited by co-released ATP and NE.
- Autonomic nerves can thus release multiple agents (ATP, small transmitters: NE & ACh, neuropeptides) which have different time courses of action. The composition of the mixture depends on the strength and duration of activation.
- Many neurons within the ENTERIC NERVOUS SYSTEM (see above) use peptides exclusively as transmitters. Examples include enkephalin, substance P, somatostatin, cholecystokinin, CGRP.

ATP - A TRANSMITTER IN THE SYMPATHETIC NERVOUS SYSTEM

- ATP is co-stored with NE in synaptic vesicles (see FIG 9) (4 ATP: 1 NE) and co-released with NE on exocytosis of synaptic vesicle in response to nerve stimulation.
- ATP has an excitatory transmitter role, along with NE, in smooth muscle of many arterioles and small arteries and of the vas deferens. It produces a rapid contraction of smooth muscle that precedes the contraction produced by NE. This action is always present since ATP is always released along with the NE. (Contrast this with the release of peptides).
• How does it work? ATP opens a ligand-gated cation channel, highly permeable to calcium ions, by binding to a so called PURINERGIC RECEPTOR.
• The increase in internal calcium triggers calcium-induced calcium release from the smooth muscle SR and a very rapid muscle contraction that precedes the contraction produced by NE at alpha_1 receptors.

**NITRIC OXIDE (NO)**

Parasympathetic stimulation can produce relaxation of certain smooth muscles (GI tract; erectile tissue of the penis). An important mediator is the gas, nitric oxide (NO).

• NO is synthesized on demand and has a brief lifetime. It is made by calcium-calmodulin-dependent NO synthetase which is activated by a rise in intracellular free calcium and converts arginine into NO and citrulline.
• NO diffuses freely across the nerve terminal membrane into the surrounding smooth muscle where it stimulates soluble guanylyl cyclase and generates cGMP.
• cGMP activates protein kinase G and causes relaxation of smooth muscle through multiple pathways that all reduce phosphorylation of myosin light chain (see Dr Karnam’s notes on smooth muscle relaxation).
• NO was first discovered as an agent generated by the endothelium of blood vessels in response to various agents, hence the name ENDOTHELium DERIVED RELAXING FACTOR or EDRF.

Figure 10
GLOSSARY OF TERMS FOR PHYSIOLOGY OF THE AUTONOMIC NERVOUS SYSTEM

The following definitions will aid in the understanding of lecture and reading material on the autonomic nervous system.

**adrenergic** - adjective pertaining to norepinephrine (NE); e.g., an adrenergic nerve is one which liberates NE as a transmitter substance.

**agonist** - (stimulant) - drug which combines with a receptor to initiate a response.

**anhydrosis** - absence or deficiency of sweat.

**antagonist** - (blocker) - drug which combines with receptor but does not initiate a response; will block access of agonist to receptor.

**A-V node** - atrio-ventricular node - area of specialized conduction tissue which transmits electrical impulses from atria of heart to the ventricles.

**bradycardia** - slowing of the heart rate.

**bronchoconstriction** - a narrowing of the lumina of air passages in lungs caused by contraction of smooth muscle in bronchi and bronchioles.

**catecholamine** - a β-phenylethylamine or ethanolamine in which the benzene ring contains hydroxyl groups in the 3 and 4 positions.

\[
\text{dopamine} = \text{norepinephrine} = \text{pinephrine}
\]

**cholinergic** - of or pertaining to acetylcholine; e.g., a cholinergic nerve liberates acetylcholine as a transmitter substance.

**cholinomimetic** - a substance that mimics the effects of acetylcholine at cholinergic receptors on a neurone or effector cell.

**chronotropic** - affecting time or rate, more specifically rate of contraction of heart; positive chronotropic effect = an increase in heart rate; negative chronotropic effect = a decrease in heart rate.

**cycloplegia** - paralysis of ciliary muscles in the eye resulting in loss of
accommodation for near vision, i.e. the ability to focus the lens.

depressor - lowering of blood pressure
depressor substance - agent that lowers blood pressure
effector cell - cell whose activity is regulated by nerve or hormone which produces an effect, e.g. contraction, secretion.
emesis - vomiting
exocytosis - process whereby the membrane of an intracellular body fuses with the plasma or cell membrane allowing expulsion of the contents of the intracellular body to the extracellular space, but retention of the membrane.
ganglia - collection of nerve cell bodies located outside the central nervous system
glycogenolysis - the splitting of glycogen to liberate glucose
junction - general term to describe area where chemical transmission of impulses occurs between 2 nerves or between a nerve and an effector cell as in neuromuscular junction or neuroeffector junction.
lacrimation - secretion of tears
lipolysis - the breakdown of fat resulting in liberation of free fatty acids
miosis - constriction of the pupil
mydriasis - dilation of the pupil
myocardial - of or pertaining to heart muscle
nerve conduction - movement of electrical impulses along an axon

neurochemical transmission the process whereby impulses are transferred from one nerve to another or from a nerve to an effector cell by means of the release of a chemical.

neuromuscular junction - the area where somatic motor nerves transmit impulses to skeletal muscle fibers.

pressor - adjective referring to an increase in blood pressure;
pressor substance - an agent that increases blood pressure
S-A- node - sino-atrial node - area of specialized myocardial tissue in the right atrium which spontaneously depolarizes giving rise to heart beat.
sympathomimetic - agonist which mimics the effects of activity of sympathetic division of the autonomic nervous system.
synapse - junction between two nerves. The signal from the presynaptic (input) neuron is conveyed to the postsynaptic (output) neuron: Conduction is unidirectional.
tachycardia - rapid heart rate.
tone - normal state of tension or activity
vasoconstriction - constriction of blood vessels
vasodilatation - dilation of the blood vessels
xerostomia - dry mouth associated with decreased production of saliva

**REVIEW QUESTIONS**: Autonomic nervous system.

Pick the single best answer

**Question 1.** The sympathetic division of the autonomic nervous system has all the following characteristics *except*:

A. the cell bodies of the preganglionic neurons lie in the intermediolateral columns of the spinal cord
B. has a well-organized ganglion system
C. all postganglionic neurons release norepinephrine
D. the system participates along with the adrenal medulla in the fight and flight response

A. This is a true statement and therefore not the correct answer. The cell bodies of the preganglionic neurons lie in the intermediolateral column.
B. This is not the exception. The sympathetic nervous system is characterized by its well-defined ganglion system.
C. This is the exception. The sympathetic postganglionic fibers innervating the sweat glands release acetylcholine rather than norepinephrine. (Postganglionic sympathetic neurons to the sweat glands of the palms of the hands do however release norepinephrine and are involved in emotional sweating (clammy hands).
D. This is a true statement and therefore not the answer.

**Question 2.** Parasympathetic stimulation causes all the following responses EXCEPT:

A. increased gastrointestinal motility  
B. constriction of the pupil (miosis)  
C. slowing of the heart (bradycardia)  
D. constriction of blood vessels

A, B & C are true. Ans D.

D is an incorrect statement and therefore the correct answer to the question. The smooth muscle of blood vessels is innervated by the sympathetic nervous system. Stimulation of the sympathetic nerves causes constriction of blood vessels via an alpha-1 adrenoceptor action of the released norepinephrine.

**Question 3.** Acetylcholine released from postganglionic parasympathetic nerves has all the following characteristics EXCEPT:

A. excitatory or inhibitory effects depending on the site of action  
B. action at the neuroeffector junction blocked by atropine  
C. coreleased with peptides at some synapses  
D. inactivated by diffusion from the site of action

A, B & C are true. Ans D. Acetylcholine is inactivated by acetylcholinesterase.

**Matching:** Answers may be used once, more than once or not at all

Direct activation of certain receptor subclasses by the relevant transmitter produces certain responses. Match the appropriate receptors with the response.

A. Muscarinic receptors  
B. Beta<sub>2</sub> receptors  
C. Alpha<sub>1</sub> receptors  
D. Nicotinic receptors

1. Increased motility of the GI tract  
2. Narrowing of the pupil (miosis)  
3. Relaxation of bronchial smooth muscle (bronchodilation)  
4. An increase in blood pressure  
5. Release of catecholamines from the adrenal medulla
6. Slowing of the heart (bradycardia)
7. Generalized sweating

Answers: 1. A; 2. A (pupillary sphincter has muscarinic receptors); 3. B (bronchial smooth muscle has beta-2 receptors); 4. C (alpha1 receptors on the smooth muscle of the blood vessels cause constriction of the blood vessel in response to released NE); 5. D (the medullary chromaffin cells have nicotinic receptors); 6. A; bradycardia is mediated by muscarinic receptors; 7. A (generalized sweating is mediated by muscarinic receptors activated by Ach released from postganglionic sympathetic nerves)

REVIEW EXERCISES FOR THE AUTONOMIC NERVOUS SYSTEM

1. Indicate which of the following types of adrenergic receptors (alpha-1, beta-1 or beta-2) are responsible for the following sympathetic effects:

   a. mydriasis (dilation of the pupil)
   b. vasoconstriction (contraction of vascular smooth muscle)
   c. tachycardia (rapid heart beat)
   d. increased myocardial contractile force
   e. vasodilation in skeletal muscle
   f. bronchodilation
   g. sweating (emotional)

Answers:

   a. alpha-1 receptors cause the radial muscle of the pupil to contract and hence produce dilation of the pupil
   b. alpha-1
   c. beta-1
   d. beta-1
   e. beta-2 (effect of EPI)
   f. beta-2 (effect of EPI)
   g. alpha-1

2. Figure out how muscarine and atropine would affect:

   a. pupillary diameter
   b. salivation
   c. G-I function
   d. urinary bladder function
   e. the heart
   f. sweat glands

Answers: muscarine

   a. miosis (constriction)
b. stimulation
c. enhanced motility and secretory activity of the GI tract
d. contraction of the bladder
e. slowing (bradycardia)
f. stimulation of sweating

atropine

a. pupillary dilation
b. inhibition of salivary secretions--dry mouth
c. inhibition of GI motility and secretory activity
d. difficulty urinating
e. tachycardia
f. inhibition of generalized sweating--dry skin