PA Physiology AY 2009-2010
Autonomic Nervous System and Adrenal Medulla

Sources of information:

The sources of information that will be sufficient for the individual student to master the specific objectives listed above include the following:

- *Guyton & Hall, Textbook of Medical Physiology*, chapter 60, pp. 748-760;
- Handouts, reprints or other supplementary materials provided by department faculty;
- The student's own lecture notes;

Key words:

Following study of the assigned text (or similar sections in other texts available to the student and approved by the instructor), the other sources of information included below, and attendance at the lectures on this topic, the student should be able to define or otherwise indicate an understanding of the following words or phrases:

Sympathetic nervous system; preganglionic neuron; postganglionic neuron; white communicating rami; gray communicating rami; sympathetic paravertebral ganglion; prevertebral ganglion; adrenal medulla; splanchnic nerves; sympathetic chain; parasympathetic nervous system; brainstem; sacral spinal cord; enteric nervous system; acetylcholine; muscarinic receptors; nicotinic receptors; vasoactive intestinal peptide; norepinephrine; adrenergic receptors; ATP; chromaffin cells; epinephrine; autonomic reflexes; epinephrine; norepinephrine; chromaffin cells; phenylalanine; tyrosine; dihydroxyphenylalanine; dopamine; norepinephrine; epinephrine; vanillylmandelic acid (VMA); metanephrines; pheochromocytoma; α_1 adrenergic receptor; α_2 adrenergic receptor; β_1 adrenergic receptor; β_2 adrenergic receptor; β_3 adrenergic receptor; adenyl cyclase; cAMP; protein kinase A; phospholipase C; IP_3; DAG; protein kinase C; fuel mobilization; metabolic effects of catecholamines; hypothalamic-pituitary-adrenocortical axis; stress response;

Learning outcomes:

Following study of the assigned text (or similar sections in other texts available to the student and approved by the instructor), the other sources of information included below, and attendance at the lectures on this topic, the student should be able to:

- Given a list of neurotransmitters (acetylcholine, norepinephrine, and epinephrine), match each neurotransmitter with one of the following sites of release: preganglionic nerve terminals, postganglionic nerve terminals, and adrenal medulla;

- Given a list of cholinergic and adrenergic receptor types, match each receptor type with one of the following locations: autonomic ganglia, parasympathetic target tissues or organs, sympathetic target tissues or organs, somatic neuromuscular junctions;

- For each of the following organs or organ systems – cardiovascular, respiratory, gastrointestinal, endocrine, and renal – identify the primary effects on the organ or organ system of sympathetic nervous system stimulation or parasympathetic nervous system stimulation;

- Describe in words the functional significance of the adrenal medulla and its hormones in overall autonomic nervous system actions;

- Recognize the structural differences between DOPA, dopamine, norepinephrine, and epinephrine;

- Identify the factors regulating catecholamine synthesis and release from the adrenal medulla, and identify the sequence of catecholamine synthesis in the chromaffin cells, beginning with tyrosine;

General Summary of Autonomic Nervous System Activity

The integrating action of the autonomic nervous system is critical for the well being of the human organism. In general, the autonomic nervous system regulates the activities of structures that are not under voluntary control and that function below the level of consciousness. Thus, respiration, circulation, digestion, body temperature, metabolism, sweating, and the secretions of certain endocrine glands are regulated, in part or entirely, by the autonomic nervous system. The autonomic nervous system can be considered to be the primary regulator of the constancy of the internal environment of the organism – *i.e.*, homeostasis.

Sympathetic Nervous System

The sympathetic system and the adrenal medulla are not essential to life in a well-controlled and stress-free environment, but the lack of sympathoadrenal functions becomes evident under circumstances of stress. Without the sympathetic nervous system, body temperature cannot be regulated when environmental temperature varies; the concentration of glucose in blood does not rise in response to urgent need; compensatory vascular responses to hemorrhage, oxygen deprivation, excitement, and exercise are lacking; resistance to fatigue is lessened; sympathetic components of instinctive reactions to the external environment are lost; and other serious deficiencies in the regulatory capacities of the body are present.

The sympathetic system normally is continuously active, but the degree of activity varies from moment to moment and from organ to organ. In this manner, adjustments to a constantly changing environment are accomplished. The sympathoadrenal system also can discharge as a unit. This occurs particularly during rage and fright, when sympathetically innervated structures over the entire body are affected simultaneously. Heart rate is accelerated; blood pressure rises; red blood cells are poured into the circulation from the spleen (in certain species); blood flow is shifted from the skin and splanchnic region to the skeletal muscles; blood glucose rises; the bronchioles and pupils dilate; and the organism is better prepared for physical activity – for "fight or flight." Many of these effects result primarily from, or are reinforced by, the actions of epinephrine secreted by the adrenal medulla.

Stimulation of α_1 adrenergic receptors causes hydrolysis of polyphosphoinositides and mobilization of intracellular Ca^{2+} as a consequence of activation of the G_q-PLC pathway. This effect in turn results in a variety of Ca^{2+}-mediated events, either directly or as a consequence of the phosphorylation of target proteins. The α_2 adrenergic receptors, on the other hand, interact with the G_i regulatory G-protein with a resulting inhibition of adenylyl cyclase leading to a decrease in cyclic AMP, activation of inwardly rectifying K^+ channels, and inhibition of voltage-gated Ca^{2+} channels. The functional consequences of these effects are hyperpolarization and inhibition of excitable membranes. The β-adrenergic receptors (β_1, β_2, and β_3) are linked to adenyl cyclase activity *via* the G_s regulatory G-protein. The increased cAMP concentration associated with β-adrenergic stimulation leads to increased PKA activity, phosphorylation of intracellular proteins, and various intracellular effects depending on the cell type being stimulation.

Epinephrine has an affinity for α_1- and α_2- adrenergic receptors that is equal to, or perhaps slightly higher than, the affinity of norepinephrine for these receptors. Epinephrine and norepinephrine have the same affinity for β_1-adrenergic receptors, whereas norepinephrine has a much lower affinity than epinephrine for β_2-adrenergic receptors and a higher affinity than epinephrine for β_3 adrenergic receptors.

Parasympathetic Nervous System

The parasympathetic system is organized mainly for discrete and localized discharge. Although it is concerned primarily with conservation of energy and maintenance of organ function during periods of minimal activity, it is nevertheless essential for life. Sectioning the vagus, for example, soon gives rise to pulmonary infection because of the inability of cilia to remove irritant substances from the respiratory tract. The parasympathetic system slows the heart rate, lowers the blood pressure, stimulates gastrointestinal movements and secretions, aids absorption of nutrients, protects the retina from excessive light, and empties the urinary bladder and rectum. Many parasympathetic responses are rapid and reflexive in nature.

As with α_1 adrenergic receptors, stimulation of M_1 or M_3 receptors causes hydrolysis of polyphosphoinositides and mobilization of intracellular Ca^{2+} as a consequence of activation of the G_q-PLC pathway. This effect in turn results in a variety of Ca^{2+}-mediated events, either directly or as a consequence of the phosphorylation of target proteins. In contrast, M_2 and M_4 muscarinic receptors inhibit adenylyl cyclase and regulate specific ion channels (*e.g.*, enhancement of K^+ conductance in cardiac atrial tissue) through subunits released from G proteins (G_i and G_0) that are distinct from the G proteins used by M_1 and M_3 receptors.

Activation of M_1, M_3, and M_5 receptors can also cause the activation of phospholipase A_2, leading to the release of arachidonic acid and consequent eicosanoid synthesis, resulting in autocrine/paracrine stimulation of adenylyl cyclase and an increase in cyclic AMP. Stimulation of M_2 and M_4 cholinergic receptors leads to interaction with other G proteins, (*e.g.*, G_i) with a resulting inhibition of adenylyl cyclase leading to a decrease in cyclic AMP, activation of inwardly rectifying K^+ channels, and inhibition of voltage-gated Ca^{2+} channels. The functional consequences of these effects are hyperpolarization and inhibition of excitable membranes. These are most clear in myocardium, where inhibition of adenylyl cyclase and activation of K^+ conductances account for the negative chronotropic and inotropic effects of ACh.

Reference Table for Autonomic Responses

The following table summarizes the major autonomic effects that PA students should master. There is obviously some memorization required here, but the effort now will certainly pay off later in the PA curriculum and in the Pharmacology course.

	Sympathetic (Adrenergic) Response		**Parasympathetic (Cholinergic) Response**	
Effector Organ	**Response**	**Receptor**	**Response**	**Receptor**
Heart				
Rate of contraction	Increase	β_1	Decrease	M_2
Force of contraction	Increase	β_1	Decrease	M_2
Duration of systole	Decrease	β_1	Increase	M_2
Blood Vessels				
Arteries (most)	Constriction	α_1 (α_2)	-	-
Skeletal muscle	Constriction or dilation	α_1 or β_2	-	-
Veins	Constriction	α_2 (α_1)	-	-
Bronchial tree	Bronchodilation	β_2	Bronchoconstriction	M_3
Uterus	Contraction	α_1	Variable	-
Vas deferens	Contraction	α_1	-	-
Gastrointestinal tract	Relaxation	α_2, β_2	Contraction	M_3
Eye				
Radial muscle, iris	Contraction (mydriasis)	α_1	-	-
Circular muscle, iris	-	-	Contraction (miosis)	M_3
Ciliary muscle	Relaxation	β_2	Contraction (accommodation)	M_3
Kidney	Renin secretion	β_1	-	-
Urinary Bladder				
Detrusor	Relaxation	β_2	Contraction	M_3
Trigone and sphincter	Contraction	α_1	Relaxation	M_2
Ureter	Contraction	α_1	-	-
Insulin release	Decrease	α_2	-	-
Fat cells	Lipolysis	β_1 (β_3)	-	-
Hepatic glycogenolysis	Increase	α_1 (β_2)	-	-
Hair follicle smooth muscle	Contraction (piloerection)	α_1	-	-
Nasal secretion	Decrease	α_1 (α_2)	Increase	-
Salivary glands	Increase secretion	α_1	Increase secretion	-
Sweat glands	Increase secretion	α_1	Increase secretion	-

Autonomic Agonists, Affinities, and Actions

(from Goodman & Gilman, Pharmacological Basis for Therapeutics)

Receptor	Agonists	Tissue	Responses
α_1	EPI ≥ NE	Vascular smooth muscle	Contraction
		GU smooth muscle	Contraction
		Liver	Glycogenolysis; gluconeogenesis
		Intestinal smooth muscle	Contraction (sphincters)
		Heart	Increased contractile force
α_2	EPI ≥ NE	Pancreatic islets	Decreased insulin secretion
		Platelets	Aggregation
		Autonomic nerve terminals	Decreased NE release (presynaptic inhibition)
		Vascular smooth muscle	Contraction
β_1	EPI = NE	Juxtaglomerular cells	Increased renin secretion
		Heart	Increased contractility, heart rate, conduction velocity
		Adipose tissue	Lipolysis
β_2	EPI >> NE	Smooth muscle (vascular, bronchial, GI, and GU)	Relaxation
		Skeletal muscle	Glycogenolysis, Increased uptake of K^+
		Liver	Glycogenolysis; gluconeogenesis
β_3	NE > EPI	Adipose tissue	Lipolysis