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chapter 2 castanzo : lecture 8,9

BOX 2.1 Clinical Physiology: Pheochromocytoma

DESCRIPTION OF CASE. A 48-year-old woman visits her physician complaining of what she calls "panic attacks." She reports that she has experienced a racing heart and that she can feel (and even see) her heart pounding in her chest. She also complains of throbbing headaches, cold hands and cold feet, feeling hot, visual disturbances, and nausea and vomiting. In the physician's office, her blood pressure is severely elevated (230/125). She is admitted to the hospital for evaluation of her hypertension.

A 24-hour urine sample reveals elevated levels of metanephrine, normetanephrine, and 3-methoxy-4-hydroxymandelic acid (VMA). After the physician rules out other causes for hypertension, he concludes that she has a tumor of the adrenal medulla, called a pheochromocytoma. A computerized tomographic scan of the abdomen reveals a 3.5-cm mass on her right adrenal medulla. The patient is administered an α_1 antagonist, and surgery is performed. The woman recovers fully; her blood pressure returns to normal, and her other symptoms disappear.

EXPLANATION OF CASE. The woman has a classic pheochromocytoma, a tumor of the chromaffin cells of the adrenal medulla. The tumor secretes excessive amounts of norepinephrine and epinephrine, which produce all of the woman's symptoms and result in elevated levels of catecholamine metabolites in her urine. In contrast to normal adrenal medulla, which secretes mainly epinephrine, pheochromocytomas secrete mainly norepinephrine.

The patient's symptoms can be interpreted by understanding the physiologic effects of catecholamines. Any tissue where adrenoreceptors are present will be activated by the increased levels of epinephrine and norepinephrine, which reach the tissues via the circulation. The woman's most prominent symptoms are cardiovascular: pounding heart, increased heart rate, increased blood pressure, and cold hands and feet. These symptoms can be understood by considering the functions of adrenoreceptors in the heart and blood vessels. The increased amounts of circulating catecholamines activated β_1 receptors in the heart, increasing the heart rate and increasing contractility (pounding of the heart). Activation of α_1 receptors in vascular smooth muscle of the skin produced vasoconstriction, which presented as cold hands and feet. The patient felt hot, however, because this vasoconstriction in the skin impaired the ability to dissipate heat. Her extremely elevated blood pressure was caused by the combination of increased heart rate, increased contractility, and increased constriction (resistance) of the blood vessels. The patient's headache was secondary to her elevated blood pressure.

The woman's other symptoms also can be explained by the activation of adrenoreceptors in other organ systems (i.e., gastrointestinal symptoms of nausea and vomiting and visual disturbances).

TREATMENT. The patient's treatment consisted of locating and excising the tumor, thereby removing the source of excess catecholamines. Alternatively, if the tumor had not been excised, the woman could have been treated pharmacologically with a combination of α_1 antagonists (e.g., phenoxybenzamine or prazosin) and β_1 antagonists (e.g., propranolol) to prevent the actions of the endogenous catecholamines at the receptor level.

BOX 2.2 Clinical Physiology: Horner Syndrome

DESCRIPTION OF CASE. A 66-year-old man who suffered a stroke on the right side has a drooping right eyelid (ptosis), constriction of his right pupil (miosis), and lack of sweating on the right side of his face (anhidrosis). His physician orders a test with cocaine eye drops. When a solution of 10% cocaine is applied in the left eye, it causes dilation of the pupil (mydriasis). However, when the cocaine solution is applied in the right eye, it fails to cause dilation of that pupil.

EXPLANATION OF CASE. The man has a classic case of Horner syndrome, secondary to his stroke. In this syndrome, there is loss of sympathetic innervation on the affected side of the face. Thus the loss of sympathetic innervation to smooth muscle elevating the right eyelid caused ptosis on the right side. The loss of sympathetic innervation of the right pupillary dilator muscle caused constriction of the right pupil. And loss of sympathetic innervation of the sweat glands of the right side of the face caused anhidrosis on the right side.

When cocaine drops were instilled in the left eye (the unaffected side), the cocaine blocked reuptake of norepinephrine into sympathetic nerves innervating the pupillary dilator muscle; with higher norepinephrine levels in those adrenergic synapses, there was constriction of the radial muscle of the iris, leading to prolonged dilation of the pupil. When cocaine drops were instilled in the right eye, because there was less norepinephrine in those synapses, pupillary dilation did not occur.

TREATMENT. The treatment of Horner syndrome is to address the underlying cause.

BOX 2.4 Clinical Physiology: Treatment of Motion Sickness With a Muscarinic Receptor Antagonist

DESCRIPTION OF CASE. A woman planning a 10-day cruise asks her physician for medication to prevent motion sickness. The physician prescribes scopolamine, a drug related to atropine, and recommends that she take it for the entire duration of the cruise. While taking the drug, the woman experiences no nausea or vomiting, as hoped. However, she does experience dry mouth, dilation of the pupils (mydriasis), increased heart rate (tachycardia), and difficulty voiding urine.

EXPLANATION OF CASE. Scopolamine, like atropine, blocks cholinergic muscarinic receptors in target tissues. Indeed, it can be used effectively to treat motion sickness, whose etiology involves muscarinic receptors in the vestibular system. The adverse effects that the woman experienced while taking scopolamine can be explained by understanding the physiology of muscarinic receptors in target tissues.

Activation of muscarinic receptors causes increased salivation, constriction of the pupils, decreased heart rate (bradycardia), and contraction of the bladder wall during voiding (see Table 2.2). Therefore *inhibition* of the muscarinic receptors with scopolamine would be expected to cause symptoms of decreased salivation (dry mouth), dilation of the pupils (due to the unopposed influence of the sympathetic nervous system on the radial muscles), increased heart rate, and slowed voiding of urine (caused by the loss of contractile tone of the bladder wall).

TREATMENT. Scopolamine is discontinued.

Challenge Yourself

Answer each question with a word, phrase, sentence, or numerical solution. When a list of possible answers is supplied with the question, one, more than one, or none of the choices may be correct. The correct answers are provided at the end of the book.

1 *Which of the following actions is/are mediated by β_2 receptors: increased heart rate, contraction of gastrointestinal sphincters, contraction of vascular smooth muscle, dilation of airways, relaxation of bladder wall?*

2 *A woman who is taking atropine for a gastrointestinal disorder notices that her pupils are dilated. This has occurred because atropine blocks _____ receptors on the _____ muscle of the iris.*

3 *Which of the following is/are characteristic of the parasympathetic nervous system but not of the sympathetic nervous system: ganglia in or near target tissues, nicotinic receptors on postganglionic neurons, muscarinic receptors on some target tissues, β_1 receptors on some target tissues, cholinergic preganglionic neurons?*

5 *Which of the following actions is/are mediated by the adenylyl cyclase mechanism: effect of parasympathetic nervous system to increase gastric acid secretion, effect of epinephrine to increase cardiac contractility, effect of epinephrine to increase heart rate, effect of acetylcholine to decrease heart rate, effect of acetylcholine to constrict airways, constriction of vascular smooth muscle in splanchnic blood vessels?*

9 *In the action of α_1 receptors, what is the correct order of steps: α_q binds to GDP, α_q binds to GTP, generation of IP_3, release of Ca^{2+} from intracellular stores, activation of protein kinase, activation of phospholipase C?*

10 *Which of the following actions are mediated by muscarinic receptors: slowing of conduction velocity in AV node, gastric acid secretion, mydriasis, contraction of gastrointestinal sphincters, erection, renin secretion, sweating on a hot day?*

CHAPTER 2

1 Dilation of airways; relaxation of bladder wall

2 Muscarinic; sphincter

3 Ganglia in or near target tissues (Hints: All postganglionic neurons have nicotinic receptors; sweat glands have sympathetic cholinergic innervation; all preganglionic neurons are cholinergic.)

5 Effect of epinephrine to increase cardiac contractility; effect of epinephrine to increase heart rate

9 α_q binds to GDP, α_q binds to GTP, activation of phospholipase C, generation of IP_3, release of Ca^{2+} from intracellular stores, activation of protein kinase

10 Slowing of conduction velocity in AV node; gastric acid secretion; erection; sweating on a hot day