Case 8

Pheochromocytoma: Effects of Catecholamines

Helen Ames is a 51-year-old homemaker who experienced what she thought were severe menopausal symptoms. These awful “attacks” were becoming more frequent. Her heart raced and pounded; she had a throbbing headache and visual disturbances; she felt hot, but her hands and feet were cold; and she was nauseated, sometimes to the point of vomiting. Mrs. Ames called her physician, who agreed that the symptoms were probably menopausal and prescribed hormone replacement therapy over the phone. Mrs. Ames took the hormones (a combination of estrogen and progesterone), but they did not relieve her symptoms. The attacks were occurring almost daily. She made an appointment with her physician.

In the physician’s office, Mrs. Ames’ blood pressure was severely elevated at 200/110, and her heart rate was increased at 110 beats/min. To rule out a pheochromocytoma (a rare tumor of the adrenal medulla), the physician ordered a 24-hour urine measurement of 3-methoxy-4-hydroxymandelic acid (VMA). To his surprise, the results of the 24-hour urinary VMA test were positive, a finding that provided nearly conclusive evidence of a pheochromocytoma. A computerized tomographic scan confirmed that Mrs. Ames had a 3-cm mass on her right adrenal gland. While awaiting surgery to remove the tumor, she was given phenoxybenzamine, an α-adrenergic antagonist. After an appropriate dosage of phenoxybenzamine was established, she was also given a low dose of propranolol, a β-adrenergic antagonist. She was cleared for surgery when the medications had decreased her blood pressure to 140/90.

QUESTIONS

1. What is the relationship of the adrenal medulla to the autonomic nervous system?

2. What hormones are secreted by a pheochromocytoma?

3. Why does an elevated urinary level of VMA (a metabolite of epinephrine and norepinephrine) suggest the presence of a pheochromocytoma? Why is it necessary to do a 24-hour measurement of VMA, rather than a spot-urine test?

4. In view of the pathophysiology of pheochromocytoma, explain Mrs. Ames’ symptoms, specifically, her increased heart rate, pounding heart, cold hands and feet, visual disturbances, and nausea and vomiting. What receptors are involved in each of these symptoms?

5. Why are two values reported for arterial pressure, and what is the significance of each value? Why were both the systolic and the diastolic blood pressures elevated?

6. Is there a plausible explanation for the fact that Mrs. Ames felt hot, even though her hands and feet were cold?

7. How did phenoxybenzamine lower Mrs. Ames’ blood pressure?

8. After the dosage of phenoxybenzamine was established, what was achieved by adding a low dose of propranolol?

9. What might have happened if Mrs. Ames had been given propranolol alone?
ANSWERS AND EXPLANATIONS

1. The adrenal medulla is a specialized ganglion of the sympathetic division of the autonomic nervous system. The preganglionic neurons have their cell bodies in the thoracic spinal cord. Axons of these preganglionic neurons travel in the greater splanchnic nerve to the adrenal medulla, where they synapse on chromaffin cells and release the neurotransmitter acetylcholine. When stimulated, chromaffin cells (the postsynaptic unit) secrete catecholamines (epinephrine and norepinephrine) into the circulation (Figure 1-12).

   *Except sweat glands, which use ACh.

Figure 1-12 Organization of the autonomic nervous system. ACh, acetylcholine; CNS, central nervous system. (Reprinted with permission from Costanzo LS: BRS Physiology, 3rd ed. Baltimore, Lippincott Williams & Wilkins, 2003, p 36.)

2. A pheochromocytoma is a tumor of the adrenal medulla gland that secretes large quantities of epinephrine and norepinephrine. As with the normal adrenal medulla, the greater secretory component is epinephrine (80%) and the lesser component is norepinephrine (20%), although the percentage of norepinephrine is higher than that in the normal adrenal.

3. 3-Methoxy-4-hydroxymandelic acid (VMA) is a major metabolite of both epinephrine and norepinephrine. When epinephrine and norepinephrine are degraded by the enzymes catechol-O-methyltransferase (COMT) and monoamine oxidase (MAO), the final metabolic product is VMA, which is excreted in urine. Thus, when a pheochromocytoma produces large quantities of epinephrine and norepinephrine, urinary excretion of VMA is increased.
A 24-hour urine sample is necessary because the tumor secretes its hormones in bursts, or pulses; a single spot-urine sample might "miss" large secretory bursts of the hormones.

4. All of Mrs. Ames' symptoms can be explained in terms of the actions of catecholamines on the various organ systems (Table 1-5). In the heart, catecholamines have three major effects, each mediated by a \( \beta_1 \) receptor: increased heart rate; increased contractility, or force of contraction; and increased conduction velocity through the atrioventricular node. In Mrs. Ames, excess amounts of catecholamines caused the sensation that her heart was racing (increased heart rate) and pounding (increased contractility). In blood vessels, primarily arterioles, catecholamines cause vasoconstriction in most vascular beds (e.g., cutaneous and splanchnic) through \( \alpha_1 \) receptors. Vasoconstriction of cutaneous blood vessels leads to decreased cutaneous blood flow and cold skin, especially in the feet and hands. In blood vessels of skeletal muscle, however, catecholamines cause the opposite effect (vasodilation) through \( \beta_2 \) receptors. The effects on vision are explained by sympathetic effects on the eye muscles. In the radial muscle of the iris, catecholamines cause contraction (\( \alpha_1 \) receptor); in the ciliary muscle, catecholamines cause dilation (\( \beta_2 \) receptor). The gastrointestinal effects of catecholamines include relaxation of the smooth muscle wall of the gastrointestinal tract (\( \alpha_2 \) and \( \beta_2 \) receptors); contraction of the gastrointestinal sphincters (\( \alpha_1 \) receptors); and increased production of saliva (\( \beta_3 \) receptors). The coordinated actions on the muscle wall and sphincters slow the motility of chyme through the gastrointestinal tract, and may lead to nausea and even vomiting.

<table>
<thead>
<tr>
<th>Organ</th>
<th>Sympathetic Action</th>
<th>Sympathetic Receptor</th>
<th>Parasympathetic Action (receptors are muscarinic)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart</td>
<td>↑ heart rate</td>
<td>( \beta_1 )</td>
<td>↓ heart rate</td>
</tr>
<tr>
<td>Vascular smooth muscle</td>
<td>↑ contractility</td>
<td>( \beta_1 )</td>
<td>↓ contractility (atria)</td>
</tr>
<tr>
<td></td>
<td>↑ AV node conduction</td>
<td>( \beta_1 )</td>
<td>↓ AV node conduction</td>
</tr>
<tr>
<td></td>
<td>Constricts blood</td>
<td>( \alpha_1 )</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>vessels in skin;</td>
<td></td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>splanchnic</td>
<td></td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>Dilates blood</td>
<td>( \beta_2 )</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>vessels in skeletal muscle</td>
<td></td>
<td>-</td>
</tr>
<tr>
<td>Gastrointestinal tract</td>
<td>↓ motility</td>
<td>( \alpha_2 ) ( \beta_2 )</td>
<td>↑ motility</td>
</tr>
<tr>
<td>Bronchioles</td>
<td>Constricts splanchnic</td>
<td>( \alpha_1 )</td>
<td>Relaxes sphincters</td>
</tr>
<tr>
<td></td>
<td>Dilates bronchiolar</td>
<td>( \beta_2 )</td>
<td>Constricts bronchiolar smooth muscle</td>
</tr>
<tr>
<td></td>
<td>smooth muscle</td>
<td></td>
<td>-</td>
</tr>
<tr>
<td>Male sex organs</td>
<td>Ejaculation</td>
<td>( \alpha )</td>
<td>Erection</td>
</tr>
<tr>
<td>Bladder</td>
<td>Relaxes bladder wall</td>
<td>( \beta_1 )</td>
<td>Contracts bladder wall</td>
</tr>
<tr>
<td></td>
<td>Constricts sphincter</td>
<td>( \alpha_1 )</td>
<td>Relaxes sphincter</td>
</tr>
<tr>
<td>Sweat glands</td>
<td>↑ sweating</td>
<td>Muscarinic (sympathetic cholinergic)</td>
<td>-</td>
</tr>
<tr>
<td>Kidney</td>
<td>↑ renin secretion</td>
<td>( \beta_1 )</td>
<td>-</td>
</tr>
<tr>
<td>Fat cells</td>
<td>↑ lipolysis</td>
<td>( \beta_1 )</td>
<td>-</td>
</tr>
</tbody>
</table>

5. Mrs. Ames' blood pressure was reported as 200/110. (Normal blood pressure is 120/80.) The two numbers refer, respectively, to systolic arterial pressure and diastolic arterial pressure. Arterial pressure is not expressed as a single value because systemic arterial pressure changes over the course of the cardiac cycle. Systolic pressure is the highest value for arterial pressure and is measured just after blood is ejected from the left ventricle into the large arteries (i.e., systole). Diastolic pressure is the lowest value for arterial pressure and is measured when the ventricle is relaxed and blood is flowing from the arteries to the veins and back to the heart (i.e., diastole).
In Mrs. Ames' case, both systolic and diastolic pressures were significantly elevated. These elevations are explained by the effects of excess catecholamines on the heart and blood vessels that have already been discussed. Catecholamines increase both heart rate and contractility. These two effects combine to produce an increase in cardiac output (the volume of blood ejected from the ventricle per minute). An increase in cardiac output means that, during systole, a greater blood volume is ejected into the arteries. This increase in arterial volume is reflected in a higher systolic pressure. In addition, catecholamines cause constriction of arterioles in many vascular beds. This constriction has the effect of "holding" more blood on the arterial side of the circulation, which increases both systolic and diastolic pressures.

The preceding explanation of the effects of catecholamines on the heart and blood vessels may be somewhat misleading because it suggests that these effects are entirely independent. They are not independent, but interact as follows. As described earlier, the vasoconstrictor effect of catecholamines in several vascular beds causes an increase in total peripheral resistance (TPR), which increases systemic arterial pressure. Systemic arterial pressure is the afterload of the left ventricle (i.e., the pressure against which the left ventricle must eject blood). An increase in systemic arterial pressure, or afterload, means that the left ventricle must work harder to eject blood. As a result, the effects of catecholamines to increase cardiac output are partially, or even completely, offset by the increase in afterload.

6. As already discussed, Mrs. Ames' hands and feet were cold because catecholamines cause arteriolar vasoconstriction in the cutaneous circulation. However, why would she feel hot? The answer lies in the role of the cutaneous circulation in dissipating the heat generated by metabolism. Normally, heat is removed from the body through responses directed by the hypothalamus. These responses include decreased sympathetic outflow to the cutaneous blood vessels, resulting in vasodilation. Warm blood from the body core is shunted to the skin surface, where heat is then dissipated by convection and radiation. When a pheochromocytoma is present, the large quantities of circulating catecholamines cancel or override this cutaneous vasodilatory response. As a result, the body retains heat from metabolism that should have been dissipated.

7. Phenoxybenzamine, an α₁-adrenergic antagonist, inhibits all effects of catecholamines that are mediated through α₁ receptors. These effects include vasoconstriction of cutaneous and splanchnic blood vessels; contraction of the sphincters of the gastrointestinal tract; and contraction of the radial muscle of the iris. As discussed earlier, one of the major reasons that Mrs. Ames' systolic and diastolic blood pressures were so high was that excess catecholamines caused vasoconstriction of arterioles (increased TPR). When this vasoconstriction was blocked by an α₁-adrenergic antagonist, TPR was decreased, and both diastolic and systolic blood pressures were decreased.

8. Once treatment with the α₁-adrenergic antagonist was established, low doses of propranolol, a β-adrenergic antagonist, could be administered to reduce blood pressure further. The drugs were intentionally given in this sequence because of the effects of high levels of catecholamines on the heart and blood vessels. Recall that constriction of arterioles by catecholamines increases arterial pressure (afterload). One effect of this increased afterload is that it is more difficult for the left ventricle to eject blood. Thus, increased afterload offsets the other effects of catecholamines to increase cardiac output.

Once Mrs. Ames' afterload was reduced by the α₁-adrenergic antagonist, the work of the left ventricle was reduced, and it was easier for the ventricle to eject blood. At this point, the effects of excess catecholamines to increase cardiac output (through increased heart rate and contractility) would have become evident. In other words, Mrs. Ames' blood pressure may have remained elevated, even in the presence of an α₁-adrenergic antagonist. Addition of propranolol, a β-adrenergic antagonist, blocked the effects of excess catecholamines on heart rate and contractility and further reduced her blood pressure.

9. It would have been dangerous to give Mrs. Ames a β-adrenergic antagonist (e.g., propranolol) without also giving her an α₁-adrenergic antagonist. As we have already discussed, excess cir-
Calculating catecholamines caused vasoconstriction of her arterioles and increased her arterial pressure (afterload). Increased afterload made it more difficult for the ventricles to eject blood. The action of catecholamines to increase contractility through cardiac $\beta_1$ receptors partially offset this difficulty. If Mrs. Ames' cardiac $\beta_1$ receptors had been blocked by propranolol (without the assistance of phenoxybenzamine to lower TPR and afterload), her heart might not have been able to eject enough blood to serve the metabolic needs of her tissues (cardiac failure).

### Key topics

- Adrenal medulla
- Catechol-$D$-methyltransferase (COMT)
- Chromaffin cells
- Diastolic pressure
- Epinephrine
- 3-Methoxy-4-hydroxymandelic acid (VMA)
- Monoamine oxidase (MAO)
- Norepinephrine
- Phenoxybenzamine
- Pheochromocytoma
- Propranolol
- $\alpha_1$ Receptors
- $\alpha_2$ Receptors
- $\beta_1$ Receptors
- $\beta_2$ Receptors
- Systolic pressure
- Total peripheral resistance (TPR)