WHAT IS ENDOCRINOLOGY?

The explosive growth of information in endocrinology made possible by unprecedented advances in technology and by expansion of the number of investigators engaged in endocrinological research presents a difficult and growing challenge to those of us who teach endocrine physiology to medical students. The scope of research has so extended the boundaries of endocrinology and blurred the distinctions among disciplines that even defining endocrinology is problematic. Additionally, it has become increasingly difficult to decide what should be taught to first-year medical students and in what context. Regulation of cellular functions by hormones represents only a subset of the larger field of chemical communication that includes aspects of neurobiology, cell biology, immunology, and developmental biology. From the perspective of the target cell, what we call a hormone is quite arbitrary. Cellular and molecular processes associated with production, secretion, and actions of hormones are no different from actions of hundreds of other paracrine and autocrine factors, immunomodulators, neurotransmitters, growth factors, and so forth. The exquisite sensitivity of molecular biological tools has uncovered hormone production and hormone receptors in the most unexpected places. A host of nonendocrine tissues produce some of the same molecules secreted by the classic endocrine glands and use them to serve as local paracrine modulators or neurotransmitters. It is now apparent that hormones act on many more cells than their classically defined targets and that virtually every tissue in the body participates in some endocrine function.

Despite all of the above, the endocrine system remains a vital component of any course in medical physiology, and mastery of the principles and phenomena it encompasses is essential for later study of clinical medicine. The role of the endocrine system is to coordinate and integrate cellular activity within the whole body, regulating cellular and organ function from a distance, with factors produced locally, often in response to hormones, governing local fine tuning. From this perspective, it becomes more logical to focus on the physiological processes that are governed by the endocrine system rather than the classical morphologically based gland by gland survey, although students need to master basic facts connected with each gland and hormone. We can regard the endocrine system as having the following physiological missions:

- Regulation of sodium and water balance: preservation of the volume/pressure reservoir required for tissue perfusion
- Regulation of calcium balance: preservation of extracellular fluid concentrations required for membrane integrity, intracellular signaling, hemostasis, etc., and preservation of skeletal integrity
- Regulation of energy balance: preserving, accessing, and interconverting metabolic fuels to meet cellular energy demands
- Coordination of processes for coping with a hostile environment
- Coordination of growth and development
• Coordination of processes associated with reproduction and lactation

From this perspective, it is clear that at least some aspect of virtually every physiological system lies within the realm of endocrine control. No single hormone or endocrine gland can accomplish any of these missions alone, and virtually every hormone participates in fulfilling multiple missions. Consequently, students need to understand not only how hormones act but also how they interact. Some basic concepts transcend the wide range of physiological actions of hormones and may provide a foundation for understanding hormonal regulation. Many of these concepts are also the bases for diagnosis and treatment of endocrine disorders.

CONCEPTS RELATED TO CONTROL OF HORMONE SECRETION

Negative feedback control. Understanding negative feedback lies at the heart of understanding endocrine control systems.

The essence of negative feedback control of hormone secretion is that some consequence of secretion blocks or dampens further secretion (Fig. 1). The model depicted would ensure constancy of a regulated parameter at some set point except for the transient negative deviations that initiate the cycle and the positive overshoots that stop it. This model is inflexible and permits no opportunity for adaptation to changing environmental demands. The added elements of changing the set point or overriding the set point, shown in Fig. 2, are more likely to meet physiological requirements.

Many biological examples appear more complex but are simply superimposition of the same principles. The pituitary and adrenal glands are in a negative feedback relationship (Fig. 3), with cortisol acting as an inhibitor of both pituitary secretion of ACTH and hypothalamic secretion of corticotropin-releasing hormone and arginine vasopressin. Hypothalamic input to the negative feedback system allows for episodic override and adjustment of the set point in response to environmental inputs. Input to the hypothalamus comes also from circadian elements that impose periodic adjustments of the set point. Positive drive to the system is imposed by stress, in this case hypoglycemia. Another aspect of negative feedback illustrated here is negation of the positive drive im-
posed by hypoglycemia when glucose production is increased as a consequence of cortisol secretion.

Negative feedback systems operating in opposite directions combine to maintain blood glucose concentrations within narrow limits (Fig. 4). This illustration also incorporates feed-forward elements. Minimizing upward deviations is facilitated by the feed-forward effects of the intestinal hormone, glucagon-like peptide 1, which stimulates insulin secretion in anticipation of absorption of a dietary glucose load. A similar but perhaps more ambiguous role is played by parasympathetic stimulation of both the α- and β-cells during the cephalic phase of eating. Override of negative feedback to permit blood glucose to increase is provided by the sympathetic innervation of the islets and circulating catecholamines from the adrenal medulla. Such a transient override ensures adequacy of high energy fuels to meet the needs of episodic muscular activity or other responses to environmentally imposed emergencies.

**Positive feedback.** In positive feedback systems, the consequences of hormone secretion feed back to reinforce the drive for secretion rather than dampen it. Rather than maintaining matters stable and unchanging, positive feedback creates instability and leads to explosive changes (Fig. 5). Consequently, positive feedback is rare in biology. The best example is oxytocin secretion by the posterior pituitary lobe during the birthing process. Stretch exerted on the uterine cervix is a powerful stimulus for oxytocin secretion and is transmitted to the oxytocin-secreting magnocellular elements in the paraventricular and supraop-
tic hypothalamic nuclei by sensory neural inputs. With progressively greater stretch sensed by cervical nerve endings by the contractions of uterine muscle, more and more oxytocin is released, stimulating escalating contractile force and stretch on the cervix. Ultimately, the cycle is broken by the explosive evacuation of the uterus with the birth of the baby (Fig. 6).

CONCEPTS RELATED TO SPECIFICITY

Because of “internal secretion” of hormones into the blood, hormones are widely disseminated throughout the body and have access to virtually all cells. However, only certain cells respond to any particular hormone. These “target” cells differ from all other cells in the respect that they express receptors for that hormone (Fig. 7). In this example, only the cells that express receptors change color in response to hormones.

Receptors are proteins located within a cell or on its surface and contain a hormone recognition site that binds its hormone with high affinity and selectivity and a signal-transducing domain. Typical cells express thousands to tens of thousands of copies of receptors for a particular hormone. Binding the hormone produces some intramolecular change that activates the signal-transducing domain. Some receptors initiate signaling through their intrinsic enzymatic activity, but most do so by the change in their interactions with other proteins that may or may not have enzymatic activity.

The information delivered to the target cell is present in the structure and three-dimensional conformation of the hormone and is sufficient only to activate the receptor. It appears that activation of the receptor is an all-or-none phenomenon, with gradations in response resulting from gradations in the numbers of receptors that are activated in each cell. The receptor, by virtue of the biochemical changes it triggers in transducing the signal, initiates a particular biochemical change or group of changes (Fig. 8). Once the
hormone has delivered its message by activating the receptor, except in very rare cases, it plays no role in shaping the response. Rather, the signals generated in the target cell are determined by the signal-transducing component of the receptor. In many cases, there is more than a single class of receptors for a particular hormone, and each class usually activates a different biochemical pathway. Only in rare instances can a receptor bind more than a single entity of hormone with high affinity, and when this occurs (e.g., parathyroid hormone and the parathyroid hormone-related peptide), both agents produce identical cellular responses. It is possible to express chimeric receptors that contain the hormone recognition component of one hormone with the signal-transducing component of a second hormone. The biochemical changes set in motion are invariably characteristic of the signaling domain of the receptor (Fig. 8).

The nature of the final response elicited in a target cell is not determined by the intracellular signal generated by the receptor but, rather, by the effective machinery expressed in the cell as a consequence of its differentiated state. For example, receptors for the parathyroid hormone are present in the basal membranes of cells of both the proximal and distal portions of the nephron (Fig. 9). Binding of the hormone initiates the same signaling cascade in both cell types, but the proximal tubules respond by decreasing phosphate reabsorption from the glomerular filtrate and increasing hydroxylation of vitamin D, while the distal cells respond by increasing reabsorption of calcium.

CONCEPTS RELATED TO TARGET CELL RESPONSIVENESS

Responsiveness of target cells to stimulation by their hormones is not constant but may vary widely in different physiological states and is often adjusted by the actions of other hormones or local paracrine or autocrine agents as well as the primary hormone.

Factors that govern the magnitude of the response to a hormone. 1) The most obvious determinant of the magnitude of the response is the concentration of hormone that is available to bind to
receptors. That concentration, in turn, is determined by

- The rate of hormone secretion
- The rate of delivery by the circulation to the target cell surface, which is slower if the hormone circulates bound to plasma proteins than if it is unbound
- The rate at which the hormone is degraded or excreted

2) Of equal importance to the hormone concentration is the number of competent target cells that express functional receptors.

3) The sensitivity of target cells to hormonal stimulation is not constant and depends on

- The number of functional receptors that are expressed
- The affinity of the receptor for the hormone
- The status of postreceptor amplification mechanisms
- The status and abundance of effector molecules

The relationship between the magnitude of response to a hormone and the concentration of hormone producing that response is described by a sigmoidal curve (Fig. 10). The sensitivity to a hormone is often defined as the concentration needed to produce a half-maximal response. Target organ sensitivity is not constant and is often adjusted in accordance with physiological circumstances. In the example shown in Fig. 10, we may assume that curve B is the basal sensitivity that may be
Specificity of hormone (H) action. Only cells that express receptors (R) for the hormone can respond to it (in this case by changing color).

Receptors contain a hormone recognition domain and a signal-transducing domain. The nature of the signal generated is a function of the receptor and not of the hormone.
increased (curve A) or decreased (curve C). With increased sensitivity, a lower concentration of hormone is required to produce a half-maximal response.

Sensitivity does not necessarily parallel hormone binding by the receptor and, therefore, is not necessarily a function of the affinity of the receptor for the hormone. Because it depends on many postreceptor events, the response to a hormone may be at a maximum at a hormone concentration that does not saturate all of the receptors (Fig. 11). When <100% of the receptors need to be occupied to obtain a maximum response, cells are said to express “spare receptors.” For example, glucose uptake by the fat cell is stimulated in a dose-dependent manner by insulin, but the response reaches a maximum when only a few percent of the available and functional insulin receptors are occupied by insulin. The affinity of the receptor for the hormone is defined as the concentration at which half of the receptors are occupied by hormone. Because the response is related to the number of receptors that are activated and can therefore produce a biochemical response, the consequence for cells that express spare receptors is that they are more sensitive to the hormone than would be predicted from their binding affinity. In the example shown in Fig. 11, a twofold excess of receptors reduced by half the concentration of hormone needed to produce a half-maximal response.
Under a variety of circumstances, cells may increase (upregulate) or decrease (downregulate) the number of functional receptors they express. Upregulation or downregulation can be achieved by adjusting the relative rates of receptor synthesis and degradation, receptor endocytosis and sequestration, or covalent modification through phosphorylation or dephosphorylation. The consequences of upregulation or downregulation for sensitivity are shown in Fig. 12. Small changes in receptor abundance are of little consequence in the presence of a large number of spare receptors but can be quite profound for cells that express no spare receptors. It is more common for cells to adjust the number of receptors rather than for receptor affinity to regulate their sensitivity to a hormone.

The apparent sensitivity to hormonal stimulation is not a function only of receptor number. Downstream events also contribute to the concentration-response relationship. On the cellular level, upregulation or downregulation of effector molecules such as enzymes, ion channels, and contractile proteins, etc., may increase or reduce the maximum capacity for a response even though the sensitivity, as defined earlier, is unchanged (Fig. 13). On a tissue or organ level, the measured response is the...
aggregate of the contributions of all of the responding cells, so that the magnitude of the response to a particular concentration of hormone is a function of the number of available cells as well as the competence of each cell. Thus a change in response capacity will result in the need for a greater or lesser concentration of hormone to produce a given level of response and, therefore, appears as a change in sensitivity, even though the concentration of hormone required for the half-maximal response may remain unchanged.

**Factors that govern the duration of the response to a hormone.** Of equal concern to the magnitude of response is its duration. Factors that govern the duration of the response to a hormone include

I) the duration of hormone availability, which is determined by

- The duration of secretion
The rate of hormone clearance from the blood, usually described as its half-life

2) whether the response results from

- A rapidly reversible covalent change, i.e., phosphorylation or dephosphorylation of key enzymes

- Or genomic events involving synthesis of proteins and the half-lives of the proteins

CONCEPTS RELATED TO INTEGRATION

Hormones seldom act alone or on a single tissue in carrying out their missions of regulation and coordination. The following examples illustrate some concepts of integration.

Additivity and synergy. Multiple hormones often work in concert, and in some instances, they may appear to be redundant. Figure 14 illustrates the interactions of glucagon, epinephrine, and cortisol to increase blood glucose concentrations. The data shown are redrawn from Eigler et al. (1). Both epinephrine and glucagon, when administered alone to dogs, produced an increase in blood glucose, and when given together, their effects were additive. Cortisol alone had little effect on the blood glucose concentration, but when epinephrine plus glucagon were given to cortisol-treated dogs, the rise in glucose was far greater than the sum of the increases produced by the individual hormones alone. These data illustrate the concept of synergism, wherein the response to a combination of hormones is greater than the sums of their individual actions.

Reinforcement. As shown in Fig. 14, the actions of several hormones may converge to regulate the process of glucose production. Figure 15 shows an example of how the diverse actions of a single hormone exerted on several different tissues may converge to reinforce a critical action. One of the primary effects of glucocorticoids is to stimulate gluconeogenesis in the liver. Cortisol increases the enzymatic capacity of the liver for gluconeogenesis and renders the hepatocyte sensitive to gluconeogenic stimulation by glucagon and catecholamines. Efficient gluconeogenesis, however, requires a supply of substrate. Cortisol promotes the breakdown of protein in skeletal muscle and the release of amino acids into the circulation. It also facilitates the breakdown of triglycerides in adipose tissue and the release of glycerol and fatty acids into the blood. Amino acids and glycerol (along with lactate) are the principal substrates for gluconeogenesis.

Push-pull. Secretion of glucose by the liver is under both positive and negative control. In emergency situations or during exercise, there is increased demand for glucose. Just increasing the secretion of glucagon and epinephrine would increase the rate of glycogen breakdown and would, therefore, increase glucose production. Stimulation by these hormones becomes much more effective if the restraining effect of insulin is simultaneously relieved. This push-pull mechanism allows for rapid, unhindered glucose mobilization (Fig. 16).

Dozens of other examples of patterns of hormone interactions at the molecular, cellular, organ, and
organismal levels can be cited to underscore concepts of integration. The concept of homeostasis is a fundamental tenet of physiology, and the endocrine system is its principal defender. The ever-changing challenges to maintaining the constancy of the internal environment and ensuring survival of the species demand that endocrine control be dynamic, adaptable, and precise. The concepts presented here will hopefully provide students with some insight into the workings of the endocrine system. The concepts presented here are not unique to endocrinology, however, and perhaps will also contribute to their understanding of physiology as a whole.

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REFERENCES