Appendix 2

The Basics of Endocrinology

Endocrinology is the study of hormones, very different sorts of messengers from the neurotransmitters of chapter 2. As a recap, neurotransmitters are released from neurons' axon terminals in response to action potentials. Once released, they travel a microscopic distance across the synapse and bind to receptors on dendrites of the second, postsynaptic neuron, thereby changing that neuron's excitability.

In contrast, a hormone is a chemical messenger released from secretory cells (including neurons) in various glands. Once secreted, it enters the bloodstream, where it can influence any cells throughout the body that possess receptors for it.* So right off the bat we have key differences. First, neurotransmitters directly affect only neurons on the other side of synapses, while a hormone can potentially affect each of the trillions of cells in the body. A second difference is the time course; neurotransmitter signaling across synapses occurs in milliseconds. In contrast, many hormonal effects emerge over hours to days and can persist forever (for example, how often does puberty go away after a while?).

Neurotransmitters and hormones also differ in the scale of their effects. A neurotransmitter binds to its postsynaptic receptor, resulting in a local change in the flow of ions across the membrane of that dendritic spine. But depending on the hormone and the target cell being considered, hormones can change the activity of particular proteins, turn certain genes on or off, alter the metabolisms of cells, cause them to grow or atrophy, to divide or to shrivel up and die.

Testosterone, for example, increases muscle mass, and progesterone causes the proliferation of cells in the uterus, causing it to thicken during the luteal phase. Conversely, thyroid hormone kills cells in a tadpole's tail as the animal is metamorphosing into a frog, and a class of stress hormones can kill cells in the immune system (helping to explain how stress makes us vulnerable to getting a cold). Hormones are extremely versatile.

Most hormones are part of a "neuroendocrine axis." Recall from chapter 2 how all roads in the limbic system lead to the hypothalamus, with its pivotal role in regulating the autonomic nervous system and hormonal systems. Here's where that second part comes in. Neurons in the hypothalamus secrete a particular hormone that travels in a tiny, local circulatory system connecting to the pituitary, just below the base of the brain. There that hormone stimulates the secretion of a particular pituitary hormone, which enters the general circulation and stimulates the secretion of a third hormone from some peripheral gland. Here's an example involving my three favorite hormones: during stress, hypothalamic neurons secrete CRH (corticotropin-releasing hormone), which stimulates pituitary cells to secrete ACTH (adrenocorticotropic hormone). Once in the general circulation, ACTH gets to the adrenal glands, where it stimulates secretion of steroid stress hormones called glucocorticoids (with the human version being cortisol, aka hydrocortisone). Other hormones (e.g., estrogen, progesterone, testosterone, and thyroid hormone) are released from peripheral glands as the final step of their own "hypothalamic/pituitary/peripheral gland axis."* As a wonderful complication, the secretion of each particular pituitary hormone is often not under the control of only a single hypothalamic releasing hormone. Instead there are multiple types of hormones serving that function, and other hypothalamic hormones that inhibit that particular pituitary hormone's release. For example, an array of hypothalamic hormones in addition to CRH regulates the release of ACTH, where different types of stressors produce different combinations of those hypothalamic hormones.

Not all hormones are regulated in this brain/pituitary/peripheral gland manner. In some cases there's a brain/pituitary two-step, where the pituitary hormone exerts effects throughout the body; growth hormone generally fits this pattern. In other systems the brain sends projections down the spine and to a particular gland, helping to regulate its hormone release; the pancreas and its secretion of insulin are an example (where circulating glucose levels are the main regulator). Then there are weirdo hormones secreted from unlikely places like the heart or gut, where the brain regulates secretion only indirectly.

Hormones, like neurotransmitters, are made cheaply. They are constructed in just a few biosynthetic steps from plentiful precursors—either simple proteins or cholesterol.* Moreover, the body generates multiple types of hormones from the same precursor. For example, the numerous steroid hormones are all generated from cholesterol.

So far we've given short shrift to hormone receptors. They do the same general job as do neurotransmitter receptors; there is a distinctive receptor molecule for each type of hormone,* with a concave binding domain whose shape is complementary to the shape of the hormone. To trot out the same cliché as was used for neurotransmitters, a hormone fits into its receptor like a key fits into a lock. And as with neurotransmitter receptors, there's no free lunch with hormone receptors. The various steroid hormones are structurally similar. Thus, if you're cheap at the production end, you need subtle, fancy receptors that differentiate among those similar hormones—you do *not* want receptors that confuse, say, estrogen and testosterone.

Hormone/neurotransmitter similarities continue. Like neurotransmitter receptors, a hormone receptor's "avidity" for its hormone can change. This means that the shape of the binding site changes a bit, so that the hormone now fits more or less snugly, thus increasing or decreasing the duration of the hormone's effects. The number of receptors for a particular hormone in a cell can also change, altering the cell's sensitivity to that hormone's effects. The number of receptors in a target cell can be as important as the levels of the hormone itself, and there are endocrine diseases where normal levels of a hormone are secreted but, because of a mutation in the hormone's receptor, no signal gets through. Hormone levels are akin to how loudly someone speaks. Receptor levels are akin to the acuity with which ears detect that voice.

Finally, receptors for a hormone typically occur in only a subset of cells and tissues in the body, meaning that only those are responsive to the hormone. For example, only tail cells contain receptors for thyroid hormone when tadpoles are turning into frogs. Similarly, only some types of breast cancer involve tumors whose cells are "ER positive"—i.e., they contain estrogen receptors and are responsive to the growth-promoting effects of the hormone.

This is our overview of how hormones alter the functions of target cells over the course of hours to days. Hormones were highly pertinent in chapter 7 when considering the effects of hormones in childhood and fetal life. Specifically, hormones can have permanent "organizational" effects during development, shaping how the brain is constructed. In contrast, "activational" effects persist

for hours to days. These two domains interact, in that organizational hormone effects on a fetal brain influence what activational effects hormones will have on that brain in adulthood.

Back to the main text to consider specific hormones.