

Hi all,

In order to get as far away as possible from reproducing the lecture notes, I've gone through the curriculum's objectives for the unit that relate to the first two lectures—this seems like the best way to identify key points. I would also suggest doing the review tests in the curriculum in order to get a sense of the question format for Dr. Katzenellenbogen's tests. I try to note here the things she has emphasized in lecture. I accidentally went beyond the first two lectures, but just left it in.

Hope this is useful,
Marie

- 1) Describe endocrine, paracrine, and neurocrine, and autocrine cell-to-cell signaling.
 - a. Endocrine signaling: The hormone is secreted into the **blood** by a gland and **acts on distant target cells**. (eg this is what is happening in anterior lobe of pituitary gland)
 - b. Paracrine signaling: The hormone is secreted by one cell and **acts on a nearby target cell** (remember: para means “around.”)
 - c. Autocrine signaling: The hormone is secreted by one cell and **acts on itself**
 - d. Neuroendocrine signaling: A chemical messenger is secreted from nerve terminals. There are three kinds of neuroendocrine transducers:
 - i. Secretomotor Neurons: These neurons control endocrine glands by direct innervation via autonomic fibers. The adrenal medulla is the only target gland that is innervated by preganglionic neurons, while everything else is innervated by postganglionic neurons.
 - ii. Magnocellular Neurosecretory Neurons. (large neurons found in Posterior pituitary gland) The cell bodies are in the supraoptic nuclei and paraventricular nuclei, and the axons run through the infundibular stem. AVP and oxytocin are synthesized in the cell bodies, transported down the axons, and accumulate in the terminals. They are then released into the nearby capillary circulation.
 - iii. Parvicellular Neurosecretory Neurons (small neurons) that secrete “hypothalamus releasing or inhibiting hormones” The axons terminate directly on the capillaries of the portal vessels in the median eminence.
- 2) Describe the negative feedback and neural control mechanisms for regulation of hormone secretion and give two examples of each.

- a. Negative feedback: A hormone is produced, has a biological effect on a particular tissue (for example the tissue expresses another hormone), and as the response is enhanced the amount of original hormone that was produced is lowered. In a **SIMPLE** feedback loop, the biological effect only acts upon the endocrine cell. In a **COMPLEX** feedback loop the biological effect might influence more than one place (think anterior pituitary gland—the target gland hormone feeds back to block output by both the hypothalamus and the anterior pituitary gland). Some things under negative feedback: ACTH, FSH, TSH, LH.
 - b. Neural control: This term describes the control over hormone secretion by the parvocellular and magnocellular neurosecretory cells. This control is exerted by monoaminergic neurons with cell bodies in the mesencephalon and lower brainstem that secrete biogenic amines. Norepinephrine, dopamine, and serotonin control the secretion of hormones from the parvocellular neurons, and Ach stimulates (while norepinephrine inhibits) the release of hormones from the magnocellular neurosecretory neurons.
- 3) Understand the concepts designated spare receptors, down regulation, up regulation, maximum responsiveness, and sensitivity as they relate to hormone target cells
- a. Spare receptors: These are the unused receptors when a target tissue is issuing a maximum response (A maximum response of a target tissue doesn't mean that every single receptor on that tissue has to be occupied by a hormone.)
 - b. Down regulation: Too much hormone around and a hormone sensitive cell may adjust down the number of cell surface receptors **for itself**. (This last bit seems important—in the review questionseg non-insulin dependent diabetes)
 - c. Up regulation: this is when the presence of a hormone increases the number of a certain kind of receptor (eg estrogen in the ovary increases LH receptors!)
 - d. Maximum Responsiveness: At a target cell's maximum responsiveness, no greater response can be elicited by the target cell, even by increasing hormone concentrations. A cell may reach maximum response when 50 to a 100 receptors are occupied, even though it has tens of thousands of receptors.
 - e. Sensitivity: This refers to the amount of hormone necessary to elicit a response in a particular target cell. The “median effective dose” (ED50) is used to measure sensitivity. This refers to the concentration of hormone required to produce a response halfway between the basal and maximum response. The higher the ED50, the more hormone is needed to provoke a response (and the less sensitive the cell).
- 4) Know the key features of the mechanism whereby many **peptide or protein hormones as well as catecholamines** act upon target cells through the adenylate cyclase-cAMP system, calcium-calmodulin system, and membrane phospholipid system.

The best way to learn this is just to review the pathways in the notes and draw them over and over again. But in general, peptide, proteins, and catecholamines bind to **membrane bound receptors** and have effects via second messengers (like cAMP, calcium, or inositol triphosphate) **Timing seems important judging from her practice questions. Within minutes of a peptide binding a G-coupled protein receptor, you see phosphorylation of intracellular proteins and increases in the intracellular levels of cAMP.**

- 5) Know key features of how steroids and thyroid hormones act on cells.
- a. Same as above. But in general, steroids and thyroid hormones act by influencing transcription and translation of particular proteins. Remember—in blood, steroid and thyroid hormones are insoluble and travel bound to plasma proteins. Only a small fraction are ever really “free.” But when a free steroid hormone binds to a receptor that is in the nucleus or cytoplasm, it forms a **hormone/receptor complex** (it doesn’t act alone, this was emphasized in lecture) and binds to an enhancer element in the DNA and affect transcription of a protein. **Emphasized in Lecture: Because steroids influence gene transcription and production, they generally have slower actions than protein/peptide hormones.** But there are some rapid effects of steroid hormones at the membranes of some cells, which implies that steroid hormones do have some actions that aren’t related to influencing transcription. **The timing of the hormone actions seems important judging by her review questions. Within minutes: the hormone receptor complex binds to DNA sites and there is increase mRNA transcription. It takes longer to see marked protein increase**
- 6) Know the roles that specific carrier proteins play in transporting hormones in the blood, and the influence of these hormone binding proteins on the disposal of hormones from the blood.
- a. Amino acid derived and polypeptide hormones dissolve! Don’t need carriers. But steroid and thyroid hormones don’t dissolve and need help. 90% of them are bound to plasma proteins, which are **globulins made in the liver**, and only the free stuff is biologically active. Some other things these carrier proteins do:
 - i. Increase the total amount of hormone that can be carried in the plasma:
 - ii. Provide a large reservoir of hormone that buffers rapid change in free hormone concentration
 - iii. Slow rate of clearance of hormones from plasma by reducing the rate of hormone degradation by the kidney and the liver and reducing the rate of entry of hormone into cells

- iv. Prolong the duration of action of hormones by extending the exit rate of hormones from the plasma to target cells (?? I don't really know what this means, but added it bc it was in her quiz.)
- 7) Know the principles of the radioimmunoassay. The Radioimmunoassay is a **competitive binding assay** that tells you how much hormone is in a given sample. The first step is to determine a standard curve. In order to do this, a **fixed amount of radiolabeled hormone** is added to a **fixed amount of antibody against the hormone in question**. After this mixture is made, the same mixture is added to a number of tubes. Then, known quantities of **unlabeled hormone is added** to the tubes describe above in increasing concentrations. A graph is plotted of the radiolabeled hormone that is bound to antibody. Competitive inhibition is at work here—when the radiolabeled hormone is the only hormone present, it will all bind to antibody. But as unlabeled hormone is added, some of the labeled hormone will be knocked off. This will show up as a smaller amount of radioactive hormone attached to the antibody (see graph in our notes). When trying to evaluate the amount of hormone in a given patient sample, the sample is added to the fixed amount of radiolabeled hormone and fixed antibody (same amounts as in original tubes used to generate the standard curve) and the quantity of radiolabeled substance is compared to the standard curve. This approach enables the detection and quantification of very small amounts of substance in the blood. But one drawback is that the test measures immunoreactivity and not biological activity. The antibodies may sometimes bind to another hormone that you do not wish to measure—for example, a precursor (eg POMC instead of ACTH).
- 8) Describe the anatomical and functional relationship between the hypothalamus and pituitary gland.
 - a. The pituitary gland sits in the sella turcica (a depression in the sphenoid bone of the skull) and is connected to the hypothalamus by the infundibular stalk. It is made up of the **adenohypophysis**, which contains the pars tuberalis and the pars distalis (anterior lobe) and the **neurohypophysis**, which is made up of the **median eminence** of the hypothalamus, the infundibular stem (inside of stalk) and the **infundibular process** (posterior lobe). The hypothalamus has a different relationship to the anterior and posterior portion of the pituitary gland. It exerts **neural control** over the posterior lobe, and controls the anterior lobe via **hypothalamic hormones**, or releasing hormones (such as GnRH, TRH, CRH, and GH) or release inhibiting neurons (like somatostatin, dopamine). (more details on this in the next two lectures).
- 9) Identify the chemical structure of the following anterior pituitary hormones: TSH, ACTH, FSH, LH, GH, somatotropin. Identify the structure of the precursor proopiomelanocortin (POMC) and know the peptides for which it is a precursor. Identify the chemical structure of the following hypothalamic neurosecretory hormones: somatostatin, corticotrophin releasing factor, GnRH, GHRH, Prolactin-inhibiting factor. More detail is given on these in the next lecture. And look at the diagrams in this lecture for details. But for now, a few basic things to help sort this out:

- a. There are four classes of hormones based on structure: glycoproteins, polypeptides, steroids, and amines. A few tips on which is which:
- i. **Steroids:** You know these: aldosterone, cortisol, estradiol, progesterone, testosterone, Vit D. **LONG HALF LIFE** (hours)
 - ii. **Amines:** Only four: two catecholamines (Epinephrine, Norepinephrine) and thyroid hormones (Thyroxine and Triiodothyronine). The catecholamines have a **very short half life** (seconds) and the thyroid hormones have **very long half lives** (hours to days)
 - iii. **Glycoproteins:** (only four, **all BIG!**): these include all of the hormones (except ACTH) produced by the anterior pituitary gland basophil cells (the “FLAT” in FLAT PIG: **FSH, LH, TSH**). This category also includes **hCG** (easy to remember—very similar structure to LH) **SHORT HALF LIFE** (minutes) (Though half life of FSH is 180 minutes). The Glycoproteins are made up of α and β subunits, and the α subunits identical (and the β subunits conferring specificity!)
 - iv. **Polypeptides:** All the rest. Of varying size, but here are some rules:
 1. Stuff from the posterior pituitary is small (9AAs: oxytocin and ADH),
 2. Stuff from the anterior pituitary is BIG except ACTH, which is small (44 AA's) There is a question in the curriculum that touches on this point!
 3. Stuff from the hypothalamus is all small (from 3 to 44 AA's) with TRH, GnRH, and somatostatin very small (from 1 to 14 AA's)
 4. Stuff from the pancreas is medium-sized (30-50AAs) except somatostatin, which has a small and medium form.
- b. POMC is a precursor for the following: (**there is a practice question on this in the curriculum**):
- i. ACTH
 - ii. α MSH, β MSH, γ MSH
 - iii. β LPH, γ LPH
 - iv. β -endorphin
- c. ACTH can be broken down to α MSH
- 10) The kinetics of receptor binding is also covered in the first two lectures, but it is laid out pretty well in the textbook (pp. 577-578).

Refs:

Bullock, J, Boyle, J, and Wang, M. (2001). NMS Physiology, 4th ed. Philadelphia: Lippincott Williams and Wilkins.

Rhoades, R. and Tanner, George. (2003). Medical Physiology, 2nd ed. Philadelphia: Lippincott Williams and Wilkins.