Classic Endocrine Glands

Throughout the body there are several endocrine glands, which produce hormones. These hormones can be classified as peptide **hormones**, **steroid** hormones and **amines**.

There are three types of horomone interactions:

- Antagonistic – two hormones have opposing actions (ie. Insulin and Glucagon).
- Synergistic – Two or more hormones necessary to produce actions.
- Permissive – When one hormone cannot fully exert its effects unless a second hormone is present. Examples of this would be cortisol for glucagon.

Hypothalamus –

Vasopressin, it is an anti diuretic hormone produced in the hypothalamus but secreted from the posterior pituitary, and without it the kidneys are impermeable to water. Therefore this hormone is able to **increase reabsorption of water**. ADH (anti diuretic hormone) is an example of a neurohormone. The Hypothalamus has two types of neurons in this case; one of them has nerve terminal on the posterior pituitary. ADH is synthesized on the hypothalamic parts of these cells; it travels on the nerve projections and is released on to the vascular system. The other type of hypothalamic neurons releases the releasing factor into a specialized cardiovascular system, where they travel to the anterior pituitary where they can inhibit or stimulate other the release of other hormones.

Vasopressin travels through the blood stream and binds to its receptor on the membrane of the collecting duct cells, which activates adenylate cyclase, which makes cAMP that signals a cascade causing the insertion of water pores (aquaporin 2) so that water can be transported from the collecting duct lumen to the blood stream. The vast majority of liquid that goes to the tubules in the kidneys are reabsorbed. However if these water pores were not triggered by Vasopressin, they would be stuck on the inside of the cells.

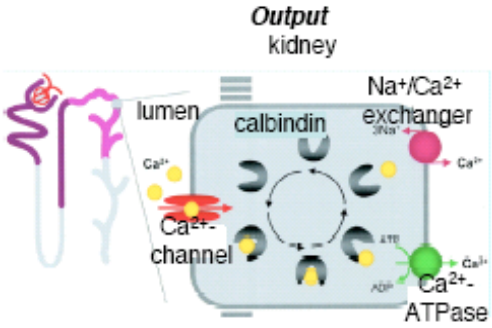
Therefore Vasopressin is stimulated by an increase of plasma osmolarity. If fluid concentrations are starting to rise, this hormone will be able to reabsorb water and try to balance these concentrations. A mutation of the gene coding for Vasopressin can cause intense thirst and excess dilute urine.

Thyroid –

Produces the **Thyroid Hormone** (**T3** which is more potent due to higher affinity of its receptor to DNA, and **T4** the more abundant one), which acts on many different homeostatic systems in our body as, stated on the table. It is controlled by TSH (Thyroid Stimulating Hormone), which stimulates its release. On the other hand TSH, which is produced in the anterior pituitary is released upon the excretion of TRH (Thyroid Releasing Hormone) from the hypothalamus. Hyperthyroidism can happen if TSH receptors are being turned on constantly, which causes an increase in the release of T4 and T3 and a decrease of TSH release. This tends to cause weight loss. If function of the thyroid gland is knocked out, hypothyroidism occurs, which is more common. This causes weight gain.

Parathyroid – One of the endocrine glands that are essential for life.

PTH is a hormone responsible for the control of Ca^{++} in the body, it acts to increase plasma [Ca^{++}] by acting directly on the bone and kidney. Its action in the bone is directly on osteoblasts, through a G-protein coupled receptor that produces cAMP. This has two complementary effects, increasing the production of RANKL (ligand) and inhibiting the production of OPG (endogenous inhibitor). RANKL binds to RANK, which is attached to an osteoclast which will in turn remove Ca^{++} from the bones. PTH can also use calcium fomr the labile pool in the bone fluid. On the kidney, PTH increases the reabsorption of Ca^{++} directly as well as inducing the production of Vitamin D, which will then increase the uptake of calcium from the small intestine. Calcium fluctuations are detected by a calcium-sensing receptor located in the parathyroid. This stimulus increases the activity of PLC, which then decreases the levels of PTH made by the parathyroid. This is a good example of negative feedback. PTH and vitamin D also control phosphate metabolism.



Hoenderop 2000 Am J Physiol Renal Physiol 278 pF352

Anterior Pituitary –

Growth Hormone is a large peptide hormone with 190aa. It is produced in the anterior pituitary, and its receptor signals through a kinase pathway, even though the receptor itself is not a kinase. **GH stimulates remodeling of the bone**, ↑ the recruitment of chondrocytes (cartilage), osteoclasts and osteoblasts. GH can act directly on these cells or it can act via IGF-1, produced in the liver. GH has a plasma binding protein, even though it is a peptide hormone. It also has anabolic effects for protein and catabolic for fat and carbohydrates. Over expression of IGF-1 in mice leads to hyperplasia and consequently cancer. Growth hormone activity is monitored by several feedback systems including GHrH (⊕ from hypothalamus), Somatostatin (Θ from hypothalamus), Ghrelin (⊕ from stomach) and IGF-1 (Θ from liver).

Pancreas –

It produces **Insulin** at βCells, which are formed from its precursos, proinsulin. Insulin is an example of an anabolic hormone, meaning that it has its main function being to use glucose to produce bigger molecules and store them in our body. It helps reducing blood glucose and store carbohydrates, fat and proteins. It has a receptor enzyme characterized by a second messenger system, which phosphorylates proteins producing a desired cellular response. Insulin release is primarily stimulated by the presence of glucose in the plasma. A transporter GLUT is responsible for bringing in glucose from the plasma into βCells and this allows for glycolysis and the citric acid cycle in these cells. Once these

processes raise the levels of ATP in the cell, a K channel is closed in the membrane of the cell, which depolarizes these cells; this is a classic example of a non-neuronal membrane depolarization. As a result Ca+ channels open which triggers the release of vesicles containing insulin. Other regulators are also present, such as miRNAs, which inhibit insulin exocytosis.

An experiment knocking out insulin receptors specifically in fat cells seemed to increase mice lifespan. This is not well understood yet.

Glucagon is another hormone produced in the pancreas by αCells. It is the antagonizing hormone for insulin; its main goal is to prevent hypoglycemia. Therefore through a G-protein coupled receptor, glucagon activates the production of its second messenger, cAMP, which results in a phosphorylation cascade. This happens in response to fasting. An interesting fact to know is that in the protein that contains the precursor of glucagon, 2 other peptides can be found, GLP-1 and GLP-2. Interestingly enough, GLP-1 inhibits glucagon release, and it stimulates insulin release.

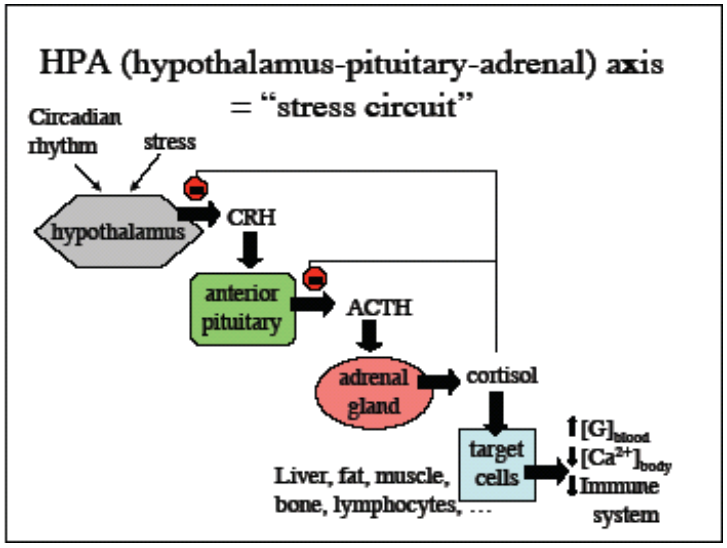
The third hormone released from the pancreas and intestine that we should know about is **Somatostatin**. This peptide hormone is produced by δCells. It is knowns as a negative hormone, since it inhibits several other endocrine (insulin, glucagon, growth hormone) and exocrine (gastric acid, etc) secretions. This hormone is an example of a precursor (preprosomatostatin followed by prosomatostatin) that can be cleaved in two different chains resulting in two different hormones, somatostatin-28 and somatostatin-14.

Adrenal Gland – The adrenal gland is located just on top of the kidneys.

The adrenal gland is responsible for the release of **Epinephrine** (catecholamine), which is a hormone that is related to acute stress. This hormone has many effects in the body, such as: glucose release (liver), fatty acid release (adipose tissue), heart contraction increase, intestinal muscle relaxation, vasoconstriction of intestine, skin and kidney, and muscle arteriole relaxation. Adrenaline can have different physiological effects via different receptors and effectors. These receptors can be G-protein coupled and can go through cAMP cascades (PKA - β1 and β2), or can directly phosphorilate PLC (Phospholipase C – α2) or they can be inhibitory like α1. Epinephrine is produced in the medulla region of the adrenal, where vesicles can also be stored.

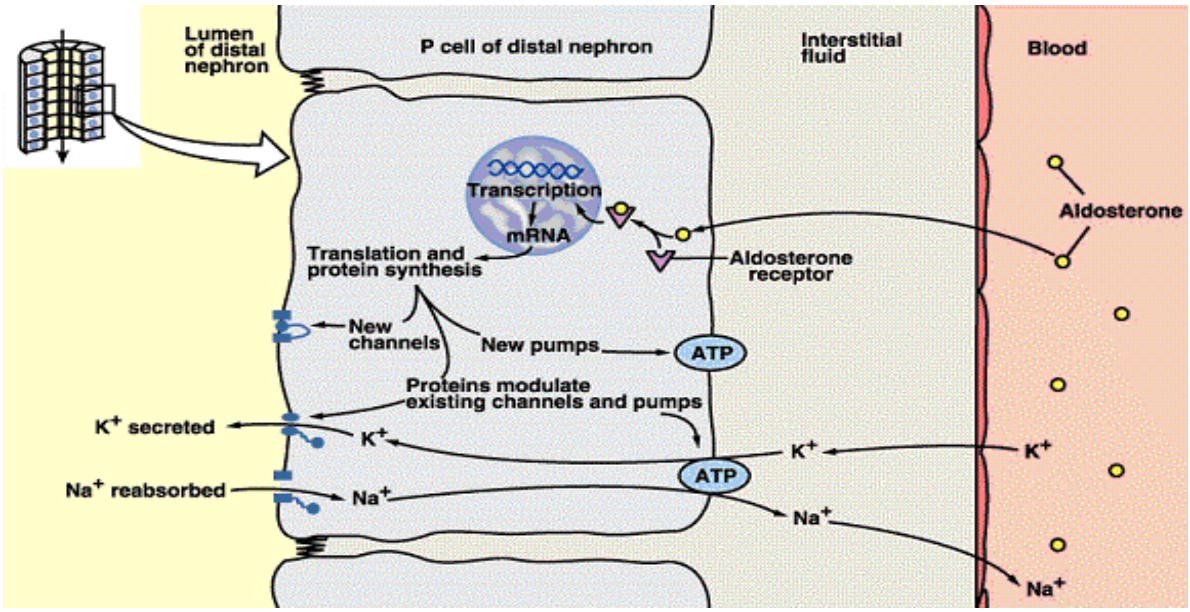
Cortisol is another important hormone produced in the adrenal gland. It is a glucocorticoid (steroid) that has catabolic actions protecting the body from hypoglycemia. It has a relatively slow effect due to its receptors being related to DNA binding proteins. This is done by the increase of gluconeogenesis from the liver, protein breakdown from muscle and fat lipolysis. It also acts to decrease [Ca^{++}] in the body, and it suppresses the immune system (decreas of cytokine release, antibody production). Even though cortisol has catabolic results in the body, it is also related to gain in abdominal fat during periods of stress. The person under stress will have urges for sweets (neurological response) that can increase the amount of adipose tissue in that area, which then releases chemicals that counteract the effects of cortisol in the brain. Cortisol is an essential hormone for life, this is mainly due to its interaction with other hormones. The release of cortisol is controlled by the hypothalamus-pituitary-adrenal axis (stress circuit). It involved the release of cortisol and its action on target cells, in addition cortisol feeds back at the level of the hypothalamus and the anterior pituitary, to regulate the release of hormones that come out of these glands.

Stress and circadian rhythms are both integrated in the actions of the hypothalamus. This is a typical hypothalamic-anterior pituitary regulation as shown on the picture below.



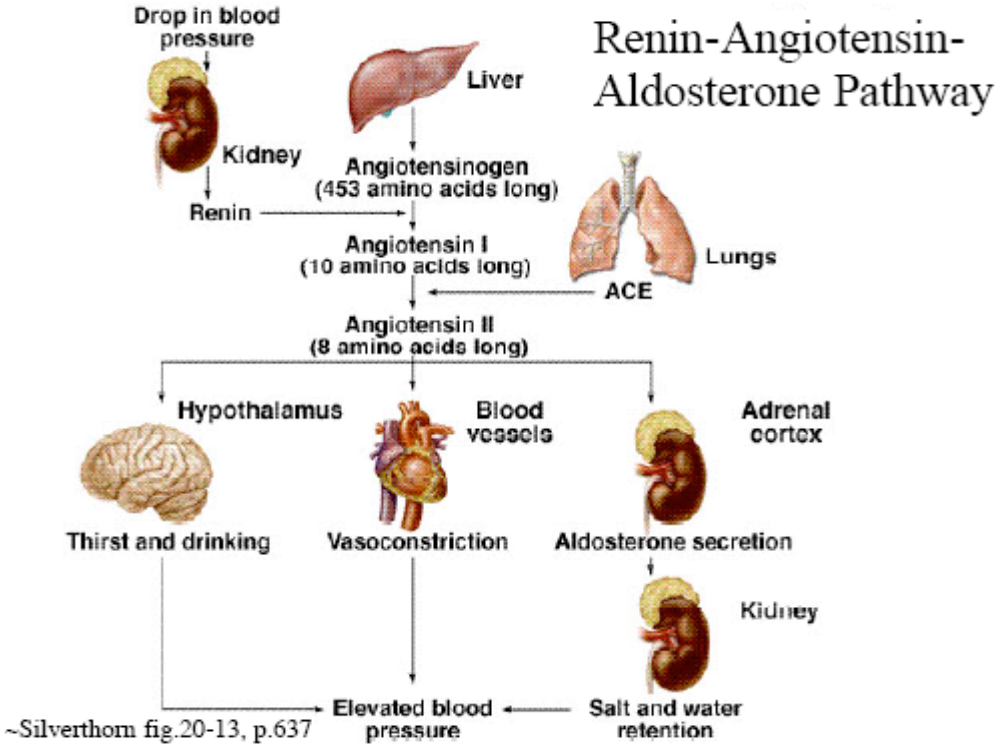
CRH peptides make up a family of peptide hormones with similar peptides that are encoded by different genes. As the figure above shows, CRH are not actually made in the adrenal, but it relates to the release of cortisol. Some of them may work on the same conditions (ie. stress) but in opposite ways. CRH peptides have roles in mood disorders, food intake, immune and cardiovascular responses. **ACTH** is another hormone that is released in response to CRH, this hormone acts on the adrenal as we have seen already, and it also works on skin pigmentation, learning capacity and immune responses. ACTH precursor encodes several other hormones as well.

Aldosterone is a steroid synthesized in the adrenal cortex, and is responsible for the **increase in sodium reabsorption**. Aldosterone induces mineralcorticoid receptor translocation to the nucleus, where it binds to transcription factors. This hormone acts on the distal tubule and the collecting duct. This distal tubule is just a portion of the nephron between the loop of Henle and the collecting duct system. So initially the aldosterone molecule binds to its receptor, which moves it to the nucleus where transcription of genes that are necessary for sodium re absorption. The movement of the Na^+ into the bloodstream, is done by active pumps, and Calcium is actively being exchanged by this pump. This is a classical example of a steroid hormone acting on the gene transcription, to give this end result of increase of sodium concentration in the blood.



The synthesis of Aldosterone is controlled by negative feedback. There are two ways of control, the simple one that takes into account K^+ and osmolarity and a complex one, dealing with the renin-angiotensin path.

Stimulators: Angiotensin II (potent) and High $[K^+]_{plasma}$.
Inhibitor: High osmolarity (extracellular fluid).



Aldosterone	Adrenal Cortex (steroid - nucleus)	Triggered by Angiotensin II, ↑ Na+ reabsorption by kidneys (↑ blood pressure)
Angiotensin II	Liver (peptide) refer to picture above	Acts on Hypothalamus (↑ Thirst), Blood vessels (Vasoconstriction), and Adrenal Cortex (secretion of aldosterone). All these contribute to ↑ of blood pressure.
Vasopressin (ADH, antidiuretic)	Hypothalamus but secreted by posterior pituitary. (Peptide) – cAMP, Gprotein	↑ H_2O reabsorption by kidneys (collecting duct)
Atrial Natriuretic peptides (ANP)	Atrium (peptide) - cGMP	It is the hormone opposing the action of Vasopressin and aldosterone. Therefore it causes a ↓ of release of rennin (enzyme that activates angiostatin II), ↓ of H_2O and Na^+ levels, and ↓ in blood pressure.
PTH (Parathyroid Hormone)	Parathyroid (peptide)	↑ plasma [Ca^{++}] acting on bones and kidney. Very important ionic control. ↓ Phosphate reabsorption in kidney.
Vitamin D	Kidney (steroid)	↑ the uptake of calcium from the small intestine. It also acts on the kidney and bones to ↑ the levels of Ca^{++} in the blood. ↑ phosphate absorption by intestine and ↑ reabsorption by kidney.
Calcitonin	C cells in Thyroid (peptide)	Plays a minor roll in adults opposing PTH actions. Me be more important for children and pregnant women.
GH (Growth Hormone, somatotropin)	Anterior pituitary (190aa Peptide)	↑ the release of IGF-1 (Insuline-like growth factor) by the liver
GHrH (GH releasing hormone)	Hypothalamus	It acts on the anterior pituitary to stimulate the release of GH.
SS (Somatostatin)	Hypothalamus	It acts on the anterior pituitary to inhibit the release of GH.
Ghrelin	Stomach	It acts on the anterior pituitary to stimulate the release of GH.
Thyroid Hormones (T4, T3)	Thyroid (amine)	↑ glucose production, ↑ lipolysis, ↑ Oxygen consumption and temperature. Has effects on the nervous system (speech, thinking and reflex), Growth and development, Cardiovascular system (blood flow, heart rate and contractility) and ↑ muscular activity.

TSH	Anterior Pituitary	Stimulates the release of T3 and T4, also appears to have receptors in precursors of osteoclasts and osteoblasts.
TRH	Hypothalamus	Stimulates the release of TSH
Insulin	Pancreas (peptide)	↑ glucose uptake
Glucagon	Pancreas (peptide)	Catabolic hormone
Somatostatin	Pancreas (peptide)	Negative effect on insulin, glucagon and growth hormone.
Adrenaline	Adrenal (catecholamine)	Glucose release, ↑ heart rate, ↓ GI activity, etc.
Cortisol	Adrenal (steroid)	Catabolic action, ↓ of [Ca^{++}] in the body, and suppression of the immune system.
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