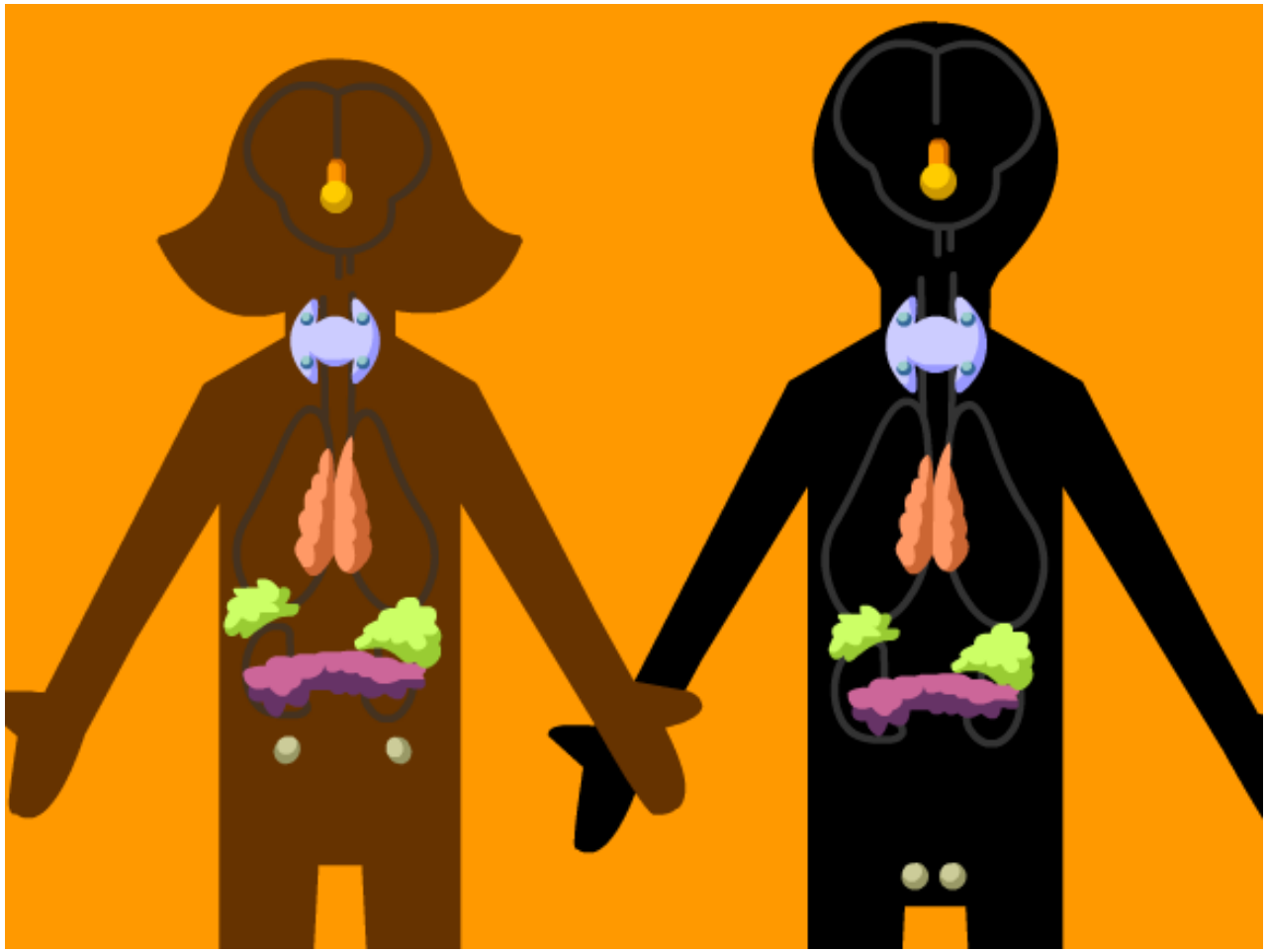


ENDOCRINE SYSTEM

Hormones

- are secreted by a cell or group of cells.
- are secreted into the blood
- are transported to a distant target.
- exert their effect at very low concentrations
- act by binding receptors.
- action must be terminated.

Peptide Hormone Synthesis, Packaging, and Release

Messenger RNA on the ribosomes binds amino acids into a peptide chain called a *preprohormone*. The chain is directed into the ER lumen by a *signal sequence* of amino acids.

Enzymes in the ER chop off the signal sequence, creating an inactive*prohormone*.

The prohormone passes from the ER through the Golgi complex.

Secretory vesicles containing enzymes and prohormone bud off the Golgi. The enzymes chop the prohormone into one or more active peptides plus additional peptide fragments.

The secretory vesicle releases its contents by *exocytosis* into the extracellular space.

The hormone moves into the circulation for transport to its target.

Steroid hormones are derived from cholesterol

They have similar structure. They are made in only a few organs.
Adrenal cortex
Gonads
Skin
Placenta

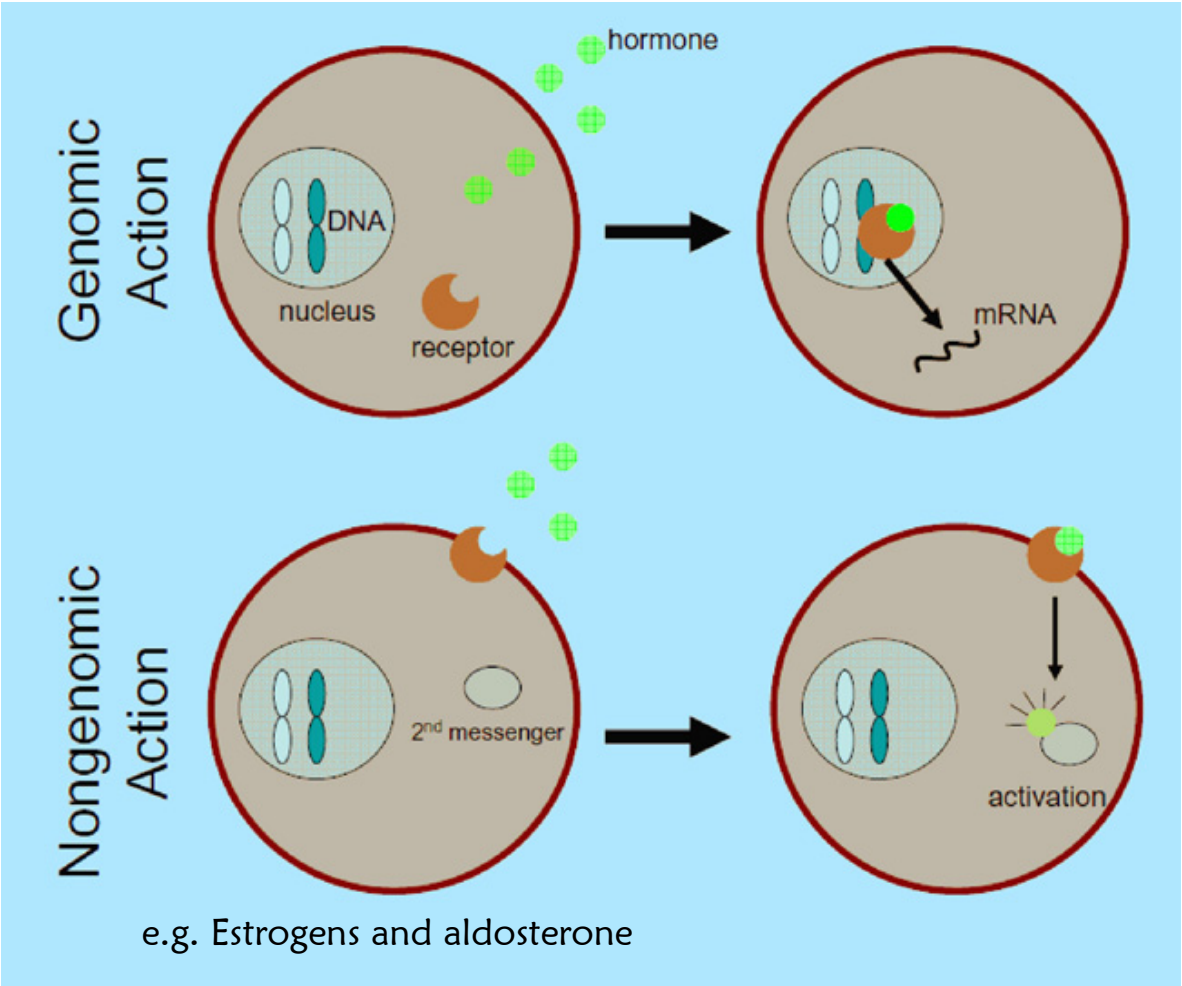
Steroids are lipophilic and diffuse easily across membranes, so cells can not store hormones in vesicles. They synthesize as needed.

Steroid hormone receptors are in the cytoplasm or in the nucleus. Ultimate destination is nucleus where the complex acts as a transcription factor, binding to DNA and by activationg or repressing one or more genes.

Activated genes create mRNA that directs synthesis of new proteins. Any hormone that alters gene activity is said to have a genomic effect on the target cell.

When hormones activates genes to direct production of new proteins, there is usually a lag time between hormone-receptor binding and the first biological effects. This lag can be as much as 90 min.

Any hormone that alters gene activity is said to have a genomic effect on the target cell.



Fast/slow response

Hormonal control

There are 3 types of hormonal control. There are steps that regulate hormone secretion. Similiar components: a stimulus, a sensor, an input signal, integration of the signal, an output signal, targets, a response
Output signal is a hormone or neurohormone
Simplest pathway are those in which an endocrine cell directly senses a stimulus and responds by secreting its hormone

Simple Endocrine Reflex: Parathyroid Hormone

PTH which controls Ca homestasis is an example.

When a certain number of Ca are bound to the receptors, PTH secretion is inhibited. If Ca falls below a certain level, inhibition stops and cells secrete PTH. PTH travels through the blood to act on bone, kidney and intestine and initiate the response to increase Ca concentration. Increase in plasma Ca is a negative feedback signal that turns off the reflex and end the release of PTH.

Multiple Pathways for Insulin Secretion

Pancreatic endocrine cells are sensors that monitor blood glucose concentration. If BG increases, beta cells respond by secreting insulin. Insulin travels through the blood to its targets which increase their glucose uptake and metabolsim. Glucose moving into cells decrease the blood concentration which act as a negative feedback signal that turns off the reflex and end the release of insulin.

Insulin secretion can also be triggered by signals from nervous system or by a hormone (**Glucagon-like peptide 1)** secreted from digestive track after a meal is eaten. The pancreatic beta cells- integrating center- must evaluate signals from multiple sources when 'deciding' whether to secrete insulin. The pathway begun by eating a meal shuts off when the stretch stimulus disappears as the meal is digested and absorbed from the digestive tract.

Pituitary Gland is a bean-sized structure that extends downward from the brain.

There are two different tissue types that merged during embryonic development.
Anterior pituitary is a true endocrine gland which is also called adenohypophysis and its hormeones are adenohypophyseal secretions.
Posterior pituitar or neurohyposis, is an extension of neural tissue of the brain. It secretes neurohormones made in hypothalamus.

Once the neurohormone is packaged into secretory vesicle, the vesicles are transported to the posterior pituitary through neurons. After vesicles reach the axon terminals, they are stored here waiting for the release signal. When a stimulus reaches the hypothalamus, an electrical signal passes from the neuron . Depolarization of axon terminal open voltage gated Ca channels, Ca enters the cell. Ca entry trigger exocytosis and vesicle contents are released into the circulation. Once in the blood, neurohomones travel to their targets.

The hypothalamic neurohormones that control release of anterior pituitary hormones are identified as *releasing* hormones or *inhibiting* hormone.

These hormones that control secretion of other hormones are known as *trophic hormones*.

To avoid dilution, hypothalamic neurohormones enter a special modification of the circulatory system called a ***portal system*** which connects the hypothalamus and anterior pituitary (hypothalamic-hypophyseal portal system)

•The hormones (not the response) are themselves feedback signal.
•Dominant feedback form is long-loop negative feedback, where the hormone secreted by the peripheral endocrine gland “feeds back” to suppress secretion of its anterior pituitary and hypothalamic hormones.
•In short-loop negative feedback, a pituitary hormone feeds back to decrease hormone secretion by the hypothalamus (PRL, GH, ACTH)

Cortisol secreted from adrenal cortex feeds back to suppress secretion on corticotropin releasing hormone (CRH) and adrenocorticotropin (ACTH). ACTH also exerts short loop negative feedback on the secretion of CRH.

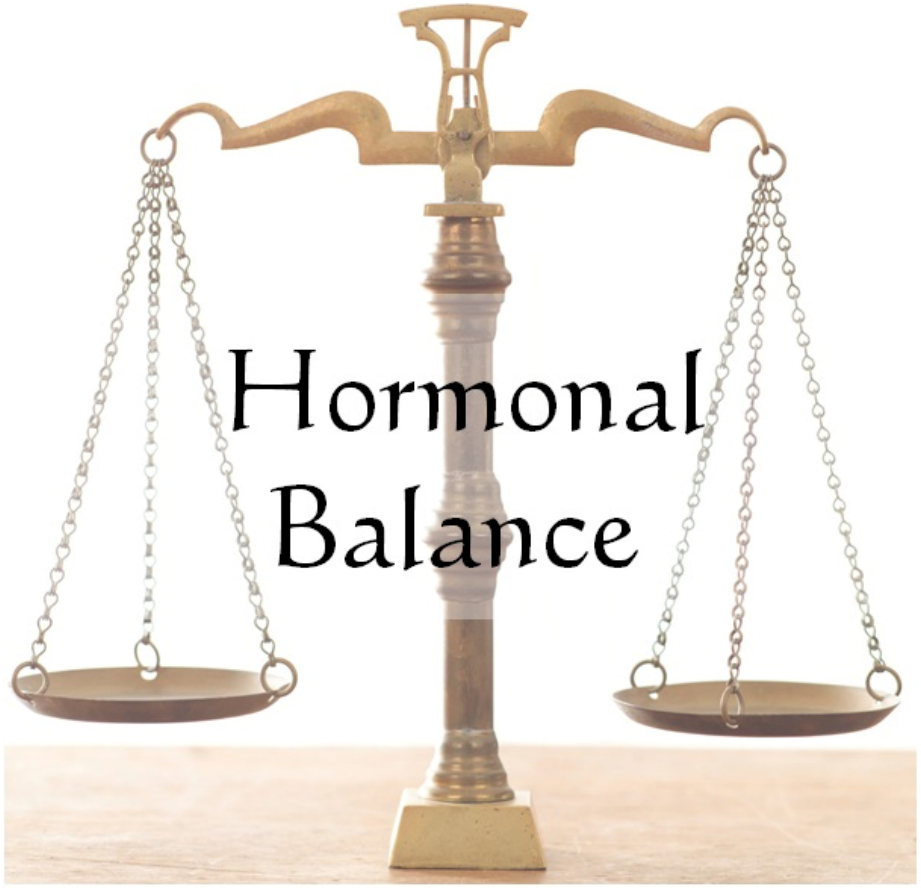
Hormone interactions:

- Synergism
- Permissiveness
- Antagonism

Synergism : the effect of interacting hormones is more than additive.

Permissiveness: one hormone can not fully exert its effects unless a second hormone is present even though the second hormone has no apparent action.

Antagonism: Two molecules work against each other, one diminishing the effectiveness of the other.



A balance of hormones is important for a healthy life. Unbalance leads to diseases.

Endocrine Pathologies

- Hormone disease is caused by an imbalance due to either excess or deficiency or abnormal responsiveness
- **Hypersecretion:** excess hormone causes exaggerated effects
  - Tumors (benign or cancerous) of glandular tissues
  - Exogenous sources- most sources are medications or supplements, *iatrogenic*
- **Hyposecretion:** deficient hormone
  - Most often low levels cause increased tropic hormone levels
  - Goiter— low secretion of thyroxin
  - Diabetes—low secretion of insulin
- **Abnormalities related to hormone response**
  - Target tissues do not respond to the hormone correctly
  - Downregulation- high hormone levels may result in a decrease of receptors as it happens in Hyperinsulinemia
  - Receptor abnormalities- the receptors may not function due to a genetic mutation as it happens in Testicular feminization syndrome

ADRENAL GLUCOCORTICOIDS

Paired adrenal glands sit on top of the kidneys which secrete multiple hormones, both neurohormones and classic hormones.

Control pathway of cortisol
Hypothalamic-pituitary-adrenal (HPA) pathway

Control pathway of cortisol is known as HPA which begins with hypothalamic corticotropin-releasing hormone. CRH stimulates release of adrenocorticotropic hormone (corticotropin) from anterior pituitary. ACTH acts on adrenal cortex to promote synthesis and release of cortisol. Cortisol then acts as a – feedback signal and inhibits ACTH and CRH.

Cortisol secretion is continuous and has a strong diurnal rhythm. Secretion normally peaks in the morning and diminishes during the night. It also increases with stress.

Steroid hormone is a typical steroid hormone and is synthesized on demand. Once synthesized, it diffuses out of adrenal cells into plasma, where most of it transported by a carrier protein, corticosteroid binding globulin. Unbound hormone is free to diffuse into target cells. All nucleated cells have cytoplasmic glucocrticoid receptors . Hormone-receptor complex enters the nucleus and alter gene expression, transcription, translation so the response occurs in 60-90 min.

Cortisol

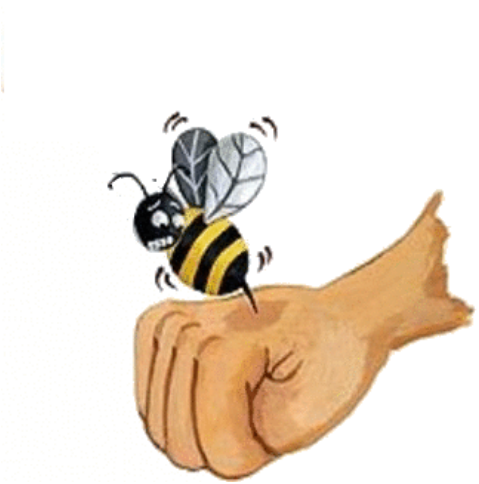
Adrenal corticosteroids are sometimes called the body's stress hormones because of their role in mediation of long term stress.
The most important metabolic effect of cortisol is its protective effect against hypoglycemia.

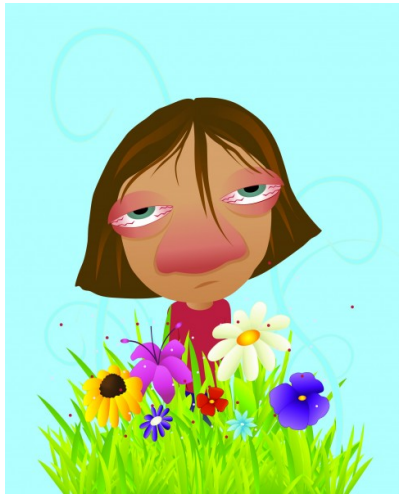
Cortisol is catabolic

- **Promotes gluconeogenesis-** stimulates the liver to increase blood glucose levels
- **Causes breakdown of skeletal muscle proteins** – releases amino acids to act as substrates for gluconeogenesis
- **Enhances lipolysis-** releases glycerol for gluconeogenesis and fatty acids for energy use
- **Suppresses the immune system-** reduces inflammation and other immune system functions.
- **Causes negative calcium balance** - reduces intestinal absorption, increases renal excretion, resulting in net loss increases bone matrix breakdown
- **Influences brain function** – affect mood, memory, and learning.

Cortisol: Therapeutic Drug

- **Suppresses the immune system** – prevents cytokine & antibody production, helps prevent organ rejection,
- **Inhibits the inflammatory response** – reduced the mobility of leukocytes
- **Used to treat:**
  - Bee stings, poison ivy, and pollen allergies
  - Prevents rejection of transplanted organs





Cortisol pathologies result from too much or to little hormone

Hypercortisolism: excess cortisol in the body

- Hormone-secreting tumors
- Exogenous administration of hormone

Hypocortisolism: are less common

- Adrenal insufficiency, Addison's disease, following autoimmune destruction of adrenal cortex
- Hereditary enzyme defects (congenital adrenal hyperplasia, adrenogenital syndrome)

THYROID HORMONES

15-20 g, one of the larger endocrine glands, has 2 cell types: C (clear) cells which secrete a calcium-regulating hormone called calcitonin and follicular cells which secrete thyroid hormone.

Thyroid hormones are amines derived from tyrosine and they are unusual because they contain the element **iodine**.

- They modulate protein, carbohydrate and fat metabolism.
- They are necessary for full expression of growth hormone, essential for normal growth and development in children.
- In first years after birth, myelin and synapse formation requires T3 and T4.
- They are thermogenic and increase oxygen consumption related to ion transport across cell membrane and mitochondrial membranes.
- There is a synergism between sympathetic nervous system and thyroid hormones.
- Stimulate heart rate and contraction.

Synthesis of thyroid hormones takes place in the thyroid follicles

Walls are a single layer of epithelial cells

Hollow center of each follicle is filled with sticky glycoprotein mixture called **colloid**

Synthesis of thyroid hormones takes place in the thyroid follicles

1. The follicular cells surrounding the colloid make a glycoprotein called **thyroglobulin** and enzymes for hormone synthesis. These are packaged into vesicles, then secreted into the center of the follicle.
2. Follicular cells also actively concentrate dietary iodide, using **sodium iodide symporter**. I- transport into the colloid is mediated by an anion transporter known as **pendrin**.
3. As I- enters the colloid, **thyroid peroxidase** removes an electron from iodide ion and adds iodine to tyrosine on the thyroglobulin molecule. The addition of one iodine to thyrosine creates MIT. The addition of a second iodine to tyrosine creates DIT.

Synthesis of thyroid hormones takes place in the thyroid follicles

MIT and DIT undergo coupling reactions. One MIT and one DIT combine and creat T3 (**triiodothyronine**) Two DIT form T4 (**tetraiodothyronine**). At this point, hormones are still attached to thyroglobulin.

4. When hormone secretion is complete thyroglobulin-T3 or T4 complex is taken back into follicular cells in vesicles.

5. Intracellular enzymes free T3 and T4 from thyroglobulin protein.

6.They are exported via protein carriers .

Thyroid hormones are uptaken into target cells via **thyroid hormone transporter** (monocarboxylate transporter, organic anion transporter) T3 is the active form in target cells so by **deiodinase** enzymes an iodine is removed from T4 and they are converted to T3. Thyroid receptors are in the nucleus. Hormone binding initiates transcription, translation and synthesis of new proteins.

Thyrotropin releasing hormone TRH from hypothalamus controls secretion of anterior pituitary hormone **thyrotropin**, also called **thyroid stimulating hormone**.

TSH acts on thyroid gland to promote hormone synthesis.

Thyroid hormone normally acts as negative feedback signal to prevent oversecretion.

THYROID PATHOLOGIES

Trophic action of TSH on thyroid gland causes enlargement, hypertropy of follicular cells. With elevated TSH levels, thyroid gland enlarges known as **goiter**. Both hyper and hypotiroidism can be associated with goiter.

HYPERTIROIDISM

- **Affects:** metabolism, the nervous system, & the heart
- **Increases oxygen consumption and metabolic heat production** – patients have a high metabolism and since they generate a lot of heat they don't tolerate hot environments well, their skin is warm and sweaty
- **Increase protein catabolism and may cause muscle weakness** – the body breaks down the protein in muscle cells which also causes weight loss.
- **Hyperexcitable reflexes and psychological disturbances** – may affect the nervous tissue structure and receptors
- **Influence β-adrenergic receptors in the heart -** increases heart rate and contraction force

Most common cause is Graves's disease.
The body produces antibodies called thyroid-stimulating immunoglobulins (TSI) which mimic TSH by activating TSH receptors on thyroid gland.
The result is goiter , T3 and T4 hypersecretion and excess hormone symptoms.
Negative feedback by high levels of T3 and T4 shuts down TRH and TSH secretion but not TSI activity on thyroid gland.

HYPOTIROIDISM

Hyposecretion of thyroid hormones

- Slow metabolic rate and oxygen consumption –
- Decreases protein synthesis –
- Slowed reflexes, slow speech and thought processes, and feelings of fatigue –
- Bradycardia –

Primary hypothyrodism is mostly caused by a *lack of iodine in the diet*. Without iodine, thyroid gland can not make hormones. Low levels of T3 and T4 mean no – feedback. In the absence of –feedback, TSH secretion rises and TSH stimulation enlarges thyroid gland (goiter).Despite hypertrophy, gland cannot obtain iodine to make hormones so the patient remains hypothyroid.

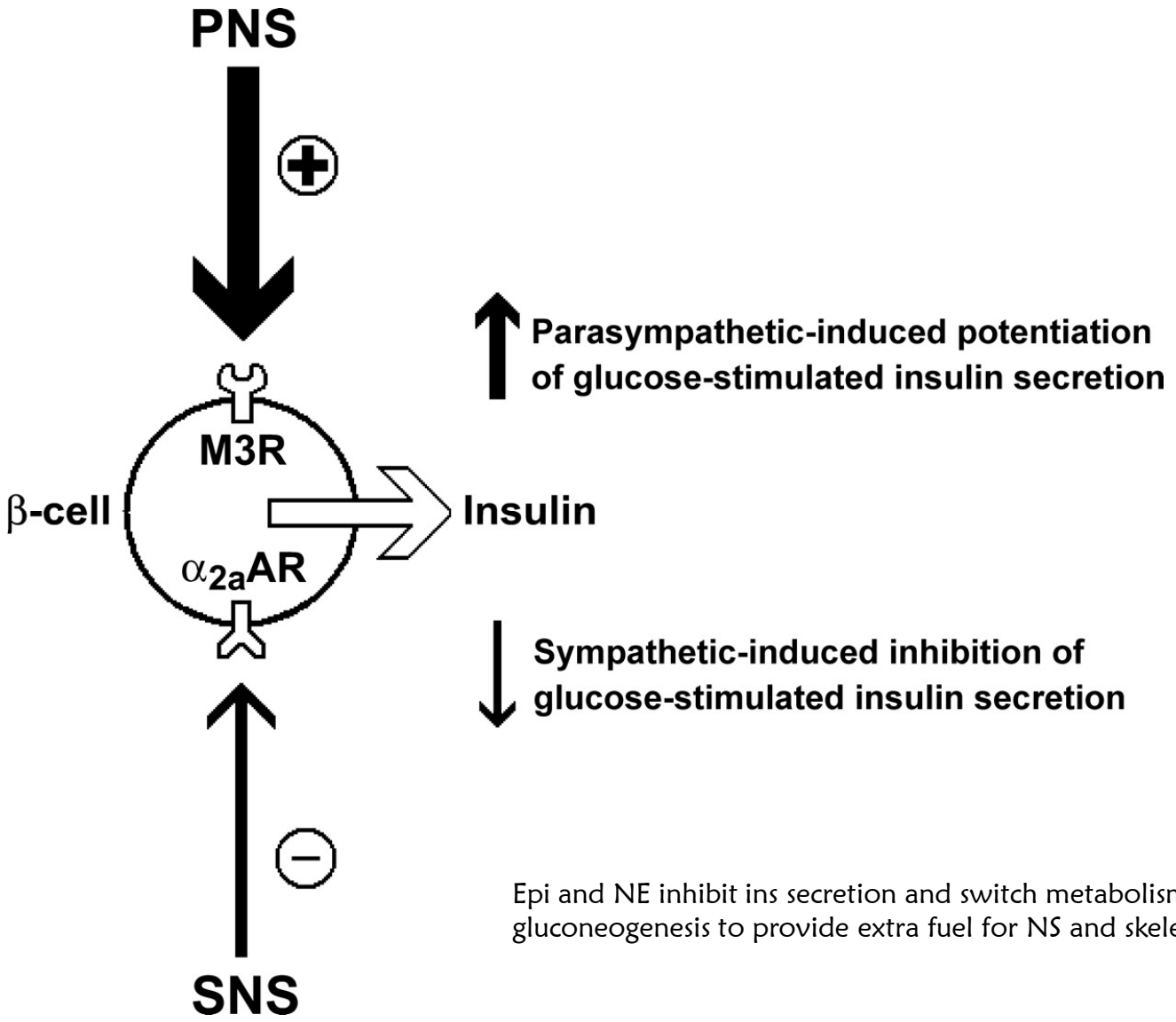
Pancreatic Hormones: Insulin & Glucagon

These two hormones secreted from pancreas regulate metabolism. Both have short lives and must be continuously secreted. There are small clusters of cells called islets of Langerhans throughout the pancreas. Most pancreas tissue is responsible for production and exocrine secretion of digestive enzymes and HCO3 but Langerhans with four types of endocrine cells secrete peptide hormones. ¾ of islet cells are beta cells which produce insulin and a peptide called amylin. %20, alpha cells secrete glucagon; most remaining are somatostatin secreting D cells. A few PP cells (or F cells) produce pancreatic polypeptide.

Factors affecting insulin secretion:

- Increased plasma glucose
- Increased plasma amino acids
- Feedforward effects of GI hormones
  - **GLP1** glucagon like peptide 1
  - **GIP** gastric inhibitory peptide
  - CCK (cholecystokinin), gastrin
- Parasympathetic activity
- Sympathetic activity

Major stimulus for insulin release is plasma glucose concentration greater than 100 mg/dL. Glucose absorbed in small intestine reaches pancreatic beta cells where it is taken up by GLUT 2 transporter. With more glucose available, ATP production increases, ATP-gated K channels close. The cell depolarizes, voltage gated Ca channels open and Ca entry initiates exocytosis of insulin.



Epi and NE inhibit ins secretion and switch metabolism to gluconeogenesis to provide extra fuel for NS and skeletal muscles.