ENDOCRINE SYSTEM

The functions of the body are regulated by two major control system:

i) Nervous system

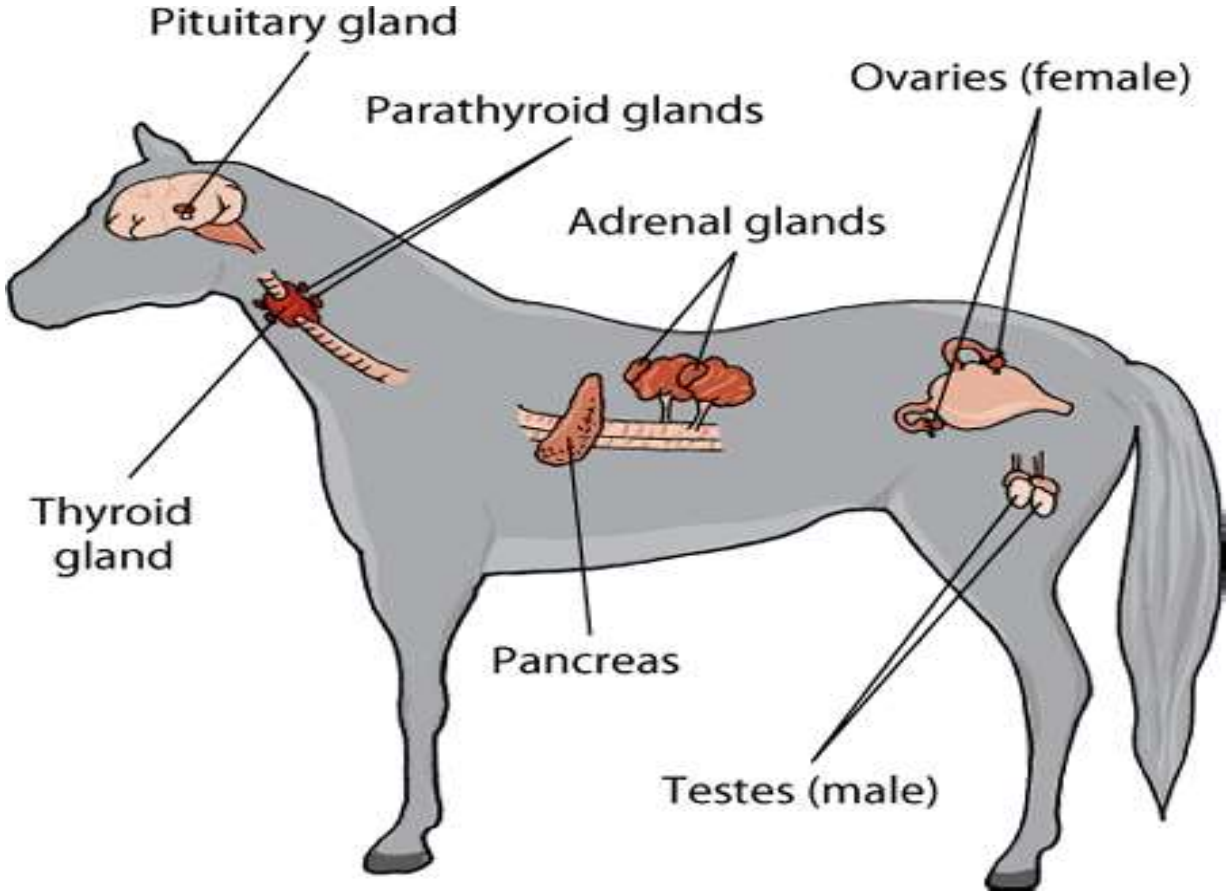
ii) Hormonal or endocrine system

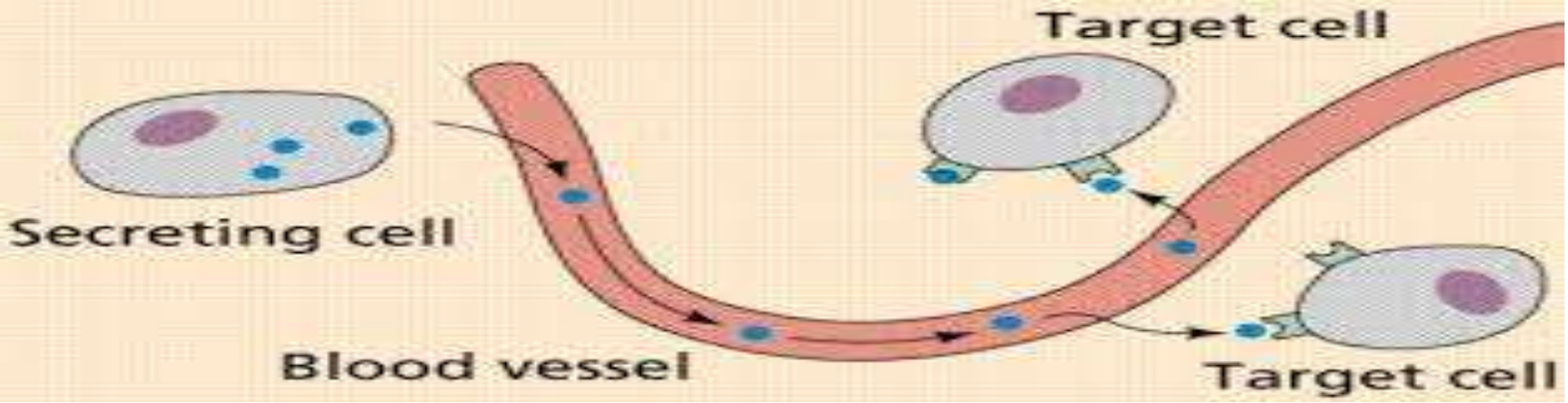
Hormones: The term hormone is applied to a chemical substance which produced in one part of the body, enters the circulation & is carried to distant organs & tissues to modify their structure & function

Endocrine/ductless gland: It is described as its secretion is not conveyed along a duct but passes directly into the blood & into the lymphatics to a target organ at some distance from the original endocrine gland

Organs usually considered endocrine in function are:-

- **Adeno-hypophyseal hormone-** Growth hormone, corticotropin, thyrotropin, follicle-stimulating hormone, luteinizing hormone, luteotropic hormone & melanocyte stimulating hormone
- **Neurohypophyseal hormones-** Anti-duretic hormone & oxytocin


Pituitary gland
Parathyroid glands
Ovaries (female)
Adrenal glands
Thyroid gland
Pancreas
Testes (male)


Target cell
Secreting cell
Blood vessel
Target cell

- **Adrenocortical hormones-** Cortisol & aldosterone
- **Thyroid hormones-** Thyroxine & calcitonin
- **Pancreatic hormones-** Insulin & glucagon
- **Ovarian hormones-** Estrogen & progesterone
- **Testicular hormones-** Testosterone
- **Parathyroid hormones-** Parathormone & calcitonin
- **Placental hormones-** Chorionic gonadotropin, estrogen & progesterone

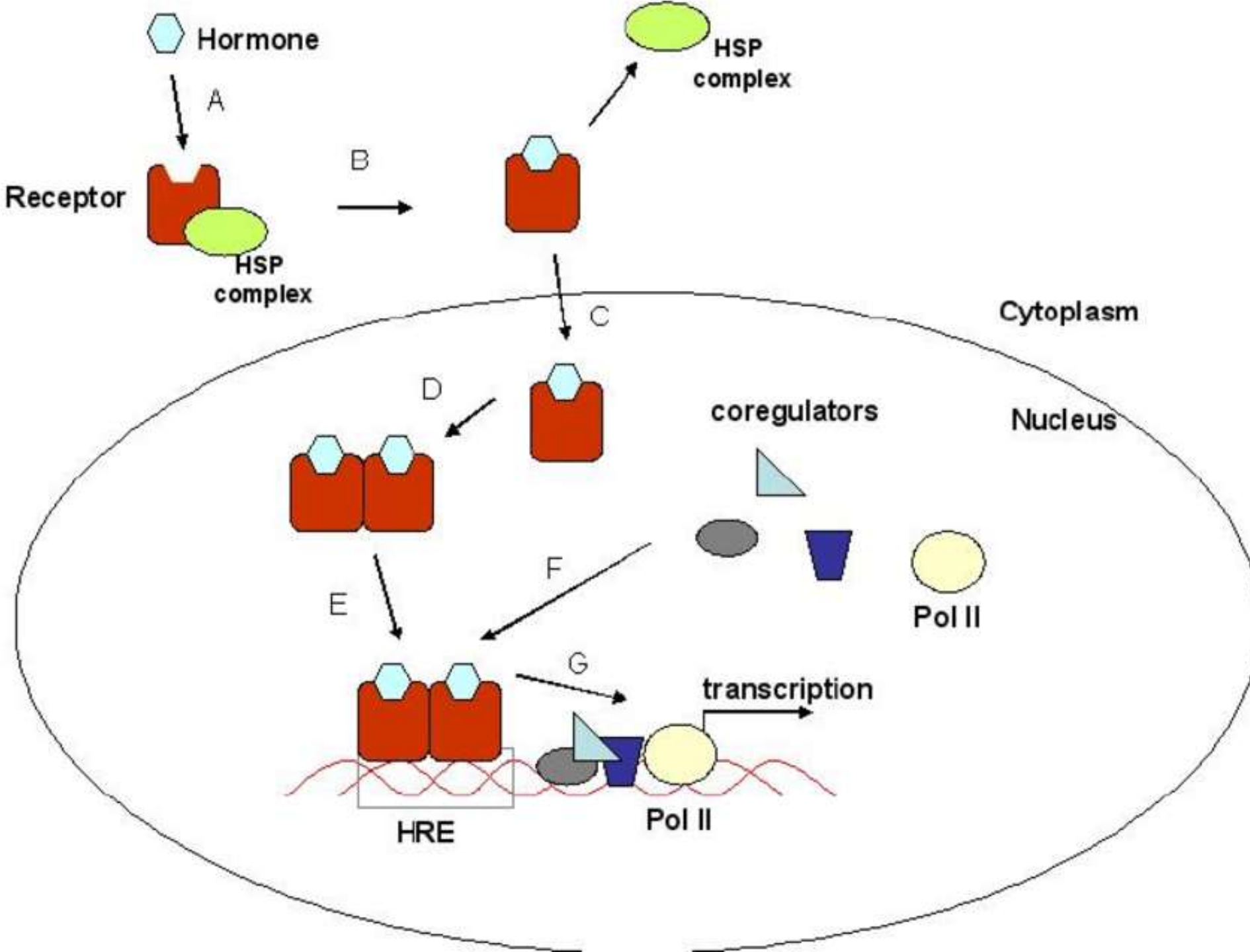
Classification: Hormones can be classified according to their chemical structure or nature of action. Chemically, they are divided into 2 groups-

- **Steroid-** The major steroid producing organs are the gonads, the adrenal cortex & certain fetal membranes
- **Protein (Polypeptides)-** Protein derivative hormones originate in either the adrenal medulla, thyroid, hypophysis, parathyroid, pancreas, fetal membranes or the endometrium. Exception is protein hormone relaxin, secreted by ovary.

- Even small changes in structure or chemical composition result in vastly different hormonal activity or possibly no activity at all, If the active sites on the molecule are changed or modified
- Some hormones affect all body tissues but others act on one organ or gland in particular
- The organ primarily affected is k/a target organ & the hormone exerting this rather specialization influence referred to tropic/ trophic hormone
- Why one type of cell responds to a specific hormone & some other cell type is yet unknown but the reason probably is related to activity of specific enzyme systems & may be associated with the binding of some hormones to certain proteins

Mode of action: There are three sites to be considered for action of normal mechanism

- The cell membrane
- Intracellular enzyme systems
- Site of protein synthesis


Hormone
A
Receptor
HSP
complex
B
HSP
complex
C
Cytoplasm
D
coregulators
Nucleus
F
E
Pol II
G
transcription
HRE
Pol II

The cell membrane:

- A hormone may act by altering the permeability or the active transport mechanisms for given molecules
- Such effects may be seen in the ↑ in glucose uptake by many tissue in the presence of insulin, in ↑ in amino acid transport into muscle cells by growth hormone & in effects of aldosterone on the movement of Na^+ through the kidney
- Such actions could wave a major effect on the metabolic activity in cells
- Some hormone activate adenylate cycalse, a membrane bound enzyme with exception of mature erythrocyte
- In the cell membrane adenylate cyclase catalyses the conversion of ATP to cyclic 3’ 5’ – adenosine mono-phosphate (cyclic AMP) & inorganic pyrophosphate
- Cyclic AMP produced within the hormonally stimulated cell alter the metabolism in a manner characteristic of the particular tissue by activated phosphokinases
- The activated phoshphokinases can then phosphorylate & change the activity of certain rate controlling enzymes

- The various effect shown in different tissues will depend upon the specificity of the particular proteins including proteins of the plasma membrane, enzymes, ribosomal proteins & nuclear proteins that a tissue contains
- Cyclic AMP being a nucleotide does not penetrate membrane easily, thus its effect may be localized in the tissue in which its formation has been stimulated termed as 2nd messanger of endocrine system, the 1st messanger being hormone cyclic AMP is destroyed by a specific enzyme k/a cyclic 3' 5'- AMP phospho-diesterase

Pre existing intracellular enzyme system-

- Some hormones would be able to ↑ the activity of cytoplasmic mitochondrial systems directly, independently any effects on protien synthesis or of any effects mediated by cyclic AMP
- While estrogens may act as hydrogen carries in trans-hydrogenase reactions & that ACTH has a direct effect on glucose 6- phosphate dehydrogenase in the adrenal cortex

By direct intracellular stimulation of cellular nuclear transcription from chromosomes-

- It may be seen in steroid hormones carried in the blood
- Hormones at the appropriate cellular sites leave the blood & cross plasma membrane into the cell end linked to a highly specific cytosol receptor to form a complex that is translocated to the nucleus
- In nucleus, the complex act on chromosomal genes to activate or to depress the process of transcription
- This results in the synthesis of mRNA which leaves the nucleus & stimulates protein & enzyme synthesis in the cytoplasm through ribosomal interaction

Second messenger concept- This concept begins with the hormone in the blood as the 1st messenger varied

- ✓ The hormones or 1st messenger binds with an specific receptor protein on the plasma membrane of the target cell
- ✓ It is postulated that this activate the membrane enzyme adenyl cyclase which ↑es the formation of cyclic 3', 5', -AMP from ATP in the cell cytoplasm

- ✓ It changes the concentration of cellular Ca^{++} affects enzyme activation, protein kinase phosphorylation and end the rate of protein synthesis & hormone secretion
- ✓ ACTH, LH, ADH, parathormone, glucagon & catecholamines act by this mechanism
- ✓ However, thyroid hormones behave like steroid hormone by attaching directly to nuclear receptors without the requirement of a cytoplasmic receptor
- ✓ The β-units of catecholamine exert their effects by activation of adenyl cyclase at the cell membrane

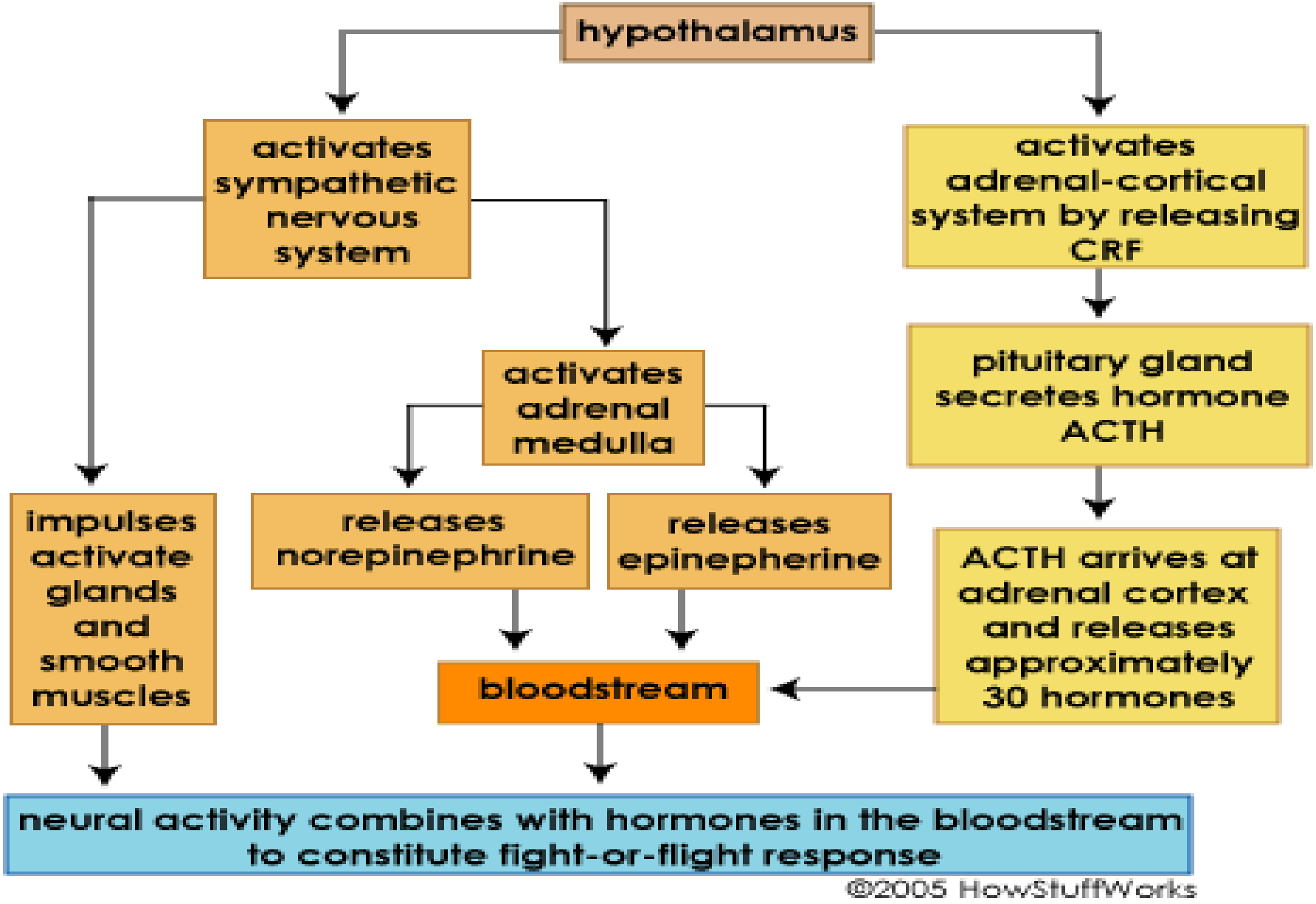
Among the hormones whose effects are mediated by cyclic AMP are-

- ➢ **Adrenaline-** acting on liver & muscle glycogenolysis, heart action, fat cell lipolysis & neuromuscular transmission
- ➢ **Nor-adrenaline-** In some actions on brain activity ↑ by melatonin synthesis in the pineal gland
- ➢ **Glucagon-** Acting to ↑ fat cell lipolysis & liver glycogenolysis
- ➢ **ACTH-** Acting to stimulate steroid hormone production in the adrenal cortex

- **LH-** Acts to ↑ steroid production in the ovary & testes
- **TSH-** Act to promote thyroglobulin hydrolysis, iodination of tyrosine residues & glucose oxidation in the thyroid gland
- **PTH-** Act on renal tubules to ↓ phosphate re-absorption & upon bone to ↑ re-absorption
- **Vasopressin-** Acting on the renal tubules to ↑ reabsorption of water

- ✓ Insulin & some prostaglandins have the ability to ↓ cyclic AMP formation in some tissues such as adipose
- ✓ Insulin can ↓ the activation of adenyl cyclase caused by adrenaline & may ↑ the activity of phosphodiesterase
- ✓ The effects of prostaglandin depends upon its type & the particular tissue
- ✓ PGE causes ↑^{ed} cyclic AMP production in ovary

Fight-or-flight Response



Sites of synthesis of new proteins:

- The transcription of structural genes for certain enzymes can be controlled by the presence or absence of certain metabolism
- Certain hormones, especially those concerned with tissue growth & maintenance are able to alter rates of enzyme synthesis
- This can be shown by the inhibition of certain hormonal effects by inhibitors of protein or RNA synthesis such as cycloheximide, puromycin & actinomycin-D
- The inhibitory effects of the latter 2 compounds are not restricted to protein & RNA synthsis effects in higher organisms
- Protein synthesis may be ↑^{ed} or ↓^{ed} in many ways

Some of the possible sites of hormonal action are indicated below:

- **Effects on DNA synthesis-** formation of multiple copies of genes

- **Gene unmasking-** to produce ↑^{ed} synthesis of specific mRNA or gene activation to ↑ the rate at which genes are transcribed
- ↑^{ing} the amount of mRNA transported out of the nucleus
- Stabilization of mRNA in the cytoplasm, that is ↑ing the useful lifetime of mRNA
- ↑^{ing} the rate of translation of mRNA into protein by activation of the necessary ribosomal enzymes or by changing the stability of poly-ribosomes or their ability to attach to the membranes of the endoplasmic reticulum
- ↑^{ed} production of new ribosome's either to bring the ribosomal population up to operational strength or to create a new population of more active or more selective ribosomes which transcribe mRNA for the particular enzyme whose synthesis is ↑^{ed} by the hormone

- The steroid hormones bind to specific proteins in the cytoplasm of their target cells
- The protein-steroid complex then enters the nucleus & bind to the nucleoprotein where it can presumably alter the extent of gene masking & subsequent transcription
- Growth hormone stimulated protein synthesis scans to be required for the ↑ in amino acid transport into muscle cells
- ↑ of RNA synthesis in liver & cells seem to depend on prior protein synthesis
- Thyroxine appears to seem ↑ basal metabolism by carrying specific synthesis of proteins involved in oxidative phosphorylation
- ACTH ↑^{es} corticosteroid synthesis by means of the production of cyclic AMP & that this effect is mediated by activation of protein phosphokinase enzymes
- The ↑ in steroid synthesis can be blocked by agents such as cycloheximide which inhibit protein synthesis at ribosome

The physiological actions of the various hormones have been explored in a number of ways-

- By studying the effects of complete removal of endocrine gland from the body
- By grafting experiments or injection of active extracts of the gland to attempt to restore the animal to normal
- By observing the effects of the administration of large amounts of the hormone to normal animals

The effects of over secretion by an endocrine gland may be relieved or caused by the surgical removal of part of the overactive tissue it will controlled but not cured

Hypothalamus: The hypothalamus extends in the third ventricle from the optic chiasma to the mamillary bodies. Association with Infundibulum, it has a unique system of arterioles & capillaries called the hypothalamo-hypophysial portal system and normal connections between them

Pituitary gland: It is located in a bony depression at the brain base called sella turcica. This further subdivided into three parts anterior, intermediate & posterior lobes.

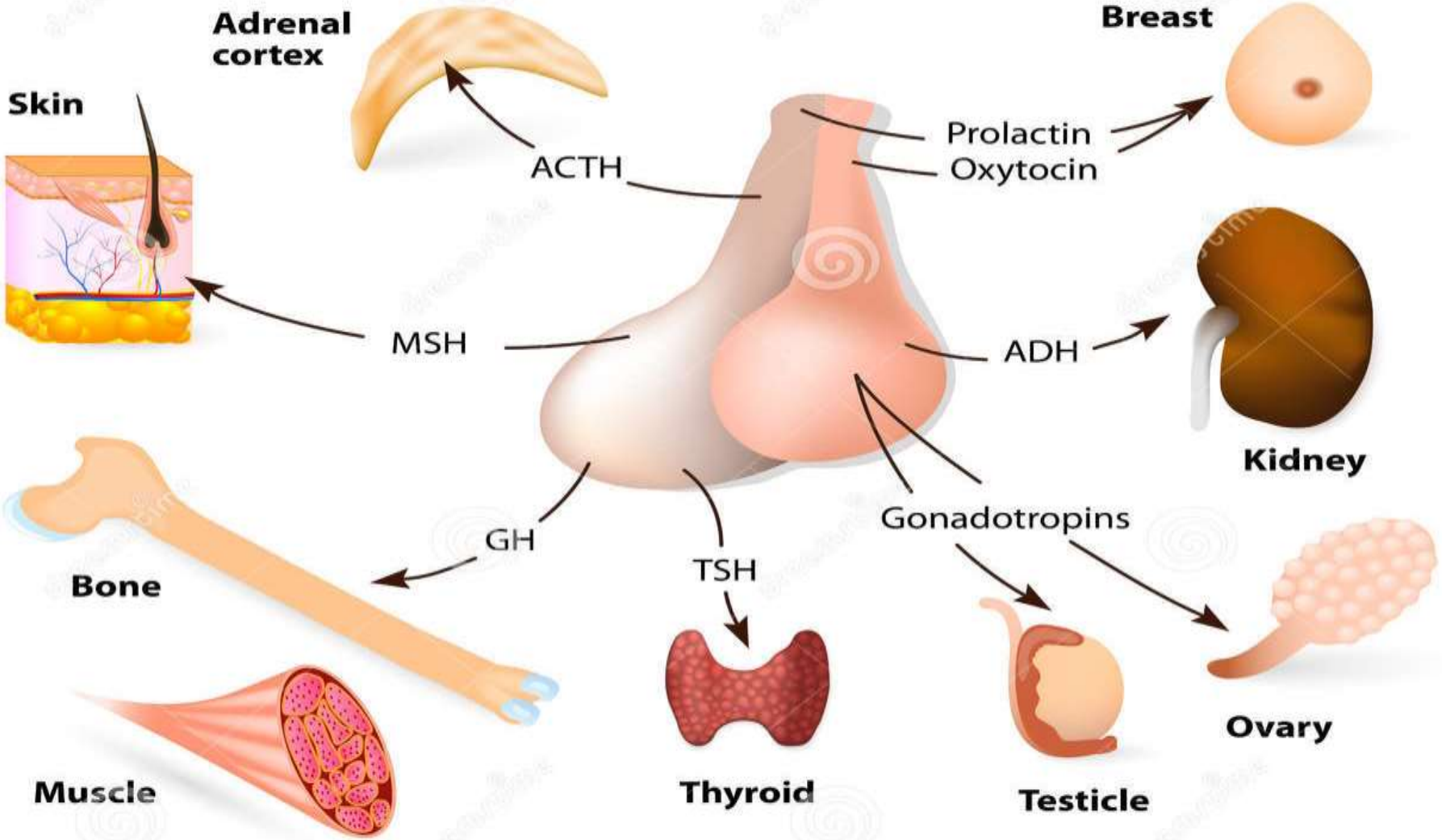
- The ant. pituitary has five different cell types secreting six hormones:-

- Somatotrophes- Growth hormone (GH)
- Corticotrophes- Adreno-corticotrophic hormones (ACTH)
- Mammotrophes- Prolactin
- Thyrotropes- Thyroid stimulating hormone (TSH)
- Gonadotropes- Follicle stimulating hormone (FSH) & Luteinizing hormone (LH)

Adenohypophyseal (ant. pituitary) hormones:

- **Growth hormone-** These are regulated by hypothalamic factors which stimulate either GHRH (somatotropin) or GHIH (somatostatin)

PITUITARY GLAND



- The levels are highest in young growing animals & acts as growth performance but in adults one growth performance is almost steady due to reduction in plasma glucose
- It acts as regulator of metabolism during starvation
- It also acts to reduce protein breakdown & the use of glucose for energy in skeletal muscle
- Somatomedins (insulin like growth factors 1 & 2 i.e. IGF-I & IGF-2) are released by the liver & cells in the area of growth plates in bone when stimulated by GH
- In older animals ↑ in body size become saturate up to a limit because only due to growth plates are closed

❖ **Adreno-corticotropic hormone-** The target cells of ACTH are of adrenal cortex (outer region of adrenal glands) that produce glucocorticoids. Its function is in the regulation of metabolism. It has three zones from outer most to inner most, they are-

- Zona glomerulosa
- Zona fasciculata
- Zona reticularis

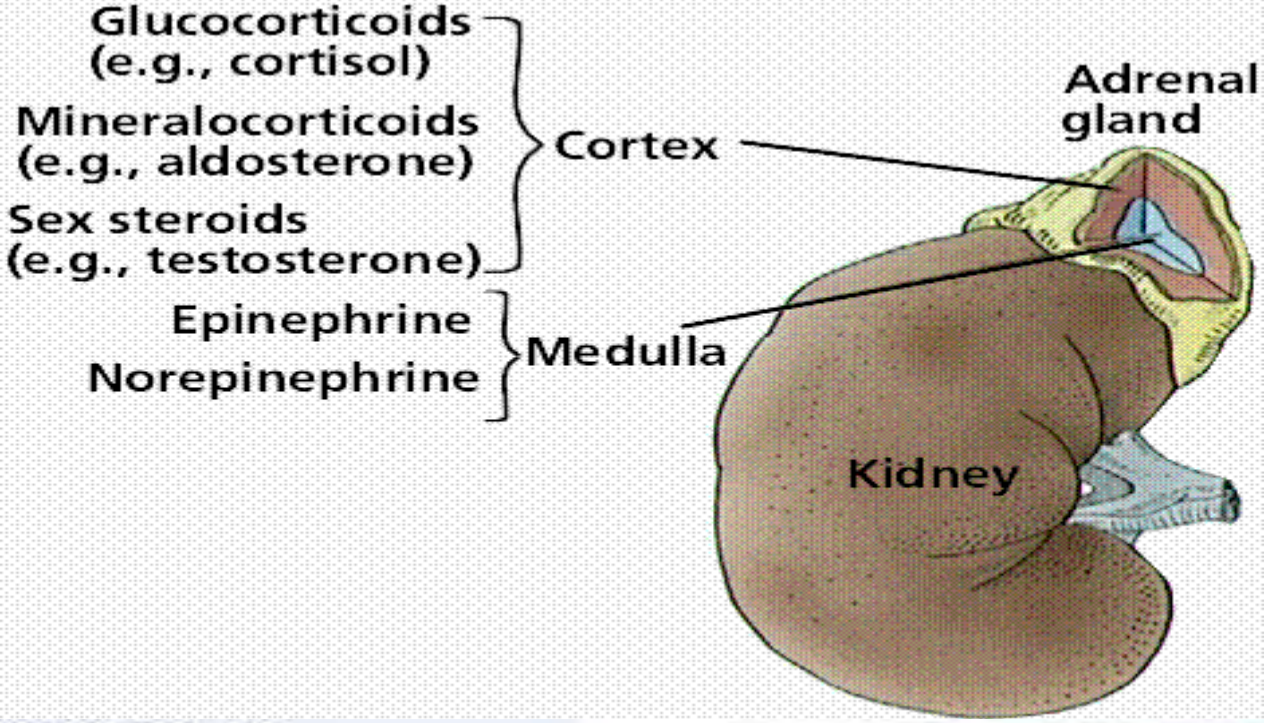
Adrenal medulla-

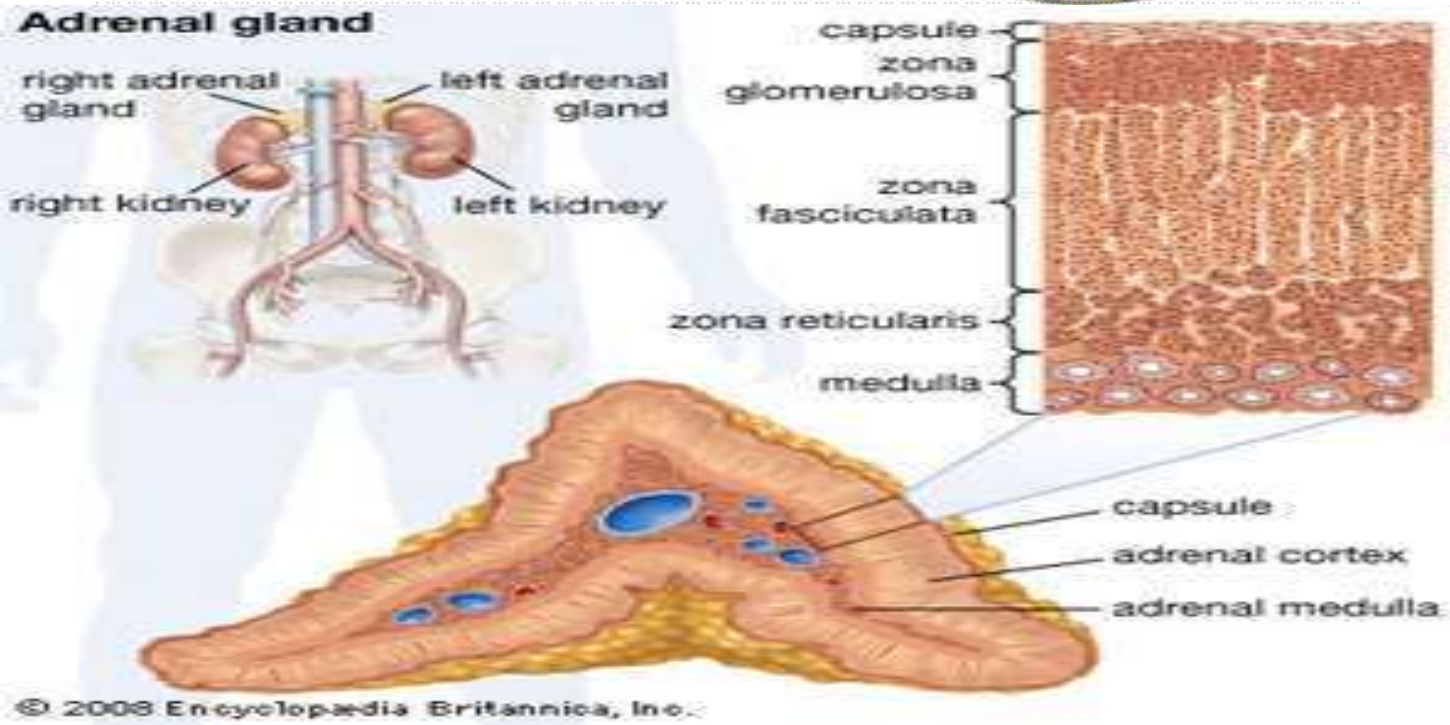
- Epinephrine (adrenaline) & nor-epinephrine (adrenergic) are classified as catecholamines being carried amino acid tyrosine derivation
- Adrenaline derivatives are classified as α_1, α_2, β_1 & β_2 according to their binding affinities for adrenergic agonists
- They are the neurotransmitter used by most peripheral neurons in ANS & CNS
- Its function is in flight n fight case

Mineralocorticoids (Aldosterone)- It secretes from the zona glomerulosa & its function is in the regulation of Na & k balance

Glucocorticoids-

- Cortisol & corticosterone are the major secretory product of the zona fasciculata & zona reticularis & are regulated by ACTH
- Zona reticularis also posses the adrenal sex hormones in very low concentration (androgens & estrogens)
- ↑ ACTH level denotes the stress condition of that animal


Glucocorticoids
(e.g., cortisol)
Mineralocorticoids
(e.g., aldosterone)
Sex steroids
(e.g., testosterone)
Cortex
Epinephrine
Norepinephrine
Medulla
Adrenal gland
Kidney


Adrenal gland
right adrenal gland
left adrenal gland
right kidney
left kidney
capsule
zona glomerulosa
zona fasciculata
zona reticularis
medulla
capsule
adrenal cortex
adrenal medulla
© 2008 Encyclopædia Britannica, Inc.

- Glucocorticoids ↑ the rate of gluconeogenesis by the liver & ↑ the rate of fatty acid mobilization from lipid tissue

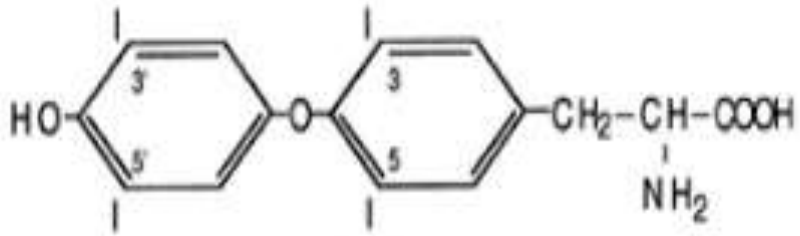
❖ **Thyroid stimulating hormone (TSH):**

- Also called thyrotropin are thyroid endocrine cells produce thyroxine (T_4) & Tri-iodothyroxine (T_3) on stimulation by TSH
- The 3 & 4 refers the no. of iodine atoms in their molecule
- These are necessary for normal growth & development in young animals & also they regulate basal metabolic rate in the adult
- **Isthmus-** Strip of thyroid tissue

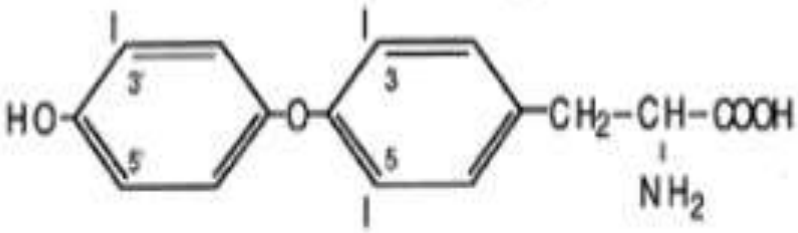
Thyroid gland:

- It is associated with the proximal part of the trachea near the larynx
- It consists of follicles & are filled with a gel like substance, colloid & it consists hormone T_3 & T_4 as iodinated tyrosine residues
- Adjacent to them, a small subset of thyroid cells, the C-cells (para-follicular cells) produce calcitonin

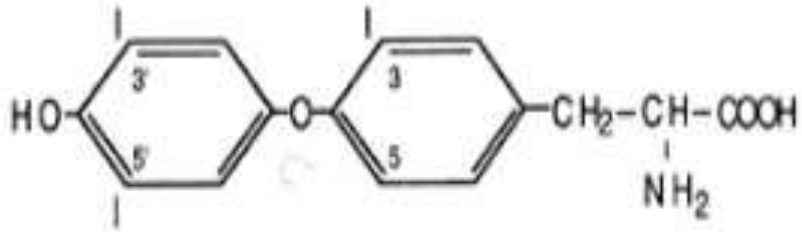
STRUCTURE OF THYROID HORMONES



L-thyroxine (T4)



3,5,3'-triiodothyronine (T3)



3,3',5'-triodothyronine (reverse T3)

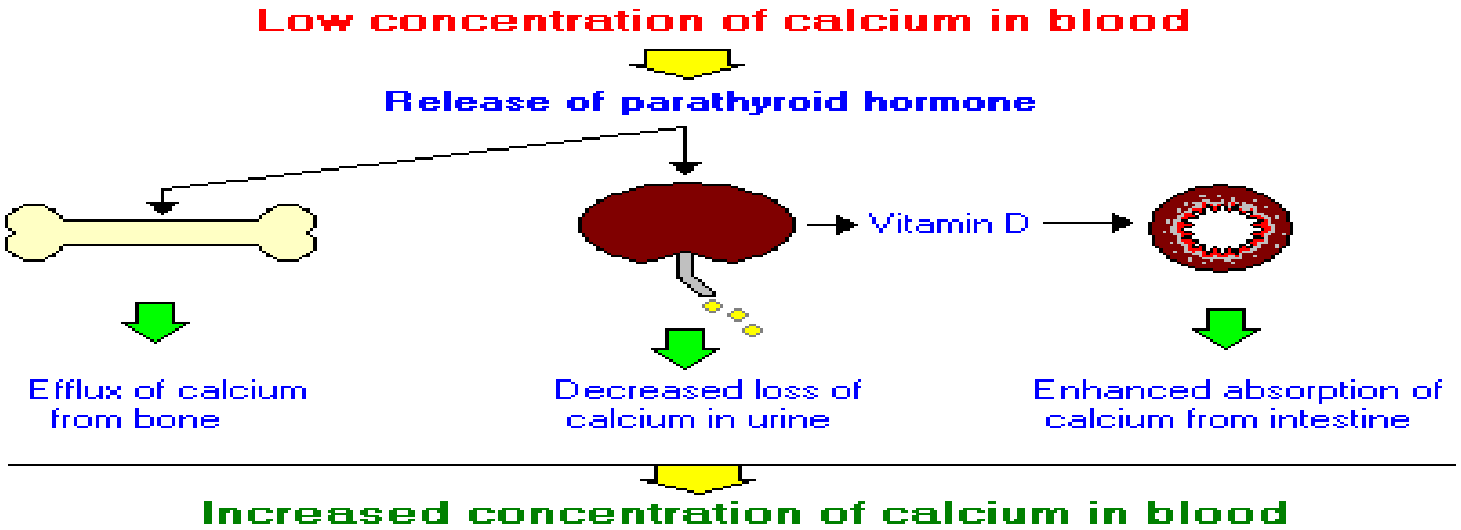
- It lowers the blood level of calcium by inhibiting the action regulated by the –ve feedback of serum Ca concentration on C-cells not by TSH
- Thyroglobulin, a protein iodine complex in colloids when get phagocytised by follicular cells
- Endocytotic vesicles containing thyroglobulins then fuse with lysosomes contains necessary enzyme for degradation of thyroglobulin & release free T_4 & T_3 from their store (Thyroghubulin) & comes into the circulation
- TSH from the adenohypophysis stimulates follicular cells to synthesis thyroglobulin to secrete T_4 & T_3 into the blood stream
- Thus TSH has the tendency to ↑ blood levels of the thyroid hormones
- The most general effect of thyroid hormone is to ↑ overall O_2 consumption & heat production
- Hypothyroidism leads to arrested physical & mental development & lowered metabolic rates by attaining the CNS abnormalities
- **Cretinism-** Congenital lack of thyroid hormone

Parathyroid glands:

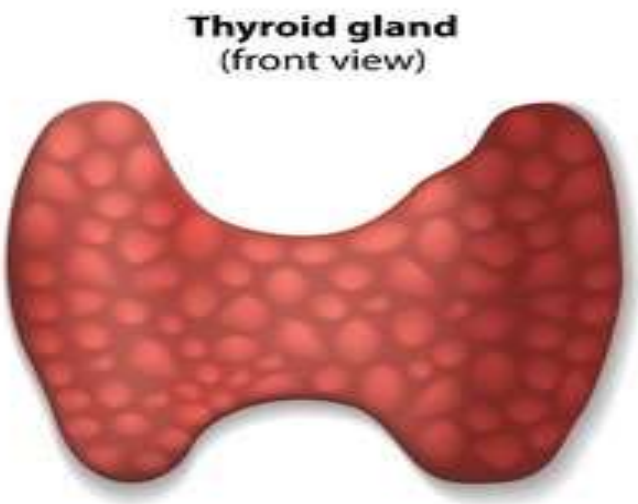
- These are small aggregates of endocrine tissue having two pair near or beneath the thyroid gland depends upon the species
- Some species have only one pair of parathyroid gland present near the thyroid gland
- Chief & Oxyphil cells are designated as two cells present in the parathyroid glands (PTH)
- Chief cells are dark cells associated with the production of PTH, parathormone
- While oxyphil cells are less and larger in size having granular cytoplasm within a small dark nucleus
- These cells are associated with senescent chief cells

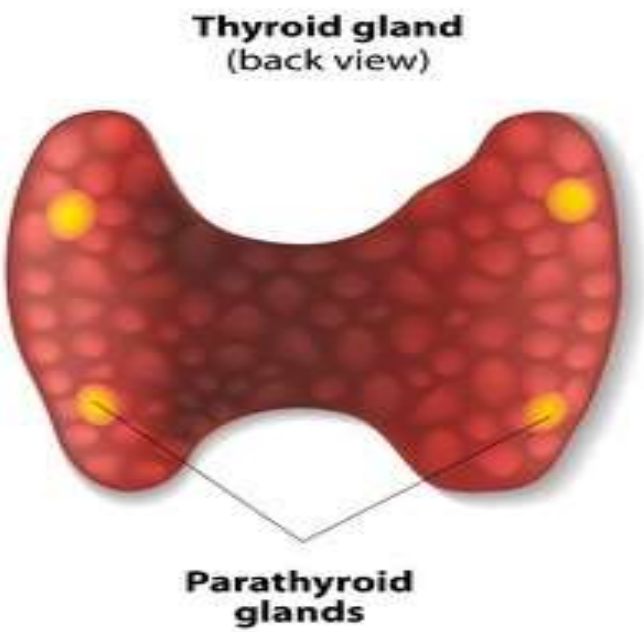
Parathormone (PTH)-

- Parathormone, a peptide hormone have a major role in balancing of the blood calcium level & phosphates
- It acts as stimulating release of Ca & P from bone, $\downarrow^{ing}$ excretion of Ca & $\uparrow^{ing}$ excretion of P by the kidney & formation of active Vit- D



THYROID AND PARATHYROID

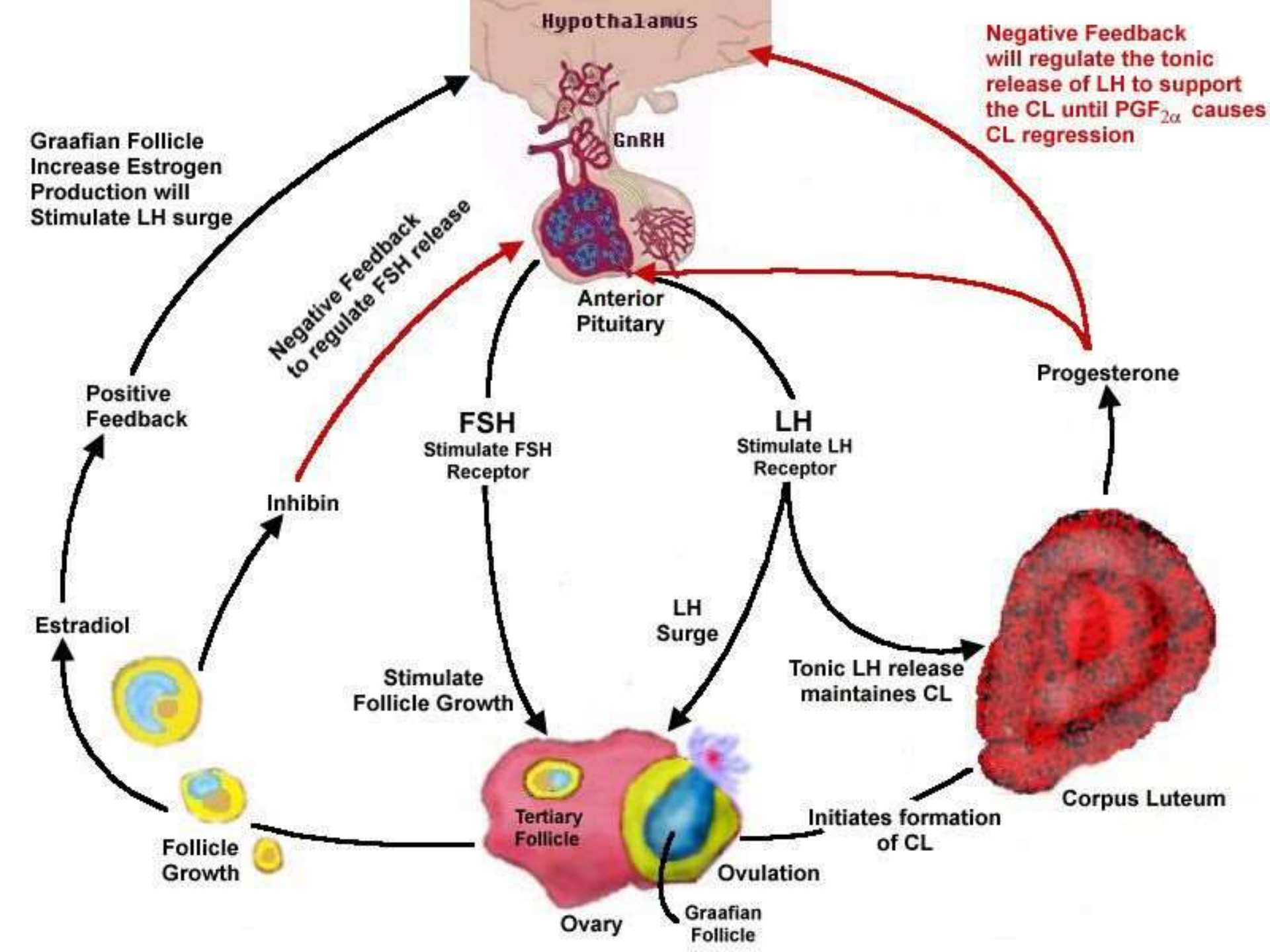


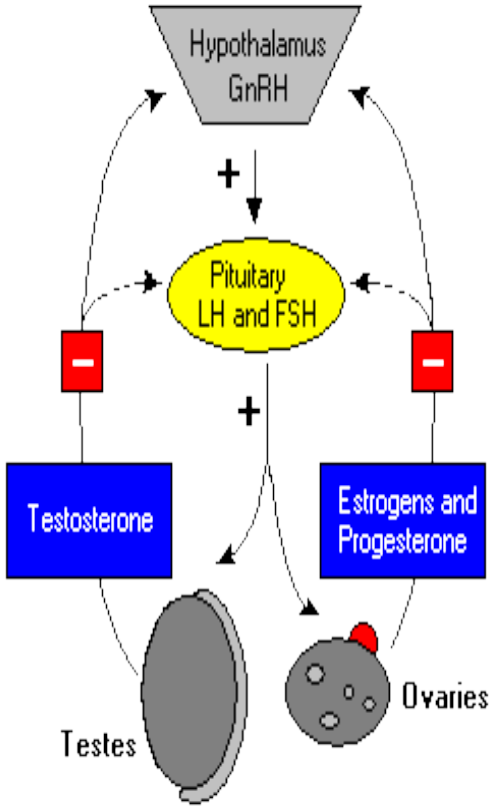


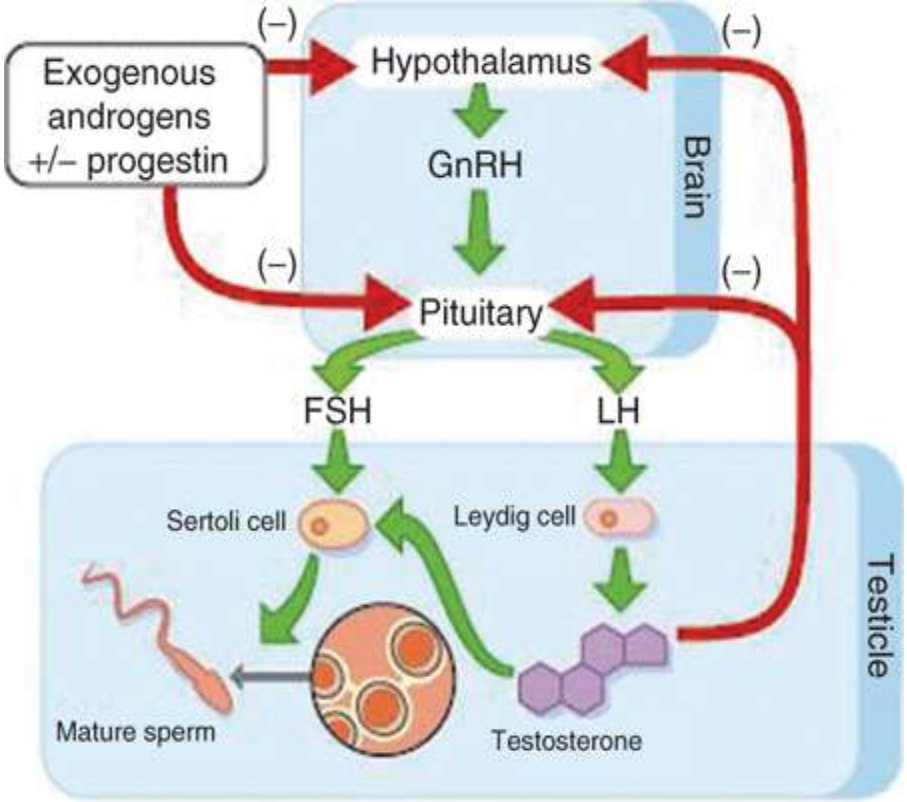
- In bone PTH acts on osteocytes to release Ca phosphate, while on osteoclasts, it degrades the bone & on osteoblasts it inhibits bone formation
- The major function of Vit-D has to ↑ the rate of Ca absorption from the G.I tract & to reduce the Ca loss from the urine
- Chief cells detect ↓ in ionized Ca concentration & respond by ↑^{ing} the secretion of PTH
- The resulting rise in plasma Ca has a –ve feedback effect on further PTH secretion

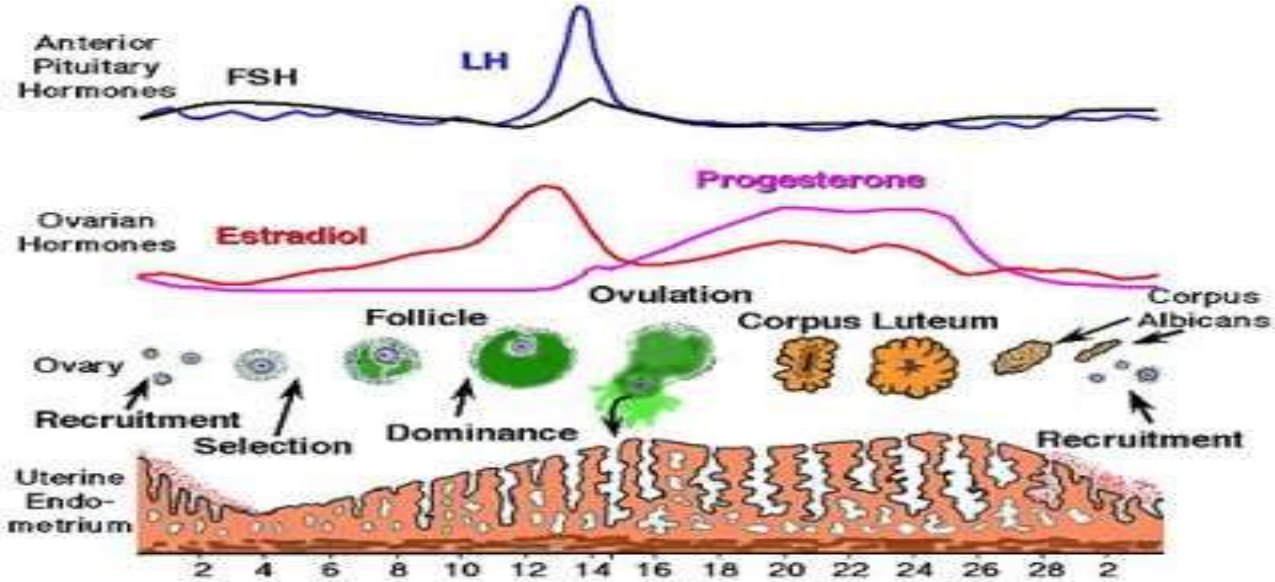
Follicular stimulating hormone:

- FSH has 2 dissimilar subunits α & β
- α subunit exist in both FSH & LH
- FSH stimulates the growth & maturation of the ovarian or graffian follicle
- In females, LH & FSH cause the secretion of estrogen
- In male, it acts on the germinal cells of the seminiferous tubules for spermatogenesis


Hypothalamus
GnRH
Anterior Pituitary
Negative Feedback will regulate the tonic release of LH to support the CL until $PGF_{2\alpha}$ causes CL regression
Graafian Follicle Increase Estrogen Production will Stimulate LH surge
Negative Feedback to regulate FSH release
Positive Feedback
FSH
Stimulate FSH Receptor
LH
Stimulate LH Receptor
Progesterone
Inhibin
Estradiol
LH Surge
Stimulate Follicle Growth
Tonic LH release maintaines CL
Corpus Luteum
Tertiary Follicle
Initiates formation of CL
Follicle Growth
Ovulation
Ovary
Graafian Follicle


Hypothalamus
GnRH
+
Pituitary
LH and FSH
−
−
+
Testosterone
Estrogens and
Progesterone
Testes
Ovaries


Exogenous
androgens
+/− progestin
(−)
Hypothalamus
(−)
GnRH
Brain
(−)
Pituitary
(−)
FSH
LH
Sertoli cell
Leydig cell
Testicle
Mature sperm
Testosterone

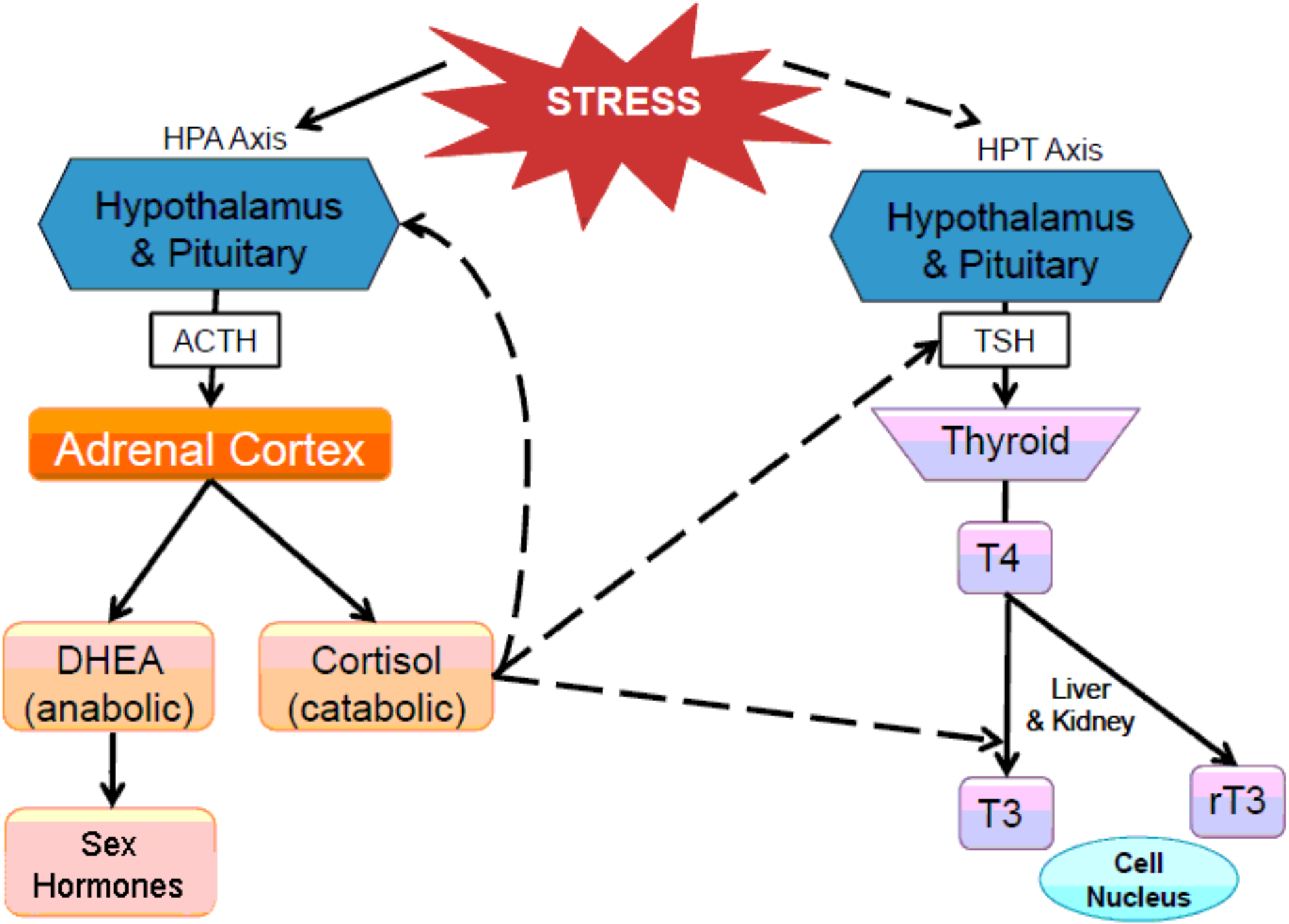

Anterior
Pituitary
Hormones
FSH
LH
Progesterone
Ovarian
Hormones
Estradiol
Ovulation
Follicle
Corpus Luteum
Corpus
Albicans
Ovary
Recruitment
Selection
Dominance
Recruitment
Uterine
Endo-
metrium
2 4 6 8 10 12 14 16 18 20 22 24 26 28 2

Luteinizing Hormone-

- It acts in conjugation with FSH to induce estrogen from the large ovarian follicle
- The pre-ovulatory surge of LH is responsible for rupture of the follicle cells & ovulation occurs
- LH stimulates the interstitial cells of both ovary & testis
- In male, LH stimulates the leydig cells to produce androgen

Prolactin:

- It is a polypeptide hormone & the molecules are more over similar to that of growth hormone
- The prolactin inhibitory factor (PIF) regulates the secretion of prolactin
- These are the catecholamines secreted from nerve terminals of the median eminence & transported through hypophyseal portal system to the adenohypophysis
- It initiates & maintain lactation & cause maternal behavior


STRESS
HPA Axis
Hypothalamus & Pituitary
ACTH
Adrenal Cortex
DHEA (anabolic)
Cortisol (catabolic)
Sex Hormones
HPT Axis
Hypothalamus & Pituitary
TSH
Thyroid
T4
Liver & Kidney
T3
rT3
Cell Nucleus

Neurohypophysis: Neurohypophysis release two hormones i.e., oxytocin (milk let down hormone) & ADH (vasopressin) which are produced in the hypothalmus. The axons of the nervous system passes these hormones from the hypothalamus to post pituitary.

Oxytocin:

- The neurons of the para-ventricular nucleus of the hypothalamus produce oxytocin & it comes into the blood stream by their axon terminals
- It induces the contraction of target smooth muscle fibres of the mammary gland & the uterus
- Oxytocin acts in the phenomenon of milk let down, wherein suckling stimulates ejection of milk from the duct system of gland
- Oxytocin causes contraction of myo-epithelial cells that surround the alveoli in the mammary gland resulting in milk letdown

- In the pregnant animal uterus, oxytocin acts on the myometrium to produce uterine contraction for expulsion of the fetus at parturition
- Ovarian oxytocin is involved in luteal function & acts on endometrium to induce PGF_2 α release causes regression of the C.L. (luteolytic action)

Antidiuretic hormone: It is produced by the neurons of the supraoptic nucleus of hypothalamus to ↑ in blood osmolality (concentration of dissolved substance) or severe ↓ in blood pressure. It also constricts the blood vessels

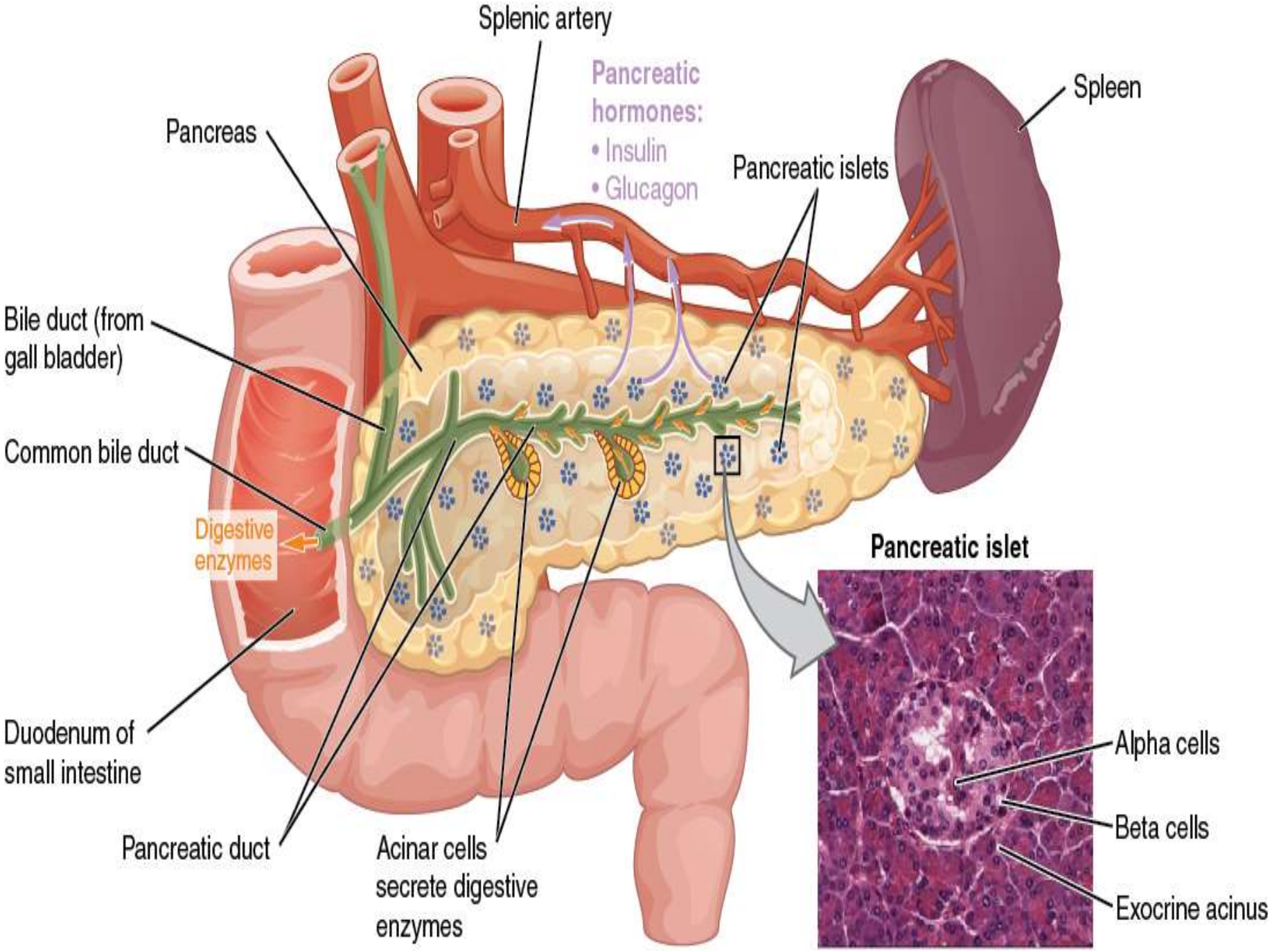
Pineal gland (Epiphysis):

- It is situated on the dorsocaudal of the diencephalon also k/a third eye
- Its function is setting daily & yearly biological cycles based on photoperiod
- It has a special cell called pinealocytes which produces serotonin & an enzyme that converts (this peptide) it to melatonin (hormone)

- Synthesis & secretion of melatonin elevates during darkness
- It is responsible for the induction of ovarian cycles
- However, the animal onsets puberty, there is ↓ or downfall in production of melatonin

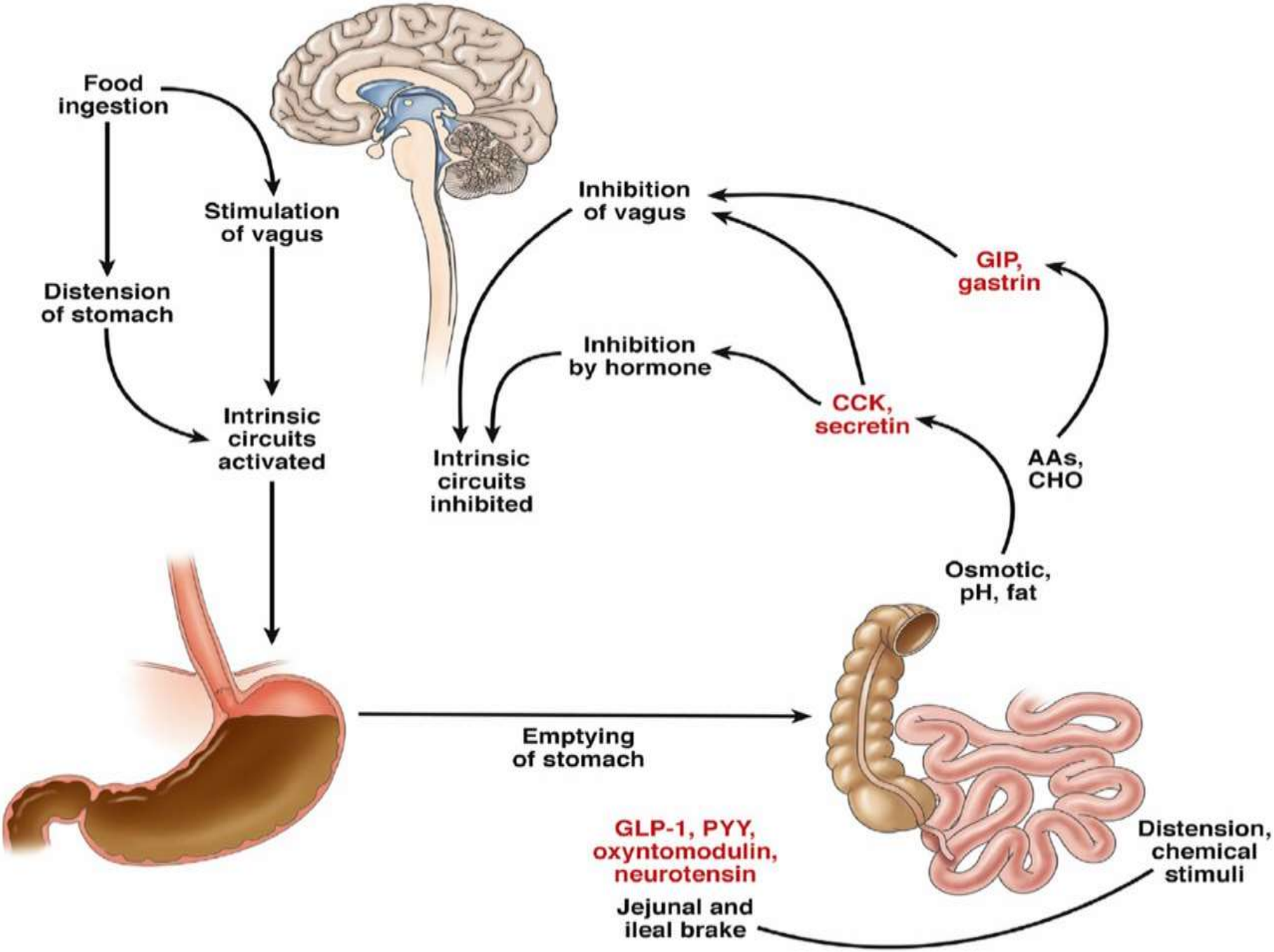
Pancreatic islets:

- It is a bi-lobed gland adjacent to the proximal part of the duodenum
- While pancreas are the exocrine glands having one or two ducts to lumen of the duodenum
- They are scattered mass from pancreas having endocrine tissue
- These pancreatic islets are arranged in irregular cords & are clumped
- The β-cells are numerous (about 75%) produce the hormone insulin
- They are sensitive to ↑ blood glucose & lowers blood glucose by stimulating the uptake of glucose by many cells of the body


Splenic artery
Pancreatic hormones:
• Insulin
• Glucagon
Spleen
Pancreas
Pancreatic islets
Bile duct (from gall bladder)
Common bile duct
Digestive enzymes
Duodenum of small intestine
Pancreatic duct
Acinar cells secrete digestive enzymes
Pancreatic islet
Alpha cells
Beta cells
Exocrine acinus

- It also stimulates skeletal muscle & liver cells to synthesis glycogen (stored glucose)
- It affects the metabolism of amino acids & lipids
- When blood glucose ↓^{es} the stimulus for insulin secretion is lost & insulin levels are extremely low
- α-cells produce glucagon causes liver cells to break down glycogen to release glucose
- It stimulates adipocytes to release fatty acids & ↑ the synthesis of glucose in the liver
- During fasting the stimulus for glucagon release ↓^{es} the blood glucose level

Gastro Intestinal Hormones: G.I. tract secretes many hormones but 3 different hormones which are responsible for peristaltic movement & digestion of the feed intake (CH_2O, fat, protein, lipids). The hormones are gastrin, secretin, cholecystokinin & gastrin inhibitory peptide

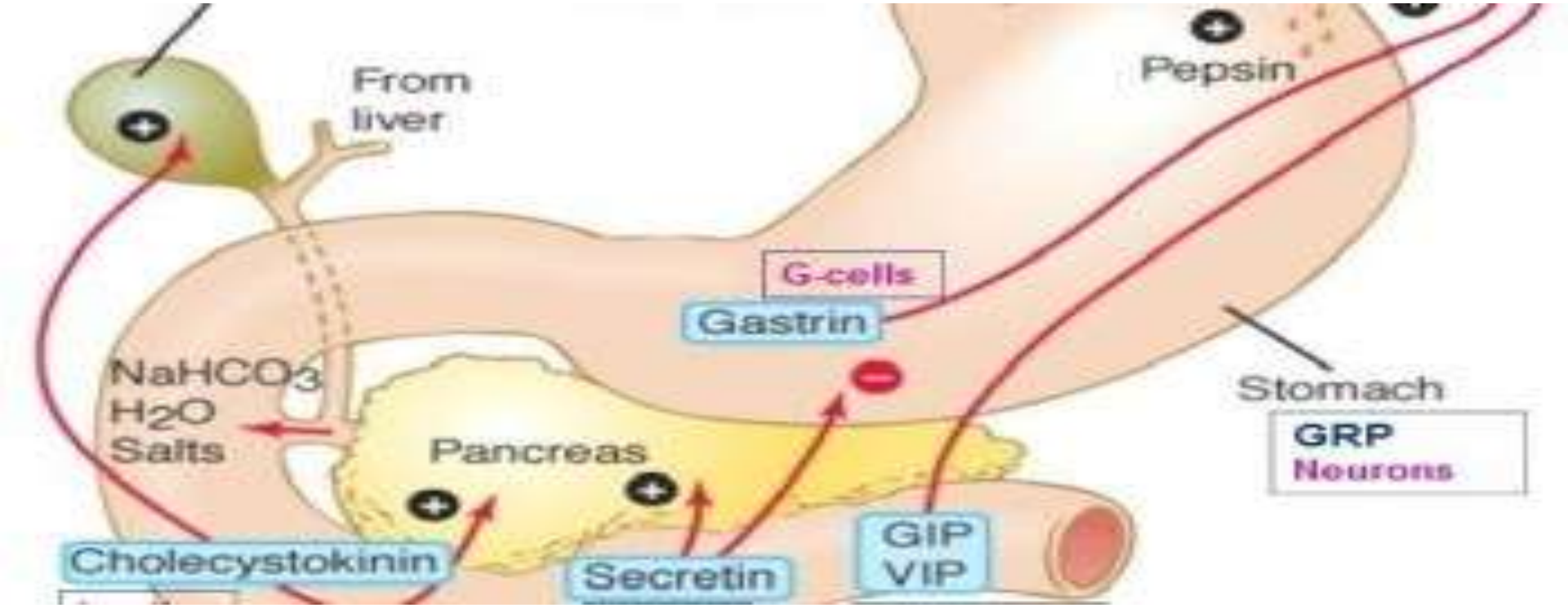

Food ingestion
Stimulation of vagus
Distension of stomach
Intrinsic circuits activated
Inhibition of vagus
Inhibition by hormone
Intrinsic circuits inhibited
GIP, gastrin
CCK, secretin
AAs, CHO
Osmotic, pH, fat
Emptying of stomach
GLP-1, PYY, oxyntomodulin, neurotensin
Jejunal and ileal brake
Distension, chemical stimuli

Gastrin:

- It is produced by the antral mucosa of stomach & also from the duodenum
- The secretion is under ANS from the stimulus food
- It stimulates HCL & pepsinogen secretion within the fundus & the enzyme activates initiates the protein digestion
- It stimulates the lower esophageal sphincter pressure, relaxation of pyloric sphincter, stimulation of pancreatic enzyme secretion, enhancement of intestine motor activity & stimulation of pancreatic bicarbonate & H_2O secretion

Secretin:

- The HCL acidify the duodenal mucosa & is the stimulus for secretin secretion
- It is a pH depended hormone needs below 4.5 for continuous release
- It also stimulates pancreatic bicarbonate secretion into the duodenum, the HCO_3^- neutralizes the H^+ from the stomach raises pH & hence $\downarrow^{ing}$ the release of secretin


From
liver
Pepsin
G-cells
Gastrin
NaHCO3
H2O
Salts
Pancreas
Stomach
GRP
Neurons
Cholecystokinin
Secretin
GIP
VIP

Cholecystokinin (CKK):

- It is present in small intestine & causes contraction & emptying of the gallbladder
- Entry of high levels of H^+ into the duodenum results in contraction of gallbladder (for release of acetylcholine) basically it acts as regulation of gallbladder
- It also stimulates pancreatic enzyme secretion, inhibition of gastric emptying
- It acts as regulator of growth of the exocrine pancreas
- It has trophic growth effect on the G.I. mucosa & of acinar cells of pancreas
- Gallbladder contraction & relaxation of the sphincter of oddi regulate the flow of bile & inhibition of gastric empting regulates the flow of chyme into the duodenum
- CCK induces satiety & reduces food intake

The other hormones are-

- **Gastric inhibitory peptide (GIP)-** It has effect on gastric secretion, pancreas & β-cells. It has metabolic effects on adipose tissue, liver, muscle, G.I. tract & brain. It helps in obesity so as the effect of insulin on incorporation of fatty acids into triglycerides.
- **Vasoactive Intestinal peptide (VIP)-** It stimulates lipolysis, glycogenolysis & insulin secretion. It also mediated the relaxation component of the peristaltic reflex.
- **Substance-P (SP)-** It has action on smooth muscle motor activity, a neuropeptide found in brain & gut. It is a natural satiator of thirst.
- **Somatostatin-** Being GH release inhibiting hormone it acts as gastrin producing & HCL acid producing cells.
- **Motilin-** Found in duodenum & stimulates gastric motor activity (emptying of chyme into the small intestine).
- **Gastrin releasing peptide (GRP)-**
- **Bulbogastrone-** inhibits gastric acids secretion.
- **Urogastrone-**

- **Glucagon like peptide 1-**
- **Villikinin-**
- **Enkephalins-**
- **Neurotensin-**
- **Peptide YY neuropeptide Y**

Exocrine pancreas: Pancreatic acinar cells have receptors or 2 hormones i.e., secretin stimulates amylase secretion whether CCK also same & mobilization of cellular Ca_2^+

GHRELIN & LEPTIN