Endocrinology

INTRODUCTION

Endocrinology

1. **Endocrinology** is the study of the endocrine system secretions and their role at target cells within the body and nervous system are the major contributors to the flow of information between different cells and tissues.

2. Two systems maintain Homeostasis
   a.

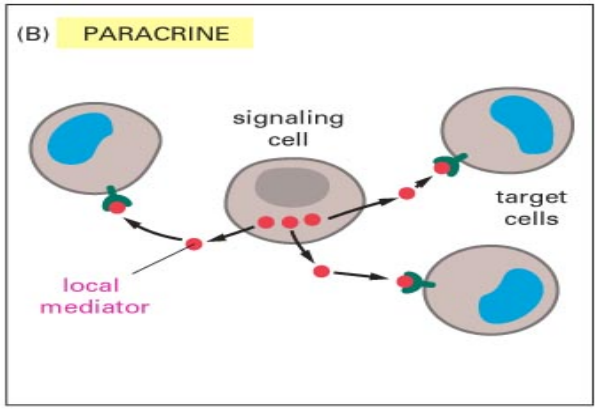
   b
3. Maintain a complicated relationship

4. **Hormones**

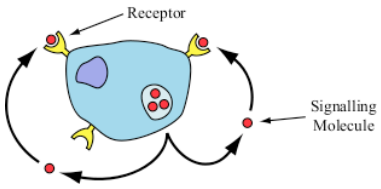
1. The endocrine system uses hormones (chemical messengers/neurotransmitters) to convey information between different tissues.
2. Transport via the bloodstream to target cells within the body. It is here they bind to receptors on the cell surface.
3. Non-nutritive

Endocrine System- Consists of a variety of glands working together.

1. Paracrine Effect (CHEMICAL)



a. **Autocrine Effect**
   i. Hormones released by cells that act on the membrane receptor



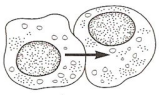
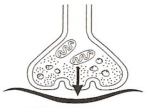
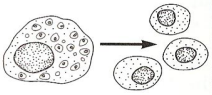
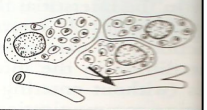
   ii. When a hormone is released by a cell and acts on the receptors located WITHIN the same cell.

_Endo_crine Secretions:

1. Secretions secreted

_Exo_crine Secretion:

1. Secretion which come from a gland
2. The secretion will be released into a specific location

	GAP JUNCTIONS 	SYNAPTIC 	PARACRINE 	ENDOCRINE 
Message transmission	Directly from cell to cell	Across synaptic cleft	By diffusion in interstitial fluid	By circulating body fluids
Local or general	Local	Local	Locally diffuse	General
Specificity depends on	Anatomic location	Anatomic location and receptors	Receptors	Receptors

Nervous System vs the Endocrine System

1. **Nervous System**
   a. Neurons
   b. Homeostatic control of the body achieved in conjunction with the endocrine system
   c. Maintain
   d. This system will have direct contact with the cells to be affected
   e. Composed of both the somatic and autonomic systems (sympathetic and parasympathetic)

2. **Endocrine System**

   a.

   b.

   c.

3. **Neuroendocrine:**
   a. These are specialized neurons that release chemicals that travel through the vascular system and interact with target tissue.
   b. Hypothalamus → posterior pituitary gland

History of the Endocrine System

Bertold (1849)-FATHER OF ENDOCRINOLOGY

1. Castrated roosters failed to develop normal size combs and wattles along with a failure to exhibit normal male behavior
2.

3.

Von Mering and Minkowski (1889)

1. First to describe diabetes mellitus by removal of the pancreas
   a. Common signs/symptoms of DM are
      I.
      II.
      III.

Banting and Best (1922)

1. Discovered insulin was produced in cell of the pancreas

Sutherland (1962)

1. Discovered the presence of cAMP

Basic Endocrinology Concepts

Homeostasis:

Feedback Mechanisms

1. ***Negative Feedback***:
   a. Very common classic feedback system
   b. Small fluctuations are the result of negative feedback
   c. An increase in a hormone will lead to a decrease in another hormone produced
   d. Hormonal level vs time on a graph, you would see small fluctuation up and down
   e. An initiation in the hormone production initiates a response to decrease the production of another hormone. This assists in maintaining a narrow range for the hormone level.

NEGATIVE FEEDBACK LOOP

Effector Hormones (T3 and T4) in blood stream reach the hypothalamus, thus, a negative feedback response is initiated. As levels increase in the blood, we tell the hypothalamus to decrease its production of TRH

Long Feedback Loop

a. GREATEST IMPACT ON THE FEEDBACK LOOP
b. Thyroxin (effector hormone) will have a *significant effect* at the hypothalamus by decreasing additional production of TRH

Short Feedback Loop

a. TSH secreted from anterior pituitary gland will have a *mild effect* at the hypothalamus by decreasing additional production of TRH

Very Short Feedback Loop

a. SMALLEST IMPACT ON THE FEEDBACK LOOP
b. TRH secreted from the hypothalamus will have *the smallest effect* at the hypothalamus by decreasing the additional production of additional TRH

2. ***Positive Feedback:***
    a. Happens *less frequently* when compared to negative feedback
    b. Results when an initial trigger significantly increases the production of a hormone. The production continues until the initial trigger is eliminated
    c. Two major examples
        a.
        b.

Positive Feedback Loops

NEUROENDOCRINE FEEDBACK LOOP

Note: Oxytocin will continue to increase until the baby is delivered followed by a decrease in release. Moreover, oxytocin can continue to be released until most of the milk has been depleted.

Receptors

A chemical structure on the surface of a cell or inside a *cell* that binds the hormone to initiate some change within the cell i.e. cell excitation via depolarization (i.e. opening of ion channels followed by local depolarization), activation of intracellular pathway and/or protein synthesis via transcription and translation (i.e. anabolic steroids)

****Side note***

1. Creatine Monohydrate
2. Two main mechanisms of action

****

Two Types of Receptors

1. **Steroid Receptors**
    a. Located within the cell
    b. Steroid analogs can pass through the cell membrane and interact with intracellular receptor inside the cell (i.e. steroid analogs)

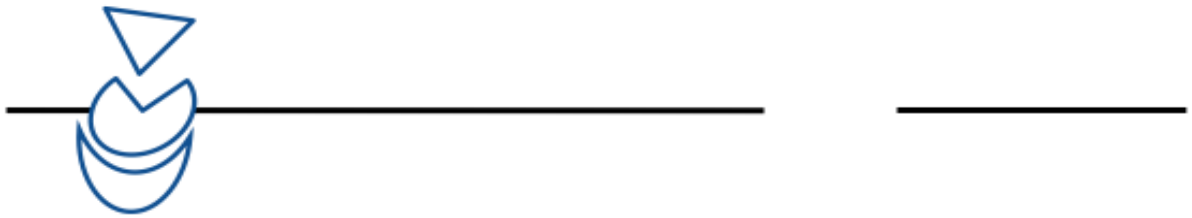
2. **Protein Receptors**
    a. Located on the cell

Hormones, Neurosecretions vs. Neurotransmitter

I. **Neurotransmitter:** *Short lasting* signal that is transmitted to a local area via an electrical impulse.

    a. i.e.

    b. Works via a second messenger cCAMP



    c. Typically transmits an electrical impulse

II. **Neurosecretion:** A *long lasting* impulse which is produced by the hypothalamus/pituitary gland, locally and at distant sites

III. **Hormones:** Produced by glands and have *longer lasting* effects; effects can be observed at tissues located far away
    a. Example:

Endocrinology Concepts

1. **Physiological regulators**
2. Active in minute amounts.
3. Fluctuations in secretions will be observed
4. Hormones will be carried by the cardiovascular system
5. Metabolized rapidly
6. Modify conditions going on within the cell

1. **Physiological Role of Hormones**
   a. **Affect cell synthesis and secretion** of other hormones within various endocrine glands and neurons
      i. *Example:* Increase in epithelial cell production and in milk production by mammary glands in women.

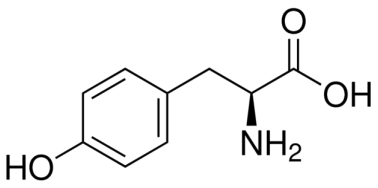
   b. Affects metabolism
      i. they can have both an anabolic (i.e. insulin, thyroid, testosterone, HGH and IGF) and catabolic metabolic processes
   c. Affects muscle function
      i. *Example*: When a person is hypocalcaemic they maintain low levels of Ca++ in their serum.

      ii. Every step in the clotting cascade requires Ca++ as a coenzyme, therefore, decreased serum Ca++

   d. Control reproduction
   e. Control cell growth
   f. Affects the movement of cations
   g. play part on effectiveness of other hormones
      i. Synergism, 1 primary agonist + another supporting hormone (i.e. HGH and IGF's)
   h. Important in normal animal behavior
      i. Testosterone/ Estrogen

Classification of Hormones

1. **Modified amino acids**: Tyrosine, Tryptophan
   a. Tyrosine will serve as the backbone, initial building block for some hormones.



TYROSINE

2. **Peptides/proteins**
    a. When we add two peptides together we remove water via a *condensation or dehydration* synthesis. Moreover, when we do the opposite by breaking the peptide bond we will undergo a *hydrolysis reaction.*
        i. **Peptide:** < 10 amino acids
        ii. **Polypeptide:** 10 – 50 amino acids
        iii. **Proteins:** > 50 amino acids
3. **Glycoproteins**
    a. These are proteins with carbohydrates attachment, (i.e. FSH, TSH and HCG). Glycoproteins hormones are usually comprised of both an α and β subunit.

4. **Steroid Hormones**
    a. **Derive their structure from the <u>cholesterol</u> backbone**. Cholesterol in body accumulates in two different ways.

    b. **Serum cholesterol** is carried in the blood in 2 distinct structures
        i. **High Density Lipoprotein** (HDL): Good cholesterol which has an increased amount of protein surrounding the cholesterol molecule

        HDL DENSITY:

        ii. Low Density Lipoprotein - Bad cholesterol which has a decrease amount of protein surrounding the cholesterol

        LDL DENSITY:

Side Note********

c. **Steroid Structure**

i. The first structural modification to create a steroid hormone

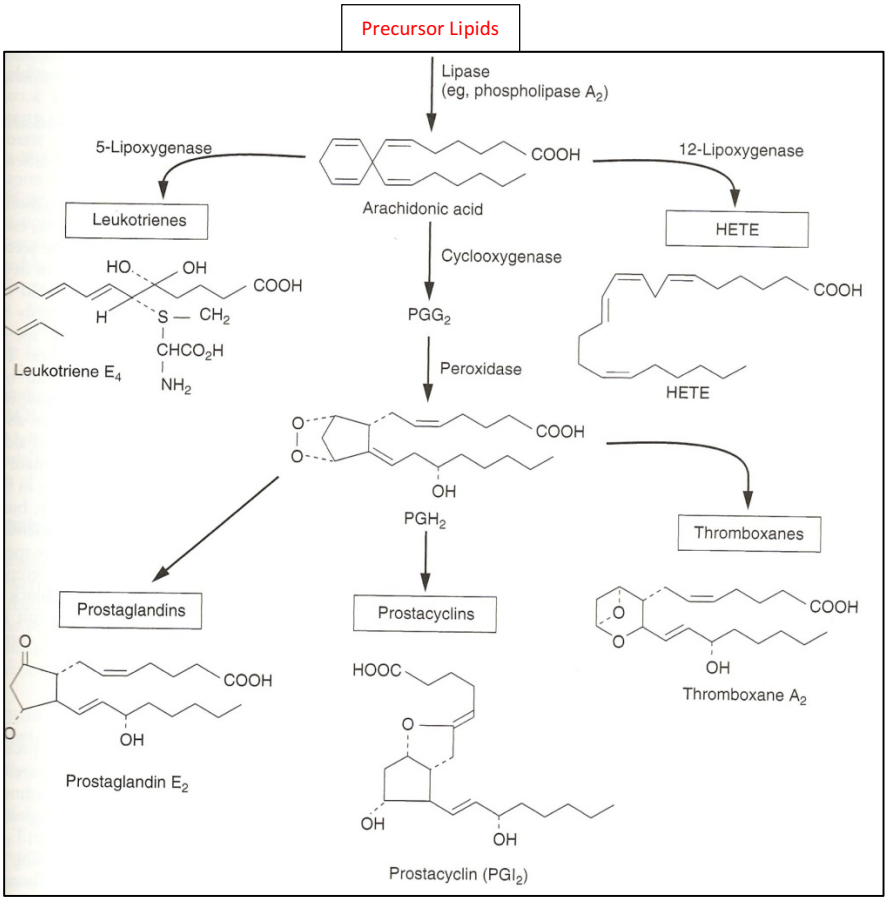
d. **Steroid Characteristics**

i. Fat soluble but not water soluble

ii. Circulatory Concentration in ng/dL

Note:

Arachidonic Acid Pathways



1. Modified Fatty Acids: Eicosanoids- *Arise from arachidonic acid*
   a. *All eicosanoids arise from the phospholipid bilayer.*
   b. Phospholipid bilayer $\xrightarrow{Phospholipase\ A_2}$ Arachidonic acid (AAA)
   c. 1 of 3 pathways possible after the synthesis of arachidonic acid
      i. **Arachidonic acid** $\xrightarrow{\boldsymbol{Cyclooxygenase\ (COX)}}$ ***Prostaglandin*** **(G)**$\boldsymbol{H_2}$

1. Examples of prostaglandins: PGE, PGA PGF2α and PGI2 (vasodilator).
   2. Prostaglandins are local tissue hormones
   3. Prostaglandins: Additional functions
      a. DECREASE in the size and function of the corpus luteum
      b.
      c.
      d. Possible correlation of menstrual cycles within species
   4. COX inhibitors
      a. COX2 inhibitors (ASA will inhibit the formation of cyclooxygenase)
   5. Prostaglandin $\xrightarrow{TXA_2}$ Thromboxane A_2
      a. Thromboxane A2 and assistance in vasoconstriction when you attempt to cut your wrist Is a powerful platelet aggregator

II. Arachidonic acid $\xrightarrow{\boldsymbol{5-Lipoxgynase\ (LOX)}}$ ***Leukotrienes***

1. AKA- SRSA (slow reacting substance of anaphylaxis)
2. Leukotrienes are produced by WBC's
3. LTC4, LTD4 and LTE4 (mixture of leukotrienes-slow reacting substances of anaphylaxis)
4.
5.

Side Note about Histamine*******

Histamine is secreted from both mast and basophiles. Anaphylactic Reaction-

iii. **Arachidonic acid** $\xrightarrow{12-lipoxygenase}$ ***HETE***

Hormone Chemistry Determines Activity

1. **Hormone Size** – Determines its half life
   a. Half life determines
   b. The size of the molecule is directly proportional to its half-life. For example the bigger the molecule the longer its half-life will be. This results the probability of the enzyme cleaving the active portion vs. not cleaving the active portion. The longer molecule will have a < chance to have the active portion *NOT* cleaved as its being broken down, thus, a longer half-life is observed.
      i. GnRH: this hormone is ~ 10 amino acids long and has a half-life of ~
      ii. FSH: this hormone is ~ 540 amino acids long and has a half-life of ~
2. **Small molecule inactivation**
   a. Epinephrine and norepinephrine can be broken down locally and in the bloodstream.
      i. **Epinepherine- released into bloodstream**
      ii. **Norepi-released at synapse, has localized effect**
   b. One pass through the liver will alter the molecule 70%.

3. **Mechanism of action of *Protein hormones vs. Lipid hormones***
   a. **Protein Hormone**:
      i. Proteins are hydrophilic

      ii. Mechanism of action requires a protein (receptor) on the cell surface
   b. **Lipid Hormone**:
      i. They are soluble in fats (hydrophobic),
      ii. Once inside the cell they can bind to their target receptor
      iii. Transport through the membrane is made possible secondary to the cholesterol in the membrane which separates the phospholipid molecules. The membrane cholesterol makes up 13% of the total membrane mass

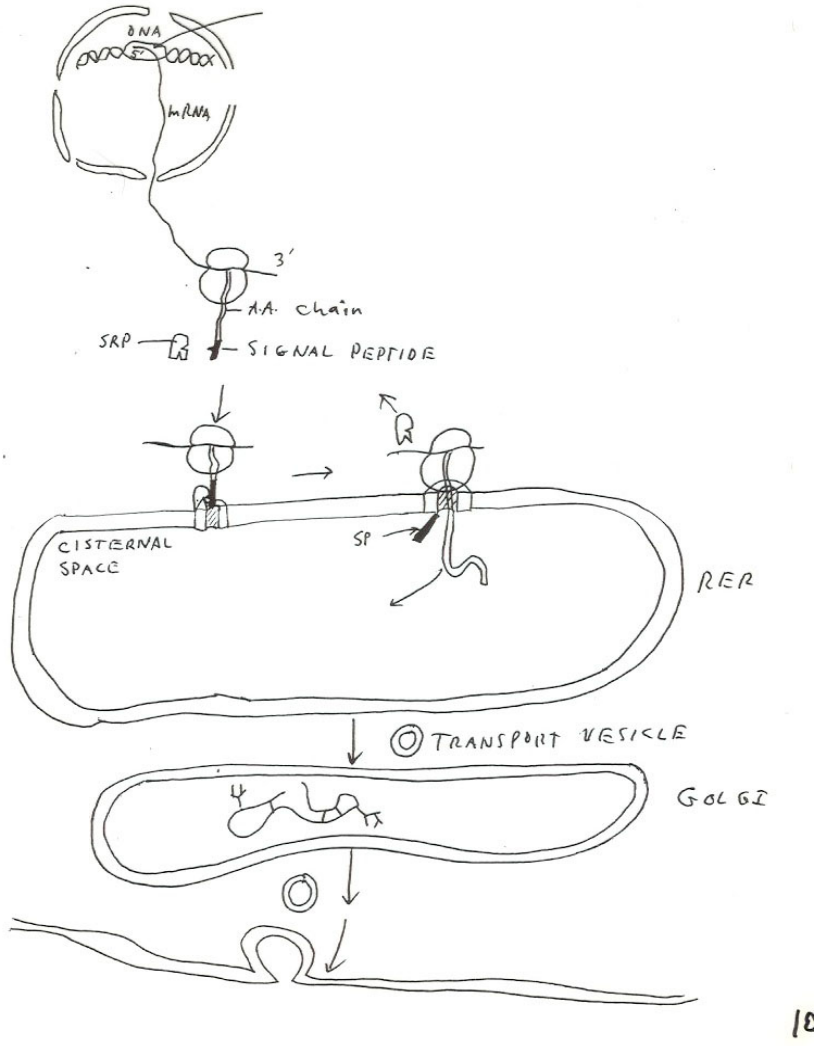
4. **Glycoproteins**
   a. Have a long half-life secondary to the sugar attached which makes them harder to break down.

Synthesis and Secretion of Hormones

Definitions:

- **Proteinaceous Hormones**: These hormones are made up of amino acids that are bound to a peptide chain one at a time, beginning from the amino terminal to the carboxyl end.
- **Pre-prohormone**: The pre-signal peptide is cleaved in the RER. This molecule has the signal peptide still attached.
- **Prohormone**: The inactive hormone is further modified somewhere around the golgi apparatus
- **Active Hormone**: The active hormone will be realeased via exocytosis. Not 100% of pre-pro hormones become active hormones.

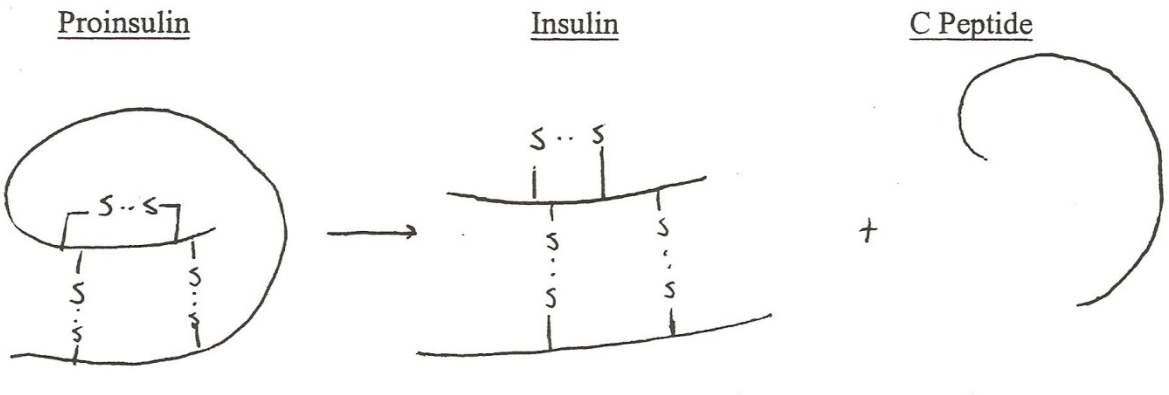
Protein Synthesis picture



Protein Synthesis overview

1. mRNA synthesized in the nucleus via transcription
2. mRNA travels out through the nuclear pores into the cytoplasm and binds to a ribosome
3. Peptide chain elongation by peptide bond formation until a stop codon is reached. The codon will be paired with its anti-codon. This results secondary to *aminoacyl tRNA synthase*. New amino acids will be bound to the growing amino acid chain via *peptidyl transferase*.
4. The *signal peptide* within the cytoplasm binds to the *signal recognition particle* (SRP) on the amino terminal of the growing peptide molecule.
5. The SRP will only facilitate guiding the protein to the endoplasmic reticulum where it will bind to a receptor/channel on the RER called a *translocon*. Thus, the developing protein into the RER. **Here is where we have the pre-hormone**.
6. The protein continues to get longer until we reach a chain terminating sequence. The protein can serve many different functions at this point. Let's consider the product another hormone.
7. The molecule with its signal peptide still attached is a pre-cursor hormone → pre-prohormone. Eventually the signal peptide can be cleaved with signal peptidase → no we have a prohormone. The prohormone will now be bud off into a transport vesicle and head to the golgi apparatus. Enzymes present in the vesicles will continue to digest the molecule into an active hormone.
8. In the golgi, N-glycosylation and disulfide bond formation will occur.
9. Hormones are packaged by the Golgi apparatus into secretary vesicles in their active form to be exocytosed from the cell

Proinsulin (84 aa long) ⟶ **Insulin (51 aa long)**



Steroid Hormone Properties and Synthesis

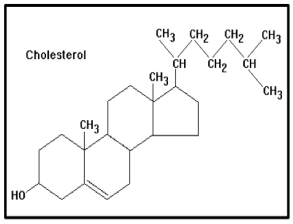
1. **Steroid Properties**
   a. absorbed through the gut
   b. Hard on the liver
      (1) Oral anabolic steroids vs. injectable and the impact on liver function.
         i. Oral anabolic:

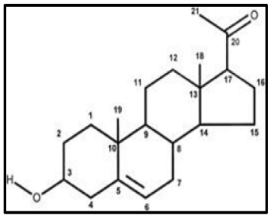
         ii. Injectables

   c. Note the way we refer to the carbons in the cholesterol molecule

Conversion of Cholesterol to Pregnenolone

Cholesterol (27 C) ⟶ Pregnenolone (21 C)



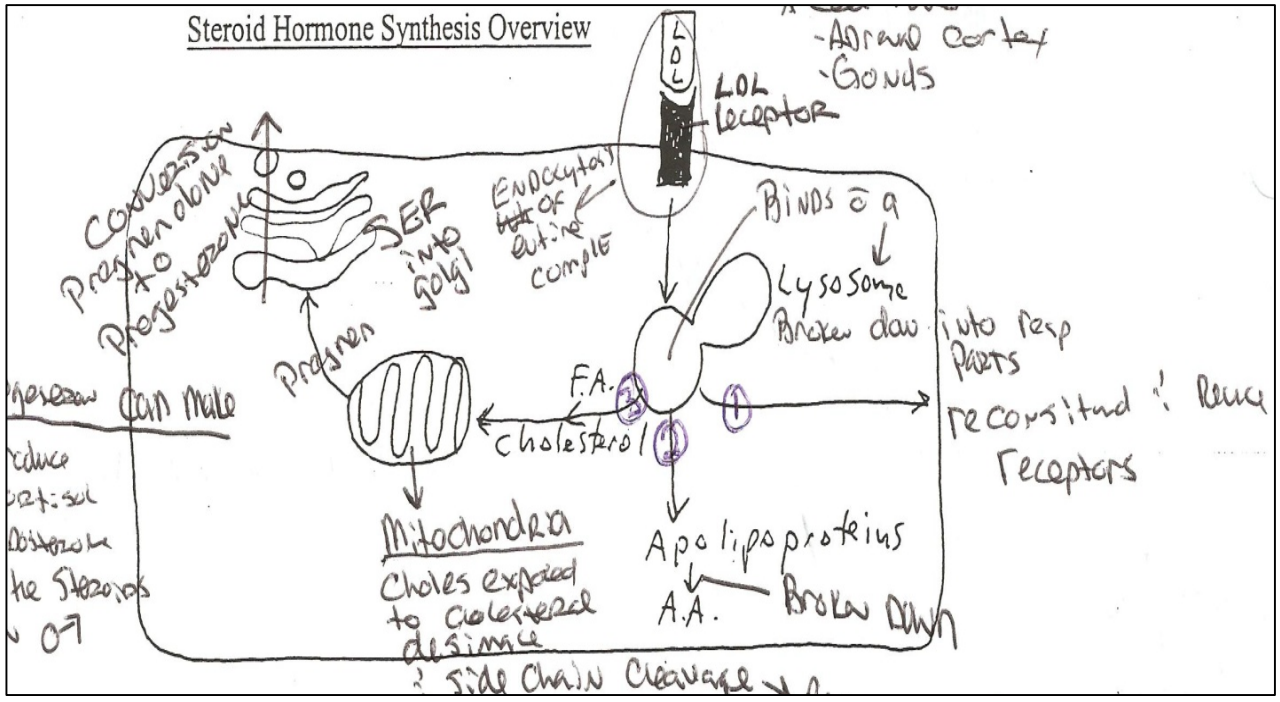


***Carbon 17 is where most of the enzyme activity occurs on cholesterol*

2. **Synthesis**
   a. Synthesis in the smooth endoplasmic reticulum
      i. Composition
      ii. Travels in the blood
   b. Cell membrane receptors for HDL's and LDL's
   c. Pregnenolone synthesis from cholesterol
   d. Pregnenolone converted to progesterone within the smooth endoplasmic reticulum
   e. Note the way we refer to the carbons in the pregnenolone molecule

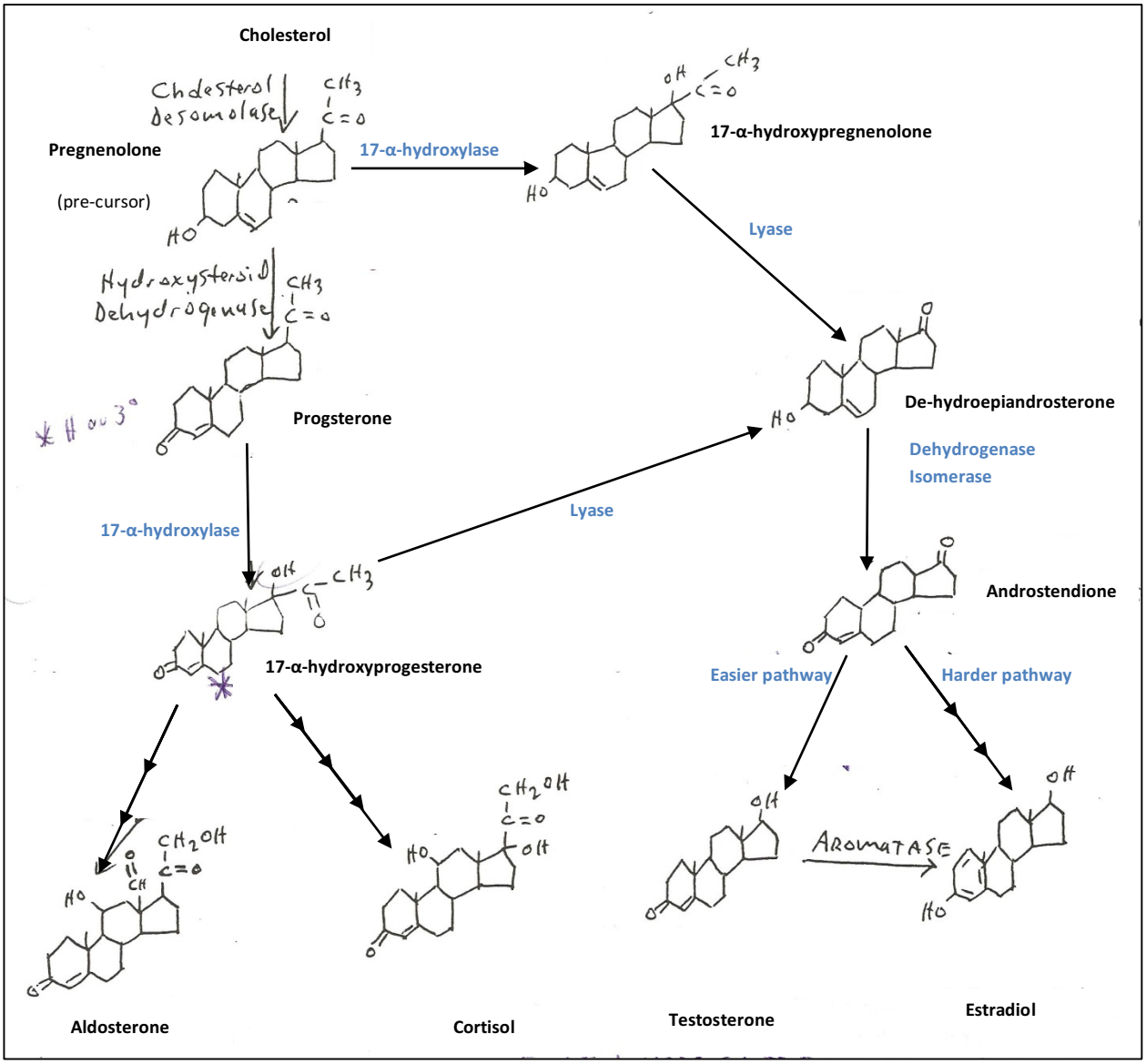
Steroid Hormone Overview

Steroid Pathway (@ adrenal cortex or gonads)



1. LDL molecule binds to the LDL receptor located on the outer membrane of the cell. Binding causes the entire complex to be endocytosed into the cell.
2. The endocytosed complex will bind with the lysosome inside the cell and be digestion into its respective parts **(apolipoproteins, cholesterol, and protein)**
3. **LDL receptors are reused/reconstituted/re-expressed on the cell surface**
4. **Apolipoproteins are broken down into amino acids and used however the body sees fit**
5. **The fatty acids and cholesterol** will be further processed by the mitochondria. Cholesterol will be exposed to the enzyme cholesterol desmolase which will cleave the side chain. Side chain removal will cause its transformation into pregnenolone.
6. Pregnenolone will travel from the mitochondria, to the smooth ER into the Golgi. It will convert pregnenolone into progesterone.
7. **ESTROGEN RECEPTORS IN THE MALE HYPOTHALAMUS DETERMINE RELEASE OF GNRH.**

Synthesis of Various Steroid Hormones



Note:

Arimidex:

FEMARA:

CLOMID:

Mechanisms of Hormone Action

1. **Steroid Hormones**
    a. Travel through the cell membrane

2. **Protein Hormones**
    a. Binding
        i. Exception- **thyroid hormones** can travel through the cell membrane and bind to an intracellular receptor

Hormonal Binding

Binding to the cell membrane will elicit one or more of the following actions

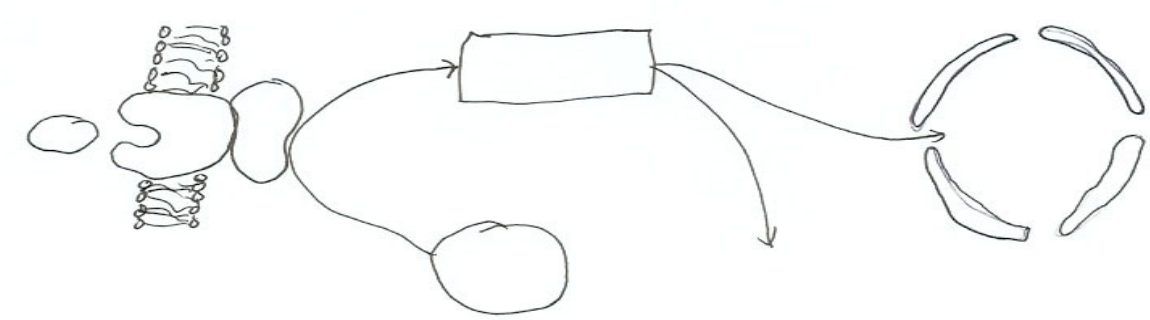
1.

2.

3.

4.

General Steps Involved in Peptide Hormone Action



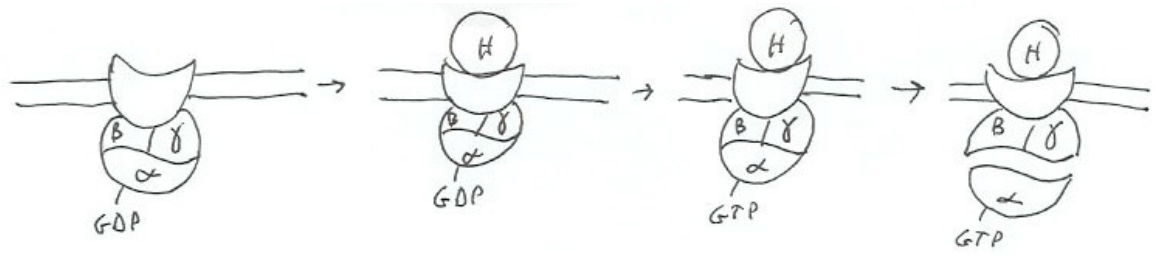
Specific Pathways of Protein Hormone Synthesis

General Terms

1. **Phosphorylase**: Specific enzyme that dephosphorylates a protein.
    a. Activation or deactivation
2. **Kinases:** A family of enzymes that phosphorylate a protein
    a. Tyrosine kinase- typically phosphorylation of the
    b. Serine/threonine kinase- typically phosphorylation

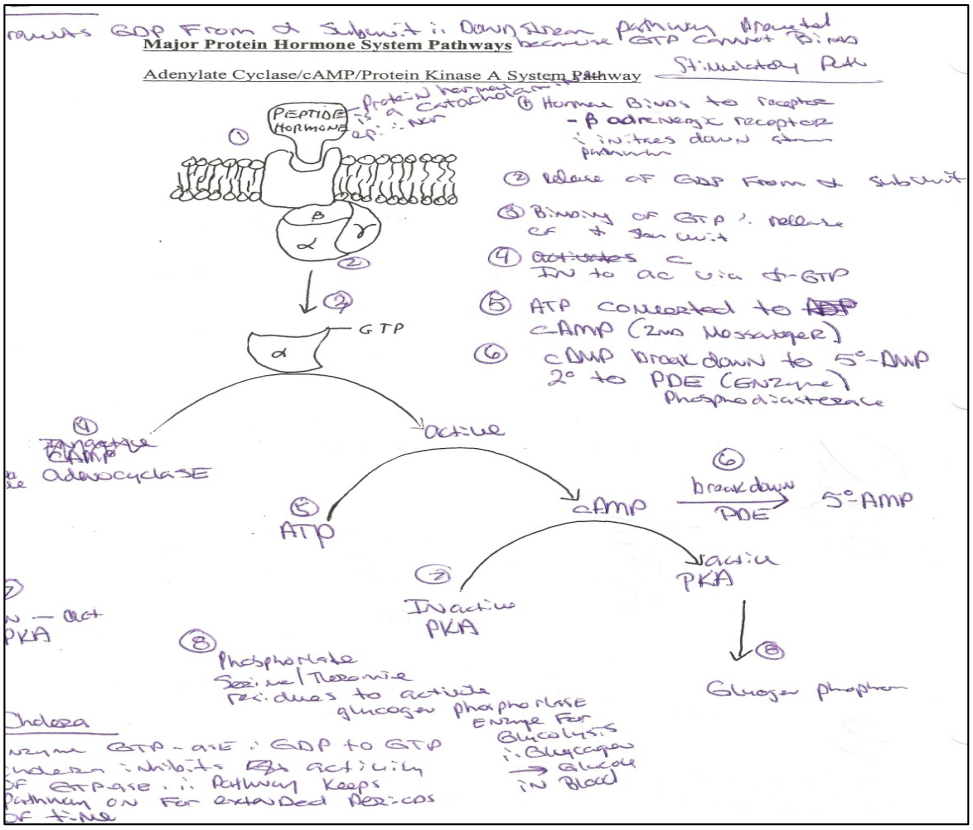
3. **G-proteins**: A protein composed of three subunits that break apart when activated to initiate reactions within the cell
    a. Types of G-proteins
        i. **Gs-protein**: Stimulatory which activated the cAMP/PKA system
        ii. **Gi-protein**: Inhibitory which inhibits the cAMP/PKA system
        iii. Gy-protein

Activated the PKC system



Protein Hormone Synthesis Pathway

Adenylate/cAMP/Protein Kinase A System Pathway



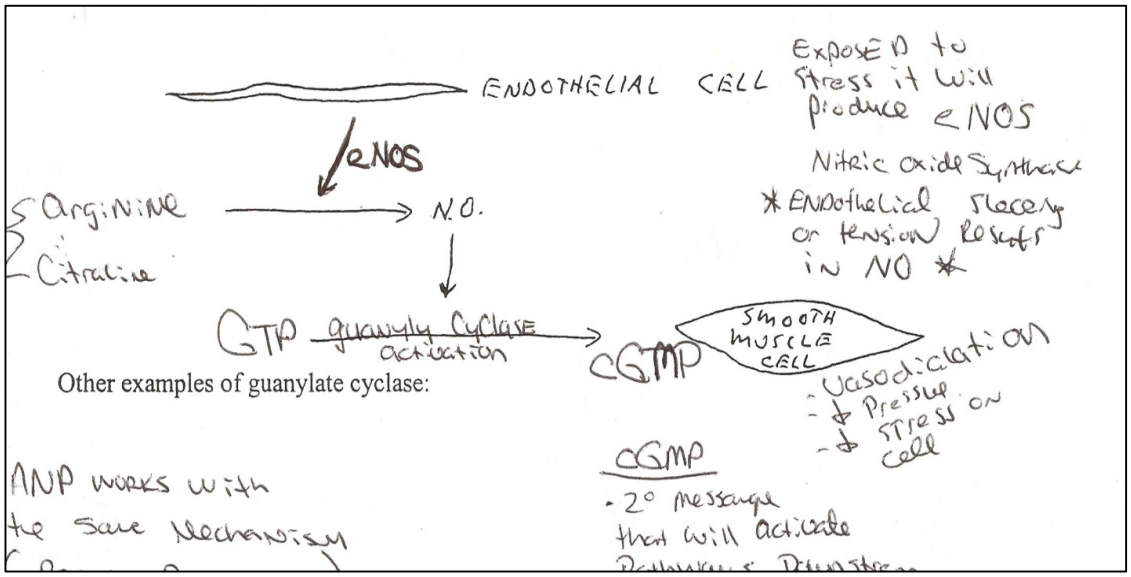
<u>Stimulatory Pathway</u> (for prior picture)

1. Catecholamine binds to a beta-adrenergic receptor and initiates a down steam pathway
2. Release of GDP from the attached α-subunit
3. Binding of GTP and release of α-subunit from G-protein
4. Inactive adenylate cyclase → active adenylate cyclase
5. ATP→ cCAMP (a 2nd messenger)
6. cAMP will be broken down into 5o-AMP
7. Inactive PKA → active PKA
8. Phosphorylation of serine/tyrosine residues to active the enzyme glycogen phosphorlase. This enzyme will enable glycogen to be transformed into glucose, thus, allowing an increase in bgl

<u>Guanylate Cyclase System</u>

1. Enzyme-Linked Receptor System is an enzyme that is bound to a receptor
2. cGMP will act as a second messenger initiating intracellular activity
   a. i.e. The downstream pathway might result in phosphorylation/de-phosphorylation of a protein.

Example of Guanylate Cyclase System: *Activation of Nitric Oxide pathway*



Nitric Oxide- overview of pathway

This process is initiated when endothelial cells which line the inside of the vascular system are exposed to stress. Stress can result from tension and/or shearing of the endothelial layer.

1. Endothelial stress/shearing release of eNOS
2. Arginine or citraline $\xrightarrow{eNOS}$ NO
3. Activation of Guanylyl cyclase
4. GTP $\xrightarrow{gyanylyl\ cycasle}$ cGMP
5. cGMP is a 2nd messenger, thus, a cascade of results will follow
   a. Smooth muscle dilation
   b. Hypotension
   c. Decreased stress on the cell

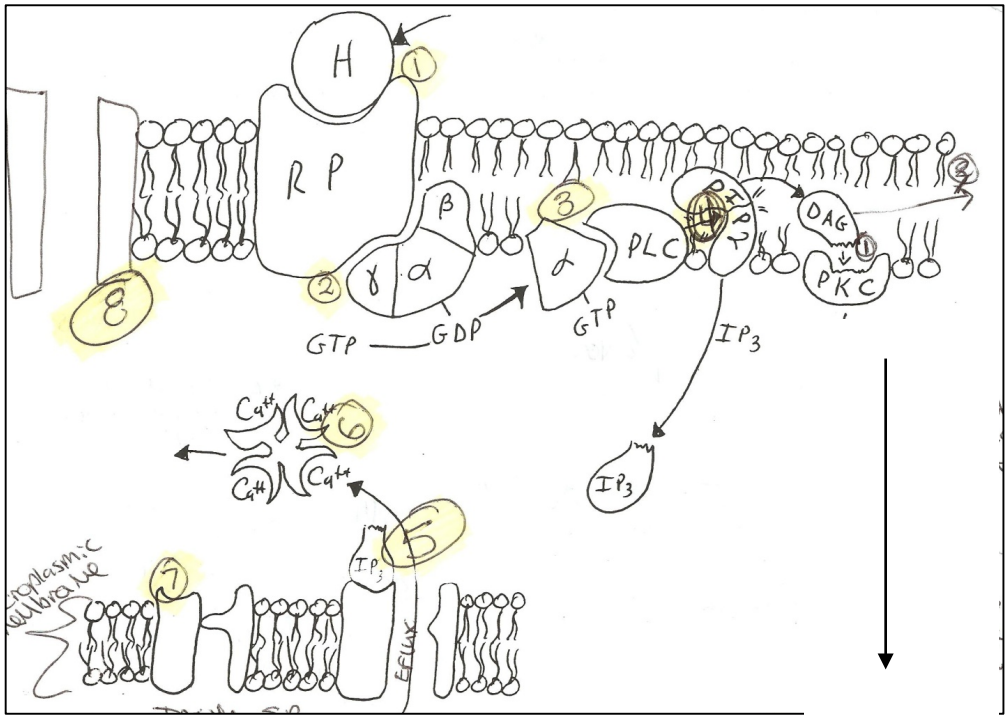
SIDE NOTE*******

Nitric Oxide supplementation will increase blood flow to the muscles, increased exchange of nutrients and wastes and also has potential positive cardiovascular effects by decreasing blood pressure.

Cardiovascular disease and supplementation with beta blockers and Ca++ channel blockers. Any hypoxic tissue will secrete angiogenin. Angiogenin will result in increased vascular tissue which may increase cardiac function demand. The effects of angiogenin won't be observed in tissue that has died.

Ca++ is a major player involved in maintaining both a resting membrane potential and skeletal muscle contraction.

Phospholipase C / DAG / IP3 / Protein Kinase C System



IP3 Pathway

1. Hormone will bind to the receptor protein
2. The G-protein binding will cause a confirmation change, thus, the GDP will disassociate from the α subunit followed by GTP binding to the α subunit initiating a confirmation change. Next the α subunit-GTP complex will disassociate from the G-protein.
3. The α subunit-GTP complex will bind with phospholipase C (PLC)
4. Activation of PLC will cause phosphotidyl inositol biphosphate (PIP2) to split into 2 molecules (IP3 and DAG). PIP2 is part of the plasma membrane. ***NOTE*** IP3 and Ca++ interact with different Ca++ ion channels via different mechanisms
5. IP3 will travel to the sarcoplasmic reticulum (SR) and bind to a IP3 receptor on the Ca++ channel in the phospholipid bilayer. Binding to the receptor will cause an efflux of Ca++ from inside the SR into the cytoplasm outside the SR.

Efflux will have 3 different fates

6. Ca++ may bind to *calmodulin* (has 4 binding sites) to initiate smooth muscle contraction.
   a. Contraction may result in cardiac (nerst potential is ~ -90mV) or smooth muscle (nerst potential ~ - mV). Thus, there is more electrical potential found outside cardiac muscle vs smooth muscle. Ca++ blockers will have more of an affect on cardiac when compared to smooth muscles resulting from the difference in electrical potential.

7. Ca++ may bind to a *Ca++ regulated ion gate* on the SR, thus, allowing a greater efflux of Ca++ to enter the cytoplasm inside the SR
8. Ca++ may also bind to the Ca++ ion channel located on the cells outer membrane. The binding here will allow Ca++ to enter the cytoplasm from outside the cell where the [Ca++] is at its greatest.
9. Diacylyl glycerol (DAG)
    a. DAG will activate protein kinase C (PKC). This Ca++ dependant. If we don't have Ca++ available in the cytoplasm this isn't a good pathway.
    b. PKC will allow for phosphorylation of seranine and threonine residues, thus, allowing for possible gene transcription/translation
    c. Arachidonic acid is created which can make prostaglandins

Steroid Hormone Mechanism of Action

<u>General Information</u>

1. Usually travel through the blood stream attached to different types of proteins
    a. Albumins

    b. Fibrins act as clotting factors
    c. Globular proteins carry various molecules in the blood. For example a steroid molecules can be carried in the blood once bound to a globular hydrophilic molecule. The hydrophilic protein carries the hydrophobic steroid. Many globular proteins are specific to specific hormones while others are not. For example
        i.
        ii.
        iii.
        iv.
    d. A small proportion of proteins travel through the blood unbound.
        i. For example hydrophobic aldosterone
        ii.
2. Three different types of carrier proteins
    a. **Non-specific**
        i. Carry many different types of hormones. Protein carrier molecules found in high concentration in the blood, therefore, carries a significant percentage of hormones within the blood
    b. **Specific**
        i. Has binding sites for specific hormones and will carry the hormone through the blood
    c. **Unbound**
        i. A small amount of hormone types are carried through the blood unbound

3. Hormone movement into target cell

a. Binding proteins release the hormone at the target cell and the steroid diffuses into the target cells cytoplasm
b. Receptors are located within the nucleus or cytoplasm of the target cell
c. Binding is to specific receptors
d. Steroid hormone receptors belong to a superfamily of nuclear and DNA binding proteins that act as transcription factors that are only active in the receptor protein/steroid hormone state.

4. Activation of a receptor

a. Hormone enters the cytoplasm possibly via diffusion and the hormone will bind to a nuclear receptor. The hormone/receptor complex will bind to the **Hormone Response Element (HRE)** and initiation of transcription will take place.
    i) Specific HRE's
        (1) ERE-
        (2) ARE-

INCREASED ESTROGEN-

INCREASED TESTOSTERONE-

MTHFR-

METHYLTESTOSTERONE-

SARMS- Selective Androgenic Receptor Modulators-

Ligandrol- LGD-4033
Andrarine-GSX-007
Cardarine- GW-501516

Non-steriodal drugs which stimulate anabolic effects.

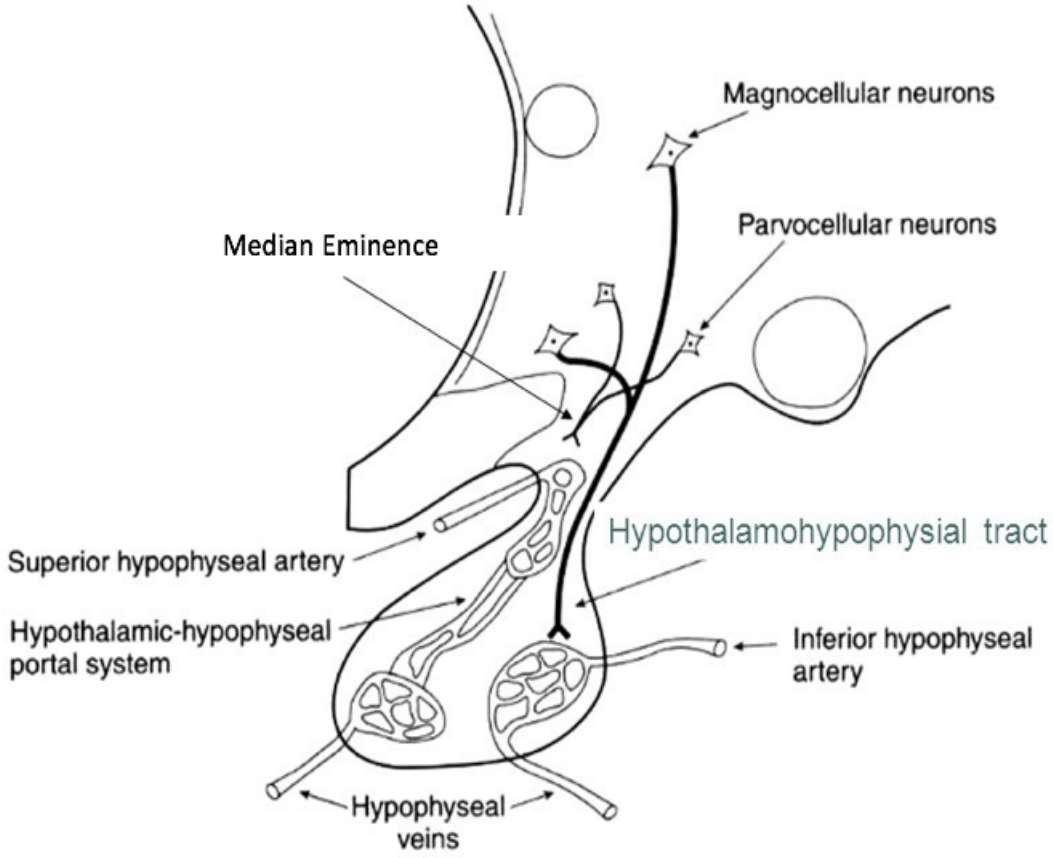
Glands of the Endocrine System

Hypothalamus:

directly controls release of hormones from anterior pituitary (master gland)

Regional Anatomy

1. The hypothalamus is located below the thalamus and is an extension of the brainstem. Hypothalamic tissue surrounds the 3rd ventricle and it creates a bowl in which the 3rd ventricle sits in which is filled with CSF. (**CSF will provide feedback to nucleus)**
2. The hypothalamus contains a large quantity of nerve cell bodies called nuclei. The nuclei are in the walls of the hypothalamus and have *short axons* which travel to either the *median eminence and terminate*. The long nuclei have axons which travel down and release their secretions into the inferior hypophyseal artery located at the posterior pituitary proper.
3. Median eminence comprises the floor of the 3rd ventricle and the base of the infundibulum.



4. Blood flow
   a. The superior and inferior hypophyseal arteries both receive blood from the *middle cerebral artery*
      i. Middle cerebral artery is the most common vessel involved in stroke. If the pre-central gyrus and post-central gyrus are the 2 most commonly affected regions. Damage to this area will result in motor and/or sensory impairments. A stroke could result in necrosis to the pituitary region which would result in hormone disturbances.

Neurophysin's

1. A hormone that is bound to another molecule which comes from the hypothalamus and is released from either the anterior or posterior pituitary gland. The bound complex will travel down the axon together. As they are released into the blood stream the complex will break apart. There is currently no known function of the binding molecule once it separates from the active hormone in the bloodstream.

Function

1. Hypothalamic neurons synthesize and secrete
2. Hypothalamic-Hypophyseal System
   a. Posterior pituitary
      i. Contain 2 main nuclei
   b. Anterior pituitary
      i. Main nuclei

Hypothalamus Hormones

1. **TRH** – Thyrotropin Releasing Hormone
   a. Functions
      i. Stimulates
      ii. Stimulates

   b. Initiating Factors
      i. *Release when exposed to cold environments → TRH stimulation → TSH →increased metabolism →*

      ii. Release
2. GnRH – Gonadotropin Release Hormone
   a. Function
      i. *GnRH → release*

   b. Initiating Factors

SIDE NOTEExogenous testosterone use will inhibit the hypothalamic-hypophyseal-gonadal axis (HHG).

GHRIH (AKA GHIH) – Somatostatin

c. Function
   i. *Thyroid*- causes a decrease release in **calcitonin.**
      A decreased release results in Ca^{2+} removal from the bones into the blood, thus, a decrease in bone density is seen.

   ii. *Pancreas:* somatostatin levels not functional during days
      (1) Inhibits insulin and glucagon production

   iii. *Pituitary*:
      (1) Inhibits growth hormone from the pituitary gland. Will inhibit at the anterior pituitary. It also inhibits the production of TSH from the anterior pituitary gland.
   iv. *GI*:
      (1) Contributes to the balance observed between production/non-production of enzymes for digestion, which enables energy to be conserved.
      (2) Inhibits secretions of all glands within the digestive system. Lumones is a generalized term for a hormone that will have an effect on the GI system.
      (3)

   v. *Brain*
      (1) It has a generalized sedative effect on the body which contributes to drowsiness

SIDE NOTE*******

The only true anabolic hormones.

The 2 main growth inhibiting hormones

3. **GHRH** – Growth Hormone Releasing Hormone
    a. Function
        i. Stimulates GH production
4. **CRH** – Corticoid Releasing Hormone
    a. Formation
        i. May be produced from the placenta

    b. Function
        i. Stimulates β-lipotropin and endorphins

SIDE NOTE **********

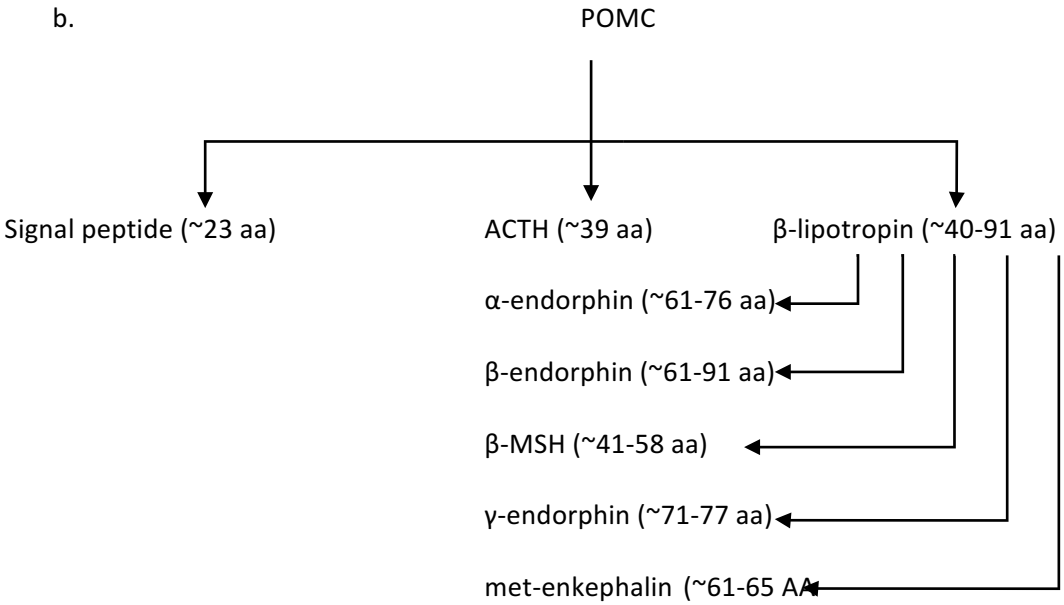
If a female in labor has pre-term labor contractions (Braxton Hicks contractions) or bleeding;

Treatment of choice-

****

5. **PRIH** – Prolactin Releasing Hormone (Dopamine)
    a. Formation:
    b. Function
        i. Inhibits prolactin release

6. **Opiates** – Endorphins/Enkephalins
    a. Formation
        i. All of the following are cleaved off of POMC.
    b.



- **Endorphin and met-enkephalins** : these are neurohormones with endogenous analgesic effects. i.e
-

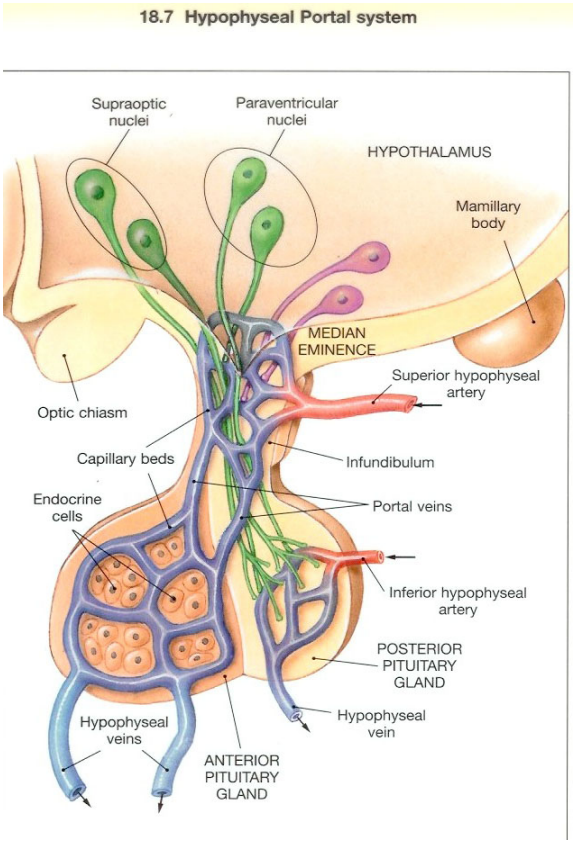
- **Long term ACTH** binding to receptors can lead to hyperpigmentation secondary to stimulation of melanocyes which will cause the skin to darken. This is a very common side effect observed in Addisons disease.

    c. Function
        i. See an increase in GH and PRL release.
        ii. In the brain the opiates have a synergistic affect by stimulating the release of epinephrine. Recall epinephrine is one of the feel good hormones.
        iii. Hypothalamus: decrease in GnRH release is observed which will also lead to a decrease in LH/FSH. Long term elevation of opioids-
        iv. 3 factors contribute to infertility in active women.

Anterior Pituitary Gland

Arose from Rathkye's pouch which was ectodermal invagination of the oral pharynx. 5 cells types distinguish by size and shape of the secretory gland, staining characteristics and cell shape

SUPERIOR HYPOPHYSEAL ARTERY



1. **Corticotrophs**
   a. **ACTH** – Adrenocorticotropin, β-lipotropin and MSH
      i. Function: stimulate adrenal cortex
      ii. Feedback regulation
         (1) Cortisol
      iii. Stimuli for ACTH release
         (1)
         (2)
         (3)
         (4)
         (5)
         (6) Physical stress
            (a) There is usually a small number of corticotrophs located within the anterior pituitary gland.

Feedback Loop for Corticotrophs

2. Gonadotrophs

a. Secrete gonadotropins (LH/FSH)

b. Synthesis of LH/FSH

i. LH- Leutinizing hormone

ii. FSH- Follicle stimulating hormone

iii. Produced in episodic bursts: once every hour which may be different between males and females.

(1) GnRH comes from the hypothalamus

(2) In males inhibin is secreted from the sustentacular cells (sertoli cells). Sustentacular cells location-

(3) Estradiol (E_2) (estrogen) confers a negative feedback response most of the time in females. However, during the ovulatory surge there is a huge positive increase in estrogen which greatly increases in GnRH, estrogen → follicular cells → increased GnRH → increased FSH/LH →

(4) Activin secretion will increase the production of FSH

c. Function

i. FSH

(1) MALES

(a) Stimulate

(b) Involved in the production

(2) FEMALES
(a) Stimulates
(b) Stimulates

ii. LH
(1) MALES
(a) Responsible for
(b) Responsible for
(2) FEMALES
(a) Stimulates
(b) Stimulates

Gonadotropin Feedback Control Loop

Negative feedback most of the time

3. Thyrotrophs

a. Produce TSH

b. Cell characteristics
i. The cells will immunostain.

c. TSH Action *** Main function
i. Increased synthesis of thyroglobulin. Thyroglobulin is the (prohormone) precursor to thyroid hormone
ii. Increased iodide transport into the follicular cells of the thyroid gland
iii. Increased endocytosis of thyroglobulin
iv. Increased exocytosis of $T_3 \; and \; T_4$ (this is truly thyroid hormone)

Feedback Control Loop for Thyrotrophs

Inhibition

4. **Somatotrophs** – Produce growth hormone
   - **a.** Growth Hormone is regulated by GHRH
   - **b.** GHRH is increased by GHIH (somatostatin)
   - **c.** Stimulation of GHRH

   - **d.** GH Action on the liver
     - i. There are many GH receptors on the liver.
     - ii. The liver produce

       (a) Serum [HGH] is pulsatile and hard to measure, thus, it is more common to see clinician's measure somatomedians (AKA IGF's). IGF's are in higher concentrations in the bloodstream, maintain a more regular release and have a longer half-life when compared to serum [HGH]

     - iii. Direct stimulation
       (a) Almost all other cells within the body will benefit from the anabolic effects of GH.
       (b) GH effects in pre-pubescent individuals -

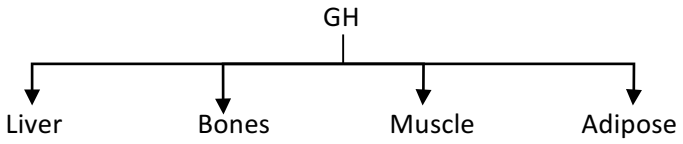
(c) An *increase in the cell size* of bones and muscle-

(d) HGH/testosterone supplementation requires a healthy diet otherwise you will create a diabetic effect and other untoward effects within your body. HGH use is nondiscriminatory.

(e) In **Paget's disease**, you may see an increase in the size of an individual's bones.

(f) An increase in protein synthesis will be observed with GH secretion
(g) An increase in fat metabolism for energy will be observed with GH secretion.
(h) An increase in glycogenolysis

iv. Growth Hormone will affect 4 different target organs



(1) Liver
   a. IGF production, specifically IGF-1

(2) Bone
   a. You will see an increase in long bone formation *but early epiphyseal plate fusion*. Therefore, an individual may have a pituitary tumor and will initially growth quickly then stop early. This person will be at an increased risk of an early death.
   b. Moreover, a dramatic increase in size will cause them to develop a "diabetic effect".

(3) Adipose tissue
   a. Increased lipolysis for energy production

(4) Muscle
   a. An increase in anabolism and works with insulin. Insulin is a highly anabolic molecule.

GH Feedback Control Loop

Somatostatin or GHIH will inhibit this feedback mechanism

5. LACTOTROPHS: (Most common cause to pituitary tumors)

a. These cells produce PRL and comprised 20 to 50% of the cells in the anterior pituitary. Inhibited by the secretion of dopamine. *PRL is similar in structure to GH and human placenta lactogen (hPL).*

b. PRL Actions

i. FEMALES

(1) Maturation of Mammary Gland

(a) PRL will cause hyperplasia of the milk glands during pregnancy. NOTE: many hormones are involved in this process/release of milk.

(2) Initiation of Lactation (Mechanism from an inhibition prospective)

(a) Progesterone inhibits lactation. Progesterone is a very dominant hormone during pregnancy.

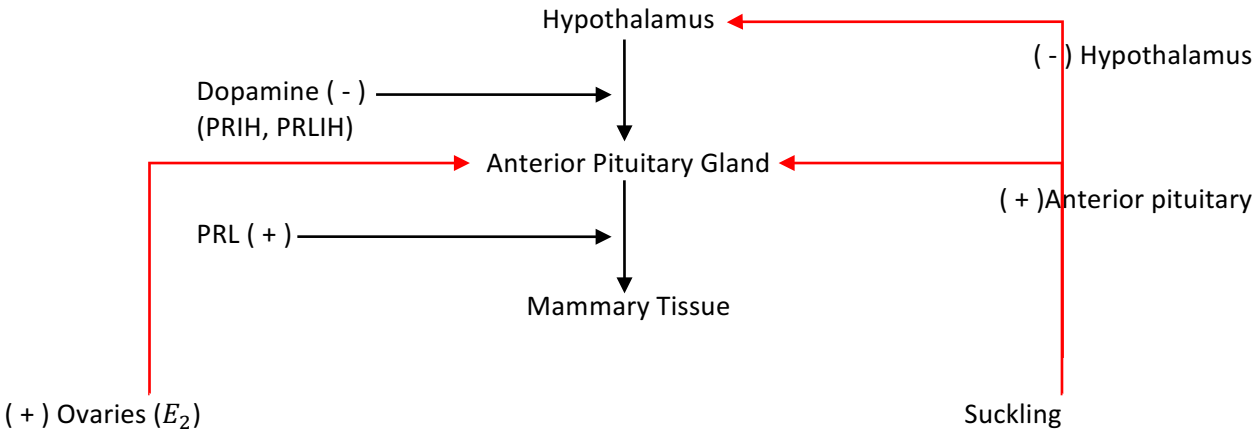
(3) Post-Partum

(a) PRL maintains lactation but *suckling in the main stimulus*

ii. MALES

(1) PRL increases the [LH receptors] on the testes and will promote testicular size.

PRL Feedback Control Loop



*** Inhibited by the secretion of dopamine, *NOTE* suckling → hypothalamus pathway***

Lack of suckling inhibits the entire feedback mechanism

PRL will cause the production/synthesis of the milk and

Oxytocin will cause the milk let down reflex

Pathophysiology of the Hypothalamus and the Anterior Pituitary Gland

1. Hypopituitarism

a. Causes

i. Pituitary tumors

ii. Hypothalamic tumors

iii. Infarction

iv. Vascular malformation secondary to a genetic condition.

(1) Empty Sella Syndrome:

b. Specific Types

i. ***Panhypopituitarism***:

(1) This condition results from a complete loss of function from the anterior pituitary gland. You may observe the following symptoms; FEMALE amenorrhea, MALES impotence BOTH will can also observe dysfunction in the other anterior pituitary hormones, i.e. no FSH/LH or TSH production. This condition may result in lethargy, stupor and even death.
Treatment:

ii. Isolated Gonadotropin Deficiency

(1) This condition typically occurs at the hypothalamic-pituitary axis. You will see a loss of GnRH, thus, in FEMALES amenorrhea, MALES a decrease in secondary sex characteristics.

iii. ACTH Deficiency

(1) This condition is relatively uncommon

iv. ***Sheehan's Disease*** *(AKA Pituitary Apoplexy)*

(1) This condition is observed secondary to post-partum anterior pituitary necrosis. It's not uncommon to see a huge increase in the number of lactrotrophs during pregnancy. This increase may create an environment in the anterior pituitary which is highly susceptible to injury.

2. Hyperpituitarism

a. These typically arise from tumors

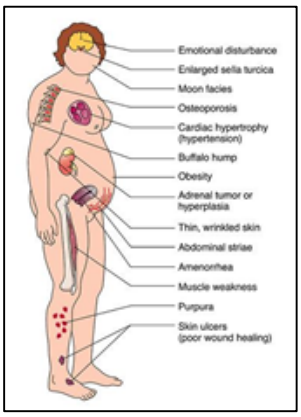
b. Precocious Puberty

i. You will observe an increase in GnRH

c. Cushing's Disease

i. This is an ACTH secreting tumor.

ii. You will observe an increase in metabolism, redistribution of body fat



iii. hyperpigmentation resulting from an increase in MSH production and possibly diabetes.

d. Prolactin Secreting Tumor

i. This is the most common of all the pituitary tumors (30% to 70%). It is 5X more common in FEMALES vs. MALES

Classic Pituitary Pathophysiology

1. Variations in Growth Hormone Production

a. ***Dwarfism***: Results from a GH deficiency

i. Congenital

(1) ***Laron's Dwarfism***

(a) The pt will have a lack of GH receptors but will produce the proper amount of GH.

(2) African pygmy

(a) The pt will have a normal [GH] but inappropriate rise in IGF. This may result from problem with GH receptors on the liver.

(3) Hereditary

(a) This stems from a gene deletion

ii. Acquired

(1) Pituitary tumors which will squeeze out the somatotrops

(2) Pituitary Infection

(a) A potential mechanism for this to happen

iii. Treatment

(1) The most common-

SIDE NOTEGH is species specific, thus, supplementation with GH from anoterh species there would be very little response. Original treatment -

b. ***Giantism***

i. An increase in GH prior to epiphyseal plate closure

ii. Signs and Symptoms for Gigantism

(1) Increase in skin thickness with (dermis and epidermis), deepening of the voice secondary to increasing length in vocal folds, overgrown skeleton, barrel chest

iii. Treatment

(1) Surgery, radiation, hormonal therapy

c. ***Acromegaly***

i. An increase in GH production after the epiphyseal plate closure. This can result from tumors

ii. Signs and Symptoms for Acromegaly

(1) Increase in skin thickness with (dermis and epidermis), deeping of the voice secondary to increasing length in vocal folds, overgrown skeleton, barrel chest, and many cardiovascular problems

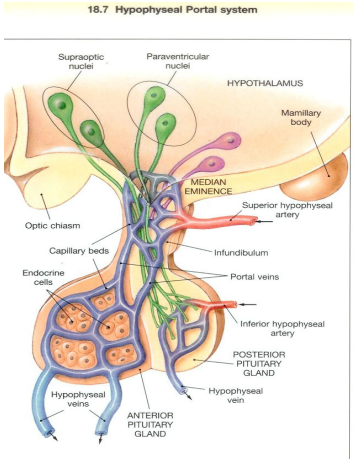
iii. Treatment

(1) Surgery, radiation, hormonal therapy

Posterior Pituitary

1) Arterial blood supply provided by the inferior hypophysial artery. Hormones of the posterior pituitary gland are produced in magnocellular cells of the hypothalamus and travel down the axon via axonplamic flow to the axon terminals located in the median eminence.

POSTERIOR HYPOSHYSEAL ARTERY



Hormones of the Posterior Pituitary

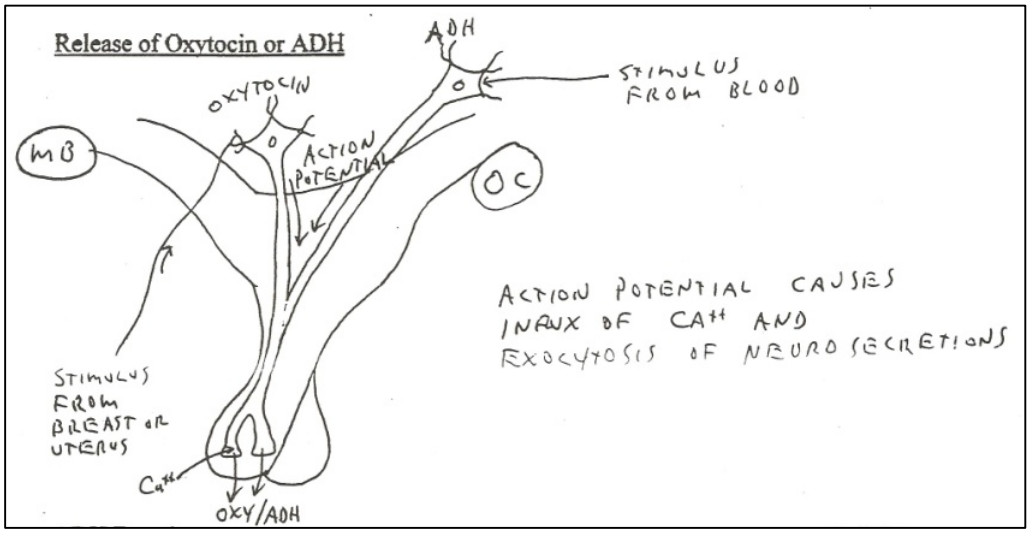
1. **Oxytocin**
   - **i.** is synthesized in the cells of the paraventricular nuclei in the hypothalamus.
   - **ii.** Function
     - **a.** Involved in the milk let-down reflex-myoepithelial cells of the mammary gland
     - **b.** will contract uterine contractions-contraction of the myometrium of the uterus

2. **Anti-diuretic hormone – (ADH)**
   - **i.** This hormone is also known as vasopressin. It is synthesized in the supraoptic nuclei of the hypothalamus.
   - **ii.** Function

Hormone Synthesis

1. Both hormones are synthesized within the rough ER of the magnocellular cells of the hypothalamus. They are packed into secretory granules that migrate down the axon bound to neurophysins [(*pressophysin neurophysin II)* from ADH and *(oxyphysin neurophysin I)* for oxytocin]. ADH also has glycoproteins which are bound. Here the hormones are cleaved into their active form and stored for release when needed

2. **Release of Oxytocin or ADH**



ADH Functions

1. **Half-life** is 15-20 minutes
2. **Osmoregulation**
   a. Osmoreceptors *(vasculosum osmoreceptors)* which line the 3rd ventricle. These magnocellular cells sense changes in the osmolality of the extracellular fluid (Na+ content).

3. **Baroregulation**
   a. Changes blood pressure (decreases), leads to an increase in ADH production to conserve water and increase blood pressure.

4. **Stimulation**
   a. Nausea and vomiting will increase ADH production
5. **Inhibition**
   a. Alcohol, caffeine, nicotine will inhibit the release of ADH

SIDE NOTE*******

PATHOPHYSIOLOGY

Malignant hypertension will cause devastating effects on the renal system.

ADH Pathophysiology

1. **Diabetes Insipidus**
   a. A decreased production of ADH or a decrease in the sensitivity of ADH receptors within the kidneys will result in a tremendous loss of water. Patients can lose-
   b. Nephrogenic cause
      i. Receptor stop working normally

c. Neurogenic cause
    i. Decreased production of ADH

2. Syndrome of Inappropriate ADH Production (SIADH)

a. This most commonly results from-

Oxytocin Function

1. Half-life ~ 3-5 minutes and its degraded by the liver
2. Milk-let down Reflex
    a. Afferent neurons in the nipples and the areola synapse on the magnocellular cells of the paraventricular nucleus causing depolarization and the release of the synaptic granules containing oxytocin.
3. Uterine Contraction and Cervical Distention during Labor and Parturition
    a. This is a positive feedback mechanism. This process is multi-hormonal. Stretching of the cervix and the myometrium releases oxytocin in normal labor. Once cortisol release from the placenta and/or the baby and an increase in [serum] will initiate this process. The uterine contractions stimulate afferent neurons in the wall of the uterus → causing the release of oxytocin → causing the myometrium to contract even more.
    b. Pitocin can be given

Oxytocin Actions

1. Lactation

a. Stimulation of

2. Parturition

a. During the last trimester of pregnancy there is an increase:

b. Moreover, as plasma oxytocin levels will increase uterine contractions will commence.

3. Testes

a. An increase in

4. Sperm Movement

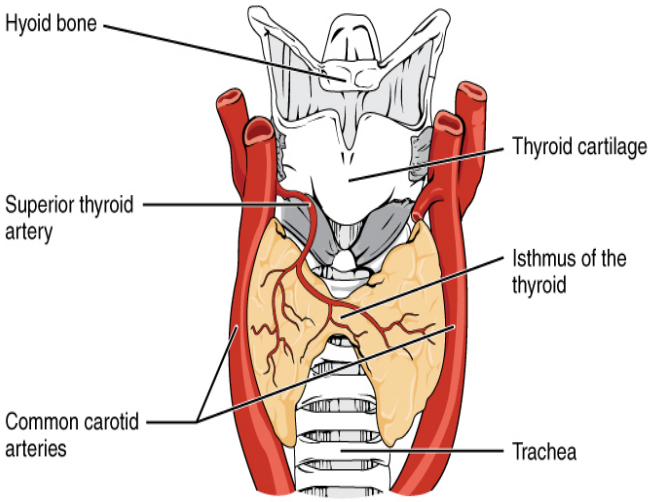
a. Oxytocin release during female climax

5. Corpus Luteum

a. Oxytocin involved in regression of the corpus luteum into the corpus albicans (luteolysis) to decrease progesterone production

Endocrinology of Metabolism

The Thyroid Gland

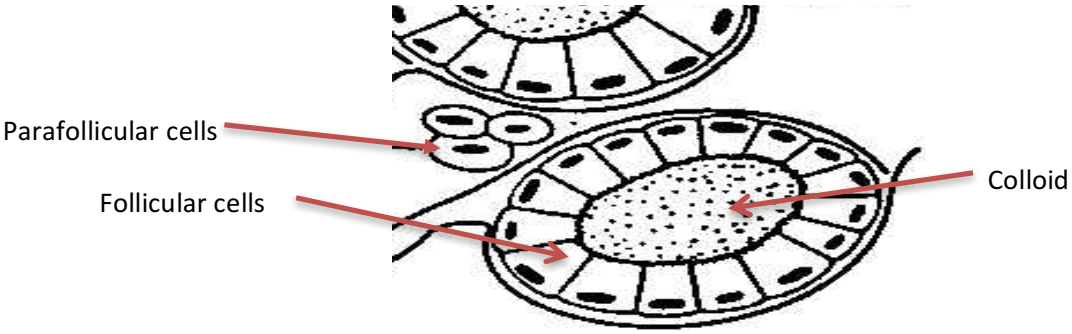


Blood supplied by two main arteries

Two lobes connected by

Cell Type

1. Follicular Cells - 3 million follicles
2. 3 million follicles which are around the edge

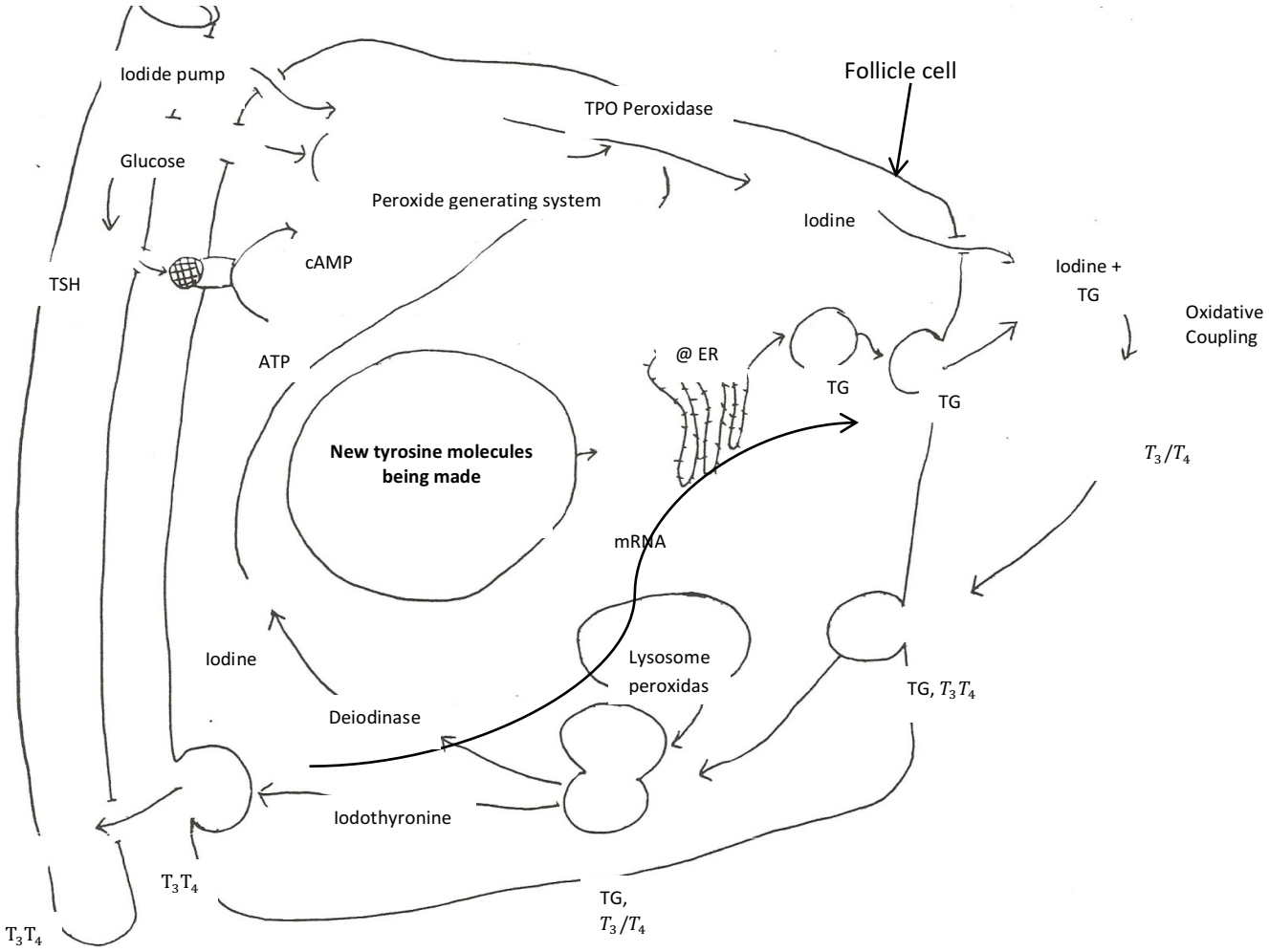


3. C-Cells **AKA**-
    a. These are interstitial cells which produce

Fetal Thyroid

1. Starts functioning at the end of the 1st trimester. Most important function of fetal thyroid is proper development of the IMMUNE SYSTEM.
2.

Thyroid Hormone Synthesis

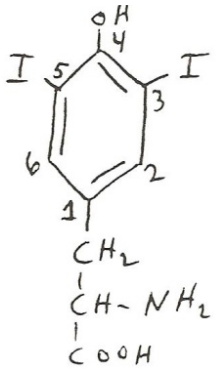


Thyroglobulin

1. This is initially synthesized in the rough ER and then gets glycosylated in the Golgi apparatus.

Iodide Pump (AKA Iodide Trapping)

1. This pump is involved in the active transport to increase the [I] within the cell.
2. Iodination of Thyroglobulin



Iodothyronine Formation

1.

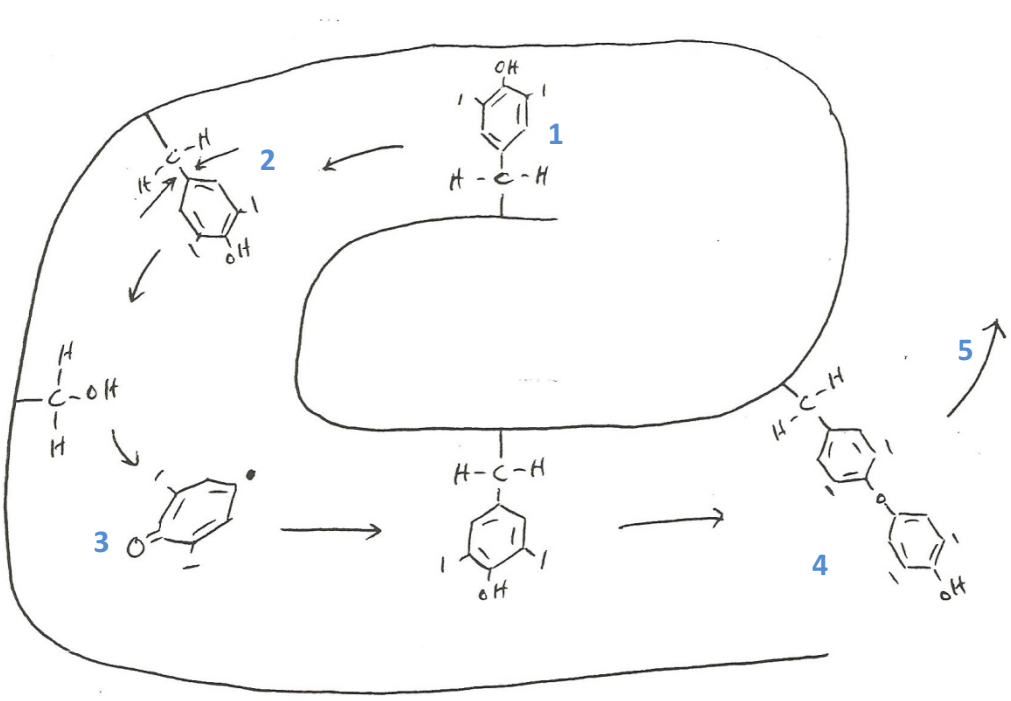
2.

3.

4.

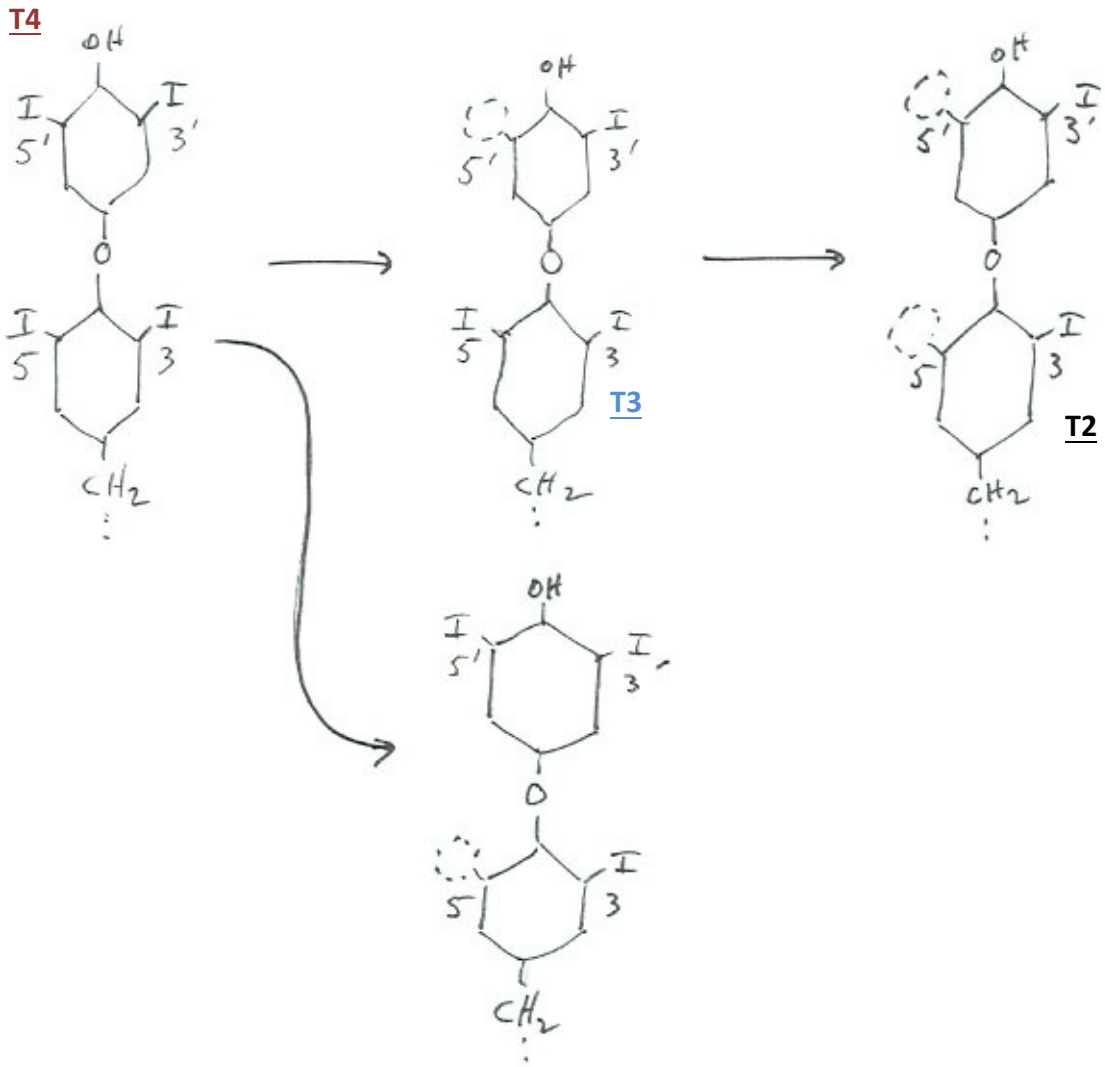
5.

6.



T3 is called **triiodothyronine-**

T4- **tetraiodathyronine** (thyroxine). Makes up 90% of the serum hormone. This is the form in which thyroid hormone travels through the blood stream.



Thyroid Hormone

Thyroid Function at the Cellular Level

1. General function is similar to a steroid hormone. It will bind to cytoplasmic receptors to induce protein synthesis
2. Primary Function
   a. Activates the cAMP pathway
   b. Involved in basal metabolic rate
   c. Increase in heat production
   d. Increase in oxygen consumption
3. Other functions
   a. Required for activation of other hormones. Especially other anabolic hormones
   b. Ramps up most other bodily functions
   c. Increase in heat production
   d. Important during pregnancy for proper fetal development

Factors Affecting Thyroid Hormone Release

1. Increase in cold →
2. Increase in warmth →
3. Decrease in stress →

Thyroid Hormone Feedback Mechanism

Side Note about free/bound T_3 and T_4

99.96% of T4 is bound to thyroid binding globulin (TBG). Thus, 0.04% if free T_4 which is in the blood and isn't bound to a protein. ~ 96% of T_3 is bound and 4% is free. Note you have more available T_3 to be shuttled into cells to be used as an active hormone

Systemic Roles of Thyroid Hormone

1. Increased heat production (Thermogenesis)
   a) Increases mitochondrial activity
   b) Increases Na/K ATPase activity which will assist cell maintain an electrochemical gradient.

   c) Increase in ATP hydrolysis

2. Dietary Roles
   a) An increase in caloric intake will increase the production and release of T_3. The increased [serum] will result in increased thermogenesis

3. Growth and Development
   a) Induces Nervous System Development
      i) Thyroid hormone is vital to proper neurological development. Thyroid deficiency from 11 weeks through 2 years of age can have dramatic effects the neurological development on a child

   b) Increases PRL formation
      i) T_3 and T_4 is anabolic, thus, is required for proper mammary gland maturation

<u>Pathophysiology of the Thyroid Gland</u>

HYPERTHYROIDISM (AKA Thyrotoxicosis)

1. General Effects

a.

b.

c.

d.

2. General Signs

a. Goiter

i. Can be caused by an increase in the colloid within the follicles.

ii. If T_3 and T_4 isn't being produced then the negative feedback mechanism isn't present. No negative feedback will allow both the hypothalamus and anterior pituitary gland to continuously produce TRH and TSH.

b. Exophthalmus

i. Bulging of the eyes which may develop from retro-orbital edema secondary to an autoimmune condition.

3. Disease Pathophysiology

a. Graves Disease is the most common.

b. T lymphocytes sensitize to antigens within the thyroid gland stimulating B lymphocytes to produce auto antibodies that bind to the TSH receptors

HYPOTHYROIDISM

1. General Effects

a. Decrease in BMR

b.

c.

d.

e.

f.

g.

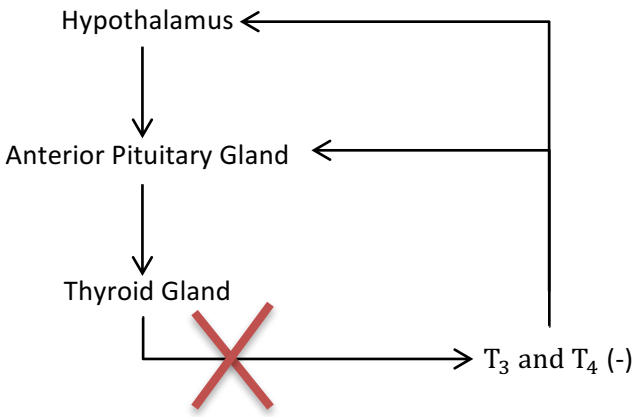
2. **Signs**
   a. Myxedema
      i. This is a generalized non pitting edema. Myexdema results from an increase concentration in the fiber deposition between the interstitial cells.

   b. Goiter
      i. A goiter will develop secondary to no T_3 or T_4 available. T_3 and T_4 cause a negative feedback mechanism. If the negative feedback mechanism isn't present them the body will consitintly produce TRH and TSH. This will result in an increase in the size of the follicular cells within the thyroid gland.

      ii. Endemic goiter

      iii. Treatment consists of surgical removal of the goiter and also medication with synthroid.

Goiter Mechanism



NOTE: If T_3 and T_4 isn't being produced then the negative feedback mechanism isn't present. No negative feedback will allow both the hypothalamus and anterior pituitary gland to continuously produce TRH and TSH. The increase production of TSH will result in an increase in the size of the thyroid follicular cells which will create a goiter

iv. Causes
   (1) Iodine Deficiency
   (2) Adult Myexdema
   (3) Onset could result from an autoimmune condition, dietary problems, surgery and radiation

c. Creatinism
   i. Generally a deficiency of thyroid hormone during neurological development of the child. Therefore, it is important the child receives proper nutrition during this developmental stage.

   SIDE NOTE:

d. Hashimoto's Disease
   i. This is a common autoimmune condition

   ii. Treatment onsists of thyroidectomy and supplementation with synthroid.

e. Thyroid Cancer
   i. Treatment
   ii. Relatively straight forward. Usually thyroidectomy and/or treatment with radioactive Iodine

Calcium Homeostasis

The parathyroid and thyroid gland will both contribute to Ca++ homeostasis

1. Ca^{2+} Functions
   a. Muscle contraction
      i. Includes skeletal muscle and cardiac muscle
      ii. smooth muscle
   b. Blood clotting cascade
      i. There is 11 steps in the entire clotting cascade and Ca++ is a cofactor in all intermediaries in every single step.
   c. Bone growth

   d. Maintain electrical membrane potential

e. Cell reproduction
   i) Mitosis and meiosis
f. Enzymatic activity

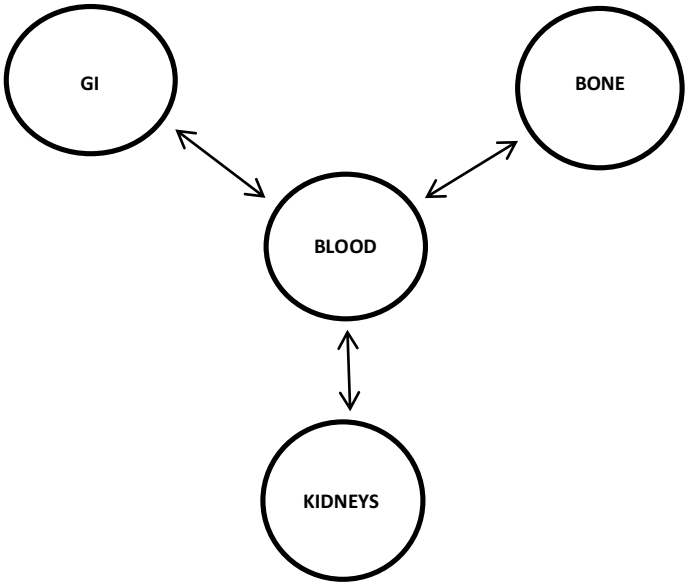
2. Target Organs
a. Bones
   i) Bones are highly vascularized structures. At any given time there is roughly 10% of your blood within your bone.
b. Liver
   i) The liver and the spleen are reservoirs for blood. If you have blood fluid volume, blood will leave the live and/or the spleen and move into the vascular tree. Pressure will move from one compartment to the other based on pressure gradient differences.
c. GI
d. Kidney

3. Ca++ homeostasis regulation is based on three different factors
a. Parathyroid hormone
b. Calcitonin
c. Vitamin D3

PARATHYROID HORMONE

1. Produced by the parathyroid gland
2. Two types of cells found here
a. Chief cells- Produce
b. Oxyntic cells
i.

3. Secretion Control
a. The parathyroid cells have Ca++ receptors on them, thus, there isn't any stimulus provided by the hypothalamus and/or the anterior pituitary gland. An increase in serum Ca++ will cause a decrease in parathyroid hormone. Moreover, a decrease in serum Ca++ will cause an increase in parathyroid hormone. The mechanism is possible via the cAMP pathway.

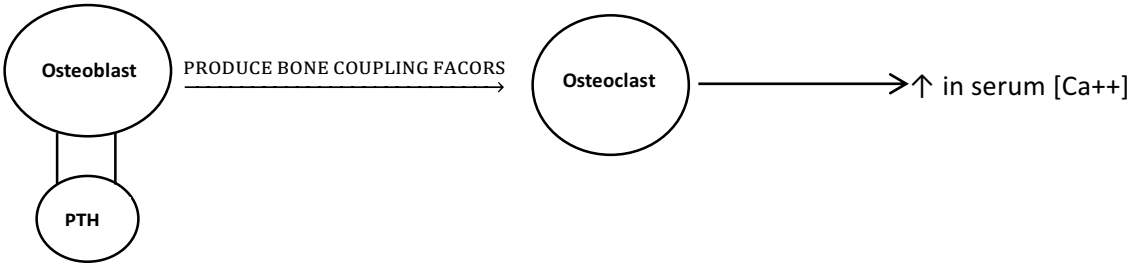


PARATHYROID HORMONE FUNCTION

1. Parathyroid Hormone Mechanism

a. Decrease in serum [Ca++] will initiate an ↑ plasma [Ca++]

i) When parathyroid hormone binds to the osteoblast receptor release of bone coupling factors will be released.



2. Renal reabsorption of Ca++

a. PTH will cause an increase in serum [Ca++]

3. **Intestinal absorption of Ca++**

- **a.** PTH will cause an increase in protein synthesis within the gut lining cells to make proteins that are transporters. These transport protein will assist by shuttling Ca++ from within the gut into the bloodstream and cause the excretion of phosphate.

Side Note: Long term prednisolone supplementation

4. **Renal excretion of phosphate**
5. **Vitamin D synthesis**
   - **a.** The active form of vitamin D is toxic. Supplementation of vitamin D will come in a different form and our body will utilize enzymes to convert it over. Some vitamin D can be synthesized from cholesterol in a reaction with the sun.

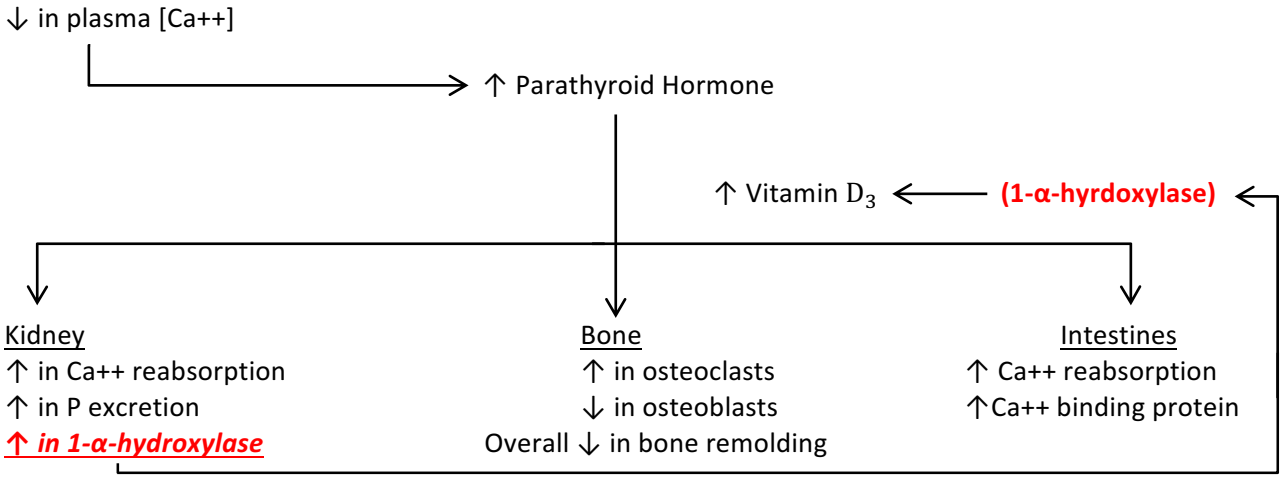
CALCITONIN

1. **Production**
   - **a.** Calcitonin is produced in the parafollicular cells of the thyroid gland

2. **Functions**
   - **a.** Decreases serum [Ca++]. Calcitonin will prevent
   - **b.** ↑in bone remodeling through an ↑ in osteoblast activity "a direct effect" → recall tones down serum Ca++, thus, it will be shuttled into the bones
   - **c.** Excretion of Na+ and Ca++ from the bloodstream with higher levels of calcitonin. Phosphate is voided in the feces and from the kidneys in the presents of calcitonin.
   - **d.** Decrease in synthesis of vitamin D_3
   - **e.** Inhibits
3. **Stimuli for calcitonin secretion**
   - **a.** ↑ in plasma Ca++ will cause
   - **b.** ↑ in circulating estrogens will result in an ↑ in calcitonin production.
   - **c.** Gastrin and CCK release will cause calcitonin to be released

4. **Calcitonin secretion decreases with age**
   a. Post-menopausal women secondary to decreased estrogen levels, sedentary lifestyles and smaller women are more prone to a decreased bone density.

Parathyroid Mechanism of Action

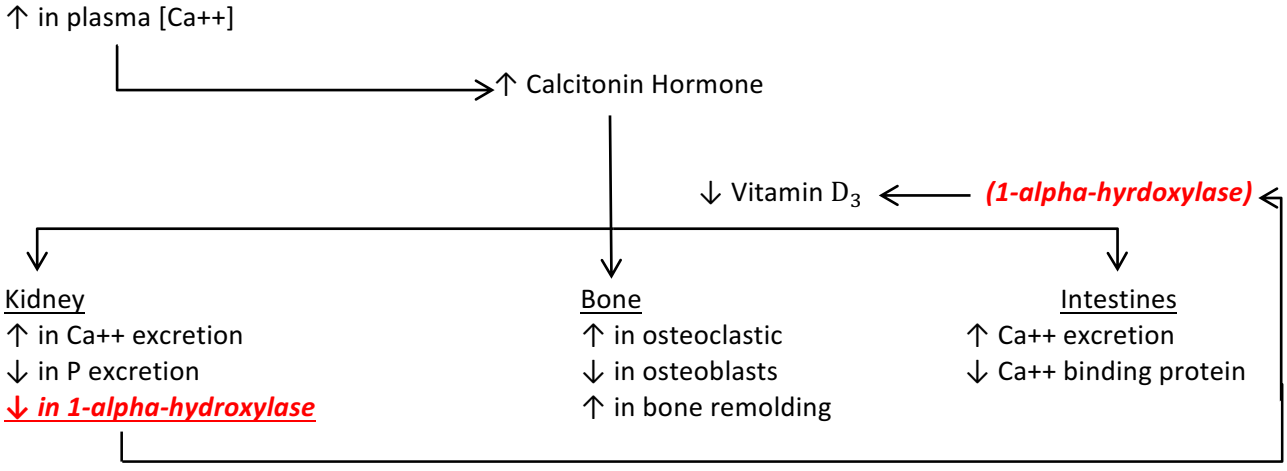


***OVERALL FUNCTION: ↑ PLASMA [Ca++] ***

HYPOPARATHYROIDISM

1. Can result from hypocalcemia secondary to hypo-polarization of the cells.

Calcitonin Mechanism of Action



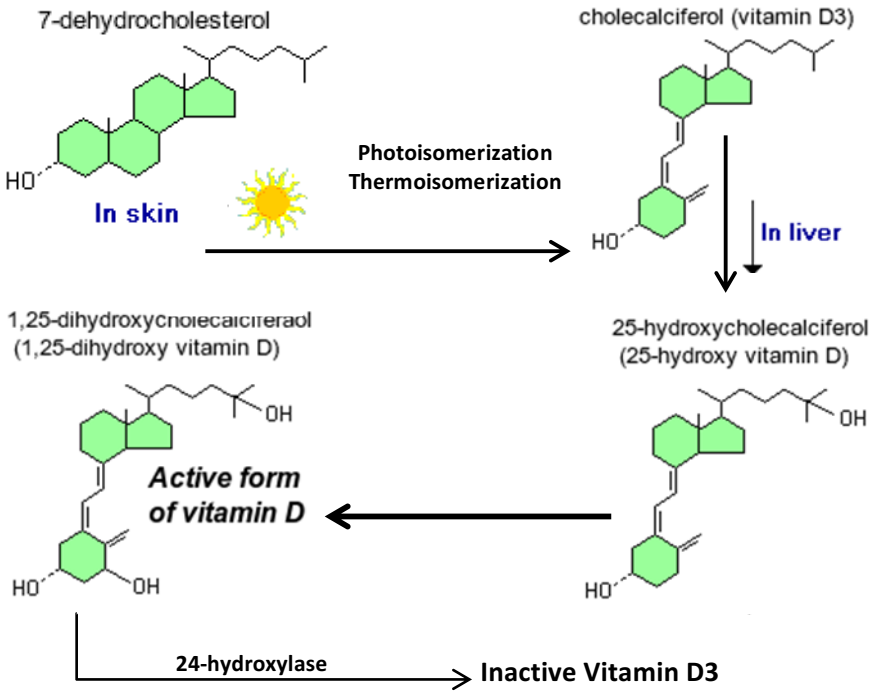
OVERALL PROCESS: ↓ PLASMA Ca++

CALCIUM HOMEOSTASIS

Vitamin D3 Pathway- (1,25-dihydroxycholecalciferol)

1. A steroid that binds to the nuclear receptors to produce mRNA for protein synthesis

SYNTHESIS LOCATION



PARATHYROID HORMONE

1. Activates 1 (alpha) hydroxylase production

Physiological Functions

1.

2.

Gastrointestinal Hormones

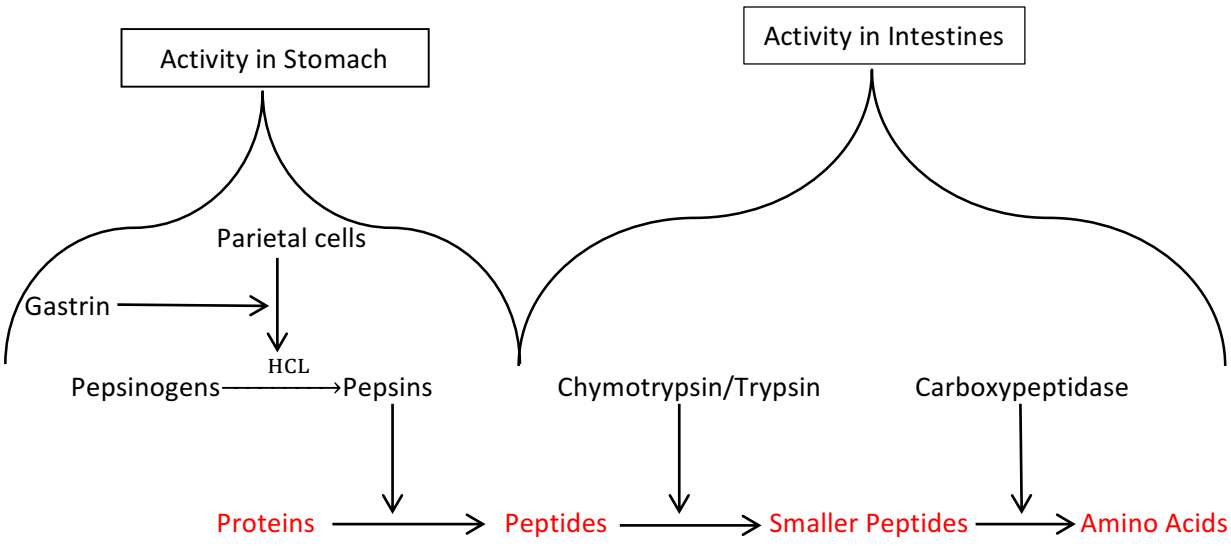
1. **Utilizes peristalsis to propel food through the digestive tract**
2. **Accessory Organs**
   a. **Pancreas**
      i. Exocrine-
      ii. Endocrine-
   b. **Salivary Glands**-Digest starches
      i. Secrete
   c. **Gallbladder**-vital for fat emulsification
      i. Function-
   d. **Liver**
      i. Metabolize nutrients traveling through it

CARBOHYDRATE METABOLISM

1. Degrade complex carbohydrates into simple sugars
   a. Saliva:
   b. Intestines:

PROTEIN METABOLISM

1. Begins in the stomach → continues in the intestines



FAT METABOLISM

Triglycerides $\xrightarrow{\text{Pancreatic Lipase}}$ Free fatty acids and glycerol

1. Begins in the intestines
2. Bile salts
3. Free fatty acids transported

GI HORMONES

1. **General characteristics**
   - **a.** Produced by
   - **b.** Clear in color
   - **c.** Diffusely located throughout the small intestines, stomach and large intestines
   - **d.** Gastroenterohepatic hormone: pancreatic hormones and enteroendocrine hormones
   - **e.** Paneth Cell-

GI HORMONE FAMILIES

1. **Gastrin family** – gastrin and cholecystokinin
   - **a. Functions**
     - **i.** ↑ in
     - **ii.** ↑in
     - **iii.** ↑ in
     - **iv.** ↑ in

overall response???

2. **Gastric acid secretion**

Pepsinogen $\xrightarrow{\text{HCl (from parital cells)}}$ Pepsin $\xrightarrow{\text{Allow for the conversion}}$ Proteins ↓ Peptides

*****An increase in HCl secretion will increase pepsin production*****

   - **a.** Gastrin, Acetylcholine and Histamine will increase in activity

GASTRIN FAMILY: (GASTRIN, CHOLECYSTOKININ)

GASTRIN

1. **Production**
   - **a.** Produced by the **G cells** in the stomach atrium and duodenum
2. **Three types**
   - **a.** A 34 amino acid gastrin molecule
   - **b.** A 17 amino acid gastrin molecule
   - **c.** A 14 amino acid gastrin molecule which
   - **d.** The last 5 amino acids in the gastrin molecule
3. **Pentagastrin**
   - **a.** This is a synthetic form of gastrin, thus, it's not uncommonly prescribe to pt's The last 5 amino acids and its COOH group is different, thus, the last 5 amino acids probably confirm most of its activity.
4. **Gastrin Release**
   1. An ↑in protein within the stomach will cause an
   2. Fats confers very little biological activity, thus,
   3. Carbohydrates will

5. **Gastrin Primary Function**
   - **a.** The main function of gastrin release is to ↑ the production of HCl secretion from partial cells***
   - **b.** HCl Functions
     - **(1)** HCl will cleave pepsinogen into pepsin. Recall this is the beginning of protein digestion
     - **(2)** HCl will kill viruses, bacteria that enter the stomach
     - **(3)** HCl is highly reactive, thus, most macromolecules can be degraded
6. **Gastrin Secondary Function**
   - **a.** ↑ production of pancreatic enzymatic secretion
   - **b.** ↑ gastric motility in the stomach and within the intestines
   - **c.** Gastrin will begin to cause relaxation of the pyloric sphincter which will allow chyme to enter the duodenum.

   - **d.** ↑ in mitotic activity within the cells lining the gut and in the acinar cells within the pancreas. The lining within the stomach is only 1 layer thick.

CHOLECYSTOKININ (CCK)

1. **CCK Production**
   a. Cholecystokinin It is produced by the **enteroendocrine "I" cells** which are located within the duodenum, jejunum and the ileum. Within the gastric pits we have the both chief cells and partial cells; these are the dominant cells within the stomach.

2. **CCK Release**
   a. CCK will be released in response to an ↑ in the concentration of amino acids, fatty acids and HCl
3. **Active CCK**
   a. Active CCK is comprised of 8 amino acids.
4. **Similar to Gastrin**
   a. The last 5 amino acids and COOH group are exactly the same as those in gastrin. CCK 7th amino acid is different from gastrin. Similar in structure but with very different function.
5. **CCK Physiological Function**
   a. ↑ in pancreatic enzyme secretion into the duodenum. Once the food starts to empty into the duodenum CCK will cause an increase in pancreatic enzyme secretion.
   b. Involved in the contraction of the gallbladder
   c. Involved in ↑ pancreatic acinar cell mitosis
   d. Stimulates intestinal cell mitosis
   e. ↓ in gastric emptying to ensure we don't overwhelm the duodenum with too much chyme
   f. Initiation of HCO_3^- secretion from the pancreas, thus, HCl will be buffered

SECRETIN FAMILY: (SECRETIN, GIP, VIP, SOMATOSTATIN)

Secretin-

1. **Production**
   a. Secretin is secreted from **enteroendocrine "S" cells** of the small intestines
2. **Actions**
   a. Induces pancreatic enzymes secretion
   b. Inhibits gastrin secretion
   c. Inhibits gastric motility
   d. Stimulates additional HCO_3^- secretion.
3. Secretin stimulation when acidic chyme enters the duodenum

Gastro-Inhibitory Peptide (GIP)

1. **GIP Production**
   a. Secreted by the **enteroendocrine "K" cells** which line the first half of the intestines. They are produced in response to either fat or glucose present within the small intestine
2. **Actions**
   a. GIP
   b. GIP
   c. GIP will inhibits glucagon by slowing down lipolysis. A ↓ lipolysis will ensure we preserve stored energy.
   d. GIP will activates lipoprotein lipase to take fats from the bloodstream and store it within cells

Vasoactive Intestinal Peptide (VIP)

1. VIP is a powerful vasodilator

Somatostatin

1. **Produced**
   a. Somatostatin is produced by the **"Delta" cells** of the pancreas
2. Somatostatin Actions
   a. Generally inhibitory 4 – 6 hours after meals
   b. ↓ in pancreatic activity (acinar and Islets)
      i) ↓ in insulin and glucagon production
   c. ↓ in acid production within the stomach

Ghrelin

1. Released from stomach and liver

Amylin

1. Co-secreted with insulin from B cells in pancrease

Oxyntomodulin

Leptin

1. Made by adipose cells

Motilin

1. Secreted by enteroendocrine cells

ANS Control of the Digestive System

Anticipation Phase

1. Acetylcholine is released and targets muscarinic receptors. The stimulus results from Vagus nerve signals.
2. Stimulates gastric acid secretion.
3. Stimulates salivary gland secretion

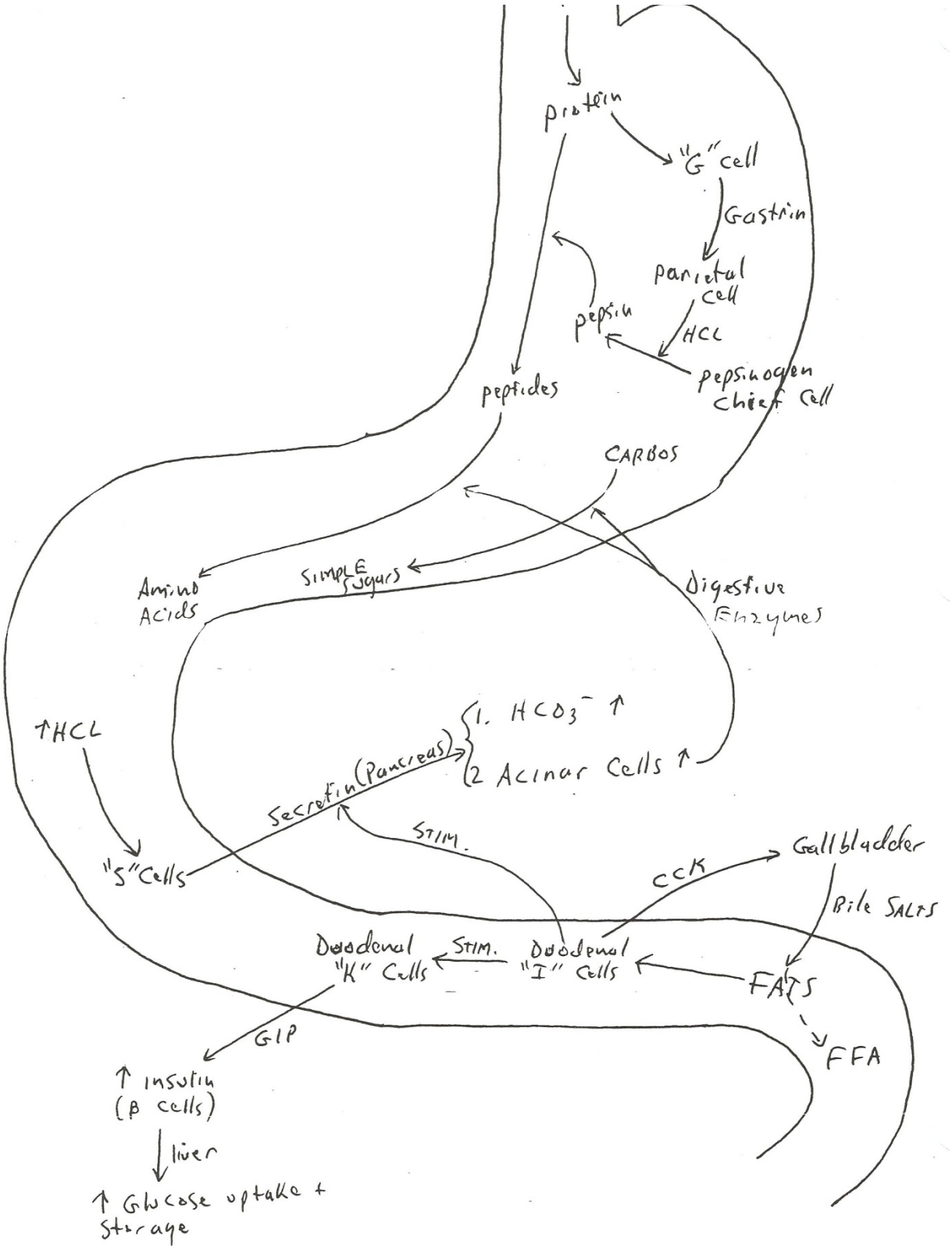
Digestion Phase

1. Tactile phase resulting from food in the gut. This results in a dramatic ↑ in enteroendocrine cell production

Intrinsic Nervous System

1. **Myenteric Plexus**
   a. Plexus innervates the outer two layers of the intestines and is responsible for peristalsis and churning of the intestines. The outer two layers contain circular muscle fibers and horizontal muscle fibers.
2. **Submucosal Plexus**
   a. Innervates the muscular mucosal layer (inner muscular layer) of the intestines and is responsible for assisting in intestinal folding
   b. Is capable of also causing contraction and vasodilation of the blood vessels surrounding the intestines which will allow for diversion of blood to other areas of the body or to increase absorption after we eat.
3. **PNS:**
4. **SNS:**

Digestion Overview



PANCREATIC SECRETIONS

Exocrine Pancreas: Main function of digestion via the acinar cells

1. **Ductal Cells**
   a. Produce HCO_3^- to buffer the acidic chyme.

2. **Acinar Cells**
   a. Digestive enzymes are produced here

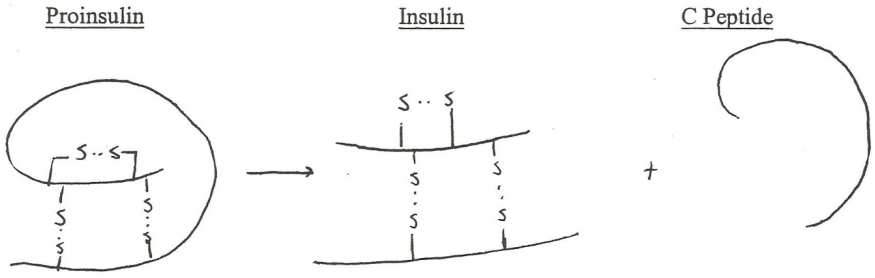
Endocrine Pancreas- 5% of the mass is represented by the Islets of Langerhans

1. **α Cells**- Glucagon secertion
2. **β Cells**- Insulin, amylin, C peptide-proinsulin
3. **Δ Cells**- Somatostatin

Insulin Structure

A protein consisting of 2 polypeptides units: α Subunit and β Subunit

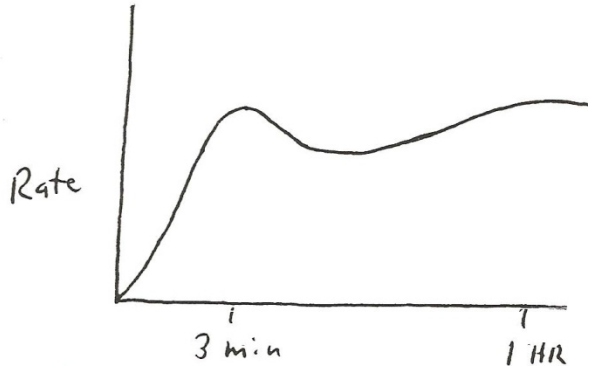
Synthesized initially from a single gene as pro-insulin



Synthesis and Secretion of Insulin

BIPHASIC RELEASE

1. Initial Release
2. Sustained Release



FACTORS CONTROLLING THE RELEASE OF INSULIN

1. **Glucose Levels**
   a. An unidentified sensing mechanism exists. Probably an unidentified membrane receptor-membrane receptor on beta cells
2. **Ingestion of proteins/fats-** Especially proteins
3. **Autonomic Nervous System**
4. **Other Hormones**
5. **Glucose Sensing Mechanism**

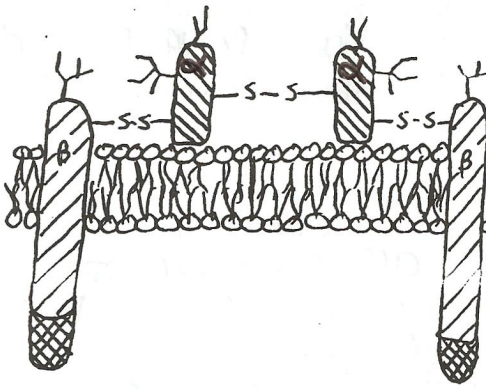
DEGRADATION OF INSULIN AT 3 MAIN SITES

1. **Liver**
   a. Has an ` ½ life of 5 minutes and the sulfide bonds are degraded

2. **Kidneys**
   a. Via glomerular filtration
3. **Pancreas**
   a. Insulin protease via cleavage

INSULIN TRANSMEMBRANE RECEPTOR

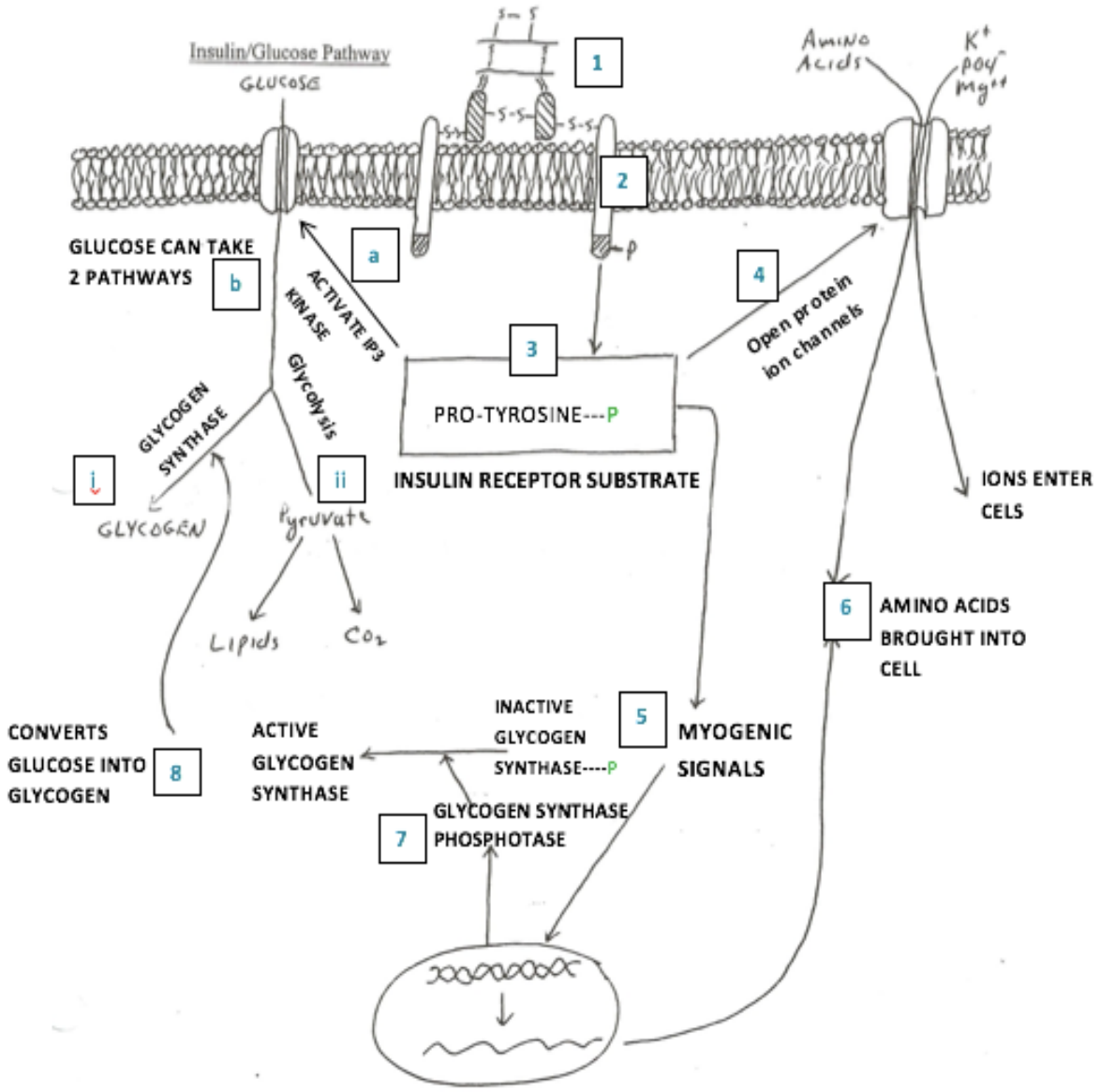
1. **General Characteristics**
   a. **α Subunit:** Attached to the cells outer membrane within the extracellular matrix on
   b. **β Subunit:** Has a receptor tyrosine kinase which is located within the cell



Insulin Function within the Target Cell

1. Insulin binds to the α subunit
2. Activation of tyrosine kinase
3. Phosphorylation of cellular proteins
4. Activation of phosphotase
5. Transport of glucose across the membrane

INSULIN/GLUCOSE PATHWAY



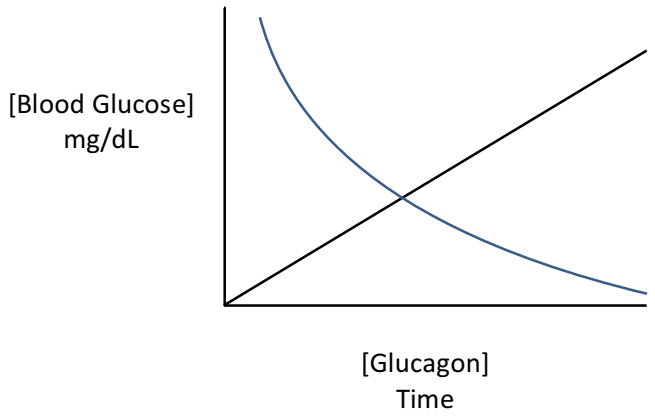
INSULIN/GLUCOSE PATHWAY MECHANISM

1. Insulin binds to alpha receptor followed by activation of the tyrosine kinase residues
2. Tyrosine-protein molecule is brought in, ATP → ADP. The tyrosine-protein is phosphorylated to activate the intracellular pathway. **The phosphate comes from the ATP**
3. Insulin Receptor Substrate- Phosphorylates to activate the protein
   a. IP3 kinase is activated to open GLUT 4 transporter which will allow glucose to enter the cell
   b. After glucose enters 2 pathways are possible
      i. Glycogen Synthase- glucose storage after conversion to glycogen
      ii. Glycolysis → sugar → 2 pyruvates → CO2 and glucose
4. Activated phosphorylated protein will open other extracellular channels to allow other amino acids and electrolytes to enter the cell. These substrates will assist in protein formation
5. Activated phosphorylated protein → myogenic signals where transcription factors are activated followed by initiation of the RAS MAPK pathway.
6. Protein synthesis begins from raw materials which were brought into the cell.
7. Glycogen synthase phosphatase will convert inactive glycogen synthase into active glycogen synthase.
8. Active glycogen synthase will convert glucose into glycogen

GLUCAGON

1. Involved in glucose homeostasis
2. Functions:
3. A member of the secretin family. Glucagon maintain a very similar structure to the secertin family but exhibits a very different function

[Glucagon] and [Glucose] Over Time



*****As serum [glucose] decrease, the [glucagon] will increase*****

GLUCAGON SECRETION

1. Possibly a glucose sensory mechanism on the alpha cells
2. Secondary response
   a. An increase in protein release into the blood will cause
   b. Amino acids
   c. Fats
      i. ↑ in free fatty acid circulation within the blood

MECHANISM

1. **Primary Actions**
   a. **Glycogenolysis:**
   b. **Gluconeogensis**: Creation of glucose or other energy sources from molecules other than glycogen
2. **Secondary Actions**
   a. **Lipolysis:** Breakdown of fats into free fatty acids that will enter the bloodstream and be available as a source of energy. If the free fatty acids aren't used as energy they will be restored within the cells.

SOMATOSTATIN

Somatostatin Production

1. Produced

Somatostatin Functions

1. **Pancreas:** Inhibited
2. **Calcitonin:** tones down serum Ca++ and ↑ one remodeling, thus, somatostatin will inhibit calcitonin
3. **Pituitary Gland:** Inhibits HGH production
4. **GI Hormones**: Inhibits digestion

Diabetes Mellitus

Symptoms

1.
2.
3.
4.

TYPES OF DIABETES

a. Insulin Dependent (IDDM, Type I

i. ↓ in β cells and a ↓ in insulin production

b. High levels of auto antibodies against tissue

c. Treatment: Insulin

d. Brittle or Labile Diabetes-hard to control type 1 diabetes

Latent Autoimmune Diabetes of Adulthood

b. Non-insulin Dependent (NIDDM, Type II

a. Insensitivity to insulin

b.

c. Almost non-existent-

c. Alzheimer's Disease

a.

b.

c.

d. Maturity Onset Diabetes of the Young

a. Typically inherited. Compared to type II diabetes

b. Usually not overweight

e. Gestational Diabetes

a.

b.

f. Daibetes Insipidus

a.

b.

c.

Pre-receptor resistance, receptor resistance and post receptor resistance.

We can develop antibodies to insulin receptors, blocking intracellular activation of insulin. There are insulin receptor mutations seen in conditions like Donohue's syndrome where these patients have elf-like characteristics-this condition used to be called leprechanism. Insulin is produced but is not able to bind to the receptor as in familial partial ppilodystrophy. We can see a decreased number of receptors commonly seen in Polycystic ovarian syndrome.

i) ß-Cell Burn out: Pancreatic ß-cells are unable to produce sufficient insulin to maintain normal blood sugar levels.

(1) If exercise does not help pre-and post-work out blood sugar, then patient most likely has this condition.

(a) Are these cells being destroyed (decreasing beta cell numbers) or are they simply not able to produce enough insulin because of overuse, much like adrenal fatigue.

INSULIN ABSENCE OR INSULIN RECEPTOR ACTION

1. Inactive Glycogen Synthetase

2. Increased Lipolysis/Decreased Cellular Glucose

a. A ↑ in serum free fatty acids and glycerol secondary to the breakdown of triglycerides. Moreover, ketone body formation from the utilization of other molecules as an energy source.

i. **Metabolic Acidosis:**

ii. **Beta hydroxybutyric acid has a low pKa which helps drive the blood to acidity**

(2) Ketones are excreted from the body in urine:

(3) With the excretion of Na+

(a) NaHCO3 is lost in urine decreasing the buffering capability of blood.

TREATMENT IN Type 2 diabetes

1. **Decreased tissue response to insulin** : Increases the need for insulin
   a. Decreased Insulin demand
      i. Obtained via weight reduction with exercise
   b. Oral Treatment
      i. **Sulfonylureas:** ↑ insulin production and release
2. **Diet** : GOAL →
   a.
   b.
   c.
   d.
3. **Exercise**
   a.
   b.
   c.
4. **Hypoglycemic Agents for type 2 diabetics**
   a. Oral Treatments
      i. **Sulfonylureas:**
      ii. **Meglitinides:**
      iii. **Biguanides:**

iv. **Dipeptidyl peptidase (DPP-4) Inhibitor:**

Type 1 Diabetes -Humalog

NOTES PAGE

(Fasting BS, A1C, Post Prandial BS) + Side Note: Diabetes Implications of Cardiovascular Disease and Polyneuropathy

1. **Metabolic Syndrome**
   a.
   b.
   c.

2. **Blood Sugar levels**
   a.
   b.
   c.

3. **Fasting Blood Sugar levels**
   a.
   b.

4. **A1C**
   a.
   b.
   c.
   d.
   e.
5. **Polyneuropathy**
   a. **Vessels basement membranes thicken=endothelial damage of very small delicate capillary beds**

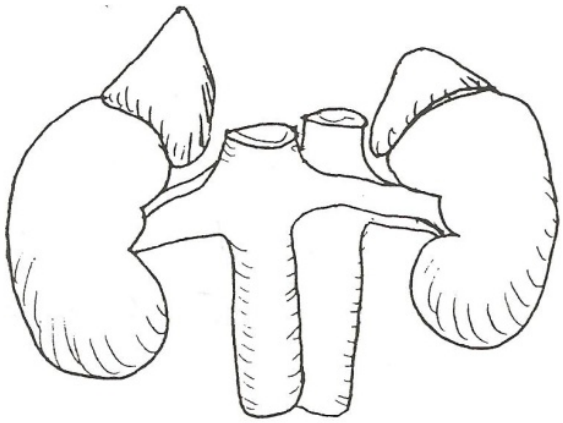
6. **Cardiovascular disease-global endothelial damage.**

ADRENAL MEDULLA

The Catecholamine:

1.
2.

Adrenal Glands



1. **Cortex**
   a. Steroidgenic Cell Types
   b. Secretes
2. **Medulla**
   a. Neural Crest Tissue:
      i. Derived from neural tissue which was originally ectoderm
   b. Adrenal medulla + Sympathetic nervous system =
   c. Secretes catecholamines:
      i. **Epinephrine** (~80%) – Broken down by
      ii. **Norepinephrine** (~20%)- Broken down by

NOTE: The sympathetic nervous system mainly secretes

AUTONOMIC NERVOUS SYSTEM:

1. ANS neurons innervate viscera vessels, skin, heart, GI tract, skeletal muscle, kidneys, bronchial passageways and potentially the pancreas and liver
   a. Vasomotor Neurons
   b. Secretory Neurons

Parasympathetic Nervous System:

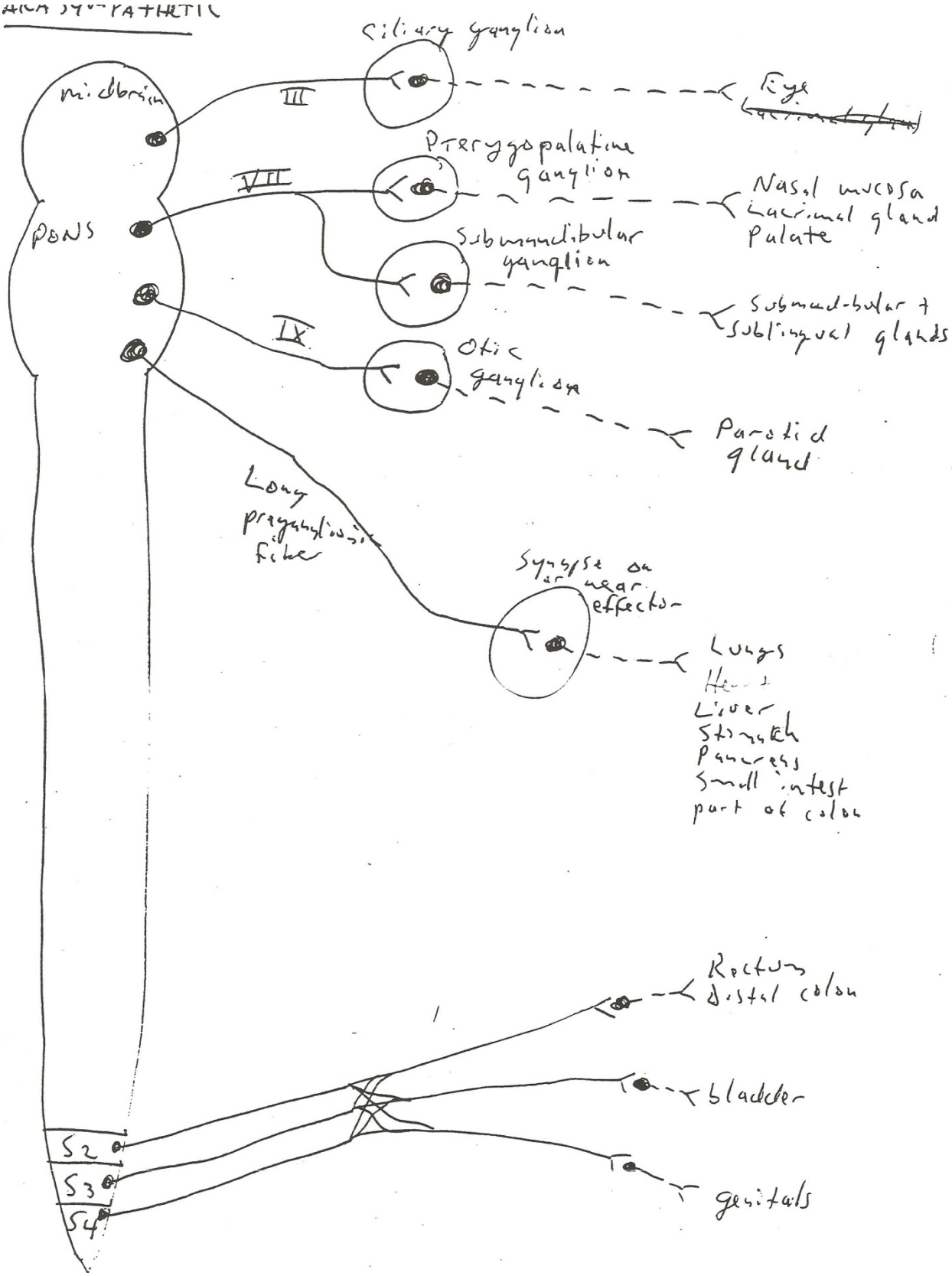
1. Nerve origination is off of the brainstem and off of S1, S2 and S3 (pelvic splanchnic nerves)

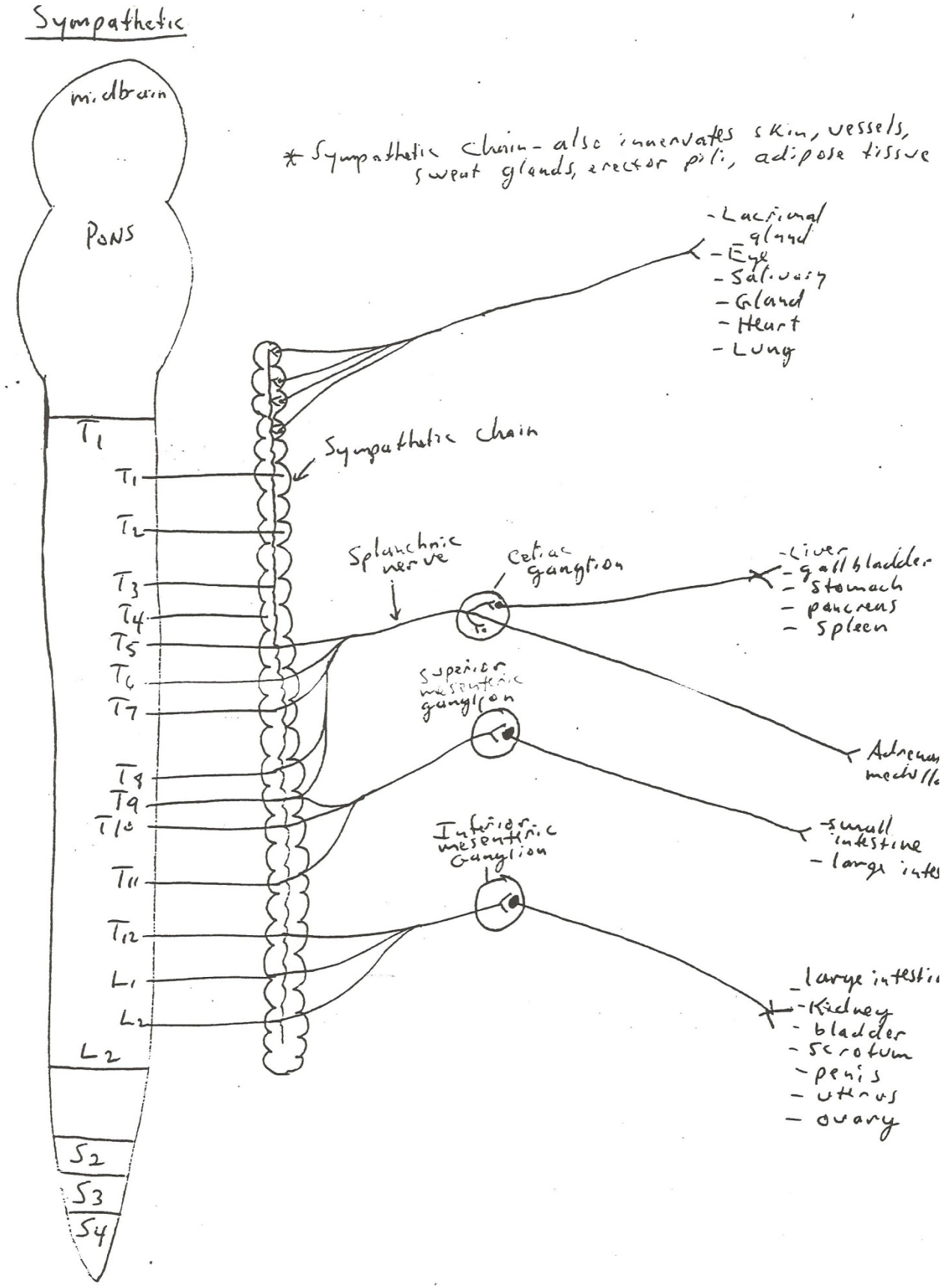
Sympathetic Nervous System:

1. Nerves originate off of T1 – L2
2. Celiac, Superior mesentery and Inferior mesentery ganglion

Preganglionic Neurons

1. Postganglionic – Parasympathetic NS
2. Postganlionic – Sympathetic NS

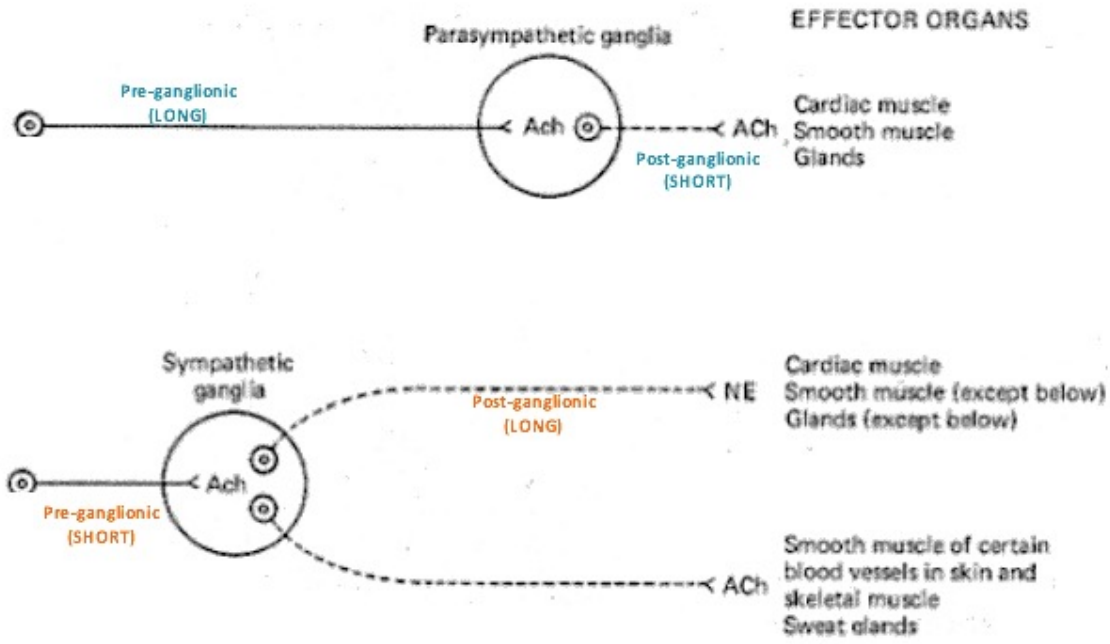

PARASYMPATHETIC
midbrain
PONS
III
VII
IX
Ciliary ganglion
Eye
Pterygopalatine ganglion
Nasal mucosa
Lacrimal gland
Palate
Submandibular ganglion
Submand-bular + Sublingual glands
Otic ganglion
Parotid gland
Long preganglionic fiber
Synapse on or near effector
Lungs
Heart
Liver
Stomach
Pancreas
Small intest
part of colon
Rectum
distal colon
bladder
genitals
S2
S3
S4


Sympathetic
midbrain
PONS
* Sympathetic chain - also innervates skin, vessels, sweat glands, erector pili, adipose tissue
- Lacrimal gland
- Eye
- Salivary Gland
- Heart
- Lung
Sympathetic chain
T1
T1
T2
T3
T4
T5
T6
T7
T8
T9
T10
T11
T12
L1
L2
L2
S2
S3
S4
Splanchnic nerve
Celiac ganglion
- Liver
- gall bladder
- stomach
- pancreas
- Spleen
Superior mesenteric ganglion
Adrenal medulla
- small intestine
- large intes
Inferior mesenteric ganglion
- large intesti
- Kidney
- bladder
- Scrotum
- penis
- uterus
- ovary

ADRENAL MEDULLA

Autonomic Neurotransmitters

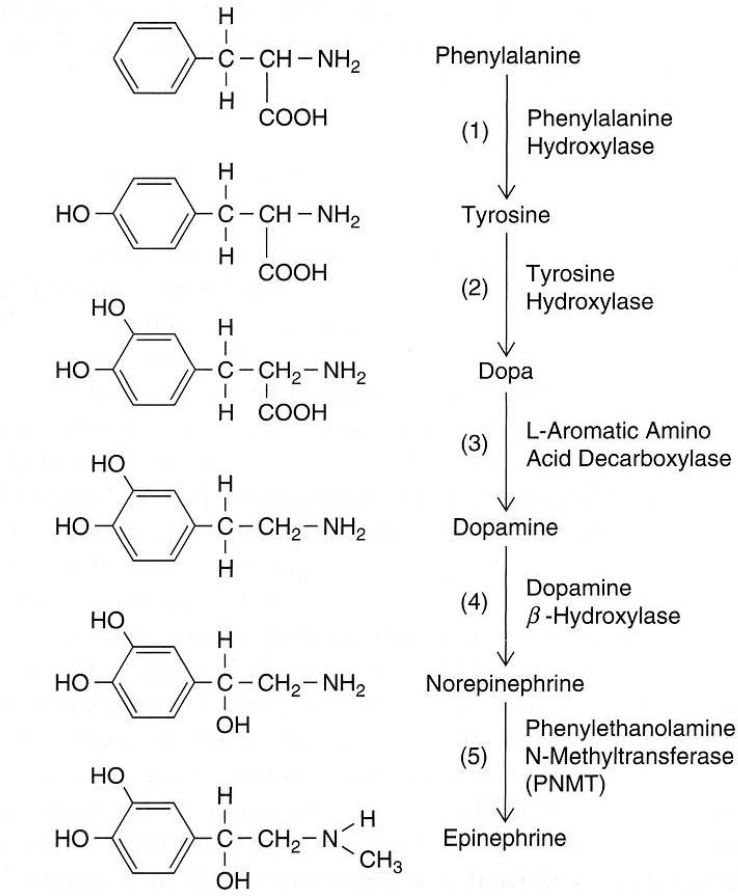
1. **Cholinergic Fibers release acetylcholine (ACH)**
   - **a.** ACH is released from all preganglionic ANS fibers. This includes both parasympathetic and sympathetic fibers.



   - **b.** ACH is released from all postganglionic parasympathetic fibers. The effects are short lived and local secondary to the presence of acetylcholinesterase.
2. **ACH Post-Synaptic Receptor Sites**
   - **a.** The effects on the target organ dependent on the receptor on that organ
     - **i. Nicotinic Receptors**
       - **(1)** Receptor for ACH on the post-ganglionic synapse (dendrites + cell body).
       - **(2)** Results: They will cause firing of all the parasympathetic and sympathetic postganglionic nerve fibers.
     - **ii. Muscarinic Receptors**
       - **(1)** Receptor for ACH on all the parasympathetic target organs and some sympathetic target organs.
       - **(2)** Results: The results are variable; can cause excitation or inhibition. It just depends on the organ

CATECHOLAMINE SYNTHESIS

1. Phenylalanine is the precursor for tyrosine



Parkinson ’s disease

DOPA will cross the blood brain barrier but dopamine will not.

ADENORECEPTORS

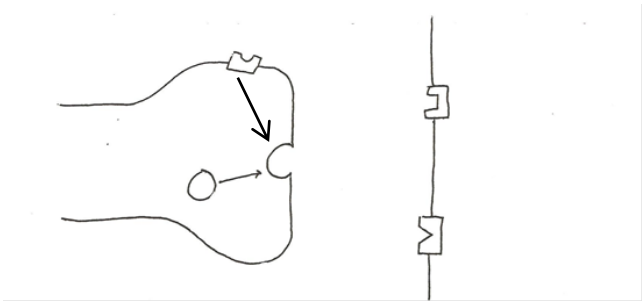
1. **Alpha Receptors (α)**
   - **a. α_1 Receptors**
     - **i.** PRIMARILY STIMULATORY
     - **ii.** Postsynaptic receptor
     - **iii.**
     - **iv.** PKC activating
   - **b. α_2 Receptors**
     - **i.** PRIMARILY INHIBITORY
     - **ii.** Presynaptic receptors
     - **iii.** Will bind catecholamine's
       - **(1)** Bind epi/norepi on the presynaptic receptor to prevent future release of epi/norepi
       - **(2)**
       - **(3)** Receptors also found on the cholinergic neurons (secrete ACH).
       - **(4)**
       - **(5)** Also present in vascular smooth muscle to induce contraction; activate G Inhibitory protein
2. **Beta Receptors (β)**
   - **a. β_1 Receptors**
     - **i.** Cardiac muscle – on both the atria and ventricles
       - **(1)**
       - **(2)**

NOTE: Beta Blockers

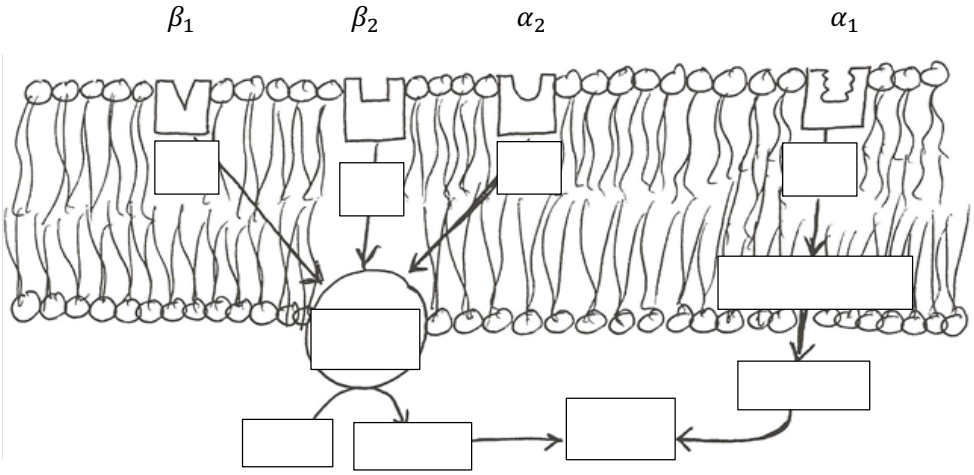
     - **ii.** Adipose tissue
       - **(1)**
   - **b. β_2 Receptors**
     - **i.** Location
       - **(1)** Vascular
       - **(2)** Bronchiolar
       - **(3)** Uterus smooth muscle
       - **(4)** Skeletal muscle
       - **(5)** Liver

     - **ii.** Will cause vasodilation

SYMPATHETIC NS NEGATIVE FEEDBACK MECHANISM



MULTIPLE MECHANISMS FOR SIGNAL TRANSDUCTION



Physiological Actions

Primarily to maintain homeostasis. Any decrease in blood pressure, plasma glucose or O2 levels will increase activity to reverse these processes

1. **Cardiovascular System**
   - **a.** Heart
     - **i.**
   - **b.** Vascular Smooth Muscle
     - **i.** ↑ in vasoconstriction
     - **ii.** Coronary, bronchial and skeletal muscle vasodilation

2. **Respiratory System**
   a. Bronchial smooth muscle relaxation via
3. **Metabolism**
   a. **CHO**
      i. ↑in serum glucose levels via hepatic gluconeogenesis
      ii. Promotes glycogen secretion via
      iii. Inhibition of insulin from pancreas via
   b. **Fat**
      i. Promote lipolysis via β1receptors
4. **Secondary Functions**
   a. **Adrenal Cortex**
      i. Induces the formation of (PMNT):

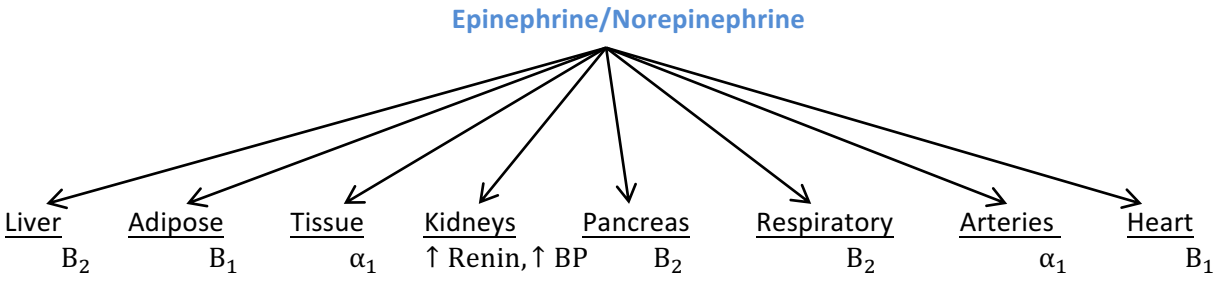
      ↑ in cortisol → ↑ in PMNT production → ↑ the release of norepi → ↑ the release of epi

   b. **Renin-Angiotensinogen Aldosterone System**

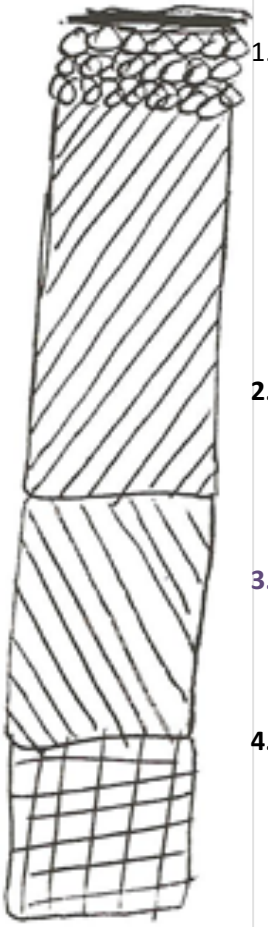
NOTE:

   c. **Pancreas**
      i. β_2 receptors → ↑ glucagon secretion
      ii. α_2 → ↓ insulin production

GENERAL CATECHOLAMINE FEEDBACK MECHANISM



HORMONES OF THE ADRENAL CORTEX



1. **Zona Glomerulosa:** (Outermost Zone)

   Produces Mineralo-Corticioids

2. **Zona Fasiculata:**

   Involved in producing Glucocorticoids:

   i.

   ii.

3. **Zonal Reticularis:** (Inner most Zone)

   Produces small amount of

4. **Medulla**

CONTROL OF THE DIFFERENT SECTIONS

1. **Glucocorticoids**
   - **a.** Produced in the **zona fasciculata** and regulated by
     - **i.** Hypothalamus
     - **ii.** Anterior Pituitary
   - **b.** Primary Action
     - **i.** Regulates carbohydrate metabolism and stimulates glycogenolysis

c. Diurnal Release: _____

i. Release affected by

(1) Fever

(2) Psychosis

(3) Stress

(4) Hypoglycemia

2. Physiological Action: Almost every cell in the body has receptors for cortisol, but there are a large number of receptors on

a.

b.

c.

The Nuclear Receptor: A DNA binding protein

Activation of DNA Binding Protein: Occurs through a conformational change

3. Intermediary Metabolism

a. Increase in synthesis of gluconeogenic enzymes

b. Catabolic reactions

c. Amino acid transport to the liver

d. Glucose uptake by tissues

4. SYNERGISTIC ACTIONS: Synergistic action to other hormones

a. Required for proper SNS function

b. Helps maintain temp

c. Synergistic to EPI and glucagon

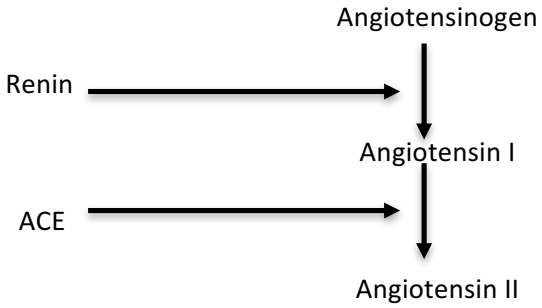
ANTI-INFLAMMATORY RESPONSE: Stages of Inflammation

1. Vascular Stage-

2. Cellular Stage-

NOTE: Glucocorticoids slow down or inhibit many processes and inhibit the immune system-

5. **Aldosterone** Produced by the **zona glomerulosa** of the adrenal cortex



   a. **Location for Renin production:**
      i. **Renin's primary role:**

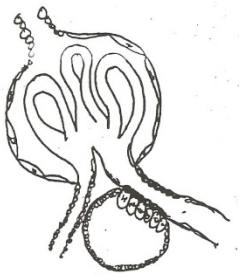
      ii. **<u>Renin's effect on the adrenal cortex</u>**

   b. **Aldosterone's effect on the kidney's**:

<u>Target Cells:</u> Collecting duct

Various hypotheses on how aldosterone works on these cells

Blood Volume and Blood Pressure Regulation



ALDOSTERONE FUNCTIONS

Renin/Aldosterone System

1. The Juxtaglomerular Apparatus

a. The JG cells

b. The Macula Densa

2. The Secretion of Renin

a. A decrease in extracellular volume

b. Stimulation of the SNS

c. Decrease firing of the stretch receptors in afferent arteriole

ANGIOTENSIN II FUNCTIONS

1. A very powerful vasoconstrictor

a. Aldosterone

b. Smooth muscle

c. Neurons of brain

d. Ganglionic transmission

e. Norepi synthesis

f. Thirst

2. Overall Function: _____

a. Angio II type I receptor

b. Angio I type II receptor

REGULATION OF H_2O /Na^+ BALANCE

1. Atrial Natriuretic Peptide release

a. Functions:

i. _____

ii. _____

iii._____

iv._____

b. General Stimulus for release: _____

c. Overall Result: _____

2. Aldosterone

3. ADH

a. Produced: _____

b. Function: _____

i. Baroreceptor

(1) Carotid and aortic arch

(2) Low pressure in the left atria

(3) High pressure in the aortic/carotid arteries

ii. Hypothalamic Osmoreceptors

iii. Angiotensin II

iv. Norepinephrine

c. Actions of ADH

i. V1 receptors

ii. V2 receptors

iii. Renal

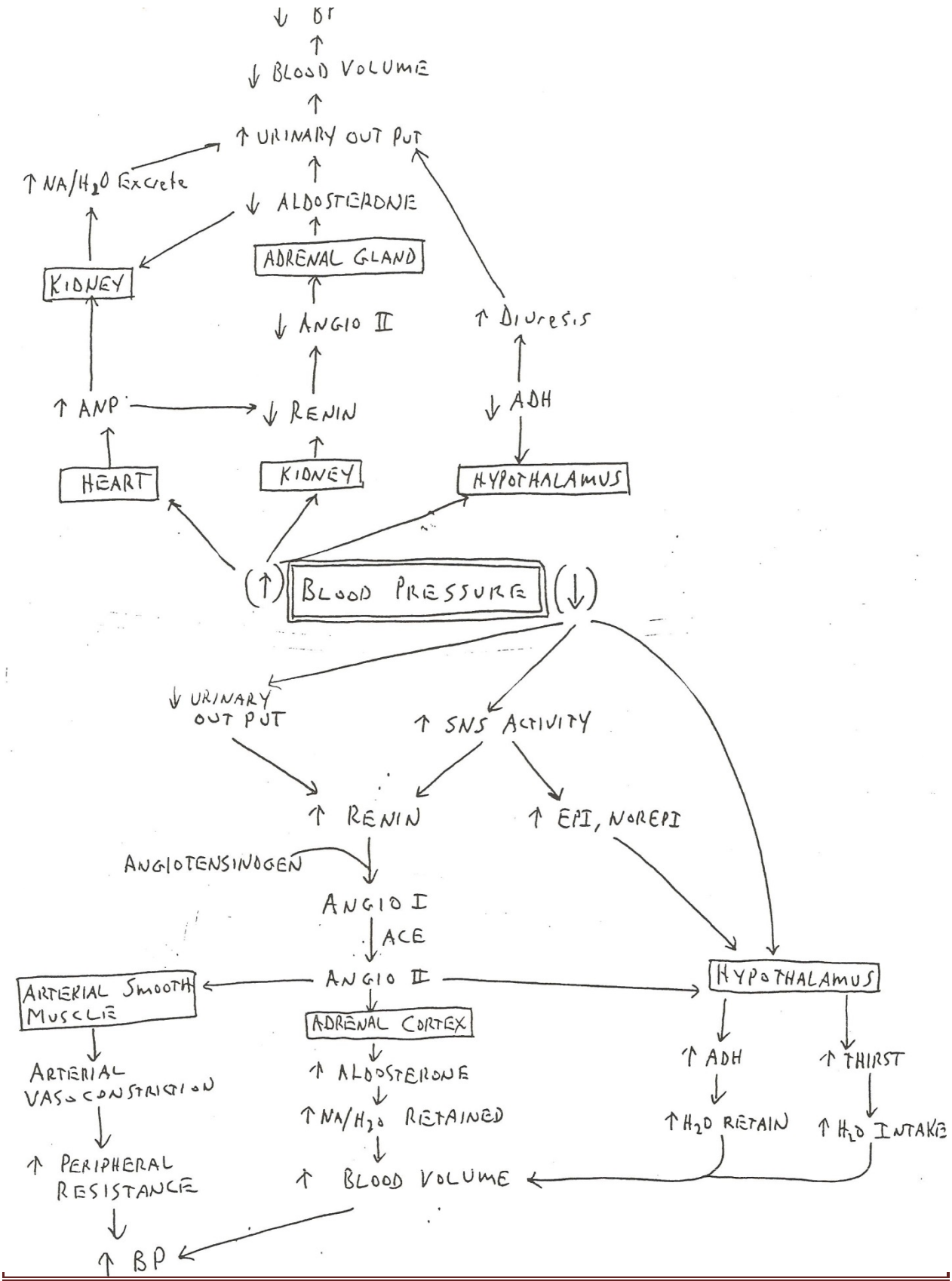
iv. Vascular smooth muscle

v. Liver

EPO-

Addison's Disease-

Cushing's Disease-


↓ BP
↓ BLOOD VOLUME
↑ URINARY OUT PUT
↑ NA/H2O Excrete
↓ ALDOSTERONE
ADRENAL GLAND
KIDNEY
↓ ANGIO II
↑ Diuresis
↑ ANP
↓ RENIN
↓ ADH
HEART
KIDNEY
HYPOTHALAMUS
(↑) BLOOD PRESSURE (↓)
↓ URINARY OUT PUT
↑ SNS ACTIVITY
↑ RENIN
↑ EPI, NOREPI
ANGIOTENSINOGEN
ANGIO I
ACE
ARTERIAL SMOOTH MUSCLE
ANGIO II
HYPOTHALAMUS
ADRENAL CORTEX
ARTERIAL VASOCONSTRICTION
↑ ALDOSTERONE
↑ ADH
↑ THIRST
↑ PERIPHERAL RESISTANCE
↑ NA/H2O RETAINED
↑ H2O RETAIN
↑ H2O INTAKE
↑ BLOOD VOLUME
↑ BP

Reproductive Endocrinology

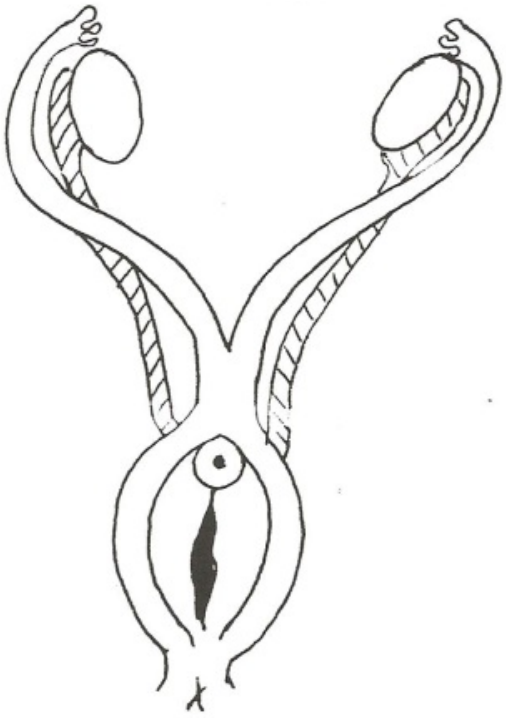
General Genetics

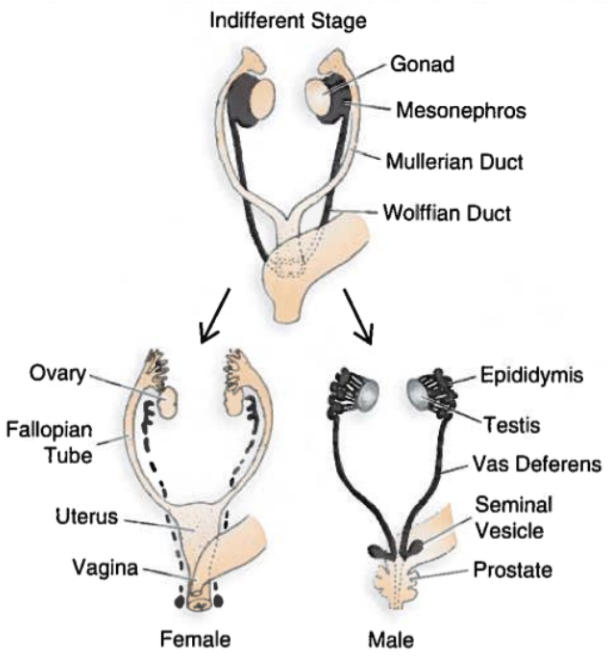
1. Gametes
    - **a.** Ova 23 chromosomes, donates
    - **b.** Sperm 23 chromosomes, donate

Sex Differentiation

1. Gonads

- **a.** The sex of an individual is generally determined by hormones produced at the testis or ovary.

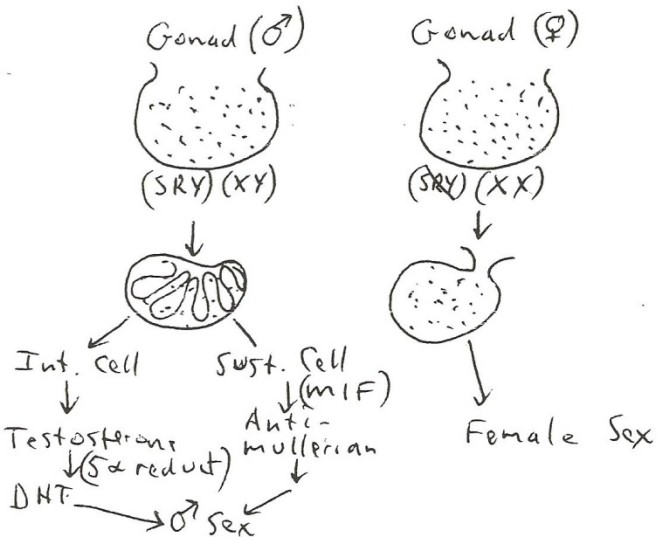




- **b.** The gonads regulate:
    - i. Functional development of reproductive tract
    - ii. Adult sex characteristics
    - iii. Adult male and female brain

c. Gonads are divided into two regions:
Cortical Region – outer region,
Medullary Region – inner region,

SEX DETERMINATION



1. Sex is determined by the **male gene**
- **a.** Testicle formation begins
- **b.** Ovary formation occurs

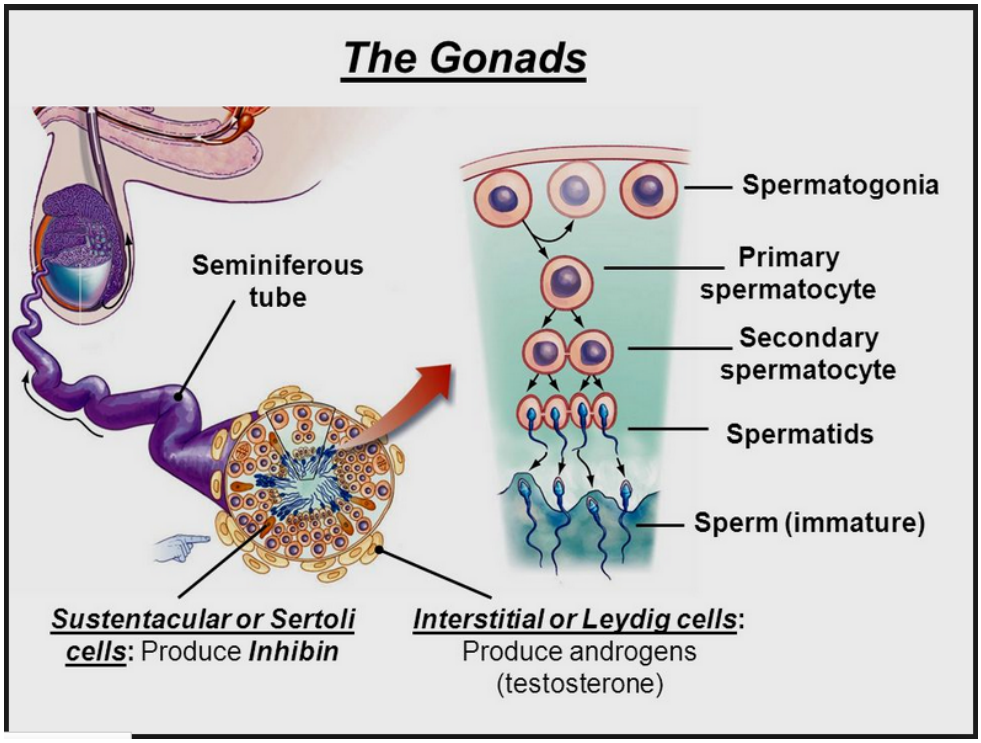
2. Sex Determining Y Gene (SRYGene)
- **a.** Determines
  - **i.** SRY proteins are turned on
  - **ii.** If the SRY gene is present the embryo will develop

3. TDF (Testis Determining Factor)
- **a.** Transcription factor that initiates downstream production and regulation

b. Interstitial cell produces testosterone. Testosterone is important in male reproductive tract development

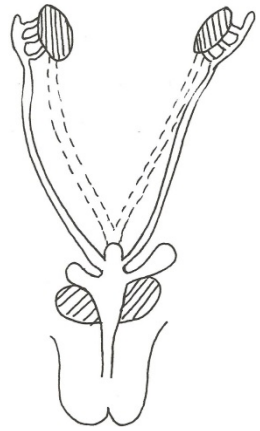
c. Testosterone exposed to 5 α reductase converts testosterone

d. Sustentacular cells – produce

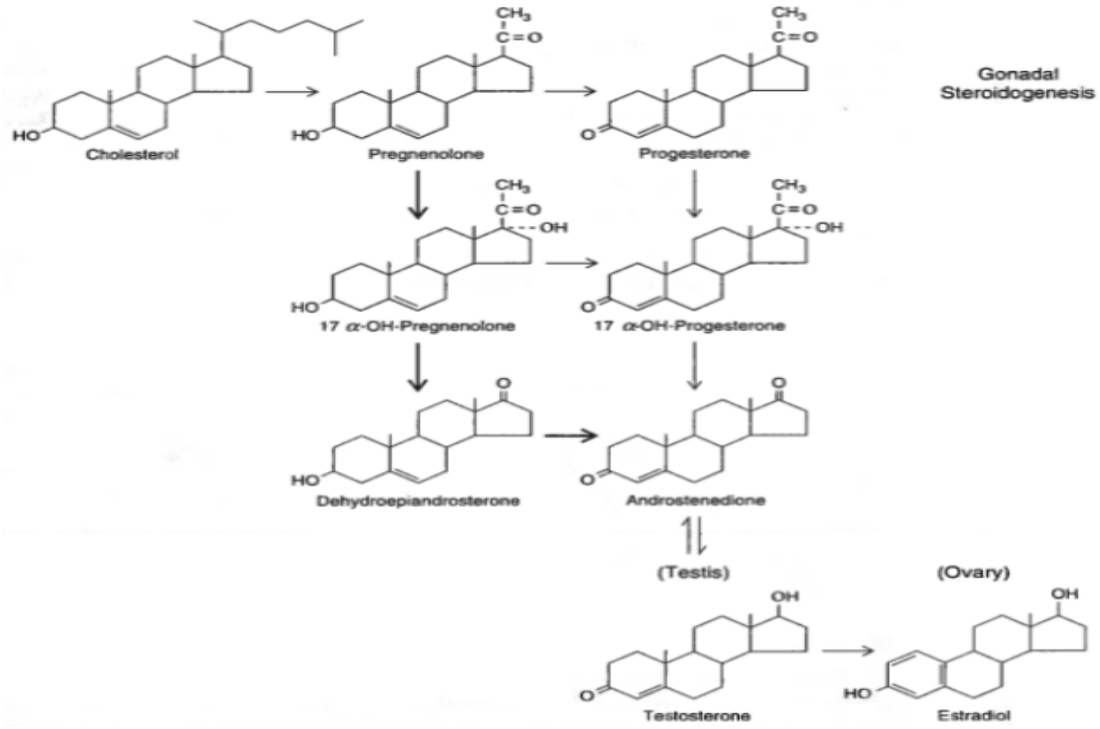


Embryonic Development of the Human Reproductive System

1. Wolfian Ducts (SRY gene present)
   a. SRY→ produce TDF→ Embryonic Testes→ Sustentacular Cells – MIF: degenerate female reproductive system



b. Interstitial Cells (Leydig Cells) – Testosterone

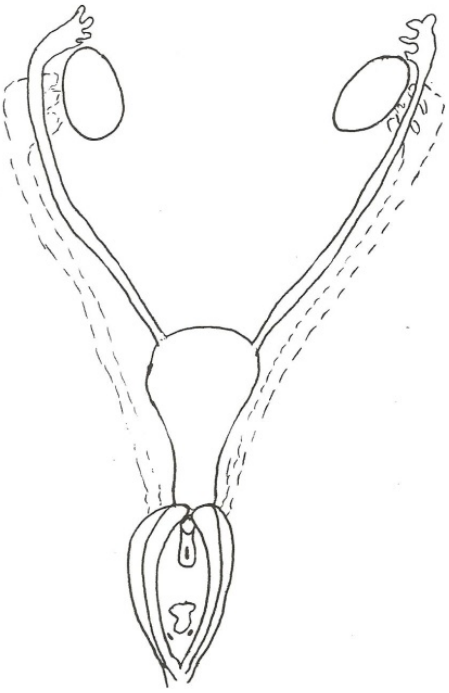


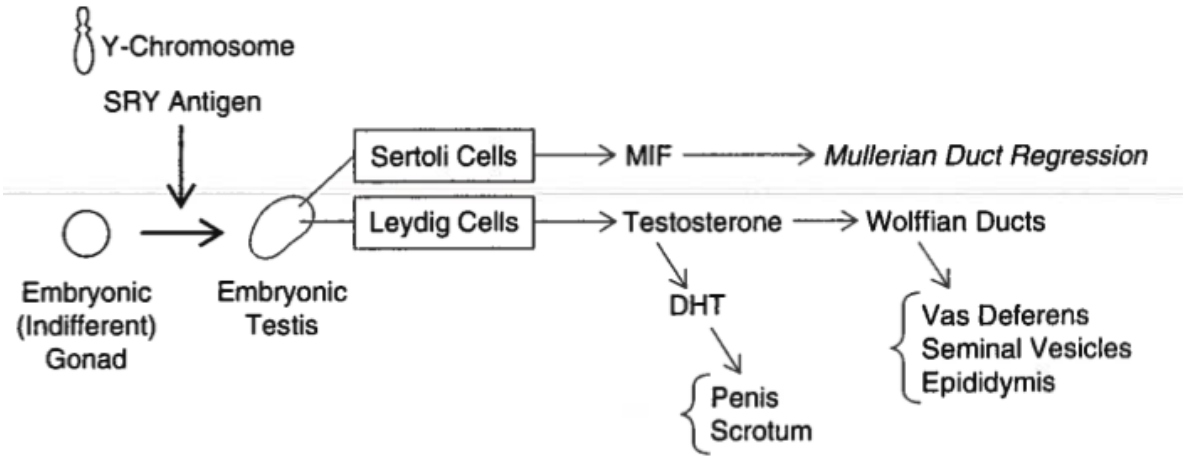
Dihydrotestosterone-

Gynecomastia -

2. Mullerian Duct (SRY gene absent)

a. No SRY→ so no MIF→male wolfian ducts deteriorate

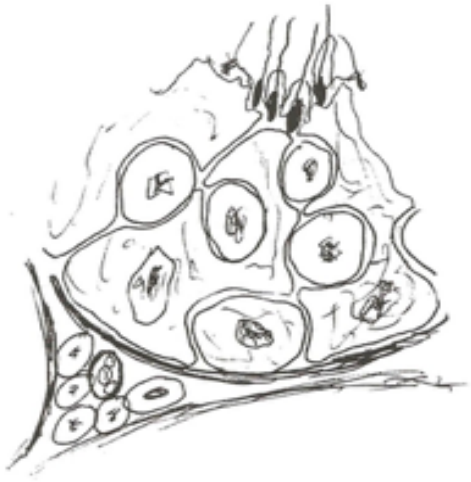



Y-Chromosome
SRY Antigen
Sertoli Cells
MIF
Mullerian Duct Regression
Leydig Cells
Testosterone
Wolffian Ducts
Embryonic (Indifferent) Gonad
Embryonic Testis
DHT
Vas Deferens
Seminal Vesicles
Epididymis
Penis
Scrotum

MALE REPRODUCTIVE ANATOMY

Sustentacular Cells (Sertoli Cells)

2. **Involved in Sperm Maturation**.
    a.
    b.
    c.
3. **FSH effects on Sustentacular Cells**
    a.



3. **The Blood Testes Barriers**
    a.

4. **Inhibin Production**
    a.

5. **Interstitial Cells**
    a.

Hormonal Effects on Brain Structure

1. Human Male

d. continuous secretion of GNRH (hypothalamus), FSH, LH (ant. pituitary)

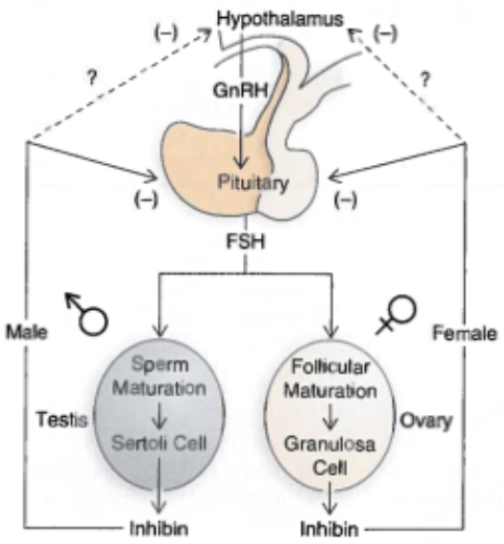
2. Human Female

a. cyclical production of GNRH (hypothalamus), FSH, LH (ant. pituitary)

b. Factors to turn on switch for puberty

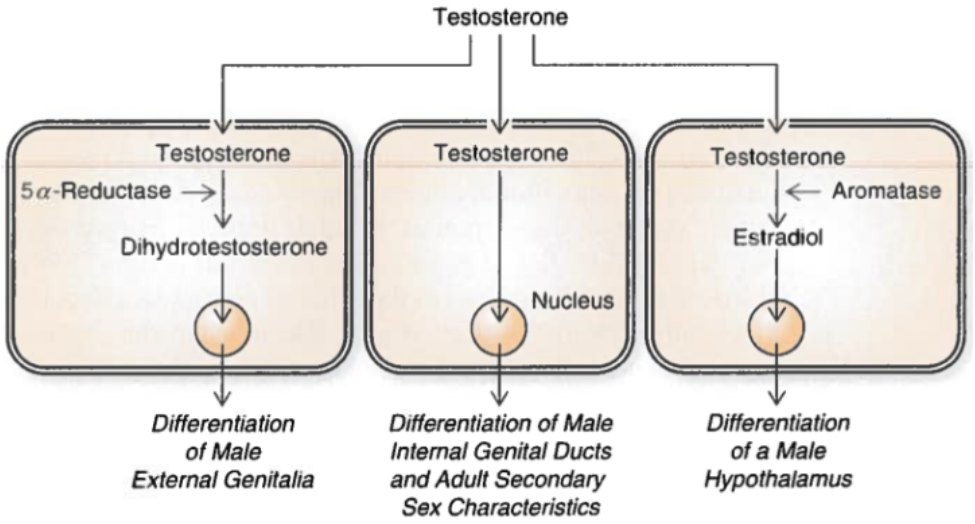
3. **Control of gonadotropins** by: hypothalamus preoptic area
   a. Effect of Testosterone on hypothalamus –during neonatal period the hypothalamus is sensitized providing continuous secretion of GNRH for male reproduction.

   b. Testosterone effect on preoptic Area of Hypothalamus – increase in size and number of the cells in the preoptic nucleus.



Effects of Testosterone and Estrogen on Reproductive Development

1. **Male reproductive Development**



2. Maturation and Endocrine Development of the Female Brain
   a. E2 regulates masculinization of the male brain. Why not the female brain?
      i. Estradiol levels are low during the prenatal desensitization period.
      ii. **FEBP – Fetoneonatal estrogen binding protein**

Male Reproductive Anatomy

Sustentacular Cells (Sertoli Cells)

Involved in Sperm Maturation

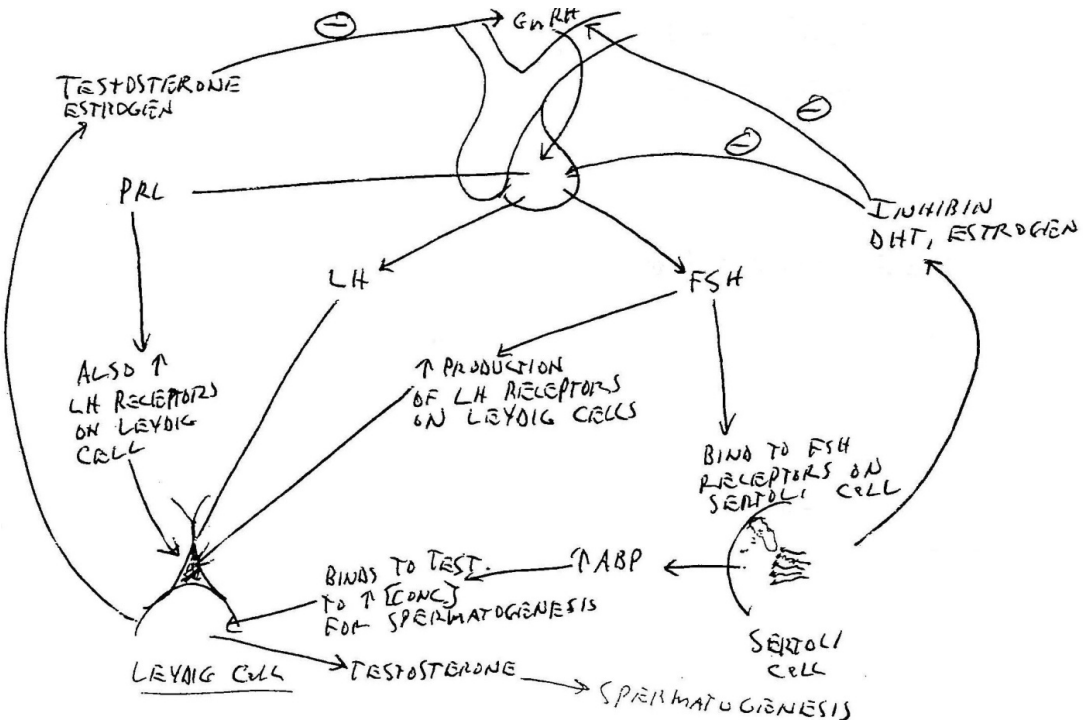
FSH effects on Sustentacular cells-

The blood testes barrier –

Inhibin Production - hormone produced by testis for negative feedback -> slows down sperm production –

Interstitial cells –

The Male Reproductive Hormonal Feedback Mechanism



Anatomy of the Male Reproductive system

1. **Prostate Gland** – 1/3 seminal volume
2. **Seminal Vesicles** – 60% of seminal volume
3. **Epididymus** – continuation of sperm maturation

Functions of Testosterone on Male Reproductive System

3. **Anabolic Effects** – increase growth of muscle mass tissue increase hair growth, deepening of voice, increase muscularity.

4. **Synthetic Androgens**
   - **a.** Negative Feedback Mechanism – give exogenous testosterone will decrease GNRH, LH, FSH production – DHT 2 ½ more times more potent than testosterone need 5 α dehydrogenase.
   - **b.** Testosterone Receptor Binding.
   - **c.** Secondary Sex Characteristics –

Reproductive Endocrinology of the Female

1. Ovarian Function

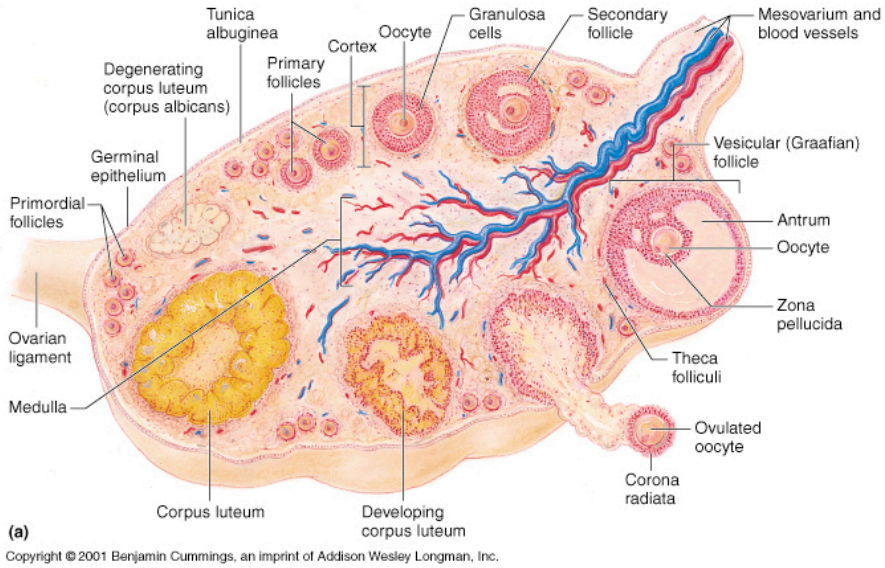
a. Produce gametes

b. Make hormones

2. Tissue Types

a. Epithelial Tissue: provides support

b. Mesenchymal Tissue: produces estrogen



Oogenesis

This the process by which female gametes are produced in the ovaries. Unlike in males, the primary oocyte are produced during fetal development:

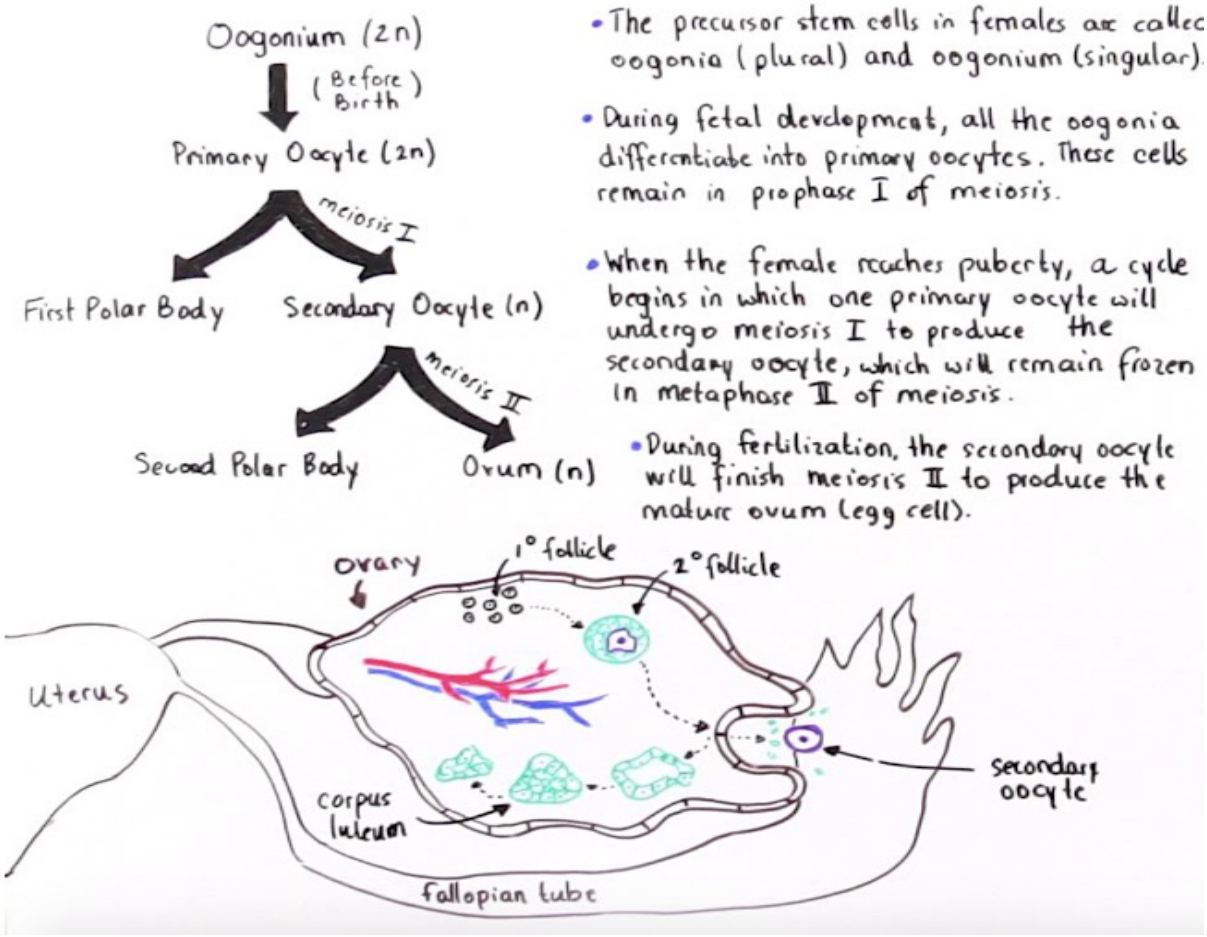
Ovarian Follicle

An ovarian follicle is a fluid filled structure that consists of the developing oocyte as well as other cells involved in the maturation process.

a. The Primordial Follicle (At Birth) – 2 million at birth, 400,000 at puberty

- **i.** Menarc =
- **ii.** Menopause =

b. How Many eggs ovulated in lifetime?



Ovarian Follicle

a. There are two types of cells that make up the ovarian follicle

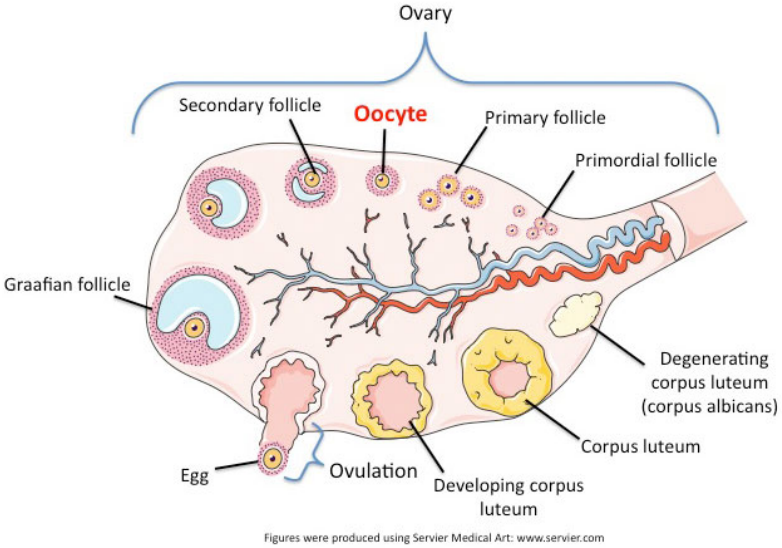
- **i.** **Thecal Cells** – develop from Mesenchymal Tissue, ovarian stomal cells, produce testosterone
- **ii.** **Theca Interna-**
  Secrete androgens, converted to estrogens via aromatase
- **iii.** **Theca Externa-**

1) Thecal Vascularization – thecal cells produce angiogenin (increase in blood flow and supply to developing follicle, after ovulation stays in ovary

2) Development of the antrum- steroid growth factors and electrolytes 100-200 times higher here thaan other parts of the body. Liquor folliculi-

iv. Granulosa Cells – derived from epithelial tissue, proliferate as oocyte enlarges directly surround oocyte (species specific), produce aromatase to to convert testosterone to estrogen.

The Anatomy of the Human Ovary



GnRh -low frequency pulses
-high frequency pulses

very little fluctuation in men
significant fluctuations in women

Ovarian Cycle

First half of the cycle termed the Follicluar Phase

- **Day 1-5:** Develop primary follicles
- **Day 6-10:** Primary follicle (initially 25)→**Atresia (deteriorate)**: Function is to produce significant amount of estrogen → The follicle that develops the fastest begins secreting

estrogen at a rapid rate and cause a negative feedback to the hypothalamus causing FSH production to decrease making other follicles→secondary follicle – estrogen in high levels. Follicles with fewer FSH receptors will not be able to develop further, thus indergoing atresia.

- **Day 13: Graafian follicle** – spike in LH – follicle ruptures, thecal cells stay behind, granulosa cells continue with egg, leaving the ovary

    - **Characteristics of secondary Graafian follicle**:
        - Increase LH receptors on thecal cells-bind LH for increased Plasminogen Activator and icreased production of androstenedione as a testosterone precursor
        - increase vascularity in thecal cells
        - increase inhibin to decrease FSH production

Follicular Phase (First Half) - During this phase plasma level of FSH

Functions of FSH

causes an increase in LH receptors on granulosa cells
causes follicular growth
increases the activity of

Follicular Phase (Second Half) - Now a decrease in FSH is noted, while an increase in estrogen from follicular production, and an increase in LH, inhibin, and E2 are noted. Estradiol and inhibin produced by the dominant follicle cause a decrease in FSH this increases the testosterone/estradiol ratio in the non-dominant follicle. More testosterone= atresia (death of that follicle)

Ovulation

- **Day 14**: **Ovulation-** occurs due to **spike in LH**
    - Both FSH and LH are needed for ovulation to occur
    - LH peak is noted prior to ovulation due to a gradual increase in estrogen
    - Plasminogen Activator- a protease which thins the follicular wall strip for ovulation. Initially, it was thought that FSH was the stimulus for

plasminogen activator, but now it is known that LH is equally potent to stimulate plasminogen activator.

- Day 12-13- Both FSH and LH are needed for ovulation to occur, FSH= a rise in estrogen which = a rise in LH receptor expression on the mature follicle making it sensitive to increased LH during this time.

Mittlesmerz-

- An increase in E2 causes an increase in number of GnRH receptors on the hypothalamus

Second half of the Ovarian Cylce is termed the Luteal Phase

- **Day 15-17: corpus hemorrhagicum** – outer thecal cells with blood center,

- **Day 18-28: corpus luteum**
  - Corpus luteum lifecycle varies, depending on whether a female is pregnant or not.
    i. **Pregnant Female**: If fertilization of egg occurs, the zygote releases a hormone hcG that maintains the corpus luteum which in turn will release progesterone to maintains the endometrium for implantation and vascularity of the endometrium.

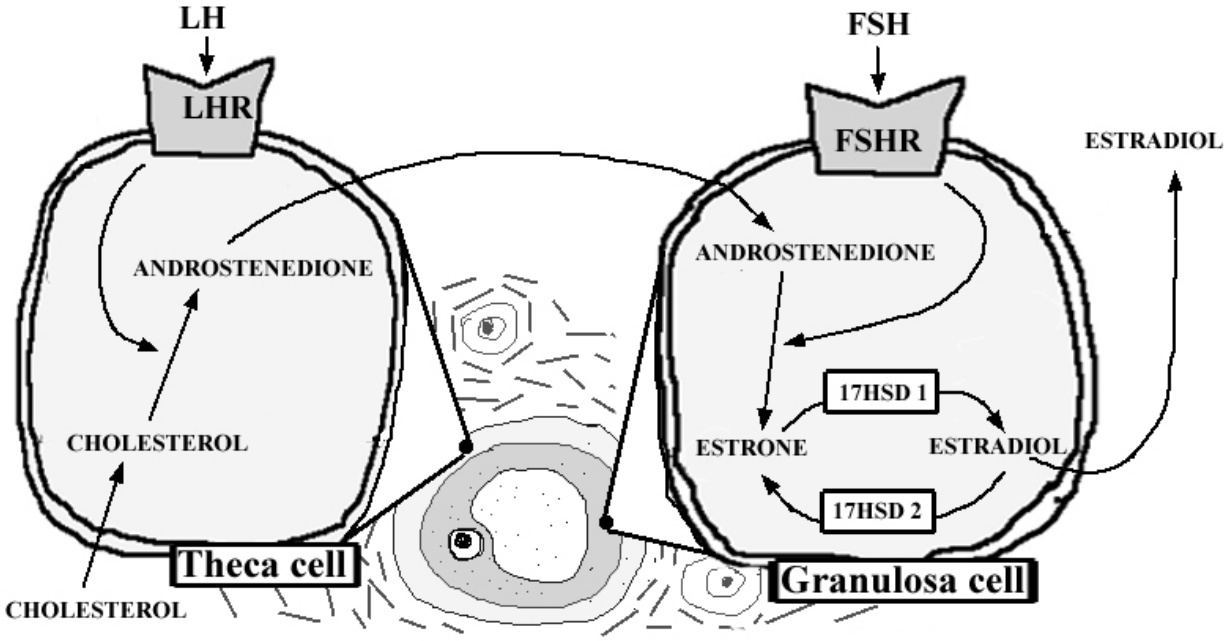
    ii. **Non-Pregnant Female**: A decrease in progesterone levels out about 14 days post ovulation, begin the process of luteolysis. The breakdown of the corpus luteum into the corpus albicans, then the process starts over.

- **Day 29-31:** corpus albicans –

Luteal Phase - Second half of the entire cycle - During this phase of the cycle an increase in progesterone, and estradiol are noted.
A decrease in LH and FSH are seen during this time.

Hormonal Input and Follicular Development

The Synthesis of Estrogen



1. **Thecal cells** are analogous

2. **Granulosa Cells** – early in cycle (analogous to)have only FSH receptors – LH receptors develop later from increased estrogen levels so they can bind to LH for the second ½ of the cycle. FSH induces granulosa cells to express LH receptors, when circulating LH binds to the receptors proliferation of granulosa cells stops.

3. **Estrogen**
   a. Estrogen levels decrease after menopause and there are E2 receptors on osteoblasts.

   b. There are 3 types of **estrogen**
      i. **Estrodiol – β-17** –
      ii. **Estrio**l –
      iii. **Estrone** –

Hormones of the Menstrual Cycle

Cycles of the Endometrial Lining

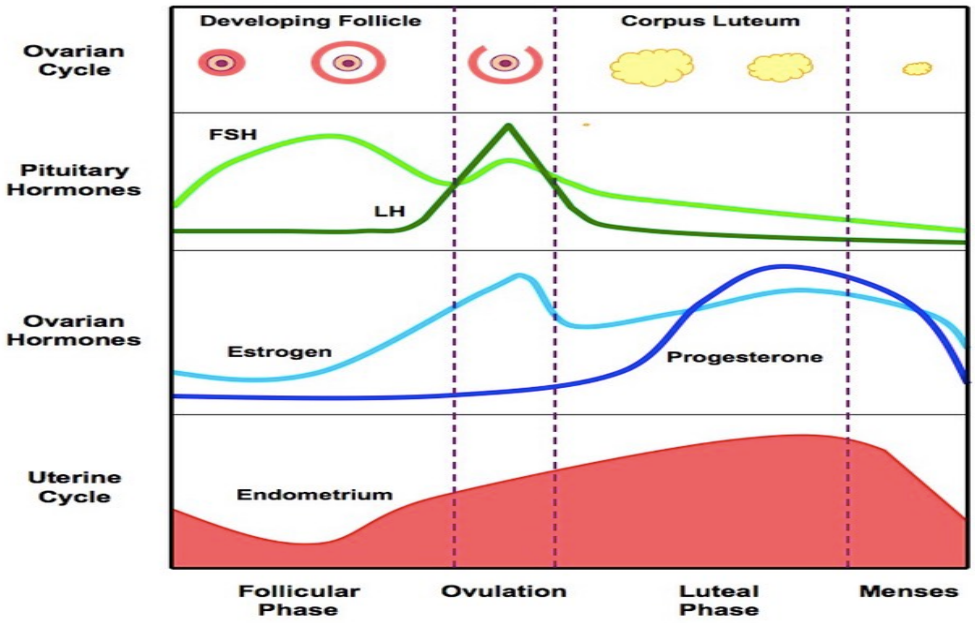
There are two Phases:

1. **Proliferative phase**- due to production of estradiol from the developing follicles the endometrium gradually thickens.

2. **Secretory Phase**- during the second half of the cycle the endometrium maintains thickness and begins to increase vascularity for implantation of the zygote and also increases glandular secretions. A decrease in hormonal levels (progesterone and estradiol) causes atrophy of the new vascularity which allows for sloughing of the endometrial lining.

Luteolysis

1. A continual and gradual increase in progesterone=



Fertilization awareness

Basil body temperature 0.5-1.6 degree increase

Fertile mucus – vaginal mucus –

Cervical changes in position and texture.

Fertile –

Non-Fertile –

Vulva (external female genitalia)

Birth Control

1. **Contraceptive Pill** – prevents ovulation by suppressing the release of gonadotropins.
   a. Progesterone has a negative feedback on the release of GNRH. Progesterone tells the hypothalamus to stop producing GNRH. Decrease estrogen production because no follicles are being produced – less able to support egg plantation. Progesterone inhibits sperm penetration through the cervix.

   b. 2 main types
      i. Combined- estrogen and progesterone –synthetic,

      ii. Progesterone only-

      iii. Conraceptive patches, NuvaRing (Vaginal rings do the same thing)

2. **RU486** – **morning after pill**, (Mifepristone) – abortifacient
   95% effective in first 50 days of pregnancy

   Note-progesterone inhibits uterine contractions and a decrease in progesterone increases uterine contractions.

Pregnancy and the Corpus Luteum

→ **Fertilization occurs**:

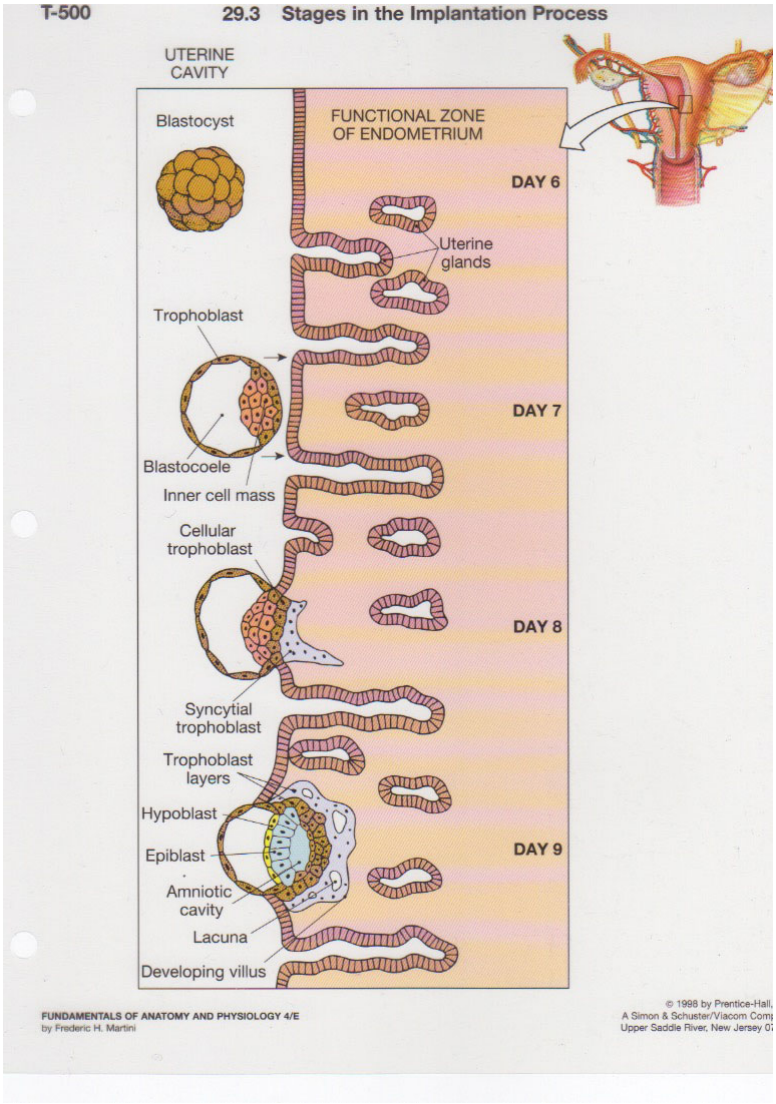
Pregnancy Timeline

1. The zygote enters the uterus
2. Implantation-
    a. At this time the "blastula" has two separate cell layers.

        i. **Cytotrophoblast**: the inner cell mass that makes up the components of the embryo.
        ii. **Syncytial Trophoblast**: The outer layer of the trophoblast that actively invades the uterine wall, rupturing maternal capillaries and thus establishing the interface between maternal blood and embryonic extracellular fluid.

→ **Syncytial trophoblast** –

Note that **HCG** is produced only when an egg has been implanted.



The Hormones of the Placenta

→ If fertilization occurs, the zygote releases a hormone called

Pregnancy test-
Ovulation test-

a. **Human Chorionic Gonadotropin (hCG)** from the embryonic tissues increases the production of progesterone within the first two weeks after ovulation. hCG is very similar in structure to LH and FSH, so it binds to LH receptors on the corpus luteum,

b. The placenta produces hCG at approx.

c. These levels continue to increase too at about 9 weeks post conception then slowly decline to about near the end of the second trimester.

3. **Function**: maintains the luteal phase to increase and maintain progesterone by the corpus luteum and the production of relaxin, used by fertility specialists in lieu of LH to trigger ovulation-

   a. Then the corpus luteum regresses. Also a critical time in fetal development - If the fetus does not take over hormone production then the pregnancy is not viable

   b. The corpus luteum also produces relaxin in response to hCG. This hormone serves several functions:
      i. Relaxes
      ii. Relaxes

1. **Progesterone**
   a. Produced by the corpus luteum up to six weeks post conception and then by the placenta from 6 weeks until the end of the pregnancy.

      Functions:
      a.
      b.

   b. **Function**: Maintain uterine vascularity and thickness, maintains uterine relaxation prior to delivery. Inhibits FSH and LH production during pregnancy. Initiates the development and growth of breast tissue.

      Braxton-Hicks/preterm labor-
      Placenta Previa/abruptia-

3. **Estrogen** – estriol (estradiol, E2) is the major estrogen produced during pregnancy in the corpus luteum.

   Maintains endometrial thickness, upregulates oxytocin receptors in endometrium

4. **LH during pregnancy**
   a. increased levels of progesterone causes decreased levels of LH secretion
   b. increased levels of estrogen causes a decrease in LH synthesis

5. **Human placental lactogen (chorionic somatomammotropin)**
   a. Produced by :
   b. Similar to GH and Prolactin in structure and functions overlap, seen in womens plasma after (10 days) conception
   c. As placenta grows HPL levels increase
   d. Function:

Sensitivity of the hormones

Fetal steroids are commonly sulfated which protects the fetus from high exogenous steroid levels

1. **α-feto proteins**: (analogs of serum albumin) glycoproteins synthesized by the yoke sac in the liver and excreted into the amniotic fluid.
   a. **Function**:

   b. Increased levels can indicate-

   c. Decrease in α feto proteins indicates –

2. **D.O.C. – deoxycorticosterone**: mineral corticoid causes salt and water retention (20 times increase)

Breast-Feeding

1. This mechanism suppresses release of GnRH
2. This mechanism stimulates the release of endorphins, which suppress the release of GnRH→ decrease chance of pregnancy when breast feeding

Tubuloalveolar cells-

Ductal cells-

Lactation

The Mammary Glands - These modified sweat glands contain a large blood supply.

a. **Prolactin** (secretory cells): *Milk production*- Epithelial cells- cells that produce the milk, during lactation their metabolic machinery works of a high rate.

    Decrease in progesterone as well after placenta leaves mother-increase in milk formation.

    i. PRL major hormone in the production of milk - E2 and Progesterone are involved in the maturation of the ducts and epithelial cells. An increase in suckling causes an increase in PRL. PRL levels are high at parturition but drop off significantly about three days after birth.

b. **Oxytocin**: *Milk letdown*- Myoepithelial cells- muscle cells that serve to contract to squeeze milk into the ductules
    i. This is a **neural reflex**. Stimulation of the nipple or a stimulatory thought process (hearing a baby crying) initiates release of oxytocin from the posterior pituitary gland to cause contraction of the Myoepithelial cells and smooth muscle cells of the ampulla. These contractions cause milk: to be released from the breast.

Parturition – baby birth

1. **Fetal ACTH**
    a. Increases cortisol synthesis
    b. Causes shift from progesterone production to more estrogen production
    c. Ratio change increases uterine contracting through increase in prostaglandin production

Fetus initiates parturition- For parturition to occur, progesterone production by the placenta must be terminated. As fetus grows in a restricted environment, it becomes stressed. This stress leads to a rise in fetal ACTH. The ACTH rise stimulates cortisol production in the fetal adrenal glands -causing an increase in the estrogen:progesterone ratio by upregulating aromatase enzymes- converting androgens to estrogens which upregulate uterine prostaglandin production thus beginning labor. (This allows the uterus to become susceptible to oxytocin for uterine contractions.) Once this occurs we see an pulsatile production of oxytocin from posterior pituitary gland as labor builds.