Student Notes

PHYSIOLOGY

1st Edition

Unit 7

Endocrinology

Preface

Dear Medicos,

Agam Medical Organization has been dedicated to fostering a culture of academic excellence and knowledge sharing among medical students. Our organization has always recognized the importance of passing on the torch of learning to the next generation. Today, we are proud to present the culmination of years of dedication and hard work: the Agam Medical Organization's Physiology Study Material.

This comprehensive study material is not just a book; it's a testament to the spirit of collaboration and the unwavering commitment of our fellow students to their academic pursuits. As we navigate the challenging journey of medical education, we understand the significance of having reliable and concise resources at our disposal. This study material has been meticulously crafted with this understanding in mind.

The material within these pages is the result of countless hours of research, study group sessions, and the collective wisdom of our seniors. It has been designed to aid you in comprehending the intricacies of physiology and, more importantly, to empower you to excel in your undergraduate university exams.

Each chapter within this book delves into various aspects of physiology, offering not just theoretical knowledge but also practical insights. We have strived to simplify complex concepts, making them accessible to all readers, regardless of their level of familiarity with the subject.

Furthermore, we have incorporated summaries, and diagrams to facilitate effective revision. We firmly believe that learning should be a dynamic process, and this study material encourages active engagement with the subject matter.

As you embark on your journey through the pages of this book, remember that you are not alone. You have the collective wisdom and support of Agam Medical Organization and its members behind you. We are here to help you succeed.

We extend our heartfelt gratitude to all the contributors, without whom this project would not have been possible. Their dedication and passion for the subject shine through in every page.

We hope that this Physiology Study Material serves as a valuable companion on your academic path, guiding you toward a deeper understanding of the human body and fostering a love for the subject. May it be a beacon of knowledge that illuminates your path to success.

Best wishes,

Agam

Acknowledgment

In the journey of creating the Agam Medical Organization's Physiology Study Material, we have been fortunate to receive support, guidance, and inspiration from numerous sources. We would like to extend our heartfelt gratitude to:

Contributors:

We are deeply appreciative of all the individuals who contributed to this material, whether through research, content creation, or editorial work. Your collective efforts have resulted in a resource that will benefit countless students. A special thanks to **Jwala S**, for leading the team to bring the material in perfect form. We would like to express our deepest appreciation to:

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Abdul Gafoor

God:

We begin by expressing our gratitude to the Almighty for bestowing upon us the wisdom, strength, and determination to undertake this endeavour.

Pioneers in the Field of Physiology:

We stand on the shoulders of giants—those pioneering scientists and researchers who paved the way for our understanding of the human body's intricate workings. Their dedication to advancing the field of physiology has been our guiding light.

Doctors and Professors:

To the medical professionals and educators who have tirelessly imparted their knowledge and expertise to generations of students, we owe a debt of gratitude. Your dedication to teaching and healing has inspired us to strive for excellence.

Seniors:

A heartfelt thanks to our senior colleagues who generously shared their wisdom and experiences with us. Your mentorship and guidance have been invaluable in shaping this study material.

Supportive Families and Friends:

Behind every student is a network of family and friends who offer unwavering support. We thank our loved ones for their patience, encouragement, and understanding throughout this journey.

The entire Agam Medical Organization:

To our dedicated members and the organization itself, thank you for providing a platform where students can collaborate, learn, and grow together. Your commitment to knowledge-sharing is the driving force behind this initiative.

Fellow Students:

Last but not least, we extend our gratitude to our fellow students who will use this study material. It is for you that we embarked on this journey, and we hope that this resource empowers you to excel in your academic pursuits.

This study material is a testament to what can be achieved through collective effort and a shared passion for learning. As we move forward, let us remember the importance of giving back and supporting one another in our pursuit of knowledge.

With sincere thanks,

Agam

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ESSAY

SHORT NOTES:

ESSAY

GROWTH HORMONE: SYNTHESIS, STORAGE, FUNCTIONS, DISORDERS RELATED TO GH

Synopsis:

1. Introduction
2. SSS -structure, synthesis, secretion
3. Plasma level of growth hormone
4. Metabolism of growth hormone
5. Growth hormone receptor
6. Mechanism of action of growth hormone
7. Regulation of growth hormone secretion
8. Abnormalities of growth hormone secretion

INTRODUCTION:

- Growth hormone/somatotropin: most important hormone for post-natal growth and development to adult size.
- Helps to maintain lean body mass and bone mass in adults

STRUCTURE:

- Single unbranched chain
- 191 amino acids
- Molecular weight;2000
- GH exhibit species specificity.

SYNTHESIS:

- GH is synthesized by acidophilic cells called somatotrophs of anterior pituitary.

SECRETION:

- GH is released in pulsatile fashion.
- Increased by sleep, stress and starvation.
- Decreased by obesity, hyperglycemia, pregnancy.
- Somatomedins decrease secretion of GH.

PLASMA LEVELS OF GH:

- Basal plasma GH level;2-4 ng/ml
- Its concentration graph shows fluctuation. after every 1-2 hr interval there is rise in plasma GH level.
- Diurnal variation in plasma levels of GH is seen.
- Levels of GH increase from birth to early childhood.
- Puberty is associated with peak period plasma GH levels.

CIRCULATION: GH bound to plasma protein. (GH binding protein)

HALF-LIFE: 0-20 min

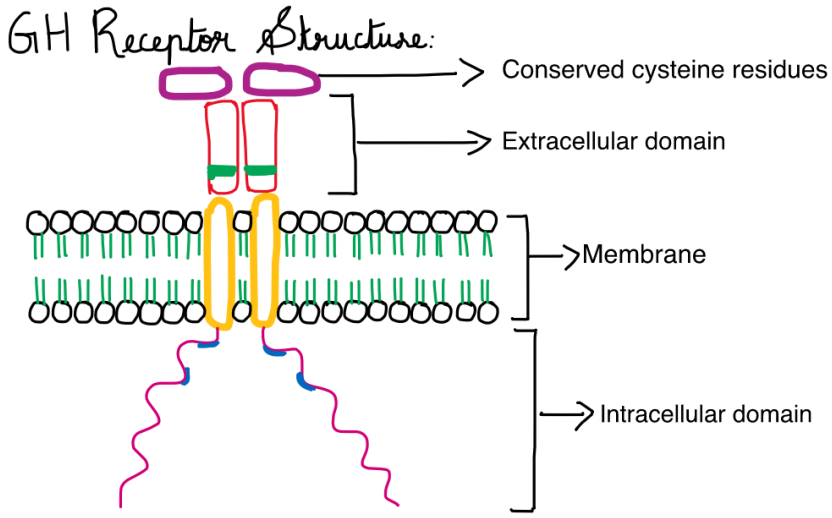
DAILY GH OUTPUT: 0.2-1.0 mg/day

METABOLISM;

- GH is metabolized rapidly in the liver.
- Metabolic clearance rate: 350 L/day

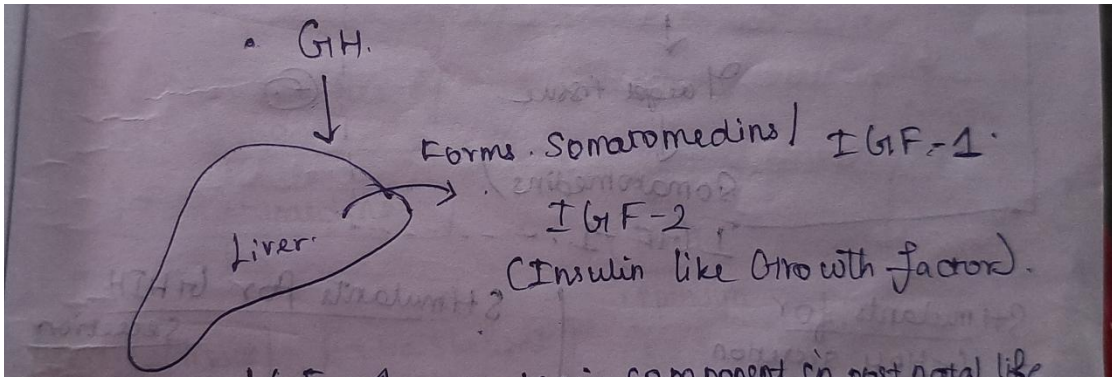
GH RECEPTORS;

- Present in liver and adipose tissue
- Vary in size
- Belongs to cytokine family of receptors.
- Large extracellular portion- a transmembrane domain
- Large intracellular portion -cytoplasmic portion



Mechanism of action:

On cartilage directly or indirectly



IGF-1 → main component in post-natal life
IGF-2 → responsible for intrauterine development

GH + receptor = GH secretagogue receptor (GHS - R)

↓

Transmembrane receptor

↓

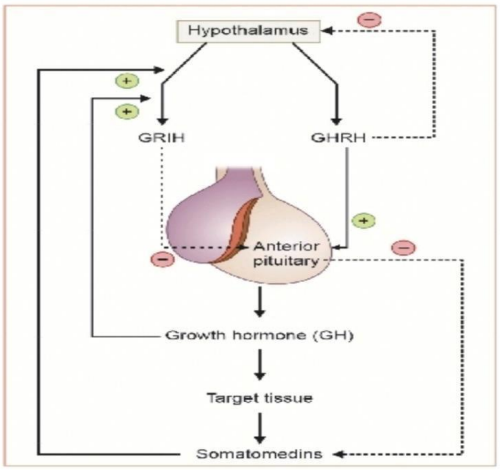
Present in liver cells mainly

↓

Induce **JAK - STAT pathway** and transcription of genes responsible for production of proteins required for growth.

REGULATION:

◆ Hypothalamic control by growth hormone releasing hormone and growth hormone inhibiting hormone from ant pituitary.



Stimulant for GHRH secretion:

- ✔ Hypoglycemi**a**
- ✔ Physical stress
- ✔ Emotion
- ✔ Ghrelin
- ✔ Slow wave phase of sleep

Stimulant for GHIH secretion:

- ✔ Hyperglycemia
- ✔ Increase free fatty acids in plasma
- ✔ IGF - inhibit GHRH from hypothalamus
  - inhibit GH from pituitary
- ✔ GH (autoregulation)

GHRH- inhibition on hypothalamus

Negative feedback control mechanism for GH involves he role of

- Somatomedins
- GH
- GHRH

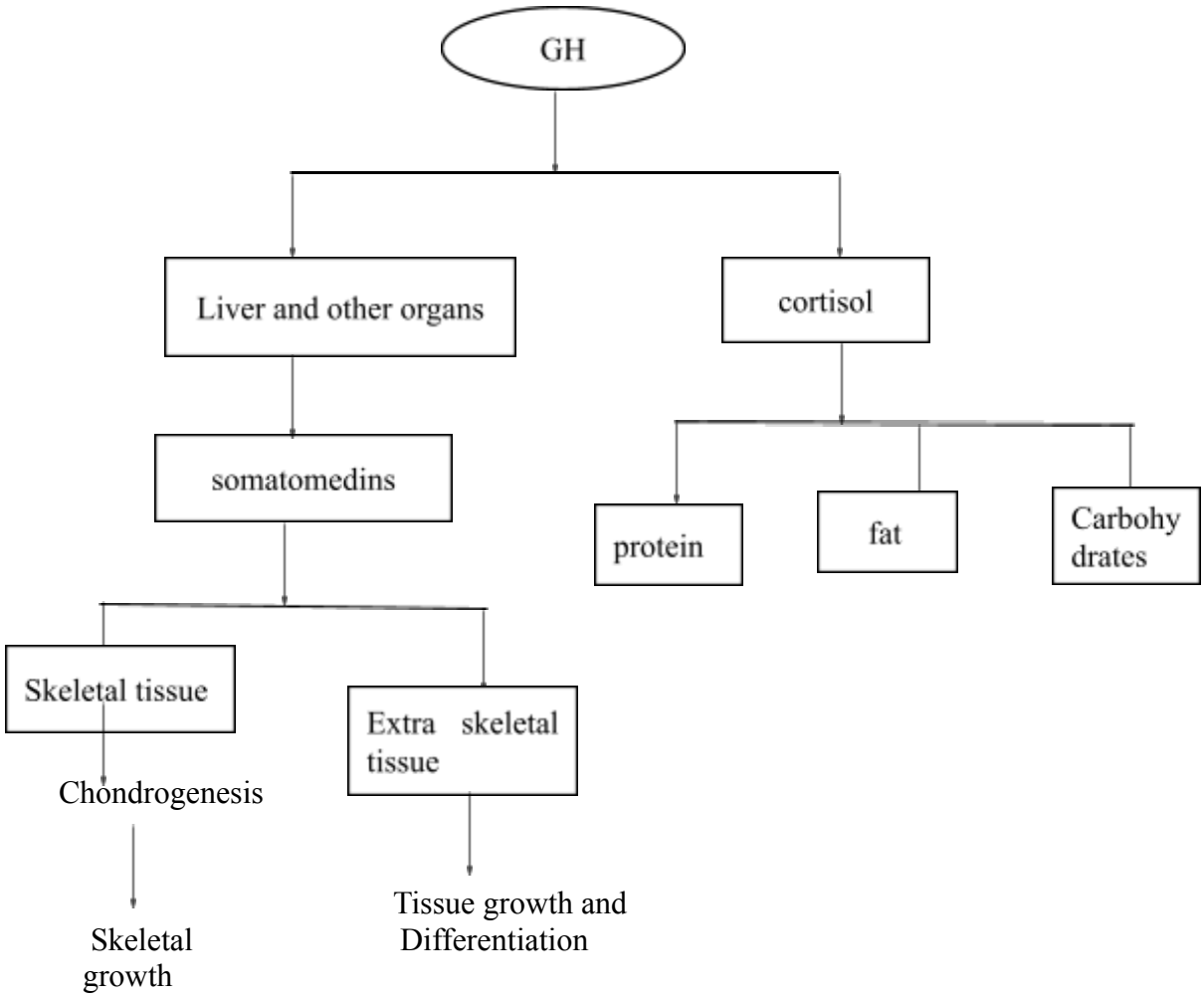
OHER FACTORS;

- THYROXINE, CORTISOL: +ve production of GH
- INSULIN: -ve GH gene expression
- OBESITY: -ve GH response
- ESROGEN: -ve GH secretion

ACTIONS OF GH;

- Growth promoting actions
- Metabolic actions

HYPOTHALAMUS → GHRH → ANTERIOR PITUITARY → GH



Physiological function:

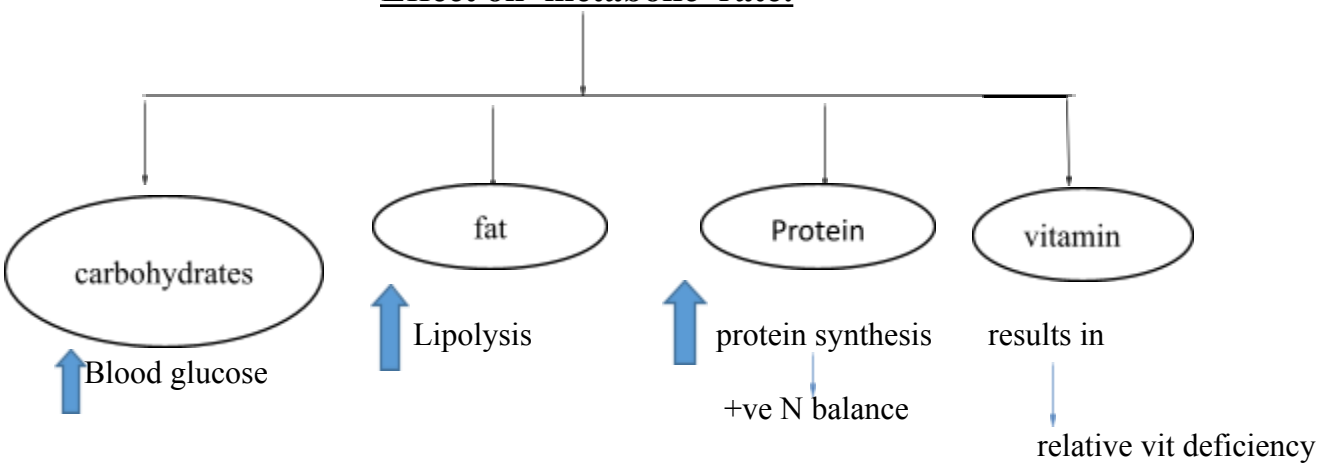
◆ Growth and development:

- ❖ Increase in protein synthesis ⟶ skeletal development ⟶ tissue differentiation.
- ❖ Development of neurons and dendritic development.

◆ Effect on metabolic rate:

- ↑ BMR and O2 consumption except retina, brain, gonads, spleen, lungs.

Effect on metabolic rate:



Effect on respiration;

↑ Resting respiratory rate, minute ventilation, O2 carrying capacity

Effect on CVS;

↑ Contractility by action of adrenaline- HR ↑

CO ↑ systolic BP

Peripheral vasodilatation ↓ diastolic BP

Effect on CNS;

↑ Critical for development of CNS
wakefulness, responsiveness, speed of reflexes
Potentiates catecholamine associated effects.

Effect on GIT;

↑ Appetite and food intake
Secretion of juices
Motility of gut

Effect on reproductive system;

- Responsible for proper functioning of reproductive system
- In males in aids in libido
- In females it regulates menstrual cycle.

Effect on kidney;

↑GFR and T max

ABNORMALITIES OF GH SECRETION;

HYPERSECRETION	HYPOSECRETION
GIGANTISM	DWARFISM[CHILDREN]
ACROMEGALY	MILD ANEMIA [IN ADULT]

1. **Gigantism:**

Introduction:

Clinical condition characterized by increased secretion of GH prior to the epiphyseal closure .

Etiology:

It is usually due to a pituitary tumor secreting excess GH.

Clinical features:

- Abnormal height: Affected individual is very tall around 7-8 feet with long bones.
- Large hand and feet.
- Gynecomastia due to prolactin like effect.
- Coarse facial features - thick lips, broad nose, macroglossia.
- Hyperglycemia due increased GH secretion.
- Headache, vomiting, diplopia, visual field defect.

Diagnosis:
Tumor by CT scan / MRI high GH level in plasma.

Treatment:
Surgical removal of tumor.

2. **<u>Acromegaly</u>**:

Introduction:
Clinical condition that occurs due to increase in GH in adults after epiphyseal closure of long bones causing excessive growth in those areas where cartilage persists.

Clinical features :
- Acromegalic face: thick lips, macroglossia, broad and thick nose , prominent eye browse.
- Prognathism ----- protrusion of lower jaw.
- Acral par abnormalities.
- Kyphosis.
- Increased sympathetic activity.
- Excessive growth of internal organs, cardiomegaly, splenomegaly, hepatomegaly.

3)Hyposecretion:
Mild anemia in adults

Features:
- ✧ Reduction in muscle mass
- ✧ Hypoglycemia

Treatment : Hematinic like iron

4. Dwarfism:

Introduction: Short stature due to deficiency of GH.

Etiology:

Endocrinal causes	Non-Endocrinal causes
GH deficiency Hypothyroidism Cushing syndrome Pan Hypopituitarism	Malnutrition syndrome Maternal nutritional deficiency Psychological dwarfism Congenital heart disease Pulmonary disease

Growth hormone- related dwarfism;

- PITUITARY DWARFISM – GH deficiency in childhood
- retarded growth in all parts of the body
- 20yrs looks like 7-10 years of age

FEATURES

- Shortness of stature
- normal mental activity
- Plumpness-fatness
- Immature face
- Delicate exremities
- No sexual maturity due to gonadotrophin deficiency

DIAGNOSIS: low level of GH/ IGF1 in plasma

TREATMENT: administration of GH preparation using recombinant human GH

❖ IGF synthesis in liver → AFRICAN PYGMIES

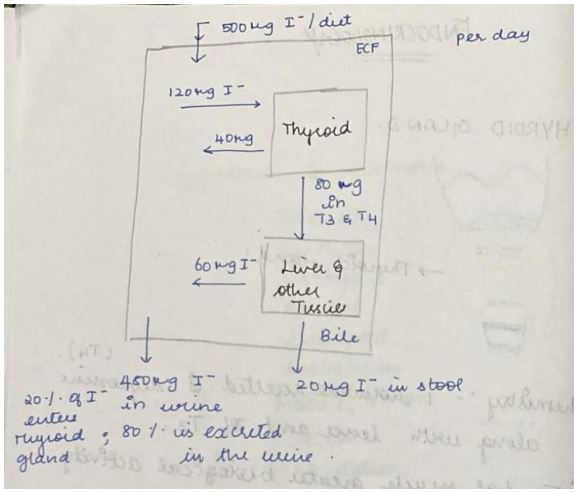
❖ or unresponsive GH receptors → LARON DWARFISM/ GH INSENSITIVITY SYNDROME

THYROID GLAND

CHEMISTRY

Primary hormone secreted is thyroxine T4 along with lesser amounts of T3. T3 has much greater biological activity than T4.

Both hormones are iodine containing amino acids.



SYNTHESIS

1. Iodine homeostasis: - Iodine is an essential raw material for thyroid hormone synthesis. Dietary iodide is absorbed by intestine and enters the circulation.
2. Iodine pump/ tapping: - Transport of iodide from blood into thyroid cells and follicles. This pump is achieved by sodium - iodide sympathetic which cotransports one iodide ion with two sodium ions across basolateral membrane. The energy for this IODINE transport comes from ATPase pump. This process of concentrating the iodide in the cells is called iodide trapping. A protein called PENDRIN helps transport iodide out of thyroid cells into colloid.
3. Formation and secretion of thyroglobulin: - A large glycoprotein is synthesised by endoplasmic reticulum and Golgi apparatus and secreted into follicles. For one molecule of thyroglobulins is equal to 70 tyrosine amino acid. They are the major substrates that combine with iodine to form thyroid hormones.
4. Oxidation of iodide ion: - This oxidation of iodide is promoted by enzyme PEROXIDASE and its accompanying hydrogen peroxidase in membrane of cells.
5. Organification of thyroglobulin: - The binding of iodine with thyroglobulin molecule is called oganification of thyroglobulin. The first product formed is monoiodothyronine.
6. Coupling of iodotyrosine residues: -

MIT + DIT ——> T3

DIT + DIT ——> T4

Small amount of reverse T3 is also formed.

STORAGE

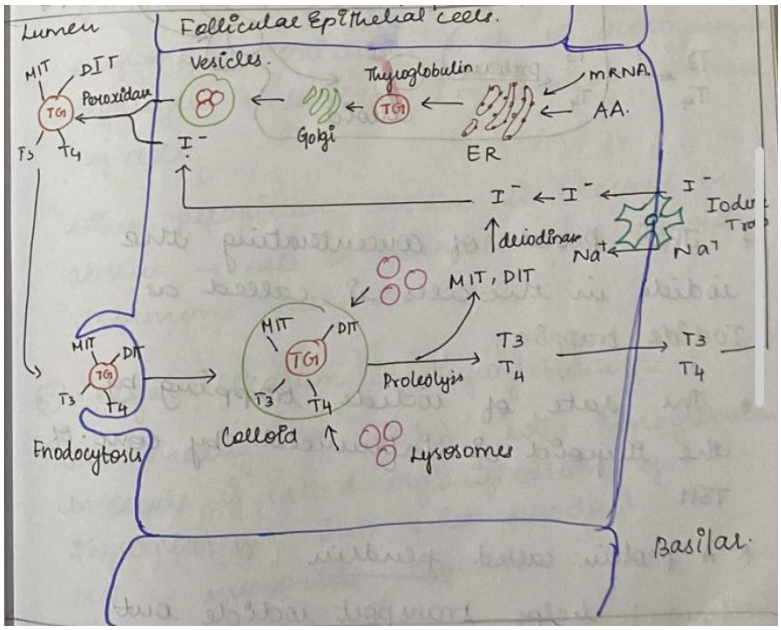
Thyroid gland has ability to store large amount of hormone. In normal human thyroid the average distribution of iodinated compounds is

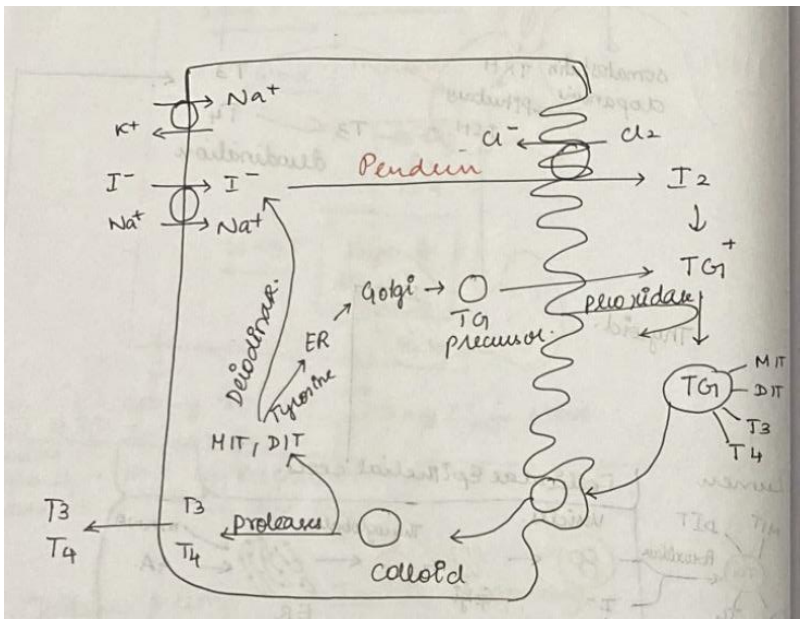
3% of MIT

33% of Di iodide thyroxine

35% of T4

7% of T3





RELEASE

a. MIT and DIT are rapidly deiodinated by deiodinase with follicular cells
b. Iodine and tyrosine are recycled for resynthesis of thyroid hormone.
c. Thyroid cells at the apical surface extended around small portion of colloid to form pinocytic vesicles.
d. Pinocytic vesicles enters thyroid cells.
e. Lysosome fused and digest thyroglobulin in pinocytic vesicles.
f. T3 and T4 are in free form are released into cells, into surroundings capillaries and thus enters into circulation.

MECHANISM OF ACTION

1. At cellular level: -

- T3 and T4 diffuse into cell and combine with nuclear receptor. This acts as DNA and increase the mRNA. rRNA increases and increases, functional and structural proteins synthesis.
- Increase in number and activity of mitochondria, which in turn increases the rate of ATP to energise cellular functions.
- Increase in activity of sodium potassium ATPase. This leads to hydrolysis of ATP, releasing energy and heat.

2. Effect on growth: -

- Promote growth and development
- Growth and development of brain during foetal life and for first few years of postnatal life
- In adult, brain, T3 and T4, stimulate synapse formation, branching myelination of nerve fibres, neurotransmitter, synthesis and vascularity

3. Effect on metabolism: -

A. Carbohydrates metabolism: -

- Increase glucose absorption
- Increase gluconeogenesis
- Increase glycogenolysis
- Accelerates insulin breakdown
- Increasing blood glucose level
- Hyperthyroidism- increase in blood glucose
- Hypothyroidism- decrease in blood glucose

B. Fat metabolism: -

- Thyroid hormone promotes cholesterol synthesis. At same time promote a hepatic break down and military excretion of cholesterol.
- Hyperthyroidism- decrease in blood cholesterol
- Hypothyroidism- increase in blood cholesterol

C. Protein metabolism: -

- Hyperthyroidism causes breakdown of protein
- Potassium excretion- breakdown of tissues

D. BMR: -

- Stimulate metabolism of tissues
- Hyperthyroidism- BMR is high (intolerance to heat)
- Hypothyroidism- BMR is low (intolerance to cold)

E. **Thermogenesis: -**

- T3 and T4 increases heat production in body.
- T3 and T4 increases, futile cycles, in which oxidative phosphorylation dissociated from ATP generation. This happens in brown fat and caused by a protein called thermogenin.

4. **Effect on systems: -**

A. CNS: -

- Essential for growth and activity of CNS
- Adult brain, hormone stimulates branching of dendrites and increases number of synapses
- Thyroid hormone deficiency during development causes mental retardation, motor rigidity and deaf mutism.
- Hypothyroidism- low memory, slowness of thought and speech, low IQ
- Hyperthyroidism- irritable, emotional, restless, anxious and paranoia

B. CVS: -

- Increase in blood flow meets the need for heat elimination from the body. As a consequence of the increase in blood flow., cardiac output also increases
- Increase in heart rate
- Increase in heart strength
- Mean arterial pressure is normal. Increase blood flow through tissues between heart beats the pulse pressure is often increases with the systolic pressure elevated in hyperthyroidism and diastolic pressure reduced.

C. Blood: -

- Stimulates erythropoiesis and necessary for maturation of RBC.
- Hyperthyroidism- polycythaemia
- Hypothyroidism- Anaemia

D. GIT: -

- Stimulates appetite and food intake, motility and secretion of digestive juice
- Hyperthyroidism- diarrhoea
- Hypothyroidism- constipation

E. RS: -

- Increase in carbon dioxide formation, increase in oxygen utilisation, increases rate and depth of respiration

F. GONADS: -

- In males hyperthyroidism- impotence, hypothyroidism- loss of libido
- In females hyperthyroidism- oligomenorrhoea, hypothyroidism- menorrhagia and amenorrhea

G. Effect on function of muscles.

- Both in hyper and hypo - present of muscle weakness
- In hypothyroidism weakness is due to general depression of metabolism.
- In hyperthyroidism weakness is due to thyrotoxic myopathy. And also increase in irritability of CNS.

H. Skin: -

- In hypothyroidism- accumulates, promoting water retention. Puffiness of skin.
- In hyperthyroidism- excess, heat is produced so it dissipates, with increase in sweat production

I. Effect on kidney: -

- Maintain renal plasma flow, GFR, reabsorption of secretory activities.

REGULATION

1. Effects of TSH on thyroid secretion: -

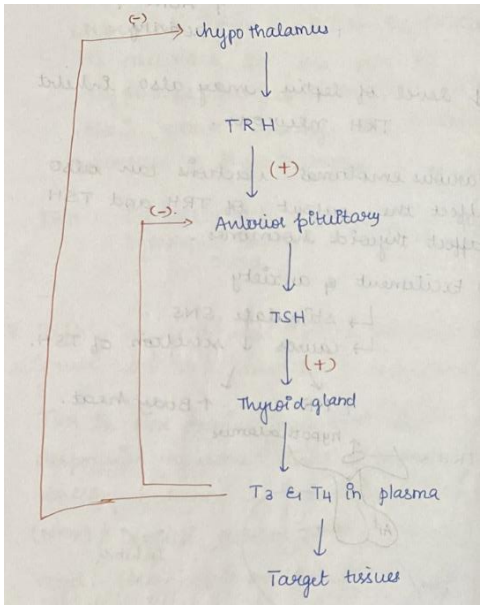
- Present in anterior pituitary
- Increases secretion of T3 and T4

2. TSH is regulated by TRH from hypothalamus: -

- TSH is controlled by TRH which is synthesised by neurons in the PVN of hypothalamus and secreted from their nerve endings in median eminence of hypothalamus.

3. Feedback effect: -

- Thyroid hormone has a negative feedback effect to prevent over secretion of hormone or overactivity of target tissues.



APPLIED/ CLINICAL ASPECTS

HYPERTHYROIDISM

- Primary hyperthyroidism- hyperactivity of gland, follicular carcinoma, LATS
- SECONDARY HYPERTHYROIDISM- Due to increase secretion of TSH and TRH
- Graves diseases- autoimmune disease in which antibody called TS immunoglobulin form against the TSH receptor in thyroid gland. High level of TH secretion caused by TSIs in turn suppress anterior pituitary.
- Thyroid Adenoma: - as long as adenoma, continues to secrete, large quantities of thyroid hormone, secretory function in the remainder of thyroid gland is almost totally inhibited because thyroid hormone from the adenoma depress production of TSH.

SYMPTOMS: -

- Exophthalmos: - protrusion of eyeball, epithelial surface of eyes becomes dry and irritated and often infected, resulting in ulceration of cornea. Oedematous swelling of retro orbital tissues and degenerative changes in extraocular muscles.
- Decrease body weight
- Insomnia
- Restless, emotional, anxious, highly irritable.
- Hand tremor - increase secretion of catecholamines
- Polycythaemia
- Intolerance to heat- increase sweating
- Hypertension
- Varying degree of diarrhoea
- Muscle weakness
- Hyperglycaemia

HYPOTHYROIDISM

- Primary hypothyroidism: - defect in gland itself
- Secondary hypothyroidism- either due to decrease in TSH or TRH
- Hashimoto disease: - the autoimmunity destroys the gland rather than stimulates it.
- Thyroiditis: - causes progressive deterioration and finally fibrosis of gland, with resultant diminished or absent of thyroid hormone.
- Hypothyroidism in infants: -

a. Persistence of physiological jaundice
b. Difficulty in feeding
c. Delay in eruption of teeth

- Persistent untreated hypothyroidism in infants leads to CRETINISM
- **CRETINISM**: - characterised by failure of body growth and by mental retardation.

Features: -

- Infantile features are seen- nose broad, flattened widely placed eyes, large protruding tongue

- Non pitting oedema
- Dwarf stature
- Mentally retarded, low IQ, myelination and synapse formation affected.
- Dry, rough and scaly skin
- Hypogonadism - impotence and sterility are common.
- Sluggish slow and lethargic movement.
- Low BMR

SYMPTOMS: -

- Myxoedema feature of hypothyroidism
- Swelling of thyroid gland- goitre
- Puffy face
- Hoarseness of voice
- Dry, rough and scaly skin
- Anaemia
- Atherosclerosis- decrease in thyroid hormone and increase in quantity of blood cholesterol.
- Intolerance to cold.
- Constipation
- Low sperm count in male
- Abnormal menstrual cycle in females

Myxoedema Madness - untreated cases- severe mental deficiency

Myxoedema Coma- medical emergency in which there is depressed level of consciousness with body temperature going down to 25 degree C

GLUCOSE HOMEOSTASIS; HORMONES INVOLVED AND THEIR EFFECTS; ADD A NOTE ON DIABETES MELLITUS

NORMAL PLASMA GLUCOSE LEVEL

- Normal fasting plasma glucose level is 70-99mg/dl.
- After food intake, this value increases, but remains within 200mg/dl. Therefore, random blood glucose when <200mg/dl is considered clinically normal.
- The normal postprandial 2 hours blood glucose level is <140mg/dl

FACTORS REGULATING BLOOD GLUCOSE LEVEL

LIVER

- Liver is the main organ in regulation of blood glucose level.
- It serves as a receiving (glycogen synthesis), manufacturing (gluconeogenesis and glycogenolysis), storing (glycogen storage) and distributing centre for glucose
- Glycogen is the storage form of glucose

- The secretion of glucose by the liver raises the blood glucose
- Removal of glucose by actively metabolizing tissues by the liver lower blood glucose level

GLYCOGENESIS - When the blood glucose level is high, liver takes up the glucose and stores it as "Glycogen" under the influence of Insulin

GLYCOGENOLYSIS - When the blood glucose level is low, glycogen breakdown happens and the glucose output to the blood stream increases under the influence of glucagon and epinephrine

- The liver thus functions as a GLUCOSTAT maintaining a constant circulating level of glucose

HORMONES:

- Insulin and glucagon are the main hormones that regulates blood glucose level in the body

Insulin

- It is a peptide hormone secreted by β cells of pancreas
- Elevation of glucose level in plasma is an important stimulator of insulin secretion
- It facilitates glucose entry into the hepatic cells
- It stimulates glycolysis, lipogenesis, and glycogen synthesis
- It inhibits glycogenolysis and gluconeogenesis
- Therefore, the primary function of the insulin is to lower the plasma glucose concentration
- It is the only hormone that decreases the plasma glucose level (only effective anti-diabetogenic hormone)

Glucagon

- It is a peptide hormone secreted by α cells of pancreas
- Physiological action of glucagon is almost opposite to that of insulin
- It stimulates glycogenolysis and gluconeogenesis
- It inhibits glycogen synthesis by inhibiting *glycogen synthase*
- It facilitates lipolysis and thus increases free fatty acids in the blood
- It especially facilitates hepatic glucose output and thus increases blood glucose level

INSULIN-GLUCAGON RATIO:

- Ratio of Insulin to the Glucagon is the I/G ratio
- Because of their opposing effects, a balance should be maintained between the secretion of insulin and glucagon for maintaining normal metabolic functions
- Therefore, insulin-glucagon molar ratio (I/G ratio) in plasma is more important than their individual concentration.
- Normally, the I/G ratio following a balance diet is approximately 3
- Following overnight fasting, it decreases to 1, and after prolonged fasting the ratio may be as low as 0.4
- Following glucose infusion, the ratio may rise to 30.

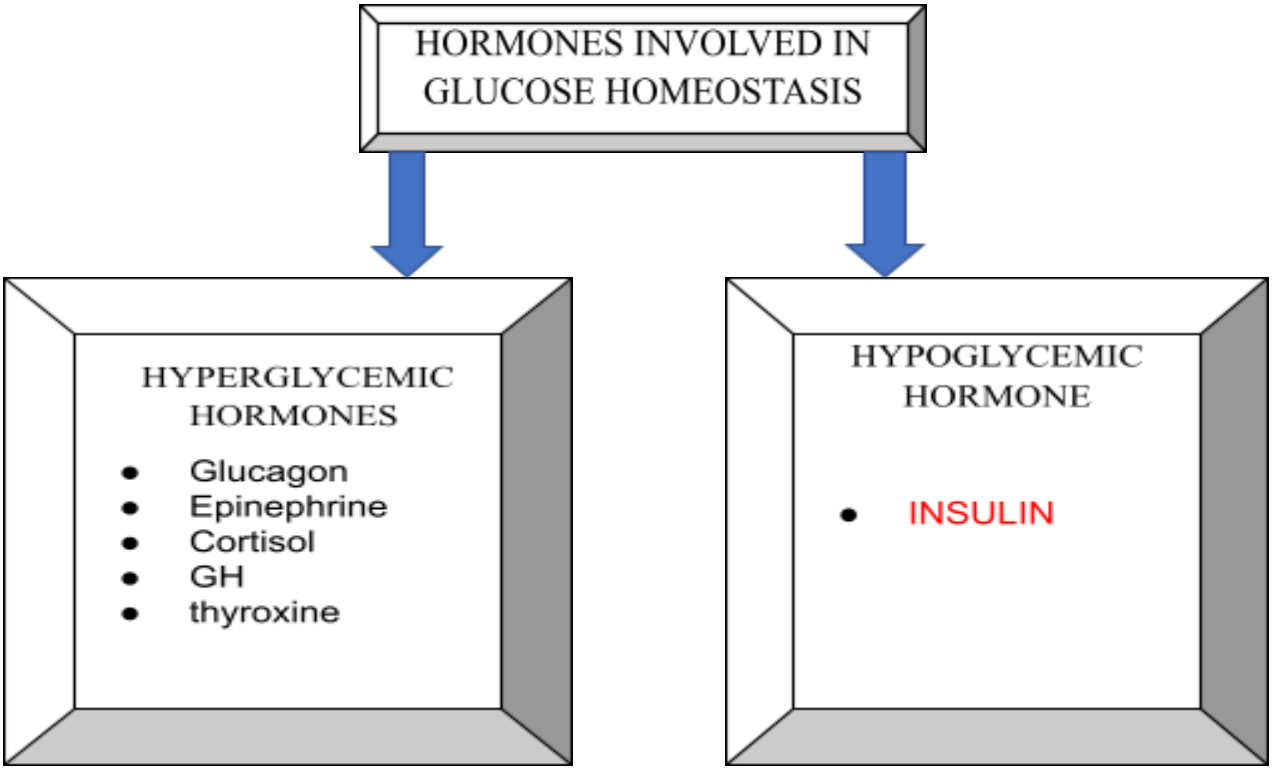
PHYSIOLOGICAL SIGNIFICANCE:

a) During starvation: -
Low I/G ratio □ glycogen break down and gluconeogenesis □ increases glucose level

b) During high-fed state: -
High I/G ratio □ favouring deposition of nutrients in the form glycogen, protein and fat □ decreases glucose level

c) In diabetes: -Inappropriate I/G ratio influences metabolic status
   - Secretion of glucagon is inappropriately elevated in insulin deficiency

- The metabolic derangements are affected by this abnormal ratio.



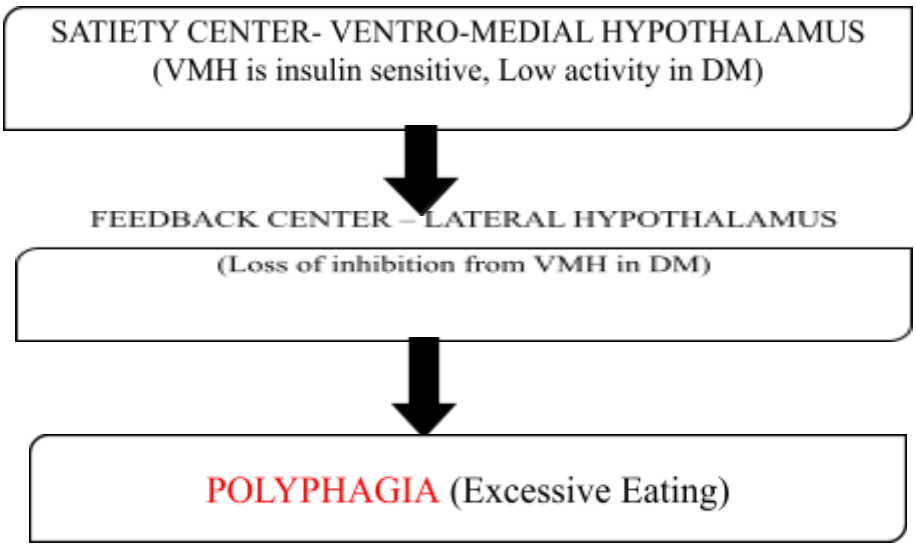
DIABETES MELLITUS

- It is a group of metabolic diseases due to destruction of β cells of pancreas or decreased sensitivity of insulin receptors (insulin resistance) characterized by hyperglycaemia.
- Diabetes is called "*a disease of starvation in the midst of plenty*"

TYPE 1	TYPE 2
Develops in childhood before the age of 40 (Juvenile diabetes mellitus)	Develops after the age of 40 (Maturity onset diabetes mellitus)
Plasma insulin level - low	Plasma insulin level – Normal or high
Cause: Autoimmune Destruction of β cells	Cause: Insulin resistance, β cell morphology is normal
Not obese	Obese
Hyperglycaemia with high incidence of ketoacidosis	Hyperglycaemia with low incidence of ketoacidosis
Genetic susceptibility is less than 50 %	Genetic susceptibility is more than 50 %
Treatment: Insulin replacement	Treatment: sulphonyl urea, biguanides, exercise, diet control, yoga

FEATURES OF DIABETES MELLITUS:

POLYPHAGIA:



POLYURIA: When plasma glucose level exceeds renal threshold (180 mg/dl),glucose appears in urine

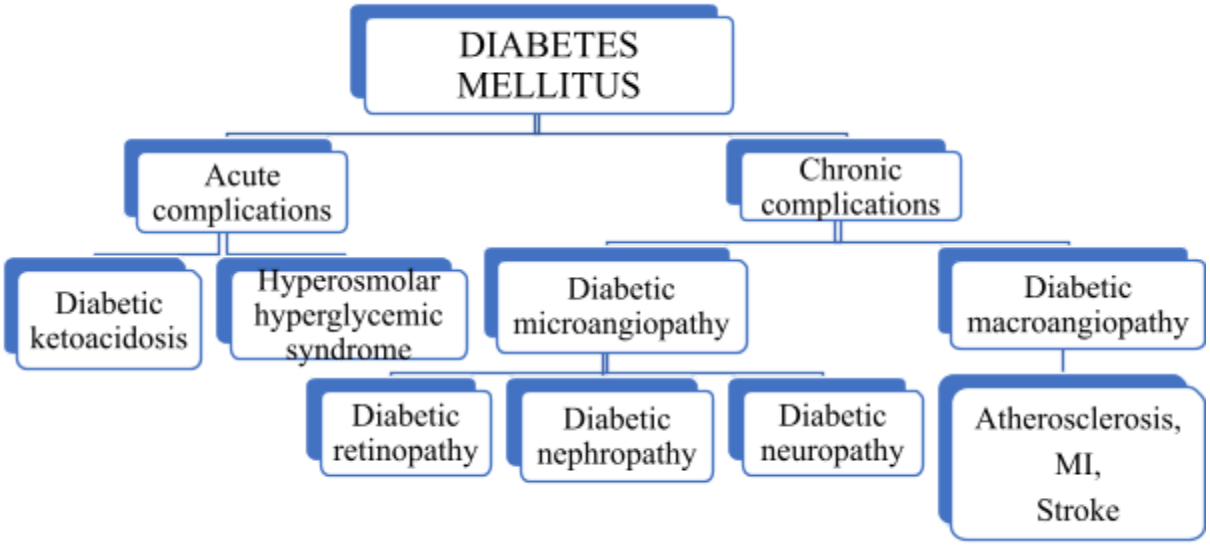
POLYDIPSIA: Osmotic diuresis(dehydration) & hyperglycaemia □ increased osmolality of blood which acts on thirst centre (pre-optic area) □ polydipsia

HYPERGLYCEMIA: Glucose cannot enter the cells in the absence of insulin □ High plasma glucose

GLYCOSURIA: Occurs when plasma glucose level exceeds renal threshold (180 mg /dl)

WEIGHT LOSS: Glucose is not utilized by the cells

COMPLICATIONS:-



INVESTIGATIONS: -

	Fasting Blood Glucose	Glucose Tolerance Test	HbA1c
NORMAL	< 99 mg/dl	< 140 mg/dl	< 5.7%
PREDIABETES	100- 125 mg/dl	140- 199 mg/dl	5.7 -6.4%
DIABETES	> 126 mg/dl	> 200 mg/dl	> 6.5%

ADRENOCORTICAL HORMONES

INTRODUCTION

Outer adrenal cortex:

- 80% - 90% of adrenal gland
- MESODERM origin
- Secretes steroid hormones

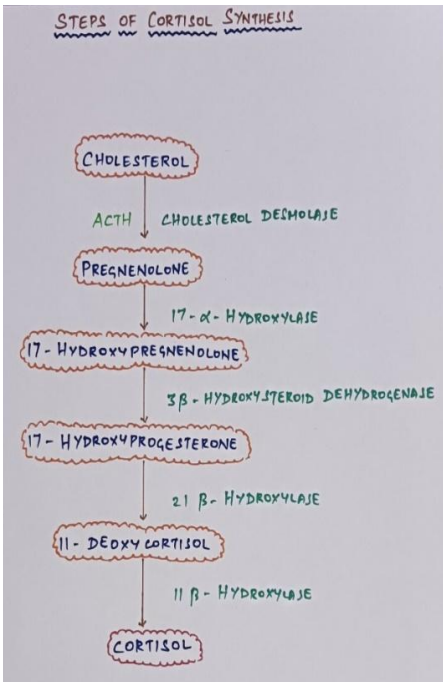
Inner adrenal medulla:

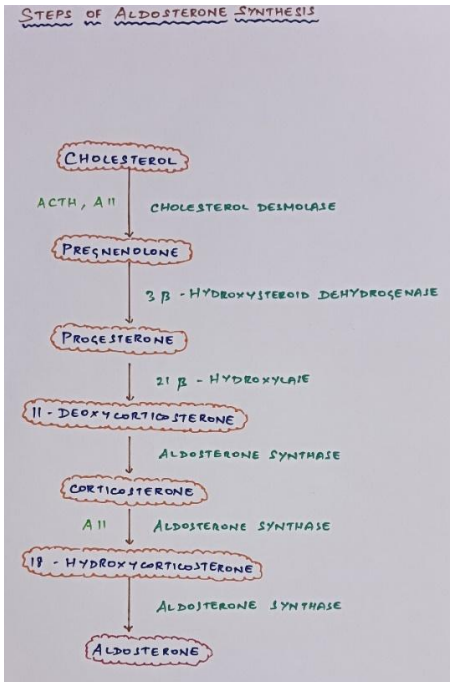
- 10% - 20% of adrenal gland
- NEUROECTODERM origin (related to sympathetic ganglia)
- Secretes catecholamines

	GLUCOCORTICOIDS	MINERALOCORTICOIDS	SEX STEROIDS
HORMONES	Cortisol Corticosterone	Aldosterone Deoxycorticosterone	Dehydroepiandrosterone Androstenedione
SECRETED FROM	Only Zona fasciculata (Long columnar cells)	Mainly Zona glomerulosa (Small clumps of cells)	Mainly Zona reticularis (Network of intercalated cells)
FUNCTIONS	Metabolic Anti inflammatory Immunosuppressant	Maintenance of extracellular fluid volume and electrolyte balance	Maintenance of secondary sexual characteristics

FUNCTIONAL ANATOMY

SYNTHESIS:





ENZYME DEFICIENCIES

- 21 β hydroxylase deficiency
    - Causes congenital adrenal hyperplasia
    - Decreased glucocorticoid, mineralocorticoid
    - Increased pregnenolone due to feedback increase in ACTH levels
    - Excess production of androgen – virilization
    - It is known as ADRENOGENITAL SYNDROME characterised by hirsutism, small breast, heavy arms and legs, clitoromegaly, receding hairline, male distribution of suprapubic hair, androgenic flush. In severe forms it may cause female pseudo hermaphroditism
    - Also causes hyponatremia
    - (SALT LOSING FORM OF CONGENITAL VIRILIZING ADRENAL HYPERPLASIA)

- 11 β hydroxylase deficiency
    - Increased 11 β deoxy cortisol / 11 β deoxy corticosterone levels
    - Excess mineralocorticoid leads to hypertension
    - (HYPERTENSIVE FORM OF CONGENITAL VIRILIZING ADRENAL HYPERPLASIA)

- 17 α hydroxylase deficiency: Causes hypertension and hyperkalaemia

- 3 β hydroxysteroid dehydrogenase deficiency: Masculinization of females and hypospadias in males

- Cholesterol desmolase deficiency: Fatal; causes termination of pregnancy

METABOLISM:

- Average plasma concentration
  Aldosterone – 0.0006 µg/dl
  Cortisol – 14 µg/dl
- Binds to TRANCORTIN (80%)
  ALBUMIN (10% - 15%)
  Remaining 5% - 10% free form
- Cortisol is metabolised in liver and excreted in kidneys
- 17 keto steroids (etiocholanolone) is metabolite of adrenal androgen; its accumulation in blood causes ETIOCHOLANOLONE FEVER

PHYSIOLOGICAL IMPORTANCE (of metabolism): -

- Normal transcortin level is 3mg/dl
  It is elevated in pregnancy
  Hence in pregnancy, the symptoms of cortisol excess does not appear even when cortisol is synthesised excess (more cortisol will be bound to more transcortin)
- Half life of cortisol is 60-90 mins whereas of aldosterone is 20 mins as aldosterone is less protein bound

GLUCOCORTICOIDS

Follows the pattern of ACTH secretion (diurnal variation)

ACTH and cortisol levels peaks at early morning 4am to 10am

PHYSIOLOGICAL IMPORTANCE: -

- Steroids should not be stopped abruptly
- It causes suppression of HPA axis
- If stopped patient may not tolerate stress and may collapse
- It takes about 10 months for pituitary to function normally after a prolonged steroid therapy
- Hence steroid dose should be tapered and gradually reduced over weeks

FUNCTIONS OF GLUCOCORTICOIDS: -

1)EFFECT ON CARBOHYDRATE METABOLISM:

- Increases blood glucose levels
- Stimulates gluconeogenesis
- Increases secretion of glycogenolytic hormones
- Anti insulin effect
- Physiologic importance – Complicates diabetes, defensive role in fasting

2)EFFECT ON PROTEIN METABOLISM:

- Facilitates proteolysis
- Inhibits protein synthesis

3) EFFECT ON FAT METABOLISM:

- Promotes lipolysis
- Promotes ketogenesis

4) EFFECT ON FOOD INTAKE:

- Increases appetite by increasing neuropeptide Y
- Increases leptin levels
- Causes redistribution of fat

5)PERMISSIVE ACTIONS: Glucocorticoid is essential for some physiological actions of other hormones to take place

6)EFFECTS ON CARDIOVASCULAR SYSTEM

- Increases myocardial performance
- Maintains vascular reactivity and increases responsiveness of arterioles to catecholamines and angiotensin II

7)EFFECT ON CENTRAL NERVOUS SYSTEM

- Influences mood and behaviour
- Decreases REM sleep, excessive levels cause insomnia
- Impairs memory
- Decreases responsiveness to stimuli

8)EFFECT ON MUSCULOSKELETAL SYSTEM

- Increases performance of cardiac and skeletal muscles by increasing acetyl choline synthesis
- In excess causes proteolysis, decreases muscle mass and strength
- Inhibits bone formation
- Decreased bone mass and mineralisation – in excess cause osteoporosis

9)EFFECT ON CONNECTIVE TISSUE

- Inhibits collagen synthesis
- Decreases thickness of skin and capillary walls
- Excess causes intracutaneous rupture (increased capillary fragility)

10)EFFECT ON KIDNEY AND WATER METABOLISM

- Increases GFR
- Inhibits ADH secretion
- Infusing iv solution in cortisol deficit patients – water intoxication

11)EFFECT ON FETUS

- Causes maturation of CNS in intrauterine life
- Essential for lung development – pulmonary surfactant synthesis

12)EFFECT ON BLOOD CELLS: Causes mild leucocytosis, erythrocytosis and thrombocytosis

13)EFFECT ON ALLERGY: Anti allergic, prevents release of histamine and growth of mast cells

14)EFFECT ON GIT:

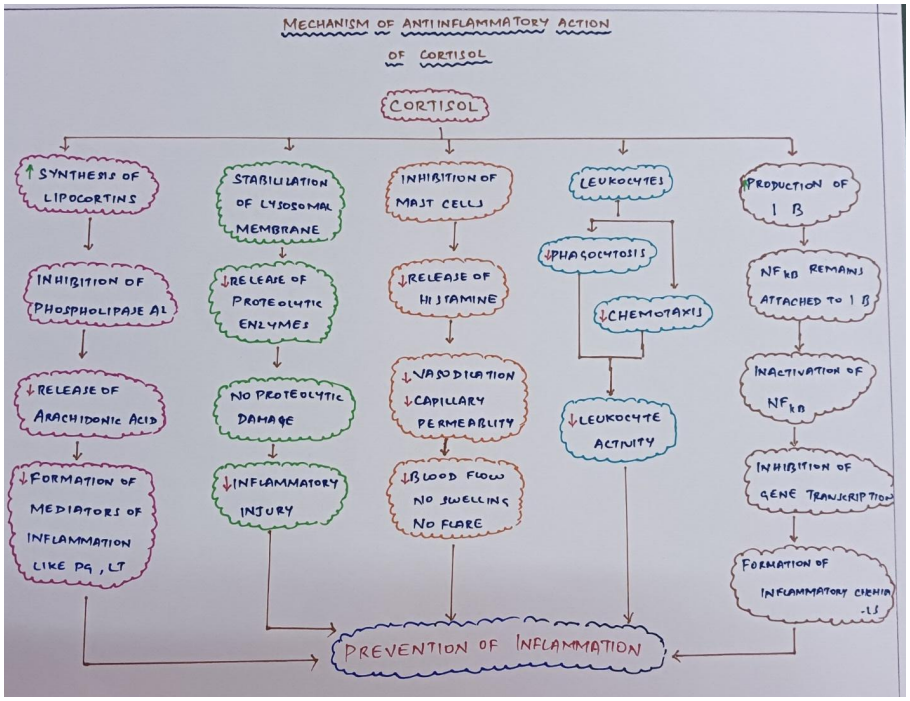
- Stimulates HCl secretion, causes gastritis
- Decreases Calcium absorption

15)EFFECT ON OTHER ENDOCRINE HORMONES: Inhibits secretion of GH, TSH, ACTH

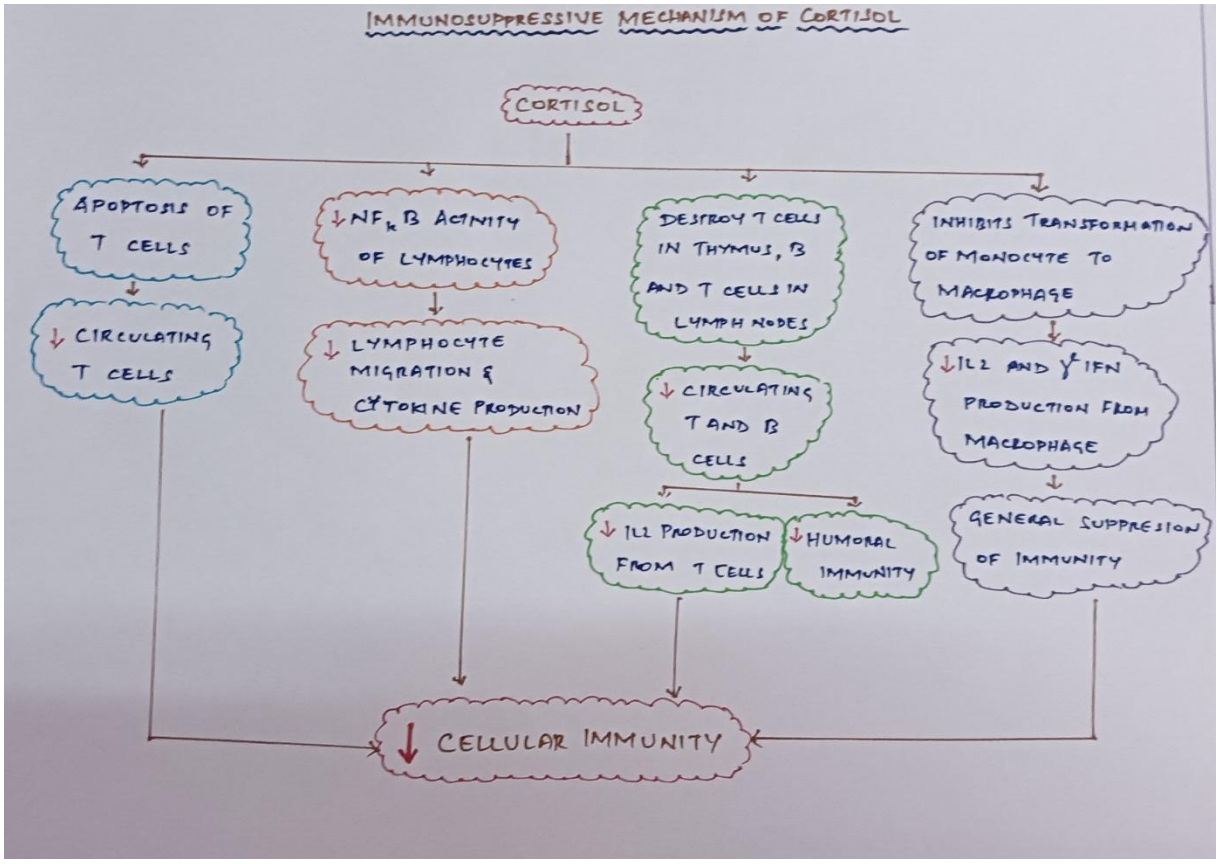
16)ROLE IN STRESS

- Stress is defined as condition in which plasma ACTH is high
- Things that increase plasma ACTH – Stressors
- In cortisol deficiency ACTH levels will high so the patient will succumb
- Glucocorticoids are essential for FFA mobilisation and for maintenance of vascular reactivity hence to withstand stress

17)EFFECT ON INFLAMMATION



18) EFFECT ON IMMUNITY



HYPERSECRETION OF GLUCOCORTICOIDS (CUSHING SYNDROME):

ETIOLOGY

- Excess cortisol
- ACTH independent : Tumor of adrenal cortex
- Exogenously administered excess steroids
- ACTH dependant : Tumors of pituitary (CUSHING DISEASE)
- The common causes include
    - Adrenal hyperplasia
    - Adrenal tumors
    - Adrenal macronodular hyperplasia
    - Familial adrenal dysplasia (CARNEY SYNDROME)
    - Iatrogenic (prolonged use of steroids or ACTH)

FEATURES OF CUSHING SYNDROME

- Centripetal obesity and weight
- Buffalo hump
- Moon face: Due to fat deposition, salt and water retention

- Fatigability and weakness
- Hypertension: Glucocorticoid excess has significant mineralocorticoid activity
- Hirsutism and amenorrhoea: Due to increased adrenal androgens
- Reddish purple striae: Excess fat deposition in abdomen causes rapid stretching of skin that results in striae
- Ecchymoses: Capillaries become thin and fragile – subcutaneous and intracutaneous haemorrhages
- Proximal myopathy: Legs – thin proteolysis of muscles and reduced bone mass
- Poor wound healing: Due to hyperglycemia
- Hyperglycemia: 20% develop insulin resistant diabetes mellitus
- Osteoporosis: May cause pathological fractures
- Emotional changes
- Hyperacidity and peptic ulcer
- Hairs – thin and scraggly

DIAGNOSIS

- Increased plasma cortisol
- Failure to suppress cortisol levels by dexamethasone (DEXAMETHASONE SUPPRESSION TEST)
- Plasma ACTH levels (High – ACTH dependant, Low – ACTH independent)

TREATMENT

- Surgical resection
- Inhibiting steroidogenesis by ketoconazole

ADRENOCORTICAL INSUFFICIENCY:

PRIMARY ADRENAL INSUFFICIENCY: - (ADDISON'S DISEASE)

- Atrophy
- Surgical removal
- Infection
- Bilateral hemorrhage into gland
- Metastatic invasion
- Drugs like ketoconazole

SECONDARY ADRENAL INSUFFICIENCY

- Pituitary disease (Decreased ACTH)
- Hypothalamus disease (Decreased CRH)

ADDISON'S DISEASE – ETIOLOGY

- Atrophy – idiopathic (Mostly autoimmune)
- Tubercular infection of adrenal gland
- Secondary metastasis to gland
- Amyloidosis
- Cytomegalovirus infection

CLINICAL FEATURES: -

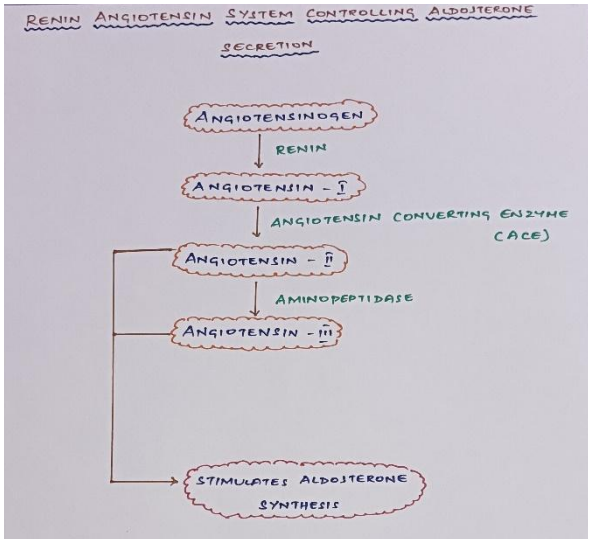
- Loss of weight and easy fatigability
- Pigmentation of skin: Hyperpigmentation of skin over pressure points, sun exposed areas, scar marks due to increased levels of ACTH (As ACTH has MSH activity – pigmentation)
- Hypotension: Due to decreased mineralocorticoid activity
- Hypotensive shock – in severe cases
- Anorexia, nausea, abdominal pain
- Hyponatremia
- Eosinophilia: As cortisol causes eosinopenia, deficiency causes eosinophilia
- Rapid hypoglycaemia on fasting
- Collapse during stressful conditions

DIAGNOSIS: Decreased cortisol + Increased ACTH

TREATMENT: Hormone replacement therapy

MINERALOCORTICOID

REGULATION OF ALDOSTERONE SECRETION



HYPERKALEMIA

- Aldosterone synthesis stimulated by increased K+ levels in ECF
- Rise in ECF K+ activates voltage gated calcium channels that increases intracellular calcium
- Increased cytosolic calcium increases aldosterone secretion
- Acute decrease in Na+ levels also stimulate its secretion
- K+ levels – natural regulator of K+ in ECF

ANGIOTENSIN RECEPTORS

- AT I – Present on Zona glomerulosa of adrenal cortex
- AT II – Binds to AT I receptor increases intracellular calcium that facilitates aldosterone secretion

MECHANISM OF ACTION

- Binds with glucocorticoid receptor in cytoplasm
- Displaces inhibitory heat shock protein from receptor
- Causes hyperpolarisation of receptor
- Binds with specific glucocorticoid regulatory elements on target DNA molecule
- Translation of mRNA's that regulate various genes

ACTIONS

- Increase Na+ and water reabsorption
- Promote K+ and H+ excretion

MECHANISMS

- Increases number of Na+ channels in tubular epithelium
- Stimulates Na+ - K+ activity
- As Na+ is reabsorbed Cl- is transported same direction to maintain electrical neutrality
- Reabsorption of Nacl – osmotic reabsorption of water
- Reabsorption of salt and water – ECF expansion

ALDOSTERONE ESCAPE PHENOMENON

- Increased reabsorption of salt and water – ECF expansion
- Increased ECF volume – increases venous return to heart
- Causes distension of atria during filling
- Atrial stretching increases secretion of ANP (Atrial natriuretic peptide)
- ANP causes profound natriuresis and diuresis
- Thus, ECF volume return back to normal – kidney escapes from the effect of aldosterone

HYPERSECRETION OF ALDOSTERONE

PRIMARY HYPERALDOSTERONISM

- Due to adrenal adenoma, adrenal hyperplasia, adrenal carcinoma
- Renin secretion – decreased (feedback)

CONN'S SYNDROME

- Due to adenoma of zona glomerulosa of adrenal gland
- Hypertension (sodium retention, ECF expansion)
- Muscle weakness (potassium depletion)
- Polyuria (impairment of urine concentrating ability)
- Edema – usually not a feature
- Hypokalemia, hypernatremia, low renin, metabolic alkalosis – lab findings

SECONDARY HYPERALDOSTERONISM

- Activation of RAAS due to increased renin
- Occurs in congestive heart failure, cirrhosis of liver, nephritic syndrome, renin secreting tumors
- Edema – usually present

BATTER SYNDROME

- Due to hyperplasia of JG cells
- Mutation in Na+K+2Cl- co transporter gene
- High renin and increased aldosterone synthesis
- Hyperaldosteronism – K+ depletion
- Hypokalemic alkalosis and hypercalciuria – common features
- BP remains normal and no edema

HYPOSECRETION OF ALDOSTERONE

CAUSES

- Adrenal insufficiency
- Inherited defects in aldosterone synthesis
- Decreased renin production (Hyporeninic hypoaldosteronism)
- Surgical removal of gland
- Protracted heparin administration
- Pretectal disease of nervous system
- Severe postural hypotension
- Unresponsiveness to Ang II (Hyperrenimic hypoaldosteronism)

CALCIUM HOMEOSTASIS

PLASMA LEVEL OF CALCIUM:

Normal plasma Ca^{2+} concentration – **9-11 mg/dl** (avg: 10 mg/dl)

PHYSIOLOGICAL FUNCTIONS OF CALCIUM

- Activation of enzymes
- Blood coagulation
- Contraction of muscles via calmodulin
- Development of bone and teeth
- Exocytosis (for secretion of various exocrine and endocrine glands)
- Genesis of pacemaker potential and maintenance of action potential
- Hormonal actions [Ca^{2+} acts as **2nd messenger**]
- Integrity of cell membrane
- Junction – for neurotransmitter release in neuromuscular junction & impulse transmission

MNEMONIC: **"ABCDE GHIJ"**

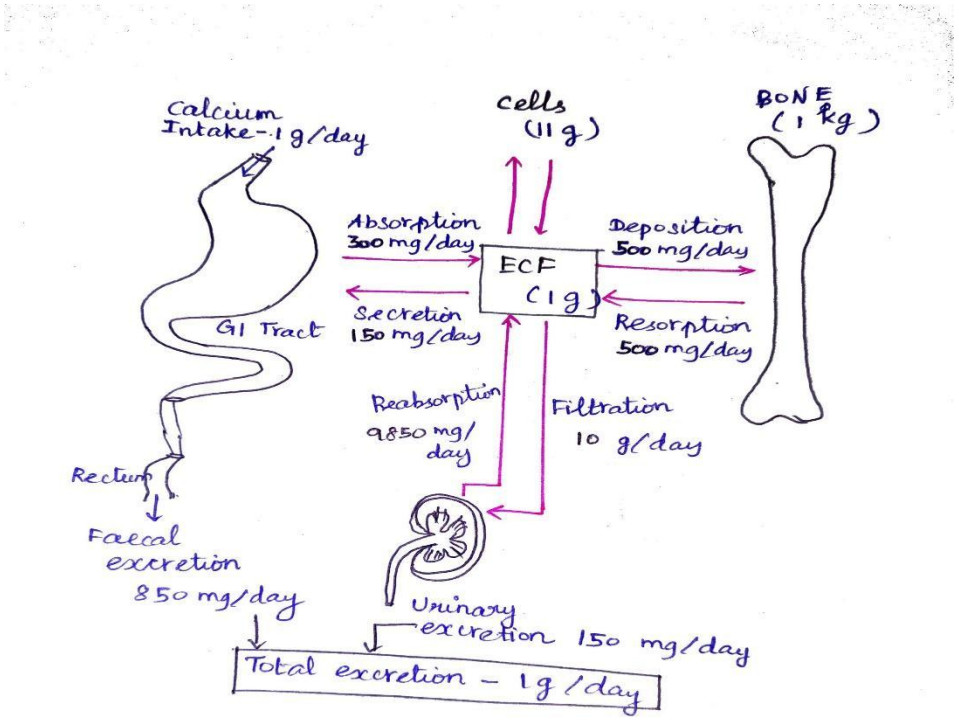
DISTRIBUTION IN BODY

Total body content	1200g average
In bones and teeth	99% of total
In ICF	0.9%
In ECF	0.1%

VARIOUS FORMS OF CALCIUM

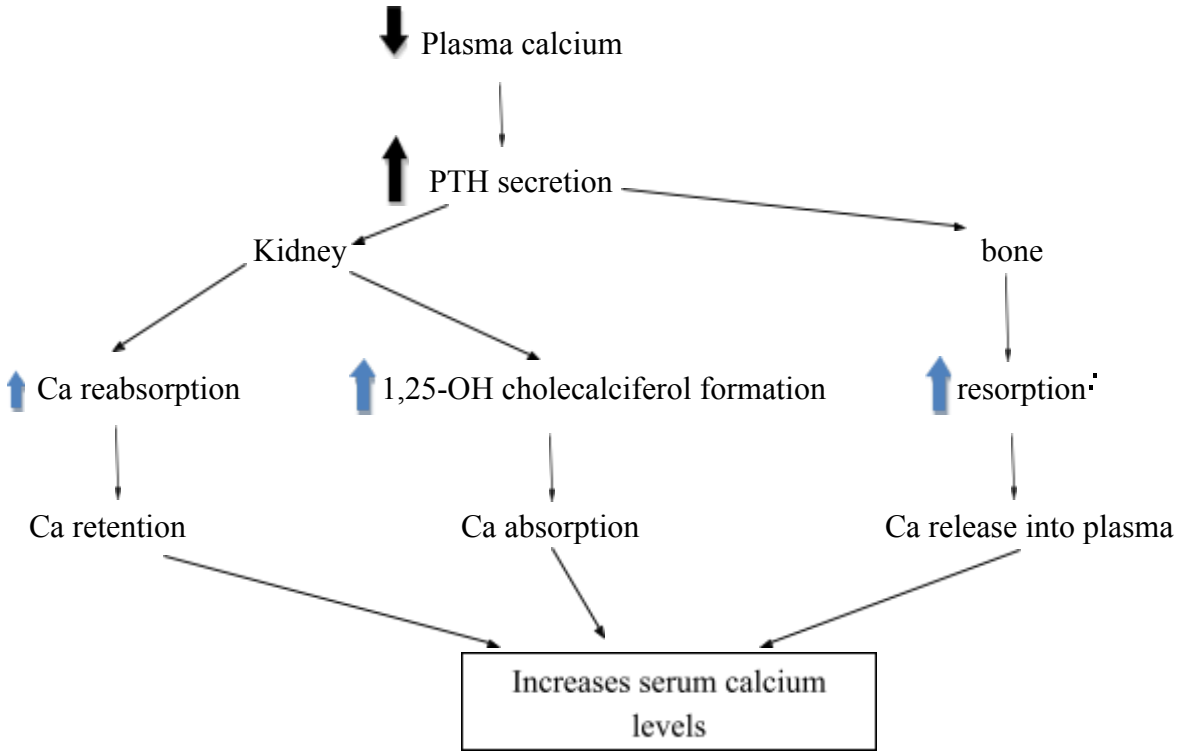
1. Ionized form = 50% (**biologically active form)**
2. Protein bound = 40%
3. Non ionized form= 10%

METABOLISM OF CALCIUM INSIDE BODY:

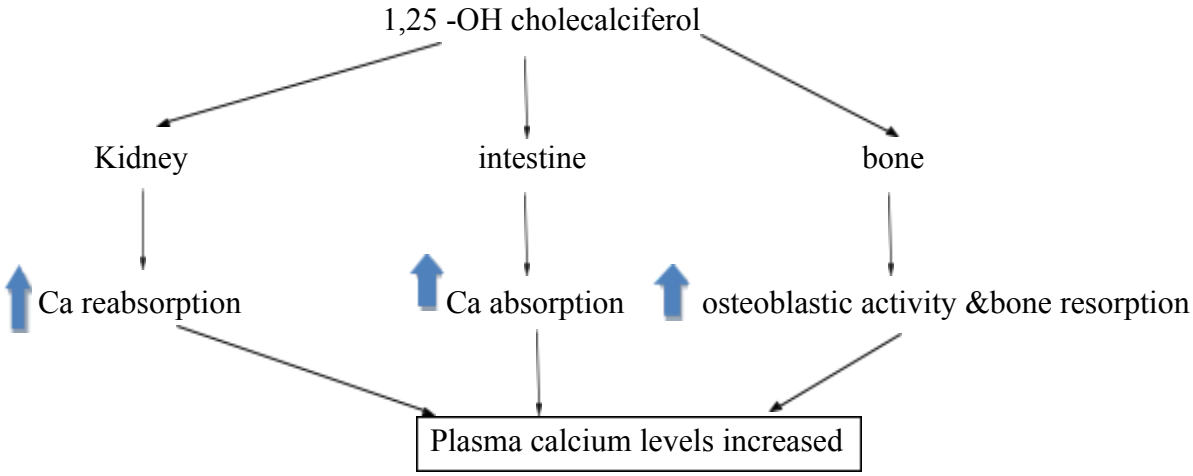


ROLE OF VARIOUS HORMONES:

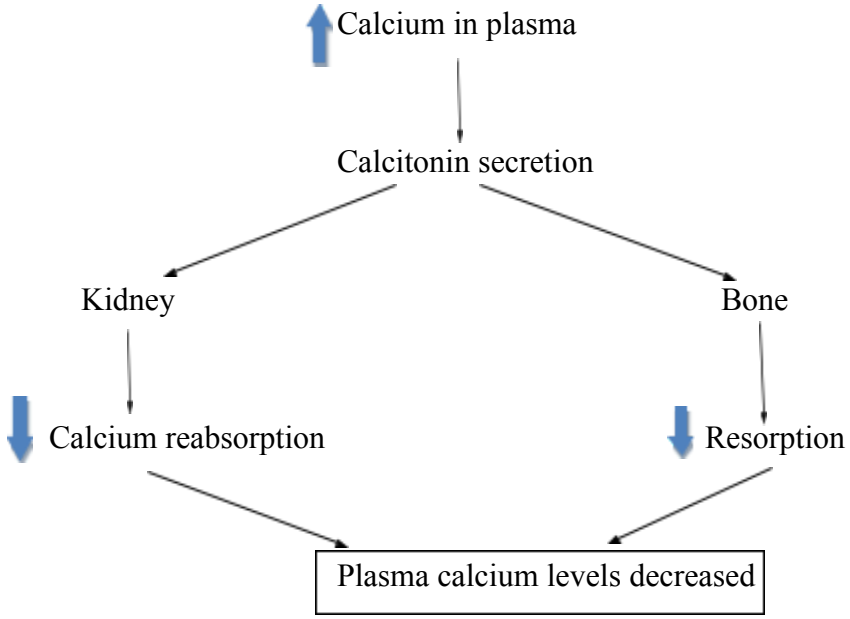
1)PTH: increases plasma calcium



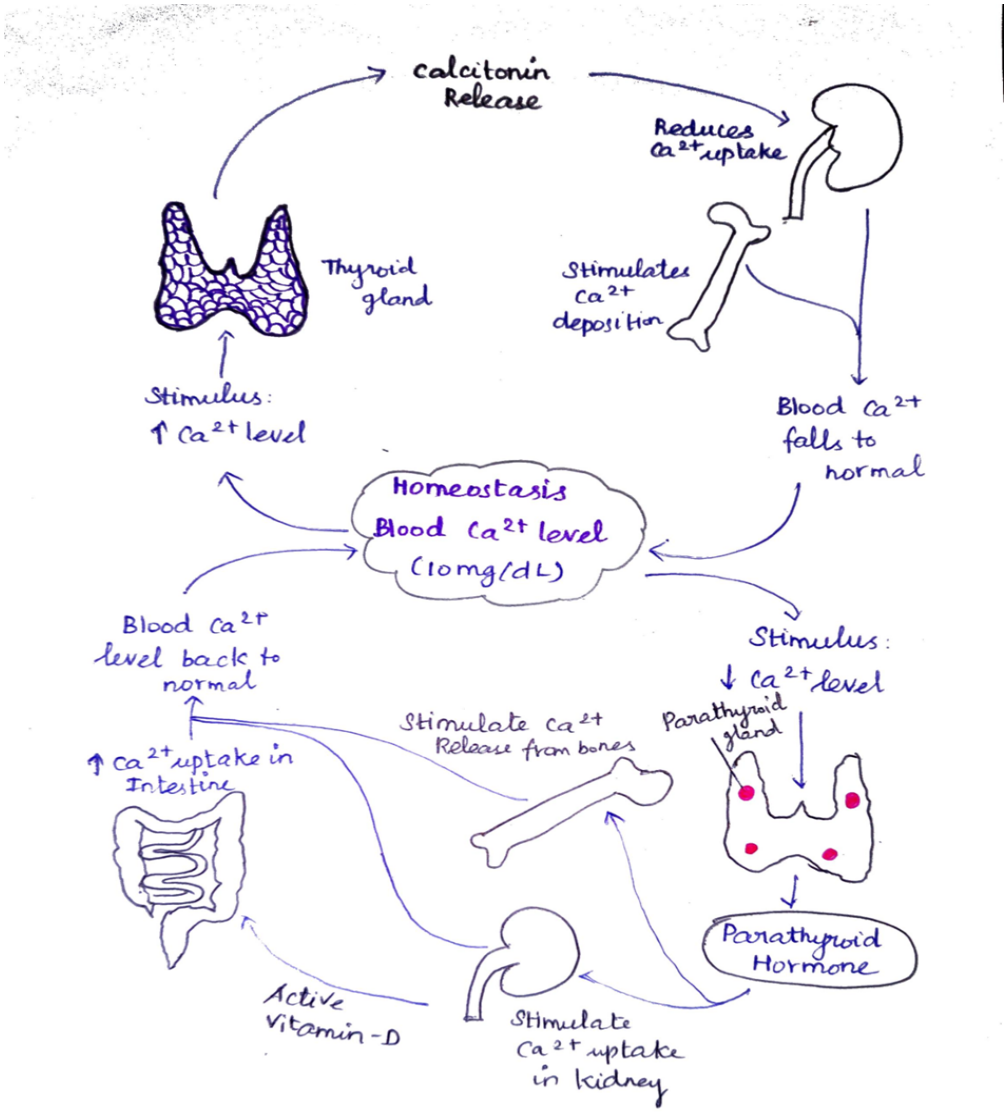
2. VITAMIN D :



3.CALCITONIN:



SUMMARY OF CALCIUM HOMEOSTASIS:



APPLIED ASPECT:

OSTEOPOROSIS:

- decrease in bone mass and density
- types: involutional and post-menopausal
- as age progresses, osteoclastic activity increases and osteoblastic activity decreases reduction in bone mass

CAUSES:

- ❖ hyperparathyroidism
- ❖ hyperthyroidism
- ❖ alcoholism
- ❖ vitamin c deficiency
- ❖ Smoking
- ❖ Ovarian diseases
- ❖ Cushing's syndrome
- ❖ Inadequate dietary Ca

CLINICAL FEATURES:

- ✔ Increased susceptibility of bone fracture common in elderly
- ✔ Trabecular bones are lost more rapidly
- ✔ Commonly affected: vertebra, hip bone, bones in distal forearm

TREATMENT:

- Administration of calcium tablets
- Vitamin d tablets
- Estrogen therapy (rarely)

SHORT NOTES

FUNCTIONS OF INSULIN, MECHANISM OF ACTION, NOTE ON SOMATOMEDIN C

INSULIN:

- Insulin is a peptide hormone (51 amino acids) consisting of A and B chain connected by Disulphide bond
- Insulin was discovered by Banting and best in 1921
- It is secreted by the β cells of pancreas
- Insulin secretion is regulated by plasma glucose concentration
- Normal basal rate of insulin release is 1- 2Units/hour

FUNCTIONS OF INSULIN:

ON CARBOHYDRATE METABOLISM

- The primary function of insulin is to lower the plasma glucose concentration (Insulin is secreted at the fed state)

In skeletal muscle and adipose tissues,

- Insulin facilitates glucose entry by activating hexokinase and GLUT-4 activity

In liver,

- Insulin promotes glycogen synthesis by activating glycogen synthetase
- It inhibits hepatic glycogenolysis by inhibiting glycogen phosphorylase and glucose-6-phosphatase
- It inhibits gluconeogenesis by inhibiting enzymes participating in gluconeogenesis
- It stimulates glycolysis by activating the enzymes phospho-fructo kinase and pyruvate kinase
- It facilitates glucose entry into hepatocytes by stimulating glucokinase

ON FAT METABOLISM:

- Insulin is the only anti-ketogenic hormone in the body
- It promotes lipogenesis and increases the entry of free fatty acids, glucose into the adipose tissue
- It stimulates lipoprotein lipase and inhibits hormone sensitive lipase

ON PROTEIN METABOLISM:

- Insulin promotes protein synthesis in ribosomes and increases uptake of amino acid into liver and skeletal muscle cells

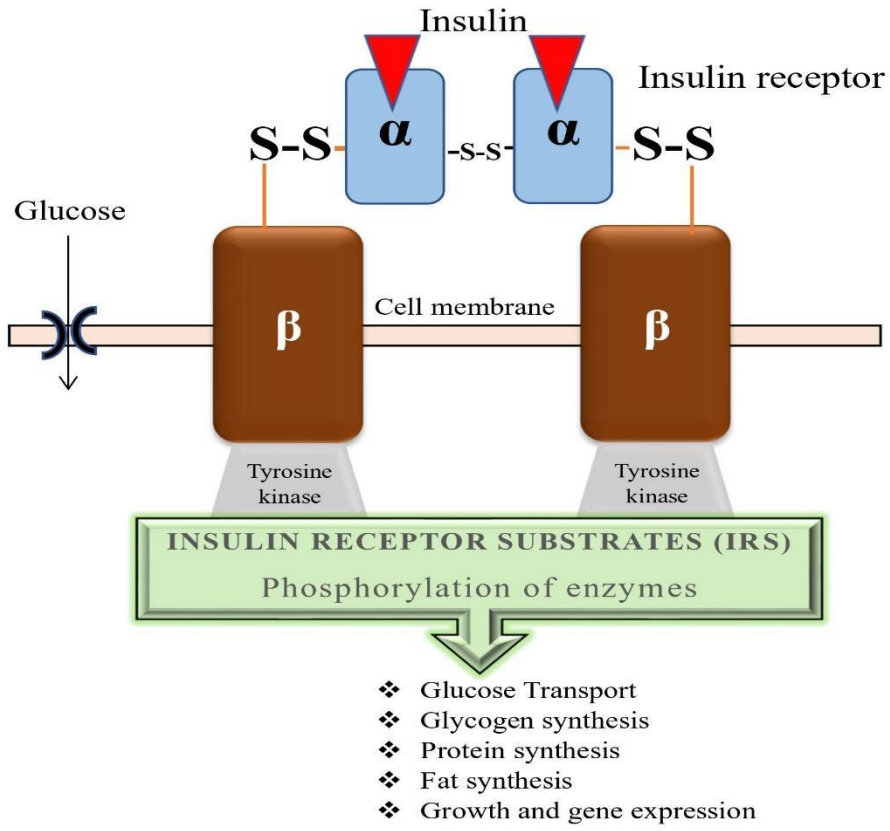
ON MINERALS:

- Insulin causes rapid entry of K^+ into the cell, thus causing hypokalaemia
- It stimulates renal reabsorption of K^+ , Na^+ and phosphates

GROWTH PROMOTING ACTION

- Insulin stimulates transcription of genes for growth factors such as IGF-I and II

MECHANISM OF ACTION:



SOMATOMEDIN- C:

- Insulin like growth factor- I (IGF- I) is also called as "Somatomedin- C"
- IGFs are polypeptide(70 amino acids) growth factors synthesized mainly in liver and it mediates the effect of growth hormone
- IGF- I is secreted independent of GH before birth. After its secretion and actions are dependent on GH
- It peaks at puberty and declines in old age
- Plasma concentration – 10 -700ng/ml
- ACTIONS:
  - Growth stimulating activity
  - Control of skeletal and cartilage growth

ADRENAL MEDULLA

CHROMAFFIN CELLS

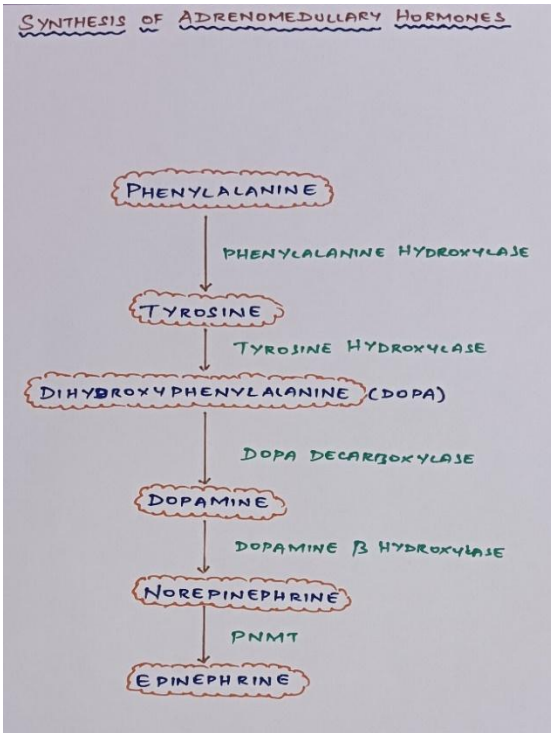
- Gland has clumps of chromaffin cells
- Store catecholamines
- Epinephrine secreting type (90%) - Larger and less dense granules

HORMONES

- Epinephrine
- Norepinephrine
- Dopamine
- Adrenomedullin
- Enkephalin
- Endorphins
- Neuropeptide Y
- Chromogranin

CATECHOLAMINES

SYNTHESIS



REGULATION

- Glucocorticoid – increases synthesis of epinephrine
- 21β hydroxylase – necessary for development of adrenal medulla
- Exercise, hypoglycaemia, trauma, anger, anxiety, pain, cold – increases synthesis

METABOLISM

- Under the influence of COMT and MAO epinephrine and norepinephrine are converted to Vanillylmandelic acid (VMA)
- Urinary excretion of VMA is 400 – 600 µg , its urinary excretion is the index of sympathetic activity

ACTIONS

Acts through α and β receptors

METABOLISM

- CARBOHYDRATE: Increase plasma glucose levels
- FAT: Promote lipolysis and stimulates FFA and ketone body formation
- THERMOGENESIS: Increases BMR
- FIGHT OR FREIGHT RESPONSE
  - Increases cardiac output
  - Promote blood flow to organs
  - Increase ventilation
  - Stimulate energy supply
  - Relax smooth muscles of GIT and urinary system
  - Causes piloerection
- EFFECT ON CVS
  - Increases heart rate, force of contraction and hence increases cardiac output
  - Cause selective arteriolar constriction in renal, splanchnic, cutaneous vascular bed
  - Pulse pressure widens
  - Diverts blood and maintains cerebral and coronary blood flow
- EFFECT ON GIT: Inhibit gastrin secretion and motility
- EFFECT ON RS: Cause bronchial dilatation and stimulate respiration
- EFFECT ON EYE: Pupillary dilation
- EFFECT ON ENDOCRINE GLANDS
  - Stimulate ADH release
  - Increase renin secretion
  - Increase thyroid hormone secretion and promotes peripheral conversion of T4 to T3
- EFFECT ON KIDNEY
  - Increases Na+ reabsorption
  - Increases renin formation and increases Na+ and water retention
- EFFECT ON ELECTROLYE BALANCE
  - Stimulate entry of K+ into muscle cells
  - Decrease plasma K+

ACTIONS OF DOPAMINE

- Renal and mesenteric vasodilation
- Vasoconstriction in other parts
- Positive inotropic effect and increases cardiac output
- Increases systolic pressure
- Natriuresis

USES OF CATECHOLAMINES

- AGONISTS – nasal decongestant, appetite inhibitor, stimulation of general body functions
- ANTAGONISTS – Hypertension, Hyperthyroidism, treatment of shock

PHEOCHROMOCYTOMA

- Tumor of adrenal medulla
- Hyperplasia of chromaffin cells
- Proliferation of chromaffin cells of paraganglia
- Concentration of epinephrine and norepinephrine is very high

FEATURES

- Sustained hypertension
- Increased metabolic rate
- Tachycardia
- Hyperglycaemia
- Loss of body weight and appetite
- Burst of catecholamine release during change in posture or sympathetic stimulation – severe headache, tachycardia, palpitation, extreme anxiety, perspiration, pallor/ flushing, severe rise in BP, feeling of impeding death

DIAGNOSIS

- Increased catecholamines in blood
- Urinary excretion of metanephrine and VMA (Vanillylmandelic acid) also increased

TREATMENT

- Surgical removal of tumor
- α blocker

ROLE OF CATECHOLAMINES IN STRESS

- Stress activates CRH and ADH which in turn increases catecholamine levels
- They together increase glucose concentration in plasma
- They also shift glucose utilization from peripheral tissues to neural tissues
- Increases supply of FFA to heart
- Increase cardiac output and BP
- In chronic stress, reproductive functions, sexual activity, feeding – suppressed

MILK EJECTION REFLEX

DEFINITION:

Discharge or expulsion of milk from the breast of the mother into mouth of the baby when baby suckles during breastfeeding is called milk ejection reflex

SIGNIFICANCE:

- It is an example of **neurohumoral reflex** ~ hormones form efferent limb in reflex pathway
- Involves both neurons and hormones in the reflex pathway

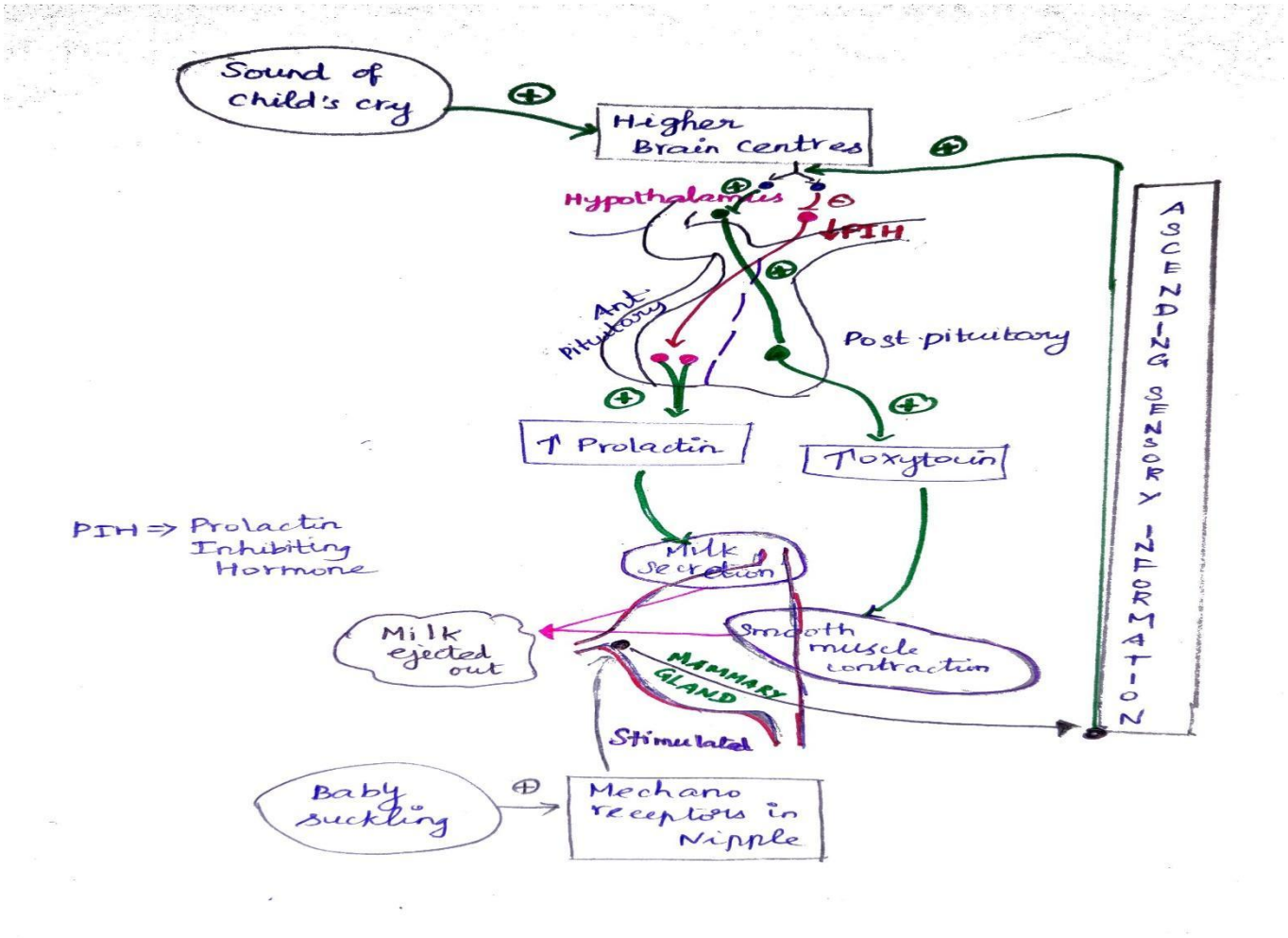
RECEPTORS:

- **TACTILE** [touch] receptors in and around the nipple

REFLEX ARC:

- STIMULUS: Nipple stimulated by suckling of baby
- AFFERENT: Neural impulses from nipple ⟶ spinal cord ⟶ **spinothalamic tract** to brain stem
- CENTRE: **HYPOTHALAMUS** (para ventricular nucleus)
- EFFERENT: Via hypothalamo-pituitary axis, **oxytocin** is released from **posterior pituitary**
- EFFECTS: Oxytocin causes contraction of myoepithelial cells of alveoli

Due to initiation of this reflex, milk from mother's breast is forcefully discharged into baby's mouth. So, it is called milk ejection reflex



GIGANTISM

- Also called as pediatric Gigantism / Giantism
- It is due to the **overproduction of GH** during adolescence (before epiphyseal closure) and is characterized by excessive growth of long bones.

Causes:

- Adenoma: tumor of the pituitary gland

  Adenoma of pituitary gland

  ↓

  Excessive production of GH

  ↓

  Gigantism

- A hypothalamic tumor causing excess GHRH can also cause gigantism.

Features

1. Tall Stature (excessive) tallness as much as 2.5metre or 8 feet
2. Bilateral gynecomastia (enlargement of breast)
3. Large hands and feet
4. Associated Features
    i. Coarse facial features
    ii. loss of libido
5. The patient will have all features of acromegaly except the acromegalic facies.

Treatment

- Surgery - to remove the pituitary tumor
- Radiotherapy – to slow me growth of the tumor
- Growth hormone antagonists

ACROMEGALY

- It is due to the excessive secretion of GH during adulthood (after epiphyseal closure)
- In 20-40% it is associated with hyper secretion of prolactin
- It causes excessive growth in those area where cartilage persist

Causes:

- ❖ Occurs due to tumor of the somatotroph of anterior pituitary
- ❖ Or also occurs due to the excess secretion of hypothalamic GRH (extra pituitary causes)
- ❖ In most of these patients, there is also consequent prolactin increase that is associated with proliferation of lactotrophs.

Features

- Enlargement of acral parts of the body, especially hands and feet.
- prognathism: enlargement of mandible and protrusion of lower jaw.
- Cardiomegaly

- Hepatomegaly
- Thickening of skin
- Splenomegaly
- Hypertrophy of tongue and muscles
- Acromegalic facies: overgrowth of malar, frontal and facial bones
- Increased amount of body hair
- Osteoarthritis due to skeletal changes
- Glucose intolerance
- Hirsutism
- Bitemporal hemianopia: due to the compression of the tumor on the optic chiasm.

Treatment

- Growth hormone antagonists
- Surgery or radiation to remove for reduce the size of tumor

DIFFERENCE BETWEEN GIGANTISM & ACROMEGALY

Gigantism	Acromegaly
Hyper secretion of GH before the closure of epiphyseal center	Hyper secretion of GH after the closure of epiphyseal center

DWARFISM

- It is due to the deficiency of GH secretion in immature individual
- It results in stunted growth

Causes

Endocrinal causes

- Growth hormone deficiency (Pituitary Dwarf)
- Panhypopituitarism
- Hypothyroid dwarfism
- Cushing's syndrome

Non- Endocrinal Causes

- Familial dwarfism
- Achondroplasia
- Nutritional defects
- Chromosomal abnormalities

Features

- Retardation of growth in all parts of body
- Normal mental activity (except in cretinism where the baby will have mental retardation)
- Plumpness (Fatness)
- Immature faces
- Delicate extremities
- Low levels of IGF-1 in plasma

Laron Dwarfism

- It is due to be abnormality of GH receptors
- It is a congenital defect and is otherwise called growth hormone insensitivity syndrome

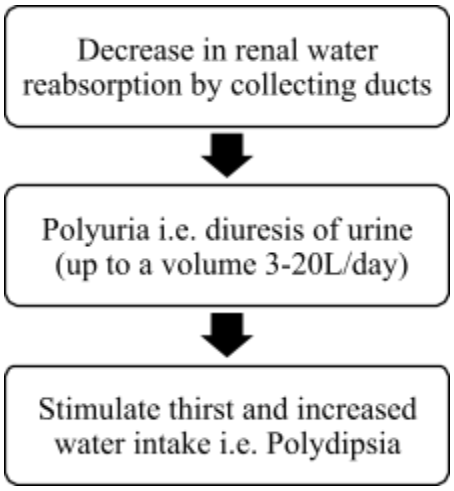
Treatment

- Surgical treatment correcting the direction which bones are growing
- Placing a short to remove excess fluid around the brain (If hydrocephalus has occurred)
- Recombinant human growth hormone

DIABETES INSIPIDUS & ITS TYPES

- **Definition**: Deficiency of ADH in which an abnormally large volume of dilute urine is produced.
- **Clinical Features**

  - Polyuria (3 to 20 L/day)
  - Polydipsia (Secondary to dehydration caused by Polyuria)
  - Dehydration



*Polyuria and Polydipsia are also featuring of Diabetes Mellitus

Diabetes Mellitus	Diabetes Insipidus
• Mellitus means tasty i.e. sweet in taste • It is hyperosmolal, due to loss of Glucose and urine > 1200 mOsm/L	• Insipidus mean tasteless, hence urine will be tasteless. • It is dilute urine, there is pure water loss, osmolality is < 300 mOsm/L

There are two types of Diabetes Insipidus

Nephrogenic

1. Kidney not responsive to ADH
2. ADH secretion is normal, but there is receptor deficiency or abnormality
3. The causes are genetic or acquired
4. The genetic causes are
    a. Autosomal Defect: Aquaporin 2 deficiency
    b. X-linked recessive disease: V2 receptor gene deficiency
5. Acquired causes are
    a. Metabolic Disorder
        i. Hypercalcemia
        ii. Hypokalemia
    b. Ischemia
        i. Acute tubular necrosis
    c. Infiltrative diseases
        i. Neuro Sarcoidosis
        ii. Amyloidosis
    d. Drugs
        i. Demeclocycline
        ii. Rifampicin
        iii. Aminoglycoside
        iv. Lithium
        v. Cisplatin
        vi. Amphotericin B

Neurogenic/ Central

1. Deficiency of ADH secretion
2. Causes are
    a. CNS Diseases
        i. Hypothalamus (Central Diabetes Insipidus)
        ii. Hypothalamo-hypophyseal tract (Neurohypophyseal Diabetes Insipidus)
        iii. Post pituitary (Pituitary diabetes Insipidus)
    b. Head Injury, tumors
        i. Craniopharyngioma
        ii. Suprasellar Pituitary tumors
        iii. Infections
            1. Meningitis
            2. Encephalitis
        iv. Vascular lesions
            1. Sheehan's syndrome
            2. Aneurysm of ICA
        v. Congenital/genetic defects

Treatment

- Vasopressin Injection
- Clofibrate therap

SYNDROME OF INAPPROPRIATE ADH SECRETION

- Excessive secretion of ADH occurs in clinical syndrome.
- ADH secretion is inappropriately high relative to serum osmolality.
- Syndrome of Inappropriate ADH is seen in:
  ➔ Head injury
- Ectopic produces of ADH
  - Some malignant tumors
  - CA lungs, pancreas, ovary, bladder

  ➔ Neurologic diseases like
    - Multiple sclerosis
    - Guillain Barre syndrome
    - Brain abscess
    - Meningitis
    - Encepliatis

  ➔ Drug
    - Desmopressin
    - Chlorpropamide
    - High dose of oxytocin
    - Phenothiazine
    - Carbamazepine

- In SIADH, there is dilutional hyponatremia caused by increased absorption of large quantity of water and natriuresis secondary to decreased aldosterone secretion
- If the SIADH is due to brain disease, the condition is called cerebral salt wasting.
- If the SIADH is due to lung diseases, then the condition is called pulmonary salt wasting.

Vasopressin escape:

- In lung cancers and other malignant tumors, ADH secretion is very high.
- In such conditions, the water retaining action of ADH is countered by a process called vasopressin escape that limits the degree of hyponatremia
- This escape phenomenon occurs due to the down regulation of aquaporins in the collecting duct.
- Thus, the urine output increases despite high levels of ADH in plasma, which indicates that the kidney has escaped from the effects of vasopressin.

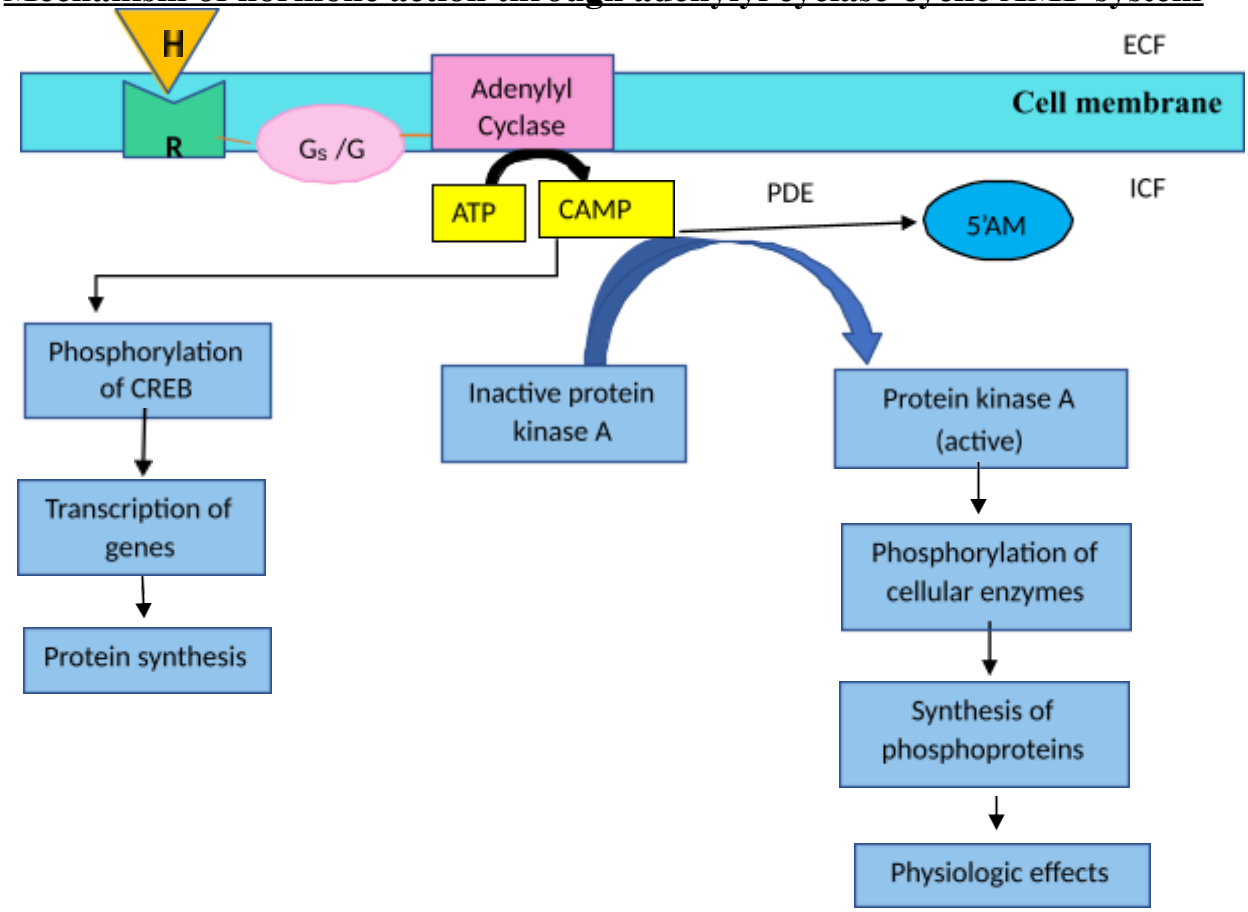
SECONDARY MESSENGER MECHANISM

- **Secondary messengers:** The intracellular signal molecules that are formed by a series of enzymatic reactions subsequent to the formation of HR complex are designated as second messengers.
  - Second messengers are formed depending on the hormone signaling of the effector cells.
  - The signal transduction pathways are activated depending on G protein activation of membrane enzymes.
  - E.g.: cyclic AMP, diacylglycerol (DAG), inositol triphosphate (IP3), cyclic GMP, phosphoproteins, transcript new mRNAs, and intra-cellular calcium.

Second messengers are formed by activation of four main transduction systems:

- Adenylyl cyclase–cyclic AMP system
- Membrane phospholipase–phospholipid system
- Guanylyl cyclase cyclic GMP system
- Transcription of mRNAs.

Mechanism of hormone action through adenylyl cyclase-cyclic AMP system

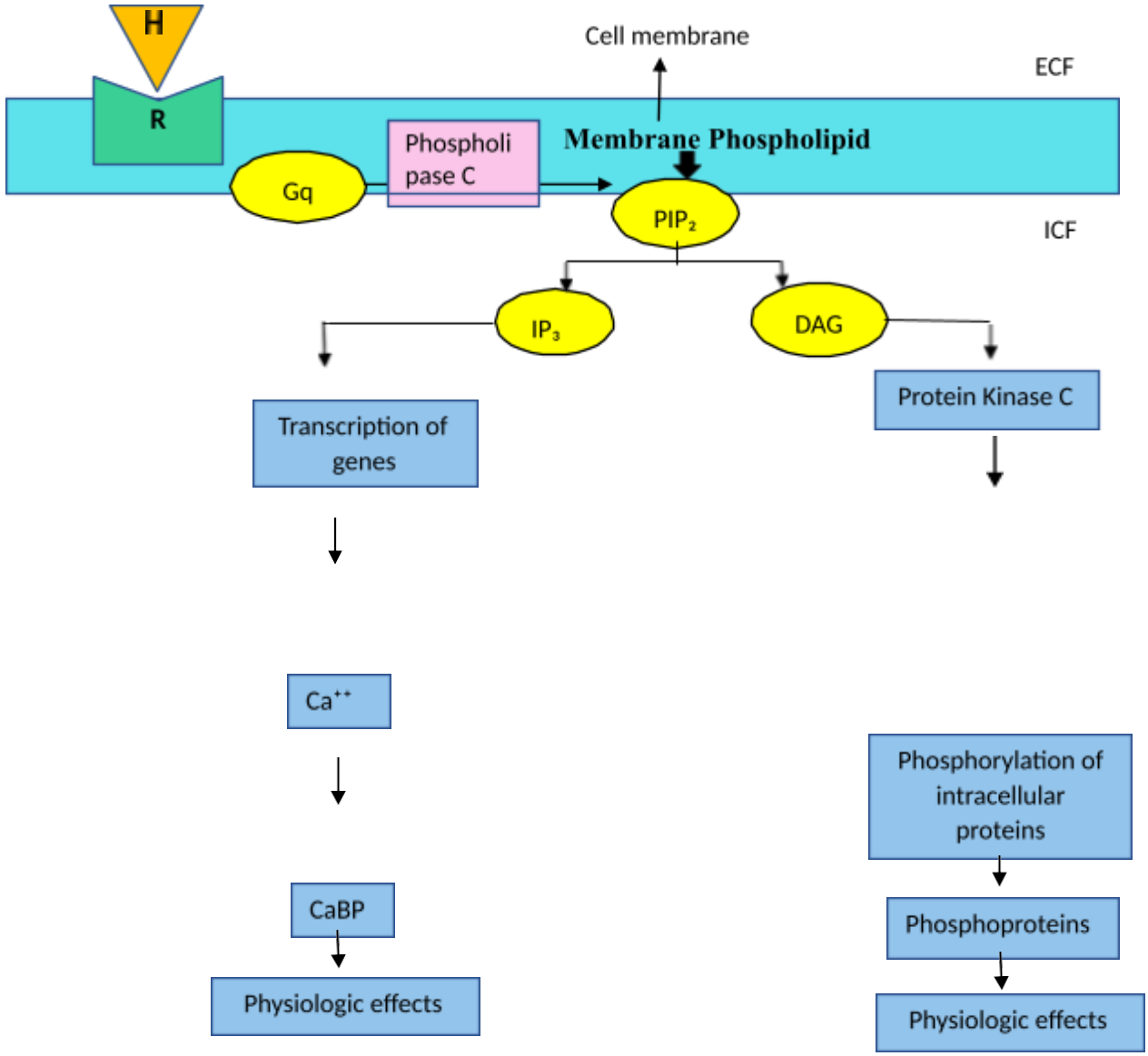


- Termination of cAMP Actions: cAMP is degraded to 5'-AMP in the cell by the cytoplasmic enzyme phosphodiesterase (PDE)

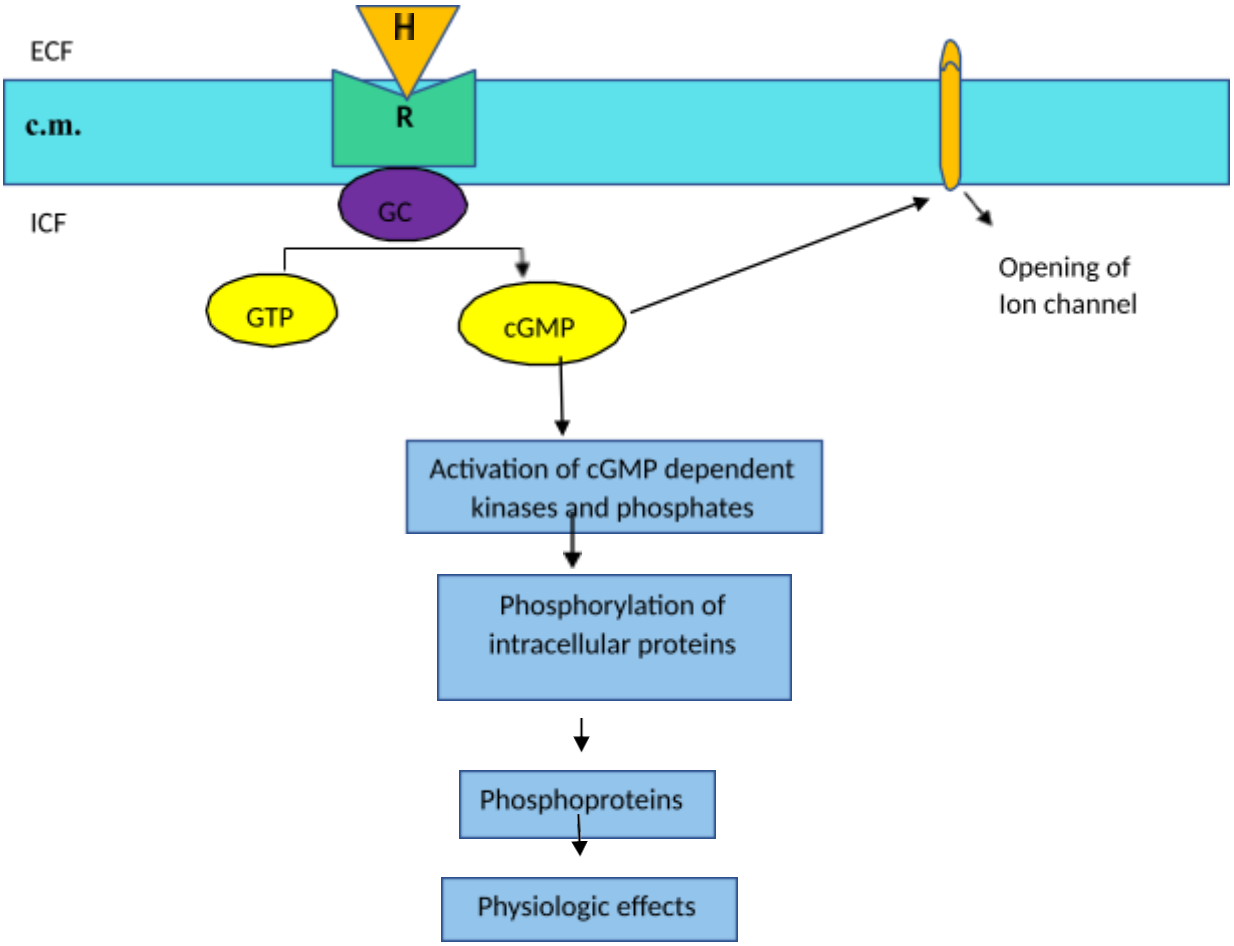
Clinical importance:

- Not only many hormones act through cAMP, but also, toxins released by various pathogens produce toxic features by altering cAMP concentration in the cell
- Cholera and pertussis toxins are examples of stimulation and inhibition of cAMP respectively

Membrane phospholipid-Phospholipase System (via IP3 and DAG)



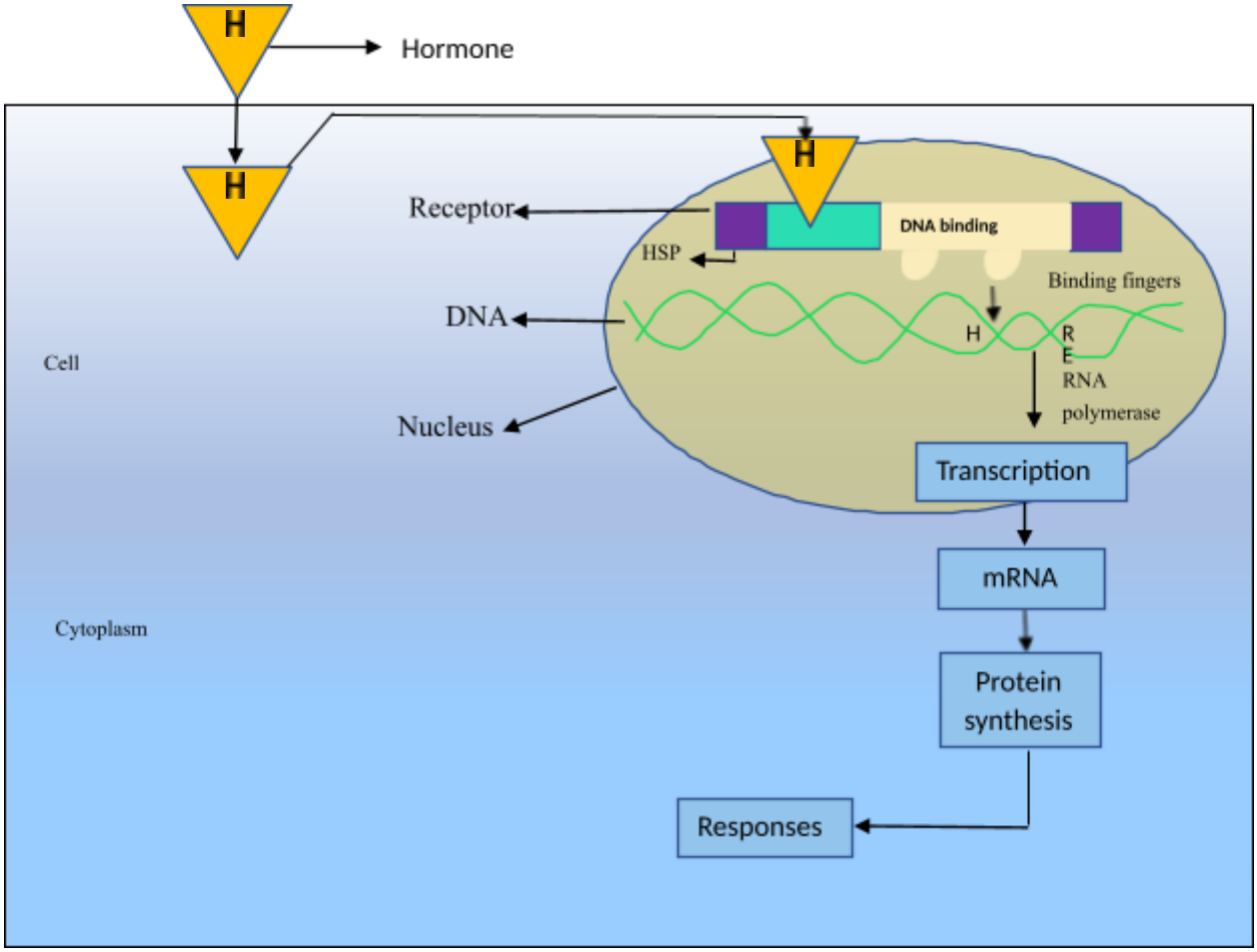
Guanylyl Cyclase-Cyclic GMP System



Intracellular Receptor (Transcription of mRNA) System:

- The receptors for thyroid and steroid hormones, 1,25-dihydroxycholecalciferol and retinoids are located inside the cell.

Intracellular receptor system



CUSHING'S SYNDROME

DEFINITION: It is a pathological condition with cortisol excess (Hypersecretion of glucocorticoids)

CAUSE:

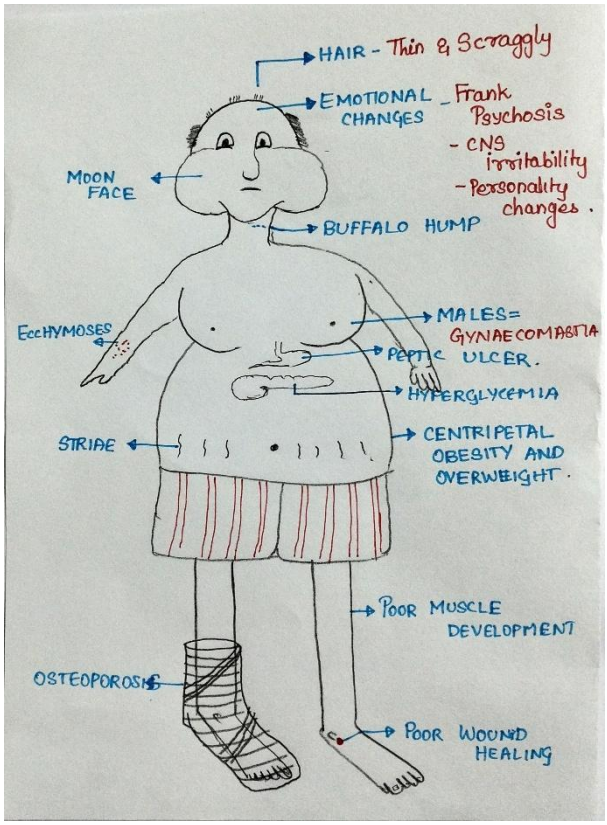
ACTH DEPENDENT

- Pituitary tumors (Cushing disease)

ACTH INDEPENDENT

- Adrenal hyperplasia
- Adrenal macro nodular hyperplasia
- Adrenal tumors
- Familial adrenal hyperplasia (Carney syndrome)
- Prolonged use of cortisol

CLINICAL FEATURES:



Mnemonic:

C: centripetal obesity and comedones (acne)

U: urinary free cortisol excess

S: suppressed immunity

H: hyperglycemia, hypertension, hypercortisolism, hypercholesterolemia, healing of wound is poor

I: iatrogenic (increased administration of corticosteroid)

N: Neoplasms

G: growth impairment

M: moon faces, myopathy of the proximal muscles

O: obesity

O: osteoporosis

N: neurological problems (Frank psychosis)

S: striae and ecchymosis

DIAGNOSIS:

1. Increased plasma cortisol levels
2. Dexamethasone suppression test

TREATMENT:

1. Surgical resection of tumor
2. Medical adrenalectomy
3. High dose of ketoconazole: inhibit cortisol synthesis

PHEOCHROMOCYTOMA

DEFINITION:

- Tumor of adrenal medulla
- Occurs due to hyperplasia of chromaffin cells
- Causing the increase in concentration of both epinephrine and norepinephrine.

FEATURES:

- Most common feature -SUSTAINED HYPERTENSION
- Cardiovascular feature
    - Tachycardia
    - Palpitations
    - Perspiration
    - Flushing
    - Rise in bp

- Metabolic features
    - Hyperglycemia
    - increased metabolism
    - Weight loss
    - Loss of appetite
- Gastrointestinal features

    - Nausea
    - Vomiting
    - Constipation

DIAGNOSIS:

- BLOOD-Increased concentration of catecholamine
- URINE-excretion of metanephrine and VMA increases

TREATMENT: Surgical removal of tumors

ADDISON'S DISEASE

DEFINITION:

1. Hyposecretion of glucocorticoids
2. **CAUSE**: progressive destruction of adrenals
    - o Idiopathic
    - Autoimmune destruction (hypothesis)
    - TB infection of adrenals
    - Secondary metastasis of tumor
    - CMV infection
    - Amyloidosis

CLINICAL FEATURES:

A -anorexia, abdominal pain (nausea, vomiting)

D-Dark skin (hyperpigmentation -less cortisol will increase ACTH by feedback mechanism and ACTH has intrinsic MSH activity)

D-decreased vascular reactivity

I-irritability

S-salt craving, stress, shock (hypotensive)

O-orthostatic hypotension

N-Na low (hyponatremia), hyperkalemia

ADDISONIAN CRISIS:

Addisonian crisis is a serious medical condition caused by the body's inability to produce a sufficient amount of cortisol in response to a sudden stress event, such as an illness or infection.

- Hyponatremia
- Hyperkalemia
- Hypoglycemia
- Hypotension
- Dehydration

DIAGNOSIS: decreased plasma cortisol level

TREATMENT: hormone replacement therapy

MYXEDEMA

Hypothyroidism in adult is known as myxedema. Characterised by generalised oedematous appearance.

Hypothyroidism

Primary hypothyroidism	**Secondary hypothyroidism**
Due to defect in thyroid gland.	Due to defect outside thyroid gland.
1.Autoimmune: Hashimoto's thyroiditis	1. Pituitary resection, pituitary tumour
2.Thyroidectomy	2. Injury involving hypothalamus, tumour
3.Iodine deficiency	3. Thyroid hormone resistance
4.Excess of iodine, excess use of Antithyroid drugs.	
5.Congenital hypothyroidism	

Signs and symptoms:

Typical feature is oedematous swelling, associated symptoms-

1. Swelling of face
2. Bagginess under eyes
3. Non pitting oedema-accumulation of **hyaluronic acid** and **chondroitin sulphate**
4. Fatigue and muscular sluggishness
5. Increase in body weight, BMR decreases
6. Decrease in cardiovascular functions(**bradycardia**)
7. Depressed hair growth
8. Cold intolerance
9. Thick and husky voice
10. Menorrhagia

Diagnosis: -

T_3 and T_4 levels are decreased but TSH is increased

Treatment: -

Thyroid hormone replacement. T_4 is instituted at a dose to maintain normal level in plasma.

CRETINISM

- Hypothyroidism in children is known as cretinism.
- Hypothyroidism develops from or before birth.
- Patient is called as **cretins**

Causes:

1. Maternal iodine deficiency during pregnancy
2. Maldevelopment of thyroid gland during foetal life
3. Inborn errors of thyroid hormone synthesis
4. Hypopituitarism in foetal life
5. Use of antithyroid drugs during pregnancy

Features:

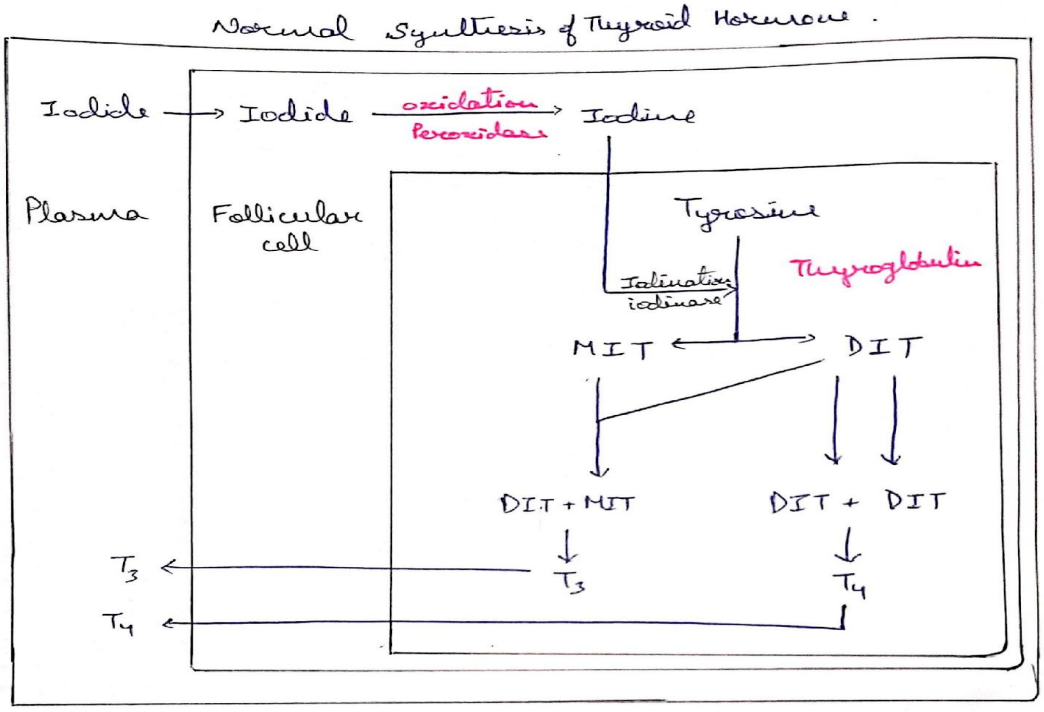
1. Dwarf
2. Bloated body (pot belly)
3. Protrusion of tongue
4. Mentally retarded
5. Reproductive system affected
6. Other features of hypothyroidism also present

Treatment:

- Mental retardation can be prevented if the disease is diagnosed and treated immediately after birth.
- Thyroid hormone replacement early in infancy can totally cure the disease.
- Prompt replacement of thyroxine.

HASHIMOTO'S THYROIDITIS

- It is an auto-immune disease.
- Common in late middle-aged women.
- In most patients start with glandular inflammation called thyroiditis caused by autoimmune antibodies.
- Antibodies act against thyroglobulin and thyroid peroxidase.
- Therefore, thyroid cells are damaged.



MIT → Monoiodotyrosine.
DIT → Di-iodotyrosine.

In Hashimoto's thyroiditis →

Antibodies against { Thyroglobulin
Thyroid peroxidase

∴ Iodide ⟶ Iodine

& Tyrosine ⟶ MIT / DIT

Therefore, no T_3, T_4.

Clinical features:

- Cold intolerance
- Weakness, easy tiredness
- Dry, thick skin
- Loss of hair
- Poor memory
- Inability to concentrate
- Constipation
- Weight gain despite poor appetite
- Thick and husky voice
- Yellow skin due to carotenemia
- Psychosis
- Menorrhagia, galactorrhoea, infertility
- BMR decreases to about -40, elevated plasma cholesterol levels
- Diastolic hypertension, decreased reaction time of tendon reflexes
- Carpal tunnel syndrome, periorbital oedema

Treatment:

- Thyroid hormone supplements
- T4 at a daily dose of 25mcg then increased/decreased based on the patient response.
- Serial T3 and T4 level monitoring required.

GRAVE'S DISEASE

Autoimmune disease and most common cause of hypothyroidism.

There is diffuse enlargement of thyroid gland usually associated with exophthalmos.

1. Due to autoantibodies against TSH receptors. Antibodies activate receptors.
2. Thyroid gland becomes hypertrophied and hyperactive.
3. Plasma level of T_3 and T_4 is very high.
4. TSH concentration is less as excess thyroid hormones inhibit TSH secretion.

Signs and symptoms: -

1. Intolerance to heat
2. Increased sweating due to vasodilatation
3. Decreased body weight
4. Increase in BMR
5. Diarrhoea due to increased GI motility
6. Nervousness, extreme fatigue, tremors
7. Tachycardia
8. Toxic goitre

9. Exophthalmos occurs due to swelling of extraocular muscles and oedematous swelling of retro-orbital tissues.
10. Oligomenorrhea or amenorrhea.

Treatment: -

The Disease is treated by using antithyroid drugs, by decreasing thyroid hormone synthesis, or by reducing the amount of thyroid tissue.

- Treatment of radioactive iodine I^{131}
- Subtotal thyroidectomy

HYPOTHALAMO PITUITARY AXIS

1)Tubero-infundibular tract and hypothalamo–hypophyseal portal system

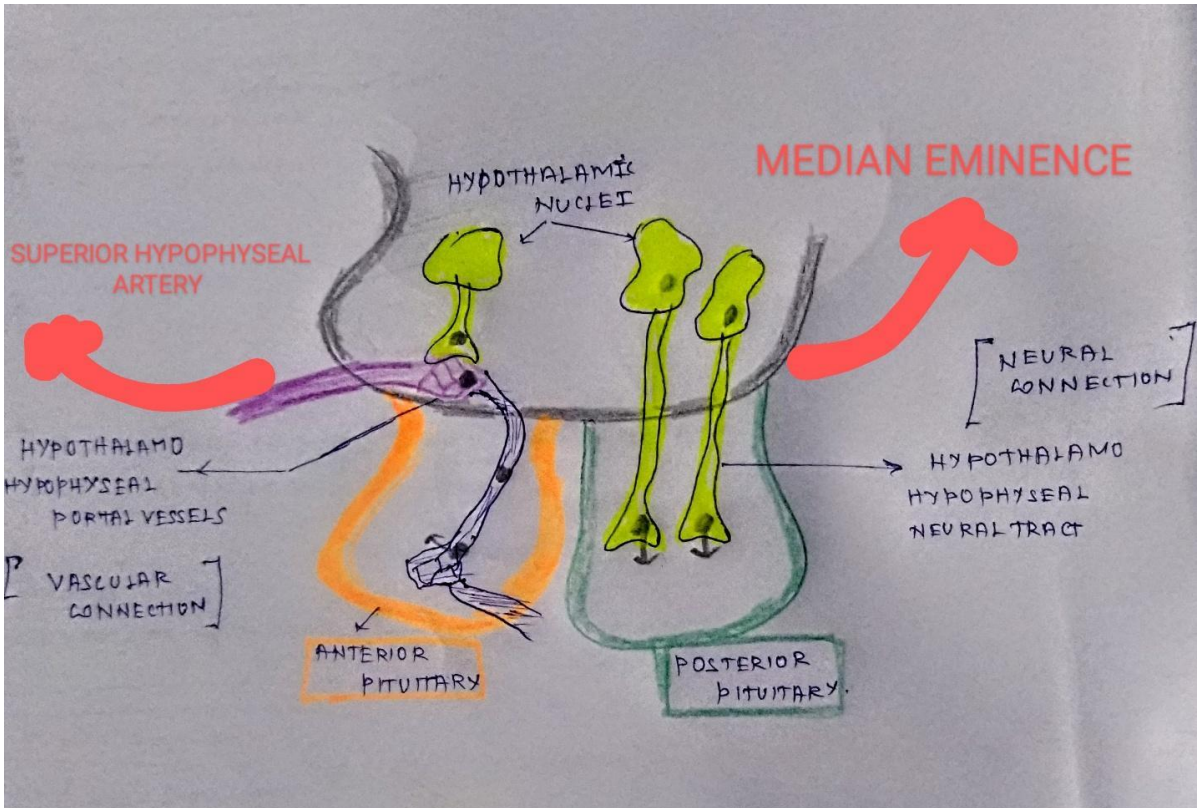
Fibres arising from the arcuate nuclei of the tuberal region of the hypothalamus and extends to the median eminence

↓

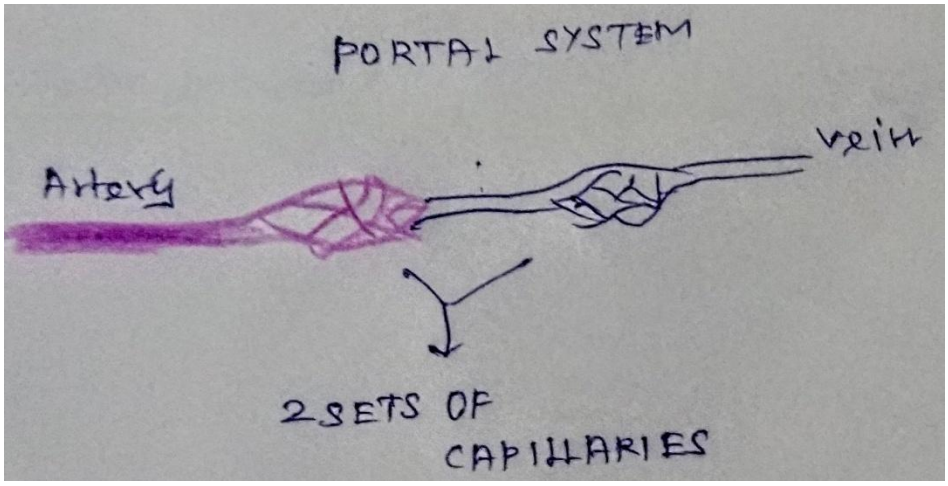
Cell bodies of these hypothalamic neurons synthesize hypothalamic hormones (Releasing and inhibiting hormone) to the median eminence region Where they are stored in the nerve terminals

↓

From where enter the capillary plexus of the Superior hypophyseal artery are transported down the portal vessels (long portal veins) and then exit from the secondary capillary plexus to reach the endocrine target cells in the adenohypophysis where they regulate the secretion of it



- The releasing hormones secreted from the hypothalamus reach the anterior pituitary via the hypophyseal tract. These hormones are also called as hypophysiotropic hormones
- Hypophysiotropic hormones are synthesised in the hypothalamic neurones (parvocellular neurones), the axon terminals contact the capillary network in the medial eminence and infundibulum that give rise to long portal vessels
- Short hypophyseal vessels communicate with the capillaries of anterior pituitary with the capillaries of the posterior pituitary which derives blood from the inferior hypophyseal artery.



2)Hypothalamo–hypophyseal tract:

It arises from the posterior pituitary and the hypothalamus. It is a completely neural connection.

The neurones for this tract are larger than the other neurones and are called as magnocellular neurons.

Axons of the large neurosecretory cells of the supraoptic and paraventricular nuclei of the hypothalamus (secrete peptide hormones i.e vasopressin and oxytocin)

↓

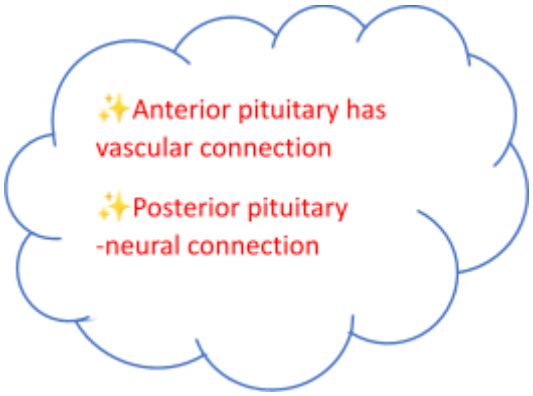
These Fibres pass to neurohypophysis through the infundibular Stem and form a series of dilated terminals known as Herring bodies.

↓

Upon stimulation of the cell bodies, the granules are released from the Axonal terminals by exocytosis.

↓

Hormones then enter the peripheral circulation via the capillary plexuses of Inferior hypophyseal artery



G PROTEIN COUPLED RECEPTORS

- Transmembrane receptors winds around cell membrane 7 times (serpentine receptor)
- G protein coupled receptors belong to several families of intrinsic membrane proteins that link receptors to the nearby effector molecules.
- G protein coupled receptors convert the signals to biological activities

Mechanism:

Hormone binds to receptor ---□ confirmational change ----□ Receptor binds to G protein intracellularly ---□ protein gets activated and bound to GTP ----□ alpha subunit dissociates from beta and gamma ----□ alpha subunit activates effector (Gs ,Gi,Gq)

Types of GPCR:

the classification is based on the alpha subunit of the GPCR

Gs:

- It uses the enzyme adenylyl cyclase
- The second messenger used is cAMP
- Effects: increase cell functions and increase protein synthesis

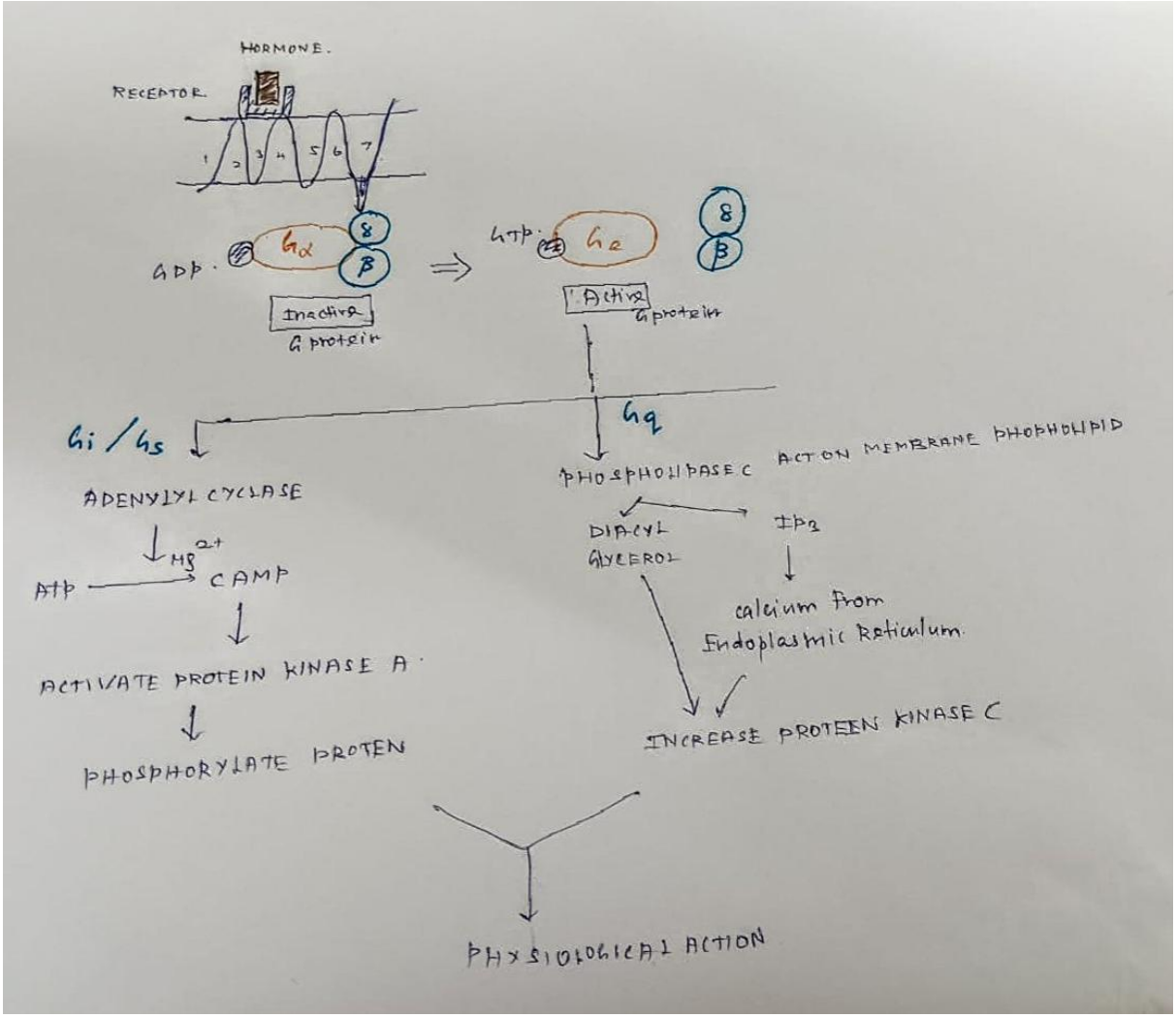
Gi:

- It inhibits the adenylyl cyclase enzyme
- As a result, it decreases the functions of cAMP that causes a decrease in cell protein synthesis

Gq:

- It uses the second messenger IP3-DAG

- It uses the enzyme phospholipase C that increases the activity of protein kinase C that cauzes the activation of many intracellular enzymes and proteins.



PROLACTIN

(Hormone for milk synthesis)

STRUCTURE

- Polypeptide hormone
- 198 AA
- Similar structure with human GH

SOURCE & SYNTHESIS

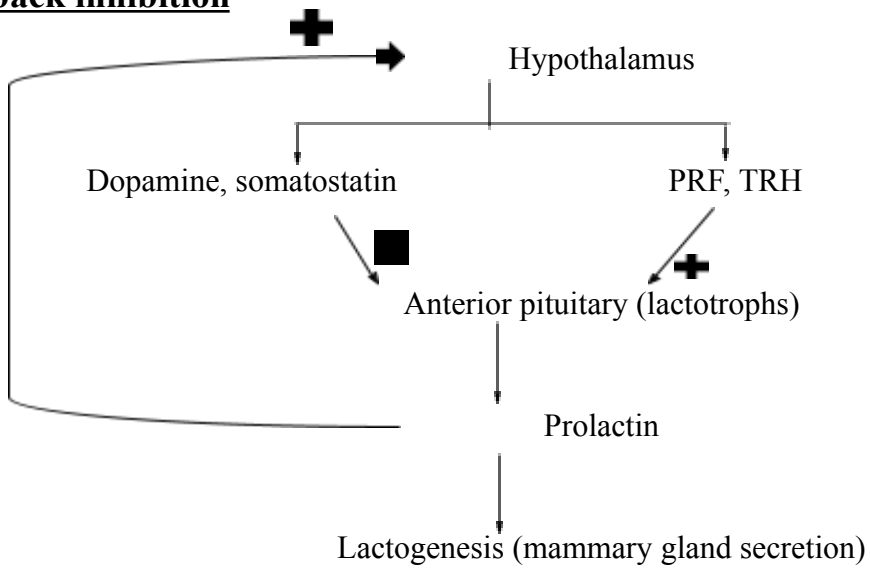
- Secreted from acidophilic cells of anterior pituitary

Preproprolactin ⟶ proprolactin ⟶ prolactin ⟶ stored in lactotrophs

REGULATION OF SECRETION

Factors that increase secretion	Factors that decrease secretion
Prolactin releasing factor, TRH Pregnancy Estrogen therapy Breastfeeding Sleep Oxytocin	Dopamine Somatostatin Feedback inhibition

Feedback inhibition



FUNCTIONS

- Stimulate the milk synthesis
- Hyperplasia of breast tissue, increase the lobules of alveoli of mammary gland
- In females: inhibits hypothalamic GnRH in high prolactin concentration, prevent ovulation, inhibit libido &stimulate maternal behavior
- In males: decreased spermatogenesis,
- Immunogenic balance of maternal tissue to fetal tissue
- Increased synthesis of synlactin in liver (intermediary GF from liver)

CLINICAL ASPECT

Lactational Amenorrhea

- Prevents ovulation
- Also called physiological contraception

Amenorrhea galactorrhea syndrome

- Excess production from tumor lactotrophs (hyperprolactinemia) causes amenorrhea & infertility
- Treatment: Dopaminergic drugs

INSULIN LIKE GROWTH FACTORS (SOMATOMEDINS)

- The indirect effect of GH on cartilage and protein depends on the production of IGFs
- Growth hormone stimulate IGFs production by gene expression by tyrosine phosphorylation of signal transduction & activation of transcription (STAT)

TYPES

IGF- 1	IGF- 2
Also called somatomedin Receptor: similar to insulin receptor Secretion: before birth independent of GH After birth its secretion stimulated by GH Effects: skeletal and cartilage growth	Multiplication stimulating activity (MSA) Receptor: mannose 6 phosphate Secretion: independent of GH its level remains constant Effects: major role in fetal growth