THE ENDOCRINE SYSTEM

Major control systems of body

Nervous system
- Rapid
- Thru electrical signals
- Effect is for short time

Endocrine system
- slow
- Thru chemical messg
- prolonged effects.

- Hormone :- greek - "To arouse or excite"
- An endocrine hormone is a substance that is produced by endocrine glands or group of endocrine cells in response to a stimulus and is carried by blood to the target tissues where it ~~they~~ exerts its physiological actions.

- Target cells of Hormones
  - ① Various types of cells eg GH, thyroxine
  - ② Specific type of cell.

Some hormones exert their action on a variety of cells

eg :- GH causes growth of most parts of body

Thyroxine ↑ rate of chem reactions in many types of cells.

⇒ Types of Chemical Messengers

Name	Rlzd by	Rlzd into	Act on / location of Target cell
(1) Neurotransmitter	Neuron terminal	Synaptic junction	Act on post synaptic mem locally.
(2) Endocrines	Endocrine cells	Blood	Located at a distance
(3) Neuroendocrine	Neuron	..	..
(4) Paracrine	Cells	ECF	different type of cell in neighborhood
(5) Autocrine	cells	ECF	Same cells that produced them
(6) Cytokine eg:- interleukin lymphokines	cells	ECF	Can be Endo or Auto or Para crine

- Multiple hormone systems play a key role in regulating almost all body's functions.

⇒ Paracrine secretions

- Act on the target cells in the neighborhood of site of secretion
- Rapidly inactivated by enzymes in ECF → prevent entry in blood.

- Dispersed by simple diffusion → constructs action to short distances.

eg:- Histamine
~~Norepinephrine~~
Neurotransmitters like ACH } Act on parietal cells of stomach mucosa — ① Ac

PGE2 - cervical dilatation

⇒ Autocrine secretions :-

eg:- Norep :- inhibits further secretion from adrenal medulla

Insulin :- acts on β cells → inhibits furth secretion of insulin.

⇒ Feedback control of Hormone secretion :-

- Several control systems are present that regulate the level of hormone very precisely.

- Three levels of feedback control :-

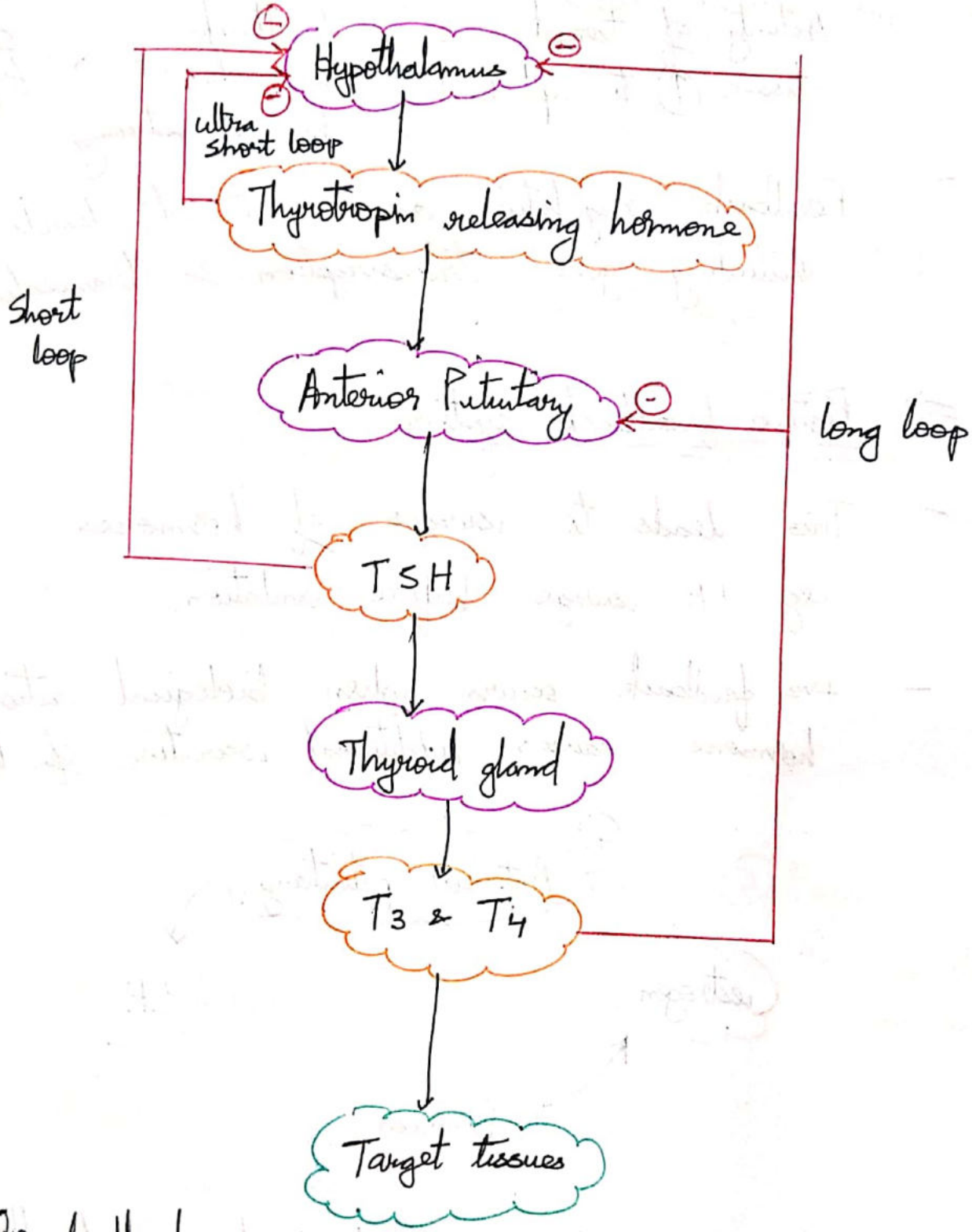
① Long loop control :-
The peripheral endocrine hormone inhibits hypothal and pituitary gland.

② Short loop control :-
The anterior pituitary hormone inhibits hypothalamu

③ Ultra short loop control :-
Releasing hormone secreted by hypothalamus itself

inhibits hypothalamus

eg :- Thyroid hormones & their control.



- -ve feedback control prevents overactivity of the glands.
- The hormone or one of its products has a -ve feedback effect to prevent oversecretion of hormone or overactivity of target hormone.

- The controlled variable is sometimes the degree of activity of tissue.

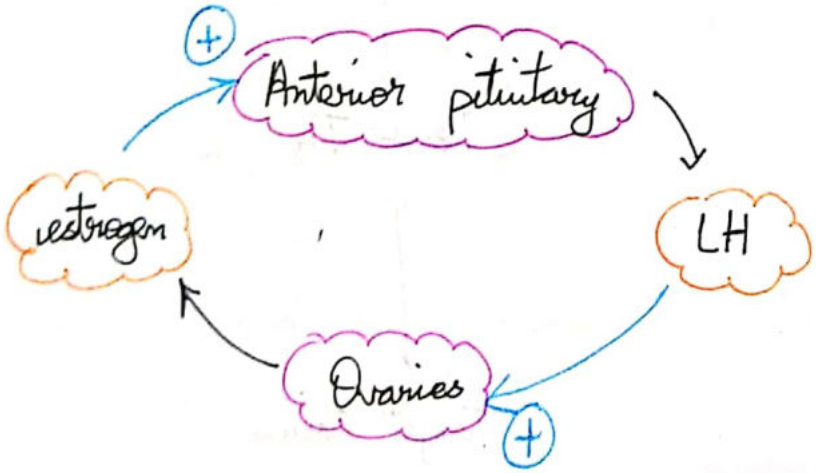
  Activity of target tissue ↑ to apt level → feedback signals become strong → Slow further secretion

- Feedback regulation occurs at all levels including gene transcription & translation.

⇒ Positive feedback system

- This leads to surges of hormones eg LH surge before ovulation.

- +ve feedback occurs when biological action of hormone causes additional secretion of hormone.



- When LH reaches an apt level -ve feedback start

⇒ Cyclical release of Hormones :-

- In addition to feedback control there is also periodic variation in release of ~~endocr~~ hormones influenced by seasonal changes, various stages of dev diurnal cycle, sleep etc
- eg :- GH ↑ during early period of sleep but ↓ " late stages " "
- Variations can be due to changes in activity of neural pathways involved in controlling hormones reln.

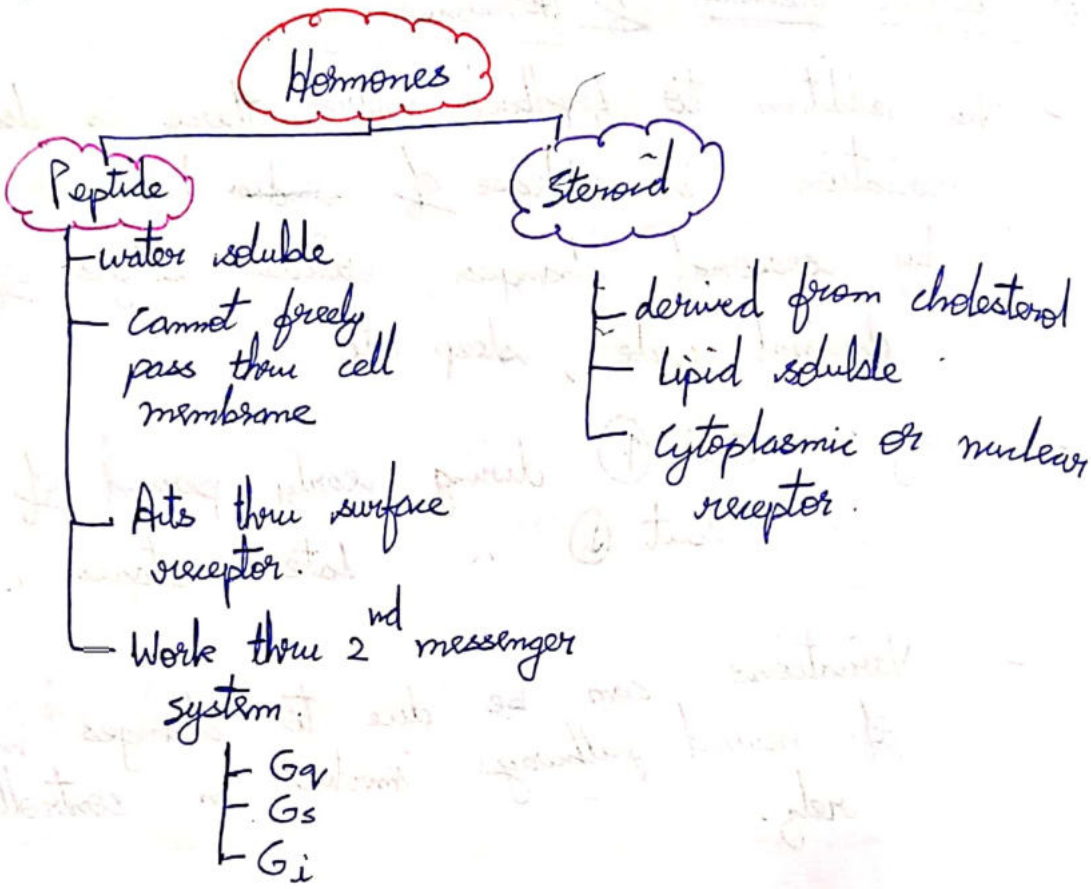
⇒ Types of Hormones :-

① Amines :-
- dopamine by hypothalamus [PIF]
- $T_3 > T_4$ by thyroid
- Catecholamines

② Steroids :-
- Cortisol, Aldosterone } Adrenal cortex
- Testosterone by Testis
- Estrogen & progesterone by Ovaries
- 1,25 - dihydroxy cholecalciferol.

③ Peptides :- Rest of the hormones

RECEPTOR PATHWAYS :-



=> G Protein coupled receptors :- GPCR

- "Seven pass" transmembrane receptor / Serpentine receptor.
- It is coupled with G proteins - GTP-binding prts.
- Peptide / Protein / catecholamine hormones → peripheral transmem prtn.

Binding of hormone

↓

changes 3D structure of GPCR [inside portion]

↓

Activates G_s protein

↓

displaces GDP and binds to GTP

↓

G_s goes & attaches to effector enzyme →

The enzyme [Adenylate cyclase] becomes super active

GTP → GDP + Pi

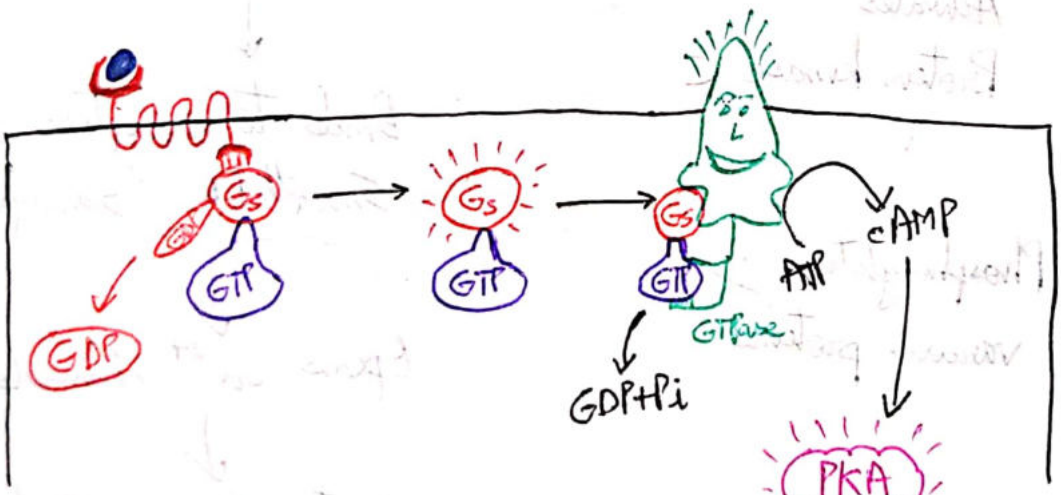
uses the energy rlzd by the conversion of GTP to GDP to convert ATP → cAMP

G_s prtn is turned off

Activates Protein kinases

Phosphorylation of various prtns → Activates enzymes

Can control transcription



PKA

Phosphorylation of various prtns

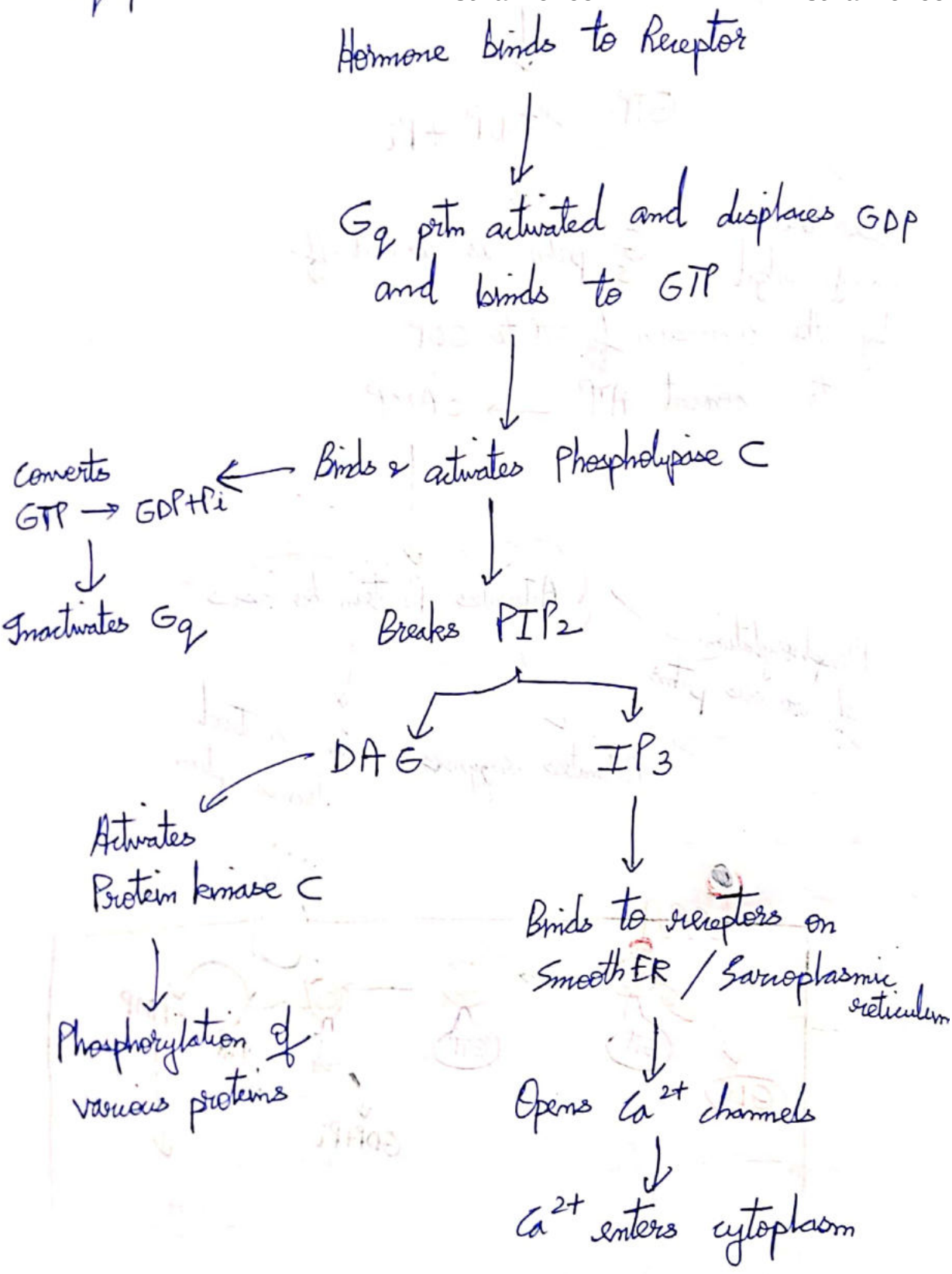
Activates enzymes

Regulates transcription

Ion channels

Cell proliferation

Gq protein



Nuclear receptors

- Steroid hormones mainly.
- Normally bound to heat shock prtns

Hormone binds to receptor

↓

HS proteins are displaced

↓

Receptor becomes active

↓

Can bind to specific gene sequence

(Hormone response element)

↓

Synthesis of prtns.

Hormone Receptor interactions :-

⇒ Synthesis of Hormones

① Peptides / Polypeptides :-

- Most of the hormones in the body are peptides / proteins
- They range in size from 3 amino acid containing peptides [eg:- Thyrotropin releasing hormone] to 100 amino acids containing proteins [GH & prolactin].
- Steps in the synthesis of peptide / prtn hormones are as follows :-
  1.) They are first syn as pre prohormones - large and biologically inactive
  2.) These prepprohormones are cleaved by endoplasmic reticulum to form smaller prohormones.
  3.) Prohormones are packed into secretory vesicles by golgi apparatus
  4.) Enzymes of vesicles convert / cleave prohormones to form biologically active hormones.
- Secretion of the hormones is by exocytosis
- Stimulus for exocytosis → ↑ Ca^{2+} conc of cytoplasm
  → ↑ cAMP → activation of protein kinase
- They are stored until secretion
- Are water soluble.

Steroid hormones :-

- Chemical structure is similar to cholesterol and most of them are synthesised from cholesterol.
- There is very little hormone storage in steroid prod endocrine cells
- Much of the cholesterol for steroid syn comes from plasma but there is also de novo syn within cells.
- They are highly lipid soluble and can simply diffuse across cell membrane.

(3) Amine hormones :-

- derived from Tyrosine
- Thyroid hormones are syn and incorporated into macromolecules of the protein thyroglobulin.
- Stored in large follicles until secretion.
- After entering blood much of the thyroid hormones bind to plasma proteins especially thyroxine binding globulin.
- Catecholamines are syn by adrenal medulla and stored in preformed vesicles.
- Stored until their secretion.
- In blood they can either bind to plasma prtns or circulate freely.

Hormone secretion, transport & clearance from blood.

- Hormone secretion & duration of action :-

- Each hormone has its own characteristic onset and duration of action - each tailored to perform its specific control function.

  eg :- duration of action of catecholamines - few seconds to min.

  Thyroxine or GH may require ~~full~~ months for full effect.

- Transport of Hormones :-

Water soluble	Lipid soluble
• Peptides / prtns / catecholamines	• Thyroid / steroids
• Dissolve in plasma & circulate freely	• Circulate in blood mainly bound to plasma prtns
• Diffuse out from capillaries into ECF & ultimately to target cells.	• Usually less than 10% of steroid / thyroid exist free in plasma.

- Protein bound hormones cannot easily diffuse out of capillaries and act on the target cells. Hence plasma prtn bound hormones are biologically inactive.

- The relatively large amounts of hormones bound to plasma prtns act as reservior replenishing the

Secretion of hormones whenever needed.
- This binding also (↓) their clearance from plasma.

- Metabolic clearance rate :-

- MCR = Rate of disappearance of hormone from plasma / Concentration of hormone
[mg/min] / [mg/ml]

- Hormones are cleared from plasma in several ways
  1.) Metabolic destruction by tissues
  2.) Binding to tissues
  3.) Excretion by liver into bile
  4.) " " kidney " urine.

- (↓) MCR ⇒ (↑) conc of hormone in blood.

⇒ Mechanism of Action of Hormones :-

- First step of a hormone's action is to bind to specific receptors
- When a hormone combines with its receptor it initiates a cascade of reaction in the cell.
- A receptor is specific for a particular hormone.
- The tissues which have the receptors for a hormone will only respond to the particular hormone.
- The no of receptors in a target cell usually does not remain constant.

Regulation of receptors

Downregulation

↓ in the no of receptors in response to high conc of hormone

↓

1. Inactivation of some receptors
2. Inactivation of some of intra-cellular protein signalling molecules.
3. Temporary sequestration of receptor to inside of cell → destruction by lysosomes
4. ↓ prod of receptors.

The target tissue's responsiveness is reduced.

Upregulation

↑ in the no of receptors due to sustain low exposure to a hor

Targe tissue becomes more responsive to hormone

- Hormone receptors can be classified based on location
  1. Membrane receptor :- Specific mainly for peptide / ptn / catechdamines
  2. Cytoplasmic receptors :- Mainly for steroid hormones
  3. Nuclear " :- Thyroid hormones and are located in direct association

More receptor interactions :-

① Ion channel linked receptor :-

eg:- Neurotransmitters like Ach, Epinephrine

Neurotransmitter binds to receptor

↓

Change in the structure of receptor

↓

Opening or closing of ion channels

↓

Movement of diff ions across the post synaptic mem.

② G protein coupled receptor :-

- Indirectly regulate the activity of target prtns → Ion channels / Enzymes
- Coupled with heterotrimeric GTP binding prtn or G proteins.
- The receptors have seven transmem segments which loop in and out of cell mem.
- The G proteins contain 3 subunits α, β, γ
  Inactive state – GDP is bound to α subunit and α, β, γ form a complex.
-

G protein

- G_s → stimulates the target protein [enzyme]
- G_i → Inhibits the target enzyme

Hormone binds to receptor

↓

Receptor undergoes conformational change.

↓

Receptor is activated

↓

G protein becomes activated

↓

GDP bound G protein associates with cytoplasmic part of receptor and exchanges GDP for GTP

↓

α subunit dissociates from trimeric complex & to associate with other intracellular signalling prtns

↓

Activated G prtn induces intracellular signals that either

- Open / close ion channels
- Change activity of enzyme
  - ↓
  - eg:- adenylyl cyclase
    Phospholipase C
- Activate gene transcription.

terminated when the hormone is removed. → α subunit dissociates → GTP converts to GDP → α, β, γ again form a complex → inactive G protein.

(3) Enzyme - linked Receptor :-
Tyrosine kinase associated receptor.

- Some receptors when activated function directly as enzymes or are closely associated with enzymes.
- Hormone binds to extracellular part of receptor
↓
Enzyme immediately inside the cell is activated
- Many enzyme linked receptors have intrinsic enzyme activity and some are associated with enzymes
- Example :- → Homodimer
  - Leptin receptor is a member of large family cytokine that functions thru associated enzymes
  - One of the signalling pathways occurs thru a tyrosine kinase of Janus kinase (JAK) family JAK 2
  - Some effects of leptin occur rapidly whereas some occur slowly & involve protein synthesis.

Leptin binds to its receptor

↓

Phosphorylation & activation of JAK 2

↙ ↓

Also Activates other enzymes → Rapid effects of leptin

Phosphorylation of signal transducer and activator of transcription factor (STAT)

↓

Transcription of target genes

↓

Synthesis of proteins

(4) Intracellular receptors :-

eg :- Steroid hormones
Vit A, D
Thyroid hormones
} lipid soluble
Readily cross cell mem.
→ bind to receptor

↓

Hormone receptor complex binds to specific regulatory sequence of DNA called hormone response element

↓

Activates / Represses transcription

↓

mRNA is formed

↓

Translation → ptn syn.

Many diff tissues have identical intracellular hormone receptor but the genes that the receptors regulate are different. in various tissues

- An intracellular receptor can activate a gene response only if the appropriate combination of tissue specific gene regulatory proteins is present.

- Effects of hormone → Steroid hormones
  - Genomic effects → Gene transcription
  - Non genomic effects → Steroid induced modulation of cyto / cell mem bound regulatory proteins

Characteristics :-

1. Rapid effects
2. Observed in highly splzd cells that do not accomplish mRNA & prtn syn [eg :- spermatozoa]
3. Can be elicited with steroids even when they are coupled with high mol wt prtns
4. Not blocked by inhibitors of mRNA / prtn syn
5. Not blocked by antagonists of classic genomic steroid receptors.

Second Messenger Mechanisms :-

- **Second messenger :-**

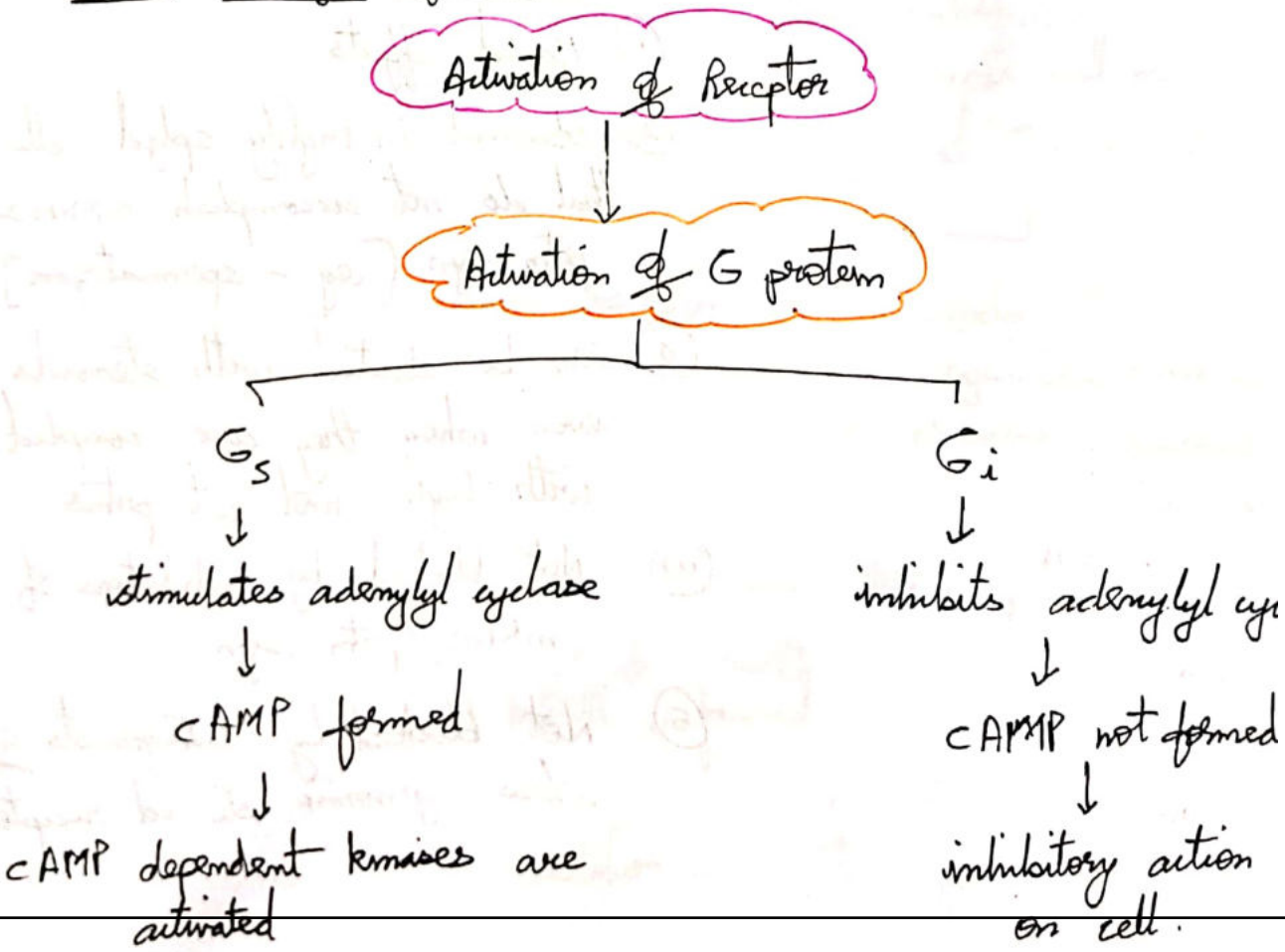
They are molecules or substances that help to communica signals from cell surface to specific target sites within the cell either in cytoplasm or nucleus.

- They significantly amplify the strength of the signa

- **Second messengers :-**

1. cAMP
2. cGMP
3. IP_3
4. DAG
5. Ca^{2+} ions

- **cAMP messenger system**



deposition of protein kinases phosphorylates specific cell proteins triggering biochemical reactions that ultimately lead to the cell's response to the hormone.

- One cAMP is formed → activates a cascade of enzymes.

- ∴ slightest amount of hormone acting on cell surface can initiate a powerful cascading activating force for the entire cell.

- Cell membrane phospholipid 2nd monger system :-

Receptor activated

↓

Attached to inside projections of Receptors ← Phospholipase C enzyme activated

↓

Causes breakdown of phospholipids in cell mem especially phosphatidyl inositol diphosphate [PIP_2]

PIP_2

- IP_3 → mobilises Ca^{2+} from mitochondria & ER → These Ca^{2+} ions have their own 2nd monger effects such as smooth muscle contraction & changes in cell secretion.

- DAG → Activates protein kinase C → Phosphorylates large no of proteins → cell's response.

Note:-
lipid portion of DAG is Arachidonic acid which is the precursor for prostaglandins and other local hormones.

- Ca^{2+} - calmodulin 2nd messenger system :-
  - calcium entry can be thru
    - opening ~~closing~~ of Ca^{2+} channels by change in mem pot
    - ligand gated Ca^{2+} channels
  - Ca^{2+} + calmodulin
    ↓
    Ca^{2+} - calmodulin complex
    ↓
    Activation or inhibition of prtn kinases
    ↓
    kinases via phosphorylation activate or inhibit several prtns ⟶ cell's response

eg:- myosin light chain kinase is activated by Ca^{2+} calmodulin ⟶ smooth muscle contrctn

- Normal Ca^{2+} conc of cell :- 10^{-8} to 10^{-7} mol/L

$[R] = 10^{-5}$ to 10^{-9} mol/L → enough binding occurs.

www.FirstRanker.com

⇒ Hormones that act on genetic machinery of cell :-

Action of steroid hormones

↓

Syn of prtns in trgt cells

↓

Proteins

↓

Enzymes | Structural prtns | Trans prtns

- Sequence of events in steroid func :-

Steroid hormone diffuses across cell mem

↓

Binds to specific receptor

↓

Hormone receptor complex enter nucleus

↓

Binds to specific pts of DNA on chromosomes

↓

Transcription & translation

↓

New prtns are formed.

Thyroid hormones → ↑ gene transcription

First Bind to receptors called
Activated transcription factors
located within chromosomal complex

↓

Control func of gene promoters
gene transcription

↓ ↓

Activate genetic mech for
formation of many prtns

↓

Most of them are enzymes

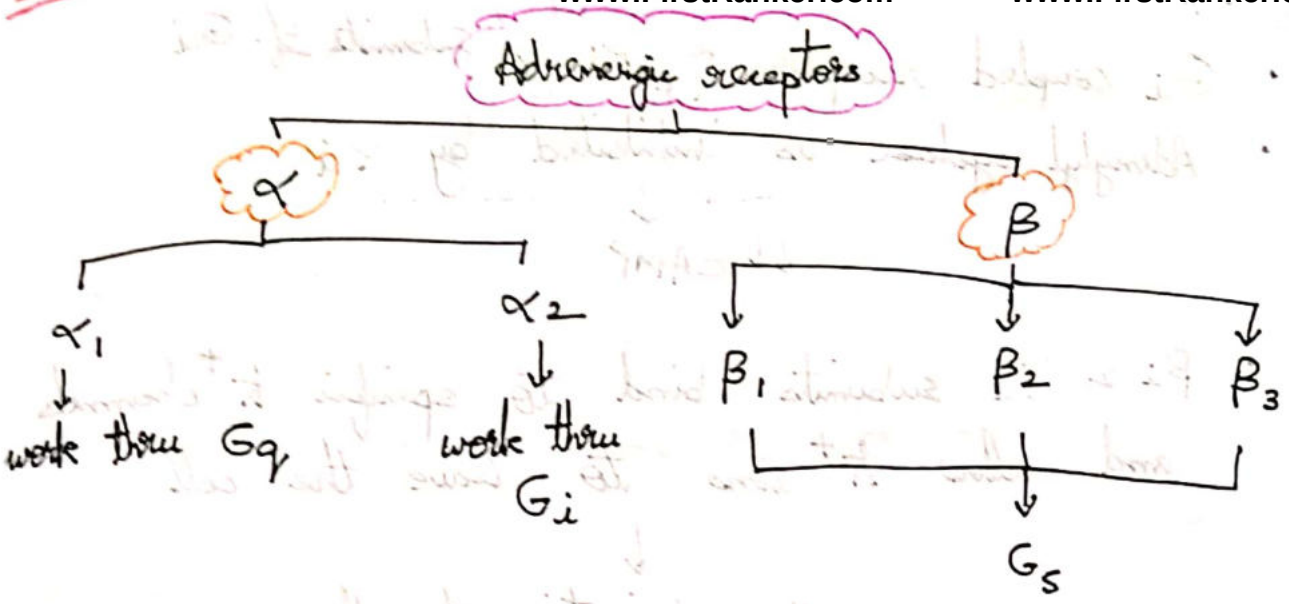
↓

Promote enhanced intracellular
metabolic activity

One bound to
intranuclear receptors

↓

continue to express
their control func
for days or weeks.



- α_1 :-

- works thru G_q coupled receptors
- Both Epi & Norepi can act on it
  - ↳ has higher affinity.
- G_q activates phospholipase C → IP_3/DAG 2nd messenger system
  - ↑↑ Ca^{2+}
    - ↓
    - Ca^{2+} - calmodulin complex
  - Activates PKC
  - → Phosphorylate proteins
    - ↓
    - Activate / Inhibit various prtns.
      - Ion channels
      - Enzymes

- G_i coupled receptors ← α_i, β_i, γ_i } Subunits of G_i
- Adenylyl cyclase is inhibited by α_i

↓

↓↓ cAMP

- β_i & γ_i subunits bind to specific K^+ channels and allow K^+ ions to leave the cell

↓

Hyperpolarisation of cell.

- β_1 / β_2 / β_3
  - G_s coupled receptor
  - Adenylyl cyclase activated → ↑↑ cAMP

↓

Phosphorylation of prtns as cAMP activates protein kinase A

- Effect on blood flow :- Tunica media has many adrenergic receptors

① Blood flow to integumentary system / skin.

- vascular smooth muscle of skin → α_1
- SNS activates → Epi → α_1 receptor

↓

G_q activates → smooth m/s contract [vasoconstriction] → ↓↓ Blood flow → Pale skin

② Arrector pili muscle :-
- α_1 adrenergic receptor
- contraction of muscle → Hair stand up

③ Kidneys :-
- Blood flow to kidneys :- vasoconstriction
  - α_1 adrenergic receptors → ↓↓ BF → less urine is produced

④ GIT :-
α_1 AR → vasoconstriction → ↓↓ BF → ↓ digestion absorption

⑤ Blood flow to skeletal m/s :-
β_2 adrenergic receptors → ↑↑ cAMP → ↑↑ PKA (initiates a pathway)
↑↑ PKA → vasodilation → ↑↑ BF

⑥ Blood flow to Heart :-
- Eq amnt of α_1 and β_2
- Coronary circulation is mainly under metabolic regulation

⑦ Blood flow to CNS :-
- Eq amnt of α_1 and β_2 AR
- BF under autoregulation by myogenic mechanism.

Receptors of Eyeball :-

- Target muscles
  - ciliaris should relax
  - dilator pupillae should contract

- ciliaris muscle relaxed → ciliaris / zonules / suspensory lig become tight → lens becomes flat → far vision

- dilator pupillae contraction → pupils dilate → far vision
  - → α_1 AR

Salivary glands :-

- β_2 AR → saliva
  - ↓ H_2O & electrolytes → Thicker saliva
  - ↑ mucin ptns
  - ↑ salivary enzymes

- Blood vessels → vascular smooth m/s → α_1 AR → ↓↓ BF → ↓ H_2O & electrolyte supply

- α_2 AR on presynaptic nerve terminals in SNS

α_2 AR binds to NE / E

↓↓ PKA → ↓ opening of voltage gated Ca^{2+} channels

↑ K^+ efflux → Hyperpolarises the axon terminal

↓↓ rly of Norepi/epi

- Heart:- Nodal system

SAN, AVN, Bundle of His

β_1 AR ← Myocardium of Hrt

β_1 AR

↑↑ Action pot in SAN, AVN → ↑ HR → ↑ CO → ↑ BP

↑↑ contractility → ↑ SV → ↑ CO → ↑ BP

Muscles

- M/s spindles have β_2 adrenergic receptors
  - proprioceptors
  - ↓
  - ↑ m/s spindle firing
  - ↓
  - Tremors ← ↑ contraction of m/s

- GIT :-
  - GI motility inhibited.
    - β_2 AR present thruout GI smooth ms
    - ↓ GI motility
    - ↓ GI secretions
  - Sphincters of GIT ← Pyloric sphincter, Internal anal sphincter
    - ↓
    - α_1 AR
    - ↳ constricts → prevents movt of food.

- Kidney :-
  - JG cells – β_1 adrenergic receptors
  - Smooth m/s – β_2 ..
    - ↳ ureteric relax.
  - detrusor m/s of urinary bladder – β_2, β_3 – recent research
    - ↳ Relaxes bladder.

Internal urethral sphincter → α_1 AR → constriction

- Adipose tissue :-

lipolysis – β_3 receptors

- Pancreas

α cells rly glucagon

↓

α_2 AR

↓

(+)

β cells rly insulin

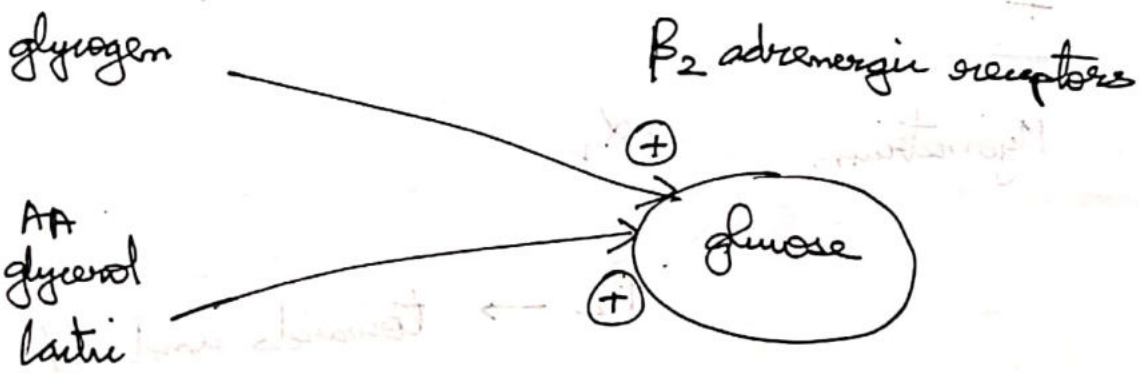
↓

α_2 adrenergic receptors

↓

(−)

- Liver :-



- Respiratory system :-

Bronchial smooth m/s – β_2 AR → relaxation

↓

(↑) Bronchial diameter

↓

(↑) Ventilation

Mast cells — β_2 AR → inhibit from rel. histamine & ~~sensitization~~

- Repro system ♂

Parasympathetic → point - erection

Sympathetic → shoot - ejaculation.

Smooth m/s of epididymis & vas deferens → α_1 AR

Smooth m/s of seminal vesicle & prostate gland → α_1 AR

♀

Myometrium → α_1

β_2 → towards end of gestation.

↓

prevents premature labour contraction

We give tocolytic agent - binds to β_2

- Platelets :-

α_2 AR → Platelets rel → Thromboxane A_2, Serotonin, ADP

ADP → Cause platelet aggregation

- Respond to Ach.

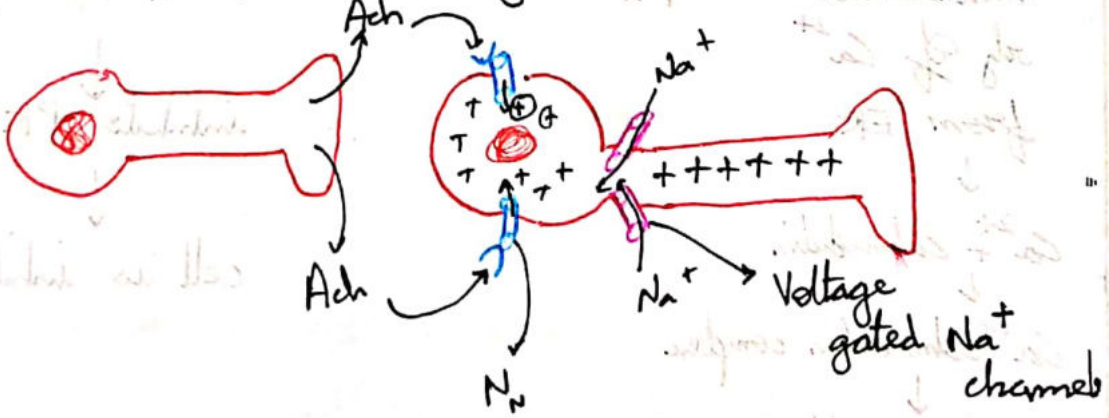
Cholinergic Receptors

- Nicotinic (R) → Respond to Nicotine also
  - N_N present on neurons
    - Autonomic ganglia
    - CNS
  - N_M present on skeletal m/s [NMJ]
- Muscarinic receptors
  - Also responds to muscarine
  - M_1 (+), M_2 (−), M_3 (+), M_4 (−), M_5 (+)
  - G protein coupled receptor
  - metabotropic receptor

- Ligand gated ion channels
- ionotropic receptors

N_N

- Neurons in the autonomic ganglia. [post synaptic mem]
- ligand gated ion channels.
- Ach binds to receptor → opening of ion channel → Na^+ influx [E.P.S.P] → RMP starts rising → when threshold pot is reached → voltage gated Na^+ channels open → AP



- Significance :-
  1. Ach plays an important role in Memory
  2. Arousal
  3. Analgesia

• Neuromuscular junction.

– Muscarinic receptors :–

Muscarinic receptors

$M_1/M_3/M_5$	M_1	M_2	M_3	M_4	M_5	M_2/M_4
+	+	–	+	–	+	–

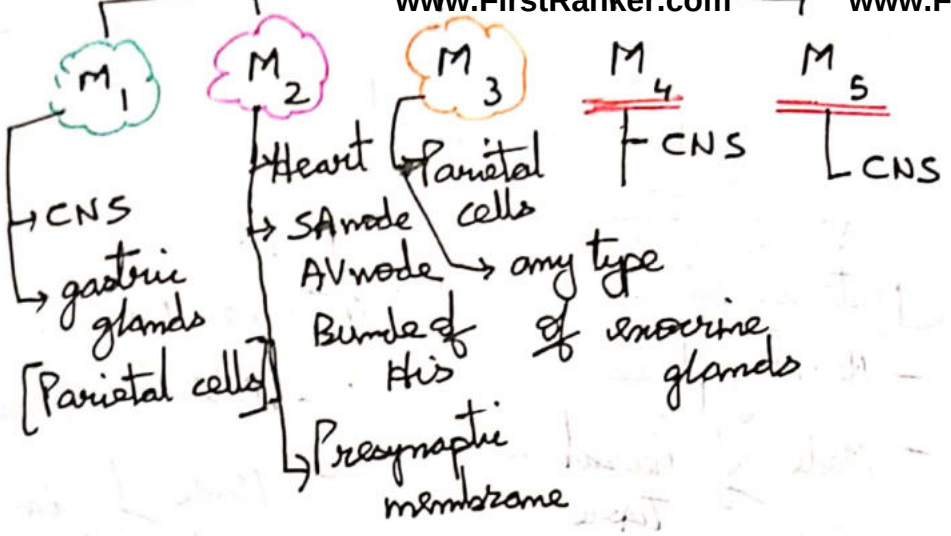
$M_1/M_3/M_5$ (+) → Gq pathway → Phospholipase C activated → Splits PIP_2

- IP_3 → stimulates intracellular rly of Ca^{2+} from ER → Ca^{2+} + calmodulin → Ca^{2+} calmodulin complex → Activates Ca^{2+} calmodulin Kinase
- DAG → activates PKC

M_2/M_4 (–) → Gi pathway

- αi → inhibits adenylyl cyclase → cAMP prod (↓) → inhibits PKA → cell is inhibited.
- βi & γi → K^+ efflux → Hyper-polarisation

Muscarinic Receptors



- Ach binds to M_2 on presynaptic mem → prevents Ca^{2+} entry
  → Prevents rel of Ach

- M_3 :- ① any exocrine glans
  - Lacrimal
  - sweat
  - Pancreas
  - salivary
  - gastric glands
  - ② β cells of Pancreas

③ Present on smooth mcs of bronchi → broncho constriction.

④ .. .. GIT → peristalsis

⑤ Can cause bladder contraction

⑥ Internal anal sphincter – defecation

⑦ Ciliaris & iris [constrictor pupillae] lens becomes globular.
↳ Activity opp to SNS – Near vision

Hypothalamic - Pituitary axis :-

- Stalk connecting the hypothalamus to Pituitary - Infundibulum
-

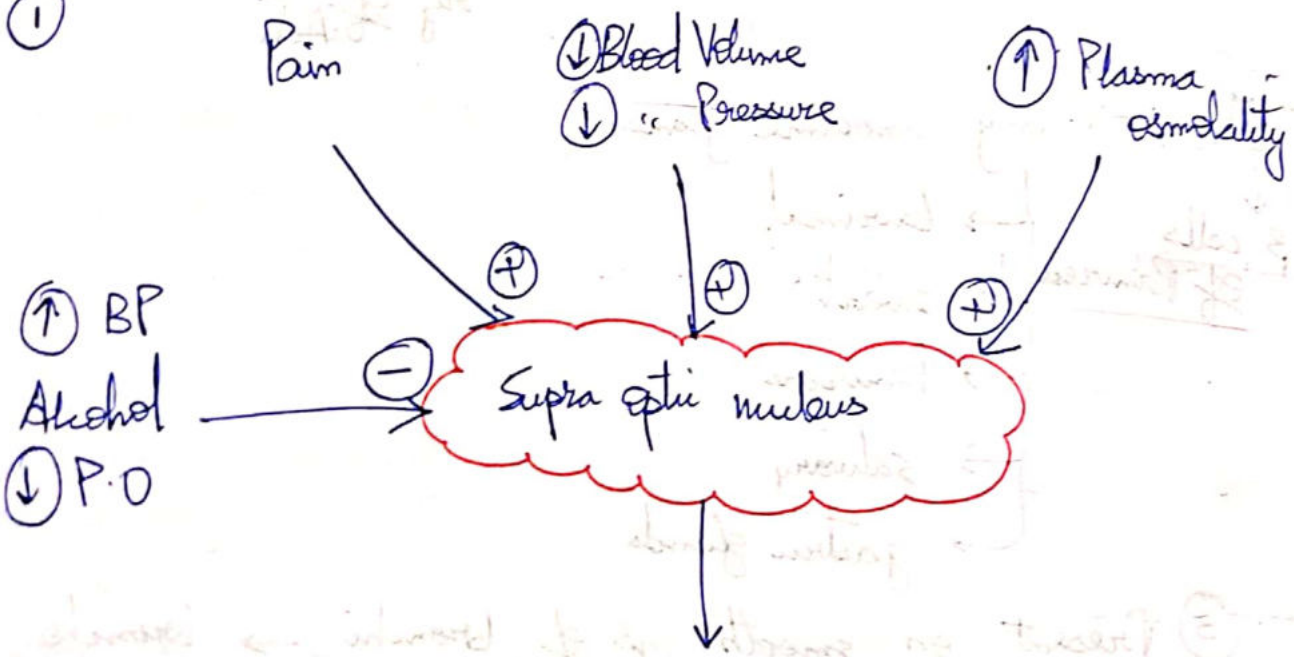
Pituitary gland

Posterior pituitary
- Neurohypophysis
- Made of Neural tissue [Pituicytes]

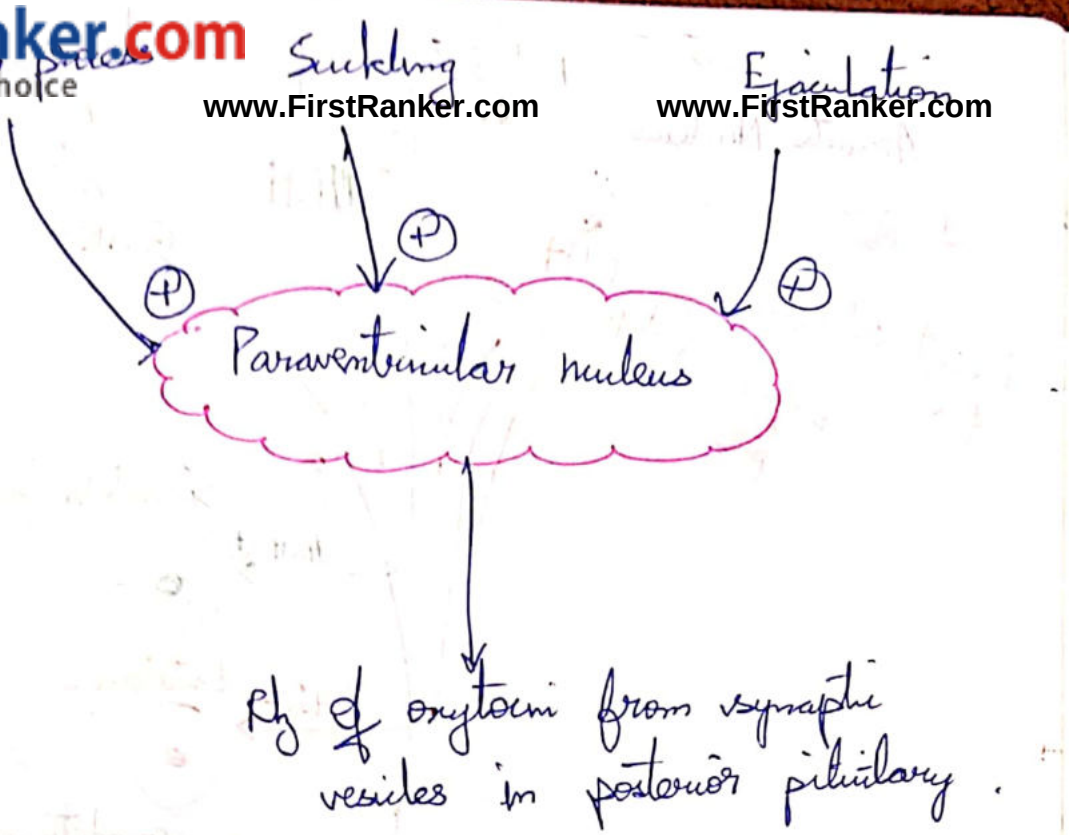
Anterior Pituitary
- Adenohypophysis
- Made of glandular cuboidal epithelium
- derived from rathke's pouch.

- Hormones of Posterior pituitary :-

(1)



Rx of ADH from synaptic vessicles of nerve endings of Supra optic nucleus axons in Posterior pituitary

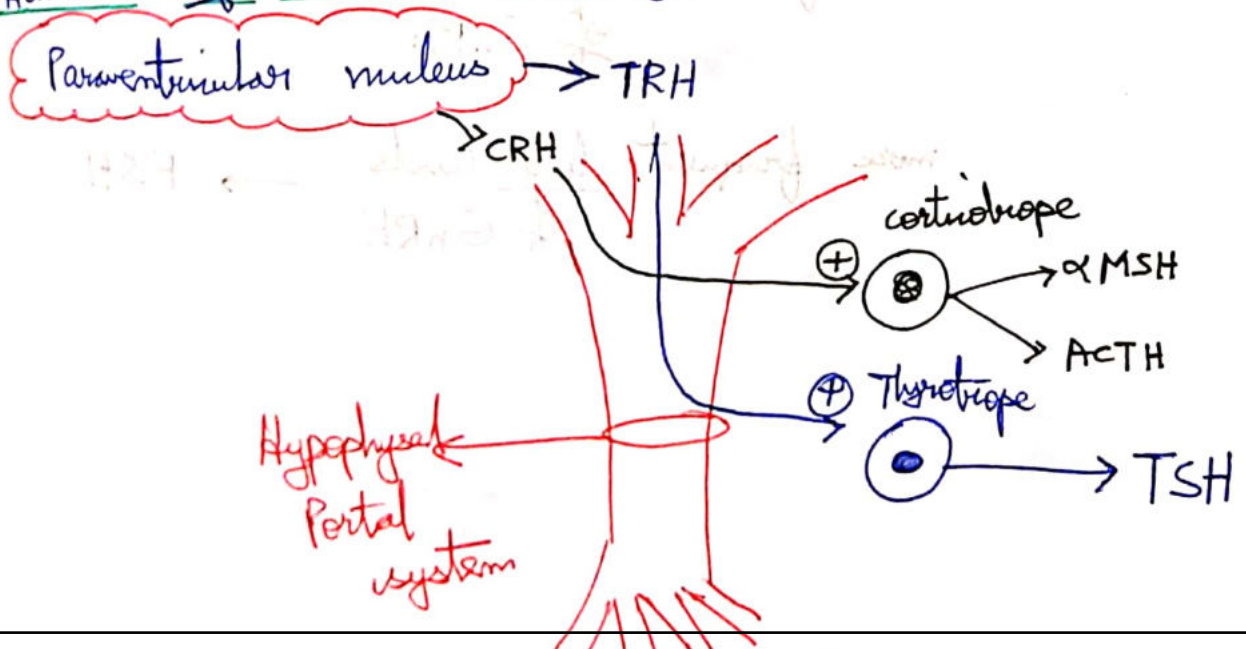


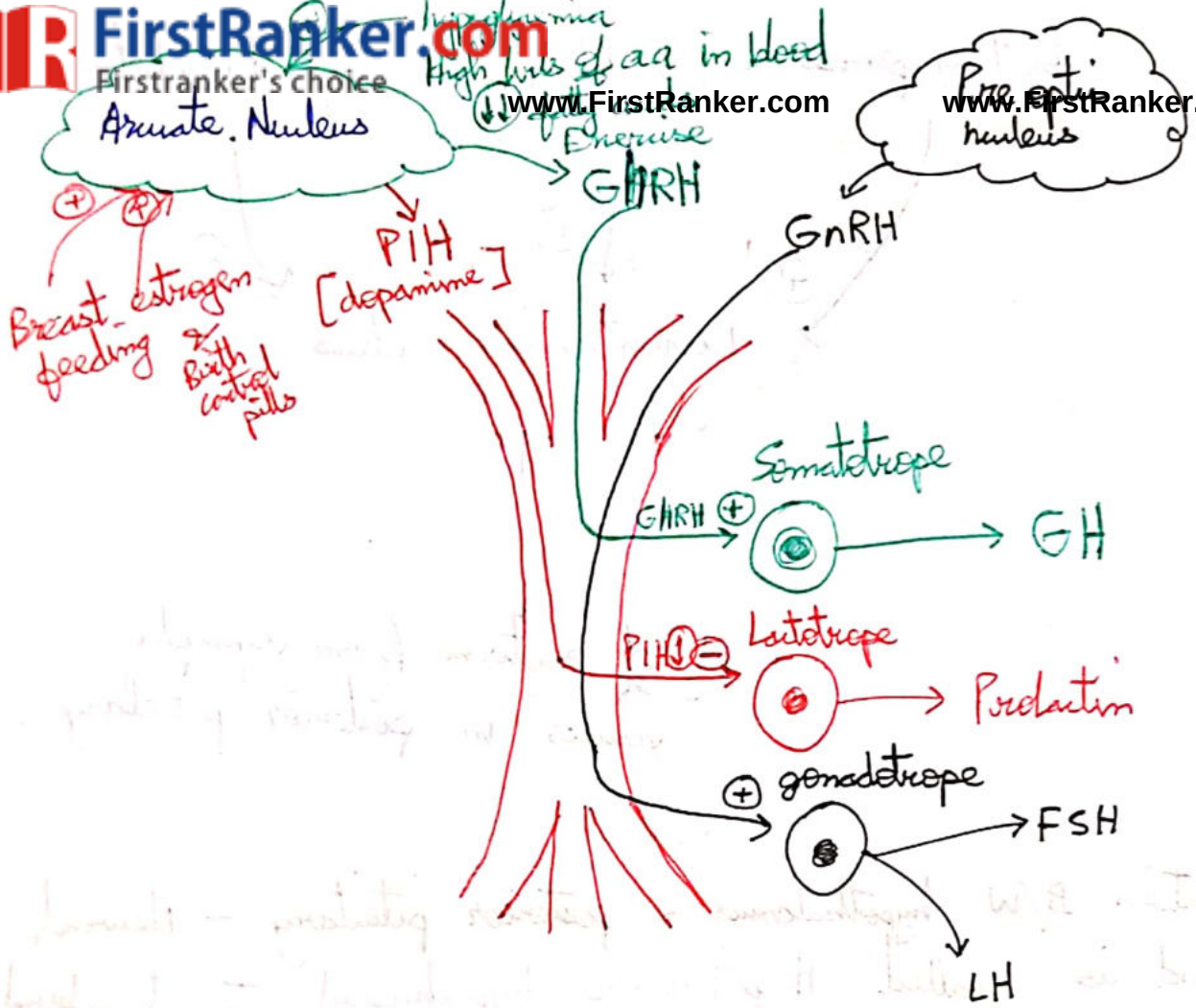
Rly of oxytocin from synaptic vesicles in posterior pituitary.

- Connection B/W hypothalamus & posterior pituitary - Neural and is called Hypothalamic hypophyseal tract - bundle of axons

- Connection B/W hypothalamus & anterior pituitary - Portal system called hypophyseal portal system

- Hormones of Anterior Pituitary

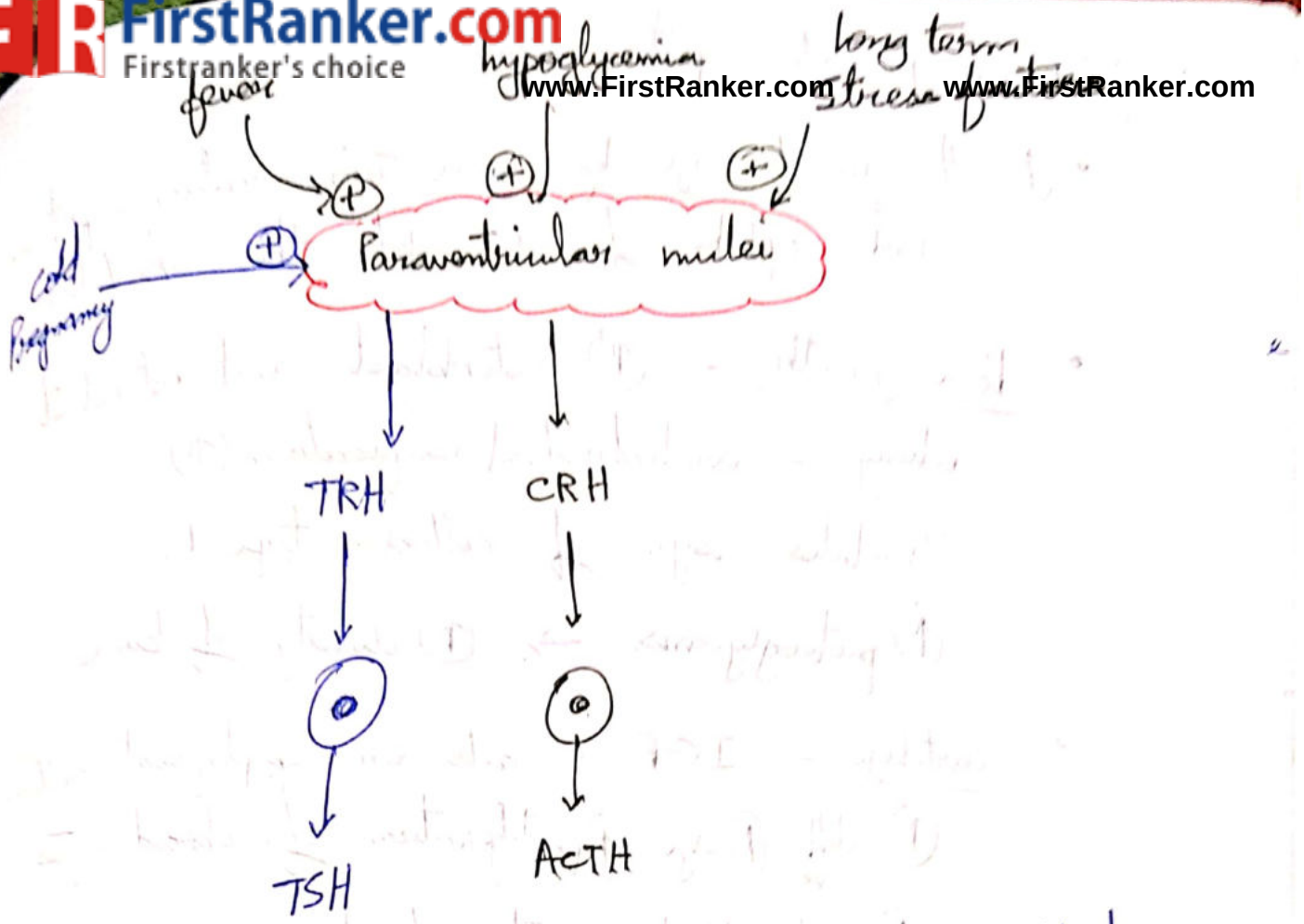




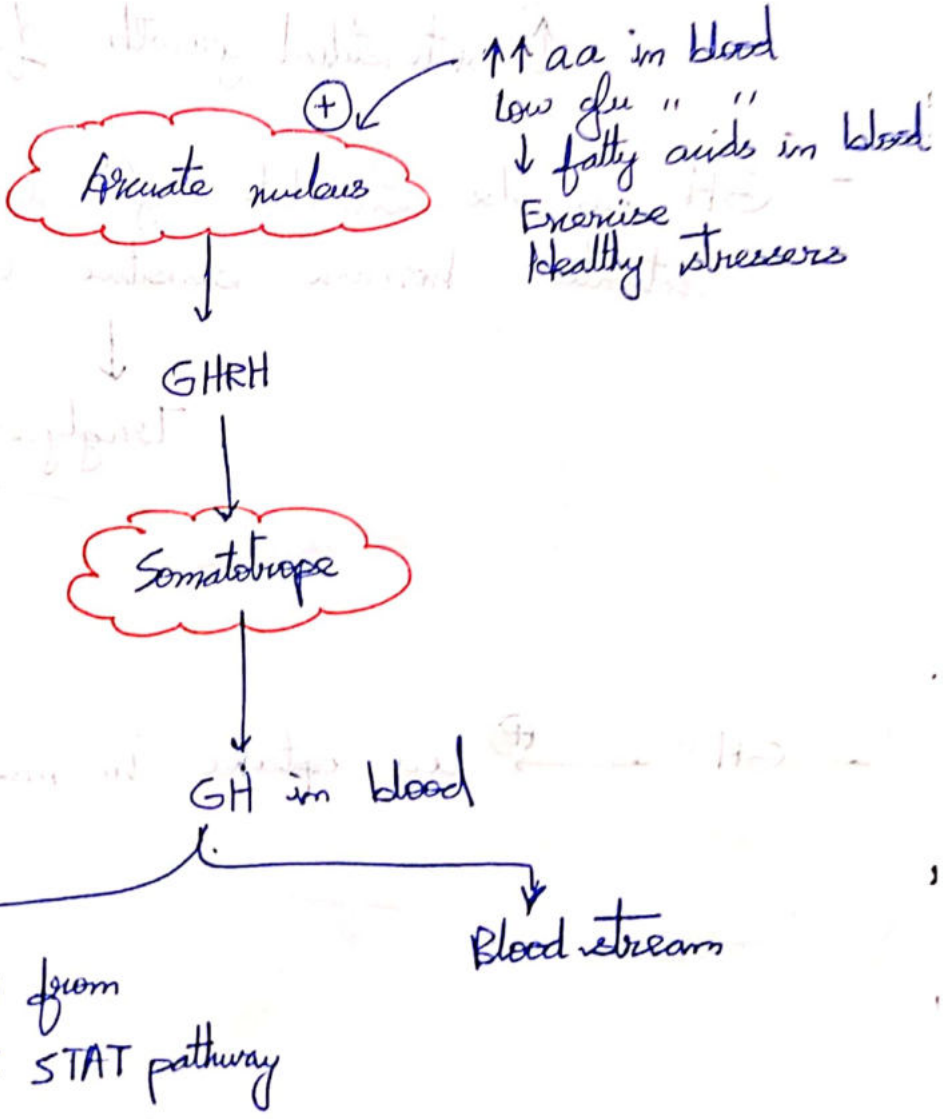
Note:- The amount of LH/FSH rlzd depends on frequency of GnRH

more frequent high levels of GnRH → LH

more frequent low levels of GnRH → FSH



Growth Hormone :-



IGF promotes prtn syn

- ↑ the muscle size by gene transcription & prt syn and uptake of aa into the m/s fibre.
- Bone growth - ↑ osteoblast and osteoclast activity - endochondral ossification ↑
  Stimulates syn of collagen type 1.
  ↑ proteoglycans. → ↑ density of bone
- Cartilage - IGF-1 acts on epiphyseal cartilage
  ↑ diff ↑ size, ↑ proliferation of chondrocytes
  ↑ interstitial growth of bones.

- GH can also stimulate gluconeogenesis
  activates hormone sensitive lipases
  ↓
  Triglycerides → Fatty acids
  → glycerol
  ↓
  glucose

- GH —⊕→ aa uptake in muscles.

PITUITARY GLAND

- Small gland wt = 0.5 - 1g diameter = 1 cm
- location :- sella turcica [bony cavity]
- Connected to hypothalamus by Pituitary stalk
-

Pituitary gland

Anterior pituitary
- Adenohypophysis
- dev from Rathke's pouch - an invagination of pharyngeal epithelium
  ↓
  Reason for epithelioid nature of cells
- 6 major peptide hormones and other hormones of less importance

Posterior pituitary
- Neurohypophysis
- dev from outgrowth of hypothalamic neural tissue
  ↳ glial type cells called pituicytes
- 2 major peptide hormones prod by hypothalamus

Anterior pituitary

- Acidophils [eosin stain]
  - Somatotropes – HGH
  - Lactotropes – Prolactin
- Basophils [hematoxylin stain]
  - Corticotropes – ACTH
  - Thyrotropes – TSH
  - Gonadotropes – ~~GnRH~~ FSH LH

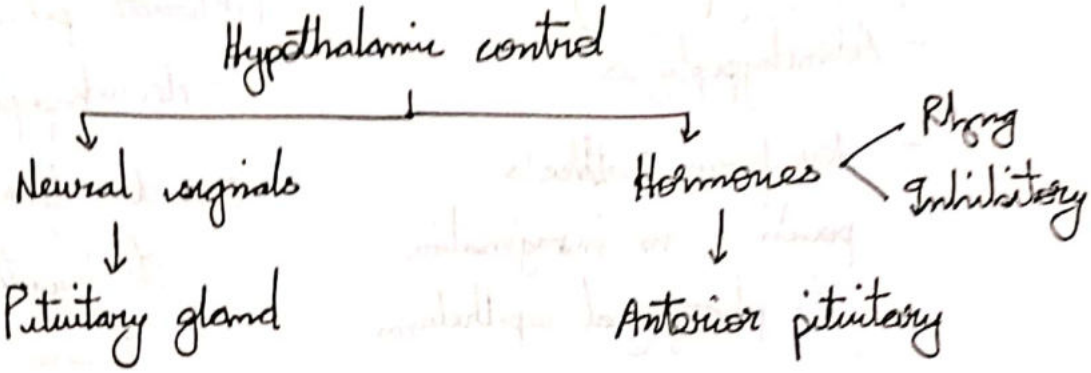
30-40% of Anterior pit. cells are somatotropes.

20% are corticotropes.

Each of the other cell types - 3-5% of total.

- Pituitary tumours that secrete large amnt of HGH - Acidophilic tumours.

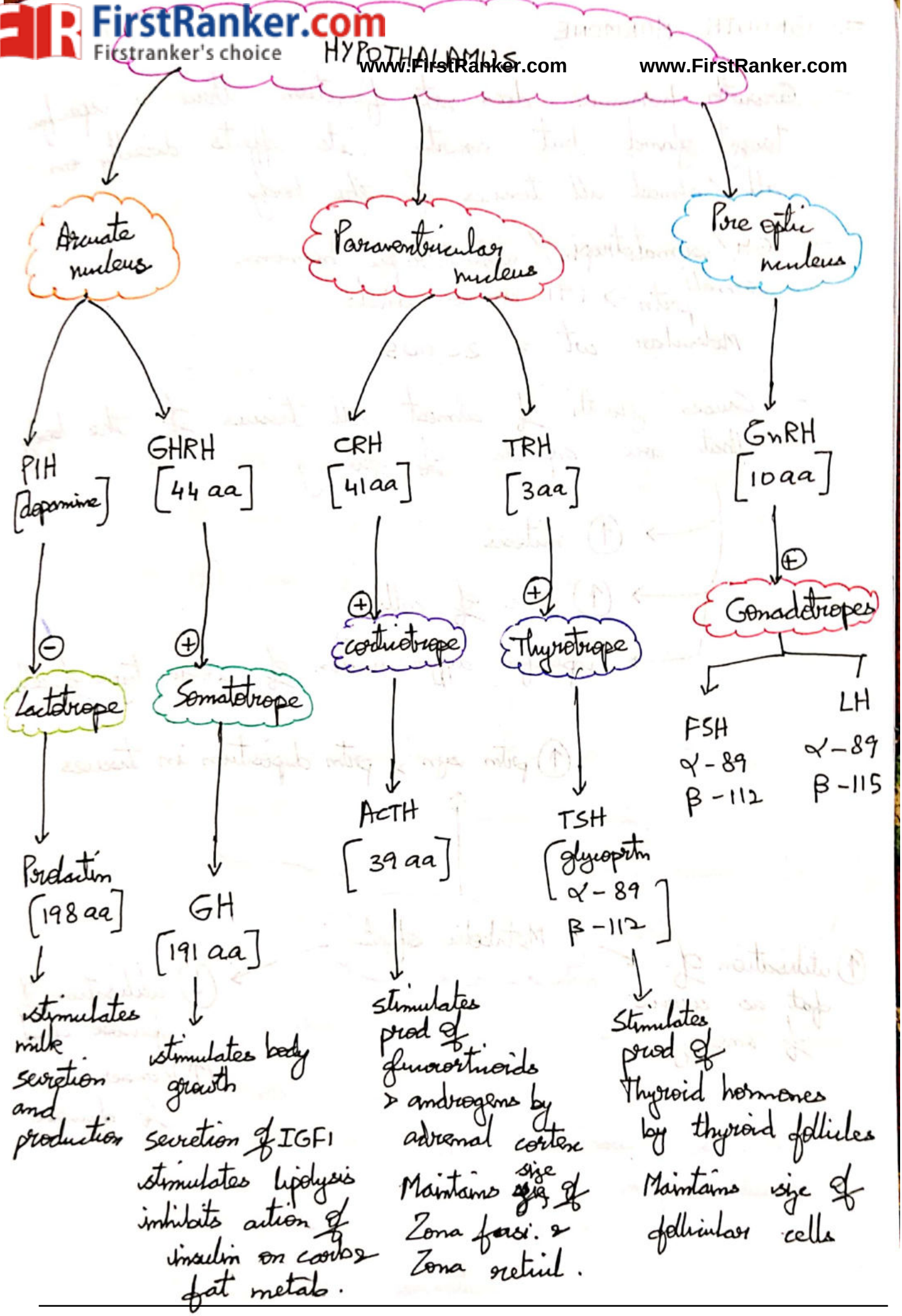
⇒ Hypothalamic control over pituitary



- Hypothalamus recvs signals from many sources in the nervous system and is a collecting center for info concerning internal well being of the body - This info is used to control secretions of the many imptnt pituitary hormns.

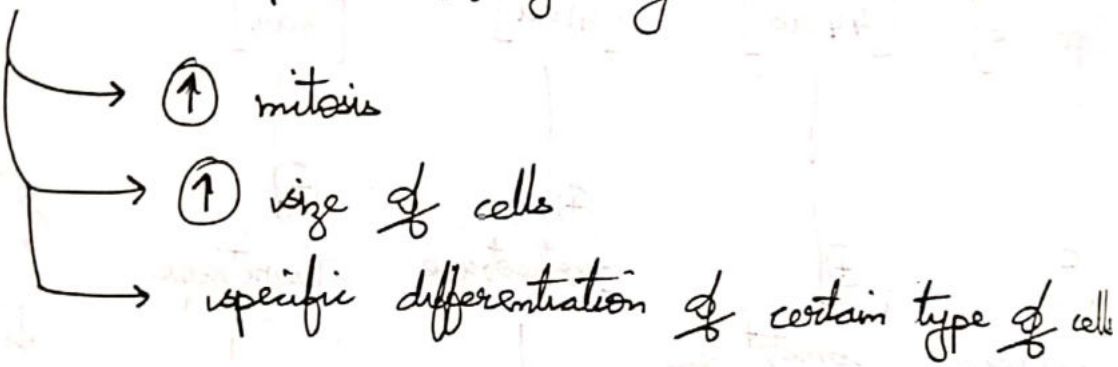
- There exists a portal system B/W hypothalamus and pituitary gland called hypothalamo hypophyseal portal system.

The vessels of this system are responsible for transporting the hypothalamic releasing and inhibitory hormones. - These hormones are syn by spcld neurons of hypothalamus.

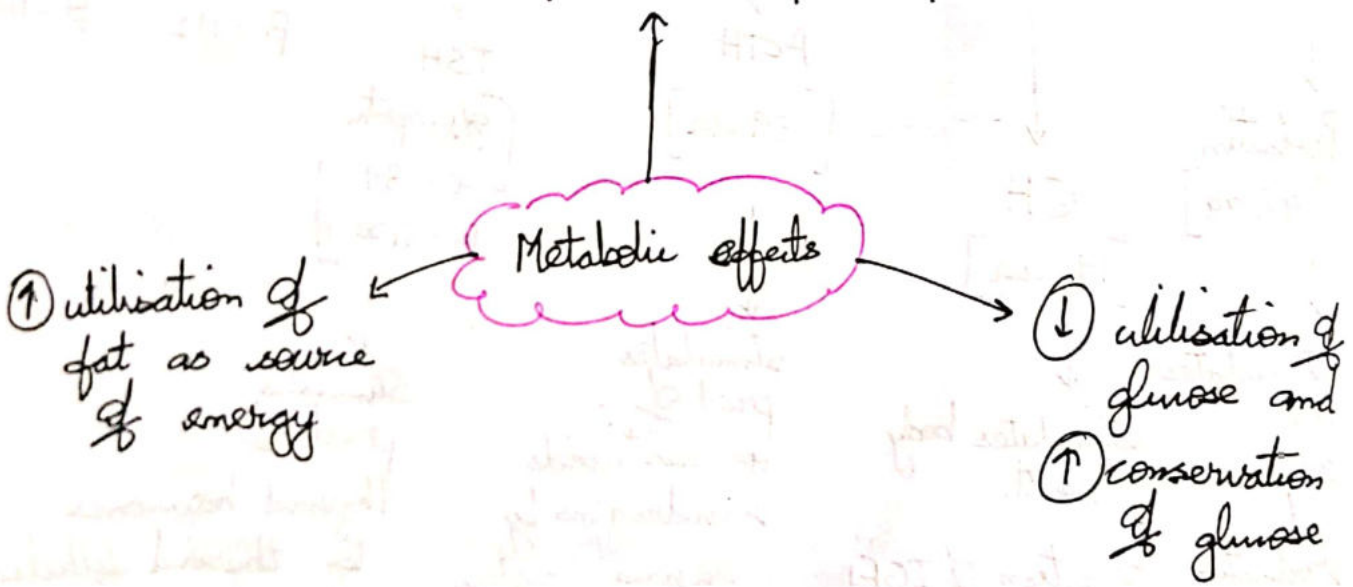


GROWTH HORMONE

- Growth hormone does not function thru a specific target gland but exerts its effects directly on all / almost all tissues of the body.
- GH / somatotropin / somatotropic hormone
  small ptn → 191 amino acids
  Molecular wt = 22,005
- Causes growth of almost all tissues of the body that are capable of growing



↑ ptn synthesis → ptn deposition in tissues



① GH ↑ protein deposition in tissues :-

- Enhancement of amino acid uptake by tissues
- " " RNA translation to form new proteins
- ↑ transcription of DNA to RNA → over more prolonged periods [24 - 48 hrs] GH causes this effect
- ↓ catabolism of ptns and amino acids.

② GH ↑ utilisation of fats as source of energy :-

- ↑ mobilisation of fat from adipose tissue
- ↑ conc of FA in blood
- ↑ convertion of Fatty acids into acetyl coA

↓

↑ utilisation as a source of energy

* excess GH – ketogenic effect

↳ very high fatty acid mobilisation causes formation of large amnts of aceto acetic acid by liver — ketosis

This also frequently causes fatty liver.

③ GH conserves glucose :- Hyperglycemia

- ↓ utilisation of glu by tissues such as skeletal m/s and adipose tissue
- ↑ gluconeogenesis by liver
- ↑ insulin secretion

These effects are due to GH induced insulin resistance — Thus ↓ the effect of insulin to enhance glu uptake & utilisation by skeletal mfs & adipose tissue

↓

hyperglycemia

↓

↑ insulin secretion

- Heme Effects of GH — diabetogenic
- Adequate insulin activity and adequate availability of carb are necessary for GH to be effective
  carb — to provide energy for growth
  insulin — enhances a.a uptake.

(4) GH effect on mineral metabolism :-
- ↑ Ca^{2+} absorp from GIT
- ↓ Na^+, Ca^{2+}, K^+, PO_4^{3-} excretion from kidneys

(5) GH effect on muscle :-
- ↑ muscle mass
- ↑ prtn deposition

(6) GH effects on organs and soft tissues
↑ growth of all internal organs and soft tissues

GH stimulates bone growth :-

- ↑ prtn deposition by chondrocytes and osteoblasts
- ↑ mitosis of these cells
- ↑ conversion of chondrocytes into osteogenic cells causing deposition of new bone — endochondral ossification

- GH causes two types of bone growth

Interstitial growth

↑ in the length of long bones

- This occurs at the epiphyseal cartilages
- First there is deposition of new cartilage followed by its conversion into new bone thus elongating the shaft
- At the same time the epiphyseal cartilage is used by late adolescence epiphyseal fusion takes place and there is no lengthening of bone afterwards

Appositional growth

↑ in the width of bones especially membranous bones

- osteoblasts deposit new bone whereas osteoclasts remove old bone
- GH strongly stimulates osteoblasts than osteoclasts

↓

Rate of deposition is more than that of resorption

↓

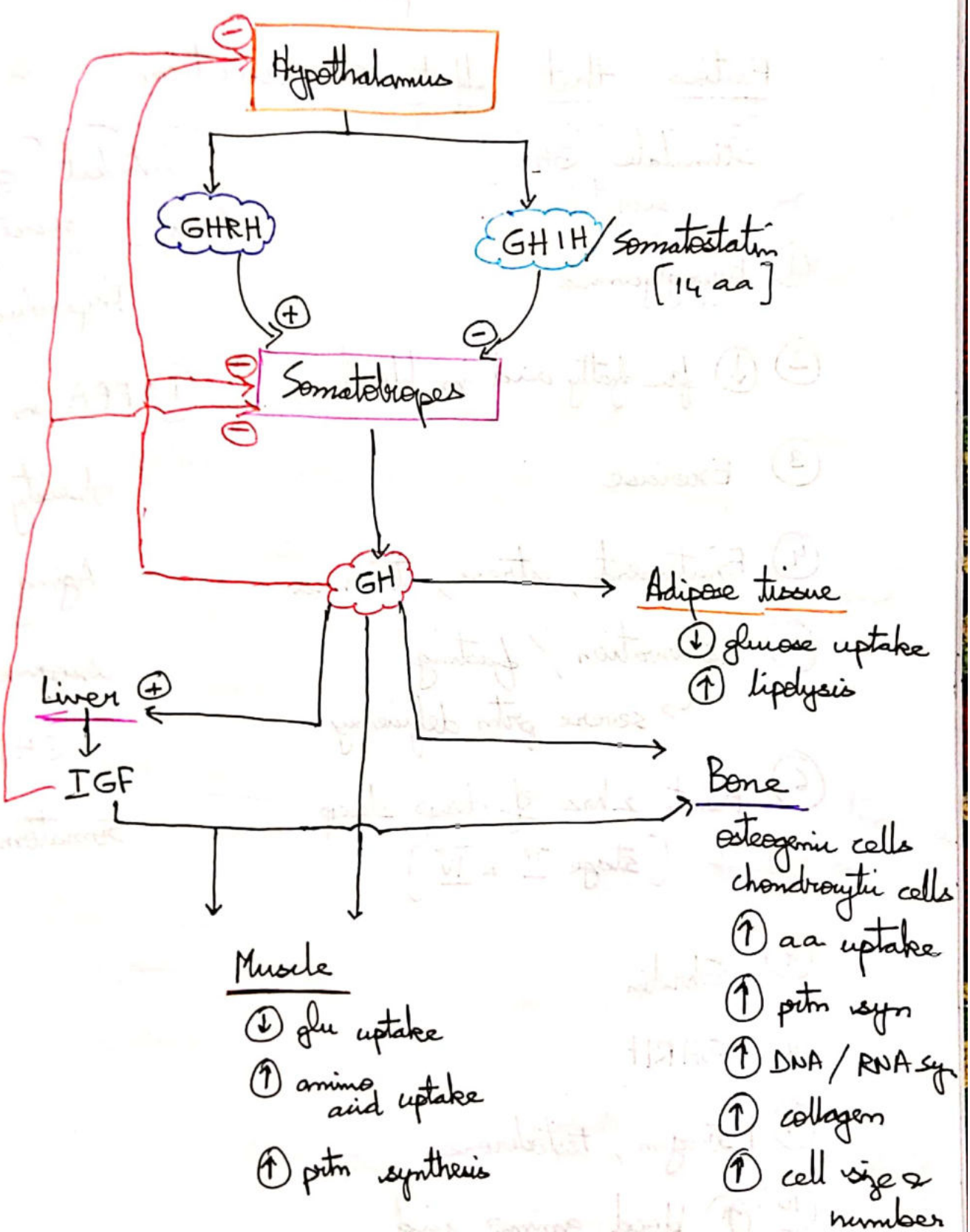
Bones can continue to become thicker through out life

Somatomedins / IGF's :-

- GH exerts much of its effects through somatomedins
- GH $\xrightarrow{(+)}$ Liver $\longrightarrow$ Somatomedins
  ↓
  Potent effect of (+) all aspects of bone growth
- Effects on growth similar to insulin. Hence called IGF
- Most imptnt one — Somatomedin - C / IGF-1
  molecular weight — 7500
  Its conc in plasma closely follows ~~that of~~ the rate of growth hormone secretion.
- GH attaches weakly to plasma prtns → rlyd from the blood into the tissues rapidly →
  Half time < 20 min

  IGF-1 attaches strongly to the carrier prtn → rlyd slowly from blood into tissues →
  Half time = 20 hrs
  ↳ This slow rly greatly prolongs the growth promoting effects of the bursts of GH secretion.
- IGF-1 → muscles — (↑) aa uptake & prtn syn
  (↓) glu utilisation

dwarf have the inability to syn significant amts of IGF's. Although their GH conc in plasma is normal their growth is stunted.



→ Regulation of GH secretion :-

- After adolescence secretion ↓ slowly with aging
  at very old age - 25% of adolescent level.
- GH is secreted in pulsatile manner.
- Factors that effect GH secretion

Stimulate GH secretion

1. Hypoglycemia
2. ↓ free fatty acid in blood
3. Exercise
4. Excitement, stress, trauma
5. Starvation / fasting
   ↳ severe prtn deficiency
6. First 2 hrs of deep sleep
   [stage II & IV]
7. Ghrelin
8. GHRH
9. Estrogen, testosterone
10. ↑ blood amino acid

Inhibit GH secretion

Hyperglycemia

↑ FFA in blood

Obesity

Aging

exogenous GH

GHIH

Somatomedins

GH in adults = 1.6 - 3 ng/ml of blood

in child/adolescent = 6 ng/ml

during prtn deficiency = can reach 50 ng/ml

- Acute conditions → hypoglycemia is a potent stimulus
  Chronic conditions such as starvation → cellular prtn depletion is a potent stimulator.

  Reason why Kwashiorkor treatment requires protein restoration - prtn treatment
  Here carb treatment is not efficient and does not bring GH levels back to normal.

- Hypothalamic signals depicting emotions, stress, trauma can all affect hypothalamic control of GH secretion

catecholamines
dopamine
serotonin
→ (+) GH secretion

- GHRH - cAMP pathway
  - short term effect → ↑ Ca^{2+} → ↑ synth of GH
  - long term → ↑ transcription → ↑ synth of GH

The major regulatory function controlled by GH is long term state of nutrition of tissues, especially their level of protein nutrition

⇒ Abnormalities of Pituitary secretions :-

① Panhypopituitarism :-

↓ secretion of all anterior pit. hormones

Congenital	Acquired in adults due to
ie. by birth	① craniopharyngomas
	② chromophobe tumours that compress the gland & finally destroy it
	③ Thrombosis of Pituitary blood vels → develops when a new mother develops circulatory shock after delivery.

Effects :-

- Hypothyroidism
- ↓ conc of glucocorticoids – ↓ rly from adrenal cortex
- ↓ rly of gonadotrophins – loss of sexual functions
- Lethargy
- Excess wt (due to ↓ GH, ↓ thyroid ↓ ACTH, ↓ adrenocortical hrms)

(2) Dwarfism

Dwarfism

due to panhypopituitarism [congenital] → sexually immature & does not go thru puberty

due to only GH deficiency → sexually mature and can have children.

- In general all physical parts of the body develop in apt proportion to each other but the rate of development is greatly reduced.
- Treatment :- By administration of Human GH prod by escherichia coli with the help of recombinant DNA technology

[cannot use GH prod by other animals as GH is species specific]

- dwarfs due to pure GH defiency can be completely cured if treated early in life.

(3) Gigantism :- Excess secretion of GH mainly due to acidophilic tumours of pituitary gland

- If this occurs before addescence ie before epiphyseal fusion → Ht (11) → person becomes a giant upto 8 ft

Clinical features

① Ht ↑ upto 8 ft tall
② Large hands & feet
③ Soft tissues grow rapidly
④ Hyperglycemia — leads to degeneration of β cells of Pancreas due to overactivity
10% of giants — full blown diabetes mellitus
⑤ All features of Panhypopituitarism if the cause is due to tumour
- Weight gain
- loss of sexual func
- ↓ immunity
- hypothyroidism
- Adrenocortical insufficiency.

- Treatment :— microsurgical removal of tumour or by irradiation of the pituitary gland.

④ Acromegaly :— Excess GH after adolescence ie fusion of epiphyses
- person cannot grow taller but bones become thick
- clinical features :—
1.) Marked enlargement of hands & feet
2.) Enlargement of mem. bones
- cranium
- nose
- supraorbital margin

- bossing of forehead
- protrusion of lower jaw - prognathism
- Portions of vertebrae (↑) in size

3.) Enlargement of organs
- Tongue enlarged
- Hepatomegaly
- cardiomegaly
- splenomegaly
- Renal enlargement.

Posterior Pituitary :-

- The posterior pituitary hormones are produced by spl magno-cellular neurons in Hypothalamus

Supra optic nucleus ⟶ ADH/AVP
Paraventricular nucleus ⟶ Oxytocin

- The posterior pituitary acts as a storage house of these hormones
- It is composed of glial like cells called pituicytes acts as support & do not secrete hormones.
- The hormones syn by supra optic & paraventricular nuclei are transported down the axons of their neurons, bound to a carrier protein called Neurophysin.

They are then stored in the synaptic knobs present within posterior pituitary until they are rlyd.

- Functions :- regulate conc ① secretion of H_2O ② reabsorption of H_2O from DCT & CD.

higher conc → vasoconstriction of arterioles

↓

↑ in BP

- ADH
  - absent → DCT & CD become impermeable to H_2O ↓ reabsorption of H_2O ↑ water loss
  - Present → opposite effects → ↑ water conservation

- Mech of Action :-

Tubular epithelial cells with spl vesicles that have highly water permeable pores called Aquaporins

↓

ADH combines with membrane receptors

↓

Activates cAMP pathway

↓

Phosphorylation of elements in spl vesicles

↓

Vesicles get inserted into apical mem

↓

water permeability ↑

All these events occurs in 5-10 min.

Factors controlling ADH prod ⇒ secretion :-

① ECF osmolarity :-

- ↑ ECF osmolarity ⟶ (+) ADH prod ⇒ secretion
- Somewhere in/near the hypothalamus are sptd neuron receptors called osmoreceptors

When ECF osm ↑ ⟶ ECF too concentrated

↓

H_2O moves out of osmoreceptors [exosmosis]

osmoreceptor size ↓ ⟵ nerve signals are initiated ⟵ (+)

Hypothalamus ⟶ ↑ ADH secretion.

When ECF osm falls ⟶ opp happens ⟶ ADH secretion ↓

∴ conc body fluids stimulate Supra optic nucleus
⇒ dilute body fluids inhibit

② Blood volume & BP

↓ Bld vol ⇒ ↓ BP ⟶ (+) ⟶ rly of High conc of ADH

↓

BP ↑ ⟵ Vasoconstriction

BP detected by stretch receptors in Atria, baroreceptors of carotid, aortic & pulmonary regns.

- When Bld vol ↓ 15-25% → secretory rate of ADH 50× norm

=> Oxytocin :-

- Functions

(1) Oxytocin causes contraction of Pregnant uterus :-

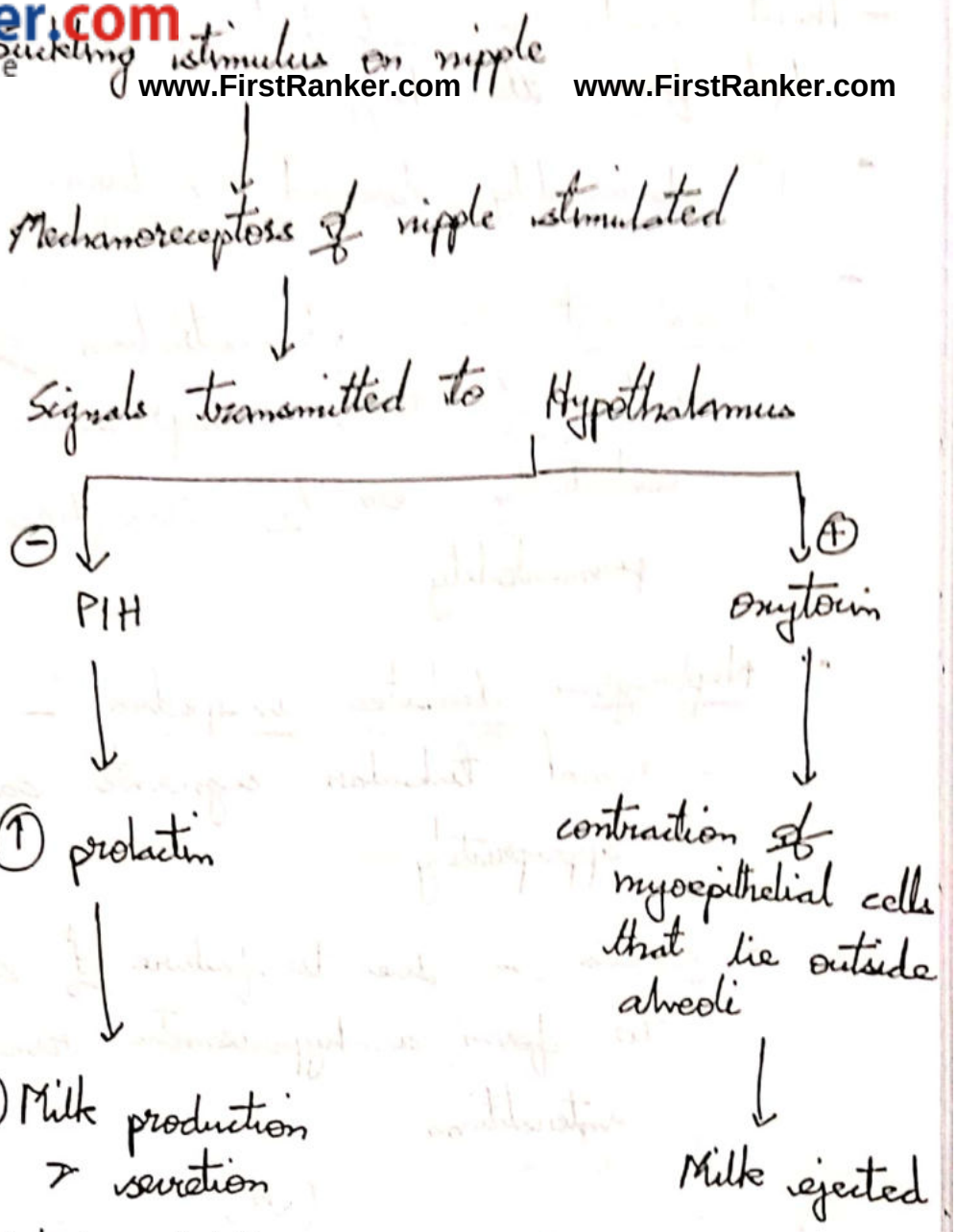
↳ powerfully stimulates contraction of uterus towards end of gestation

May be partially resp for ~~labour~~ causing birth of baby as :-

- In a hypophysectomised animal duration of labor is prolonged
- Amnt of oxytocin ↑ during the last stage of labor
- stimulation of cervix elicits nervous signals → ↑ ↑ secretion of oxytocin.

(2) Oxytocin aids in milk ejection by breasts :-

- In lactation oxytocin causes milk to be expressed from alveoli into ducts of breast so that they can obtain it by suckling.



⇒ Disorders of Posterior pituitary

① Diabetes insipidus :-

- Central diabetes insipidus :-
  inability to prod / rel ADH from posterior pituitary
  caused by
  a) Head injuries
  b) Infections
  c) Congenital causes.

distal segments cannot absorb water in absence of ADH → formation of large volume of dilute urine upto 15 l/day

- Thirst mech are activated when excessive water is lost from the body
- 1° abnormality observed → large vol dilute urine
- Treatment :- administration of a synthetic analog of ADH, desmopressin which acts selectively on V_2 receptors to ↑ H_2O permeability
- Nephrogenic diabetes insipidus :-
  - renal tubular segments cannot respond appropriately
  - causes :- due to failure of counter current mech. to form a hyperosmotic renal medullary interstitium

    (or)

    failure of DCT & CD to respond to ADH
  - Large vol of dilute urine are formed This causes dehydration unless fluid intake is ↑ by the same amnt
  - Treatment :- Correct the underlying renal disorder Hypernatremia can also be attenuated by a low Na^+ diet and administration of a diuretic that enhances renal sodium excretion

② SIADH – syndrome of Inappropriate secretion of Anti diuretic hormone.

- It is a syndrome of Na^+ & H_2O imbalance
- Manifested hyptonic hyponatremia and impaired urinary dilution
- causes → Exogenous
  → Endogenous
  → Idiopathic
  - Endogenous → ADH secretion ↑ from hypothalamus
    → ADH from ectopic prod such as carcinoma
    → drugs that potentiate ADH effect
  - Exogenous → administration of ADH
    → .. analogs like desmopressin

- Features :-
  a) ↓ in effective plasma osmolality (<275 mosm/kg)
  b) ↑ in urinary ~~dilution~~ osmolality (>100 mosm/kg during hypotonic conditions)
  c) ↑ urinary Na^+ (> 40 mmol/kg)
  d) clinical euvolemia
  e) Normal thyroid & adrenal func
  f) No history of recent use of diuretics

Management :-

a) Addressing all correctable causes
b) correcting hyponatremia — ↑ Na^+ in die
c) restricting fluid intake
d) Administering vasopressin receptor antagonist if hyponatremia persists.