Lecture 1

Histamine

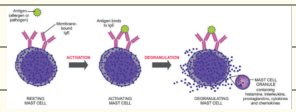
biogenic amine,which triggers vasodilatation and increases vascular permeability. It is stored in granules of circulating basophiles and mast cells and released immediately when these cells are injured.

It is synthesized by decarboxylation of histidine by Histidine decarboxylase.

Locations: Everywhere, intestinal mucosa, lungs, skin, mast cells, basophiles, CNS (role as a neurotransmitter)

Histamine is released by two ways :

Specific (antigen-mediated)



Antigen-Antibody interaction → mast cell degranulation

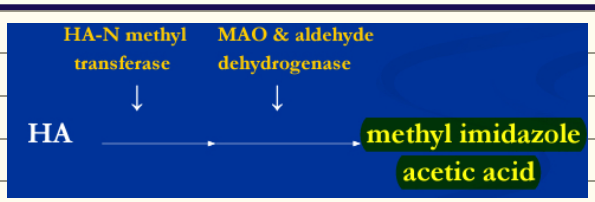
Non-specific (non-antigen-mediated)

Drugs (antibiotics, anticancerous agents, compound 48/80…etc), dyes, venoms, mechanical or thermal stress

Histamine receptors

	H1	H2	H3	H4
Major Tissue Locations	Smooth muscle(B.V and bronchi), endothelial cells	gastric parietal cells	CNS	mast cells, eosinophils, T cells, dentritic cells
Major biologic function	acute allergic responses	Secretion of gastric acid	Modulating transmission	Regulating immune response
Agonists	Compound 48/80	Compound 48/80 Apromidine	Compound 48/80 Betahistine(Partial agonist)	—
Antagonists	Classical Antihistamines Sedating and Non-sedating	Cimetidine Ranitidine Famotidine Nizatidine	Betahistine (effective in Meniere's disease, obesity and atypical depression)	—

Metabolism of Histamine:



Responses to Histamine

Bronchoconstriction (predominant H1)

Increased acid secretion (H2)

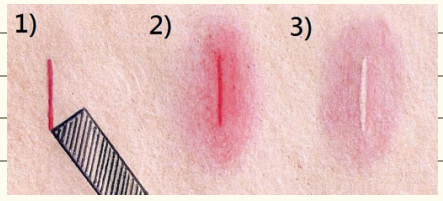
+ ve chronotropic & inotropic effect (H2)

Lewis triple response (hypersensitivity reaction; H 1 & H2)

1) Dilatation of capillaries → red spot (flush) or red line

2) Dilatation of arterioles → flare

3) Increased capillary permeability → whitish swelling (wheal)



***Inhibitors of histamine release (Mast cell stabilizers) :**

1) Cromolyn sodium (sodium cromoglycate)
2) Nedocromil sodium
3) Ketotefen

inhibit mast cells degranulation
Do not block Ag-Ab binding to mast cells
Do not lead to bronchodilatation

Used mainly as a prophylactic agents in patients with:

- Mild to moderate asthma (Ag, exercise, dry air-induced)
- Hay fever
- Conjunctivitis
- Systemic mastocytosis

We have certain drugs that increase levels of cAMP, thus decrease histamine release like :
Epinephrine, Isoproterenol, Theophylline

***Classical Antihistamines**

Major side effects to antihistamines
- Sedation and drowsiness - Anticholinergic effect - Teratogenicity
- Overdosage → convulsions and coma

Sedating (1st generation) more lipid soluble → CNS:

Diphenhydramine, Dimenhydrinate, Chlorpheniramine, pyrilamine,Carbinoxamine, Triprolidine, Tripelennamine, Promethzine, Meclizine, Cyclizine, Cyproheptadine…

Non-sedating (2nd generation) :

Astemizole, Loratadine , Desloratadine, Fexofenadine,Citrizine…etc

Major clinical uses for antihistamines:
- Allergic reactions (acute hives, urticaria, hay fever, allergic rhinitis, mild anaphylaxis…etc)
- Motion sickness (antiemetic effect)
- Sleeping aid (OTC preparations)

*Classical antihistamines are effective orally and parenterally , and some of them may have anti-cholinergic, local anesthetic effects .

**Antihistamines cannot block totally hypersensitivity reactions.

Prostaglandins and leukotreines

Involved in

- Platelet aggregation
- Control of B.P (diameter of blood vessels)
- Contraction of the uterus
- Protection of the stomach and duodenum…etc

Involved in

- Allergic reactions

SRS-A (slow reacting substance of anaphylaxis) : Believed to be a mixture of LTB LTD 4 , LTC and is responsible for the severe bronchoconstriction in patients with anaphylaxis or bronchial asthma

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Cell membrane phospholipids

Glucocorticoids
Phenothiazines
Local anesthetics
Antimalarial agents

(X) Phospholipase A2

Arachidonic acid

NSAIDs (Aspirin, Ibuprofen, Indomethacin, Piroxicam, ~~Diclofenac Na+ K+, Mefenamic acid, Sulfenpyrazone, Phenybutazone, Sulindac...etc~~)

Nonselective: Block COX 1 & COX 2

Cyclooxygenase (PG synthase)

Zileuton (X) Lipoxygenase

5-HPESE

Selective: Block only COX 2

Meloxicam, Rofecoxib, Etoricoxib; Etodolac, Valdecoxib; Nabumetone

PGD, PGH2, PGG2

LTB4 , LTC4 , LTD4

antagonists

Zafirlukast, Montelukast

	PGE2	PGF2α	PGE1	PGI2	TXA2
Abortifacient, labor inducers:	Dinoprostone	Dinoprost	Gemeprost	—	—
Antiplatelet, peripheral vascular disease, Raynaud's disease	—	—	—	Epoprostenol Iloprost	—
Keeping patent ductus arteriosus, impotency	—	—	Alprostadil	—	—
Postpartum hemorrhage	—	Carboprost	—	—	—
Peptic ulcer disease	—	—	Misoprostol	—	—

Thromboxane synthase inhibitors : Dazoxiben, Hydralazine

Aspirin

Has the best antiplatelet activity (inhibits vascular cyclooxygenase reversibly and platelet cyclooxygenase irreversibly)

#Has the best antiinflammatory effect (inhibits PG synthesis and increases synthesis of natural antiinflammatory substances e.g. lipoxins and resolvins)

#Large doses of aspirin inhibits both cyclooxygenase and lipoxygenase enzymes

PG's mechanism of action :

It is receptor mediated , so for example PGI2 *activates adenylate Cyclase and increases cAMP levels* while TXA2 does the opposite

- **Major pharmacological effects to PGs:**
- **CVS:** $E, I_2 \rightarrow$ vasodilatation $\rightarrow \downarrow$ B.P
  $TXA_2 \rightarrow$ vasoconstriction
- **Blood:** E_1, I_2 (prostacyclin) $\rightarrow \downarrow$ platelet aggregation
  $TXA_2 \rightarrow \uparrow$ platelet aggregation
- **Bronchi:** $I_2, E \rightarrow$ dilatation
  $F \rightarrow$ constriction
- **Uterus:** $E, F_{2\alpha}$ strong contractors
- **Stomach:** E, A, I_2 $\downarrow$ acid $\uparrow$ mucus

**Clinical application is based on either mimicking physiological effects by exogenous PGs or, in pathological situations, preventing their synthesis

Lipooxygenase: Lungs, W.B.C's, Platelets

Cyclooxygenase (COX): All tissues

COX_1: Stomach, Kidneys, Platelets

COX_2: Other tissues

Prostacyclin synthase: Blood vessels

Thromboxane synthase: Platelets

Lecture 2

Endocrine system

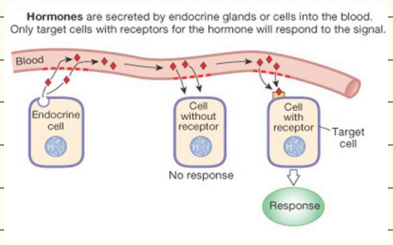
- Coordinates the function of cells
- Uses chemical signals (hormones) for cell to cell communication
- Response to an endocrine signal occurs within minutes to hours (ductless glands)

The importance of Hormonal regulation

- Growth & development
- normal homeostasis
- Response to environmental situations (stress…)
- Reproduction, fertility, sexual function

Hormones

Chemical substances synthesized in and released from highly specialized cells collectively known as endocrine glands



Considered cell to cell communication molecules

Transported by blood , to act at Distant or local target tissue receptors to Activate physiological response

Chemical nature of hormones

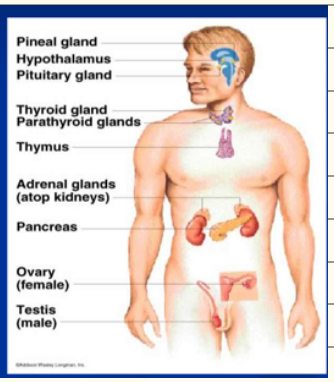
Steroids:
Cortisol; Aldosterone; Estrogen; Progesterone; Androgens

amino acid derivatives:
T3 ; T 4 ; Dopamine (precursor=Tyrosine)

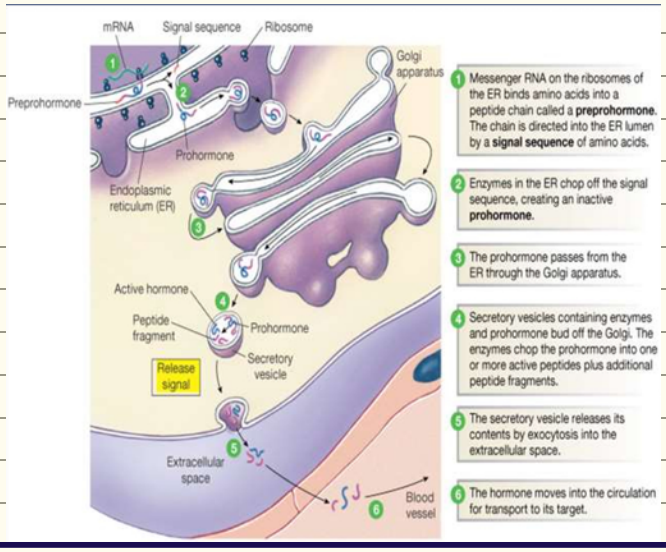
Receptor locations
- Surface (Dopamine)
- Intracellular (nuclear; T 3 & T 4)

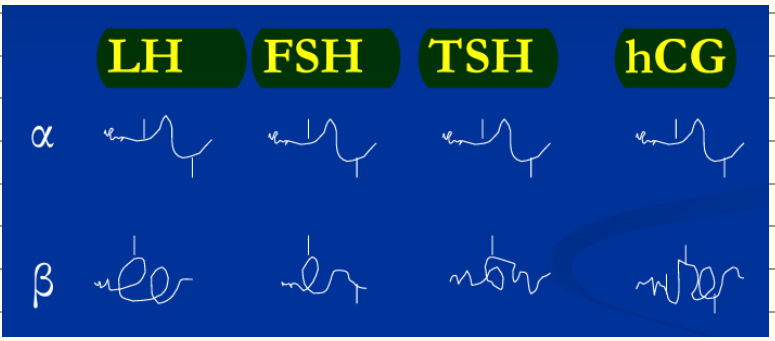
Small peptides; polypeptides; large proteins or glycoproteins:
Hypothalamic hormones; GH; PRL; Insulin; Glucagon; LH; FSH; TSH…

** Glands
Ductless
Hypothalamus
Pituitary
Thyroid
Parathyroid
Pancreas
Adrenals
Ovaries
Testes

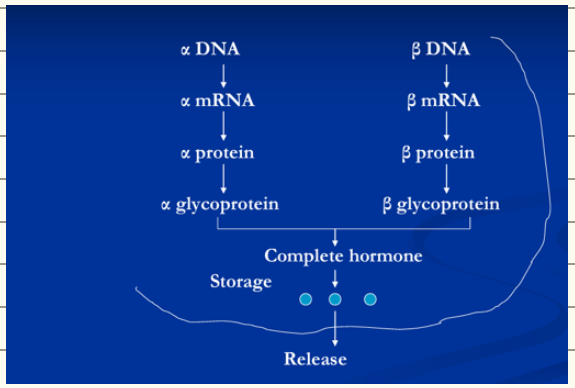


Protein and Polypeptide Hormones: Synthesis and Release



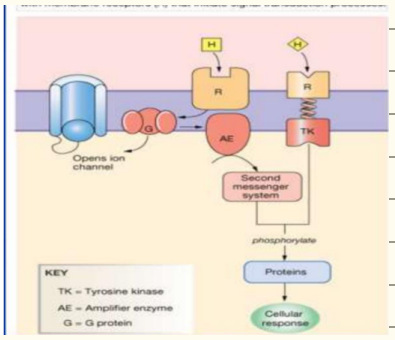


This picture illustrates that those hormones have the same alpha subunit , but they differ in their Beta subunit meaning that the basis behind the differences in their actions is due to the difference in the Beta subunits



The figure shows the Cascade of events from DNA towards the release of the hormone. Any step along this pathway can be targeted by drugs. Drugs targeting the synthesis process of these proteins are of slow-onset of action while those targeting the release process are of rapid-onset.

✓ Protein hormones can't penetrate the cell membrane and therefore bind **cell surface receptors**, thereby inducing a conformational change leading to **signal transduction**:
- **System activation** (Tyrosine kinase pathway activation by insulin).
-**Open ion channel** via either Enzyme activation, Second messenger systems or Protein synthesis



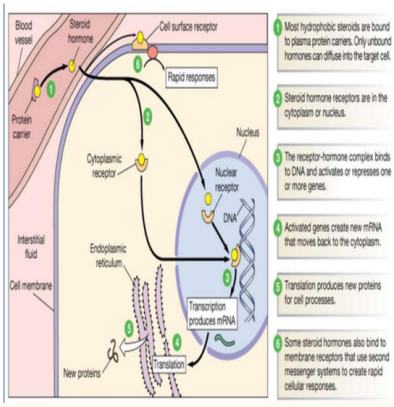
- **Steroid Hormones and their Receptors**:

Synthesized by glands and then secreted to travel throughout the blood in the bound form (bound to carrier proteins), only the unbound hormones can then affect their target cells via 3 routes:

1- Pass through the membrane to bind **cytoplasmic receptors** forming complexes that then go towards to nucleus to regulate DNA-expression.
2- Pass through the membrane to immediately bind **nuclear receptors**
3- Some of these hormones bind **cell surface receptors** to elicit a rapid cellular response.

Route 1,2 usually require time because the process of protein synthesis while Route 3 elicits a faster response.

Note: Steroid hormones are hydrophobic substances and therefore cannot freely in the hydrophilic environment of the blood and thus need carrier proteins.



Hormones are subjected to 2 phenomena:

Desensitization (Down-regulation) : decrease in the number and/or affinity of receptors. It is considered the underlying mechanism behind DM where the patients are irresponsive to insulin despite being in high levels in the blood

Sensitization (Up-regulation): increase in the number and/or the affinity of the receptors for that hormone. Clinically, Oral hypoglycemic agents are used to induce the up regulation of Insulin receptors for the treatment of DM type 2.

The time the hormone spends in high amounts inside blood depends on :

- *Efficiency of degradable enzymes & clearance Metabolism &excretion.*
- *Extent of protein binding*
- *Efficiency of negative feedback mechanisms*

Sources of hormones:

- ***Natural From Humans:*** **GH** was previously extracted via a nasal procedure but not anymore due to bad SE. Also, **LH and FSH** are taken from the Urine of postmenopausal women. Finally **HCG**, known as the hormone of pregnancy, is produced by the placenta and therefore is found in high amount in Urine of pregnant women.
- ***Natural From Animals:*** Animal **Insulin** and (**T3,T4** from pigs and cows) are theoretically humans but with low bioavailability, thus replaced by synthetic Recombinant insulin and T3,T4.
- ***Synthetic:*** Most supplied hormones and Their antagonists, synthesized by many techniques including Recombinant DNA.

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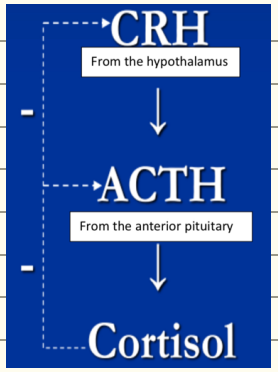
*Basal conditions are defined as body conditions whereby we have minimal release of hormones

Stimuli for hormones release :

- **Nerve impulse**
- **Change in composition of ECF**
- **Another hormone (tropic hormone)**

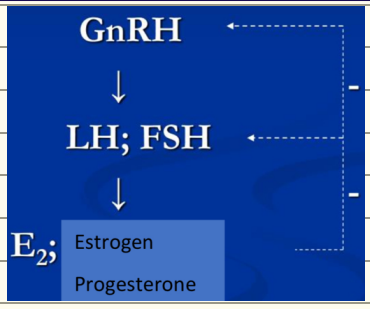
- Hormones reach blood → target cells → receptors → initial change → cascade of reactions → recognizable changes including:

1- **Change in cell permeability**
2- **Stimulation or inhibition of protein synthesis** (Regulation of Transcription or translation)
3- **Stimulation or inhibition of mediator release (second messenger)** which can be proven by using laboratory methods, Examples on 2ndry messengers: cAMP; DAG; Ca++; ITP (IP3)...



This figure represents the ***Hypothalamic- pituitary-adrenal axis*** which is controlled by Cortisol, feeding back into ant-pituitary or the hypothalamus inhibiting ACTH, CRH release.

Clinically, when dealing with Cortisol deficiency, we can identify the origin of the deficiency using Hormone assays (expensive). Thus, it better to **treat with replacement therapy regardless of the origin of the deficiency**. (**1ry** intrinsic to adrenal gland, **2ry** in the pituitary or **3ry** in the hypothalamus).

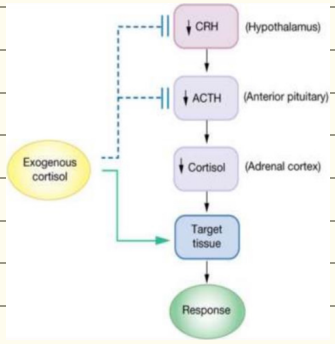


In females, this is the ***hypothalamic pituitary gonadal axis,***

In postmenopausal women, there is a decrease in estrogen and progesterone and consequently, there will be an increase in LH, FSH which can be detected in urine test.

Clinical correlate: Oral contraceptives usually contain estrogen and progesterone in certain amounts that can lead to suppression of the axis. In 90% of cases this suppression is reversible. In 10% of cases, the reversal takes from 6 month to even a case of irreversible suppression leading to infertility. ***Therefore, Newlywed ladies are advised not to use such agents*** before their first pregnancy in order to diagnostically tell whether their infertility is an intrinsic disorder or whether its extrinsic due to taking these oral contraceptives.

This figure illustrates the effect of **exogenous administration of cortisol** on the adrenal axis. Upon chronic administration, there will be suppression of all CRH, ACTH, endogenous cortisol synthesis and secretion.



This is why patients taking Cortisol for long periods of time are advised not to abruptly stop using the drug to avoid Adrenal suppression (decrease in the endogenous synthesis of cortisol).

Clinical uses of hormones:

Deficiency states, for instance **cortisol deficiency**, treated by **HRT** (Hormone replacement therapy) by using Physiological dosages (10^-13-10^-9) .

Excess production of a specific hormone by using **Inhibitors to the synthetic machinery** or **Release inhibitors** or **Specific antagonists** or **Surgery**.

Anti-inflammatory effects (**non-endocrine related diseases**) by using supraphysiological dosages.

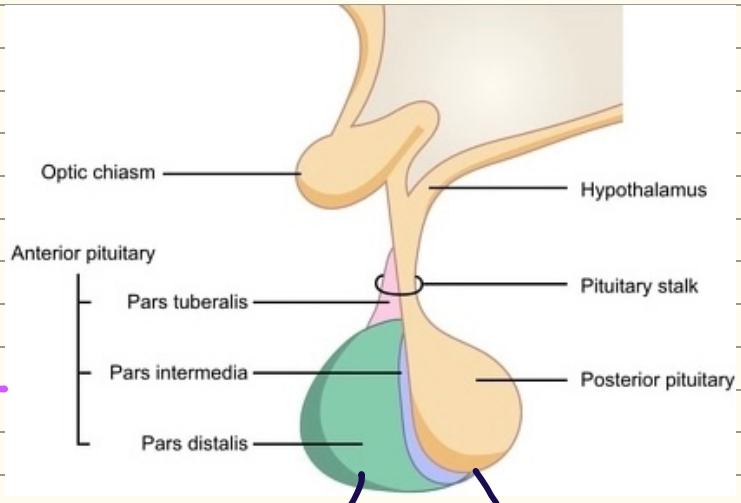
as diagnostic tool (**TRH test ...**)

Final notes:

- we can use some drugs which are not hormones but used in the management of diseases of endocrine origin, Examples: **Antithyroid drugs, oral hypoglycemic agents.**
- Some drugs are used to treat diseases not related to the endocrine system but affecting it Example: Anticancerous drugs → leading to ♂ & ♀ infertility.
- The use of hormones as contraceptives is controversial as discussed before.

Lecture 3

Hypothalamus → Hormones → network of capillaries (portal system)→ Anterior pituitary



Hypothalamus → ADH & Oxytocin → neuro-secretory axons→ Posterior pituitary

stimulatory and inhibitory control

stimulatory control

GH, PRL, MSH | **ACTH, TSH, LH, FSH** | **ADH , Oxytocin**

 # Derived from larger precursor (Proopiocortin)
 # it increases cortisol release

Undergoes circadian rhythm (It has a diurnal variation) :

- It has a higher production and release during the Day
- It has a lower production and release during the night
- This has a clinical significance→Because whenever we use it in HRT, we try as much as possible to mimic

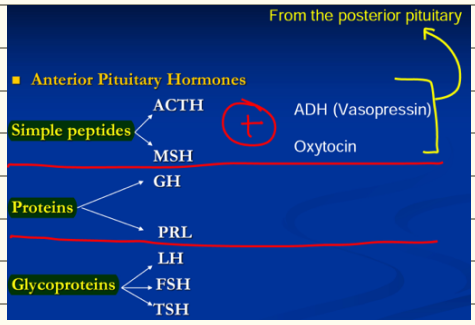
Acthar and Cosyntropin **(tetracosactrin; Cortrosyn) are synthetic analogs**

Uses:
Diagnostic use (given I.V or I.M)
Certain cases of adrenal insufficiency

↑ T3 & T4 through ↑ cAMP, ↑ Iodine uptake ↑ iodination and hydrolysis of thyroglobulin

**** it has diagnostic use to detect (hypo or hyper)-thyroidism or other thyroid disorders**

Chemical Classification of Hormones :



Has Prolactin like activity

GH (Somatropin) stimulates * growth of soft tissues and bones *↑ lipolysis*↑ gluconeogenesis & ↓ glucose utilization (diabetogenic effect)

MOA unclear, its effects believed to be mediated through IGFs (Somatomedins) which are formed in the liver , kidneys, muscles and other tissues

 # Has GH like activity

 # Dopamine **is a major regulator of prolactin synthesis and release by the anterior pituitary. In order to increase prolactin→We have to inhibit dopamine.**

In **males :**
it increases **testosterone** production by testes and hence **spermatogenesis**

But ↑ PRL → ↓ LH & FSH → *impotency & infertility*

In **Females :**
Breast development (puberty; pregnancy)
Lactation

But ↑ PRL → ↓ LH & FSH → galactorrhea amenorrhea syndrome

Factors ↑ GH release:	Factors ↓ GH release:
Sleep, Arginin, Insulin, Hypoglycemia	Bromocriptine in acromegalics
β- adrenergic antagonists, Clonidine,	Somatostatin synthetic analogs
Bromocriptine and levodopa in normal individuals	

Factors/drugs ↑ PRL:	Factors/drugs ↓ PRL:
Pregnancy, sleep, nursing, stress (surgery, exercise)	DA agonists (Bromocriptine, pergolide, levodopa)
TRH, Estradiol, DA antagonists (antipsychotics= phenothiazines and haloperidol; metoclopramide..)	apomorphine, clonidine ,
Methyldopa, reserpine, diazepam, opiates, meclizine, imipramine…	MAO inhibitors (pargyline)

GH- replacement therapy

recombinant human GH preparations:

-Somatropin (Humatrope)

-Somatrem (Protropin)

recombinant human IGF-1 preparations:

-Mecasermin (recombinant human IGF1);

-mecasermin rinfabate (recombinant human IGF-1 + IGF binding protein-3 [IGFBP-3])

Given in dwarf with IGF-1 deficiency not responding to GH

The most important adverse effect observed with ***mecasermin*** is **hypoglycemia**

Prolactin- suppression therapy

bromocriptine is the drug of choice in cases of Hyperprolactinemia in both males and females irrespective of the cause

bromocriptine is also indicated for :

Suppression of lactation

Acromegaly

Parkinson's disease

DM type II

Side effects: Rare, pulmonary fibrosis; confusion; hallucinations; MI…

Side effects of synthetic rHGH products:

Water retention, the development of antibodies to HGH, insulin resistance and diabetes, hypertension, carpal tunnel syndrome, abnormal bone growth, reduced life span, disturbed insulin metabolism, leukemia, overgrowth of connective tissue, and tumors, ↑ intracranial pressure with papilledema

Disorders affecting GH secreting cells:

Hyposecretion

In children it leads to **dwarfism** manifested by a very short trunk, short neck, shortened arms and legs, average- sized hands and feet, broad rounded chest

Rx of dwarfism → GH replacement therapy

In adults leads to a higher level of body fat, especially around the waist, anxiety and depression, decreased sexual function and interest, fatigue, less muscle…

Rx of GH deficiency in adults → loss of weight, good sleep, high protein low carbohydrate diet, exercises + GH replacement therapy

Hypersecretion

Gigantism, Acromegaly

Rx

Surgery

Somatostatin synthetic analogs

DA agonists (Bromocriptine; Cabergoline)

Pegvisomant (GH receptor antagonist, given SC, major side effects include abnormal liver enzymes and some reports indicated increased growth of GH- secreting pituitary tumors)

Hypothalamic hormones

TRH, GHRH, GnRH, GHIH, Dopamine (DA), CRH

A 40 a.a peptide
synthetic preparations are available (**Hexarelin, Sermorelin**)

Diagnostic use and in the management of certain cases of dwarfism

A 41 a.a peptide
It stimulates synthesis and release of ACTH
stress ↑ CRH release

Diagnostic use (CRH test)

Tri peptide
synthetic analogs are available (**Protirelin**)
Stimulates TSH synthesis and release

MOA: Activation of **phospholipase C** to increase intracellular **IP3 & DAG** Also, TRH has been found to increase **PRL** release through **2nd messenger Ca ++**

Mainly used:
As a diagnostic tool (TRH test)
To treat certain cases of hypothyroidism

A 14 a.a peptide
↓ secretion of GH, ACTH, TSH, Insulin, Glucagon, Gastrin , Serotonin

Its effects on blood glucose levels are dose dependent :
Low doses → hypoglycemia (↓ glucagon secretion)
High dose → hyperglycemia (↓ insulin secretion)

synthetic analogs are available (**Octreotide, Lanreotide**)
Those synthetic analogs are used mainly for :
Acromegaly
Carcinoid syndrome
Insulinomas, gastrinomas
Esophageal varices
?? Diabetes mellitus

They are still under clinical evaluation because of the side effects that are produced, particularly on platelets.

Major side effects for Ocreotide and lanreotide : Gall bladder stone formation and platelet abnormalities

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- Anterior pituitary hormones
  - Hypothalamic lesion or removal ➔ ↓ Ant. Pit H's **except PRL**
  - Hypothalamic stimulation ➔ ↑ Ant. Pit H's **except PRL**
    - That gives you an idea that prolactin is mainly under the (↓) **inhibition by the hypothalamus** through a hormone or substance that **inhibits the release and synthesis of prolactin** from AP, namely, **Dopamine**.

■ **General characteristics of hypothalamic hormones:**
TRH, CRH, GHRH, GHIH, GnRH, Dopamine (DA)
- **Small peptides and polypeptides** (exception DA) of low M.W
- Needed in very low concentrations (*pg*)
- Have short $t_{1/2}$
- Act on receptors on plasma membrane