ENDOCRINE SYSTEM

Pharmacology

Lec. 2

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*ما ينطق به الدكتور من شرح سيكون باللون الاحمر
*وما يكون مهم في شرح الدكتور يكون باللون البنفسجي
*ما يكون مهم في السلايدات يكون بخطين أو بخط

Hypothalamic Hormones

*Neurohormones:
Hormones released by a **neuron**.

- Hypothalamus →produce ADH & Oxytocin (posterior pituitary hormones) → through neuro-secretory axons→ Posterior pituitary
- Hypothalamus → Hormones of anterior pituitary →through network of capillaries (portal system)→ Anterior pituitary
- Anterior pituitary hormones like:

✓ ACTH, TSH, LH, FSH are under stimulatory control

✓GH(growth hormone), PRL(prolactin), MSH (melanocyte stimulating hormone) are under stimulatory and inhibitory control by hypothalamus.

- General characteristics of hypothalamic hormones:

TRH, CRH, GHRH, GHIH (somatostatin), GnRH, Dopamine(DA) as a hormone not a neurotransmitter.

1- Small peptides and polypeptides (exception DA which is an amino acid derivative) of low M.W

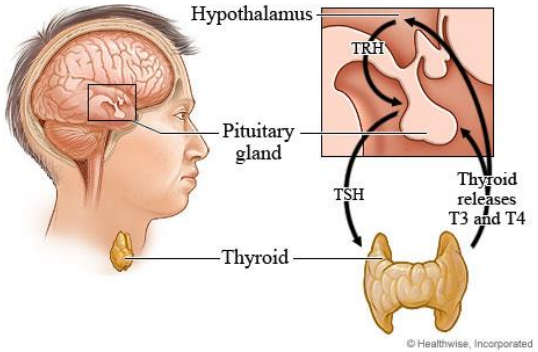
2- Needed in very low concentrations (pg)

3- Have short t1/2

4- Act on receptors on plasma membrane

- **TRH=Thyroid Releasing Hormone (Protirelin)**

Additional



Tri-peptide (3 AAs), synthetic analogs are available

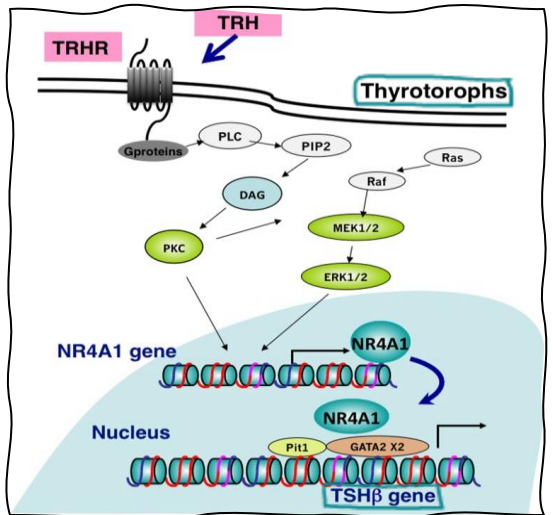
Effective orally and I.V

Stimulates TSH synthesis and release through the (Hypothalmus 'TRH'-Pituitary 'TSH'-Thyroid 'T3 and T4') axis.

Additional

MOA: Activation of phospholipase C to increase intracellular IP3 & DAG which act as second messengers mediating the effect of TRH.

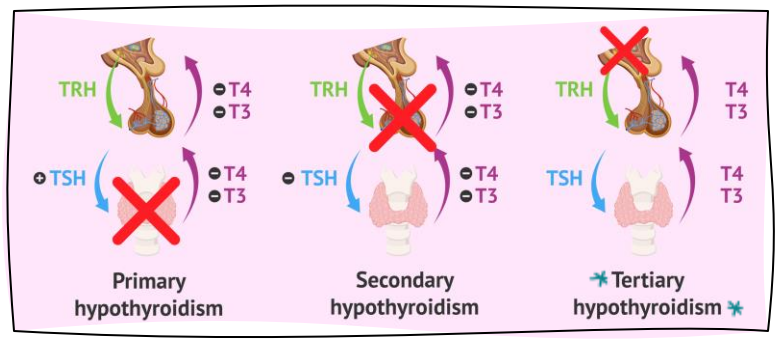
Also, TRH has been found to increase PRL release through 2nd messenger Ca++



Mainly used:

- As a diagnostic tool (TRH test), to assess the function of TSH secreting cells.

- To treat certain cases of hypothyroidism, provided that the anterior pituitary and thyroid gland are functional and hypothyroidism has arisen due to a deficiency in TRH secretion from the hypothalamus. Recall that the major cause of hypothyroidism is tertiary.
- So tests must be performed to determine the deficient hormone causing hypothyroidism.



Additional

DOA = Duration of action

Dose: 50 µg I.V, 5 mg orally, maximum response in 15-30 min, DOA 2-4 hrs

- **CRH=Corticotropin Releasing Hormone**

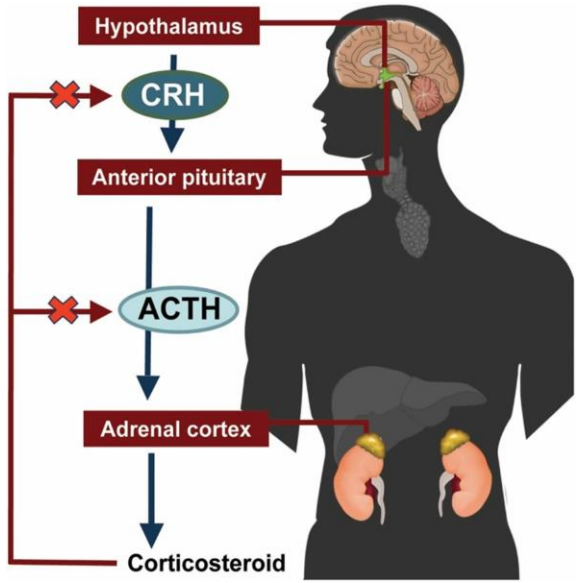
*Tetracosactide is a synthetic analog to ACTH.
Characterized by short duration of action and short half-life.

41 a.a peptide stimulates synthesis and release of ACTH which stimulate cortisol secretion from the adrenal gland through the axis (CRH 👉 ACTH 👉 Cortisol), when stress ↑, CRH is released

Diagnostic use (CRH test)

ACTH is used in adrenal insufficiency if the problem is in pituitary rather than adrenal gland (SEE THE PIC)

Additional



- **GHRH (Hexarelin, Sermorelin)**

40 a.a peptide, synthetic preparations are available

Diagnostic use and in the management of certain cases of dwarfism tertiary to a defect in the hypothalamus (it is given SC, SubCutaneous)

‘Very interesting hormone’

- **GHIH (Somatostatin)**

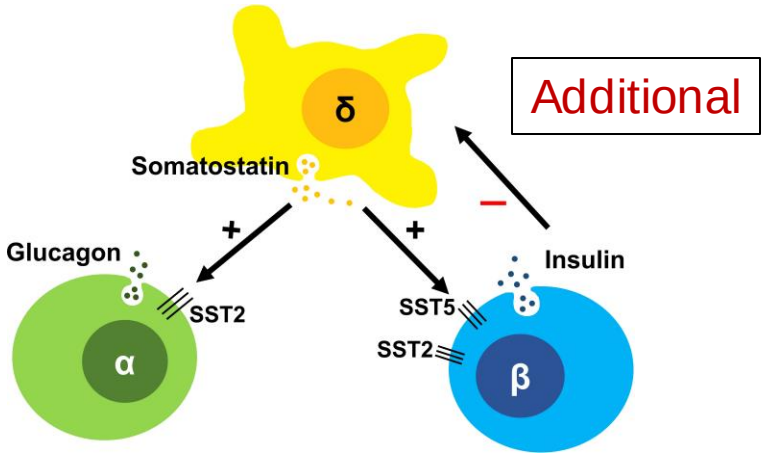
14 a.a peptide

↓ secretion of GH, ACTH, TSH, Insulin, Glucagon, Gastrin, Serotonin (inhibitory)

Its effects on blood glucose levels are <u>dose dependent</u>

Low doses ⟶ hypoglycemia (↓ glucagon secretion)

High dose ⟶ hyperglycemia (↓ insulin secretion) , role of somatostatin in the management of D.M .



Octreotide & Lanreotide

Given SC and IM

Major side effects: Gall bladder stone formation and platelet abnormalities

Synthetic analogs to **somatostatin** with longer t1/2 are mainly used in the management of:

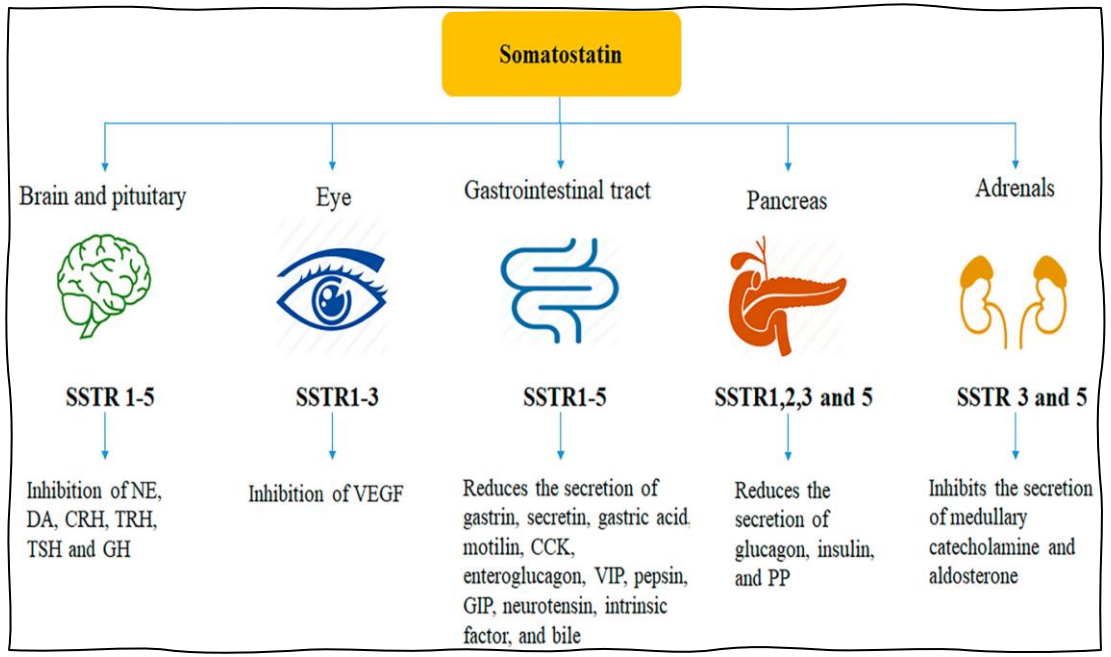
- **Acromegaly**, characterized by excess production of GH. Mainly treated by surgical removal of the tumor causing this hypersecretion, nevertheless some medications show success in lowering GH levels.
- **Carcinoid syndrome**, characterized by a carcinoid tumor affecting EC cells in the intestines ,leading to high level of serotonin, major manifestation is severe intractable diarrhea. It's the drug of choice in carcinoid syndrome as it's highly effective 💥
- **Insulinomas** tumor affecting beta cells in the pancreas which releases high amounts of insulin.Somatostatin inhibits insulin secretion ⍰

- -**Gastrinoma**, tumor characterized by high levels of gastrin secretion. Somatostatin also inhibits gastrin secretion ?

- **Esophageal varices ,** somatostatin increases platelet aggregation which prevents bleeding, but not that successful. Other drugs may be used to prevent bleeding as vasopressin .

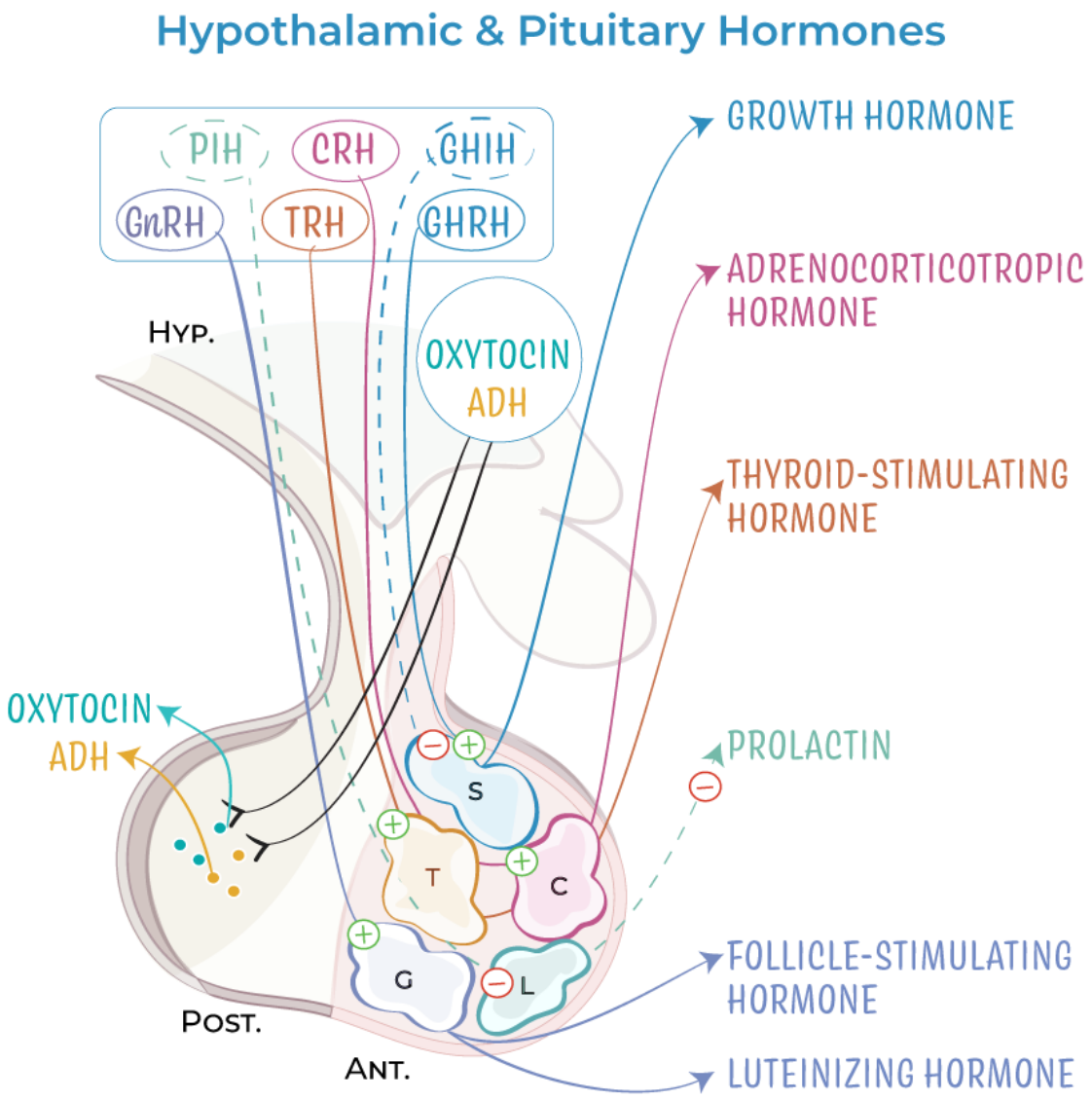
- ?? **Diabetes mellitus**

Additional: as you can see, somatostatin has many targets and is effective against various tissues among the body . Spotlight on this figure 👉



Additional

Pituitary Hormones



Anterior Pituitary Hormones

Classified chemically into:

- **Simple peptides**
  - ACTH
  - MSH
- **Proteins**
  - GH
  - PRL
- **Glycoproteins**
  - LH
  - FSH
  - TSH

- **Posterior Pituitary Hormones**

Simple peptides (9 a.a)

-ADH (Vasopressin)

-Oxytocin

- Hypothalamic hormones regulating the anterior pituitary hormones reach the anterior pituitary through a network of capillaries (portal system) whereas ADH and oxytocin reach the posterior pituitary via neurosecretory axons

Posterior pituitary releases and doesn't synthesize hormones !!

Anterior Pituitary Hormones

Hypothalamic lesion or removal → ↓ Ant. Pit H's except PRL

Hypothalamic stimulation → ↑ Ant. Pit H's except PRL

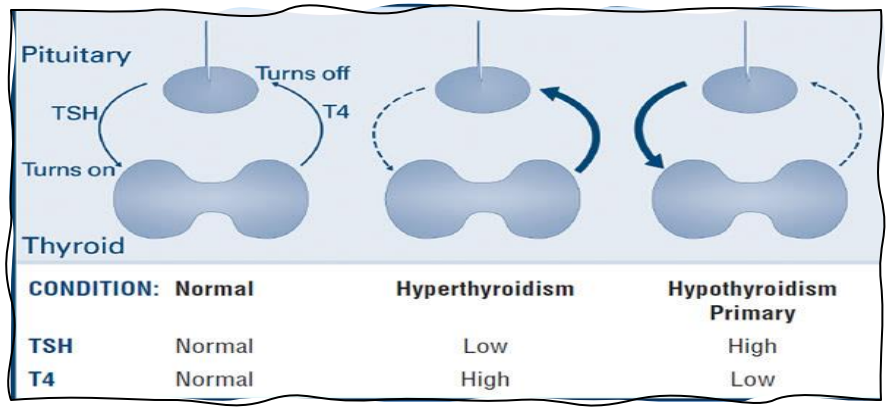
PRL is under inhibition by hypothalamus.

- **TSH (a glycoprotein which interacts with surface membrane receptors)**

increase↑ T3 & T4 through ↑ cAMP (second messenger), ↑ Iodine uptake

Final outcome is **synthesis** of thyroid hormones: ↑ iodination and hydrolysis of thyroglobulin

** diagnostic use to assess the function of thyroid gland.



Additional

Iodine is only needed for thyroid hormones synthesis as the first step is iodine uptake.

TSH binds to TSH receptors on thyroid follicles.

- **ACTH**

Derived from larger precursor (Pro-opiocortin)

Leads to↑ cortisol **release**

Undergoes circadian rhythm , cortisol is high during the day and low during night.

Corticotropin (**tetracosactrin** trade name Acthar®) and **cosyntropin** (Cortrosyn®) are synthetic analog to ACTH

*Cortisol levels peak in the early morning after waking up and decline throughout the day.
And this switches in people who work at night and sleep during the day.

*Tetracosactrin is a synthetic analog to ACTH.
Synthetic analogs are characterized by short duration of action and short half-life.
We try to synthesize analogs that are capable of mediating similar biological effects to the original hormones. However, they differ from each other in the pharmacokinetic properties.

Uses:
- Diagnostic use (given I.V or I.M)
- Certain cases of adrenal insufficiency if the problem is in anterior pituitary rather than the adrenal.

- **Growth hormone (Somatropin)**

- Species specific (human’s GH is different from animal’s, unlike insulin which is similar)

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

- GH stimulates growth of soft tissues and bones

- ↑ lipolysis

- ↑ gluconeogenesis & ↓ glucose utilization (diabetogenic effect)

- PRL(prolactin)-like activity , so we can conclude there is similarity in their chemical structure. Likewise, oxytocin and ADH which are similar in structure have similar activities.

Some information about GH:

*There is a big difference between animal GH and human GH, so we can not use it from animal.

*GH is not trophic hormone. Does not affect other endocrine glands in order to enhance or inhibit the release of their hormones .

*GH effects are mediated through IGF-I (somatomedian) from liver.

*GH deficiency can be caused by damage or absence of GH gene which causes dwarfism . Another cause is due to the deficiency of IGF-I, tissues won't respond to GH, and the treatment won't include GH therapy in this case.

*If the epiphyseal plate is closed, GH will not affect the length of the bone.
GH affects the length of children because the epiphyseal plate is still open.

*Deficiency in males above 16 yrs or females above 14 yrs isn't significant, except for glucose levels' regulation.

*Acromegaly is a side effect to administration of synthetic analogs of GH.

We use these factors to manage low secretion of GH

- **Factors ↑ GH release:**

- Sleep(maximal levels during night in children), Arginin, Insulin, Hypoglycemia
- β-adrenergic antagonists, Clonidine, Bromocriptine and Levodopa in normal individuals

Bromocriptine in normal individuals is a dopamine agonist, it increases GH.
However, in acromegalics it decreases GH synthesis and release.

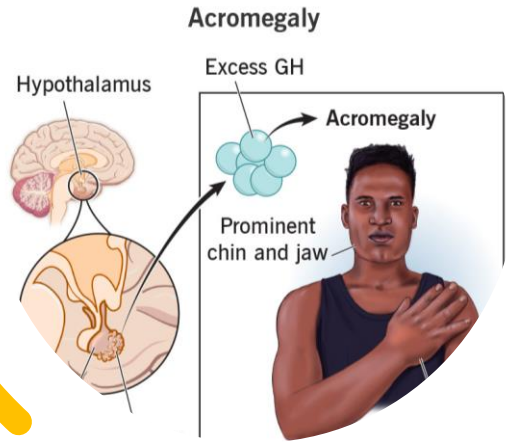
- **Factors ↓ GH release:**

- Bromocriptine in acromegalics
- Somatostatin synthetic analogs

Its effects on decreasing GH levels make sense as it's a dopamine agonist which inhibits prolactin release and prolactin is known to have GH like activities. But acting as an enhancer of GH release in normal individuals is not comprehensible . Unfortunately, causes for this paradoxical effects are not yet well understood 🤯

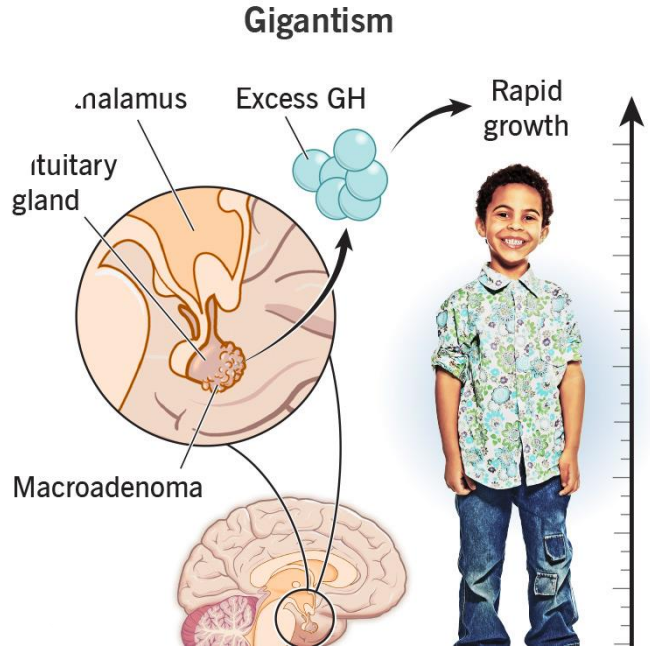
- **Disorders affecting GH secreting cells:**
- **Hypersecretion** → Gigantism in children ,
- Acromegaly in adults

Additional



- Rx (treatment):

- - Surgery (surgical removal of the pituitary gland tumor should be considered the primary treatment, we have reached a point of cure using surgical removal)
- - Somatostatin synthetic analogs
- - DA agonists (Bromocriptine; Cabergoline) and
- - Pegvisomant (GH-receptor antagonist, given SC(subcutaneously), major side effects include abnormal liver enzymes and some reports indicated increased growth of GH-secreting pituitary tumors)



Hyposecretion of GH

- In children it leads to dwarfism manifested by a very short trunk, short neck, shortened arms and legs, average-size hands and feet, broad rounded chest…
- In adults Not so common but it may lead to a higher level of body fat, especially around the waist, anxiety and depression, decreased sexual function and interest, fatigue, less muscle… Replacement of GH may be used.

Rx of dwarfism → GH replacement therapy

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

In adults, we should try first lifestyle modification. However, in certain cases we use GH replacement therapy.

*Rx = Treatment

GH replacement therapy

- GH-replacement therapy with S.C(subcutaneous) or I.M(intramuscular) recombinant human GH preparations:

  Somatropin (Humatrope)

  Somatrem (Protropin)

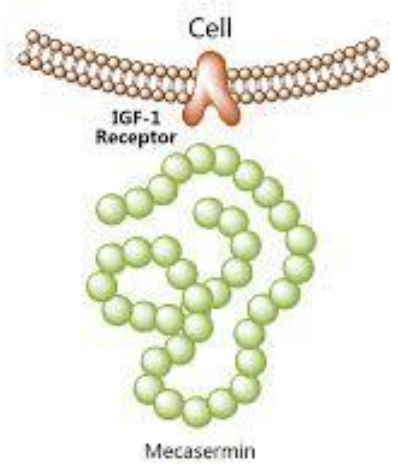
In hormone replacement therapy, we try as much as possible to mimic physiology, so GH is usually given at night as its maximual levels are reached during night. For example, if the patient is 9 years old, we give him S.C or I.M GH daily at night until he/she becomes 15-16 years old or until the epiphyseal plate closes, its closing can be assessed by clinical test.

- **Mecasermin** (recombinant human IGF-1); Another preparation is : **mecasermin rinfabate** (recombinant human IGF-1 +IGF binding protein-3=IGFBP-3), given SC, this extends the duration of action of Mecasermin as it's given twice daily, while Mecasermin rinfabate is given once daily in dwarf with IGF-1 deficiency not responding to GH, hypoglycemia is a major side effect

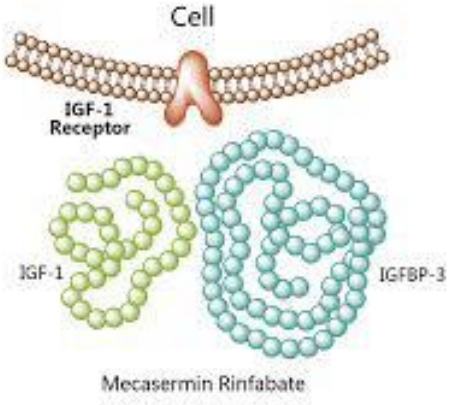
GH is normal, the deficiency is in IGF-1 secretion. Treatment with GH won't solve the problem as we mentioned previously. This also strengthens the clues provided to prove that GH effects are mediated through IGF-1

Mecasermin rinfabate is similar to Mecasermin in that both drugs contain recombinant DNA origin insulin-like growth factor 1 (IGF-1). **Mecasermin rinfabate** however, is already bound to recombinant DNA origin insulin-like growth factor binding protein 3 (IGFBP-3). The binding of IGF-1 to IGFBP-3 is said to extend the half life and reduce the clearance of IGF-1 in patients with growth hormone resistant syndromes and low levels of IGFBP-3 though this may represent <500 patients worldwide

Both mecasermin and mecasermin rinfabate are usually given SC



Mecasermin



Mecasermin Rinfabate

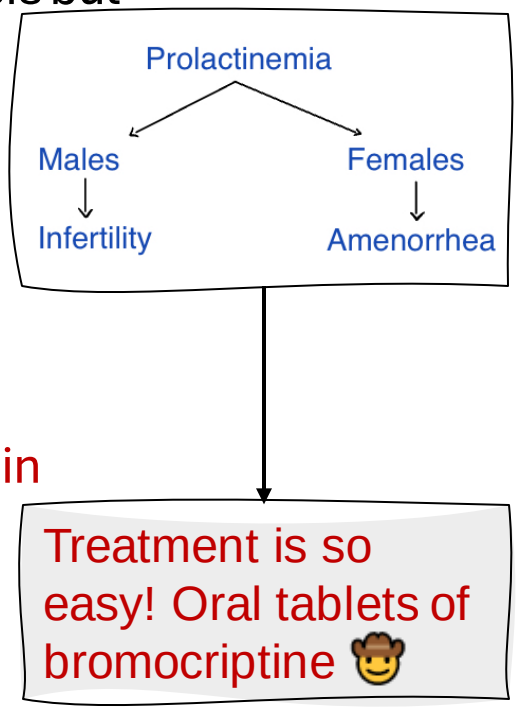
- Side effects of synthetic rHGH(recombinant human GH) products:

  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

- **Prolactin (PRL)**

- Ant. Pit(anterior pituitary hormone); released by Placenta during pregnancy, reaches its highest level at time of delivery and it is responsible for milk production.
- ** Dopamine (DA) is the major regulator of prolactin synthesis and release, it's inhibitory so in order to increase prolactin we inhibit dopamine.
- ** Has GH-like activity

- In ♂s(males) PRL increases testosterone production by testes and hence spermatogenesis but ↑ PRL → ↓ LH & FSH → ♂hyperprolactinemia ➡ impotency & infertility in MALES



- In ♀s(females):
- - Breast development (puberty; pregnancy)
- - Lactation (milk **production**, remember milk **ejection** is function of **oxytocin**)
- - ↑ PRL → ↓ LH & FSH (galactorrhea amenorrhea syndrome: absence of menstrual period in females but in male increase prolactin does not affect sexual function but affect spermatogenesis through inhibition of FSH leading to infertility)

- **Factors/drugs ↑ PRL:**

- Pregnancy, sleep, nursing, stress (surgery, exercise)

- TRH, Estradiol, DA antagonists (antipsychotics= phenothiazines and haloperidol; metoclopramide..)

- Methyldopa, reserpine, diazepam, opiates, meclizine, imipramine…(drugs of addiction and that's why most addicts are infertile!)

- **Factors/drugs ↓ PRL:**

DA agonists (Bromocriptine, pergolide, levodopa)

apomorphine, clonidine , MAO inhibitors (pargyline)

MAO = monoamine oxidase

- **Clinical uses to dopamine agonists:**

Bromocriptine, Cabergolin…

- Hyperprolactinemia in ♂s and ♀s irrespective of its causes (drug of choice)
- Suppression of lactation (like in cases of death in utero)
- Acromegaly (inhibits prolactin and GH)
- Parkinson's disease
- Cushing's syndrome (Dopamine agonists have been found to inhibit ACTH release)
- DM type II

Dopamine agonists are given orally

Side effects:

Rare, pulmonary fibrosis; confusion; hallucinations; MI…

Past paper

Which of the following does NOT cause hyperprolactinemia:

- A. Pregnancy.
- B. High dose estrogen therapy.
- C. Reserpine.
- D. Dopamine.
- E. Stalk effect.

- Answer: D

Which of the following is not considered a general characteristic to hypothalamic hormones and their synthetic analogs:

- A. Most are peptides or polypeptides.
- B. They have low molecular weight.
- C. They have short biological half-life.
- D. Most interact with surface membrane receptors.
- E. They are ineffective orally.

- Answer: E

The secretion of this hormone is not regulated by the hypothalamus:

- A. Prolactin.
- B. LH.
- C. Human chorionic gonadotropin.
- D. Growth hormone.
- E. ACTH.

- Answer: C

Pegvisomant is an example of:

- Answer: growth hormone antagonist

True regard octreotide:

- Answer: somatostatin analog

Wrong Regard TRH:

- Answer: Ineffective orally