



Hypothalamic and pituitary hormones : محاضرة

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لجان التفتعات



Introduction to the Endocrine System  
&  
Hypothalamic and Pituitary Hormones  
(Growth Hormone agonists and antagonists)

Pharmacology II

Dr. Heba Khader

الهرمونات : **biochemicals** بتفرزها الغدد وبتنتقل عن طريق الدم  
لمناطق ثانية بالجسم وبتعمل تأثير ، اذا صار عنا نقص بهرمون  
معين بنعطي بداله **replacement**

# Introduction

- **Hormones** are regulatory biochemicals that are produced by glands, and transported by the circulatory system to a distant target organ to exert their action.
- They are often used as replacement therapy (e.g. exogenous insulin for treatment of diabetes mellitus).
- However, they can also be used for a variety of other therapeutic and diagnostic purposes.
- Certain drugs such as thyroid-hormone inhibitors and oral antidiabetic agents, although not hormones themselves, influence the synthesis or secretion of hormones.

بنستخدم الهرمونات كعلاج او ك **diagnostic procedure**

في ادوية بتكون **hormone inhibitors**, اذا كان في زيادة بإنتاج هرمون معين بنعطي هاي  
الادوية

# Introduction

هرمونات بنقدر نستخدمهم كعلاج :

- Therapeutically useful hormones and related drugs include:

1 • The pituitary hormones

2 • The gonadal hormones

3 • The adrenocorticosteroids

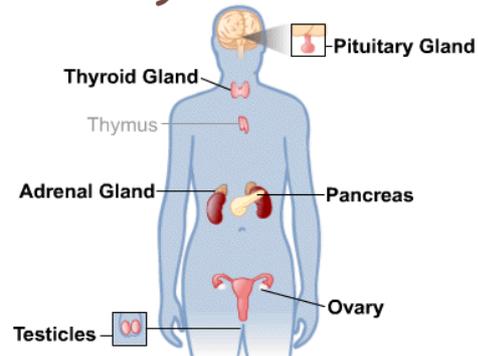
4 • The thyroid hormones and (inhibitors) ⇒ اذا زيادة بالهرمون

5 • The antidiabetic agents



Hormones replacement

Hormone inhibitors



# Introduction

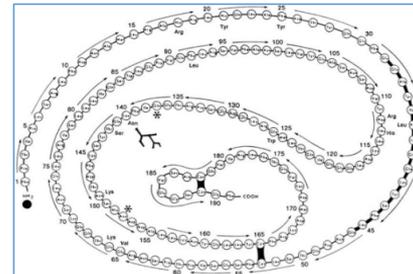
Two main structural classes of hormones:

1. Peptide hormones (e.g. growth hormone, FSH, insulin, calcitonin, somatostatin)

- Short plasma half-life **تأثيرهم بالجسم اقل من دقائق**
- No carrier proteins
- Water-soluble (hydrophilic, unable to cross membranes)
- Activate cell surface receptors: **المستقبلات وشغلهم بكون عال cell surface**

causing intracellular amplification response (short onset and offset)

- Not orally active, so most given IV, IM, S.C or intranasally.



Human growth hormone

كل هذول الانواع ولا واحد منهم  
بنقدر نعطيها **orally** لانه **unstable**  
بال **stomach and intestine**  
فالجسم ما يستفيد منهم ، فبعطيهم  
**IV , IM ,subcutaneous**



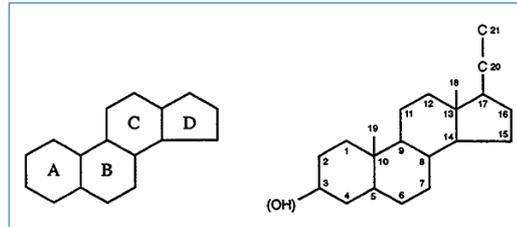
Peptide hormone

# Introduction

## 2. Steroid hormones (e.g. estradiol, testosterone)

- Long plasma half-life
- Mainly bound to carrier proteins like albumin **ممکن يرتبطوا مع بروتينات الدم**
- Fat soluble (lipophilic, free hormone enters cell, can cross membranes)
- Activate intracellular receptors that act in the nucleus (turn on genes, takes a while to occur and for effect to dissipate)
- Orally active **ممکن نعطيه orally وفي منها injections**

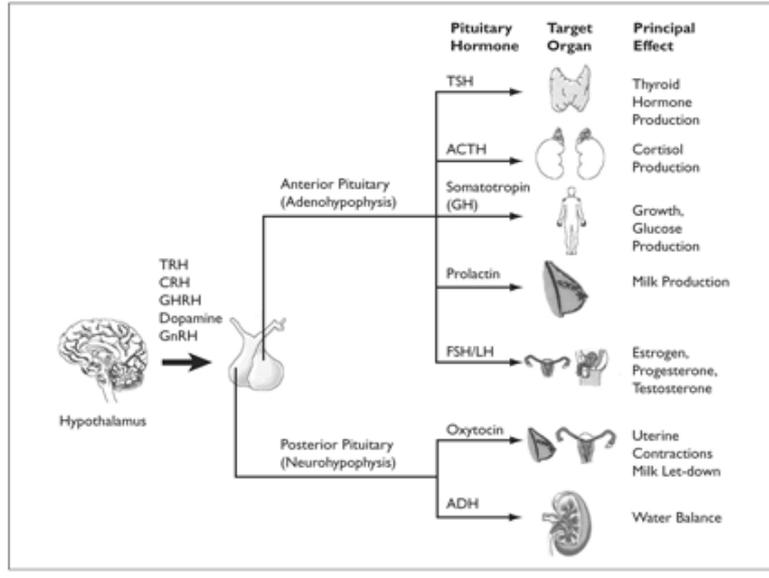
تأثيرهم يكون طويل لانهم بوخدوا وقت لحتى يبين  
تأثيرهم على الجسم ، لأنه هاد النوع لازم يدخل جوا ال  
**cytoplasm** لأنه ال **receptors** تبعتهم فيه ، زي ال  
**corticosteroids receptors** ، بعد ما يرتبط الهرمون  
بالمستقبل الي جوا السيتوبلازم يدخل ال **nucleus**  
فبتحفز انتاج بعض البروتينات (بتحفز بعض ال **genes**  
جوا ال **nucleus**)  
عشان هيك هاي العملية بتوخذ وقت عشان يبين تأثيرها  
على الجسم



Main regulator for all hormones in the body

# Hypothalamic and Pituitary Hormones

Figure 2. Hypothalamic-pituitary Hormone Relationships



TRH indicates thyrotropin-releasing hormone; CRH, corticotropin-releasing hormone; GHRH, growth hormone releasing hormone; GnRH, gonadotropin-releasing hormone; TSH, thyroid-stimulating hormone; ACTH, adrenocorticotropic hormone; FSH, follicle-stimulating hormone; LH, luteinizing hormone; ADH, antidiuretic hormone. Adapted from *Acromegaly* by AG Harris, 2001.

## اختصارات الهرمونات

### ACRONYMS

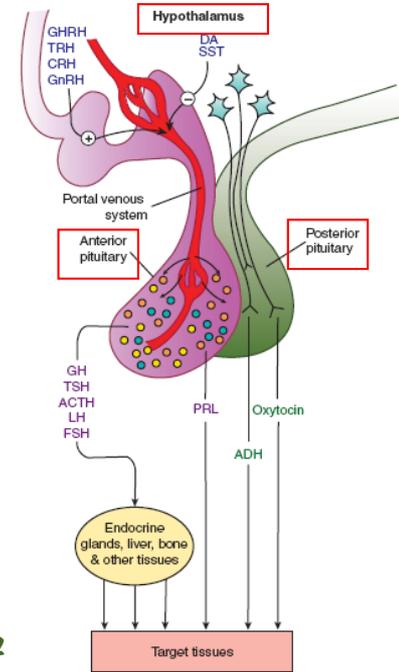
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<b>ACTH</b>	Adrenocorticotrophic hormone (corticotropin)
<b>CRH</b>	Corticotropin-releasing hormone
<b>FSH</b>	Follicle-stimulating hormone
<b>GH</b>	Growth hormone
<b>GHRH</b>	Growth hormone-releasing hormone
<b>GnRH</b>	Gonadotropin-releasing hormone
<b>hCG</b>	Human chorionic gonadotropin
<b>hMG</b>	Human menopausal gonadotropin
<b>IGF</b>	Insulin-like growth factor
<b>LH</b>	Luteinizing hormone
<b>PRL</b>	Prolactin
<b>rhGH</b>	Recombinant human growth hormone
<b>SST</b>	Somatostatin
<b>TRH</b>	Thyrotropin-releasing hormone
<b>TSH</b>	Thyroid-stimulating hormone (thyrotropin)

ال **hypothalamus** وال **pituitary** gland مرتبطين كثير مع بعض ومرتبات صعب نفرقهم بال **structure**

# Hypothalamic-Pituitary Endocrine System

- The hypothalamus and the pituitary gland are closely connected, and together they provide a means of communication between the brain and many of the body's endocrine organs.
- Hypothalamic factors regulate the release of anterior pituitary hormones.
- The pituitary gland is recognized for its essential role in body homeostasis, and for this reason it is often referred to as the “master gland”.



1- ال **pituitary** تحت ال **hypothalamus** بالزبط ، ال **pituitary** بتفرز معظم الهرمونات للجسم فبسموها **master gland** وكمان بتعمل **regulation** لغدد الجسم .

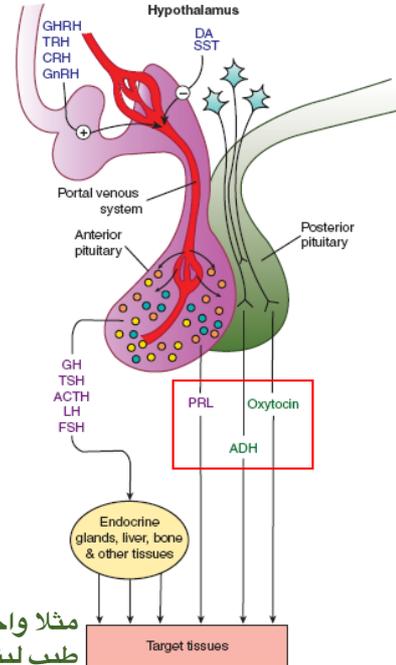
2- ال **hypothalamus** بتفرز هرمونات بتعمل **regulation** لإفراز ال **pituitary** هرمون تاني خاصة منطقة ال **anterior pituitary** ، وال **interior** بتفرز هرمون بحفز إفراز هرمون تاني من **gland** تانية .

3- ال **interior** كل الهرمونات الي بتفرزها بتحفز إفراز **other peripheral hormones** من ال **glands** وال **liver** ما عدا ال **prolactin** ما بحفز إفراز اشفي هو الي يشتغل ، مثلا ال **interior** بتفرز **TSH** فهو بوصل عال **thyroid gland** وبحفز إفراز ال **thyroxine**

# Hypothalamic-Pituitary Endocrine System

- Except for prolactin, anterior pituitary hormones stimulate hormone production by peripheral endocrine glands or liver.
- **Prolactin** and posterior pituitary hormones **vasopressin (ADH)** and **oxytocin** act directly on target tissues.

هدول ال 3 هرمونات تأثيرهم مباشر  
على الجسم ، الباقي بحفزوا انتاج  
هرمون ثاني



مثلا واحد عنده **hypothyroidism** ( نقص انتاج ال **thyroxine** ) عشان اعالجه بعطيه **thyroxine**.  
طيب ليش ما اعطيه **( TSH ( thyroid stimulating hormone ) ؟**

ل لأنه ممكن يآثر على اشياء ثانية وكمان تأثيره بالجسم ما راح يكون نفس تأثير ال **thyroxine** لأنه  
مش ضروري تكون المشكلة نقص ال **TSH** ف كعلاج بعطي الهرمون نفسه مش الي بحفز انتاجه لأنه  
**more selective**

# Hypothalamic-Pituitary Endocrine System

**TABLE 37-1** Links between hypothalamic, anterior pituitary, and target organ hormone or mediator.<sup>1</sup>

Anterior Pituitary Hormone	Hypothalamic Hormone	Target Organ	Primary Target Organ Hormone or Mediator
Growth hormone (GH, somatotropin)	Growth hormone-releasing hormone (GHRH) (+) Somatostatin (-)	Liver, bone, muscle, kidney, and others	Insulin-like growth factor-I (IGF-I)
Thyroid-stimulating hormone (TSH)	Thyrotropin-releasing hormone (TRH) (+)	Thyroid	Thyroxine, triiodothyronine
Adrenocorticotropin (ACTH)	Corticotropin-releasing hormone (CRH) (+)	Adrenal cortex	Cortisol
Follicle-stimulating hormone (FSH) Luteinizing hormone (LH)	Gonadotropin-releasing hormone (GnRH) (+) <sup>2</sup>	Gonads	Estrogen, progesterone, testosterone
Prolactin (PRL)	Dopamine (-)	Breast	—

<sup>1</sup>All of these hormones act through G protein-coupled receptors except growth hormone and prolactin, which act through JAK/STAT receptors.

<sup>2</sup>Endogenous GnRH, which is released in pulses, stimulates LH and FSH release. When administered continuously as a drug, GnRH and its analogs inhibit LH and FSH release through down-regulation of GnRH receptors.

(+), stimulant; (-), inhibitor.

# Hypothalamic-Pituitary Endocrine System

- Because of the greater ease of administration of target endocrine gland hormones or their synthetic analogs, the related hypothalamic and pituitary hormones (TRH, TSH, CRH, ACTH, GHRH) are used infrequently as treatments.
- Some, such as ACTH, are used for specialized diagnostic testing.

**TABLE 37-2** Clinical uses of hypothalamic hormones and their analogs.

Hypothalamic Hormone	Clinical Uses
Growth hormone-releasing hormone (GHRH)	Used rarely as a diagnostic test for GH and GHRH sufficiency
Thyrotropin-releasing hormone (TRH, protirelin)	May be used to diagnose TRH or TSH deficiencies
Corticotropin-releasing hormone (CRH)	Used rarely to distinguish Cushing's disease from ectopic ACTH secretion
Gonadotropin-releasing hormone (GnRH)	May be used in pulses to treat infertility caused by GnRH deficiency  Analogues used in long-acting formulations to inhibit gonadal function in children with precocious puberty, in some transgender/gender variant early pubertal adolescents (to block endogenous puberty), in men with prostate cancer and women undergoing assisted reproductive technology (ART) or women who require ovarian suppression for a gynecologic disorder
Dopamine	Dopamine agonists (eg, bromocriptine, cabergoline) used for treatment of hyperprolactinemia

# Hypothalamic-Pituitary Endocrine System

- Whereas all the pituitary and hypothalamic hormones are available for use in humans, only a few are of major clinical importance. These include:
  1. GH
  2. SST
  3. LH
  4. FSH
  5. GnRH

1

راح نشوف انه دائماً عندي **hormone inhibitors** و **hormone** لأنه كمية ال **hormone** الي يحتاجها الجسم لازم تكون **balanced** لا تكون الكمية كبيرة ولا قليلة

# Growth Hormone **GH** بصيرله **inhibition** عن طريق هرمون تاني اسمه **somatostatin**

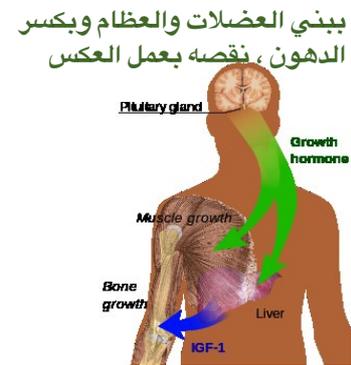
- Growth hormone (GH) is also known as **somatotropin** or **somatropin**.
- Somatotropin is a large polypeptide that is released by the anterior pituitary in response to growth hormone-releasing hormone (**GHRH**) produced by the hypothalamus.
- Somatotropin release is inhibited by **somatostatin**.
- GH is secreted by the anterior pituitary in a pulsatile fashion, with several short bursts that occur mostly at night. The greatest amount of GH secretion occurs during the night within the first 1 to 2 hours of sleep.
- Daytime GH pulses are most likely to occur after meals, following exercise, or during periods of stress.

ال **GH** مسؤول عن نمو الجسم بشكل عام ، افضل كمية ينتجها الجسم من هاد الهرمون خلال النوم خاصة اول ساعتين عشان هيك النوم مهم خاصة للأطفال ، اثناء النهار برضو بنفرز بس بكميات قليلة **As pulses** . ممكن تزيد كمية الافراز بعد وجبات الأكل او اذا بذل جهد جسدي زي الرياضة

يعمل **insulin like growth factor stimulation** في علاقة قوية بين **GH** و **insulin** بشتغلوا عكس بعض ، كل ما زاد **GH** بتقل **insulin** وبصير **hypoglycemia** والعكس ، فالناس الي بقل عندهم ال **GH** يزيد ال **insulin**

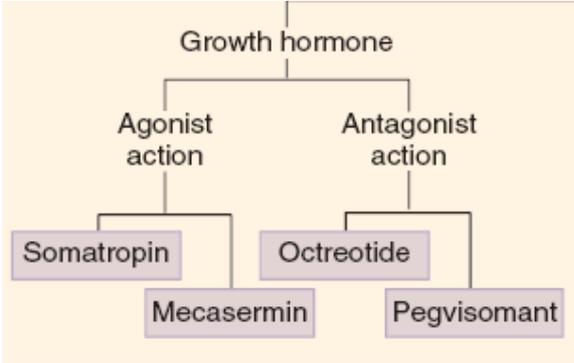
# Growth Hormone

- GH stimulates **insulin-like growth factor (IGF1)**, also called somatomedin C) production by organs like the liver.
  - IGF1 is responsible for many of the actions of GH.
  - GH and IGF1 effects include:
    - longitudinal bone growth <sup>طول العظم ، عشان هيك الأطفال الي عندهم نقص بال **GH** ما بطولوا</sup> until the epiphyses close—near the end of puberty.
    - GH has anabolic effects in muscle and catabolic effects in lipid cells that shift the balance of body mass to an increase in muscle mass and a reduction in adiposity.
    - The direct and indirect effects of GH on carbohydrate metabolism are mixed, in part because GH and IGF-I have opposite effects on insulin sensitivity.
      - GH reduces insulin sensitivity
- بينني العضلات والعظام ويكسر الدهون ، نقصه بعمل العكس
- whereas IGF-I has insulin-like effects



تأثيره زي تأثير ال **insulin**

# Growth Hormone Agonists and antagonists



# Somatropin

1. **Somatropin**, the recombinant form of human GH, is used for:

1) GH deficiency in children and adults.

- In childhood, GH deficiency typically presents as short stature, often with mild adiposity. Another early sign of GH deficiency is hypoglycemia due to unopposed action of insulin, to which young children are especially sensitive.
- adults with GH deficiency often have generalized obesity, reduced muscle mass, and reduced cardiac output.

حكيانا اذا الطفل عنده نقص بالهرمون يكون عنده **short srature** يعني اقصر من الاطفال الي بعمره ، فلازم نراقب طول الطفل ، كمان بصير عنده **mild adiposity** يعني قصير وناصح ، وعنده كمان **hypoglycemia**

اذا الشخص كبر وطول بعدين صار عنده نقص بال **GH** ، بنصح وكمية ال **fat** كثير عالية وال **muscles** قليلة جداً فهاد راح يآثر عال **cardiac output**

من الاسباب الشائعة لنقص ال **GH** ، سرطان بال **pituitary** فبستأصلوا جزء منها فيصير عنده نقص بهرمونات كثير

طيب اذا حدا كبير و قصير ممكن اعطيه هاد الهرمون عشان يطول ؟ لا لأنه طول العظم بوقف فترة المراهقة

يعني اذا مع عنده نقص فيه واخذ زيادة بتقل كمية ال **Fat** بجسمه

وبتزيد العضلات فيستخدموه ب كمال الاجسام وهاد اشئ غلط اما اذا اصلا عنده نقص عادي لأنه الجسم بصير طبيعي

اذا واحد صار معه نقص بال **GH** اول اشئ بشوفه انه نصح كثير وكمية العضلات قليلة ومشاكل تانية بتصير

# Somatropin

1. **Somatropin**, the recombinant form of human GH, is used for:

- 2) The treatment of children with diseases associated with short stature (chronic renal failure and genetic diseases such as Turner syndrome).
- 3) Muscle wasting in AIDS patients.
- 4) GH is also used by athletes for a purported increase in muscle mass and athletic performance and is one of the drugs banned by the Olympic Committee and professional sports associations.

2- يستخدم هاد الهرمون للاطفال الي عندهم **short stature** وبنفس الوقت نقص بال **GH** , مرات يكون الطفل طول اقصر من الطبيعي بس مشكلته اشي ثاني مش بال **GH** ، بجربوا يعطوه ال **GH** وبعد وقت طويل ما بنلاحظ بفرق بالطول معناته مستوى الهرمون طبيعي

3- مرضى الايدز بصير عندهم تدمير بخلايا العضلات **muscle wasting** فبعطوه الهرمون

4- بال **body building** و الها محاذير كثير ، مرات اذا استخدم اللاعب الهرمون بكمية كبيرة بعنبروه استخدم منشطات

# Somatropin

المشكلة مش بال GH يكون عنده **idiopathic short stature** فيكون استخدام الهرمون بزيده بس 1.5 \_ 3 inches

1. **Somatropin**, the recombinant form of human GH, is used for:

5) A controversial but approved use of GH is for children with **idiopathic short stature**. In this group of children, multiple years of GH therapy at great cost and some risk of toxicity results in a small (1.5-3 inches) average increase in final adult height.

- Somatropin is administered **subcutaneously** 6–7 times per week. **Injection** مرة باليوم
- Children generally tolerate GH treatment well. Adults tend to have more adverse effects from GH therapy. **Peripheral edema, myalgias, and arthralgias (especially in the hands and wrists)** occur commonly but decrease with dosage reduction.

استخدام ال GH كعلاج ما بعمل عندهم **side effects** تقريباً أما ال **adults** بصير عندهم مشاكل مرتبطة بالجرعة كل ما زادت بتزيد الاعراض

# Mecasermin

هاد **human insulin like growth factor 1** , بعض الاطفال. الي عندهم **short stature** لما اعطيهم **GH** ما يستحيبوا لانه يكون المشكلة عندهم نقص بهاد ال **IGF-1** ف بنعطيهم اياه ك بديل لل **GH** بس مشكلة ال **IGF-1** انه يشتغل زي ال **insulin** فلازم دائما الطفل دائما يكون معه سناكس عشان ما يصير **hypoglycemia**

## 2. Mecasermin

- Small group of children with growth failure unresponsive to GH therapy are deficient in IGF-1.
- Mecasermin, recombinant human IGF-1, is administered parenterally to children with IGF-1 deficiency.
- Its most important toxicity is hypoglycemia, which can be prevented by consumption of a snack or meal shortly before mecasermin administration.

اذا في مشكلة بنقص ال **GH** في عنا خيارين يا بعطيه **GH** يا **IGF-1**

# Growth Hormone Antagonists

- Growth hormone-secreting pituitary adenomas cause **acromegaly** in adults and, rarely, **gigantism** in children and adolescents who have not completed their growth phase.

العلاج عن طريق 3 انواع GH antagonists

- Pharmacologic treatment of GH excess seeks to inhibit GH secretion or interfere with GH effects, which include:

1. Somatostatin analogues (**octreotide** and **lanreotide**)
2. Dopamine D<sub>2</sub> receptor agonists
3. Pegvisomant

الجسم بفرز somatostatin بعمل inhibition لل GH ف عندي somatostatin analogous drugs

اذا في زيادة بال GH شو راح يصير بالجسم يعني طفل انولد معه زيادة فيه ؟  
يعمل مشكلتين ، اول وحدة **acromegaly** عند ال adults والثانية عند الاطفال **gigantism** .  
الثنتين عبارة عن تضخم ( عملاقة ) يكون مش طبيعي

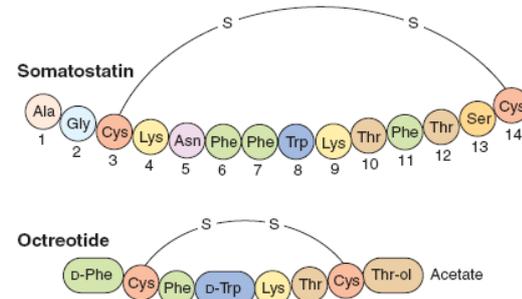


شو اسباب الزيادة ؟ غالباً **autoimmune diseases** او سرطان بالغدد او طفرة **genetic mutation**

# Somatostatin Analogues

يعمل **inhibition** لهدول الأربيع هرمونات

- Somatostatin, a 14-amino-acid peptide, **inhibits the release of GH, glucagon, insulin, and gastrin.**
- **Octreotide** and **lanreotide**, long-acting synthetic analogs of somatostatin, are used to treat:
  - Acromegaly (excess GH) **تضخم عند ال adults**
  - Gastrinoma (excess gastrin) **نوع سرطان ، زيادة الخلايا الي بتفرز ال gastrin**
  - Glucagonoma (excess glucagon) **الفا cells بتزيد افراز ال glucagon**
  - Other endocrine tumors.



# Somatostatin Analogues

احد الاثنياء الي بنعاني منها مع  
المريض

①

- Regular octreotide must be administered subcutaneously 2–4 times daily.

② • whereas a slow-release intramuscular formulation of octreotide or lanreotide is administered every 4 weeks for long-term therapy.

في فرق بالسعر بين هالدول ال 2

- Octreotide and lanreotide cause significant gastrointestinal disturbances, gallstones, and cardiac conduction abnormalities.

حصى بالمرارة

# Dopamine D<sub>2</sub> receptor agonists

تأثيره عال **prolactin** اكثر من **GH release**

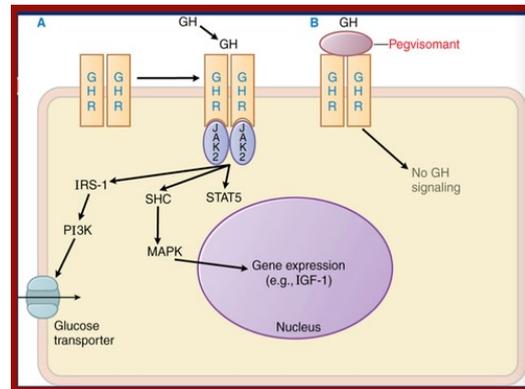
- Dopamine D<sub>2</sub> receptor agonists such as **bromocriptine** are more effective at inhibiting prolactin release than inhibiting GH release.
- However, high doses of D<sub>2</sub> receptor agonists have some efficacy in the treatment of small GH-secreting tumors.

كيف يستفيد من ال **bromacriptine** ؟ اذا اعطيته بجرعة عالية كثير فبعمل **GH release** ل **inhibition**

# Pegvisomant Competitive antagonist

شغله على ال **receptors**

- **Pegvisomant** is a GH receptor antagonist approved for treatment of acromegaly.
- Normally, GH, which has 2 distinct receptor binding sites, initiates cellular signaling cascades by dimerizing 2 GH receptors.
- Pegvisomant is a long-acting derivative of a mutant GH that is able to cross-link GH receptors but is incapable of inducing the conformational changes required for receptor activation.



عندي **two receptors** لل **GH** جنب بعض عال **cell membrane** , الدوا يرتبط على واحد منهم وبنفس الوقت بعمل **inhibition** لل **receptor** الثاني ، يعني عشان ال **GH** يعطينا مفعول لازم يرتبط بهطول ال **2 receptors** فال **pegvisomant** راح يرتبط على واحد منهم فال **GH** هيك يرتبط بس بواحد فما بصير في تأثير لل **GH** ، بنفس الوقت **pegvisomant** بس يرتبط ويعمل **block** لل **receptor** ما بحفره هو شكله كتير مشابه لل **GH** بس ما بقدر يعمل ، بنفس الوقت **pegvisomant** الي هي تغييرات بال **receptors** الي بتعمله **activation**

Questions??