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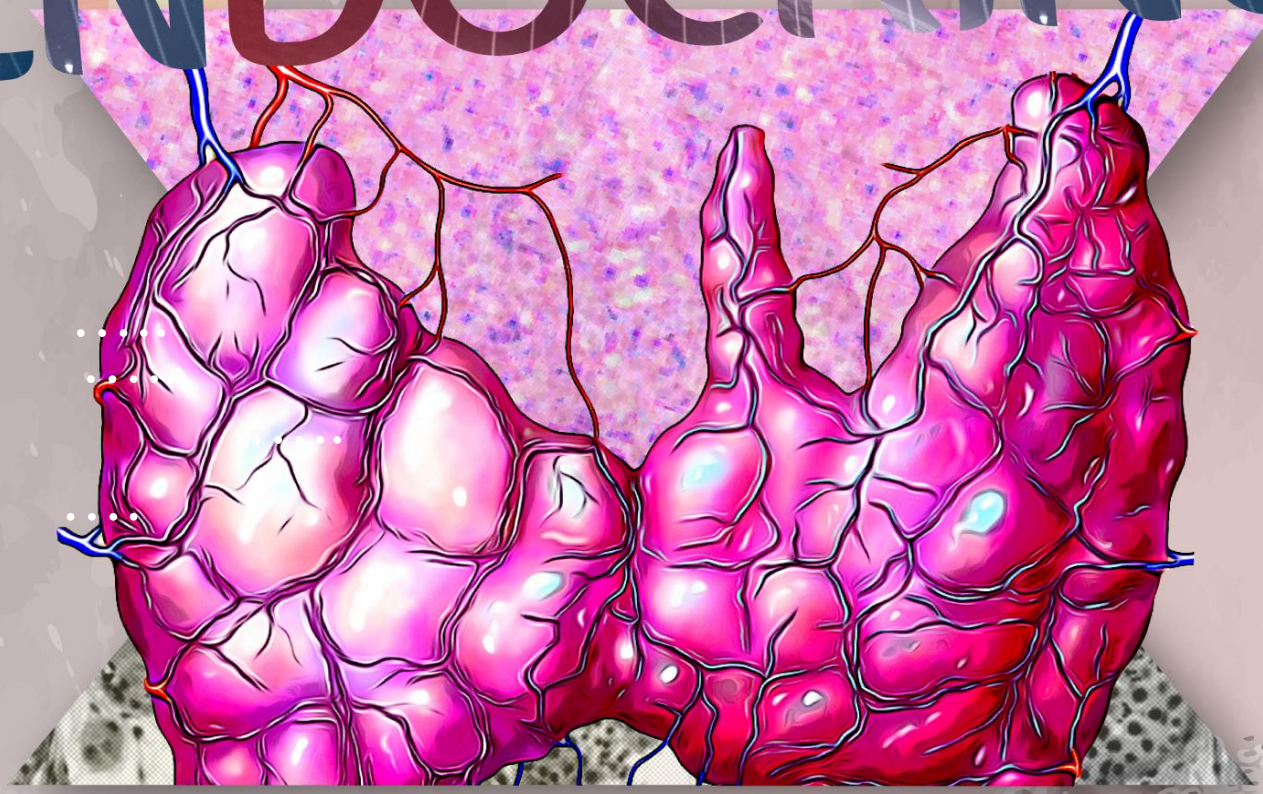
ENDOCRINE



SUBJECT: Pharamacology

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The Hypothalamus:

It controls most of our body organs. The hypothalamus does this by sending neuronal signals or by secreting hormones that act on the pituitary gland and cause it to also release hormones. These pituitary hormones in turn will go to endocrine organs (suprarenal, thyroid, etc.) that release hormones as well. In some exceptional cases the anterior pituitary hormones will go to a nonendocrine organ (ex. the liver which produces something other than a hormone like IGF-1.)

The end message thus doesn't always have to be a hormone. It can be a protein, amino acid, etc.

*** Hormones from the hypothalamus that go to the pituitary through a neuronal pathway: ADH and oxytocin. These are fast hormones that go directly to the target tissue, as they are needed urgently and cannot afford to go through intermediate organs.

Pharmacological Applications:

There are drugs that mimic or block the effects of the hypothalamic or pituitary hormones. They are used in these applications:

1. In replacement therapy for hormone deficient patients. This is critical to maintain body balance, because hormone deficiency will have vast effects on many processes that happen in the body (ex. GH controls metabolism, muscle mass, lipid tissues etc.) In this therapy we deal with hormones at a very low concentration (nanogram), which makes it difficult to monitor the patient. Still, you have to observe them carefully and monitor their progress for ex. changes in BMI.

2. As antagonists for diseases that are characterized by an excess production of pituitary hormones.

3. As diagnostic tools to identify several endocrine disorders and confirm them (ex. Dwarfism, no ovulation, absence of GH or GHRH). For instance, take a woman who's not ovulating, the problem could originate from the

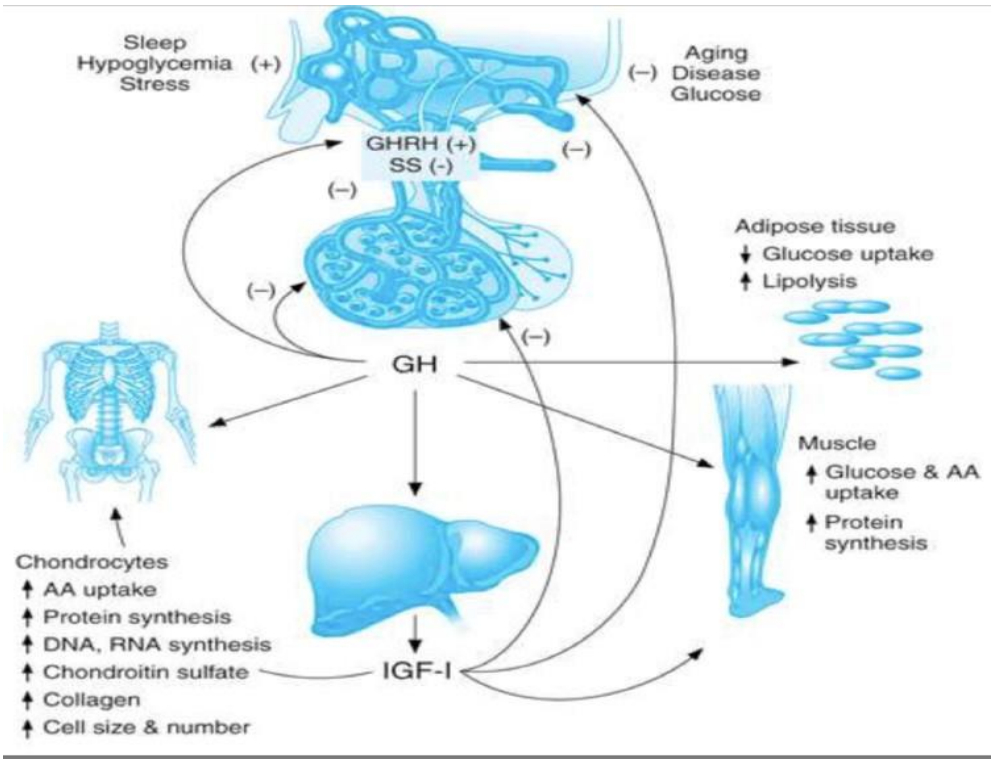
hypothalamus or the anterior pituitary or the gonads and so to determine the problem the hormones will be used as a diagnostic tool.

Anterior Pituitary Hormones:

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) (+)[2]	Gonads	Estrogen, progesterone, testosterone
Prolactin (PRL)	Dopamine (–)	Breast	—

** PRL does not have an inducer only an inhibitor / Dopamine has a negative effect on PRL

Growth Hormone:



GH stimulants:

- Sleep (peaks after 1st or 2nd hour of sleeping/ most important time of release)
- Hypoglycemia
- Stress
- Exercise
- Increased amino acid concentration
- Hyperlipidemia

GH inhibitors:

- Aging: it's concentration in our body decreases as we get older.
- Disease
- Glucose

GH effects:

- Adipose tissue: decreased glucose uptake and increased lipolysis mostly by GH
- Muscles: increased glucose and amino acid uptake, and increased protein synthesis
- Chondrocytes: increased amino acid uptake, protein synthesis, DNA and RNA synthesis, chondroitin sulfate, collagen, and increased cell size and number (in bones). **the number of cells does not increase in muscles

This effect is mediated through IGF-1→ it goes to the muscles and bones, whereas GH on its own goes to the adipose tissue.

Bodybuilding Supplements:

Bodybuilders aim to gain muscle and increase lipolysis. This is done through:

1. Androgens- (ex. Testosterone)

2. GH- (increases body mass and lipolysis) GH is considered to be the expensive alternative. You can determine if the person took GH by touching their skin. It increases body mass and lipolysis.

GH is a 191 amino acid peptide with 2 sulfhydryl bridges. It is given to patients as recombinant human GH (rhGH) available clinically called Somatropin.

GH is released in a pulsatile manner mostly during sleep-pulses generated by the interplay of GHRH and somatostatin. GH secretion decreases with age. However, Somatropin is not used for antiaging.

Physiological actions of GH:

In childhood: GH promotes linear growth, growth of long bones, cartilage, muscles and organ systems. GH is given to them in the case of deficiency.

In adulthood the major effects are metabolic:

- It increases protein synthesis and bone density
- Promotes lipolysis and inhibits lipogenesis
- Promotes gluconeogenesis and glucose release
- Opposes insulin induced glucose uptake in adipose tissue
- Reduces insulin sensitivity

Children can have GH deficiency, and it has been discovered that adults can have it as well newly. There are some extreme cases (old, very obese, little muscle mass and malaise). These people are new cases that have started to appear and show symptoms similar to GH deficiency. They have an imbalance in protein synthesis (low) compared to increased fat and adipose tissue. They also lack energy, and glucose utilization is minimal. These people can be given GH treatment.

Features of GH deficiency:

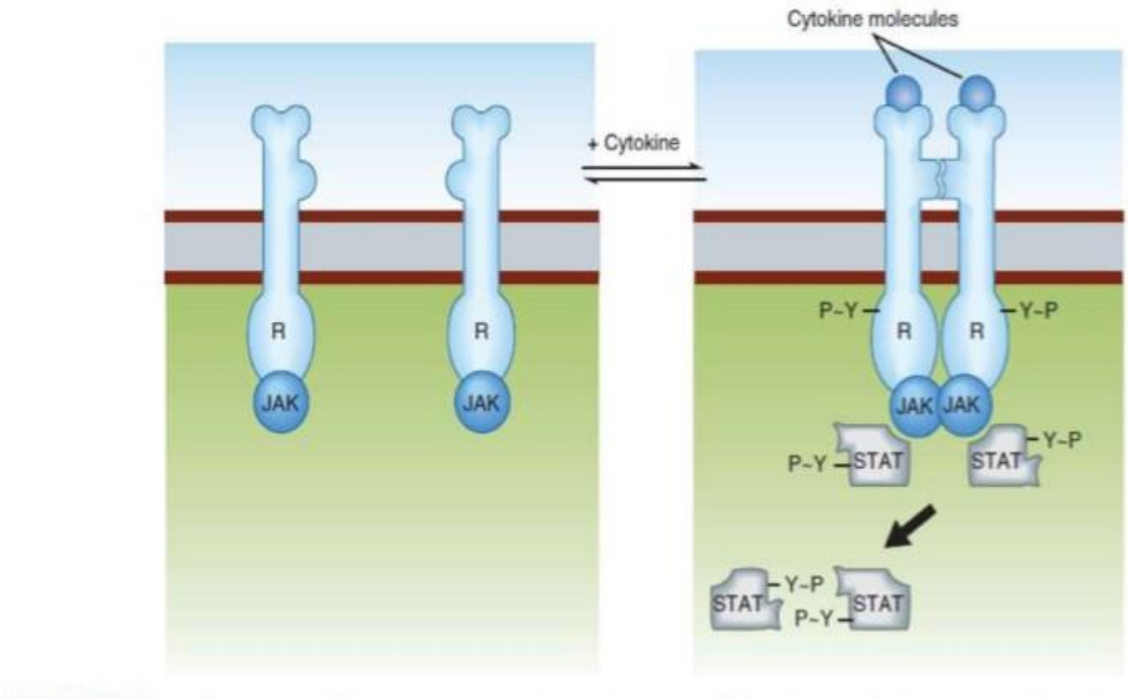
Children: it results in short stature, adiposity, and hypoglycemia. This is most commonly due to a deficiency of GHRH.

Adults:

- Changes in body composition: increased generalized adiposity
- Decreased skeletal muscle mass and strength
- Decreased bone density
- Cardiovascular changes; cardiac muscle atrophy, atherogenic blood lipid profile
- Fatigue, weakness, depression, overall malaise.

Note: (this could be a continuation of childhood onset disease or it could be due to a pituitary problem)

Growth hormone mechanism of action:



- We have growth hormone dimers. They are two receptors onto which GH binds.
- The effects are mediated through binding to a cell surface receptor of JAK-STAT cytokine receptor superfamily.
- Dimerization of the 2 GH receptors by a single GH molecule activates signaling cascades mediated by receptor-associated JAK (Janus-kinase) tyrosine kinases and STATs (signal transducers and activators of transcription).

Pharmacodynamics:

GH has complex effects on growth, body composition and carbohydrate, protein and lipid metabolism. The growth promoting effect is mediated mainly through production of insulin-like growth factor 1 (IGF-1), mainly by the liver, but also in bone, cartilage, muscle, kidney and other tissues where it has autocrine or paracrine roles. It also stimulates longitudinal bone growth until the epiphyses close near the end of puberty.

In both children and adults, it has anabolic effects in muscles and catabolic effects in adipose tissue→ 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, partly because GH and IGF-1 have opposite effects on insulin sensitivity.

GH leads to→ hyperglycemia

IGF-1 leads to→ hypoglycemia (insulin like effect)

GH reduces insulin sensitivity by stimulating gluconeogenesis in the liver, thus resulting in mild hyperinsulinemia, and increased blood glucose level. In elderly, if they have excess GH this causes acromegaly which may produce DM (rare cases).

However, the presence of IGF-1 has opposes the previous effect. It has insulin-like effects on glucose transport, lowers serum glucose and increases its uptake.

** Together GH and IGF-1 balance each other out.

Note: GH does not cause DM in children. Also, in acromegaly, it does produce DM but in rare cases and the resulting hyperglycemia is clinically irrelevant.

Adults with GH deficiency>> have generalized obesity, reduced muscle mass, lack energy, asthenia, diminished bone density, dyslipidemia, and reduced cardiac output.

There are patients who have normal GH levels but have a lack of GH effects manifestation (severe GH resistance). Why does that happen? Some patients have a genetic polymorphism in the GH receptor (recall pharmacogenetics), which leads to an ineffective receptor that is mutated and does not stimulate the effect. It could also be due to post-receptor signaling mutations, or GH antibodies. This patient does not have GH deficiency but rather a deficient GH function. This can be due to a mutation in JAK or STAT, thus neither of them go to the genes to produce IGF-1.

Treatment→ I give the patient IGF-1. The administration of recombinant IGF-1 may cause hypoglycemia because of insulin-like effects, as there is no GH to oppose the function of the IGF-1.

Therapeutic uses:

- Replacement therapy for deficient states.

TABLE 37–4 Clinical uses of recombinant human growth hormone.

Primary Therapeutic Objective	Clinical Condition
Growth	Growth failure in pediatric patients associated with:
	Growth hormone deficiency
	Chronic renal insufficiency pre-transplant
	Noonan syndrome
	Prader-Willi syndrome
	Short stature homeobox-containing gene (SHOX) deficiency
	Turner syndrome
	Small for gestational age with failure to catch up by age 2 years
	Idiopathic short stature
Improved metabolic state, increased lean body mass, sense of well-being	Growth hormone deficiency in adults
Increased lean body mass, weight, and physical endurance	Wasting in patients with HIV infection
Improved gastrointestinal function	Short bowel syndrome in patients who are also receiving specialized nutritional support

- The most important thing to know: idiopathic short statures. In this case, the child doesn't have a GH deficiency, but he isn't growing tall and is shorter than the average children in his age (if he is two standard deviations away from the normal he is an outlier). The solution is growth hormone.

- Growth hormone is also used to improve the metabolic state, increase lean body mass and sense of well-being.

- It can also be used in patients with AIDs to combat wasting in body mass.

- Is used in gastrointestinal function in people who have short bowels and weak nutrition. Giving the patient GH will help them undergo active utilization of the nutrients they eat, to build more protein.

**These are the only approved uses of GH. The role of GH in anti-aging is a controversial issue.

Toxicity & Contraindications:

In children (are relatively rare):

1. Increase in intracranial pressure in children (pseudotumor cerebri) manifested as changes in vision, headache, nausea and vomiting.
2. Slipped capital femoral epiphysis>> GH stimulated growth leads to this.
3. Progression of scoliosis during rapid growth.
4. Hypothyroidism is commonly discovered during GH treatment.
5. Hyperglycemia.

In adults (more than children):

1. Peripheral edema, myalgia, arthralgia (hands and wrists). In reality when you increase the metabolism in an old patient, he can no longer handle this effect which leads to these effects.

2. Carpal tunnel syndrome.

3. Increased activity of cytochrome P450 enzymes>> increased metabolism of some drugs and reduction of their blood levels in the liver. This will impact the metabolism of the other drugs that the patient is taking, which makes its excretion faster thus diluting its effect. Solution: increase dose of the drugs.

4. Proliferative retinopathy.

5. Contraindicated in patients with active malignancies>> particularly IGF-1. IGF-1 is overexpressed in many cancers. It transforms into an oncoprotein in tumors, thus giving more GH promotes the growth of the cancer. Ex. Should not be given in children with acute lymphocytic leukemia. In adults, it is contraindicated in cancer, and in history of cancer.

6. Use in critically ill patients increases mortality>> giving GH will put them under metabolic stress

Mecasermin:

A small number of children with growth failure have severe IGF-I deficiency that is not responsive to exogenous GH.

- May be caused by mutations in GH receptor and in the GH, receptor signaling pathway, neutralizing antibodies to GH, and IGF-I gene defects.
- Mecasermin and mecasermin rinfabate may be used for treatment of this condition.
- Mecasermin is a recombinant that is administered subcutaneously. However, it has a short half-life. To prolong its half-life, we attach it to carrier proteins.
- Mecasermin rinfabate is a complex of rhIGF-I and recombinant human insulin-like growth factor-binding protein-3 (rhIGFBP-3) which is the transport protein that carries the IGF-1.
- This binding protein significantly increases the circulating half-life of rhIGF-I.

Adverse effects:

1. Hypoglycemia (this is the most important)>> eat sweets 2 hours before the injection

2. Increased intracranial pressure.

3. Adenotonsillar hypertrophy>> is idiopathic

4. Elevation of liver enzymes>> it will affect the metabolism of the other drugs that the patient is taking.