• Introduction to GH in general, chemistry, anaphylactic shock, GHBP, bioassays, GHRH, SS, glucostats and catecholamines

• GH regulates protein, fat and carbohydrate metabolism and is regulated by proteins, FFA, glucose and other factors. GH indirect effects are mediated by liver somatomedins (insulin-like growth factors or IGF)

• Mechanism of action: GHRH, SS, GH, IGF

• Pubertal growth spurt in humans, an example of activation of the GH axis

• Pathologies: dwarfism, gigantism, acromegalia, clinical tests. GH use/abuse
Introduction

- GH, GHRH, SS
- GH effects
- Mechanism of action
- Puberty
- Pathologies

The median eminence (ME) is the link between the brain and the anterior pituitary.

- GH is a protein
- similar to Prl / hPL
- heterogeneity
- anaphylaxis
- GH - BP & GH / T
- evolution
- bioassay vs RIA
- regulation

The median eminence (ME) is the link between the brain and the anterior pituitary.
Introduction

- GH, GHRH, SS
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- Puberty
- Pathologies

The median eminence (ME) is the link between the brain and the anterior pituitary.
Introduction

• GH, GHRH, SS

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• Mechanism of action

• Puberty

• Pathologies

GH secretion is controlled by hypothalamic neurohormones and by IGF.

• SS and GRH
• short loop feedback
• SS / GRH feed-back
• IGF
• long loop feedback
• VMN /glucostat /GH
• GH pulsatile release
• SS / GRH & pulses
• CAs and steroids

GH secretion is under the direct dual control of a stimulatory (GHRH) and an inhibitory (SS) input.
Introduction

- GH, GHRH, SS
- GH effects
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- Pathologies

The hypothalamic median eminence (ME) is the link between the brain and the endocrine system.

Main neurohormones involved in the neuroendocrine control of growth, SS, GHRH and Ghrelin.
Introduction

- GH, GHRH, SS
- GH effects
- Mechanism of action
- Puberty
- Pathologies

Growth, effect of growth hormone - releasing hormone (GHRH) on plasma GH, placebo vs GHRH

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Introduction

- GH, GHRH, SS
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Somatostatin and ocreotide

Native somatostatin 14

Octreotide

Ocreotide is a long-lasting somatostatin analog used in medicine
Introduction

- GH, GHRH, SS
- GH effects
- Mechanism of action
- Puberty
- Pathologies

Somatostatin, octreotide and GH secretion

Ocreotide is a long-lasting somatostatin analog used in medicine

Serum GH levels and octreotide therapy

Ocreotide is a long-lasting somatostatin analog used in medicine
Introduction

- GH, GHRH, SS

- GH effects

- Mechanism of action

- Puberty

- Pathologies

LH / FSH
TSH
PRL
ACTH
GH

GH, as many anterior pituitary hormones, has a circadian secretion pattern

Introduction

- GH, GHRH, SS

- GH effects

- Mechanism of action

- Puberty

- Pathologies

before T4
after T4

GH secretion is partially dependent of T3, a thyroid hormone

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Growth Hormone (GH) effects

- GH, GHRH, SS
- GH effects
  - Stimulates body growth and is anti-insulinic
  - Decreases fat and increases lean body mass
  - Involved in cardiac and immune function
  - Involved in mental agility and aging
- Mechanism of action
- Puberty
- Pathologies

A summary of GH effects and of its current therapeutic uses

GH has direct and indirect effects, the latter being mediated by the IGFs
Growth Hormone (GH) effects

- GH, GHRH, SS
- GH effects
  - Mechanism of action
  - Puberty
  - Pathologies

GH has direct and indirect effects, the latter being mediated by the IGFs.
Growth Hormone (GH) effects

- GH, GHRH, SS

- GH effects
  - lowers blood aminoacid concentrations
  - lowers blood urea nitrogen. Positive N balance
  - increases DNA, RNA, and protein synthesis
  - elevates glycemia by decreasing CH utilization and sensitivity to the insulin-hypoglycemic effect
  - elevates fat oxidation. Lowers respiratory quotient
  - induces growth in general mostly through IGFs
  - stimulates growth and calcification of cartilage
  - GH abuse causes diabetes mellitus by exhaustion of β-cells overstimulated by high glycemia (meta-hypophyseal diabetes). Impaired glucose tolerance in acromegaly might be related to this interaction

- Mechanism of action

- Puberty

- Pathologies

GH promotes the use of fat depots as energy source rather than glucose (sparing effect of glucose)
Growth Hormone (GH) effects

- GH, GHRH, SS
- GH effects
- Mechanism of action
- Puberty
- Pathologies

The effect of GH on intermediary metabolism is characterized by a glucose sparing effect.

Direct and indirect actions of GH on growth and metabolism.
Growth Hormone (GH) effects

- GH, GHRH, SS

  - GH effects
  - Mechanism of action
  - Puberty
  - Pathologies

Growth Hormone (GH) effects

- GH, GHRH, SS

  - GH effects
  - Mechanism of action
  - Puberty
  - Pathologies

GH effect on growth requires the presence of insulin for optimal performance.

GH effect on growth requires the absence of cortisone for optimal performance.
GHRH and SS

- GH, GHRH, SS
- GH effects
  - Mechanism of action
- Puberty
- Pathologies

Most of the effects of GHRH and of SS are mediated by AC and PLC.

GHRH and SS

- GH, GHRH, SS
- GH effects
  - Mechanism of action
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- Pathologies

Most of the effects of GHRH and of SS are mediated by AC and PLC.
GHRH and SS

- GH, GHRH, SS
- GH effects
  - the GHRH peptide:
    - GPCR, AC, cAMP, PLC/IP3, PLA/PGE
    - sexual dimorphism (DHT), receptors for SS
  - the SS peptide:
    - GPCR, Gi, AC, open K channels, hyperpolarization, lower Ca influx

- Mechanism of action
- Puberty
- Pathologies

Most of the effects of GHRH and of SS are mediated by AC and PLC

Growth Hormone (GH)

- GH, GHRH, SS
- GH effects
  - GH, GHRH, SS
  - GH effects
    - Mechanism of action
    - Puberty
    - Pathologies

The effects of GH are mediated by single transmembrane domain receptors

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Growth Hormone (GH)

- GH, GHRH, SS
- GH effects

- Mechanism of action
- Puberty
- Pathologies

The effects of GH are mediated by single transmembrane domain receptors

The effects of GH are mediated by single transmembrane domain receptors
Growth Hormone (GH)

- GH, GHRH, SS
- GH effects
  - GH receptors do not have a kinase
  - Dimerization, if GH excess inhibition
  - Ligand binding results in rapid phosphorylation of cell proteins on Tyr

- Mechanism of action
  - Janus (JAK) kinases are cytoplasmic tyrosine kinases which physically associate with box 1-box 2 domains of the ligand bound receptor leading to auto-phosphorylation on Tyr residues and phosphorylation of transcription factors called “signal transducers and activators of transcription” or in short “STATS”

- Puberty
- Pathologies
  - Most GH effects are mediated by IGFs

The effects of GH are mediated by single transmembrane domain receptors
Growth Hormone (GH)

- GH, GHRH, SS
- GH effects
  - Mechanism of action
- Puberty
- Pathologies

The effects of GH are mediated by single transmembrane domain receptors

IGFs and other Growth Factors

- GH, GHRH, SS
- GH effects
  - Mechanism of action
- Puberty
- Pathologies

The effects of IGFs are mediated by single transmembrane domain receptors
IGFs and other Growth Factors

- GH, GHRH, SS
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- Pathologies

The effects of IGFs are mediated by single transmembrane domain receptors

Growth Factor families
- Insulin
- EGF (>10), FGF (9), IGF (2), NGF (4), PDGF (2), TGF-β (24), EPO

Erythropoietin (U/l) vs. Haemoglobin (g/l) graph showing a negative correlation between EPO levels and haemoglobin levels.

The effects of IGFs are mediated by single transmembrane domain receptors
IGFs and other growth factors

- GH, GHRH, SS
  - Unlike hormones, GFs are produced by many tissues. They are not produced in specific glands. They are secreted proteins exerting multiple effects on cell growth, metabolism, differentiation, and on growth / development of organisms. Binding proteins control growth factor availability

- GH effects
  - GFs actions might be endocrine, paracrine, juxtacrine, autocrine, and intracrine (PDGF)
  - Cytokines, secreted proteins produced by macro-phages, lymphocytes, and blood cell precursors controlling the immune and hematopoietic systems
  - GFs have Tyr-K except TGFβ which phosphorilates Ser / Thr residues, receptor dimerization
  - amplification through multiple kinases & stats (signal transducers and activators of transcription)
  - long-term effects of GFs are dependent on shifts in gene expression

- Mechanism of action
  - IGF regulates somatic growth in direct relation to GH
  - Plethora of actions attributed to GFs, but precise role in growth and development is still partially unresolved.
  - Examples:
    - EGF induce wool shedding & is used for shearing sheep
    - FGF induces limb development. Exp. in chick embryos
    - NGF induces sympathetic ANS. Ab experiment in rat embryo. Target-derived neurotrophic factor hypothesis
    - PDGF is involved in wound healing. Multiple sclerosis
    - TGFβ in immune function, inflammation, reproduction. Activins stimulate FSH secretion. MIH, involved in sexual differentiation has 30% aa identity with TGFβ. Stimulates wound healing. TGFβ excess causes fibrosis

- Puberty
  - Pathologies

The effects of IGFs are mediated by single transmembrane domain receptors
IGFs and other growth factors

• GH, GHRH, SS

• GH effects
  • Mechanism of action
  • Puberty
  • Pathologies

The effects of IGFs are mediated by single transmembrane domain receptors

Aminoacids in black are in identical position in A and B chains of insulin
Insulin and IGF-1 receptors are structurally related heterotetrameric glycoproteins.
Pubertal growth in humans

- GH, GHRH, SS
- GH effects
- Mechanism of action
- Puberty
- Pathologies

Growth acceleration at puberty is associated with increased GH

Hormonal regulation of growth at different stages of life. IGFs = insulin-like growth factors; GH = growth hormone; T3 = triiodothyronine.
Pubertal growth in humans

- GH, GHRH, SS
- GH effects
- Mechanism of action
  - Puberty
  - Pathologies

Growth acceleration at puberty is associated with increased GH

![Graph showing height velocity chart and GH secretion over time.](image)
Pubertal growth in humans

- GH, GHRH, SS
- GH effects
- Mechanism of action

- Puberty
- Pathologies

Growth acceleration at puberty is linked to increased GH, IGF1 and IGF-BP3

GH secretory episodes are increased in frequency and amplitude by testosterone
Human Endocrine Diseases

- GH, GHRH, SS
- GH effects
- Mechanism of action
- Puberty

Pathologies

A GH hypersecretion: Harvey Cushing’s first acromegalic patient

GH-related human endocrine diseases
Endocrine pathologies related to GH and the IGF axis

- GH, GHRH, SS
- GH effects
- Mechanism of action
- Puberty
- Pathologies
  - GH hyposecretion leads to dwarfism. Tom Thumb
  - Idiopathic short stature due to low GH, GRH, IGFI
  - Laron dwarfism due to low GH/IGF, GHR, & GH-BP
  - GH bioassay, epiphyseal growth plates, steroids
  - GH hypersecretion before puberty and gigantism
  - GH hypersecretion after puberty and acromegaly
  - bST and milk production or pushing the envelope
  - illegal bST use in athletes. Acromegaly / diabetes

Endocrine pathologies related to GH and the IGF axis
Human Endocrine Diseases

- GH, GHRH, SS
- GH effects
- Mechanism of action
- Puberty
  - Pathologies

A pathology related to a GH deficiency of hypothalamic origin

Human Endocrine Diseases

- GH, GHRH, SS
- GH effects
- Mechanism of action
- Puberty
  - Pathologies

Growth acceleration at puberty is associated with increased GH
Human Endocrine Diseases

- GH, GHRH, SS
- GH effects
- Mechanism of action
- Puberty

**Pathologies**

Serum IGF-1 and IGF-2 in normal, acromegalic and GH deficiency patients

Serum IGF-1 and IGF-2 in normal, hypopituitary dwarfism and in pygmies
Human Endocrine Diseases

- GH, GHRH, SS
- GH effects
- Mechanism of action
- Puberty

Pathologies

- Laron's syndrome, a pathology related to a GH receptor deficiency
- Gigantism due to AP hyperfunction after a surgery procedure at age 12

Mother & son.

At 8-foot-4, Leonid Stadnik, 33 years old, is the tallest human being on the planet (2005)