The GH/IGF-I Axis

- Synthesized in the anterior lobe of the pituitary gland in somatotroph cells
- ~75% of GH in the pituitary and in circulation is 191 amino acid single chain peptide, 2 intra-molecular disulfide bonds
- Weight: 22kD
- Amount of GH secreted:
  - Women: 500 µg/m²/day
  - Men: 350 µg/m²/day

Pulsatile Pattern of GH Secretion in a Healthy Adult

GH Secretion: Primarily Regulation by two hypothalamic hormones

- GHRH induces GH synthesis and secretion in somatotrophs
- Somatostatin: Decreases to allow GH secretory bursts
- Growth Hormone Releasing Hormone Stimulatory of GH Secretion
- Somatostatin Inhibitory of GH Secretion
- Growth Hormone Release
- GH Secretion
Pharmacologic Agents Used to Stimulate GH Secretion

- GHRH +
- GH
- L-dopa
- Clonidine

Inhibit Somatostatin

Hypoglycemia (Insulin)

Arginine

Pyridostigmine

Other Physiological Regulators of GH Secretion

- Sleep
- Exercise
- Stress
- Amino Acids
- Fasting
- Glucose
- Hypothalamus
- Pituitary

Inhibits Somatostatin

Stimulates hypothalamic GHRH

Insulin-like growth factor I (IGF-I)

- 70 amino acid polypeptide
- Produced predominantly in the liver
- Endocrine and autocrine/paracrine actions
  - Mediates major anabolic and growth-promoting effects of GH
  - Insulin-like effect, independent of GH
- Does not mediate the lipolytic effects of GH

Major Determinants of Circulating IGF-I Levels

- Growth Hormone
  - Increases IGF-I production in liver, major source of circulating IGF-I
- Nutritional Status
- Age
- Genetic Factors
- Binding proteins
- Increased levels in pregnancy and puberty

GH Secretion & IGF-I Levels Across Lifespan

- GH secretion declines with age
- Serum IGF-I levels also decline with age.
Disorders of GH Secretion

• **GH Excess:**
  - GH overproduction by a GH secreting pituitary tumor - ACROMEGALY

• **GH Deficiency:**
  - Childhood onset
  - Adult onset

**Biochemical Diagnosis of Acromegaly**

**Growth Hormone**
- Random GH Levels
- GH Suppression after Oral Glucose: Failure of GH to Fall < 1 µg/L

**Serum IGF-I Level:**
- Elevated above age-adjusted normal range

**Prevalence of Clinical Features at Diagnosis**

- Acral enlargement and/or coarse features
- Sweating
- Menstrual Disorders
- Headache
- Arthritis
- Carpal tunnel syndrome
- Diabetes or impaired glucose intolerance
- Impaired potency and/or libido
- Hypertension
- Visual field defect
- Obstructive sleep apnea
- Galactorrhea
- Coronary artery disease

**Current Therapies for Acromegaly**

• **Primary therapy**
  - Transsphenoidal surgery
  - Medical therapy

• **Adjunctive therapy**
  - Medical therapy
    - Dopamine agonists
    - Somatostatin analogs
    - GH receptor antagonist
  - Radiotherapy (+ interim medical therapy)
Role of Surgery for Acromegaly

First Line Therapy in Nearly All patients:

- Potential for cure
- Leads to immediate decline in GH level
- Reduces tumor size and relieves mass effect
- Surgical complication rate is low

Somatostatin Analogs (SA)
- Directly inhibit GH secretion

Dopamine Agonists (DA)
- Directly inhibit GH secretion

Growth Hormone Receptor (GHR) Antagonist (pegvisomant)
- Blocks the GH receptor, negating effects of GH in periphery
- Directly inhibits IGF-I secretion

Somatostatin-14 Analogs: Clinical Use

Lanreotide
- GH molecule that has been mutated to function as a receptor antagonist
- GH Receptors are blocked.
- GH does not fall, but GH actions are blocked.
- IGF-I levels fall and clinical symptoms of acromegaly improve

Octreotide
- Functional GHR Dimerization is Prevented

Goals of Therapy

- Biochemical control
  - GH suppression
  - IGF-I normalization
- Relieve signs and symptoms
- Reduce tumor size & mass effect
- Preserve pituitary function
- Minimal side effects

Etiologies of Clinical Syndromes of Growth Hormone Deficiency

Hypothalamic Disease: GHRH Deficiency

Pituitary Disease: Failure to Secrete GH

Liver & Other Tissue
- Deficiencies of GH or IGF-I receptors in liver; IGF-I not produced; GH resistance, GH not low.
Etiologies of Adult Onset of GH Deficiency

<table>
<thead>
<tr>
<th>Cause</th>
<th>N=1034</th>
<th>Percent</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pituitary tumor</td>
<td>53.9</td>
<td></td>
</tr>
<tr>
<td>Craniopharyngioma</td>
<td>12.3</td>
<td></td>
</tr>
<tr>
<td>Idiopathic</td>
<td>10.2</td>
<td></td>
</tr>
<tr>
<td>CNS tumor</td>
<td>4.4</td>
<td></td>
</tr>
<tr>
<td>Empty sella syndrome</td>
<td>4.2</td>
<td></td>
</tr>
<tr>
<td>Sheehan's syndrome</td>
<td>3.1</td>
<td></td>
</tr>
<tr>
<td>Head trauma</td>
<td>2.4</td>
<td></td>
</tr>
<tr>
<td>Hypophysis</td>
<td>1.6</td>
<td></td>
</tr>
<tr>
<td>Surgery other than for pituitary treatment</td>
<td>1.5</td>
<td></td>
</tr>
<tr>
<td>Granulomatous diseases</td>
<td>1.3</td>
<td></td>
</tr>
<tr>
<td>Irradiation other than for pituitary treatment</td>
<td>1.1</td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>4.0</td>
<td></td>
</tr>
</tbody>
</table>


Clinical Consequences of Adult Onset GH Deficiency

- Increased cholesterol and increased levels of some cardiovascular risk markers eg. CRP.
- Abnormal body composition; increased central body fat.
- Decreased bone density
- Decreased quality of life

Therapy of GH Deficiency:
- Requires daily subcutaneous injections of human growth hormone. (Some newer formulations may be longer acting)
- Effect in GH deficient adults; Modest improvements in the effects of GH deficiency listed above.

Regulation of Prolactin Secretion

**Stimulated by:**
- Sleep
- Food
- Stress
- Pregnancy
- Nursing
- Breast stimulation

**Suppressed by:**
- Dopamine

Hyperprolactinemia

- Defined as excess serum prolactin: Prolactin >20 µg/L in men or >25 µg/L in women
- Most common endocrine disorder of the hypothalamic-pituitary axis
- Prevalence: 0.4% in unselected normal adult population
- Many different etiologies
- Prolactinomas are the most frequent cause of hyperprolactinemia

Pathological Causes of Hyperprolactinemia

<table>
<thead>
<tr>
<th>Pituitary/Hypothalamic Disorders</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prolactinoma</td>
</tr>
<tr>
<td>Acromegaly</td>
</tr>
<tr>
<td>Other sellar masses</td>
</tr>
<tr>
<td>Infiltrative disorders</td>
</tr>
<tr>
<td>Hypothalamic and pituitary stalk disease or damage</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Other Causes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary hypothyroidism</td>
</tr>
<tr>
<td>Seizures</td>
</tr>
<tr>
<td>Polycystic ovary disease</td>
</tr>
<tr>
<td>Neurogenic causes (chest wall trauma or surgery, herpes zoster)</td>
</tr>
<tr>
<td>Renal insufficiency</td>
</tr>
<tr>
<td>Cirrhosis</td>
</tr>
<tr>
<td>Medications</td>
</tr>
</tbody>
</table>

Pharmacologic Causes of Hyperprolactinemia

<table>
<thead>
<tr>
<th>Antihypertensives</th>
</tr>
</thead>
<tbody>
<tr>
<td>Verapamil</td>
</tr>
<tr>
<td>Methyldopa</td>
</tr>
<tr>
<td>Reserpine</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>GI Medications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chlorpromazine</td>
</tr>
<tr>
<td>Metoclopramide</td>
</tr>
<tr>
<td>Domperidone</td>
</tr>
<tr>
<td>H2 blockers</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Antipsychotics</th>
</tr>
</thead>
<tbody>
<tr>
<td>Phenothiazines</td>
</tr>
<tr>
<td>Butyrophenones</td>
</tr>
<tr>
<td>Atypicals</td>
</tr>
<tr>
<td>Antidepressants</td>
</tr>
<tr>
<td>Tricyclics</td>
</tr>
<tr>
<td>MAO inhibitors</td>
</tr>
<tr>
<td>SSRI's</td>
</tr>
<tr>
<td>Other</td>
</tr>
<tr>
<td>Cocaine</td>
</tr>
<tr>
<td>Opiates</td>
</tr>
<tr>
<td>Protease Inhibitors</td>
</tr>
</tbody>
</table>
### Clinical Manifestations of Hyperprolactinemia

Hyperprolactinemia: Suppresses gonadotropins - leads to varying degrees of gonadal dysfunction.

<table>
<thead>
<tr>
<th>Women</th>
<th>Men</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oligo-amenorrhea</td>
<td>Decreased libido</td>
</tr>
<tr>
<td>Infertility</td>
<td>Erectile dysfunction</td>
</tr>
<tr>
<td>Galactorrhea</td>
<td>Gynecomastia</td>
</tr>
<tr>
<td>Estrogen deficiency</td>
<td>Galactorrhea</td>
</tr>
<tr>
<td>Acne/hirsuitism</td>
<td>Infertility</td>
</tr>
<tr>
<td>Osteopenia</td>
<td>Osteopenia</td>
</tr>
</tbody>
</table>

### Treatment of Hyperprolactinemia

- Dopamine agonist therapy is primary treatment for almost all patients
- Surgery and radiation therapy occasionally used
- Careful follow-up without treatment is an option for patients if they do not have a macroadenoma, are asymptomatic, have normal gonadal function, and are not seeking fertility

### Dopamine Agonists used to treat Hyperprolactinemia/Prolactinomas

- Bromocriptine
- Cabergoline

### Hyperprolactinemia: Treatment Goals

- Restore gonadal function
- Improvement in sexual dysfunction
- Fertility
- Resolve galactorrhea (if bothersome)
- Reduce/stabilize tumor size
- Reverse mass effects
- Preserve/restore pituitary function
- Normalize PRL level

### Pituitary Tumors

- Nearly all benign
- Can be: Non-secreting, Hormone Secreting
  - Prolactin
  - Growth Hormone
  - ACTH- Cushing’s
  - TSH, LH, FSH
- Cause Disease: Problems related to: Excess hormone
  - Pressure of tumor on: optic nerves, other surrounding
  - Or normal pituitary - pituitary insufficiency

### Evaluation of the Patient for Pituitary Disease

- History and Physical examination
- Laboratory: Pituitary hormone overproduction and hypopituitarism
  - Prolactin
  - Free T4, TSH
  - Cortisol, ACTH
  - GH, IGF-I
  - LH, FSH, testosterone
  - Pregnancy test
- MRI
- Visual fields