**Pituitary**

February 10, 2009

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**Hypothalamic-Pituitary Axes**

- **Anterior Hypothalamic Factors**
  - Releasing/Inhibiting

- **Posterior Pituitary Hormones**
  - ADH, oxytocin

**Circulating Hormones**

**Target Gland and Tissue Effects**

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**Growth Hormone**

- Synthesized in the anterior lobe of the pituitary gland in somatotroph cells

- ~75% of GH in the pituitary and in circulation is a 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

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**The GH/IGF-I Axis**

- **Somatostatin**
- **GHRH**

**Hypothalamus**

**PITUITARY**

**GH**

**IGF-I Synthesis**

**LIVER**

**CIRCULATION**

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**Pulsatile Pattern of GH Secretion in a Healthy Adult**

![Graph showing pulsatile pattern of GH secretion with peaks during sleep and troughs during wakefulness.](image)

From: “Acromegaly” by Alan G. Harris, M.D.

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**GH Secretion: Primarily Regulation by two hypothalamic hormones**

- **GHRH**
- **Somatostatin (SMS)**

- **GHRH** induces GH synthesis and secretion in somatotrophs

- **Somatostatin** decreases to allow GH secretory bursts

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From: “Acromegaly” by Alan G. Harris, M.D.
Pharmacologic Agents Used to Stimulate GH Secretion

- L-dopa
- Clonidine
- Hypoglycemia (Insulin)
- Arginine
- Pyridostigmine

Stimulate hypothalamic GHRH or Inhibit Somatostatin

GHRH + SMS

GH

Other Physiological Regulators of GH Secretion

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

GHRH

Hypothalamus

SMS

Pituitary

GH

Target Tissues

IGF-I

Metabolic & Growth Promoting Effects

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

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

GH Secretion & IGF-I Levels Across Lifespan

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

GH & IGF-I Actions

- GH & IGF-I regulate metabolic and growth effects in various tissues.
Disorders of GH Secretion

- **GH Excess:**
  GH overproduction by a GH Secreting pituitary tumor - ACROMEGALY

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

**GH/IGF-I Axis**

Acromegaly

- Somatostatin(-)
- GHRH (+)
- PITUITARY
- GH
- Local IGF-I Synthesis
- LIVER
- IGF-I Synthesis
- CIRCULATION
- IGFI

Prevalence of Clinical Features at Diagnosis

<table>
<thead>
<tr>
<th>Clinical Feature</th>
<th>% of Patients</th>
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<tbody>
<tr>
<td>Acral enlargement and/or coarse features</td>
<td>90</td>
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<tr>
<td>Sweating</td>
<td>70</td>
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<tr>
<td>Menstrual Disorders</td>
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<td>Headache</td>
<td>30</td>
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<td>Carpal tunnel syndrome</td>
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<td>Diabetes or impaired glucose intolerance</td>
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<tr>
<td>Hypertension</td>
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<td>Impaired potency and/or libido</td>
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<td>Visual field defect</td>
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<td>Obstructive sleep apnea</td>
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<td>Galactorrhea</td>
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<td>Coronary artery disease</td>
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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

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

Increased somatic growth & metabolic dysfunction

Pegvisomant
- 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

IGF-I Levels Fall

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

Failure to generate IGF-I peripherally
- 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

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<thead>
<tr>
<th>Cause</th>
<th>N=1034</th>
<th>Percent</th>
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<tr>
<td>Pituitary tumor</td>
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<tr>
<td>Craniopharyngioma</td>
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<td>Idiopathic</td>
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<td>CNS tumor</td>
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<td>Empty sella syndrome</td>
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<td>Head trauma</td>
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<td>Surgery other than for pituitary treatment</td>
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<tr>
<td>Other</td>
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</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.

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

**Pituitary/Hypothalamic Disorders**
- Prolactinoma
- Acromegaly
- Other sellar masses
- Infiltrative disorders
- Hypothalamic and pituitary stalk disease or damage

**Other Causes**
- Primary hypothyroidism
- Seizures
- Polycystic ovary disease
- Neurogenic causes (chest wall trauma or surgery, herpes zoster)
- Renal insufficiency
- Cirrhosis
- Medications

Regulation of Prolactin Secretion

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

**Suppressed by:**
- Dopamine
- Under Tonic Inhibition

Pharmacologic Causes of Hyperprolactinemia

- Antihypertensives
  - Verapamil
  - Methyldopa
  - Reserpine
- GI Medications
  - Chlorpromazine
  - Metoclopramide
  - Domperidone
  - H2 blockers?

- Antipsychotics
  - Phenothiazines
  - Butyrophenones
  - Atypicals
- Antidepressants
  - Tricyclics
  - MAO inhibitors
  - SSRI's
- Other
  - Cocaine
  - Opiates
  - Protease Inhibitors?
Clinical Manifestations of Hyperprolactinemia

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

**Women**
- Oligo-amenorrhea
- Infertility
- Galactorrhea
- Estrogen deficiency
- Acne/hirsutism
- Osteopenia

**Men**
- Decreased libido
- Erectile dysfunction
- Gynecomastia
- Galactorrhea
- Infertility
- Osteopenia

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

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
  - are not seeking fertility

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

Dopamine Agonists used to treat Hyperprolactinemia/Prolactinomas

- Bromocriptine
- Cabergoline