Pituitary

February 11, 2008

Hypothalamic-Pituitary Axes

Hypothalamic Factors
Releasing/Inhibiting

Anterior Pituitary Hormones
ACTH, PRL, GH, LH, FSH, TSH

Circulating Hormones

Target Gland and Tissue Effects

Posterior Pituitary Hormones
ADH, oxytocin
The GH/IGF-I Axis

- **Somatostatin**
- **GHRH**
- **Hypothalamus**
- **PITUITARY**
- **GH**
- **IGF-I**
- **LIVER**
- **CIRCULATION**

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, with 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 (µg/L)

Sleep

0900 2100 0900

Clocktime

From: "Acromegaly" by Alan G. Harris, M.D.

GH Secretion: Primarily Regulation by two hypothalamic hormones

GHRH +

GHRH induces GH synthesis and secretion in somatotrophs

- SMS

Somatostatin Inhibitory of GH Secretion

Somatostatin: Decreases to allow GH secretory Bursts
Pharmacologic Agents Used to Stimulate GH Secretion

Stimulate hypothalamic GHRH or Inhibit Somatostatin

L-dopa
Clonidine

Hypoglycemia (Insulin)
Arginine
Pyridostigmine

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
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.

GH & IGF-I Actions

- GHRH
- SMS
- Hypothalamus
- Anterior Pituitary
- GH
- Bone
- Fat
- Muscle
- Liver
- Target Tissues
- IGF-I
- Metabolic Effects
- Anabolism Growth

IGFBP-1
IGFBP-2
IGFBP-3
IGFBP-4
IGFBP-5
IGFBP-6
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**

- Somatostatin(-)
- GHRH (+)
- GHRH (+) stimulates GH secretion
- GH stimulates IGF-I synthesis in the liver
- Local IGF-I synthesis in circulation

**Acromegaly**

- GH increases GH and IGF-I levels
- IGF-I synthesis in local tissues
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

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**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

Targets of the GH/IGF-I Pathway for Medical Therapy of GH Producing Pituitary Tumor

- Somatostatin
- GHRH
- Growth hormone-secreting tumor
- IGF-I
- Increased somatic growth & metabolic dysfunction
**Somatostatin**

Somatostatin-14

- Amino acids common to native hormone & analog.

**Analogs: Clinical Use**

- **Lanreotide**
  - Thr
  - Cys
  - Val
  - Lys

- **Octreotide**
  - D
  - Trp
  - D
  - Phe
  - Lys
  - Thr

**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
- Failure to generate IGF-I peripherally
  - Deficiencies of GH or IGF-I receptors in liver; IGF-I not produced; GH resistance, GH not low.

Liver & Other Tissue

IGF-I
Etiologies of Adult Onset of GH Deficiency

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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

Under Tonic Inhibition

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

Pharmacologic Causes of Hyperprolactinemia

**Antihypertensives**
- Verapamil
- Methyldopa
- Reserpine

**GI Medications**
- Chlorpromazine
- Metoclopramide
- Domperidone
- H2 blockers?

**Antipsychotics**
- Phenothiazines
- Butyrophenones
- Atypicals

**Antidepressants**
- Tricyclics
- MAO inhibitors
- SSRIs

**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/hirsuitism
- Osteopenia

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

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
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