ENDOCRINES

LEARNING OBJECTIVES

- Basic function of each endocrine system
- Pathophysiology
- Interrelationship between endocrine systems
- Treatment options
  - Replacement therapy
  - Attenuation of hyperactive system
  - Indirect treatment
- Mechanism of action of therapeutic agents
- Limitations of treatment
- Adverse consequences of treatment
ENDORCINES
ORGANIZATION

- HYPOTHALAMUS
- ADRENALS
- TARGET TISSUES
- T.T. HORMONES
- CALCIUM-REGULATING HORMONES
- PANCREATIC HORMONES
I. INTRODUCTION TO ENDOCRINES

A. Secretory glands
   1. Exocrine glands have ducts — secrete sweat, tears, saliva, gastric acid, digestive enzymes, etc.
   2. Endocrine glands are ductless -- release hormones directly into the circulation.

B. Hormones
   1. secreted by endocrine gland
   2. transported in the circulation
   3. exerts their effects distant from site of excretion
   4. physiological role is understood.
I. INTRODUCTION TO ENDOCRINES

C. Endocrine Glands (target tissues)
Most hormones have a specific site of action
1. Hypothalamic hormones act on pituitary
2. Pituitary hormones act on target tissues -- thyroid, ovary, testis, adrenal cortex
3. Exceptions are growth hormone and thyroid hormones which effect most tissues.
I. INTRODUCTION TO ENDOCRINES

D. Physiological Function of Endocrine System

1. Homeostasis -
   a) ANS produces quick transient changes; the ES produces a slow prolonged response
   b) homeostatic mechanisms involve most physiological processes.

2. Growth (to adulthood)

3. Body development (pubertal changes)
I. INTRODUCTION TO ENDOCRINES

E. Regulation of Hormone Secretion.

Proper function of the ES is dependent upon complex regulation of hormone secretion.

1. Nonhormonal control
   a) Blood glucose controls insulin and glucagon levels
   b) Blood Ca++ controls PTH and C levels
   c) ADH and oxytocin
I. INTRODUCTION TO ENDOCRINES

E. 2. Hormonal Control

a) Releasing Hormone (RH) + Hormone (H)
   Negative Feedback
I. INTRODUCTION TO ENDOCRINES

E. 2. Regulation of Hormonal Release
   b) Releasing Hormone (RH) + Inhibiting Hormone (IH)
II. HYPOTHALAMIC HORMONES

A. Gross Anatomy

HYPOTHALAMUS

Anterior Pituitary

Posterior Pituitary

Intermediate Lobe
II. HYPOTHALAMIC HORMONES

B. Function of Hypothalamic Hormones

1. Posterior Pituitary Hormones (ADH and oxytocin) — synthesized in the hypothalamus no control over other hormones.

2. Regulatory Hormones regulate the release of other hormones
II. HYPOTHALAMIC HORMONES

C. Physiological Release of Hormones
1. Anterior pituitary hormones
2. Posterior pituitary hormones
II. HYPOTHALAMIC HORMONES

C. 1. Release of Anterior Pituitary Hormones

Hypothalamus nerve fibers liberate regulatory hormones

Portal system system carries these regulatory hormones to the anterior and intermediate lobes
Oxytocin and ADH are transported down the axons to the nerve endings in the posterior lobe of the pituitary where they are stored until released.
II. HYPOTHALAMIC HORMONES

D. Regulation of Release

1. Releasing hormones + neg. feedback

- Anterior
  - ACTH
- Steroids
  - Estrogens
  - Androgens
- Sex Organ
- Thyroid
- Adrenals
- CRH
- TRH
- GnRH
- LH
- FSH
- TSH
- ACTH
II. HYPOTHALAMIC HORMONES

D. Regulation of Release

2. Releasing hormones + inhibiting hormones

- GHRH + GHRIH
- PRH + PRIH
- MRH + MIF

Anterior

GH

Intermediate

MSH

Prolactin
II. HYPOTHALAMIC HORMONES

D. Regulation of Release

3. Hormones not under hormonal control
   a) ADH — water osmolarity
   b) Oxytocin — uterine contractions
II. HYPOTHALAMIC HORMONES

E. General characteristics of regulatory hormones

1. Small polypeptides
2. Not active orally
3. Short-acting when given intravenously
4. Synthetic derivatives prepared relatively easily
II. HYPOTHALAMIC HORMONES

F. Summary

1. Regulatory hormones - most prominent effect is regulation of synthesis and release of pituitary hormones
2. Distinct mechanism for regulatory hormone release
3. Regulatory hormones are small polypeptides
4. Posterior pituitary hormones
5. Distinct mechanism for posterior pituitary hormone release
III. ANTERIOR PITUITARY

A. Hypopituitarism

1. Adult
   a) Causes — Sheehan's syndrome
      Tumor
      Hypophysectomy—treatment for cancer, diabetes mellitus
   b) Consequences
      atrophy of gonads (FSH), thyroid and adrenal cortex
      decreased metabolic rate (TSH)
      hypoglycemia, increased sensitivity to insulin (GH)
      suppression of lactation (Prolactin)
      depressed spontaneous activity (TSH & ACTH?)
      loss of libido (LH & FSH)
      increased sensitivity to stress (ACTH)
III. ANTERIOR PITUITARY

A. Hypopituitarism

2. Juvenile

   a) Cause -- pituitary doesn't develop during embryogenesis

   b) Consequences

      1. normal longevity
      2. dwarfism
      3. no sexual development
      4. thyroid and adrenal hypoactivity
III. ANTERIOR PITUITARY

A. Hypopituitarism

3. Therapy (Adult vs. juvenile)
   a) Replacement with glucocorticoids, thyroid and sex hormones — GH, MSH and prolactin are absent.
   b) Pituitary hormones usually not used because they
      1. have no advantages over above hormones
      2. expense
      3. antibody formation
      4. must be injected
      5. emphasis is on target hormones
III. ANTERIOR PITUITARY

B. Hyperpituitarism

1. Cause -- pituitary tumor
2. Consequences
   a) gigantism and acromegaly
   b) goiter and enlarged adrenal cortex
   c) precocious sexual development
   d) Cushing's syndrome
   e) occasionally lactation

3. Treatment - surgical removal of tumor
III. ANTERIOR PITUITARY

C. Growth Hormone (somatotropic hormone or somatotropin)

1. Chemistry — 191 amino acids
   Sequence is known. GH activity resides in an "active core" of the molecule.

2. Regulation of release (next slide)
   a) GHRH and GHRIH
   b) GH — levels fluctuate greatly during 24 hours in large response to metabolic alterations and rate of secretion of other pituitary hormones. GH levels probably play minor role in release of GHRH & GHRIH.
III. ANTERIOR PITUITARY

C. Growth Hormone

2. Regulation of release (cont.)

- Exercise
- Stress
- Sleep
- Excitement
- Insulin

GHRIH

GHRH

Free Fatty Acids
Hyperglycemia
Glucagon
ACTH
Glucocorticoids

Increased release

TIME

Basal Levels

GH Levels

Increased release
III. ANTERIOR PITUITARY

C. Growth Hormone

3. Pharmacology of GHRH
   a) Structure — 2 releasing factors isolated from pancreatic islet cells contain 40 and 44 amino acids.
   b) Physiological Effects — elevate GH levels in normals and in GH deficiency. Effective i.v. (1-2 µg/kg) or intranasally.
   c) Pharmacological Effects — stimulates prolactin release
   d) Therapeutic Use
      Diagnostic for idiopathic GH deficiency in order to characterize pituitary responsiveness
      Promising for stimulating growth in patients with responsive pituitary and bone.
   e) Preparation — GHRH44 is available from Bachem.
      Sermorelin is an analog used for diagnostic purposes
III. ANTERIOR PITUITARY

C. Growth Hormone

4. Pharmacology of Somatostatin (GHRIH)
   a) Structure -- tetradecapeptide
   b) Physiological effects -- described above
   c) Pharmacological effects:
      1) Inhibits secretion of insulin and glucagon from pancreas. Leads to increase in FFA and decrease in glucose
      2) Inhibits gastrin secretion from pancreas
      3) Inhibits secretion of TSH, ACTH
III. ANTERIOR PITUITARY

C. Growth Hormone

4. Pharmacology of Somatostatin (GHRIH)
   d) Therapeutic potentials:

   GHRIH has a very short life. Analogs have greater potency, longer half-life and selective actions. Octreotide is more effective and longer acting.

   Acromegaly — GHRIH suppresses high levels of GH in acromegaly. Bromocryptine (a DA agonist) is better treatment.

   Diabetes mellitus — GH (abnormally high in diabetes) + glucagon promote breakdown of glycogen, gluconeogenesis and ketosis. GHRIH + insulin may be indicated for long-term treatment. GHRIH can prevent ketoacidosis in juvenile-diabetics who are deprived of insulin.

   Tumors — GHRIH inhibits secretion of glucagon from pancreatic tumor and gastrin from pancreatic tumor (Zollinger-Ellison syndrome)
III. ANTERIOR PITUITARY

C. Growth Hormone

5. Physiological actions of growth hormone
   a. Growth. GH stimulates synthesis of somatomedins, predominately in the liver. Somatomedins most likely promote growth processes. Promotes growth in almost every organ except brain and eyes. Promotes growth in bone until epiphyses close.

   b. Nitrogen metabolism
      1. Nitrogen is retained as protein synthesized.
      2. Sodium, calcium, potassium, phosphorus and chloride are retained.
      3. Increased amino acid transport into tissue. Increased protein incorporation.
      4. Somatomedins stimulate sulfate uptake into cartilage.
III. ANTERIOR PITUITARY

C. Growth Hormone

5. Physiological actions of growth hormone
   
c. Effects on metabolism of carbohydrate and lipid

1) GH effect is very complicated for several reasons:
   
a. Several hormones are involved in CHO metabolism
   GH & I — anabolic
   Glucocorticoids & catecholamines — catabolic and antagonistic of GH & I.

b. GH effect is very complicated for several reasons:
   Source of fuel — GH switches fuel source from CHO to fat.
   Decreased CHO utilization leads to elevated blood levels of CHO.
   Opposite insulin’s effect.

   Storage of CHO — Both GH and I promote CHO storage.

   GH can directly antagonize I action. With this antagonism and the negative feedback system, these two hormones keep each other in check.
III. ANTERIOR PITUITARY

C. Growth Hormone

5. Physiological actions of growth hormone
   c. Effects on metabolism of carbohydrate and lipid

   2) Long term effects of GH are to
      - promote CHO storage
      - switch energy source from glucose to fat

   3) GH effects also dependent upon status of the individual
III. ANTERIOR PITUITARY

C. Growth Hormone

5. Physiological actions of growth hormone

c. Effects on metabolism of carbohydrate and lipid

3) Continued

- Normal state: GH and I act together and anabolic effects are dominant (i.e., glycogen formation).

- Diabetic state: Low levels of insulin decreased utilization of CHO which is reduced further by GH. GH becomes diabetogenic because it also promotes mobilization and utilization of fat, resulting in ketosis.

- GH deficiency: insulin utilizes CHO too rapidly in the absence of GH.
III. ANTERIOR PITUITARY

C. Growth Hormone

6. Therapeutic Use

a) Human pituitary GH

1. Clinical use -- only in treatment of hypopituitary dwarfism. Only in patients with open epiphysis. Treatment continued until epiphysis close or desire height achieved.

2. Source -- extracted from human pituitary at autopsy. Only primate GH is active in humans. Was available from National Hormone and Pituitary Program as Asellacrin from Serono Labs and Crescormon from KabiVitrum.

3. Adverse effects

   a. Hyperglycemia, ketosis
   b. hypothyroidism
   c. rarely allergic reactions
   d. Creutzfeldt-Jakob disease -- apparently arose from a virus from the autopsy tissue that produces dementia, cerebellar symptoms, myoclonus and death within a year.

III. ANTERIOR PITUITARY

C. Growth Hormone

6. Therapeutic Use
   b) Synthetic GH
      2. Somatrem [Protropin] (Genentech) Product of gene splicing
         Differs from natural GH by a methionine residue
         GH def. = 0.1 mg/kg im or sc 3X/week
         Turners = 0.125 mg/kg im or sc 3X/week
      3. Somatropin [Humatrope] (Lilly) Produced by recombinant DNA techniques
         Identical to natural GH
         Dosage same as for somatrem
III. ANTERIOR PITUITARY

C. Growth Hormone

6. Therapeutic Use
   b) Synthetic GH

4. Adverse effects --
   Same as for natural GH
   Diabetogenic in insulin deficiency
   Antibody formation in 30% cases for somatrem
   Antibody formation in 2% cases for somatropin
   Except no Creutzfeldt-Jakob disease
   Evaluate patients yearly for hypothyroidism
III. ANTERIOR PITUITARY

D. Prolactin

1. Chemistry — structurally related to GH.

2. Regulation of Release
   a) Stimuli — PRIH and PRH
      Physiological factors that influence secretion of GH have similar effects on prolactin secretion.
      Prolactin levels rise during pregnancy, reaching maximum levels at term. In nursing mothers, suckling causes prolactin release.
   b) PRH stimulates the release of prolactin
      structure of PRH is unknown
      little is known about its physiological function, but apparently prolactin release is major function
      therapeutic potential of PRH would be initiation of lactation
      TRH also causes release of prolactin, but the physiological significance has not been established
III. ANTERIOR PITUITARY

D. Prolactin

2. Regulation of Release
   c) PRIH - primary control of prolactin
      PRIH is released by dopamine and dopamine agonists.
      Increased dopamine leads to increased PRIH and decreased prolactin
      Has clinical potential for inhibiting lactation
III. ANTERIOR PITUITARY

D. Prolactin

3. Physiological actions

a) Involved in the initiation and maintenance of lactation. Estrogens and progesterone block these prolactin actions during pregnancy.

b) Prepares the mammary glands for breast feeding by promoting growth (both proliferation and differentiation of mammary ductal and alveolar epithelium).

c) Inhibits LH and FSH release as well as their effects on ovaries and gonads.
III. ANTERIOR PITUITARY

D. Prolactin

4. Hyperprolactinemia
   a. Condition — excessive prolactin secretion
   b. Causes
      1. Dopamine antagonists (reserpine, haloperidol)
      2. Hypothalamic or pituitary disorder
      3. Increased TRH release (simple goiter)
      4. Oral contraceptives (E & P increase PRH release and prolactin secretion. E/P increase plasma binding of T4, decrease free T4 which stim. TRH release.
      5. Prolactin-secreting tumors
   c) Consequences:
      1. Galactorrhea — excessive lactation
      2. Amenorrhea — excessive prolactin decreases release of LH & FSH as well as blockade of their actions
      3. Infertility
      4. Impotence
      5. Mammary tumors — controversial
III. ANTERIOR PITUITARY

D. Prolactin

4. Hyperprolactinemia

d) Treatment —

L-DOPA has been tried and is moderately successful.

Bromocriptine (Parlodel) a DA agonist is more effective — high secretion of prolactin is reversed within several weeks and pregnancy becomes possible. Also has been used to treat impotence in patients with high levels of prolactin.
announcing
the first
nonestrogenic, nonhormonal agent
for prevention of postpartum lactation

Parlodel®
(bromocriptine mesylate)
TABLETS, 2.5 mg