Hypothalamus and Anterior Pituitary

- The “story line” concept: introduction to communication, “reflex arc” model, neuroendocrinology, hierarchies, integration
- The “hypothalamic - pituitary” unit: neurovascular hypothesis, hypothalamic and hypophysiotropic neurohormones to anterior pituitary.
- The “neuroendocrine control”, “hierarchies” and “integration” sites: the ME as neuroendocrine integration site, other neuroendocrine integration sites
- The “anterior pituitary”: embryological origin, amplification unit for hypophysiotropic hypothalamic signals
- Regulators of anterior pituitary secretion: regulators of ACTH and of GH secretions and their mechanisms of action
- Neurohormones (GnRH, TRH, GHRH, SS, CRH, DA): a list of hypophysiotropic neurohormones and their effects

The “Story Line” Concept

For each hormone, the student should know
1. Its cell of origin
2. Its chemical nature, including
   a. Distinctive features of its chemical composition
   b. Biosynthesis
   c. Whether it circulates free or bound to plasma proteins
   d. How it is degraded and removed from the body
3. Its principal physiological actions
   a. At the whole body level
   b. At the tissue level
   c. At the cellular level
   d. At the molecular level
   e. Consequences of inadequate or excess secretion
4. What signals or perturbations in the internal or external environment evoke or suppress its secretion
   a. How those signals are transmitted
   b. How that secretion is controlled
   c. What factors modulate the secretory response
   d. How rapidly the hormone acts
   e. How long it acts
   f. What factors modulate its action

I suggest you put this information into a table YOU design !!!
The “Story Line” Concept

S E
sensor integrator
center

a “reflex arc”
a base for a
control model

efferent
“story line”
diagram for a control system
as that present in
a refrigerator

S E
negative feedback
“story line”
effector

... if story lines are linked through an integrator and
a negative feedback then you have “control”...

The “Story Line” Concept

Blood glucose as example of a multihormonal control

e.g.
Insulin (Σ1)
Glucagon (Σ2)
Cortisol (Σ3)
Epinephrine
SS and GRH
GH
T3 - T4
others ...

S E
The “Hypothalamic- Pituitary” Unit

- Hypothalamus
- Pituitary Stalk
- Anterior / Posterior Pit.
- Hypothalamic Nuclei
  - Vascular link to AP
  - Neuronal link to PP
- Stalk transection
- Kidney transplant
- Neonate pituitary
- Harris, Halaz, Yalow, Shally, Guilleman (NTC)
- Neuroendocrine control (pulsatile, circadian, episodic)

The “Neuroendocrine Control”, “Hierarchies” and “Integrators”

- variable under control (°C / °F)
- thermostat (set point)
- °C / °F detector (feedback)
- Integrator (Σ)
- common language
- error signal (on/off)
- engine (amplifier)

NTC = neuroendocrine transducer cells

long loop negative feedback
short and ultrashort negative feedbacks
hierarchies: gonadal adrenal thyroid others

final endocrine effect
The “Neuroendocrine Control”, “Hierarchies” and “Integrators”

- variable under control (t°C / °F)
- thermostat (set point)
- t°C / °F detector (feedback)
- Integrator (∑)
- common language
- error signal (on/off)
- engine (amplifier)

feedback detector → Integrator (∑)
Error signal (NTC)
negative feedback loop
AP gland
controlled hormone

E2 / P4 receptor
Cortisol receptor
T3 receptor

E2 / P4
GnRH
CRH
TRH

N TC
adrenal hierarchy
adrenal hierarchy
thyroid hierarchy

N TC
Gonadal hierarchy
Adrenal hierarchy
Thyroid hierarchy

Corticosteroid (E2 / P4)
Adrenocorticotropic hormone (ACTH)
Thyrotropin (TSH)

The “Neuroendocrine Control”, “Hierarchies” and “Integrators”

ARN-ME and PVN, two hypothalamic integration center

ARN-ME PVN

POA

The PVN has outputs:
to ARN-ME area
to posterior pituitary
to midbrain (ANS)

GnRH
TRH, GHRH
SRIF / SS
DA, CRH, VIP

Page 5
The “Neuroendocrine Control”, “Hierarchies” and “Integrators”

ARN-ME and PVN, two hypothalamic integration center

What are integrators for, and from where do their inputs came from, and where do their outputs go to??

The “Neuroendocrine Control”, “Hierarchies” and “Integrators”

ARN-ME and PVN, two hypothalamic integration center

What are integrators for, and from where do their inputs came from, and where do their outputs go to??
The “Neuroendocrine Control”, “Hierarchies” and “Integrators”

ARN-ME and PVN, two hypothalamic integration center

What are integrators for, and from where do their inputs came from, and where do their outputs go to??

The “Anterior Pituitary”

AP function and “story lines”

Anterior Pituitary Hormones

<table>
<thead>
<tr>
<th>Hormone</th>
<th>Target</th>
<th>Major Action</th>
</tr>
</thead>
<tbody>
<tr>
<td>TSH</td>
<td>Thyroid gland</td>
<td>Stimulates synthesis and secretion of thyroid hormones</td>
</tr>
<tr>
<td>FSH</td>
<td>Ovary</td>
<td>Stimulates growth of follicles and ovary</td>
</tr>
<tr>
<td>LH</td>
<td>Testis</td>
<td>Increases serum FSH level and stimulates growth of testis</td>
</tr>
<tr>
<td>GH</td>
<td>Brain, pituitary tissue, skin</td>
<td>Promotes growth of brain, pituitary tissue, and skin</td>
</tr>
<tr>
<td>PRL</td>
<td>Mammary gland</td>
<td>Promotes milk secretion and maintains lactation</td>
</tr>
<tr>
<td>ACTH</td>
<td>Adrenal cortex</td>
<td>Stimulates and activates secretion of aldosterone</td>
</tr>
<tr>
<td>POMC</td>
<td>Pancreas, stomach, duodenum</td>
<td>Pancreatic hormone production and secretion of digestive enzymes</td>
</tr>
</tbody>
</table>
The “Anterior Pituitary”

- Embriological origin
- Anatomical / functional links to the brain
- Hypophysiotropic neurohormones
- Hormone RIAs

The pituitary gland is located in a depression of the basiesphenoid bone called the “sella turcica”
The “Anterior Pituitary”

- Embriological origin
- Anatomical / functional links to the brain
- Hypophysiotropic neurohormones
- Hormone RIAs

Hypophysiotropic Hormones

Embriological origin

Anatomical / functional links to the brain

Hypophysiotropic neurohormones

Hormone RIAs

The “Anterior Pituitary”

Hypophysiotropic Hormones

<table>
<thead>
<tr>
<th>Hormone</th>
<th>Aminoacids</th>
<th>Hypothalamic Source</th>
<th>Pituitary Action</th>
</tr>
</thead>
<tbody>
<tr>
<td>CRH</td>
<td>41</td>
<td>Neurons of the hypothalamic nucleus</td>
<td>Stimulates secretion of ACTH and TSH</td>
</tr>
<tr>
<td>GnRH</td>
<td>11</td>
<td>Anterior nuclei</td>
<td>Stimulates secretion of FSH and LH</td>
</tr>
<tr>
<td>GHRH</td>
<td>44</td>
<td>Anterior nuclei</td>
<td>Stimulates GH secretion</td>
</tr>
<tr>
<td>Ghrelin</td>
<td>28</td>
<td>?</td>
<td>Release into GHIS and may directly stimulate GH secretion</td>
</tr>
<tr>
<td>SS</td>
<td>11 or 28</td>
<td>Anterior hypothalamic nuclei</td>
<td>Inhibits secretion of GH</td>
</tr>
<tr>
<td>SHT</td>
<td>7</td>
<td>?</td>
<td>Inhibits prolactin secretion (1)</td>
</tr>
<tr>
<td>DA</td>
<td></td>
<td></td>
<td>Inhibits prolactin secretion (2)</td>
</tr>
<tr>
<td>TRH</td>
<td>15</td>
<td>Anterior hypothalamic nuclei</td>
<td>Stimulates secretion of GH and prolactin</td>
</tr>
<tr>
<td>AVP</td>
<td>9</td>
<td>Anterior hypothalamic nuclei</td>
<td>Acts in concert with CRH to stimulate secretion of GH</td>
</tr>
</tbody>
</table>

(vascular link)

(neuronal link)
The “Anterior Pituitary”

- Embriological origin
- Anatomical / functional links to the brain
- Hypophysiotropic neurohormones
- Hormone RIAs

**Hypophysiotropic Hormones**

<table>
<thead>
<tr>
<th>Hormone</th>
<th>Structure</th>
<th>Function</th>
</tr>
</thead>
<tbody>
<tr>
<td>TRH</td>
<td></td>
<td></td>
</tr>
<tr>
<td>GnRH</td>
<td></td>
<td></td>
</tr>
<tr>
<td>SS</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CRh</td>
<td></td>
<td></td>
</tr>
<tr>
<td>GHRH</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ghrelin</td>
<td></td>
<td></td>
</tr>
<tr>
<td>VP</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

How to measure Hormones

A

B

Page 10
Regulators of AP secretion

- Regulators of ACTH secretion
- Regulators of GH secretion

The hypothalamic – pituitary – adrenal hierarchy

Dopamine

Regulation of ACTH secretion

Cloridram rhythms
Stress

Regulators of ACTH secretion

ACTH --->

Peptidergic neuron
Adrenal
Regulators of AP secretion

- Regulators of ACTH secretion
- Regulators of GH secretion

POMC and biosynthesis of ACTH

Feedback associated with control of ACTH

(Addison’s disease ???)

Regulators of AP secretion

- Regulators of ACTH secretion
- Regulators of GH secretion

What does this profile suggest about the control of ACTH ???
Regulators of AP secretion

- Regulators of ACTH secretion
- Regulators of GH secretion

S → E

Regulators of ACTH secretion

Stimuli
CRH
Stress
Hyperglycemia
Surgery
Trauma
Infection
Hypoxia
Hypoglycemia
ADH
Diurnal pattern:
peak just before awakening
Anxiety, depression
α- and β-Adrenergic agonists

Inhibitors
Cortisol

Regulators of GH secretion

S → E

Regulators of AP secretion

Mechanism of action

Inhibitory hormone

Cytoplasm

Cyclic AMP-dependent protein kinases

G-Protein Functions

Intracellular
CAMP

Structural effects

Calcium fluxes

Gene expression

Membrane effects

S → E

(more info in gluco-corticoid lectures)
Regulators of AP secretion

- Regulators of ACTH secretion
- Regulators of GH secretion

SE (more info on steroids, gluco and mineralocorticoids lectures)
Regulators of AP secretion

- Regulators of ACTH secretion

- Regulators of GH secretion

Regulators of AP secretion

- Regulators of ACTH secretion

- Regulators of GH secretion

(last lecture)

(this lecture)

(lecture on growth)
Regulators of AP secretion

• Regulators of ACTH secretion

• Regulators of GH secretion

What does this experimental profile suggests?

Regulators of AP secretion

• Regulators of ACTH secretion

• Regulators of GH secretion

More on growth and metabolic actions of hormones in later lectures on metabolism of:

- water
- glucose
- mineral
- growth

GH endocrine effects are also the reason why it is abused as drug to enhance sport performance.
Regulators of AP secretion

- Regulators of ACTH secretion
- Regulators of GH secretion

GH and exercise performance

More on growth and metabolic actions of hormones in later lectures on metabolism of:

- water
- glucose
- mineral
- growth

GH endocrine effects are also the reason why it is abused as drug to enhance sport performance.

Regulators of Growth Hormone Secretion

Factors Stimulating GH Secretion

- Metabolic
  - Decreased blood glucose
  - Increased serum amino acids, particularly arginine, leucine
- Hormonal
  - GRH
  - TRH
  - ADH, glucagon
  - Dopamine
  - Uncontrolled diabetes mellitus
- Drugs
  - Dopamine agonists
- Other
  - Exercise
  - Sleep (stages III and IV)
  - Stress
  - Puberty

Factors Inhibiting GH Secretion

- Metabolic
  - Increased blood glucose
- Hormonal
  - Somatostatin
  - IGF
  - Hypothyroidism
- Drugs
  - Dopamine antagonists
- Other
  - Emotional deprivation of children
  - Aging
Regulators of AP secretion

- Regulators of ACTH secretion
- Regulators of GH secretion

Mechanism of action

Cytokine receptor activation

S

Gigantism

GH hyper-secretion before and after the closure of epiphyseal growth plate at puberty

2.3 meters (7' 6'')

1.6 meters

2.3 meters (7' 6'')

1.6 meters

Page 18
Regulators of AP secretion

- Regulators of ACTH secretion
- Regulators of GH secretion

![Graph showing changes in GH levels during Acromegaly]

Acromegaly

![Images of individuals labeled with dates]

Page 19
Hypophysiotropic neurohormones

- anatomy, embryology, and hierarchies (gonadal, thyroid, GH, adrenal, Prl, intermedin).
- TRH: structure, receptor, secreting cells, regulation, actions, clinical use.
- GHRH: structure, receptor, secretion, patophysiology, clinical use.
- SRIF: structure, receptor, secretion, analogs.
- CRH: structure, receptors, regulation, secretion and patophysiology, clinical use.
- DA: synthesis and DA neurons, regulation of Prl, receptors, hyperprolactinemia and D2R agonists.
- gases as neural messengers (neurohormones).

GnRH

- decapetide derived from a 92 aa precursor encoded by one gene which also encodes GAP
- its receptor has 7-transmembrane domains, characteristic of G protein - linked receptors. Its AP content changes with physiological states. Constant GnRH infusion downregulates the GnRH-receptor
- GnRH regulates LH / FSH synthesis and release by a Ca - dependent mechanism involving phosphoinositol - tide hydrolysis, PKC activation, and calmodulin
- Kallman syndrome, precocious puberty, hpg mouse
- sexual behavior, prostate cancer, endometriosis

TRH

- is a tripeptide amide synthesized as part of a large prohormone termed prepro-TRH which contains 6 TRH copies encoded by one gene
- its receptor has 7-transmembrane domains, characteristic of G protein - linked receptors
- TRH actions are mediated by the phosphoinositol / Ca system (IP3, DAG, calmodulin, PKC)
- distribution of TRH receptors in brain suggest TRH is also a neurotransmitter / neuromodulator
- TRH appears to function as neurotrophic factor
- used in stimulation tests prior to new TSH assays

GHRH

- 44 aa in more than a isoform coded in a large prohormone. Hypothalamic gene expression is under the control of GH, is sexually dimorphic and regulated by gonadal steroids (up by DHT)
- its receptor has 7-transmembrane domains, characteristic of G protein - linked receptors
- several second messenger systems mediate effects of GHRH: AC/cAMP, PLC/IP2, PLA/PGE
- GHRH neurons have SS receptors, GH pulses
- half of human GH - secreting tumors have point mutations of Gs gene that interfere with intrinsic GTPase activity and lead to constitutive activation
<table>
<thead>
<tr>
<th>SS</th>
<th>CRH</th>
<th>DA</th>
</tr>
</thead>
<tbody>
<tr>
<td>• a tetradecapeptide whose gene sequence is well conserved in evolution. Post-translational processing of proSS by peptidases / convertases is also conserved and determine the SS tissue specificity</td>
<td>• a 41 aa, synthesized as part of a prohormone which is processed enzymatically. The CRH gene is expressed widely. CRH-BP decreases its synaptic concentration and bioavailability</td>
<td>• is a catecholamine synthesized by hydroxylation of tyrosine and subsequent decarboxylation of L-Dopa</td>
</tr>
<tr>
<td>• its five receptor subtypes have 7-transmembrane domains, typical of G protein - linked receptors</td>
<td>• its receptor has homology to the G - protein - coupled receptor superfamily, and has been linked to GC and to an increase in Ca by cAMP</td>
<td>• D2 receptors regulate Prl. They have 7 transmembrane domains, typical of G protein- linked receptors</td>
</tr>
<tr>
<td>• SS inhibits AC activity on binding to its receptor by stimulating Gi. Additional SS open K channels hyperpolarizing the cell and decreasing Ca influx through voltage sensitive channels</td>
<td>• CRH is the primary hormonal regulator of the body’s stress response. It has a reciprocal positive interaction with AVP at the ME (?)</td>
<td>• hyperprolactinemia due to uncoupling of lactotrophs from hypothalamic DA.</td>
</tr>
<tr>
<td>• since many tumors expressed SS-receptors, SS agonists are used in their detection and treatment. SS antagonists are of potential use to increase GH</td>
<td>• CRH is used in stimulation tests, agonists in depression, anorexia nervosa, anxiety, drug withdrawal. CRH-BP antagonists increase CRH</td>
<td>• hyperprolactinemia causes hypo-gonadism, low libido &amp; galactorrhea. It is treated by DA agonists. Prl response to haloperidol is a very good predictor of its antipsychotic effects</td>
</tr>
</tbody>
</table>