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M2 Endocrine Sequence

University of Michigan Medical School

Directors:
Arno K. Kumagai, M.D.
Thomas Giordano, M.D., Ph.D.

Winter 2009
General Information

- Syllabus and Lecture notes
- Required Sessions:
  - Patient presentation: Friday, March 6th
  - Endocrine Small Groups: Thurs-Fri, March 5-6th
  - Longitudinal Case
- Endocrine Photo Gallery
Feedback loops and anterior pituitary physiology

M2- Endocrine Sequence

Arno K. Kumagai, M.D.

Division of Metabolism, Endocrinology & Diabetes

Winter 2009
### Pituitary cell types

<table>
<thead>
<tr>
<th>Pituitary cell type</th>
<th>Pituitary hormone</th>
<th>Clinical syndrome associated w/ tumor</th>
</tr>
</thead>
<tbody>
<tr>
<td>Corticotrope</td>
<td>ACTH</td>
<td>Cushing’s disease</td>
</tr>
<tr>
<td>Somatotrope</td>
<td>GH</td>
<td>Acromegaly</td>
</tr>
<tr>
<td>Gonadotrope</td>
<td>FSH and LH</td>
<td>None</td>
</tr>
<tr>
<td>Lactotrope</td>
<td>Prl</td>
<td>Prolactinoma</td>
</tr>
<tr>
<td>Thyrotope</td>
<td>TSH</td>
<td>Hyperthyroidism</td>
</tr>
</tbody>
</table>

Source: Undetermined
Hormonal Feedback Loops
You

Your thermostat

Your furnace

Source Undetermined
Hypothalamus

Pituitary

End organ

R. Lash
Adrenal axis

CRH ± AVP

ACTH

Cortisol
CRH = Corticotropin Releasing Hormone

- 41 amino acids long
- Ovine form is more potent than human form
- A trophic factor and a releasing hormone
Hypothalamic-Pituitary-Adrenal Axis

ACTH = Corticotropin
- Derived from a large molecule (POMC)
- 39 amino acids long, first 24 are the same in multiple species
  - Synthetic ACTH (aa 1-24) used clinically
- 250 µg in the pituitary - about 50 µg secreted daily
Post-translational Processing of POMC in the Normal Pituitary

POMC = Pro-opiomelanocortin

MSH = Melanocyte stimulating hormone
Growth hormone axis

GHRH → GH (-) → IGF-I (-) 

GH (+) 

SRIF (-)
Growth hormone axis

**GH Releasing Hormone (GHRH)**

- About 44 amino acids long
- Discovered in pancreatic tumors
- Men over 40 have little response to GHRH
Growth hormone axis

Somatostatin (SRIF)
- Inhibits secretion of GH and TSH
- Also inhibits GI hormones and functions
- Octreotide is a clinically useful analogue

GHRH → GH(-) → SRIF → IGF-I

GFH
(+)
(-)
(-)
(+)

GHRH

GH
(+)
(-)

IGF-I
(-)

R. Lash
Growth hormone - prolactin family

- Significant homology, less so at the protein level (16%)
- Prl & GH both activate the prolactin receptor
- Family also includes placental lactogen (PL)
Prolactin axis

Neural Stimulus (+)

'PRF' (+)

Prl (-)

Dopamine

IMPORTANT

Prolactin release is tonically inhibited by DOPAMINE

Janine Chedid, Wikimedia Commons
Regulation of prolactin = tonically inhibited

- **Prolactin-inhibiting factors (PIFs)**
  - **Dopamine**, Dopamine, Dopamine, maybe GABA
  - **Bromocriptine** is a dopamine agonist
  - Block multiple aspects of lactotrope function

- **Prolactin-releasing factors (PRFs)**
  - TRH - but probably not physiologically important
  - Other candidates: AVP, VIP, Oxytocin, PHI-27
Thyroid axis

TRH

(+)

(-)

SRIF

(+)

(-)

TSH

(+)

(-)

T₃/T₄

(-)

R. Lash
Thyroid axis

\[ T_4 \leftrightarrow T_3 \]

- TRH
- TSH
- SRIF

(+) and (-) signs indicate regulatory effects.

R. Lash
Hypothalamic-Pituitary-Thyroid Axis

TRH = Thyrotropin Releasing Hormone
- Tripeptide (3 amino acids)
- Also a potent stimulator of prolactin release
- Synthesized as a prohormone with six copies of the TRH molecule

TRH

TSH

T4 ⇌ T3

(-)

SRIF

T3/T4

(+)

(-)

R. Lash
The TRH Tripeptide

Source Undetermined
Hypothalamic-Pituitary-Thyroid Axis

TRH → (+) T4 ↔ T3 → SRIF → (-) T3/T4 → (+) TSH

TSH = Thyroid Stimulating Hormone

• AKA “Thyrotropin”
• Binds to receptors on thyroid to stimulate synthesis and release of thyroid hormones T4 (and some T3).
• Part of a glycoprotein hormone family
Thyroid stimulating hormone (TSH) is part of a family of glycoprotein hormones

- Composed of noncovalently bound $\alpha$ and $\beta$ subunits
- Both subunits are glycosylated
- $\alpha$ subunit is common
- $\beta$ subunits are unique - confer biologic and immunologic specificity
Glycoprotein hormone family

α-subunit

92 aa

TSH-β

FSH-β

LH-β

CG-β

112-147 aa
Hypothalamic-Pituitary-Gonadal Axis

GnRH

(+)

Testo (LH)

(-)

(-)

Inhibin (FSH)

(+)

LH & FSH

(+)

R. Lash
Hypothalamic-Pituitary-Gonadal Axis

- GnRH
- LH & FSH
- Testo (LH)
- Inhibin (FSH)
- T → E2

Note: (+) indicates stimulation; (-) indicates inhibition.
GnRH = Gonadotropin Releasing Hormone

- 10 amino acids in length
- Regulates both LH and FSH
- GnRH ↔ LH & FSH
- Sex steroids
Gonadotropin releasing hormone (GnRH)

- Pulsatility and pulse frequency are critical
- Pulsatile infusion stimulates LH and FSH secretion
- Constant infusion inhibits LH and FSH secretion
- GnRH can be used to induce fertility and suppress gonadal function
Hypothalamic-Pituitary-Gonadal Axis

This is where things get complicated...

GnRH

LH & FSH

Estrogen

Inhibin (FSH)

R. Lash
You

Your stereo

Your roommate
Positive feedback loop

You

That special someone

R. Lash
You

That special someone

Special someone’s significant other

(?)

(?)

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Female gonadal axis (negative feedback)

GnRH

LH & FSH

(+)

Estrogen (±)

Inhibin (FSH)

(−)

R. Lash
Female gonadal axis
(Positive feedback during ovulation)

GnRH

(+)

LH & FSH

Estrogen
(+)

R. Lash
Let’s review the major players

<table>
<thead>
<tr>
<th>Hypothalamic releasing factor</th>
<th>Pituitary hormone</th>
<th>Effect of hypothalamic factor</th>
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</thead>
<tbody>
<tr>
<td>TRH</td>
<td>TSH (and Prl)</td>
<td>Stimulatory</td>
</tr>
<tr>
<td>CRH</td>
<td>ACTH</td>
<td>Stimulatory</td>
</tr>
<tr>
<td>GHRH</td>
<td>GH</td>
<td>Stimulatory</td>
</tr>
<tr>
<td>Somatostatin (SRIF)</td>
<td>GH and TSH</td>
<td>Inhibitory</td>
</tr>
<tr>
<td>Dopamine</td>
<td>Prl</td>
<td>Inhibitory</td>
</tr>
<tr>
<td>GnRH</td>
<td>FSH and LH</td>
<td>Stimulatory</td>
</tr>
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Rhythms in endocrinology

■ Circadian rhythms
  - Occur over the course of a day, and repeat daily
  - Characteristic of most endocrine functions
  - Examples: Cortisol secretion

■ Ultradian rhythms
  - Bursts (spikes) of hormone secretion
  - Can be superimposed on circadian rhythms
  - Physiologically important, particularly in reproduction
Pulsatility in the reproductive axis

- **GnRH**
  - Pulsatile infusion at 90 minute intervals can induce ovulation in women with hypothalamic disease
  - Continuous infusion is used to suppress LH/FSH in preparation for in vitro fertilization

- **LH and FSH**
  - Puberty is associated with pulses of greater frequency and amplitude
Frequency of administration determines effect of PTH on bone cells

Osteoblast

Osteoclast

P<0.05, †P<0.01, ‡P<0.001 vs Vehicle

Dobnig and Turner. Endocrinology 1997;138:4607-4612
Things to remember if you’re just waking up

- Generally, hypothalamic hormones stimulate pituitary hormone release
- Prolactin regulation, in contrast, is primarily inhibitory
- The inhibitory hypothalamic factors worth remembering are somatostatin and dopamine
Things to remember if you’re just waking up

- Pituitary hormones fall into three groups
  - Glycoprotein hormones (TSH, LH, and FSH)
  - ACTH
  - Growth hormone and prolactin

- Negative feedback is the usual state of affairs, but not the only one

- Hormone activity depends on both the quantity present, and its mode of release
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