Hypothalamus

- Introduction to communication, “story lines”, “reflex arc” models, neuroendocrinology, hierarchies, integration, endopathologies.
- Neuroendocrine control, hierarchies, integrators. Inputs to neuroendocrine transducer cells and their effects on AP hormones. ME as a neuroendocrine integration site, other neuroendocrine integration sites.
- Neurohormones (GnRH, TRH, GHRH, SS, CRH, DA).

Today’s lecture

“story line”

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 !!!
Components of a hormone response system. Responses produced by hormones generally are sensed by whatever apparatus activated the secretion and usually decrease further secretion.
Introduction to communication

Endocrinology main functions and their basic control

- Reproduction
- Growth and development
- Maintenance of internal environment
- Energy production, utilization, and storage

S -> E
Blood glucose as example of a multihormonal control

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

Hierarchy, negative feedback and endocrine pathology

AP hormones are regulated by hierarchical control system with trophic & target hormone

Alteration of trophic vs target hormonal balance
The Hypothalamic-Pituitary axis

- 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

Mid-sagittal section of the human pituitary gland and adjacent hypothalamic structures.

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Mid-sagittal section of the human hypothalamus and pituitary. The principal nuclei of the hypothalamus are listed within the bracket.
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BUT, HOW DID WE LEARN WHAT WE KNOW

Vascular supply of the human pituitary gland. Note the origin of long portal vessels from the primary capillary bed and the origin of short portal vessels from the capillary bed in the lower part of the stalk. Both sets of portal vessels break up into sinusoidal capillaries in the anterior lobe.
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\[ \begin{align*}
\text{in vitro} \\
\text{half AP +} & \quad \text{half AP -} \\
\uparrow & \quad \uparrow \\
\uparrow & \quad \uparrow \\
\updownarrow & \quad \updownarrow \\
\updownarrow & \quad \updownarrow \\
\text{ACTH, CRF, CRH} & \\
\text{TSH, TRF, TRH} & \\
\text{LH/FSH, LRF, LHRH, GnRH} & \\
\text{GH, GRF, GRH} & \\
\text{GIF, SS} & \\
\text{PRL, PIF, DA PRF, VIP, TRH, SHT} & \\
\end{align*} \]

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\[ \begin{align*}
\text{in vivo} \\
\text{LH release} & \quad \text{into systemic blood} \\
\text{GnRH release} & \quad \text{into portal blood} \\
\text{follicular} & \quad \text{anestrus} \\
\text{time at 10 min intervals} & \\
\end{align*} \]
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- Neuroendocrine control (pulsatile, circadian, episodic)

Changes in hormone concentrations in blood may follow different patterns:
A. Hourly rhythm of LH secretion
B. Daily rhythm in testosterone secretion
C. Episodic secretion of prolactin

Neuroendocrine control, hierarchies and integrators

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

TARGET

FINAL ENDOCRINE EFFECT

hierarchies:
gonadal
adrenal
thyroid
others

short and
ultrashort
negative
feedbacks

long
loop
negative
feedback

hypothalamus

Integrator (Σ)

Error signal (NTC)

negative feedback loop

controlled hormone

feedback detector

CS

AP

gland

S E

Source

Target
Neuroendocrine control, hierarchies and integrators

The median eminence an hypothalamic integration center
Neuroendocrine control, hierarchies and integrators

The median eminence an hypothalamic integration center

GnRH
GRH/SS
TRH
CRH
ME
AP
LH / FSH
GH
TSH
ACTH

NPG
NEND
CRH
GnRH
SS

ME hypophysiotropic release to portal vessels

ACTH
LH / FSH
GH
Neuroendocrine control, hierarchies and integrators

The median eminence an hypothalamic integration center

ARN-ME and PVN, two hypothalamic integration center

ARN-ME PVN
Neuroendocrine control, hierarchies and integrators

ARN-ME and PVN, two hypothalamic integration center

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

Neuroendocrine control, hierarchies and integrators

ARN-ME and PVN, two hypothalamic integration center

hypothalamus and control of water metabolism
Neuroendocrine control, hierarchies and integrators

ARN-ME and PVN, two hypothalamic integration centers

What are integrators for and from where do their inputs came from??

ARN-ME

PVN

AP

PP ANS

S → E

S → E
Neuroendocrine control, hierarchies and integrators

ARN-ME and PVN, two hypothalamic integration centers

- 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).

Neuroendocrine control, hierarchies and integrators

Hypophysiotropic neurohormones

- GnRH, TRH, GRH, SS, CRH, DA, VIP, MSH - RF
- LH / FSH, TSH, GH, ACTH, Prl, MSH
- P4, T, E2, T3, T4, IGFs, cortisol

Page 16
Neuroendocrine control, hierarchies and integrators

GnRH

- decapeptide 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 phosphoinositide 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
### Neuroendocrine control, hierarchies and integrators

#### Hypophysiotropic neurohormones

**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 interferes with intrinsic GTPase activity and lead to constitutive activation

**SS**

- 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
- its five receptor subtypes have 7- transmembrane domains, typical of G protein - linked receptors
- 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
- since many tumors expressed SS-receptors, SS agonists are used in their detection and treatment. SS antagonists are of potential use to increase GH
Neuroendocrine control, hierarchies and integrators

**CRH**

- 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
- 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
- CRH is the primary hormonal regulator of body’s stress response. It has a reciprocal positive interaction with AVP at the ME (?)
- CRH is used in stimulation tests, antagonists in depression, anorexia nervosa, anxiety, drug withdrawal. CRH-BP antagonists increase CRH

**DA**

- is a catecholamine synthesized by hydroxylation of tyrosine and subsequent decarboxylation of L-Dopa
- D2 receptors regulate Prl. They have 7 transmembrane domains, typical of G protein-linked receptors
- DA decreases cAMP (Gi) and ICF-Ca. Prl release is inhibited by low Ca and by Ca channel blockers
- hyperprolactinemia due to uncoupling of lactotrophs from hypothalamic DA.
- hyperprolactinemia causes hypogonadism, low libido and galactorrhea. It is treated by DA agonists. Prl response to haloperidol is a very good predictor of its antipsychotic effects