Neuroendocrinology 2

GnRH

End of menstruation

Follicular phase

FSH

Estrogen

Follicle
Ovaries

(B) Theca externa
Theca interna
Granulosa cells
Liquor folliculi

Germinal epithelium
Interstitial cell mass
Blood vessels
Corpus albicans
Regressing corpus luteum

Primary follicle
Stroma
Secondary follicle

Mature corpus luteum
Erupted follicle

Primary corpus luteum
Antrum
Ovum

E₂

Progesterone
Synthesis of ovarian steroids
“Male” & “female” hormones – misleading terms

- Males express aromatase in brain and make estradiol from plasma T; males also have progesterone

- Females synthesize androgens in ovary, generally as precursors to estradiol
  - Females also have T and AE in blood
HPA axis

Stress & Energy

Gluocorticoids
DHEA

Hypothalamus

CRH

Anterior pituitary

ACTH (through blood)

Adrenal cortex

CORT, DHEA
Adrenal glands
Adrenal glands

Cortex
Medulla

(B) Adrenal cortex and medulla

Adrenal cortex
Adrenal medulla

Capsule
Zona glomerulosa
Zona fasciculata
Zona reticularis
Adrenomedullary hormones

- Monoamines - derived from single amino acid
- Catecholamines – from tyrosine
  - Epinephrine (adrenaline), norepinephrine (noradrenaline), dopamine
Adrenal glands

Cortex
Medulla

(B) Adrenal cortex and medulla

Adrenal cortex
Adrenal medulla

Capsule
Zona glomerulosa  aldosterone
Zona fasciculata  corticosterone
cortisol
Zona reticularis  DHEA
Synthesis of adrenocortical steroids

https://www.youtube.com/watch?v=sPS7GnromGo
Transport & release

- Lipid soluble hormones use carrier proteins to travel through blood, whereas protein and peptide hormones are soluble in blood.

- Lipid soluble hormones are not stored, whereas protein and peptide hormones are stored in secretory vesicles & released in response to a stimulus
Hormone receptors

- Protein or peptide hormone receptors
- Steroid hormone receptors
- Via receptors, hormones regulate levels of growth factors, neurotransmitters, enzymes etc.
Protein or peptide hormone receptors

- **3 domains:**
  - An extracellular domain – binds ligand
  - A transmembrane domain
  - A cytoplasmic domain

- Regulated
- Don’t last forever
Protein or peptide hormone receptors

- Intrinsic enzymatic activity: enzyme in cytoplasmic domain that activates intracellular proteins via phosphorylation
- Second messenger
  - E.g., cAMP – can activate protein kinases

Earl Sutherland
Nobel prize 1971

Ed Krebs
Nobel prize 1992
Steroid hormone receptors

- **Intracellular**
  - Traditional, within cell, regulate gene expression via hormone response elements, slow acting (at least 30 min)

- **Membrane-bound**
  - More recently discovered, plasma membrane or mitochondria, regulate enzymes (e.g., kinases), typically fast acting

- How to distinguish between these?
Intracellular steroid receptors

- Receptors have 3 domains:
  - C-terminal, central and N-terminal
- Receptors in cytoplasm or nucleus
- HRE - hormone response element on DNA, where ligand/receptor complex binds to promoter region to regulate gene expression
Intracellular steroid receptors

Takes time!
Membrane steroid receptors

Rapid effect of corticosterone on male sexual behavior

Binding of $^3$H-corticosterone to neuronal membranes

Negative Feedback

- Hypothalamus
  - TSH-releasing hormone
  - Anterior pituitary
    - TSH
      - Thyroid gland
        - Thyroxine and triiodothyronine
          - Excitatory effect
          - Inhibitory effect
Neurosteroids

- Steroids synthesized in the brain
- Etienne Baulieu, 1981
- Rats: have low levels of DHEA in blood
- High levels of DHEA in brain
- No effect of castration and adrenalectomy on brain DHEA levels
- Steroid levels in blood vs. brain
Neurosteroids

Neurosteroids in the male rat brain (whole brain)

<table>
<thead>
<tr>
<th>Brain (ng/g)</th>
<th>PREG</th>
<th>PREGS</th>
<th>PREGL</th>
<th>DHEA</th>
<th>DHEAS</th>
<th>DHEAL</th>
<th>PROG</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intact</td>
<td>8.9 (±2.4)</td>
<td>14.2 (±2.5)</td>
<td>9.4 (±2.9)</td>
<td>0.24 (±0.33)</td>
<td>1.70 (±0.32)</td>
<td>0.45 (±0.13)</td>
<td>2.2 (±1.1)</td>
</tr>
<tr>
<td>Orx/adx</td>
<td>2.6 (±0.8)</td>
<td>16.9 (±4.6)</td>
<td>4.9 (±1.3)</td>
<td>0.14 (±0.13)</td>
<td>1.64 (±0.43)</td>
<td>0.29 (±0.12)</td>
<td>3.2 (±1.6)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Plasma (ng/ml)</th>
<th>PREG</th>
<th>PREGS</th>
<th>PREGL</th>
<th>DHEA</th>
<th>DHEAS</th>
<th>DHEAL</th>
<th>PROG</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intact</td>
<td>1.2 (±0.6)</td>
<td>2.1 (±0.9)</td>
<td>2.4 (±0.9)</td>
<td>0.06 (±0.06)</td>
<td>0.20 (±0.08)</td>
<td>0.18 (±0.05)</td>
<td>1.9 (±0.7)</td>
</tr>
<tr>
<td>Orx/adx</td>
<td>0.3 (±0.1)</td>
<td>nd</td>
<td>1.3 (±0.3)</td>
<td>nm</td>
<td>nm</td>
<td>nm</td>
<td>0.1 (±0.1)</td>
</tr>
</tbody>
</table>

These data raised the hypothesis that DHEA is made de novo from cholesterol in the brain itself.

Alternate hypothesis?
Hippocampal synthesis of sex steroids and corticosteroids: essential for modulation of synaptic plasticity

Yasushi Hojo\textsuperscript{1,2,3}, Shimpei Higo\textsuperscript{1}, Suguru Kawato\textsuperscript{1,2,3 *}, Yusuke Hatanaka\textsuperscript{1}, Yuuki Ooishi\textsuperscript{1}, Gen Murakami\textsuperscript{1,3}, Hirotaka Ishii\textsuperscript{1}, Yoshimasa Komatsuzaki\textsuperscript{1}, Mari Ogiue-Ikeda\textsuperscript{1,4}, Hideo Mukai\textsuperscript{1,2,3} and Tetsuya Kimoto\textsuperscript{1,2,3}

<table>
<thead>
<tr>
<th>Corticosteroids</th>
<th>Hippocampus (freshly isolated)</th>
<th>Plasma</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Intact</td>
<td>ADX</td>
</tr>
<tr>
<td>-----------------</td>
<td>-------------------------------</td>
<td>--------</td>
</tr>
<tr>
<td>CORT (ng/g wet weight or mL)</td>
<td>128.1 ($n=8$)</td>
<td>2.4 ($n=11$)</td>
</tr>
<tr>
<td>CORT (nM)</td>
<td>369.8</td>
<td>6.9</td>
</tr>
<tr>
<td>DOC (ng/g wet weight or mL)</td>
<td>1.9 ($n=12$)</td>
<td>1.9 ($n=23$)</td>
</tr>
<tr>
<td>DOC (nM)</td>
<td>5.9</td>
<td>5.8</td>
</tr>
</tbody>
</table>
Endogenous Synthesis of Corticosteroids in the Hippocampus

Shimpei Higo\textsuperscript{1,9}, Yasushi Hojo\textsuperscript{1,2,3,9}, Hirotaka Ishii\textsuperscript{1}, Yoshimasa Komatsuzaki\textsuperscript{1,4}, Yuuki Ooishi\textsuperscript{1}, Gen Murakami\textsuperscript{1,3}, Hideo Mukai\textsuperscript{1,2,3}, Takeshi Yamazaki\textsuperscript{5}, Daiichiro Nakahara\textsuperscript{6}, Anna Barron\textsuperscript{1}, Tetsuya Kimoto\textsuperscript{1}, Suguru Kawato\textsuperscript{1,2,3,*}