Reproductive Endocrinology
Reproductive Endocrinology

• Hypothalamic hormones
  - Gonadotropin releasing hormone (GnRH)
    - stimulate release of
      • FSH = follicle stimulating hormone
      • LH = luteinizing hormone
    - from pituitary
  • ‘Gonadotropin’ = gonad stimulating
Hypothalamic Surge/Tonic Centers

- Neurosecretory neurons from surge and tonic centers deposit neurohormones into portal system
- Portal system delivers these hormones to the adenohypophysis
GnRH release is pulsatile

- GnRH pulse generator in hypothalamus called 'circhoral clock'
- Circhoral pulses
  - One pulse every hour
  - Each LH peak coincides with a GnRH pulse
Adenohypophysis

Neurosecretory cells of the hypothalamus
Portal vessels
Hypothalamic hormones
Endocrine cells of the anterior pituitary
Pituitary hormones

HORMONE: Growth hormone (GH) 
Prolactin (PRL)
Follicle-stimulating hormone (FSH) and luteinizing hormone (LH)
Thyroid-stimulating hormone (TSH)
ACTH
MSH
Endorphins

TARGET: Bones 
Mammary glands 
Testes or ovaries 
Thyroid 
Adrenal cortex 
Melanocytes 
Pain receptors in the brain
Pituitary Glycoproteins

FSH - LH - TSH

*Figure 5-8.* Diagram of an Anterior Lobe Glycoprotein Hormone

The α and β subunits are held together non-covalently by hydrogen bonding and van der Waals forces (dotted lines).

Carbohydrate (CHO) moieties are shown in boxes and are covalently bonded to the α and β subunit.
Pituitary Hormones

- **Follicle stimulating hormone**
  - stimulates gametogenesis in males and females
- **Luteinizing Hormone**
  - stimulates steroidogenesis in males and females
- **Prolactin**
  - stimulates the synthesis of milk in mammalian females
  - maternal behavior in some species
- **Oxytocin**
  - stimulates smooth muscle contraction
    - associated with birth and milk release
Negative Feedback

Hypothalamus

Pituitary

GnRH

Gonad

FSH/LH

Short Feedback

Negative Feedback
Negative Feedback

Hypothalamus

Pituitary

GnRH

LH

Gonad

T or E

Long Feedback
Negative Feedback & Homeostasis

- GnRH
- LH
- T or E

Graph showing hormone concentration over time.
Negative feedback

• 1. peptide hormones
  • alter G protein response

• 2. steroid hormones
  • $E_2$ and $P_4$ decrease transcription of $\beta$FSH-mRNA and levels of $\beta$FSH-mRNA
  • $P_4$ causes decrease in GnRH release
Positive Feedback & Homeostasis

GnRH

LH

Hormone Concentration vs. Time

E
Permissive action of hormones

- steroid hormones may act as permissive agents by
  - increase number of receptors
  - increase protein kinases
  - increase inhibitors of cyclic nucleotides
Other Endocrine Organs

- gonads
  - steroids
  - synthesis stimulated by LH
  - derived from cholesterol

A, B, C and D designate specific rings. Numbers designate specific carbons.
Steroidogenesis

Cholesterol

P450ssc

Pregnenolone

3βHSD

P450c17

17-OH Pregnenolone

3βHSD

P450c17

Dehydroepiandrosterone

3βHSD

P450c17

Progesterone

P450c21

17-OH Progesterone

P450c21

Androstenedione

17 Keto Reductase

P450 arom

Testosterone

17β Estradiol

Deoxycorticosterone

P450c11

Corticosterone

11 Deoxycortisol

Cortisol
Progestagens

- **Primary progestagen**
  - Progesterone

- **Secondary progestagens**
  - $17\alpha$-Hydroxyprogesterone ($17\alpha$-OHP)
  - $20\alpha$-Hydroxyprogesterone ($20\alpha$-OHP)
    - Aka $20\alpha$-dihydroxyprogesterone

- **Three nuclear receptors**
  - PR-A; PR-B and new PR-C (humans to date)

- **Membrane receptors (two distinct classes)**
  - progesterone membrane receptor component
    - (PGMRC; subtypes 1 and 2)
  - membrane progestin receptors
    - (mPR; subtypes alpha, beta and gamma)
Androgens

- Two 1° androgens
  - Testosterone (T)
  - Dehydrotestosterone (DHT)
- Two 2° androgens
  - Androstenedione (A4)
  - Dehydroepiandrosterone (DHEA)
- One nuclear receptor
  - AR
- One membrane receptor?
  - Characterization/no cloning and sequence to date
Estrogens

- in vertebrates -
  - three 1° estrogens (Oestrogens)
    - Estradiol-17β (E2)
    - Estriol
    - Estrone
  - Two nuclear receptors
    - ERα
    - ERβ
  - One membrane receptor
    - GPR30
cAMP
MAPK
E2
PLC
PKC
G
PI3K
K
NO
Non-ERE-promoter
mER
Src
AC
PKA
Akt
eNOS
Raf
Ras
RTK
AP1
p
MEK
GABAR
GIRK
µ
K+

CyclinD1
CREB
AP1
Non-ERE-promoter
FoxA1
coactivator
nER
ERE-promoter
p
p
E2
CyclinD1
FoxA1
coactivator
nER
ERE-promoter
Cholesterol

Progesterone

Testosterone

Estradiol-17β

Gain carbonyl groups
Loss carbon tail

Gain hydroxyl
Loss carbonyl & methyl
Adrenal

- **Mineralocorticoids**
  - aldosterone
- **Glucocorticoids**
  - cortisol or corticosterone
- **Weak Androgens**
  - Dehydroepiandrosterone (DHEA)
- **All derived from progesterone**
Adrenal

- **Mineralocorticoids**
  - aldosterone
- **Glucocorticoids**
  - cortisol or corticosterone
- **Weak Androgens**
  - Dehydroepiandrosterone (DHEA)
- **All derived from progesterone**
- **Major role in stress response**
Adrenal Function
Steroidogenesis

- Pregnenolone
  - NADPH + O₂ → NADH
  - 17-hydroxyprogesterone
- Progesterone
  - NADPH + O₂ → 11β-hydroxylase
  - 11-deoxycortisol
- Corticosterone
  - NADPH + O₂ → 21-hydroxylase
  - Hydrocortisone
- Aldosterone
  - NADPH + O₂ × 2
  - Cortisol or Hydrocortisone
Lipid based Hormones

**Figure 5-10.** Gonadal Steroid Synthetic Pathway

- Cholesterol (27 carbons)
- Progesterone (21 carbons)
- Testosterone (19 carbons)
- Estradiol (18 carbons)

**Figure 5-11.** Structure of PGF\(_{2\alpha}\) and PGE\(_2\)

(The dashed lines represent bonds that extend into the plane of the page)

**Prostaglandin F\(_{2\alpha}\) (PGF\(_{2\alpha}\))**

**Prostaglandin E\(_2\) (PGE\(_2\))**

**Biochemical classifications include:**
- peptides
- glycoproteins
- steroids
- prostaglandins

**Steroid hormones have a common molecular nucleus called the cyclopentanoperhydrophenanthrene nucleus.** The molecule is composed of four rings designated A, B, C and D. Each carbon in the ring has a number, as shown in Figure 5-9.
Prostaglandins

- Eicosanoids
  - Along with thromboxanes and prostacyclins
- Lipid based hormones
  - 20 carbon atoms,
  - 5-carbon ring
- Derived from arachidonic acid
Prostaglandins

- First isolated from seminal fluid in 1935
  - by the Swedish physiologist Ulf von Euler
  - and independently by M.W. Goldblatt
- believed to be from prostate
  - Actually produced by the seminal vesicles
- Produced in virtually all tissues and organs
  - autocrine and paracrine mediators
  - act upon multiple cell types
    - platelets, endothelium, uterine and mast cells
- Non-Steroidal Anti-Inflammatory Drug (NSAID)
  - Target COX and other aspects of PGs pathways
Prostaglandins

Some prostaglandins may participate in memory and other brain functions.

Some prostaglandins sensitize nerve endings that transmit pain signals to the spinal cord and brain.

Two prostaglandins relax muscles in the lungs; another contracts them.

Two prostaglandins increase blood flow in the kidney.

Two prostaglandins protect the lining of the stomach.

Some prostaglandins dilate small blood vessels, which leads to the redness and feeling of heat associated with inflammation.

Two prostaglandins contract uterine muscles; another relaxes them.

The Omega-6 Pathway
- Linoleic acid (LA) 18:2n-6
  (Soy, corn, cottonseed, safflower oils)
- Gamma-linolenic acid (GLA) 18:3n-6
  (Evening primrose, borage, black currant oils)
- Dihomo-gamma-linolenic acid (DGLA) 20:3n-6
  (Liver & other organ meats)
- Arachidonic acid (AA) 20:4n-6
  (Butter, lard, animal fats, brain, organ meats, egg yolk, seaweed)
- Docosahexaenoic acid (DHA) 22:6n-3
  (Human milk, organic egg yolks, fish liver oils, fish eggs, liver, brain, other organ meats)

The Omega-3 Pathway
- Alpha-linolenic acid (LNA) 18:3n-3
  (Flax oil, grains, green vegetables)
- Octadecatetraenoic acid 18:4n-3
- Eicosapentaenoic acid (EPA) 20:5n-3
  (Fish liver oils, fish eggs)
- Docosapentaenoic acid 22:5n-3
- Docosahexaenoic acid (DHA) 22:6n-3

Needed for development & function of brain.
Prostaglandin blockers - NSAIDs
Unintended Consequences

- FDA
  - more than 22,000 dogs have gotten sick
  - some have died after taking non-steroidal anti-inflammatory drugs
    - including Metacam, Deramaxx, Previcox and Rimadyl.

http://www.dogsadversereactions.com/nsaid/nsaidspage.html
Diclofenac (NSAID) and Vultures

• Unintended consequences
  • Not all species the same
• Diclofenac
  • Non-Steroidal Anti-Inflammatory Drug (NSAID)
• cause gout and renal failure in vultures of the *Gyps* genus
• In India 3 *Gyps* species
  • lost over 99 percent of population in a decade
• Still sold in Africa
  • Used for cattle

http://envfor.nic.in/divisions/wildlife/vulture_plan.htm
Thyroid

- thyroxin ($T_4$) or triiodothyronine ($T_3$)
- iodine as a central component
- alters metabolism
- nuclear receptor in mitochondria
Thyroid

- Two lobes in the neck
- Two hormones
  - Thyroxine (T4)
  - Triiodothyronine (T3)
  - Require iodide for synthesis
- Major role in development and control of metabolism
Thyroid follicle