Developmental Progression & Susceptibility to Teratogens & Fetal Loss
Sex Determination in Mammals Is a Process

Male

- XY chromosome with Y genes
- Sry (TDF)
- medulla
- testis
- MRF (Mullerian Regression Factor; Sertoli Cells)
- Testosterone (Leydig Cells)
- immature male genitalia + external sex characteristics
- adult phenotype

Female

- XX chromosome
- Genetic, Gametic, Chromosomal Sex
- No Sry
- cortex
- ovary
- Gonadal Sex
- immature female genitalia + external sex characteristics
- Estradiol + Progesterone
- Behavioral & Metabolic Sex
- adult phenotype
SRY Is the Male Determination Factor

Page et al. Zfy/Zfx
Berta et al. SRY

HMG Transcription Factor
Binds to sry element of Sertoli cell MIS/MRF gene (stimulates) & of Leydig cell P450 aromatase gene (inhibits) [1993]

Cytogenetic localization of SRY region (after McLaren)

Y chromosome of man
P
q

Yp
Centromere
Sxr
60 kb
Hy
Zfy
35 kb

SRY

2a
Sry (14 kb DNA fragment)

2b
XX embryo 13 days

2c
XX-Sry male

Transfection of Sry sequence in the mouse successfully transforms an XX embryo to a male, demonstrating the Sry gene is necessary and sufficient to determine maleness in a mammal (Koopman et al., Nature 351:117-121, 1991.
Genetic Cascades Involved in Testis & Ovarian Differentiation


Intermediate mesoderm → WT-1 → Genital ridge → DAX-1 → Bipotential gonad → SRY → SRY (SOX9↑) → Ovary

SOX9

Gene(s)N

Leydig Cells Aromatase

Sertoli cells → TESTES

TESTES → Sertoli cells → SF-1, SRY → AMH gene → AMH receptor → Müllerian duct regression

Leydig cells → SF-1 → Genes encoding steroidogenic enzymes, SRY

Testosterone → 5α-reductase → DHT → Androgen receptor → Stabilization of the Wolffian ducts

Male differentiation of the urogenital sinus and external genitalia
Gonadal Differentiation in the Human

Intersexes (pseudohermaphrodites) may arise from lack of androgen receptors (tfm), adrenal overproduction of androgens (congenital adrenal hyperplasia), or other disruptions of these paths. (Modified from Paxton, *Endocrinology: Biological and Medical Perspectives*, W.C. Brown, Dubuque, IA, 1986.)
Differentiation of the External Genitalia

Prostate, scrotum, & penis require 5a-reductase conversion of testosterone to 5a-dihydrotestosterone for proper development; androgen levels needed are not normally available until puberty. (Modified from Paxton, Endocrinology: Biological and Medical Perspectives, W.C. Brown: Dubuque, IA, 1986.)

Term Placenta Villi Histology
Prostaglandin Metabolism & Childbirth Initiation

Challis et al. McGill

Major changes in PG metabolites in the uterus & placenta during gestation & before parturition.

Fetal | Placenta | Decidua | Myometrium

PG | PGDH | PGs | Prehn

Cortisol | DHEA-S

Mom

PGDH prostaglandin dehydrogenase

171) Pregnancy & Childbirth
http://www.rci.rutgers.edu/%7Euzwiak/HumanSexuality/HSSpringLect7.html
Notes: 1. Cortisol may decrease progesterone production by increasing 17α-hydroxylase activity thereby shifting progesterone toward androgen or estrogen products. (This is known to occur in sheep.)

2. Progesterone blocks smooth muscle contraction induced by oxytocin or prostaglandins, it decreases the number of estradiol receptors in myometrium, it causes norepinephrine to relax smooth muscles via α-adrenergic receptors, & it may block formation of gap junctions between uterine muscle cells.

3. Placental prolactin production may also rise to the point that it assists in stimulating fetal adrenal glucocorticoid production.

4. Relaxin from the corpus luteum and endometrial granulocytes relaxes pelvic ligaments and the myometrium after estrogen priming if it is released in the presence of growth hormone.

5. The stretching of the body of the uterus in late pregnancy also tends to promote parturition by putting pressure on catecholaminergic nerves that produce the norepinephrine associated with inhibition of myometrial contraction.
Functional Breast Anatomy

Mouse

Galactopore
Nipple

Secondary Tubules
Mammary Duct
Ampulla
Lactiferous Duct
Nipple
Areola
Alveoli
Interlobular Connective Tissue & Fat

Ruminant

Gland Cistern
Teat Cistern
Lactopore

Human


Hormonal Control of Breast Development

Immature, Atrophic Ducts
Milk Secration
PRL, Adrenal Steroids

Estrogens, GH, Adrenal Steroids
Ductal Growth
Estrogen, Progesterone, PRL, GH, Adrenal Steroids

Lobulo-Alveolar Growth

Microanatomy of the Breast Alveolus

Capillaries
Arteriole
Veinule
Mypeoepithelial Cells (Rasquet Cells)
Alveolar Cells
Alveolus
Secondary Duct
Milk

Milk Production by Alveolar Secretory Epithelial Cells

Milk contains: Water, lactose, fat globules, proteins (lactoferrin, nonspecific lipase, immunoglobulins, alpha lactalbumin, casein), calcium, phosphate, other minerals, & vitamins. PRL stimulates milk production by the secretory epithelial cells. Milk let-down occurs when suckling produces an afferent neural signal for oxytocin release. Oxytocin stimulates the myoepithelial cells to contract and force alveolar contents into the collecting ducts.

Mechanism of Progesterone Suppression of Lactation Prior to Birth

During pregnancy, progesterone (acting on the secretory epithelial cells of the matured breast) inhibits milk production by lactase syntheses, converting lactose from glucose and UDP-galactose.

Loss of placental progesterone disinhibits PRL actions on alveolar secretory cell production of alpha lactalbumin & subsequently allows lactose production to occur post-partum.

Nonlactating Breast Histology

![Nonlactating Breast Histology Image]

Lactating Breast Histology

![Lactating Breast Histology Image]
Initiation of Puberty & LH Changes during Adolescence

Peripubertal Changes in LH Secretion

Female LH across Puberty

- LH changes independently of the gonadal feedbacks of the ovary. Therefore, only changes in the hypothalamic-pituitary complex are needed to bring about the pubertal rise in gonadotropic hormones. (Modified from Grumbach, In Krieger & Hughes (ed) Neuroendocrinology, Sinauer: Sunderland, MA, 1990.)

Male LH Changes across Puberty

- LH pulses > 120 min apart
- LH pulse amplitude & frequency even during the day increase
- LH pulse frequency stabilizes at 1 per 90 - 120 min day & night
The GONADOSTAT Theory of Regulation of LH Control & Timing of Puberty

Maturation of negative feedback mechanism

Increased pituitary responsiveness to GnRH
Rising gonadotropin levels

Increased gonadal responsiveness to gonadotropins
Rising sex steroid levels

Sleep associated increase in LH secretion: episodic secretion of LH

Activation of positive feedback mechanism

Free Sex Steroids
Serum SHBG

(Modified from Grumbach et al., Hypothalamic-pituitary regulation of puberty: Evidence and concepts derived from clinical research, in Grumbach et al. (ed) Control of the Onset of Puberty, John Wiley & Sons, Inc.: New York, 1974.)

Campbell's Conjecture on the physiological mechanism behind the Gonadostat Theory of LH Control: SHBG controlling free sex steroid regulates hypothalamic responses.
Normal Thyroid & Goiter Anatomy

Normal Thyroid

Goiter

Thyroid cartilage
Thyroid
Trachea

Parathyroids (PTH; involved with calcium & bone metabolism)
Parafollicular C-cells (calcitonin, PTH & calcitriol)
Calcium in
Calcium & bone metabolism
Calcium in
Calcium & bone metabolism
Highly vascular
Basal lamina are avascular
Tight junctions
(with the basal lamina seal off the lumen from other serum proteins)
Colloid, Thyroglobulin (0.57 million MW)
Thyroid Hormone Synthesis by Thyroid Follicle Epithelial Cells

Biosynthesis of Thyronines at the Apical/Lumenal Membrane of Thyroid Follicular Cells

Thyroperoxidase -- Catalyzed Iodination of Desiodo-Thyroglobulin

Thyroperoxidase -- Induced Coupling forming Nascent Thyronines

Mechanism of Thyroid Hormone Action

Dimeric TG: glycoprotein, 669 kD; monomers = 2748 aa, 134 Y residues; 25-30 Ys can be iodinated, only 4 (positions 5, 2553, 2567, & 2746) normally used to produce T4 & T3.
Pancreatic Histology
Schematic of Pancreatic Islet

Pancreatic Function

Pancreas

Blood Vessels

α-cells
- glucagon

β-cells
- insulin

Pancreatic polypeptide

Islets of Langerhans

F-cells

S-cells
- somatostatin

Islets of Langerhans Histology
Hormones from the Pancreatic Islets

**PEPTIDES OF THE PANCREATIC ISLETS**

**Human Proinsulin**
(Insulin = A + B Chains)

**Human Glucagon**

**Human Somatostatin**

**Human Pancreatic Polypeptide**

**Notes on Pancreatic Hormones**

**Insulin:**
Produced by beta cells (60% of islet cells); released from preproinsulin (proinsulin 30-53), leaving the A & B chains linked by disulfide bonds. Acts primarily on the liver and skeletal muscle to increase glucose uptake & decrease gluconeogenesis (glycogen, fat, protein). Insulin secretion is stimulated primarily by glucose, also by glucagon, peptide YY, and glucagon-like polypeptide 1. It is antagonized by epinephrine & somatostatin.

**Glucagon:**
Produced by alpha cells (25% of islet cells); cleaved from preproglucagon. Acts primarily on the liver to counter the actions of insulin (glycogenolysis, fat, protein). Glucagon secretion is stimulated primarily by glucose, also by FFAs, ACTH, and peptide YY. It is antagonized by insulin, peptide YY, and somatostatin.

**Somatostatin:**
Produced by delta cells (10% of islet cells); released from a 116 amino acid precursor, preprosomatostatin, via a 29 amino acid somatostatin, an active hormone that inhibits both insulin & glucagon release, decreases the absorption of all nutrients from the gut.

**Pancreatic Polypeptide:**
Produced by F cells in the islets of the head of the pancreas (from a 35 amino acid precursor, prepropancreatic polypeptide). It acts by stimulating gastric acid secretion, may be a satiety factor like structurally related neuroendocrine hormones NPY & PYY. Released after a protein meal.
Glucose Homeostasis

Hormonal Control of Glucose Homeostasis

<table>
<thead>
<tr>
<th>Hormone</th>
<th>Insulin</th>
<th>Glucagon</th>
<th>Epinephrine</th>
<th>Cortisol</th>
</tr>
</thead>
<tbody>
<tr>
<td>Function</td>
<td>Satisfied</td>
<td>Buffer</td>
<td>Hungry</td>
<td>Emergency</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Glucose</th>
<th>Uptake into cells</th>
<th>Glycolysis</th>
<th>Gluconeogenesis (L)</th>
<th>Glycogen</th>
<th>Synthesis / lysis</th>
<th>Fat Synthesis / lysis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glucose</td>
<td>+ M, F</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>F</td>
</tr>
</tbody>
</table>

Does not act on skeletal muscle.

Diabetes

(production of copious urine)

"Disease that mimics starvation or starvation in the midst of plenty."

Type I
- insulin dependent

Type II
- insulin independent
- insulin resistant
- some types = overprod. of GH or glucagon

Blood Glucose

Glucagon

GHRP

NPY

AgRP

Leptin

CART

POMC

Cortisol

GHR

PYY

Insulin

Insulin-like growth factors

Epinephrine

Satiety

Stress > CRH > ACTH > Cortisol

Controls on Food Intake

Hypothalamus

ARN & PVN

\( \alpha \text{MSH} \rightarrow \text{POMC} \)

\( + \text{CRH} \rightarrow \text{CART} \)

\( + \text{NPY} \rightarrow \text{AGRP} \)

\( + \text{Leptin} \rightarrow \text{ARN} \)

\( + \text{Leptin} \rightarrow \text{Body Fat} \)

Energy Expenditure

Food Intake

NPY = neuropeptide Y
CART = cocaine & amphetamine - related transcript
AGRP = agouti - gene related peptide,
        endogenous \( \alpha \text{MSH} \) antagonist
The Juxtaglomerular Apparatus: Source of Renin
Angiotensin Metabolism

Liver

ANGIOTENSINOGEN (Renin Substrate)

ANGIOTENSIN I

ANGIOTENSIN II

CONVERTING ENZYME

ANGIOTENSINASES

Smaller Fragments

Juxtaglomerular Apparatus

Adrenal Glomerulosa, Vascular Smooth Muscles
Kidney - Distal Tubule
1) Cells sensitive to the axn of aldosterone (mineralocorticoid involved in controlling [Na+] blood)
   contain MC receptor
2) Observation: Cells respond to glucocorticoids very well (reason is that cortisol + cortisone bind better to MC receptor than aldosterone does)

How does the body distinguish glucocorticoids + aldosterone to mediate MC action specifically?

Cortisol

No longer binds to aldosterone receptor

II position is reduced

MC

Multitissue Signalling Leading to Blood Pressure Elevation

- Adrenal Glomerulosa
  - Aldosterone
    - Kallikrein
      - Prostaglandins
    - Kininogen → Bradykinin

- Kidney Tubules
  - Kallikrein
    - Prostaglandins
    - Renin

- Kidney
  - Prorenin
    - Angiotensin I
      - Angiotensin II

- JG Cells
  - Prorenin
    - Angiotensin I

- Plasma Renin Substrate
  - Angiotensin II

- Systemic Arteries
  - Vasoconstriction
    - Increased Blood Pressure

- Inactive Fragments
Aldosterone Response Effectors in the Epithelium of the Kidney Distal Tubule
Cholecalciferol Metabolism

7-Dehydrocholesterol → UV (Skin) → 7,25-(OH)2-D3

25-Hydroxylase (Liver)

Vitamin D3 (Cholecalciferol) → PTH

24-Hydroxylase (Kidney)

25-OH-D3 → lα-Hydroxylase (Kidney) → lα,25-(OH)2-D3 → Biologically potent Calcitriol

24,25-(OH)2-D3 → 24,25,26-(OH)3-D3
Cellular Anatomy of Bone

Bone Cell Associations


Calcium Movement Across Bone Cells