Hormonal regulation of gonad function overview

• Role of hormones in reproductive functions
  – production and maintenance of mature gametes
  – optimization of the circumstances of impregnation
  – support of pregnancy, insuring the growth of the fetus, parturition, lactation

• Comparison of male and female gonad function
  – basic differences
  – theoretical similarities and functional analogies
  – sexual differentiation (positive and negative determination), ratio of determining hormones
Hormonal control of sexual function
the sexual determination

• genetic sex
  – determined by the chromosomes
• gonadal sex
  – the presence of ovaries or testes
• phenotypic sex
  – the presence of internal and external genitalia
Hormonal regulation of sexual function
release of pituitary hormones

- The regulating hormone is **GnRH**
  - pulsing type secretion
    - light/dark cycle
    - stress
    - odor (pheromone)
  - receptor aggregation
  - facilitate both FSH and LH secretion
  - effects
    - \( \text{Ca}^{2+} \) - calmodulin
    - \( \text{PLC} \rightarrow \text{IP}_3 \) & PKC
    - cAMP, cGMP?
Hormonal regulation of male sexual function
hormones involved in the feed-back regulation

- **GnRH**
- **LH →** Leydig cells (cAMP)
  - testosterone
  - estrogens (lesser amount)
- **FSH →** Sertoli cells (cAMP)
  - spermatogenesis
  - inhibin
- **Inhibin** \([\alpha\beta_A \text{ or } \alpha\beta_B]\) (activin \([2\beta_A \text{ or } \beta_A\beta_B]\))
  - inhibition of FSH secretion
- **testosterone, estrogens**
  - mainly inhibition of GnRH secretion
  - inhibition of FSH és LH secretion
Hormonal regulation of female sexual function

hormones involved in the feed-back regulation

- **GnRH**
- **LH** → theca interna cells
  - androgen secretion
  - luteinization
- **LH** → granulosa cells
  - estrogen! and progesterone
  - luteinization
- **FSH** → granulosa cells
  - estrogen secretion
  - inhibin
- **Inhibin**
  - inhibition of FSH secretion?
- **estrogens**
  - inhibition of FSH and LH secretion
  - increase of FSH and LH secretion
Hormonal control of sexual function
age-dependent changes in reproductive functions

• **before puberty**
  – two period of GnRH secretion
  – low hormone concentrations (FSH dominance)
    • negative feed-back is hypersensitive
    • CNS inhibition

• **puberty**
  – start is genetically (?) determined
  – CNS factors, „maturation” of the hypothalamus-pituitary-gonad chain
    • appearance of pulsatile GnRH secretion
    • LH dominance (in boys, too)
    • responsiveness of gonadal cells
Hormonal control of sexual function
age-dependent changes in reproductive functions

• **disappearance of gonadal responsiveness**
  – in males it is gradual and never complete
  – in females transition is sharper & complete (**menopause**)
    • vegetative symptoms (vascular reactions, heat waves, emotionally labile, coronary diseases are more frequent, osteoporosis)
    • increased GnRH level with FSH dominance
Hormonal regulation of male sexual function
the effects of testosterone

- **Production, transport**
  - Leydig (theca) cells
  - adrenal cortex
    - here dihydroepiandrostendione is the major androgen
  - only the free hormone is effective (cca. 2%)
    - testosterone binding globulin
    - albumin (in micro-circulation the affinity is decreased, free hormone concentration increases; 50%)

- **Effects at the cellular level**
  - in most tissues it is converted to DHT
    - greater affinity for the androgen receptor
    - the DHT/receptor complex is more effective
  - might be converted to estrogen (brain, adipose tissue)
    - libido ?
    - sexual behavior ?
    - feed-back regulation ?
Hormonal regulation of male sexual function
effects of testosterone

• **Anabolic effects**
  – increased protein synthesis (GH)
  – decreased protein breakdown (GH)
  – fuse of epiphyseal plates
  – $\text{Na}^+$, $\text{K}^+$, $\text{Ca}^{2+}$, $\text{H}_2\text{O}$, $\text{SO}_4^{2-}$ and $\text{PO}_4^{3-}$ retention

• **Secondary male sex characteristics**
  – size of internal and external genitalia
  – fructose secretion of seminal vesicle
  – psychic effects (aggressiveness)
  – deeper voice
  – generally more body hair—but scalp hair is less
  – form of pubic hair
  – body configuration (fat depots)
  – size of the muscles
  – secretion of sebaceous glands

• **Spermiogenesis**
  – blood/testis barrier, temperature
  – both FSH and testosterone act via the Sertoli cells
  – paracrine communication between Sertoli cells and germ cells

• **Inhibition of pituitary**
Hormonal regulation of male sexual function
hormonal control of spermatogenesis

• **Sertoli cells** (FSH, T)
  – blood/testis barrier, defends
    • the gametes
    • the body from auto-immune effects of testis derived products
  – regulation of sperm development
    • IGF I, stem cell factor
    • \( \text{GnRH} \)
  – inhibin production

• **Leydig cells** (LH)
  – testosterone secretion
    • very large concentration (100x)
    • paradox effect of external T
Hormonal control of female sexual function
effects of estrogens

• **Genitalia**
  – growth of follicle $\uparrow$
  – motility of uterine tubes $\uparrow$
  – secretion of tubal glands $\uparrow$
  – proliferative phase of endometrium
  – more elastic mucus by cervix
  – amount, activity, excitability of uterine muscle $\uparrow$
  – oxytocin sensitivity (depolarization, $\text{Ca}^{2+}$ binding, prostaglandin) $\uparrow$
  – vaginal cornification

• **Secondary sex characteristics**
  – enlargement of genitalia
  – body conformation, fat distribution
  – voice
  – body hair distribution (androgens from adrenal cortex)

• **Behavioral effects**
  – libido (hypothalamic neurons)
  – estrus behavior in animals

• **Other effect**
  – anabolic, closure of epiphyseal plates, water- and salt retention (ADH?)
  – plasma cholesterol level $\downarrow$, VLDL$\uparrow$
  – production clotting factors of in liver $\downarrow$
  – bone resorption $\downarrow$
  – angiotensinogen secretion $\uparrow$

• **Breasts**
  – enlargement of globular ducts
  – pigmentation of areolas $\uparrow$
  – adipose tissue$\uparrow$
Hormonal control of female sexual function
effects of progesterone

• **Genitalia**
  – motility of uterine tubes ↑
  – secretion of tubal glands ↑
  – secretory phase of endometrium
  – thick, non-elastic, non-ferning mucus of cervix
  – activity and excitability of uterine muscle ↓
  – oxytocin sensitivity ↓
    • ? number of E receptors ↓
    • ? transformation of estrogen ↑
    • ? hyperpolarization
    • ? prostaglandin synthesis ↓

• **Breasts**
  – development of alveoli

• **Other effects**
  – thermogenesis
  – ventilation ↑
    • respiratory center CO₂ sensitivity
  – potassium excretion ↓
    • block of aldosterone effect
  – appetite ↑
# Hormonal control of female sexual function

## Interaction of sexual steroids and gonadotroph hormones

<table>
<thead>
<tr>
<th>Hormone</th>
<th>Granulosa cell</th>
<th>Theca interna cell</th>
<th>Luteal cell</th>
<th>Pituitary</th>
</tr>
</thead>
<tbody>
<tr>
<td>GnRH</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>FSH &amp; LH secretion $\uparrow$</td>
</tr>
</tbody>
</table>
| FSH | LH receptor density $\uparrow$  
  E secretion $\uparrow$  
  Inhibin secretion $\uparrow$ | - | - | - |
| LH | E secretion $\uparrow$ (low)  
  E secretion $\downarrow$ (high)  
  P termelés $\uparrow$  
  luteinizáció | A secretion $\uparrow$  
  luteinisation | P secretion $\uparrow$ | - |
| E | Proliferation facilitation of FSH effect  
  LH receptors $\uparrow$ | Proliferation  
  A secretion $\uparrow$ | - | Small concentration  
  LH & FSH $\downarrow$  
  Large concentration  
  LH & FSH $\uparrow$ |
| P | - | - | P receptor $\uparrow$  
  P secretion $\uparrow$ | E absence  
  LH secretion $\downarrow$  
  E presence  
  LH secretion $\uparrow$ |
| inhibin | - | - | - | FSH secretion $\downarrow$ (?) |

E – estrogen, P – progesterone, A - androgen
Hormonal control of female sexual function
interaction of theca and granulosa cells

Theca cell

- LH
- LHR
- cAMP
- cholesterol
- progesteron
- androstenedione
- testosterone

Granulosa cell

- LH
- LHR
- FSH
- FSHR
- cAMP
- cholesterol
- progesteron
- androstenedione
- testosterone
- estrogen

Basal lamina
- capillary
- antrum
Hormonal control of female sexual function

hormonal changes during the menstrual cycle

• **Division of cycle** (length 21-35, average 28 days, start is the start of menstruation)
  – **follicular** phase
    • menstrual phase
    • proliferative (preovulatory) phase (length changes)
  – **ovulation** phase (1-3 days)
  – **secretory** (luteal, postovulatory) phase (length constant; 13-14 days)

• **Questions**
  – why only a single follicle reaches the state of ovulation?
  – what induces ovulation?
  – why does corpus luteum regress?
Hormonal control of female sexual function

- **Formation of primery follicles**
  - paracrine effect between the oocyte and the granulosa cells

- **Follicular development**
  - low initialestrogen and progesterone levels
    - FSH secretion
  - **Effect of FSH**
    - granulosa cell activation
    - estrogen synthesis
    - inhibin production
  - **Effect of estrogen**
    - proliferation
    - facilitation of FSH effect (positive feed-back)
Hormonal control of female sexual function

Oogenesis

Selection of dominant follicle

• The one with the greatest FSH sensitivity, since
  – estrogens and inhibin inhibit FSH secretion
  – atrophy of non-dominant follicles

• Effect of LH
  – androgen secretion increases in theca cells
  – progesterone secretion increases in granulosa cells (androgen, thus FSH independent) estrogen synthesis
Hormonal control of female sexual function

Oogenesis

Ovulation

• continued, increased estrogen secretion of the dominant follicle
  – GnRH/LH/FSH surge (positive feed-back)

• Effects of LH
  – first meiotic division completed
  – luteinisation starts
  – progesterone secretion of luteal granulosa cells

• Effects of FSH
  – LH receptor desity ↑
  – proteolytic activity ↑ → ovulation
  – prostaglandin synthesis ↑ → ovulation

• estrogen concentration ↓?
  – LH and FSH secretion ↓
Hormonal control of female sexual function

**Corpus luteum** (formation ?)

- Effect of LH on granulosa cells
  (large density of receptors ← FSH effect)
  - luteinisation
  - progesterone & estrogen secretion ↑

- effect of progesterone on luteal cell
  - progesterone secretion ↑ (autocrine positive feed-back)

- progesterone, inhibin, estrogens
  - pituitary hormone secretion ↓

- LH level ↓
  - hormone secretion of corpus luteum ↓

- progesterone & estrogen level ↓
  - pituitary inhibition is removed
  - FSH secretion ↑ → new cycle
Hormonal control of female sexual function
parturition

- Appearance of placenta
  - fetal digestive track and nutrient store
  - fetal lung serving the gas exchange
  - fetal kidney for removing waste products
  - endocrine organ, which influences both maternal and fetal metabolism

- Placental hormones (importance from the 8. week)
  - human chorion gonadotrop hormone (hCG)
  - progesterone
  - estrogens
  - human chorion somatomammotrop hormone (hCS) (or placenta-lactogen hormone; hPL)
  - other hormones
Hormonal control of female sexual function
endocrine regulation of parturition

• what determines the start?
  – the role of several hormones
    (cortisol, estrogens, progesterone, relaxin, oxytocin, prostaglandins, catecholamins)
    have been shown, but…
  – **signal from the fetus**
    • in the fetal adrenal gland
      androgen → glucocorticoid
  – decrease in **progesterone** level
    • is present, but its role?
  – increase in **prostaglandin** level
  – increase in **oxytocin** level
    • result and not reason
Hormonal control of female sexual function
endocrine regulation of lactation

- Regulation of **milk production**
  - proper development of breasts
  - milk secretion
  - milk ejection

- development of **breasts**
  - prolactin
  - estrogens, progesterone
  - IGF I & insulin (? GH és hPL)

- Other effects of **prolactin**
  - during lactation it inhibits reproductive functions (GnRH FSH & LH)
  - in large concentration spermatogenesis & gonadal hormone levels decrease
  - in low concentration maintenance of progesterone secretion
  - behavioral effects (decreased libido, parental behavior)

- regulation of **milk secretion**
  - prolactin
  - insulin & glucocorticoids
  - the large estrogen & progesterone levels inhibit during pregnancy

- regulation of **milk ejection**
  - effects of oxytocin on smooth muscle cells in ducts (neuro-hormonal reflex)
Hormonal control of female sexual function
endocrine regulation of lactation

• regulation of **prolactin** secretion
  – hypothalamic inhibition ($D_2$ receptor $\rightarrow$ cAMP)
  – ? PRH (TRH, VIP, ?)
  – prolactin short loop inhibition
  – facilitating effect of estrogens
    (prolactin-gene transcription)
  – mechano-receptors in breasts

• regulation of **oxytocin** secretion
  – stimulation of mechano-receptors
    in breasts & genitalia (neuro-
    hormonal reflex of milk ejection)
  – emotional effects