Reproductive Cyclicity

- Male repro: a simpler way of control
- Menstrual cycles: ovary / uterine anatomy and cell types, follicular phase, ovulation, luteal phase, cyclicity
- Race events: removal of P4 negative feedback, follicular recruitment or FSH inducing its own receptors, pulsatile LH secretion - a richer communication language, preovulatory E2 triggering the LH preovulatory surge
- GnRH network as basic model for cyclicity
- Contraception, pathology

Introduction

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
Male repro is not a cyclic event

- Reproduction
- Menstrual cycle
- Race events
- GnRH system
- Contraception
- Pathology

In male E2 do not induce a preovulatory LH surge, but POA electrical stimulation does
Male repro is not a cyclic event

- Reproduction
  - Menstrual cycle
  - Race events
  - GnRH system
  - Contraception
  - Pathology

In male E2 do not induce a preovulatory LH surge, but POA electrical stimulation does.

Male repro is not a cyclic event

- Reproduction
  - Menstrual cycle
  - Race events
  - GnRH system
  - Contraception
  - Pathology

The formation of male mammalian germ cells.

Each primary spermatogonium ultimately gives rise to 64 sperm cells. Cytokinesis is incomplete in all but the earliest spermatogonial divisions, resulting in expanding clones of germ cells that remain joined by intercellular bridges. Maturing spermatids are closely associated with and enveloped by the Sertoli cells.
Male repro is not a cyclic event

- Reproduction
  - Menstrual cycle
  - Race events
  - GnRH system
  - Contraception
  - Pathology

Schematic structure of the androgen receptor and of the mechanism of androgen action

In male E2 do not induce a preovulatory LH surge, but POA electrical stimulation does
Male repro is not a cyclic event

- Reproduction
  - Menstrual cycle
  - Race events
  - GnRH system
  - Contraception
  - Pathology

<table>
<thead>
<tr>
<th>Hypergonadism</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary</td>
<td></td>
</tr>
<tr>
<td>Leydig cell deficiency (Leydig cell agenesis)</td>
<td></td>
</tr>
<tr>
<td>Adult Leydig cell failure (male climacteric phase)</td>
<td></td>
</tr>
<tr>
<td>Seminiferous cell aplasia (Sertoli-only syndrome)</td>
<td></td>
</tr>
<tr>
<td>Secondary</td>
<td></td>
</tr>
<tr>
<td>Gonadotropin deficiency (hypogonadotropic hypogonadism)</td>
<td></td>
</tr>
<tr>
<td>Hypothalamic hypogonadism (defect in GnRH secretion)</td>
<td></td>
</tr>
</tbody>
</table>

Hypergonadism
- Primary (steroid-secreting testicular tumors)
- Virologic (androgen-secreting) Leydig (interstitial) cell tumors (macrogametosis in the prepubertal male)
- Familial (androgen-secreting) Leydig (interstitial) cell tumors
- Secondary
- Hypothalamic origin (enhanced GnRH secretion)
- Pituitary origin (hyponadotropic hypogonadism)

- Syndrome of androgen resistance
  - Testicular feminizing syndrome (absence or defect of androgen receptors)
  - Syndrome of 5α-reductase deficiency (failure to convert testosterone to DHT)

- Gynecomastia (breast enlargement)

Mutation in the androgen binding domain prevents androgen binding to its receptor
Mutation in Zn finger domain of the receptor prevents androgen-receptor complex binding to DNA
LH release is pulsatile

- Reproduction
  - Menstrual cycle
  - Race events
  - GnRH system
  - Contraception
  - Pathology

In both males and females, FSH release from the AP is controlled by inhibins and activins.

The activins and inhibins are disulfide bonded dimers of the products of three separate genes. Activins are comprised of two beta subunits.

Inhibin B is the major circulating form in the human male, and is comprised of an alpha subunit and the beta B subunit.

In both males and females, LH release from the AP is pulsatile and driven by GnRH.

Pulsatile LH is driven by GnRH

- Reproduction
- Menstrual cycle
- Race events
- GnRH system
- Contraception
- Pathology

In both males and females LH release from the AP is pulsatile and driven by GnRH

GnRH increases Gonadotropins

- Reproduction
- Menstrual cycle
- Race events
- GnRH system
- Contraception
- Pathology

GnRH cell bodies located in the POA have axon terminals in the hypothalamic ME
Pulsatile vs continuous GnRH

- Reproduction
- Menstrual cycle
- Race events
- GnRH system
- Contraception
- Pathology

Continuous GnRH release down-regulates GnRH receptors at its AP target site

E2 / P4 feedback on GnRH / LH

- Reproduction
- Menstrual cycle
- Race events
- GnRH system
- Contraception
- Pathology

E2 and P4 affect GnRH pulse amplitude and frequency and therefore LH / FSH

E2 on LH pulse amplitude

P4 on LH pulse frequency
Hormones in Menstrual Cycle

- Reproduction
- Menstrual cycle
- Race events
- GnRH system
- Contraception
- Pathology

Menstrual hormonal profile is driven by GnRH as well as AP sensitivity changes.
Hormones in Menstrual Cycle

- Reproduction
- Menstrual cycle
- Race events
- GnRH system
- Contraception
- Pathology

Menstrual hormonal profile is driven by GnRH as well as AP sensitivity changes.

Repro cyclicity is GnRH driven

- Reproduction
- Menstrual cycle
- Race events
- GnRH system
- Contraception
- Pathology

The menstrual hormonal profile can be reproduce by exogenous GnRH pulses.
Repro cyclicity is GnRH driven

- Reproduction
- Menstrual cycle
- Race events
- GnRH system
- Contraception
- Pathology

GnRH pulses


The menstrual hormonal profile can be reproduce by exogenous GnRH pulses

Cellular effects of LH and FSH

- Reproduction
- Menstrual cycle
- Race events
- GnRH system
- Contraception
- Pathology

FSH increase drives early ovarian follicular development in the menstrual cycle
The Follicle, the Ovulation site

- Reproduction
- Menstrual cycle
- Race events
- GnRH system
- Contraception
- Pathology

The ovarian follicle contains the oocyte and granulosa cells but not theca cells.

The Follicle, the Ovulation site

- Reproduction
- Menstrual cycle
- Race events
- GnRH system
- Contraception
- Pathology

If you can fully explain ovarian cycles you understand puberty, cyclicity and aging.
The Follicle, the Ovulation site

- Reproduction
- Menstrual cycle
- Race events
- GnRH system
- Contraception
- Pathology

If you can fully explain ovarian cycles you understand puberty, cyclicity and aging.

The ability to maintain a large rate of follicular growth is basic for reproduction.
The Menstrual Cycle: the ovary

- Reproduction
  - Menstrual cycle
  - Race events
  - GnRH system
  - Contraception
  - Pathology

LH and FSH drive pre-antral follicles to be Graffian follicles and then corpora lutea

The Menstrual Cycle: the uterus

- Reproduction
  - Menstrual cycle
  - Race events
  - GnRH system
  - Contraception
  - Pathology

Ovarian follicular and luteal phase match uterine proliferative and secretory phase
The Menstrual Cycle: E2 release

Theca & granulosa cell cooperation in estrogen synthesis.

The Menstrual Cycle: E2 release

Theca & granulosa cell cooperation in estrogen synthesis.

The mechanism of action of gonadotropins involve a 7tm domain receptor and AC

The two cell gonadotropin theory

Theca cell has LHr and makes androgens, granulosa cell has FSHr and produces E2
The Menstrual Cycle: E2 release

- **Reproduction**
  - The two cell gonadotropin theory
- **Menstrual cycle**
- **Race events**
- **GnRH system**
- **Contraception**
- **Pathology**

Proliferation of granulosa cells during follicular development.

Initially, granulosa cells are few and have receptors only for FSH (FR) on their surfaces. In response to continued stimulation with both FSH and estradiol, granulosa cells proliferate and by the midfollicular phase LH receptors (LR) begin to appear. By late in the follicular phase a large number of granulosa cells are present and they are responsive to both LH and FSH. They are now competent to secrete sufficient estradiol to trigger the ovulatory surge of gonadotropins.

E2 production requires LH (increases SCCE) and FSH (increases aromatase)
The Menstrual Cycle: E2 release

- Reproduction
- Menstrual cycle
- Race events
- GnRH system
- Contraception
- Pathology

The Menstrual Cycle: LH release

- Reproduction
- Menstrual cycle
- Race events
- GnRH system
- Contraception
- Pathology

"If much noise the monkey covers its ears, if too little it cups them to amplify signal"
The Menstrual Cycle: LH release

- Reproduction
  - Pulsatile LH release drives preovulatory E2 release
  - Pulsatile LH release due to pulsatile GnRH release. The pulse generator and how to assess its existence
  - Pulse frequency/amplitude as efficient signals for the neural reproductive output
  - Hypothalamic pulsar is modulated by steroids. Differential effects of cyclic E2/P4 on pulse parameters
- Menstrual cycle
  - Hypothalamic pulsar modulated by neurotransmitters (+ and - array). “Lack” of E2 receptors in GnRH neurons
- Race events
  - POA - E2 receptors & phasic GnRH release by a decreased -FB (luteolysis, 2nd derivative, “sponge” receptor, data in monkey)
- GnRH system
  - Mass follicular growth & preovulatory E2, origin of 2nd derivative input to a “sponge” E2 receptor
- Contraception
  - Relationship among preovulatory E2 secretion, hypothalamic transmitters and release of GnRH. The (+) and (-) input array
- Pathology
  - The order of these events replicates those that will be involved in the race, later

E2 drives the preovulatory surge of LH. An LH surge is obligatory for reproduction to occur.

Events driving a preovulatory surge of LH are the same in humans and other animals.
The Menstrual Cycle: ovulation

- Reproduction
  - Menstrual cycle
- Race events
- GnRH system
- Contraception
- Pathology

Laparoscopic view at the time of ovulation during the menstrual cycle, in humans

Ovulation in a rabbit. Follicular fluid, granulosa cells, some blood, and cellular debris continue to ooze out of the follicle even after the egg mass has been extruded.
The Menstrual Cycle: summary

- Reproduction
  - Menstrual cycle
    - Players involved in the cyclic events occurring during the menstrual cycle
      - menses, estrus, LH surge, repetitive events
      - differences / similarities menstrual / estrous cycles
      - main events a drop in P4, increase in E2, LH surge
      - follicular vs luteal, E2 vs P4, ovarian vs uterine phases
      - luteolysis, LH surge, ovulation as cyclic events
      - GnRH as trigger of LH surge (mouse without GnRH)
      - E2 as trigger of GnRH release (phasic vs tonic E2 r)
      - a race: FSH, follicular wave, atresia, dominant follic.
      - FSH stimulates FSH/LH receptor formation and E2
      - E2 stimulates formation of ovarian FSH receptors
      - increase follicle growth in presence of low FSH/LH

- Race events
- GnRH system
- Contraception
- Pathology

The menstrual cycle can be seen from different viewpoints, but is the same cycle.
The Menstrual Cycle: summary

- Reproduction
  - Menstrual cycle
- Race events
- GnRH system
- Contraception
- Pathology

The menstrual cycle can be seen from different viewpoints, but is the same cycle.

a view from ovary and uterus
The Menstrual Cycle: summary

- Reproduction
- Menstrual cycle
- Race events
- GnRH system
- Contraception
- Pathology

Endometrial changes during a typical menstrual cycle. Simultaneous events in the ovary are also indicated. The endometrium thickens during the follicular phase, uterine glands elongate, and spiral arteries grow to supply the thickened endometrium.

During the early luteal phase there is further thickening of the endometrium, marked growth of the coiled arteries, and increased complexity of the uterine glands. As the corpus luteum wanes, endometrial thickness is reduced by loss of ground substance. Increased coiling of spiral arteries causes ischemia and finally sloughing of endometrium. The upper portion of the figure shows the corresponding events in the ovary.

The menstrual cycle can be seen from different viewpoints, but is the same cycle.
The Menstrual Cycle: summary

- Reproduction
- Menstrual cycle
- Race events
- GnRH system
- Contraception
- Pathology

Hormonal Control of the Follicular Phase

Hypothalamus

Anterior pituitary

GnRH

(+)

LH

FSH

(+)

Ovarian follicle

Theca cells

Granulosa cells

Testosterone

(+)

Androstenedione

P4

Circulation

E2

The menstrual cycle can be seen from different viewpoints, but is the same cycle

The Menstrual Cycle “as a race”

- Reproduction
- Menstrual cycle
- Race events
- GnRH system
- Contraception
- Pathology

removal of P4 negative Fb on FSH / LH (by luteolysis) as starting point of a cyclic race to fun or problems

increase tonic FSH / LH release (amplitude, frequency), as initial response of the neuroendocrine system

increase E2 intraovarian & hypothalamic effects, as a little engine going beserk to fulfill a “sponge” goal

E2 triggers the preovulatory surge of LH

GnRH neuron “practically” lacks E2 receptors, a cause we have to care about neurotransmitters (+,- input array)

synaptic-like features among GnRH neurons and the concepts of network and subnetworks (like the heart?)

coeexistence of GnRH and galanine in a subnetwork

NPY and E2 role as an example of GnRH input array

Kisspeptine, a possible new “runner” in the race

ßEND and GnRH disinhibition as mechanism for the preovulatory surge of LH, an ovulation obligatory event

All previous different viewpoints can be merged into a single “racing” events
The Neuroendocrine Control

- Reproduction
- Menstrual cycle
- Race events
  - GnRH system
- Contraception
- Pathology

Changes in GnRH pulse amplitude and frequency link the brain and repro effects
The Neuroendocrine Control

- Reproduction
- Menstrual cycle
- Race events
- GnRH system
- Contraception
- Pathology

Based on what you have seen so far, how can you explain aging and menopause

Some Contraceptive Paradigms

- Reproduction
- Menstrual cycle
- Race events
- GnRH system
- Contraception
- Pathology

You should be able to explain each one of these methods, or you may pay later ...
Some Contraceptive Paradigms

- Reproduction
- Menstrual cycle
- Race events
- GnRH system
- Contraception
- Pathology

You should be able to explain each one of these methods, ....... or you may pay later

Polycystic Ovarian Syndrome

- Reproduction
- Menstrual cycle
- Race events
- GnRH system
- Contraception
- Pathology

Common endocrine disease in women at your age, linked to a metabolic syndrome
Hypothalamic Amenorrhea

- Reproduction
- Menstrual cycle
- Race events
- GnRH system
- Contraception
- Pathology

Naloxone, opiate antagonist, prevents action of β-endorphin, a GnRH inhibitory input

Hypogonadotrophic Hypogonadism

- Reproduction
- Menstrual cycle
- Race events
- GnRH system
- Contraception
- Pathology

Ovulation induction in women using physiological frequency - exogenous GnRH