Reproduction

The goal of these lectures is to discuss basic physiology associated with the control of reproduction (from sexual differentiation to adult reproductive function).

The sections for this lecture are:

- Introduction and GnRH
- Puberty in females
- The ovary and the menstrual cycle
- Neuroendocrine control of the ovary
- Contraceptives and abortifacients
- Reproductive pathologies

Life is a series of chemical reactions occurring in compartmentalized environments.
The main purpose of life is to keep itself alive.

Physiology, the study of how life works, is based on the simultaneous occurrence of the following three concepts:
- levels of organization
- structure / function relationship
- homeostatic regulation

Introduction
Introduction

"ability to carry a fetus to terminus" and "temporal maturational process" as definitions of female puberty and in their relationship with the black boxes of the control system

the uterus starts responding to ovarian steroids during the infantile period, well before the onset of puberty (bioassays and binding assays, ideopathic precocious puberty)

the ovary presents autonomous follicular growth during the neonatal stage, and begin to respond to gonadotrophins during the infantile period (in vivo and in vitro steroid output)

the anterior pituitary of neonatal animals responds as an adult pituitary when transplanted to adult hypophysectomized rats (pituitary transplants of neonatal pups to their mother)

the CNS negative and positive feedbacks of E2 on LH and FSH are not present in infantile period, but they become progressively active during the prepubertal period (- and + FB approaches)

while dynamic AP-ovarian relationship are operative before puberty, the onset of puberty results from the elaboration in sufficient amounts of female hormones puberty is probably brought about by removal of hypothalamic and/or extra-hypothalamic inhibitory inputs to gonadotropin secretion, resetting of the gonadostat

puberty is brought about by stimulation of facilitatory influences on gonadotropin secretion (increase in central drive), rather than by a resetting of the gonadostat

puberty onset can be considered as the climax of a cascade of developmental changes occurring harmoniously during reproductive immaturity

the cascade of events preceding puberty is elicited by hypothalamic "timekeeping" genes (homeotic genes), which activate a central drive neurogenic mechanism

Introduction

GnRH migration from olfactory placode
pulsatility intrinsic role of GnRH neuron
GnRH differentiates AP - gonadotrophs
fetal FSH / LH receptor uncoupled to AC
early neurogenic link AHA- POA & ovary
lack of fetal E2 - Fb contributes to early growth of primordial follicles
stimulatory effect of E2 on ovulatory LH surge occurs years after birth
prepubertal Prl / GH increase ability of FSH to induce LH receptors
stimulatory VIP (E2,P4), adrenergic nerves & Epi acting by β-receptors (P4) are fully established during the prepubertal period

synaptic - like contacts among GnRH neurons suggests existence of an GnRH network (GT-1 cells, PDA, pulses, anatomy)
electrical activity linked to each LH and GnRH pulse (MUA in GT-1 cells, and in monkey / ovine in vivo)
GnRH pulses precede LH pulses (portal and PPC data; GT-1 cell data)
calcium entry to culture olfactory placode GnRH neurons is pulsatile, suggesting that GnRH pulses might be Ca-driven
**GnRH (=LHRH)**

Continuous GnRH release causes down regulation of GnRH receptors in its target.

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existence of a pulse generator follows working of myocardium and presence of synapsis among GnRH cells
hypothalamic tonic and phasic feedback centers (gonadectomy and replacement therapy, HHA concept, stereotaxic steroid implants)
tonic and phasic feedback centers, the biphasic effect of E2, and the role of sexual differentiation (E2 and tonic vs phasic E2 receptors)
initiation of maturational processes associated with hypothalamic differentiation, anterior pituitary and ovaries
GnRH pulsatility an intrinsic characteristic of GnRH neuron maturation of the E2 +/- Fbs and activation of a steroid independent central drive that stimulates the GnRH network
modulatory role of Prl and GH on ovarian steroid release by affecting LH but not FSH receptors
hypothalamic precocious puberty

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GnRH pulsatility an intrinsic characteristic of GnRH neuron maturation of the E2 +/- Fbs and activation of a steroid independent central drive that stimulates the GnRH network
modulatory role of Prl and GH on ovarian steroid release by affecting LH but not FSH receptors
hypothalamic precocious puberty
Puberty

The Yin and the Yang

Pubertal Juvenile Pause
(Implies: CNS inhibition)

Prepubertal Juvenile Pause
(Implies: CNS inhibition)

Ovary

LH controls SCCE
FSH controls aromatase

Hypothalamus

GnRH

FSH controls aromatase

GnRH

LH controls SCCE

Ovary

LH

FSH

GnRH

GnRH

LH controls SCCE

FSH controls aromatase

GnRH

Puberty

The Yin and the Yang

Neurosecretory

Hypothalamus

GABA

GABA

FSH controls aromatase

Ovary

LH controls SCCE

FSH controls aromatase

GnRH

GnRH

LH controls SCCE

FSH controls aromatase

GnRH

Puberty

The Yin and the Yang

Neurosecretory

Hypothalamus

GABA

GABA

FSH controls aromatase

Ovary

LH controls SCCE

FSH controls aromatase
Pulsatile LH drives E2

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
hypothalamic pulsar modulated by neurotransmitters (+ and - array). "Lack" of E2 receptors in GnRH neurons
POA - E2 receptors & phasic GnRH release by a decreased -FB (luteolysis, 2nd derivative, "sponge" receptor, data in monkey)
mass follicular growth and preovulatory E2, origin of 2nd derivative input to a "sponge" E2 receptor
relationship among preovulatory E2 secretion, hypothalamic transmitters and release of GnRH. The (+) and (-) input array

E2 drives the LH surge

This LH surge is an obligatory event for reproduction to occur.

control surge
examples
P4
E2-As
GnRH-As
LH-As
blocked surge
Menstrual / Estrous Cycles

- Menstrual cycle
- Estrous cycle
- LH surge, repetitive events at all axis levels
- Differences and similarities menstrual / estrous cycles
- Main events: drop in P4, increase in E2, surge of LH
- Follicle vs. luteinization, estrogenic vs. progestational, ovary vs. uterus view
- Luteolysis, LH surge, ovulation as common cyclic denominators
- GnRH as trigger of the LH surge (expt: mouse without GnRH)
- E2 as trigger of GnRH surge (expt: phasic vs. tonic E2 receptor)
- FSH, follicular wave, atresia, dominant follicle, ... the race
- FSH stimulates formation of FSH / LH receptors, & E2
- E2 stimulates formation of ovarian FSH receptors
- Increase follicular growth in presence of low FSH / LH

Menstrual Cycle

- LH (milli-international units/ml)
- FSH (milli-international units/ml)
- Progesterone (nanograms/ml)
- Estrogen (picograms/ml)
- Menstruation

(view from the blood)
Menstrual Cycle

(View from the ovary and uterus)

Ovary

Lining of the uterus

Basal body temperature (°F)

Menstruation

Day of cycle

Corpus luteum

Follicle

Menstrual / Estrous Cycles

Hormonal Control of the Follicular Phase

Hypothalamus

GnRH

Anterior pituitary

FSH

LH

Ovarian follicle

Theca cells

Granulosa cells

Testosterone

Androstenedione

Estrogen

Progestrone

Hormonal Control of the Luteal Phase

Anterior pituitary

GnRH

LH

FSH

Corpus luteum

Estrogen

Progestrone

Circulation

Circulation
Menstrual / Estrous Cycles

- 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
- estradiol triggers the pre-ovulatory surge of LH
- GnRH neuron "practically" lacks E2 receptors, main cause we have worried about the neurotransmitter mess (+,- input array)
- synapsis among GnRH neurons and the concepts of network and subnetworks
- coexistence of GnRH and galanin in a subnetwork
- NPY and the role of E2 as an example of GnRH input array
- ØEND & GnRH deshinition as a mechanism for LH surge

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Menstrual / Estrous Cycles

Summary of the Menstrual Cycle

<table>
<thead>
<tr>
<th>DAY(S)</th>
<th>MAJOR EVENTS</th>
</tr>
</thead>
<tbody>
<tr>
<td>1–5</td>
<td>Estrogen and progesterone are low because the previous corpus luteum is regressing. Therefore: (a) Endometrial lining sloughs. (b) Secretion of FSH and LH is released from inhibition, and their plasma concentrations increase. Therefore: Several growing follicles are stimulated to mature.</td>
</tr>
<tr>
<td>7</td>
<td>A single follicle (usually) becomes dominant.</td>
</tr>
<tr>
<td>7–12</td>
<td>Plasma estrogen increases because of secretion by the dominant follicle. Therefore: Endometrium is stimulated to proliferate.</td>
</tr>
<tr>
<td>7–12</td>
<td>LH and FSH decrease due to estrogens and inhibit negative feedback. Therefore: Degeneration (atresia) of nondominant follicles occurs.</td>
</tr>
<tr>
<td>12–13</td>
<td>LH surge is induced by increasing plasma estrogens. Therefore: (a) Oocyte is induced to complete its first meiotic division and undergo cytoplasmic maturation. (b) Follicle is stimulated to secrete digestive enzymes and proaglandins.</td>
</tr>
<tr>
<td>14</td>
<td>Ovulation is mediated by follicular enzymes and proaglandins.</td>
</tr>
<tr>
<td>15–25</td>
<td>Corpus luteum forms and, under the influence of low but adequate levels of LH, secretes estrogen and progesterone, and so plasma concentrations of these hormones increase. Therefore: (a) Secretory endometrium develops. (b) Secretion of FSH and LH is inhibited, lowering their plasma concentrations. Therefore: No new follicles develop.</td>
</tr>
<tr>
<td>25–28</td>
<td>Corpus luteum degenerates (if egg is not fertilized). Therefore: Plasma estrogen and progesterone concentrations decrease. Therefore: Endometrium begins to slough at conclusion of Day 28, and a new cycle begins.</td>
</tr>
</tbody>
</table>
The brain is the ultimate control of cyclic ovarian function.

The GnRH neuron is the link between reproductive-related brain function and the reproductive system.

The GnRH neuron is the link between reproductive-related brain function and the reproductive system.

Neuroendocrine Control

Neuroendocrine Control
Contraception

Some Forms of Contraception in Humans and Animals

<table>
<thead>
<tr>
<th>METHOD</th>
<th>FIRST YEAR FAILURE RATE</th>
<th>PHYSIOLOGICAL MECHANISM OF EFFECTIVENESS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Barrier Methods</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Condoms (♂ and ♀)</td>
<td>12%</td>
<td>Prevents sperm from entering uterus</td>
</tr>
<tr>
<td>Dacryl vaginal sponge (♀)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Spermicides (♀)</td>
<td>20%</td>
<td>Kills sperm in the vagina (after insemination)</td>
</tr>
<tr>
<td>Sterilization</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vasectomy (♂)</td>
<td>&lt;0.5%</td>
<td>Prevents sperm from becoming part of seminal fluid</td>
</tr>
<tr>
<td>Tubal ligation (♀)</td>
<td></td>
<td>Prevents sperm from reaching egg</td>
</tr>
<tr>
<td>Intrauterine device (IUD) (♀)</td>
<td>3%</td>
<td>Prevents implantation of blastocyst</td>
</tr>
<tr>
<td>Estrogens/Progestins</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Oral contraceptive pill (♀)</td>
<td>3%</td>
<td>Prevents ovulation by suppressing LH surge (negative feedback); thickens cervical mucus (prevents sperm from entering uterus); alters endometrium to prevent implantation of blastocyst</td>
</tr>
<tr>
<td>Injectable or implantable progestins (♀)</td>
<td>&lt;0.5%</td>
<td></td>
</tr>
</tbody>
</table>


Notes:
- Spermicides are often used in combination with a diaphragm/cervical cap and condoms.
- Only condoms are effective in preserving sexually transmitted diseases.
- The effectiveness of injectable and implantable contraceptives varies; these methods are not listed because they are not reliable.
- Oral contraceptives are 99% effective in preventing pregnancy.
Animal Reproductive Techniques

Examples of some of the Reproductive Techniques used in Animal Production and in Humans:

1. Estrous, Menses Synchronization
2. Induction of Ovulation
3. Superovulation
4. Embryo Transfer
5. Cloning

Pathology

Chromosomal disorders (a few examples)
- Gonadal dysgenesis (Turner’s syndrome), XO karyotype
- Female phenotype but lack of secondary sexual characteristics (sexual infantilism)
- Seminiferous tubule dysgenesis (Klinefelter’s syndrome) XXY karyotype

Hermaphroditism
- True hermaphroditism (mosaicism)
- Both ovarian and testicular components present; equivocal external genitalia
- Male pseudohermaphroditism (testes present but partial or nearly complete female internal and external phenotypes)
- Deficient 17-ketosteroid reductase activity
- Congenital adrenal hyperplasia (due to block in pregnenolone formation)
- Leydig cell agenesis (or hypoplasia)
- Syndromes of androgen resistance
- Testicular feminizing syndrome (absence of target tissue androgen receptors)
- Syndrome of 5α-reductase deficiency (failure to convert testosterone to DHT)

Female pseudohermaphroditism
- Congenital virilizing adrenal hyperplasia (due to enzyme defect in cortisol biosynthesis)
- Progesterone administration to the mother during fetal development

Sexual precocity (precocious puberty)
- Complete (increased gonadotropin secretion of pituitary or ectopic origin)
- Incomplete (precocious pseudopuberty; development of secondary sex characteristics but lack of gametogenesis)

Adrenal steroid-secreting tumors (androgens or estrogens)
- Adrenal hyperplasia (e.g., 11β-hydroxylase or 21α-hydroxylase deficiencies; increased adrenal androgen production)
- Early masculinization in the male, masculinization of the female