Sex differentiation to puberty

- Sexual differentiation in general: chromosomal, gonadal and phenotypic sex, endocrine control of phenotypic differentiation, role of testicular hormones in male development, disorders of sexual differentiation

- Hypothalamic sexual differentiation: sexual dimorphic areas, androgenized female model, olfactory placode and GnRH migration, development and maturation of female HPG axis as intro to puberty and to adult cyclicity

- Puberty: definition, hypothesis, role of GnRH and other systems, diseases

Introduction

repro and its “story lines”
Sex differentiation

- **Sex differentiation general aspects**
- **Hypothalamic sex differentiation**
- **Neuroendo control of Puberty Onset**

![Diagram showing the process of sex differentiation]

- Genetic sex established at conception governs development of gonadal sex.
- Egg → Sperm → Genetic sex → Gonadal sex → Phenotypic sex.
- CNS regulates FSH-LH secretion, affecting sex behavior and secondary sex characteristics.
- External genitalia development influences phenotypic sex expression.

**Key terms**:
- Genome sex
- Phenotypic sex
- Urogenital system
- Secondary sex characteristics
- External genitalia
- CNS control of gonadal sex development
Sex differentiation

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sex differentiation

 XY
SRY product

 XX

 testis
ovary

 S E

 gonadal sex controls the development of phenotypic sex

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 gonadal sex controls the development of phenotypic sex
The bipotential gonad

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female pattern is default unless TDF, a transcription factor of the SRY gene, is present
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Gonadal differentiation

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TDF of SRY gene as master switch for downstream differentiation genes
- embryo without Y develops as female
- embryo with multiple X + 1Y = male
- XX injected with SRY gene --> male
- SRY turns indifferent genital ridge into medullary development of testis, testosterone production, male phenotype
- SRY gene is normally present in males but its locus was deduced from XX individuals with testis development that inherited 40kb Y chromosome (n=4)
- gain of function mutations in genes downstream might explain testis in XX

female pattern is default unless TDF, a transcription factor of the SRY gene, is present
Genes and sex differentiation

- **Sex differentiation general aspects**
  - steroid receptors, ligand-dependent transcription factors, bind unique HRE in the promoter of specific target genes
  - orphan receptors, which have been cloned by homology, have no known ligands but appear to be mediators of adult endocrine function and organogenesis

- **Hypothalamic sex differentiation**
  - SF-1 = Ad4BP is one of these receptors. It resembles the Drosophila Ftz-F1, which regulates the developmental homeobox gene fushi tarazu (for paired body components)
  - SF-1 transcripts are found in steroid-producing organs, in Sertoli cells, in pituitary gonadotrope, and in the VMN during formation of bipotential gonad, sexual differentiation (sexually dimorphic pattern), and in the adult gonad expressed in developing gonadotropes prior to expression of alpha and ß subunits of LH & FSH, but not in LHRH neurons
  - SF-1 knockout mice die of corticoid insufficiency (volume depletion, low corticosterone, high ACTH), have female external & internal genitalia regardless of chromosomal sex, do not express LH & FSH, and do not have the VMN a proposed homeostatic relay center involved in metabolic and reproductive control

- **Neuroendo control of Puberty Onset**
  - female pattern is default unless TDF, a transcription factor of the SRY gene, is present
Phenotypic differentiation

- Sex differentiation general aspects
- Hypothalamic sex differentiation
- Neuroendo control of Puberty Onset

Mullerian system regress in males (AMH) through apoptotic mechanisms (suicide)

The undifferentiated state has a bipotential gonad and both Mullerian and Wolffian systems
Phenotypic differentiation

• Sex differentiation general aspects
  - gonocytes from yolk sac move to gut and seed undifferentiated gonad: male / medulla, female / cortex
  - gonadal anlagen is visible at 4 weeks gestation, testis at 7 weeks (if the Y gene is present) and the ovary at 13-16 weeks
  - in females apoptosis of Wolffian system
  - in males anti-Mullerian hormone (AMH), a member of the TGFß family of peptides
  - female genitalia in the absence of Y
  - male genitalia is dependent on androgen production by the testis. Timing, effect of congenital adrenal hyperplasia in XX
  - testosterone, critical period, hypothalamic sexual differentiation and reproductive cycles

In the absence of testis development the genetic program stimulates development of an ovary

• Hypothalamic sex differentiation

• Neuroendo control of Puberty Onset

T induces differentiation of the internal genitalia and DHT that of the external genitalia
Phenotypic differentiation

• Sex differentiation
general aspects

• Hypothalamic sex
differentiation

• Neuroendo control
of Puberty Onset

\[ T \text{ in presence of 5a-reductase generates DHT and in presence of aromatase generates E2} \]

T and DHT are steroids and their mechanism of action involve intracellular receptors
**Phenotypic differentiation**

- **Sex differentiation general aspects**
- **Hypothalamic sex differentiation**
- **Neuroendo control of Puberty Onset**

**Endocrine pathologies** include hypofunction and hyperfunction of primary or secondary origin.

T and DHT are steroids and their mechanism of action involve intracellular receptors.
Turner syndrome patients (XO) usually have short stature and delay puberty.

Complete testicular feminization (XY, AR mutation) and an undervirilized male.
Sex differentiation disorders

• Sex differentiation general aspects
  - Virilization: fetal adrenal steroidogenesis defects
  - Hypothalamic sex differentiation
  - Neuroendo control of Puberty Onset

3βH-steroid dehydrogenase deficiency in male (top) and in female (below)
Partial (top) and complete (below) virilization in genetic females with 21 H deficiency

Hypogonadotropic hypogonadism before and after treatment with T cypionate
**Hypothalamic Differentiation**

- Sex differentiation general aspects
- Hypothalamic sex differentiation
- Neuroendo control of Puberty Onset

Male hypothalamic differentiation is caused by T to E2 aromatization in sexual dimorphic areas.

Female hypothalamic differentiation, the default program, includes the ability to induce ovulation.
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Puberty as a process and its relationship to the theoretical control

The onset of puberty as an example of the hypothalamic maturation of the theoretical neural components of a feedback system controlling pulsatile GnRH release and reproduction

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

Phenotypic changes at puberty

Female hypothalamic differentiation, the default program, includes the ability to induce ovulation
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Functional changes at puberty

- Sex differentiation general aspects
  - Infantile uterus responds to steroids well before the onset of puberty (assays and ideopathic precocious puberty)

- Hypothalamic sex differentiation
  - Neonatal ovary has autonomous follicular growth and responds to gonadotrophins during infantile period (has steroid output)
  - Neonatal anterior pituitary responds as an adult pituitary when transplanted to adult hypox rats (neonatal AP to their mothers)
  - The CNS negative and positive feedbacks of E2 on LH and FSH are not present in the infantile period, but they become progressively active during the prepubertal period (- and + FB approaches)

Hormonal change at puberty

- Sex differentiation general aspects

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Female hypothalamic differentiation, the default program, includes the ability to induce ovulation.
Theories on puberty onset

- **Sex differentiation**
  - general aspects

- **Hypothalamic sex differentiation**

- **Neuroendo control of Puberty Onset**

- while dynamic AP-ovarian relationship are operative before puberty, its onset results from the elaboration of sufficient hormones
- it is brought about by removal of inhibitory inputs to gonadotropins (reseting of the gonadostat)
- it is caused by stimulation of facilitatory inputs on gonadotropin secretion (increase in central drive), rather than by gonadostat reseting
- puberty onset is 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

Female hypothalamic differentiation, the default program, includes the ability to induce ovulation
Puberty-related Pathologies

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5 year old & 2 year old

Precocious puberty: central idiopathic (girl) & secondary to congenital adrenal hyperplasia (boy)

7 year old boy, central precocious puberty secondary to neurofibromatosis, unaffected twin

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