GENETIC DISORDERS OF GONADOTROPINS AND THEIR RECEPTORS CAUSING HYPOGONADISM

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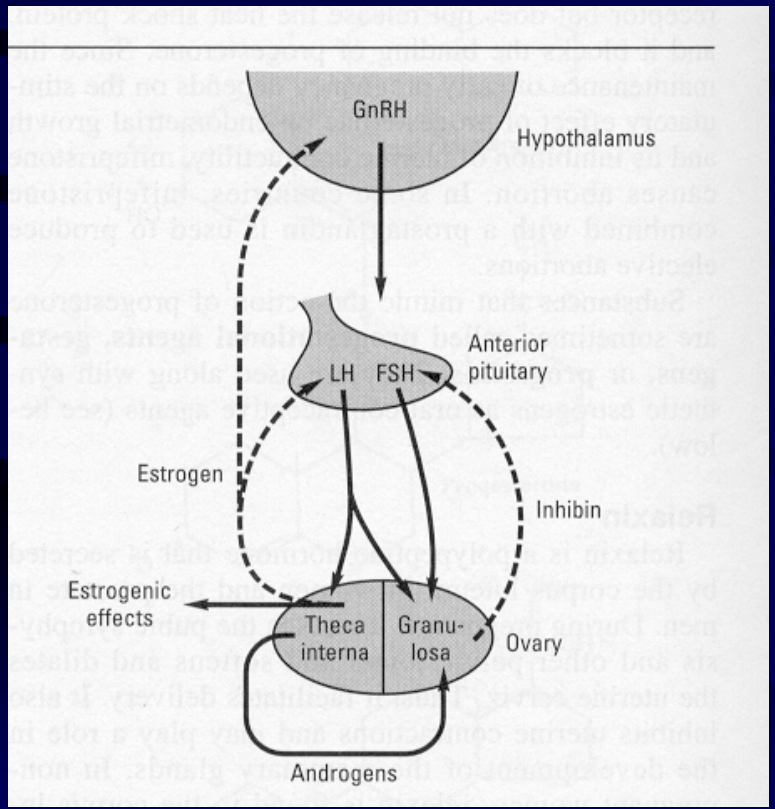
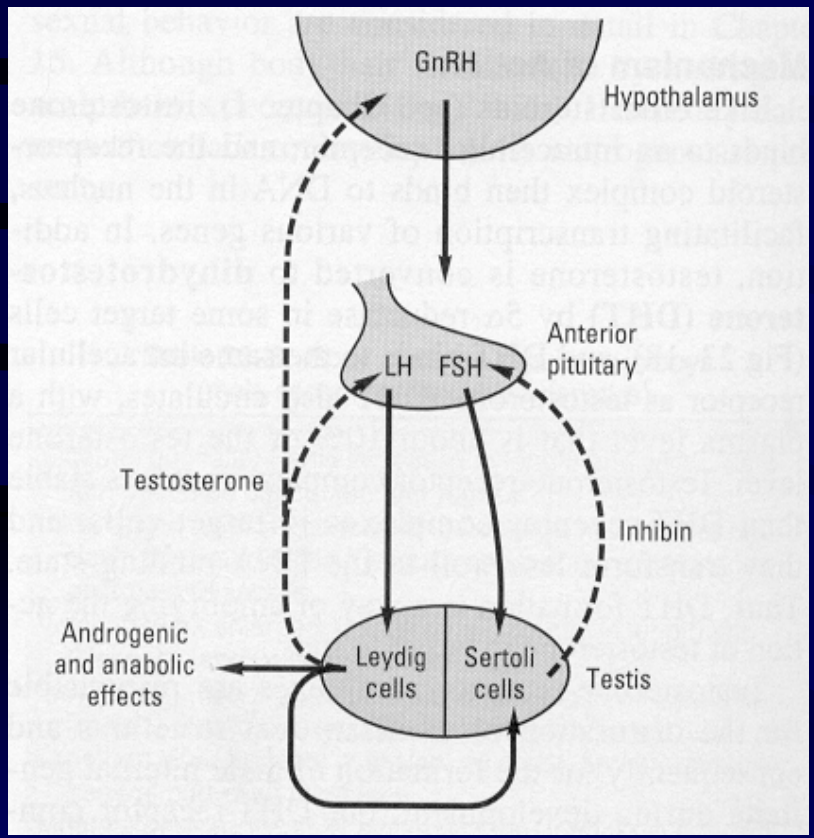
The Hypothalamo-Pituitary-Gonadal Axis in Females



- GnRH stimulates LH and FSH secretion
- Ovarian androgens and estrogens inhibit GnRH, LH, and FSH secretion.
- Inhibin from the granulosa cells inhibits FSH secretion.

The Hypothalamo-Pituitary-Gonadal Axis in Males

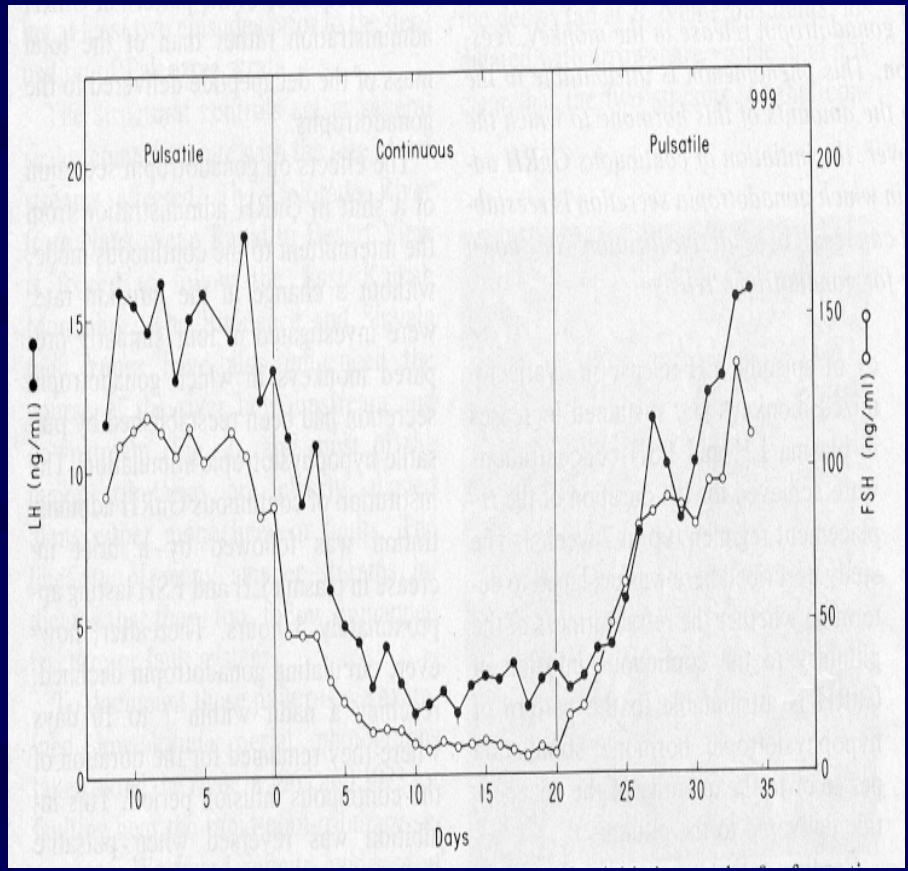


- GnRH stimulates LH and FSH secretion
- Testosterone inhibits GnRH, LH and FSH secretion
- Inhibin from the Sertoli cells inhibits FSH secretion

LH and FSH responses to GnRH

- Pulsatile administration
- of GnRH

- Continuous administration of GnRH



Belchetz, Science 202, 1978

Classical View of Gonadotropins Function I

- **FSH – in females stimulates the development of follicles in the ovary and production of estrogen by granulosa cells**
- **FSH – in males stimulates spermatogenesis**

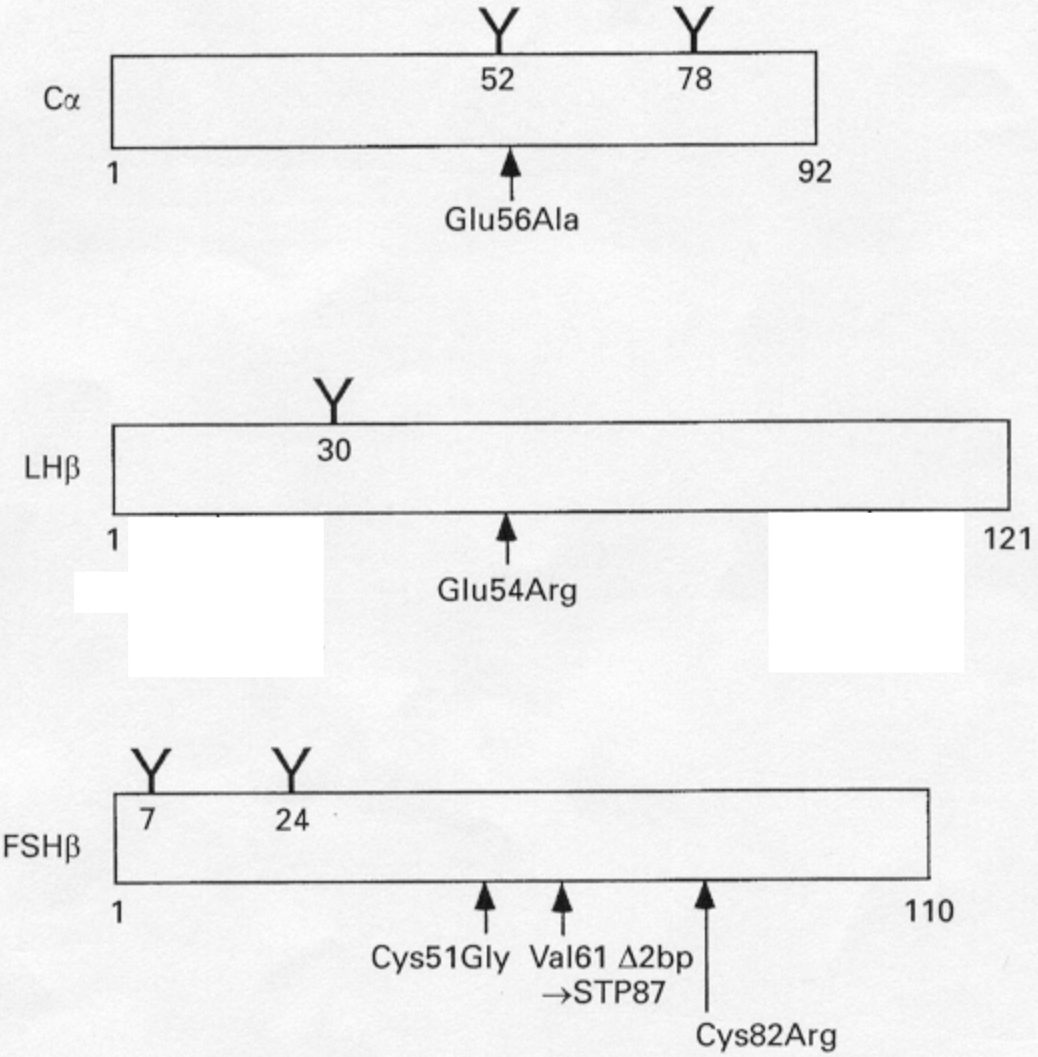
Classical View of Gonadotropins Function II

LH – in females stimulates ovulation, the formation of the corpus luteum and the production of progesterone by the corpus luteum

LH – in males stimulates the production of testosterone by the Leydig cells

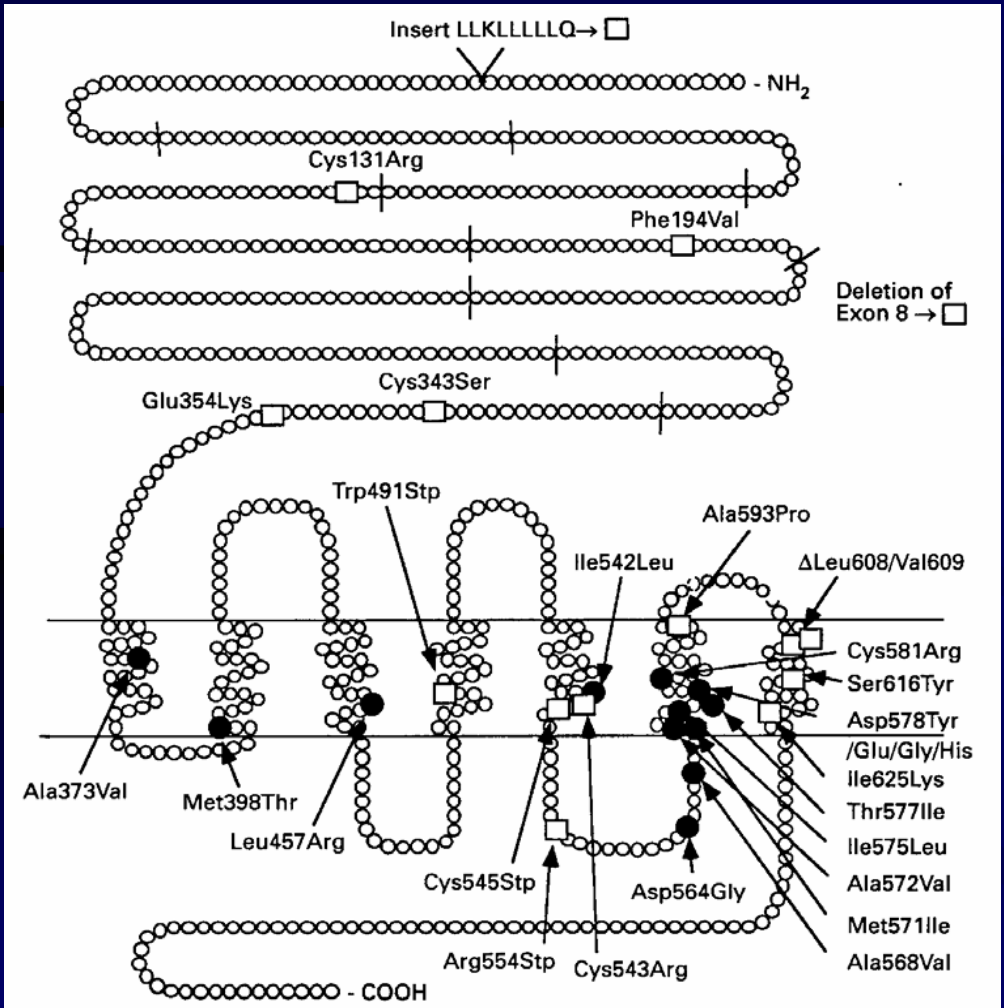
Mutations in the Gonadotropin Subunit Genes

- LH-β: only one mutation described in the human
- FSH-β: several mutations described, both in male and female patients
- Cα: no somatic mutation described in the human yet. Only one tumor secreting a mutated Cα



J Reprod Fertility 119, 2000

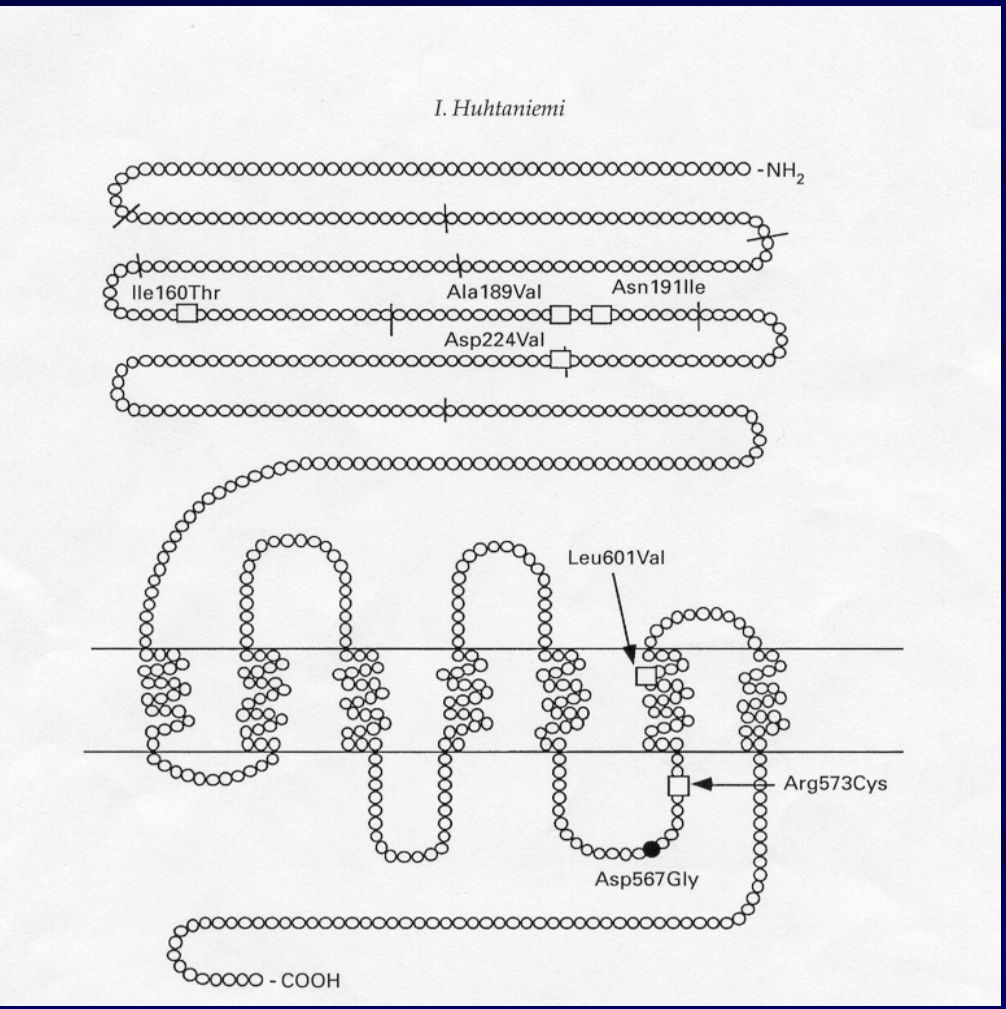
Summary of Mutations in the LH Receptor Gene



The largest number of mutations in genes of gonadotropins and their receptors have been detected in the <u>LHR gene</u>:

– 15 activating (?)
– 14 inactivating (?)

Schematic Structure of the FSH Receptor Gene



- **Only a few mutations have been identified:**
  - **– one activating (?)**
  - **– six inactivating (?)**

LH Deficiency in Females

No LH? mutation yet described in a female patient

LH-R

- normal external genitalia
- normal pubertal development
- secondary amenorrhea
- no pre-ovulatory follicles

LH Deficiency in Males

LH?

Single case described

Bio-inactive LH

? **Phenotype:**

– normal genitalia

– delayed puberty

Male heterozygotes: 3/4 infertile

LH-R

Broad spectrum of phenotypic expression

– pseudohermaphroditism and complete azoospermia

– micropenis, delayed puberty and arrest of spermatogenesis

Role of the LH/LH-R System

- Important for normal male puberty, but not female
- LH-R plays a role in spermatogenesis as well as in ovulation

LH-R is a candidate gene for male as well as female infertility

FSH Deficiency in Females

FSH?

Three cases described

- **Phenotype:**
  - delayed puberty
  - primary amenorrhea
  - normal response to FSH with achievement of fertility

FSH-R

Finnish study

- **Phenotype:**
  - primary amenorrhea
  - ovarian dysgenesis with normal XX karyotype

FSH Deficiency in Males

FSH?

Two cases described

- **Phenotype:**

1. **delayed puberty, low testosterone and absent spermatogenesis**
2. **normal puberty and virilization, spermatogenic arrest**

FSH-R

Finnish study

- **Phenotype:**

– **normal virilization**
– **decreased testicular volume**
– **variable suppression of spermatogenesis**

Role of the FSH/FSH-R System

- Important for estrogen production, follicular maturation and fertility

- Role of FSH in spermatogenesis remains unclear:
  - variable spermatogenesis in FSH-R mutations
  - absent spermatogenesis in FSH? mutations

Conclusion I

- The cloning of the genes coding for the gonadotropin subunits and their receptors has made it possible to identify patients with abberant pituitary-gonadal function in which the pathology is caused by mutations in these genes

Conclusion II

A better understanding of the molecular pathophysiology of hypogonadism/infertility should allow to:

– counsel patients about their prognosis and the risk of transmitting a condition to their children upon treatment

– to be treated more appropriately in the context of known hormonal deficits