Gonadotrophin-dependent follicle development

Juha Tapanainen

Department of Ob-Gyn
University of Oulu
Oulu University Hospital
Finland

Lisbon 2008

Objectives

- Follicular development and gonadotropin dependent phases of follicular growth
- What can be learned from gonadotropin/receptor mutations in human
- What can be learned from gonadotropin/receptor knockout models
- Follicle recruitment and dominance
- Intraovarian modulators of follicular development
- Ovulation

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Gougeon 1996

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Follicular development

- Initial follicle development
- FSH-dependent progression
- LH-responsive maturation

Hillier 2001

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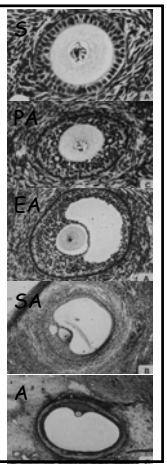
Classification of follicles

- Secondary: distinct TC layer, blood supply
- Preantral: several gc layers
- Early antral: fluid-filled patchy appear within GC
- Small antral
- Antral: large crescent-shaped cavity
- Graafian: 15-25 mm



From Gougeon 1996

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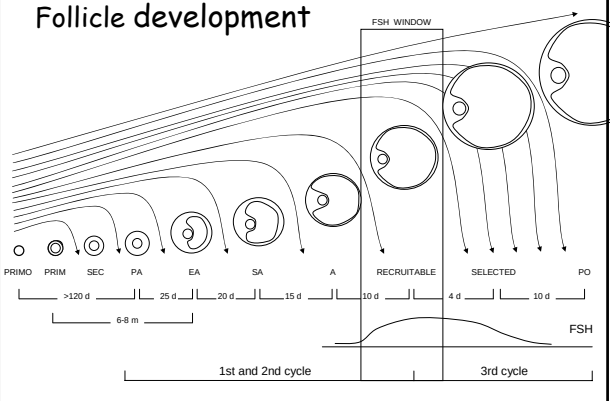
Follicle development



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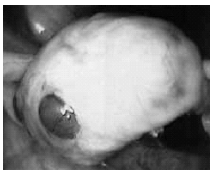
Adopted from Gougeon 1996, Welt et al. 1997, Macklon & Fauser 2001

Oocytes

- Fetus 7×10^6
- Newborn 1×10^6
- Puberty 4×10^5
  - Ovulation 300-400
- Menopause 100-1000



= 99.9% of oocytes die by the mechanism of apoptosis

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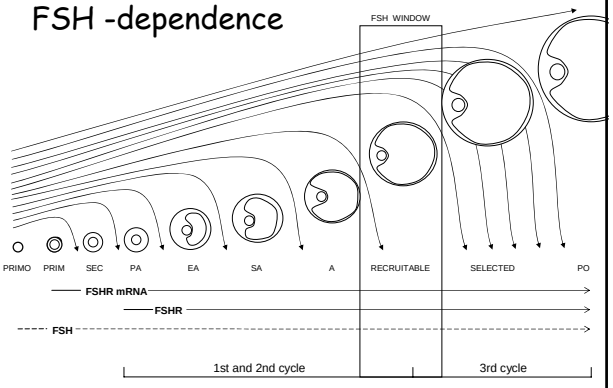
FSH -dependence



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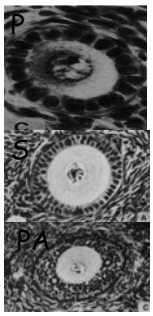
FSH-dependence

- FSHR mRNA – primary onwards
  - » Human
- FSHR – early preantral follicles
  - » Channing & Kammerman 1973, Roy et al. 1987



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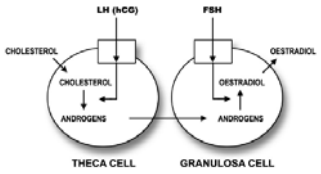
Follicle growth and steroidogenesis



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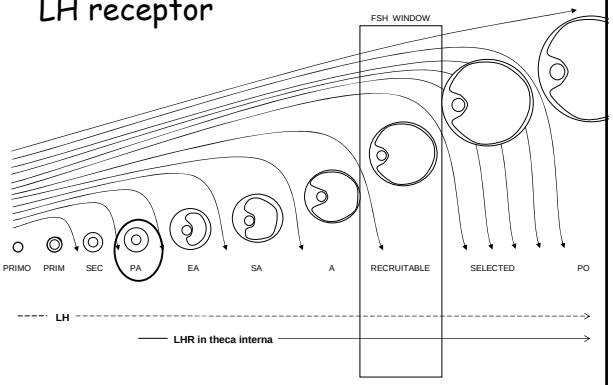
Armstrong et al. 1979, Hsueh et al. 1984

LH receptor



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Gonadotropin/receptor mutations in human

- Inactivating FSHβ
  - Layman et al al. 1997, 2002; Matthews et al. 1993
- Inactivating FSHR
  - Aittomäki et al. 1995; Beau et al. 1998;Touraine et al. 1999
- Activating FSHR (ligand hCG)
  - Smits et al. 2003; Vasseur et al. 2003
- Inactivating LHR
  - See Themmen & Huhtaniemi 2000

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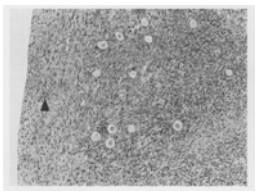
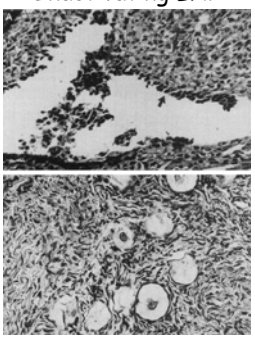
Inactivating FSHR



Aittomäki et al. 1995

Inactivating LHR



Toledo et al. 1996

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Gonadotropin/receptor knockout (KO) mice

- FSHβ - no follicles beyond preantral stage
  - » Kumar et al. 1997
- FSHR – follicles up to secondary stage
  - » Dierich et al. 1998; Abel et al. 2000
- LHβ - degenerating antral follicles, no CL
  - » Ma et al. 2004
- LHR – no follicles beyond antral stage
  - » Lei et al. 2001; Zhang et al. 2001, Pakarainen et al. 2005

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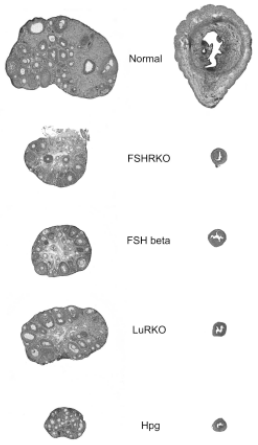

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From Ilpo Huhtaniemi

Intraovarian modulators of follicular development

- IGF system
- Epidermal growth factor (EGF) system
- VEGF system
- Transforming growth factors (TGFα, TGFβ)
- Anti-Mullerian hormone (AMH)
- Bone Morphogenetic Protein (BMP) system

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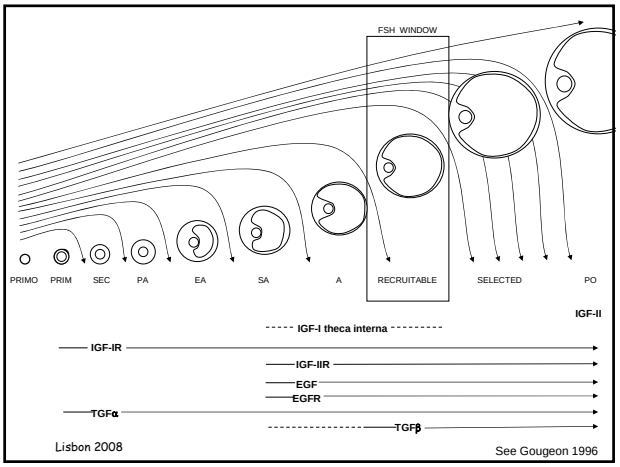
See Palermo 2007, Shimasaki et al. 2008



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See Gougeon 1996

AMH

- AMH null mice:
  - Number of growing follicles are increased
  - > follicles more sensitive to FSH
  - Lower FSH levels
    - » Durlinger et al. 1999, 2001
- In vitro:
  - AMH inhibits FSH-dependent follicle growth (gc proliferation)
    - » Durlinger et al. 2001

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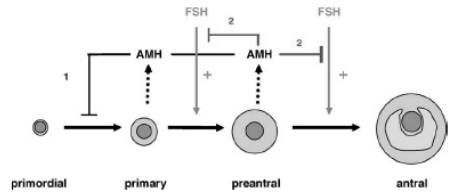
Inhibitory effect of AMH on FSH-dependent selection of follicles



Visser & Themmen 2005

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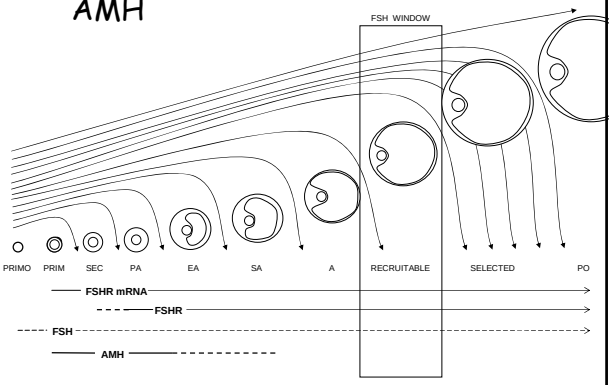
AMH



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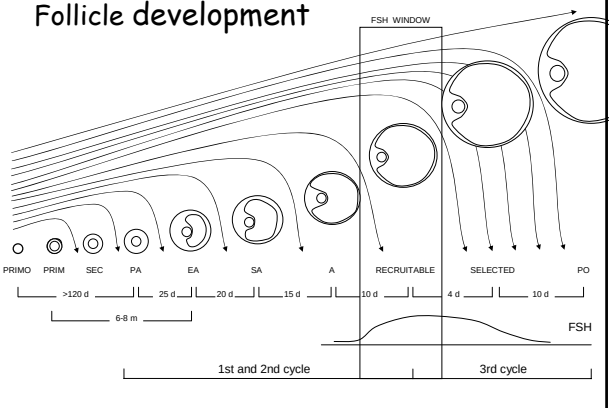
Follicle development



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Adopted from Gougeon 1996, Welt et al. 1997, Macklon & Fauser 2001

Luteal-follicular transition

- The rise in FSH is essential for recruitment of follicles into pool from which a dominant follicle is selected
- Increase in GnRH pulse frequency
- Close correlation between the rise in FSH and the increase in GnRH pulse frequency

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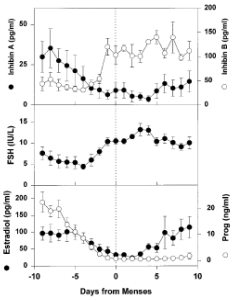
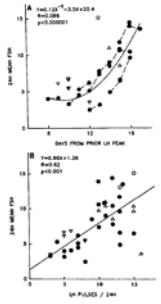
FSH and FSH pulses during luteal-follicular transition



Welt et al. 1997



Hall et al. 1992

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Selection of follicle cohort

- Selection is critically dependent on the rise of FSH
- FSH gives rise to continued growth of a limited number (cohort) of follicles
- Mechanisms by which FSH causes selection remains poorly understood
- Bidirectional communication between follicular cells (gc, tc, oocyte)
- Bone Morphogenetic Protein (BMP)-system may play a significant role

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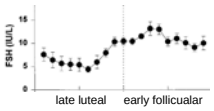
Cohort and dominance

- Some (largest) follicles more sensitive to FSH in late luteal phase
- Mitotic index of gc is important, and even smaller follicles can make up their growth delay in a few days
- In early follicular phase follicles with lower mitotic index are unable to make up the growth delay

Gougeon 1996

Selection of dominant follicle

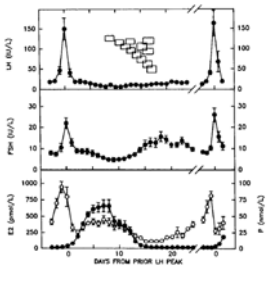
- The whole recruited cohort contributes to the initial decline in FSH levels during the first half of follicular phase
- The largest follicle has the major role in decreasing further FSH to levels below that required to support the growth of smaller follicles
- Estradiol and inhibin are the major factors produced by the selected cohort to suppress the secretion of FSH



Dominant follicle

- In the human a single follicle from the cohort is selected
- Remaining follicles enter atresia
- GCs of dominant follicle become responsive to LH (induction of LHR by FSH) and less dependent on FSH

Ovulation



Hall et al. 1992

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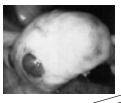
Ovulation



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Ovulation

- LH surge promotes terminal differentiation and oocyte maturation, required for ovulation of fertilizable egg
- LH directly stimulates TC and GC, but its effect on cumulus cells and oocyte are probably indirect
- Critical to LH-stimulated ovulation is the induction of EGF-like growth factors, which promote cumulus expansion and oocyte meiotic resumption
  - » Park et al. 2004, Panigone et al. 2008

Hall et al. 1992

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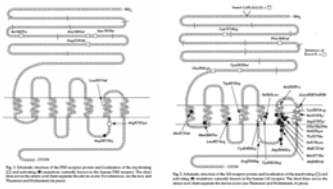
Summary 1

- Gonadotropin dependence of follicular growth starts at preantral stage
- Follicle cells (gc, tc, oocyte) are responsive to gonadotropins already earlier
- Mechanisms by which FSH causes selection of follicle cohort remains poorly understood
- In addition to ovulation the expression of LHR (= constitutive low LH activity) is essential for follicular development from antral to preovulatory stage

Summary 2

- Intraovarian modulators (growth factors) participate in the regulation of gonadotropin-independent follicle growth but they are also involved in follicular maturation and follicle selection in later stages
- Animal studies indicate that especially BMP-system and EGF-like growth factors play important roles in development of dominant follicle(s) and ovulation
- The role these factors in follicle development and ovulation in human ovary is unknown and further investigations are needed



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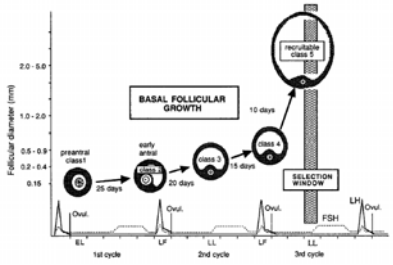

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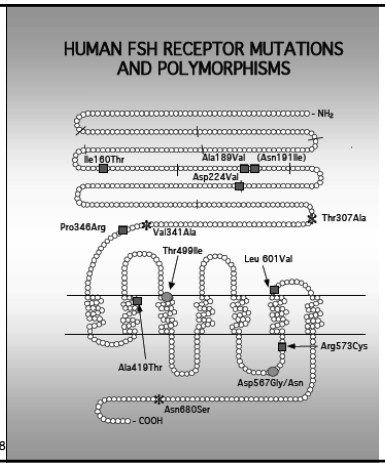

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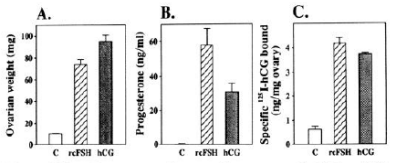

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Intraovarian peptides

- IGF-I(II)
  - Alone or with FSH stimulates proliferation of immature GC
  - Alone or with FSH stimulates aromatase
  - Stimulates progesterone production
- IGFBPs
  - Inhibit IGF-I stimulated actions

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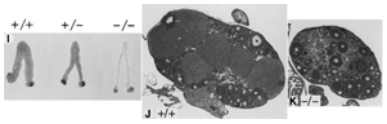
FSHR mutations

	Human female	Animals/animal models
Inactivating	Primary amenorrhea Preantral block	Preantral block Infertility
Activating	No	No

Knockout



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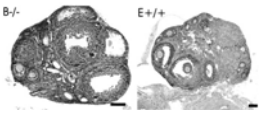
Dierich et al 1998

LHR mutations

	Human female	Animals/animal models
Inactivating	Primary amenorrhea Normal genitalia Antral follicles hCG-test negative	Antral follicles No preovulatory foll.
Activating	No female phenotype	No

Knockout



Zhang et al 2001

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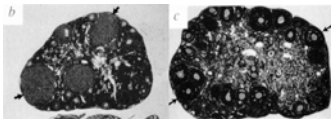
FSHβ mutations

	Human female	Animals/animal models
Inactivating	Primary amenorrhea Infertility	Preantral block Infertility
Activating	No	Cystic ovaries Infertility

Knockout



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Kumar et al 1997