Imperial College
London

Control of steroid hormone production

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Control of steroid hormone production: learning objectives

- To describe the cells of origin of steroid production by the ovary
- To describe the key enzymes in the steroidogenic pathway in the ovary
- To understand the basic principles of the regulation of steroid production by gonadotrophins and insulin/IGFs

Miller WL, Steroidogenic enzymes *Endocr Dev* 2008 **13** 1-18

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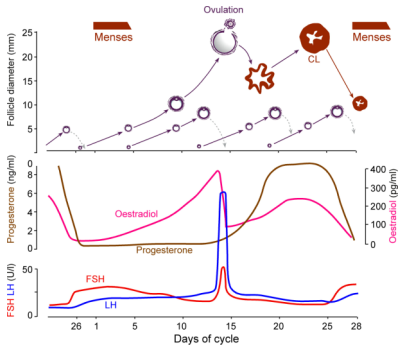
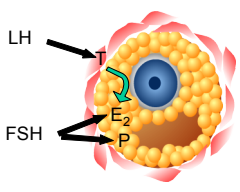
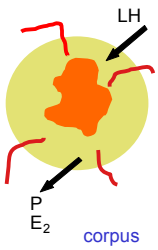


Baird, 1981

Steroidogenesis in the ovary



large antral follicle



corpus luteum

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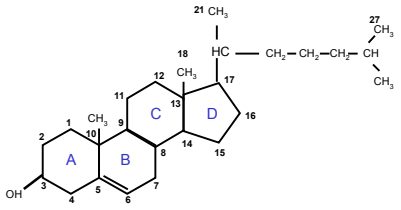
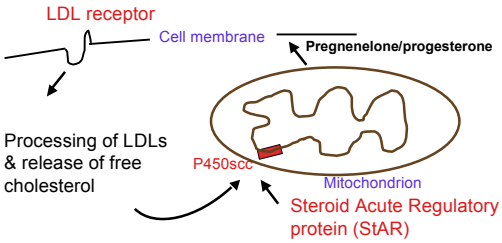
Cholesterol - the parent molecule for steroidogenesis



The steroidogenic "machinery"

- Getting cholesterol into cells (substrate)
- Getting cholesterol to the mitochondria
- Cleavage of carbon side-chains from sterol nucleus; introduction of hydroxyl groups; conversion of sterol A ring to aromatic structure
- Oxido-reductases at carbons 3,11,17,21
- Double bond reductases
- Sulfonation and sulfatases

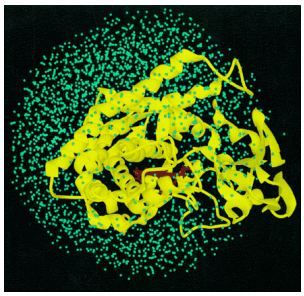
Making cholesterol available for steroidogenesis



Steroidogenic enzymes

- Cytochrome P450s
  - Cholesterol side-chain cleavage ($P450_{scc}$)
  - 17 hydroxylase/17,20 lyase ($P450_{c17}$)
  - Aromatase ($P450_{arom}$)
- Oxido-reductases (hydroxysteroid dehydrogenases)
  - 3βHSD, 17βHSD
- Steroid reductases
  - 5αReductase

Molecular model of P450c17



Auchus & Miller, *Mol Endocrinol* 1999 **13** 167-175

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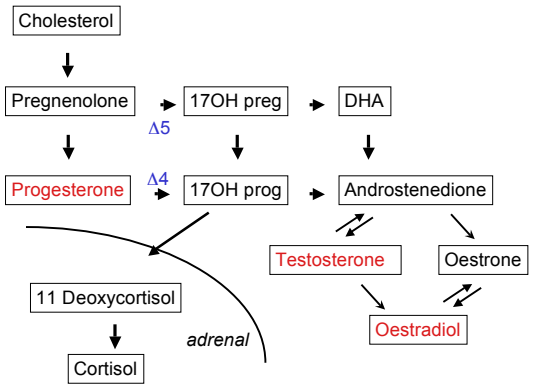
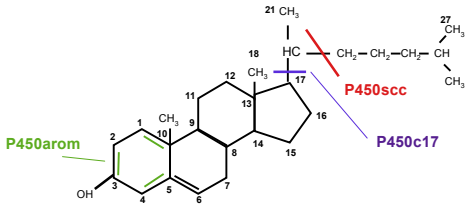
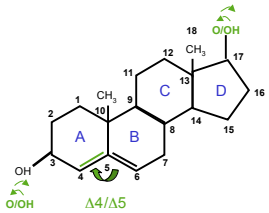
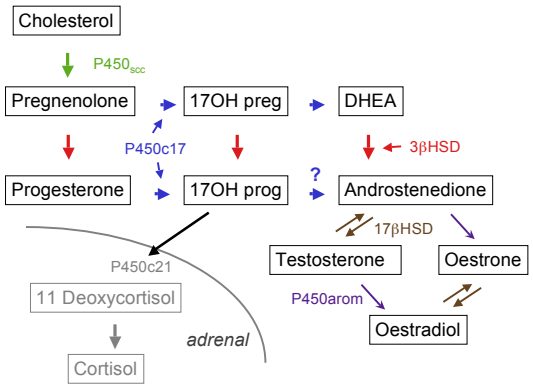


Cytochrome P450 steroidogenic enzymes



Steroid oxido-reductases 3β HSD and 17βHSD





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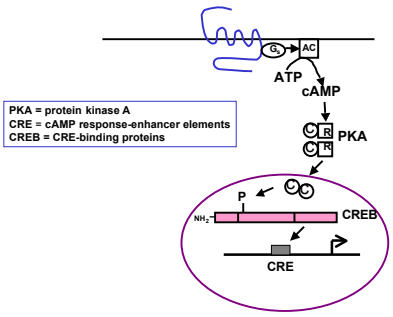
Regulation of steroidogenesis

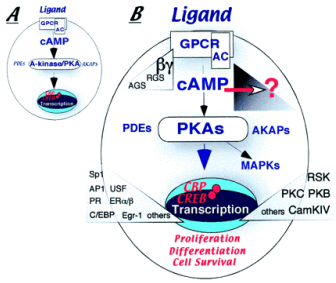
- Gonadotrophins (LH, FSH, hCG)
- Growth factors (insulin and IGFs)
- Nuclear receptors (SF-1, ERα,β)

Gonadotrophin signaling



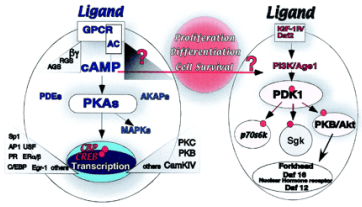
Adapted from Catt KJ "Intracellular signaling" in Hillier SG *et al* (eds) *Scientific Essentials of Reproductive Medicine*, London:WB Saunders 1996 pp45-59

Modified PKA (gonadotrophin-activated) pathway



Richards J, *Mol Endocrinol* 2001 **15** 209-18

A link between the PKA and P13-K/PDK1 Pathways?



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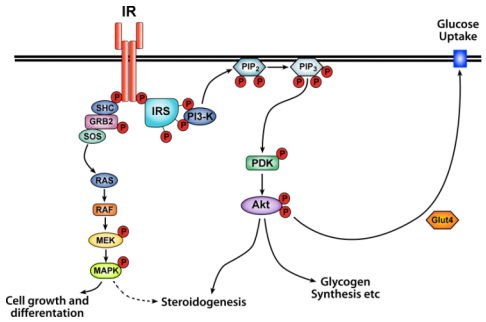
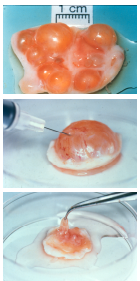
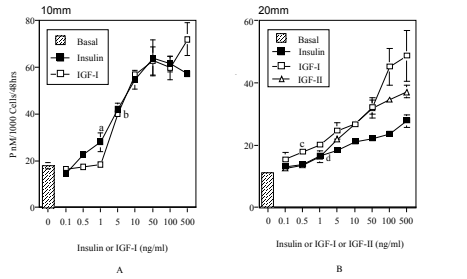
Insulin (and IGF) action in the ovary



"Harvesting" follicles from the human ovary

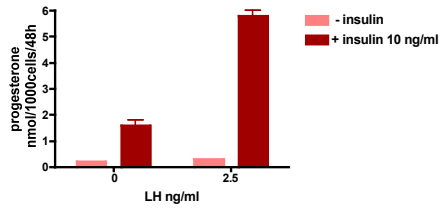


Insulin and IGFs stimulate steroidogenesis by human granulosa cells



Willis *et al*, 1998

Insulin amplifies LH-induced progesterone production by granulosa cells



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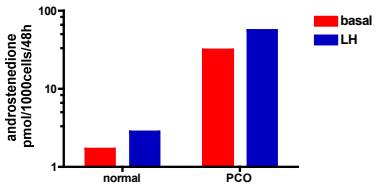
Polycystic ovary syndrome

- Polycystic ovary syndrome is the commonest cause of anovulatory infertility (>80% of cases) and of hirsutism
- The classic biochemical features are raised serum concentrations of LH and **androgens**
- It is also associated with a characteristic metabolic disturbance and increased risk of type 2 diabetes
- Its aetiology remains uncertain but familial clustering of cases suggests an important genetic component

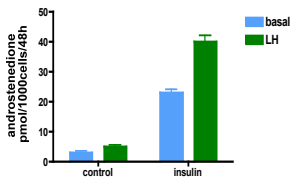
Source of excess androgen in PCOS



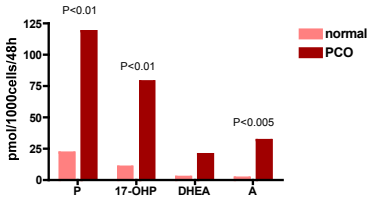
PCO theca cells produce 20-fold more androstenedione in culture than normal theca

Gilling-Smith *et al*, 1994

Insulin pre-treatment augments androgen production by human theca cells in culture

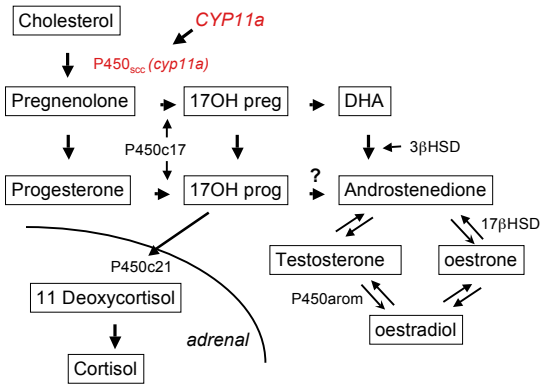


Steroid production by cultured theca cells from normal and polycystic ovaries

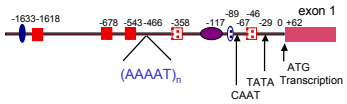


Evidence for a global abnormality of steroidogenesis

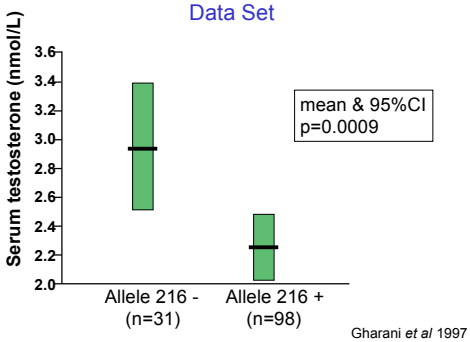
Gilling-Smith *et al, J Clin Endocrinol Metab* 1994 **79** 1158-65



Map of *CYP11a* promoter region



Association of *CYP11a* Genotypes with Total Serum Testosterone Levels in a Case-Control Data Set



Gharani *et al* 1997

Association of *CYP11a* polymorphisms with PCOS in a large case-control data set

- 371 cases of PCOS, 341 controls
- No significant differences in allele frequency between PCOS cases and controls
- No associations between any allele, genotype or haplotype and testosterone levels in the PCO cases

Gaasenbeek et al, *J Clin Endocrinol Metab* 2004 89 2408-13

Summary

- Ovarian steroidogenesis is regulated primarily by gonadotrophins
- Growth factors are important in modulating steroidogenic response to gonadotrophins
- There appears to be cross-talk between major signaling pathways in transcriptional regulation of steroidogenic enzymes
- Abnormal steroidogenesis in PCOS may result, partly, from abnormal regulation of expression of *CYP11a* (P450scc)