

Extra-testicular estrogen production and action

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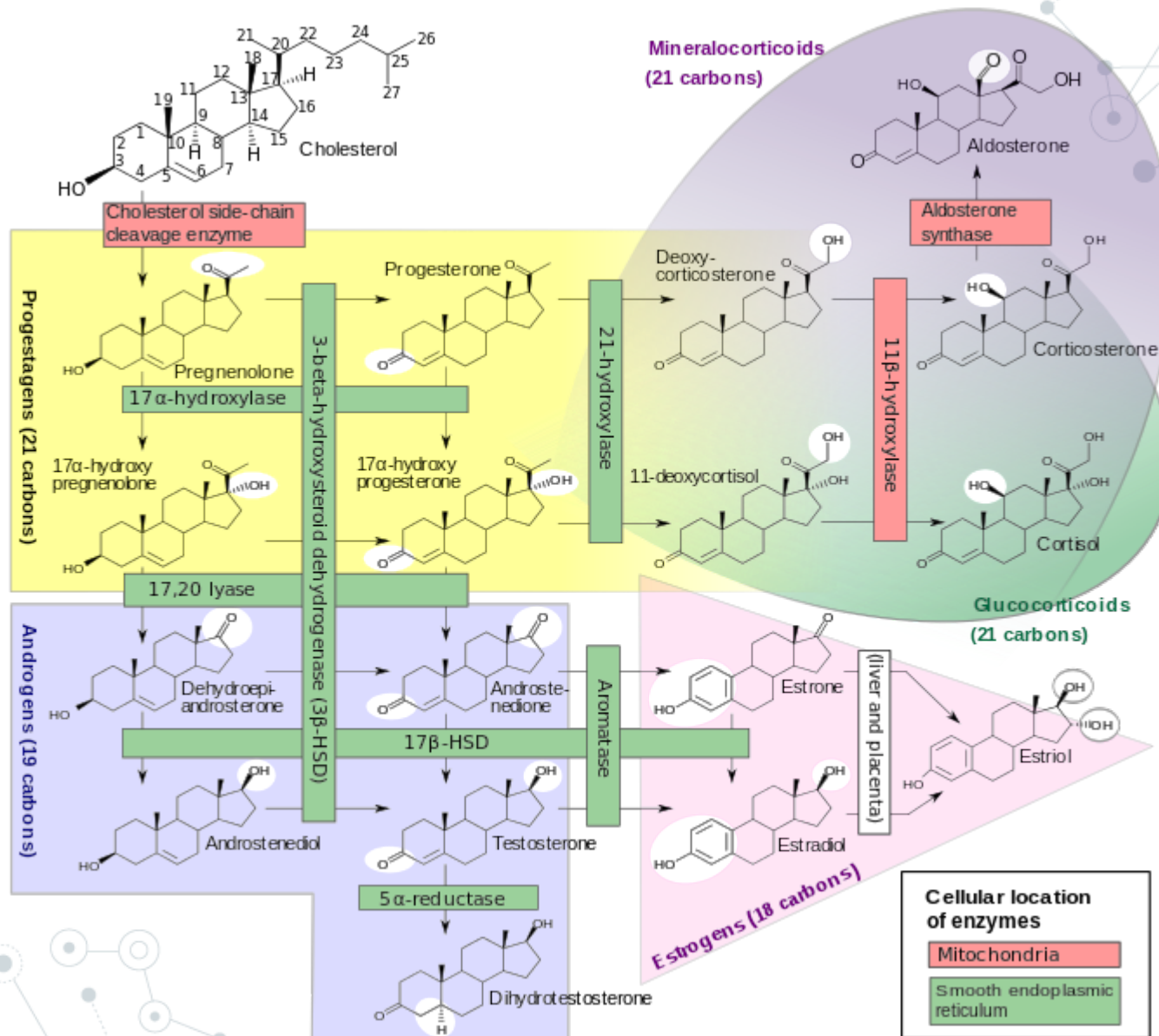
Bad estrogens?

Estrogens are produced by the ovary and are traditionally considered as exclusively female sex hormones. For years an opinion existed that these hormones have no influence in men or induce the malfunctioning of the testes.

In fact, the **excess of estrogens** in adult males may lead to:

- a feedback inhibition of the hypothalamus-pituitary-testis axis, leading to hypoandrogenemia and appearance of male hypogonadism symptoms,
- suppression of spermatogenesis and infertility.

Pathway of human steroidogenesis



Estrogens in men

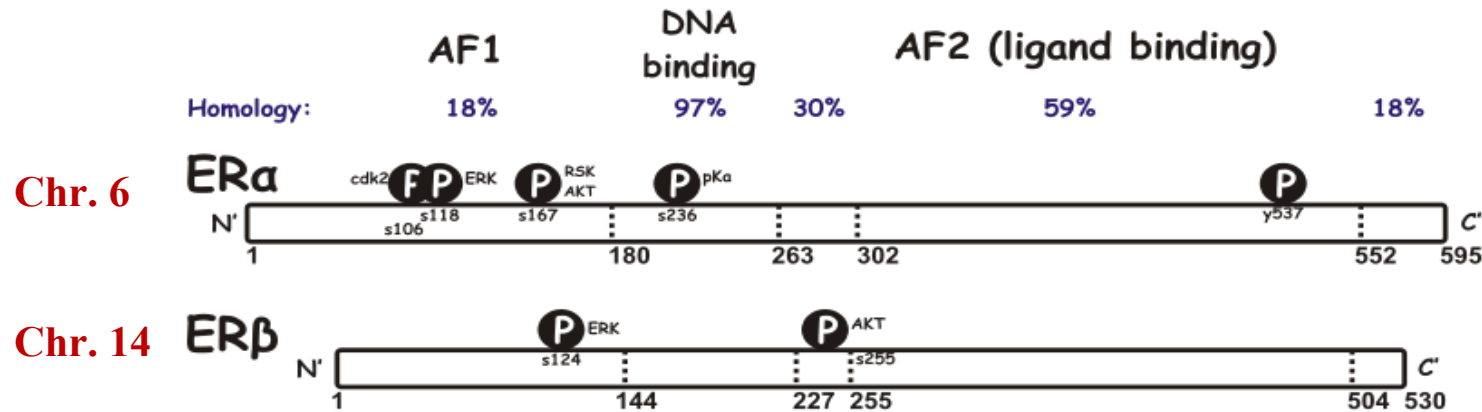
- **Testes**
 - Sertoli cell
 - Leydig cell
 - Germ cells
- **Adipose tissue**
- **Adrenals**
- **Brain**
- **Hair**
- **Liver**

Sources of estrogens in men

	Daily production (μg)	Blood concentration (pg/ml)
Estradiol	40 - 50 20 - 90*	20 - 40

Critical serum estradiol threshold 15-25 pg/ml

Nuclear estrogen receptors



ERα (ER1)

Testis (Leydig), prostate (stroma), liver, adipose, skeletal muscle, bone, breast, brain (pituitary, hypothalamus)

ERβ (ER2)

Testis (spermatocytes, spermatids), prostate (epithelium), brain (limbic system, cerebellum, cerebral cortex), colon, vascular endothelium, bone

- ER1 demonstrated in 1950
- ER2 demonstrated in 1996
- ligand-activated transcription factors
- belong to the nuclear hormone receptor superfamily

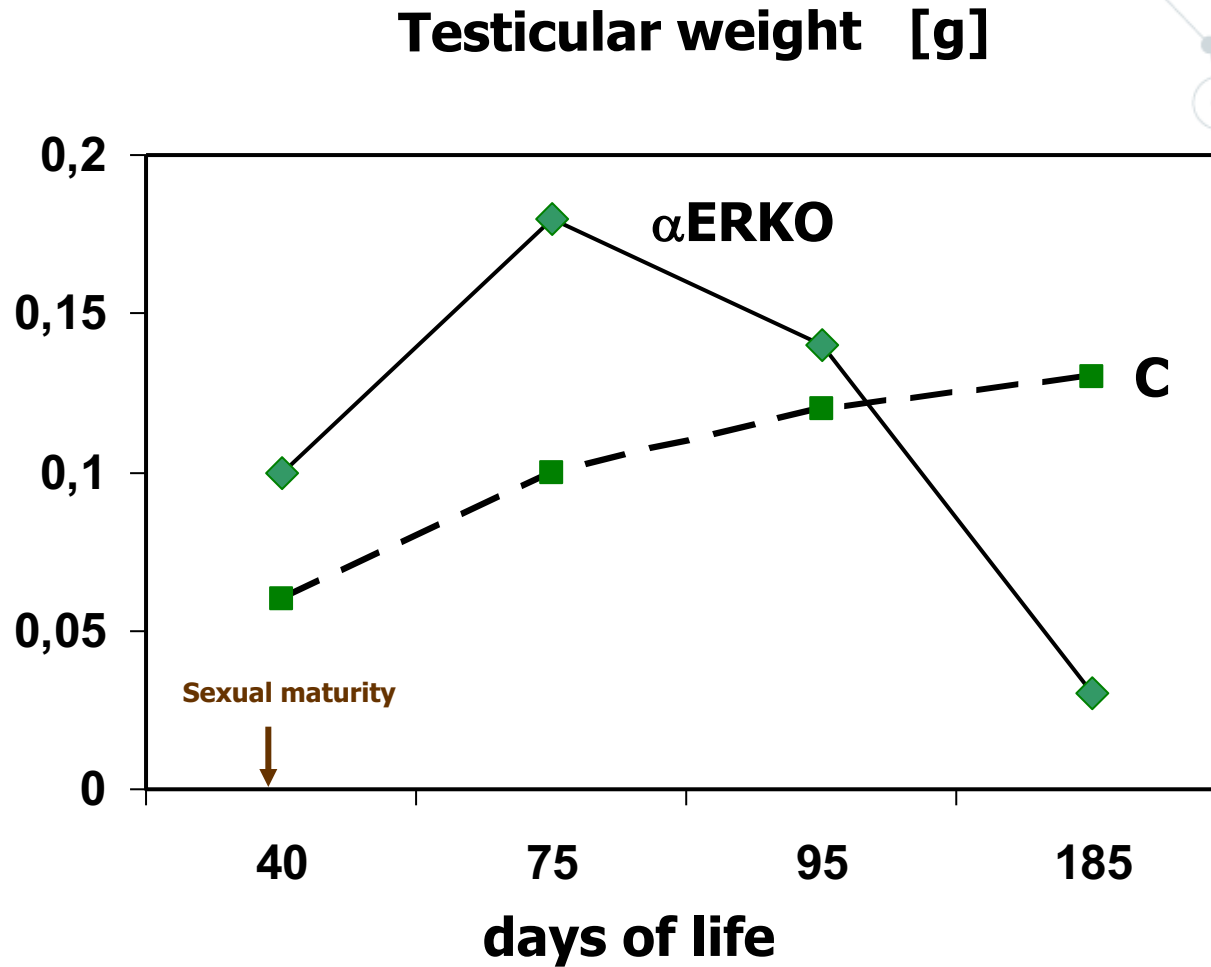
Membrane estrogen receptor

- **G protein-coupled estrogen receptor 1 (GPER)**, known also as **G protein-coupled receptor 30 (GPR30)**
- discovered in 2005
- is encoded by the *GPER* gene (**chr. 7**)
- is localized in the cellular endoplasmic reticulum
- binds to and is activated only by estradiol
- is responsible for some of the rapid nongenomic signalling events
- is expressed in testis (germ and somatic cells), brain, blood vessels, adipose, liver, pancreas, skeletal muscles

ER and aromatase deficiency in mouse model

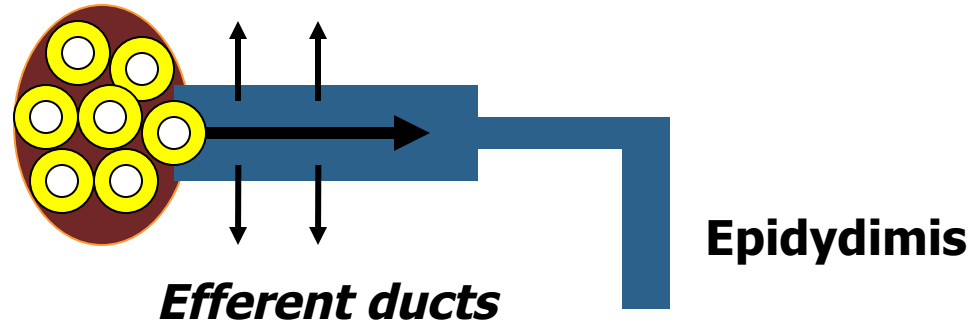
α ERKO	β ERKO	$\alpha\beta$ ERKO	ArKO
- normal development - advancing atrophy of testes - infertility (<i>↓ number of sperms, inability to fertilize egg in vitro</i>)	- normal development - normal fertility	- normal development - advancing atrophy of testes - infertility (<i>↓ number of sperms inability to fertilize egg in vitro</i>)	- normal development - advancing $\downarrow$ number of spermatids - 50% $\downarrow$ number and motility of sperms 

α ERKO mice



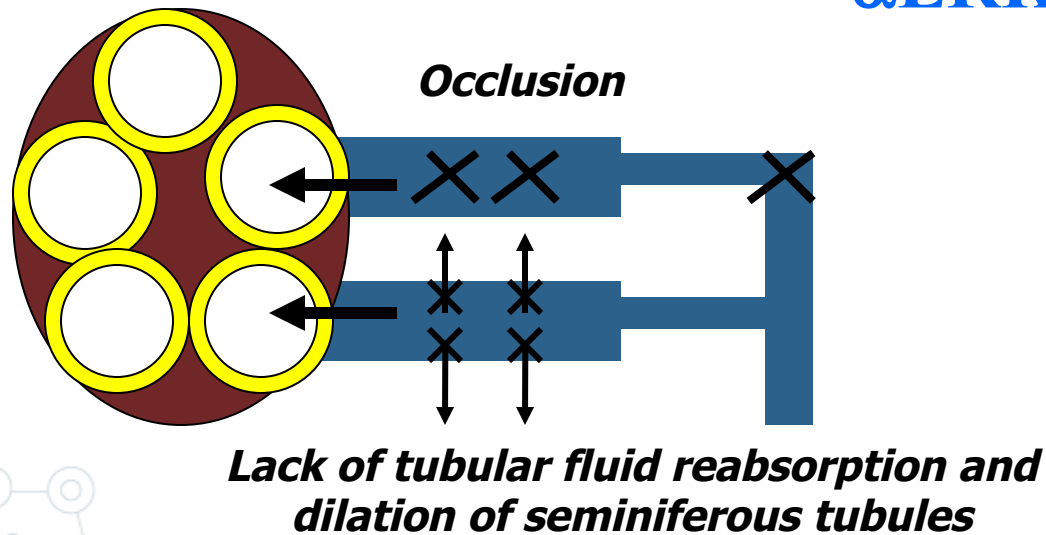
Testis

Normal mice

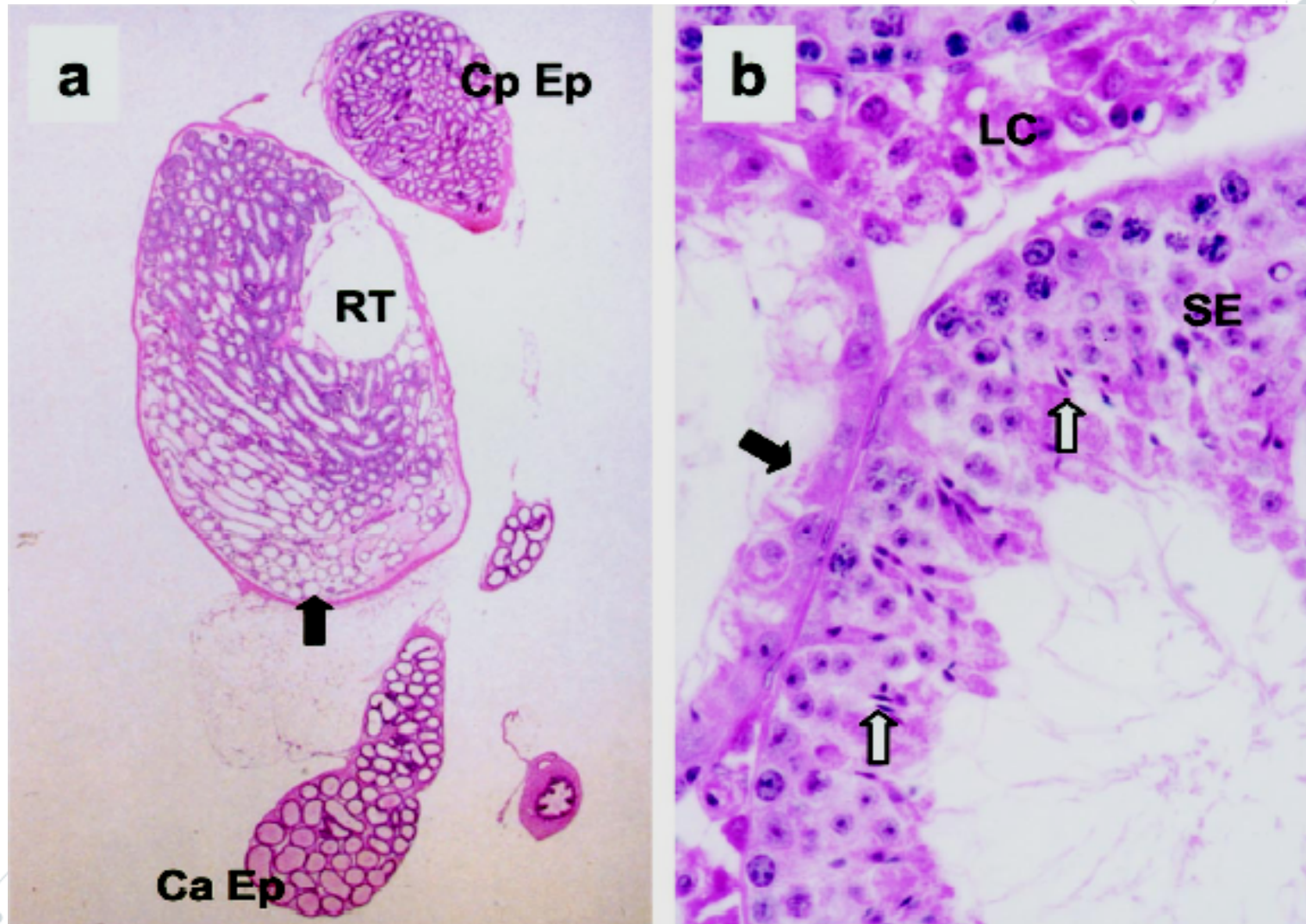


Testis

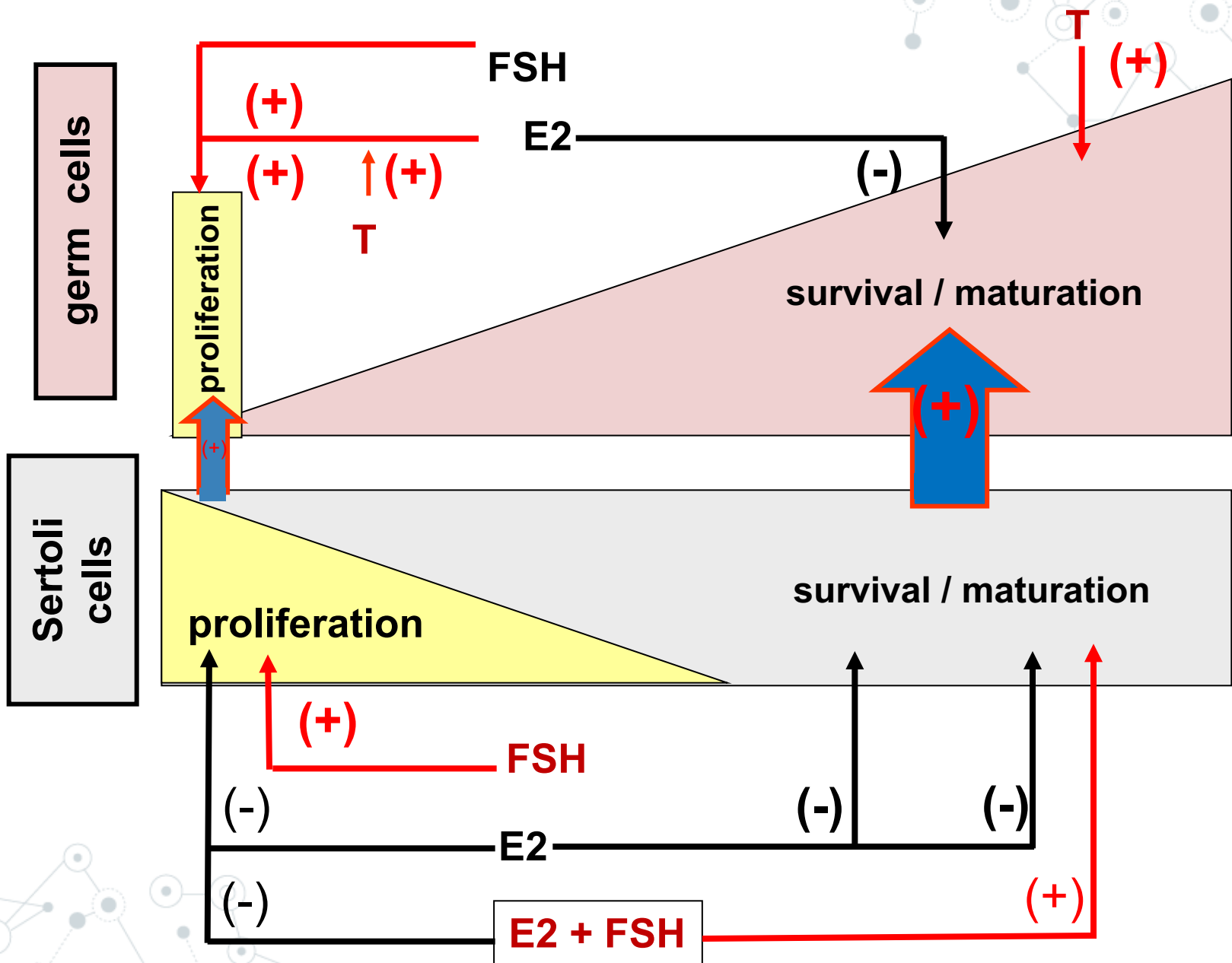
α ERKO mice



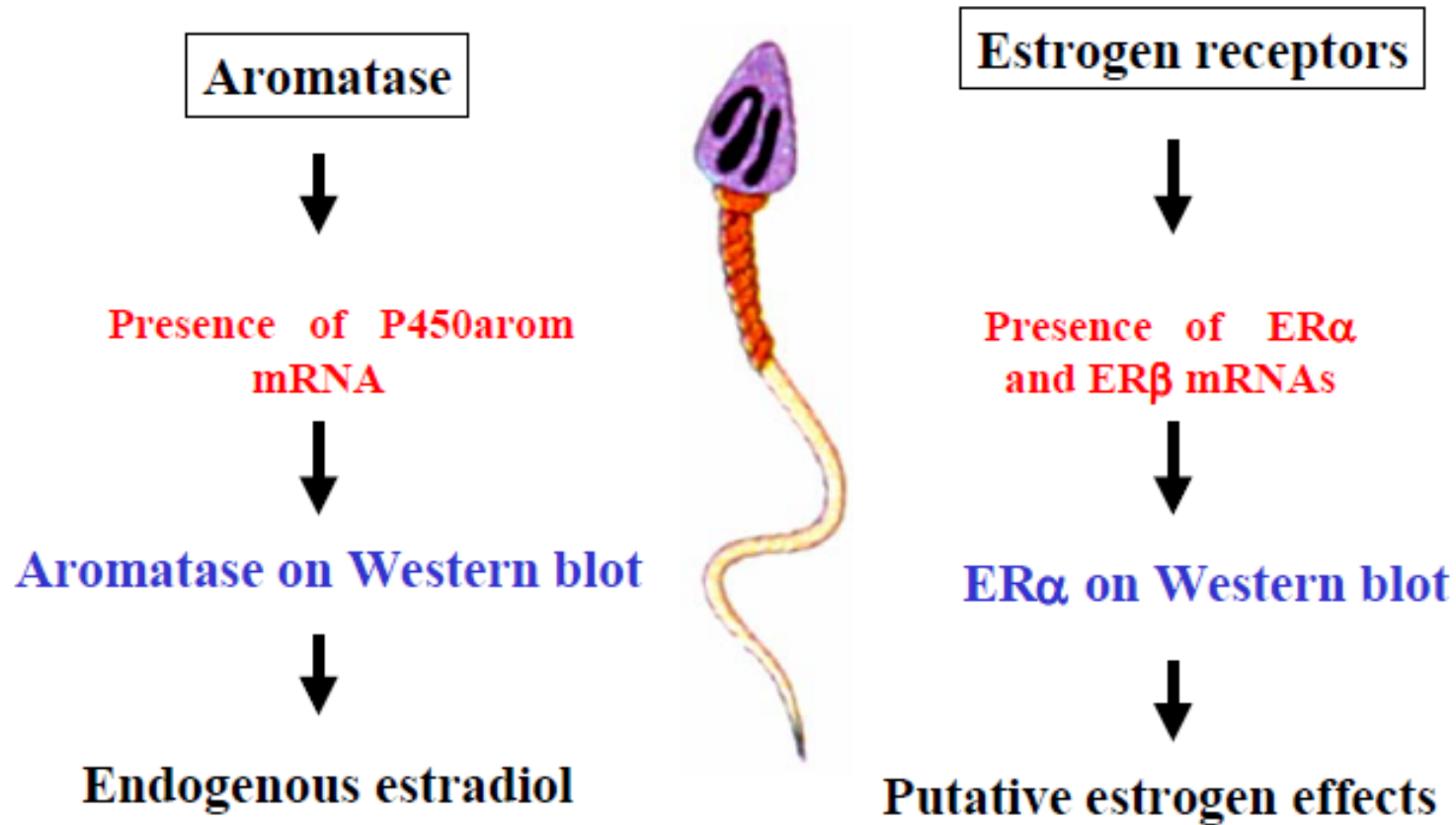
α ERKO mice



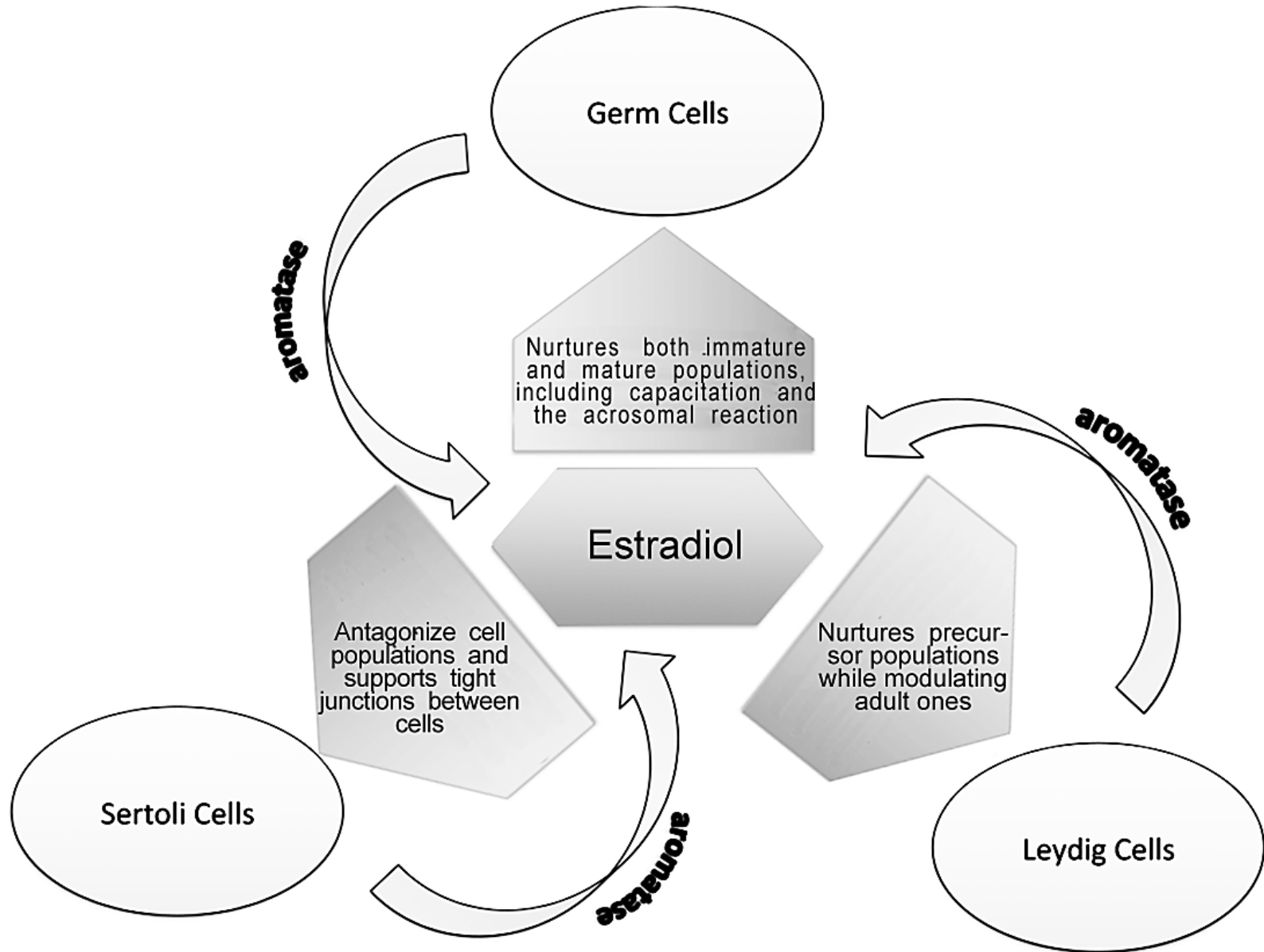
Hormonal control of spermatogenesis



Human spermatozoa – source and target of estrogens



The role of estradiol in spermatogenesis



ARKO mice



Brain

- Impairment of sexual behaviour
 - Lower copulation frequency
 - Lack of intromission and ejaculation
 - Decreased level of aggression
- Decreased physically-active behaviour
- Impaired spatial reference memory

Bone

- Osteopenia / osteoporosis

Metabolic changes

- Obesity
- Decrease in lean mass
- Hyperleptinemia
- Insulin resistance
- apoptosis of dopaminergic neurons in the hypothalamic arcuate nucleus, an area of the brain pivotal to the regulation of energy uptake, storage and mobilisation

Gonads

- Impaired spermatogenesis
- Low sperm concentration and motility
- Sperm unable to fertilize oocyte *in vitro*

Role of estrogens in central nervous system

- Affect the amount of serotonin receptors in the brain modulating mood, mental state, cognition, and emotion
- **GPER and ER α** - mediate the antidepressant-like effects of estradiol
- **GPER** - angiogenic effects
- **ER β** - anxiolytic effects
- **GPER and ER β** - activate oxytocin system
- Estrogens produced locally in the brain are not only **neuroactive steroids** but they also display many functional characteristics of **neuromodulators** and perhaps **neurotransmitters**.

ARKO mice



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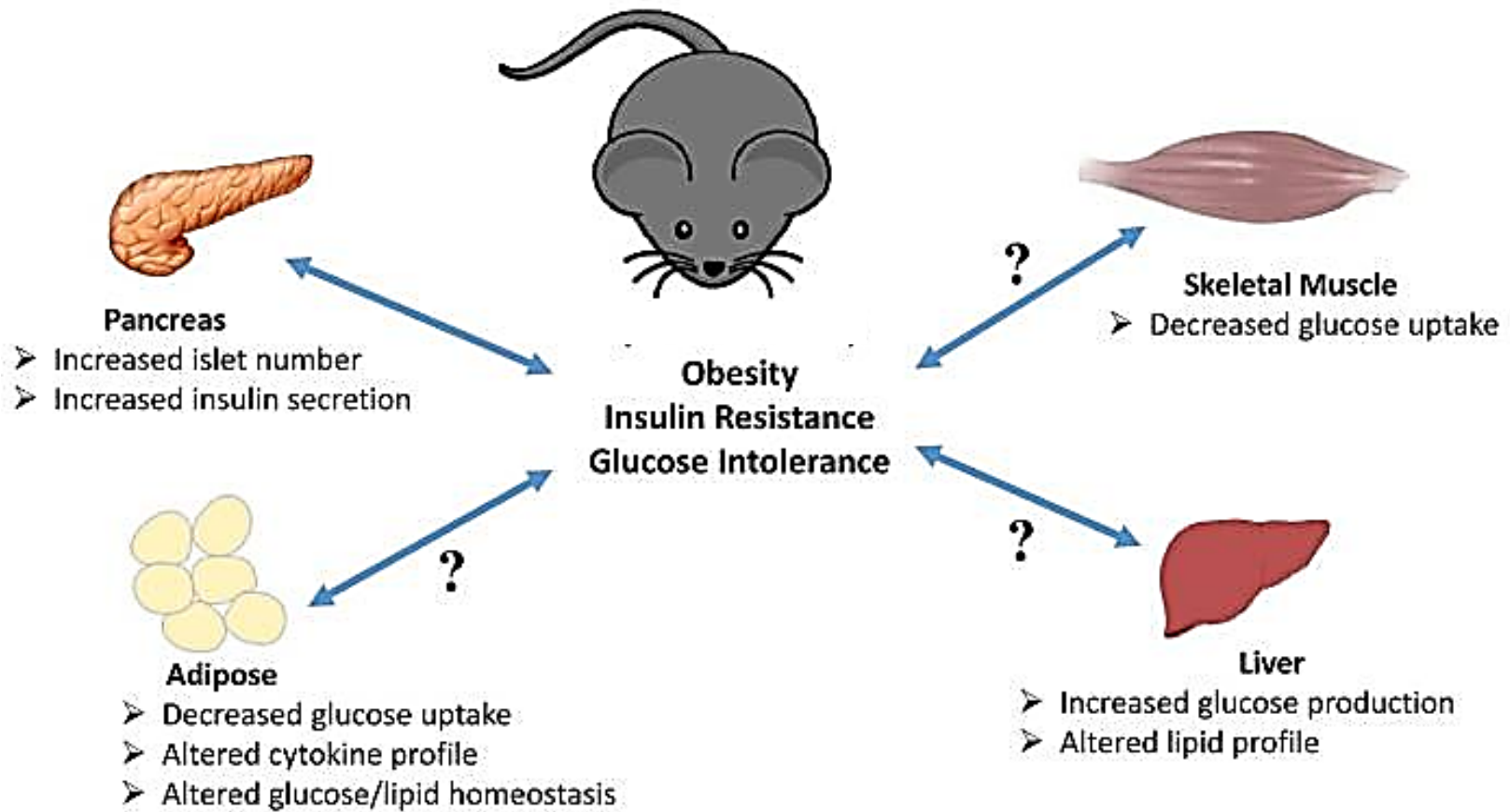
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Gonads

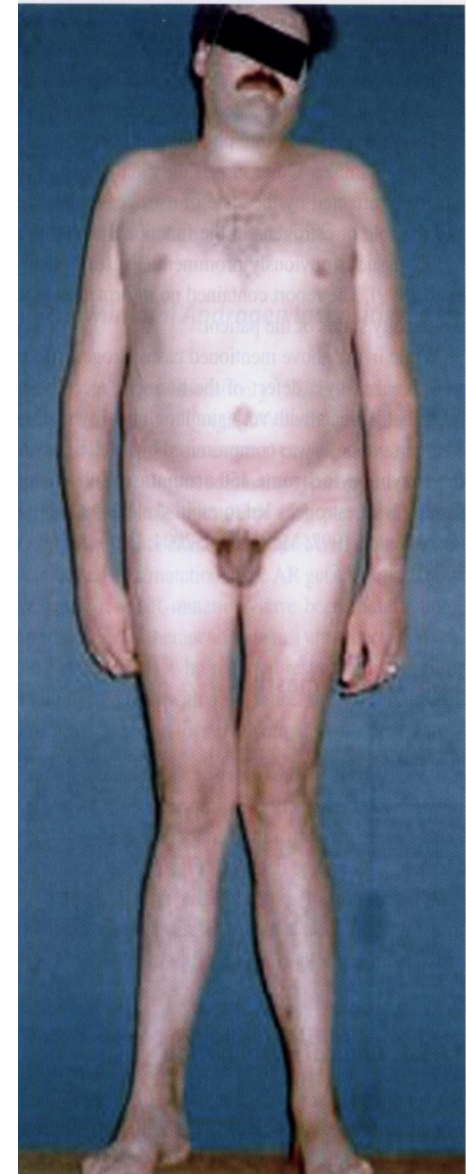
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GPRKO mice



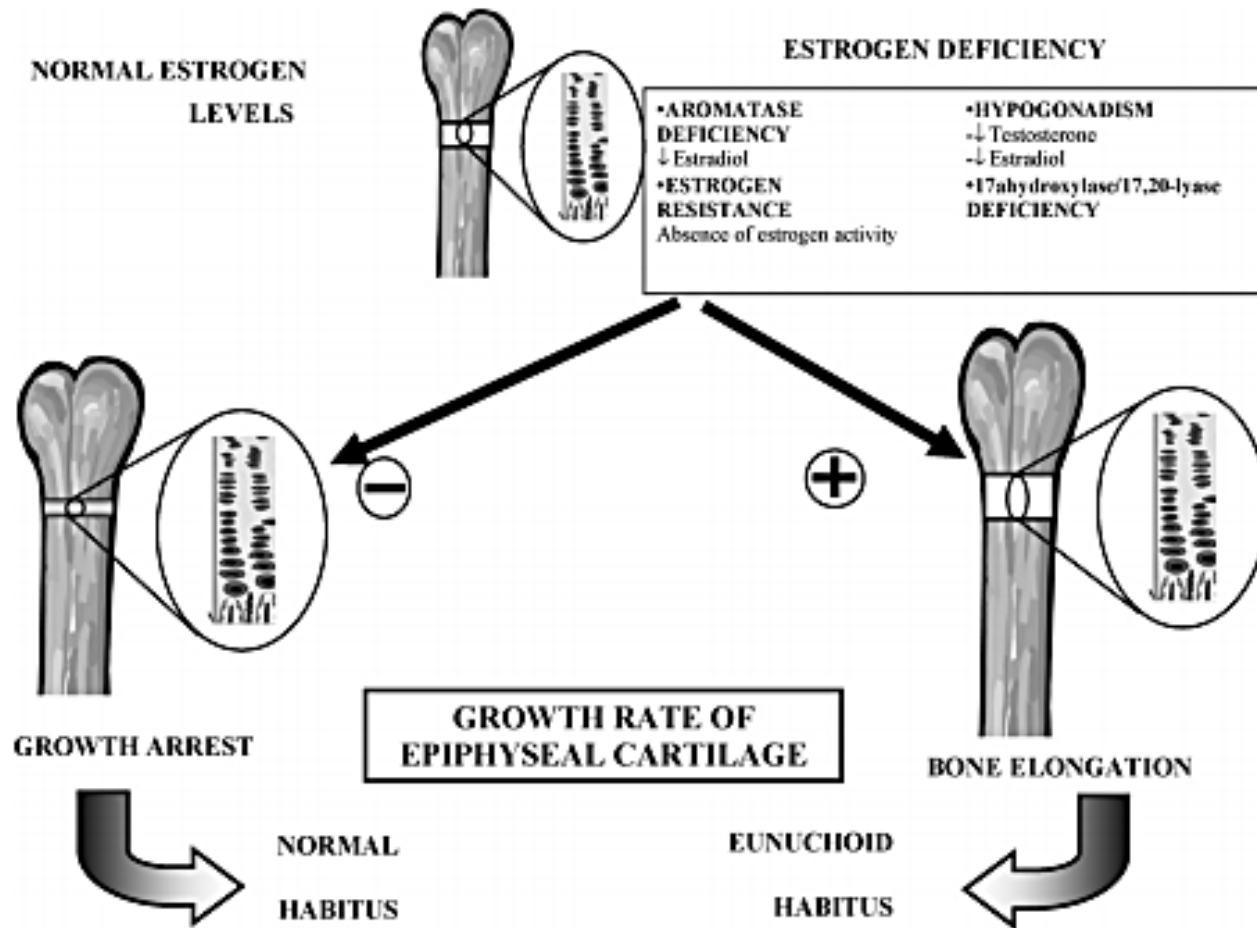
Aromatase deficiency in men

- Tall stature
- Eunuchoid body proportions and valgus knee
- Unfused epiphyses
- Decreased bone age
- Decreased BMD
- Normal age of puberty
- Normal male sexual characteristics
- Decreased testes volume
- Increased FSH, normal LH and T, and decreased E2 levels
- Severe oligozoospermia
- Male gender identity
- Heterosexual sex orientation
- Libido and sexual functions normal
- Truncal obesity
- Insulin resistance and dyslipidemia (increased total cholesterol and LDL, decreased HDL)
- Hepatic steatosis, enlargement, increased hepatic enzymes

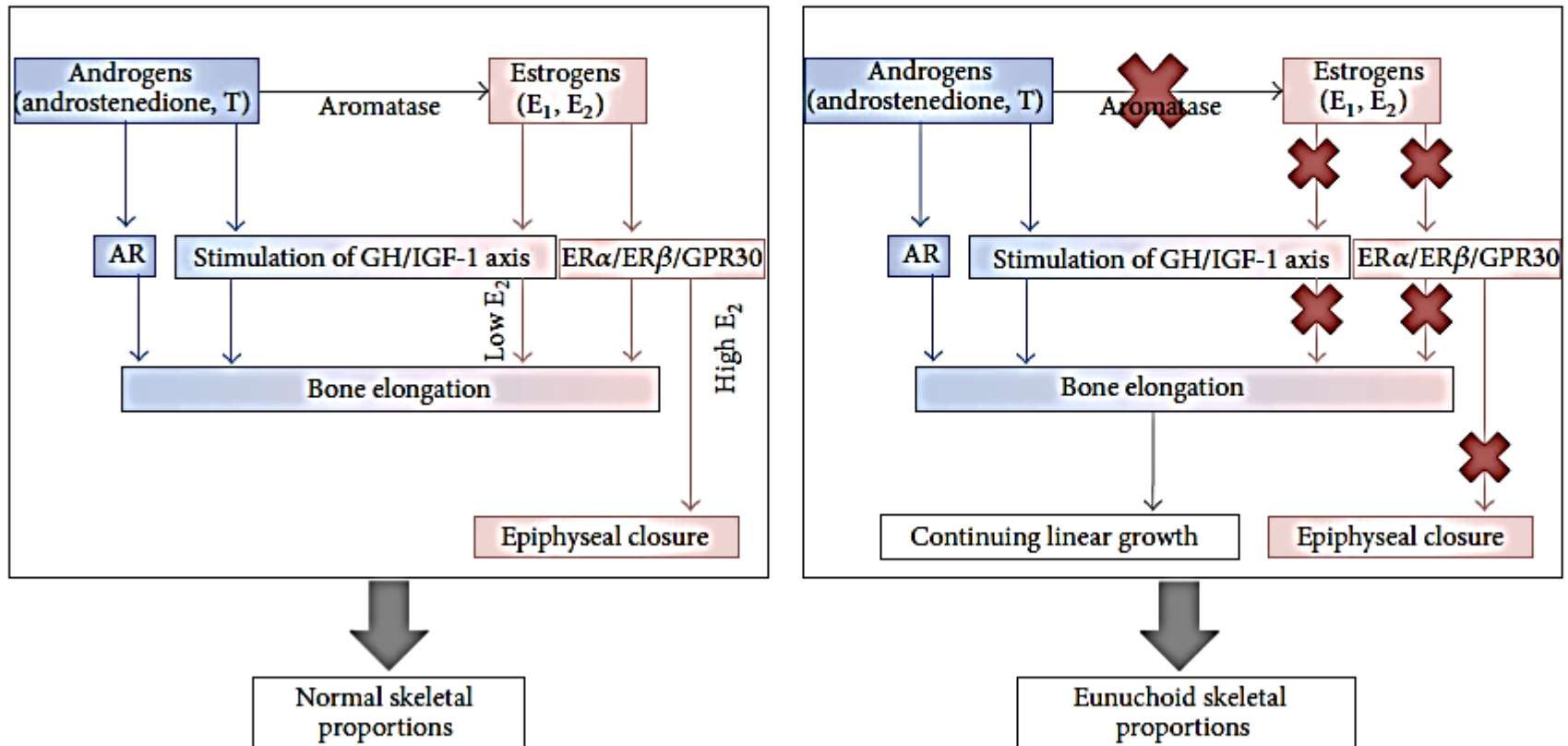


*Morishima et al., 1995; Carani et al., 1997;
Jones et al., 2006*

Role of Estrogens on Human Male Skeleton



Role of Estrogens on Human Male Skeleton

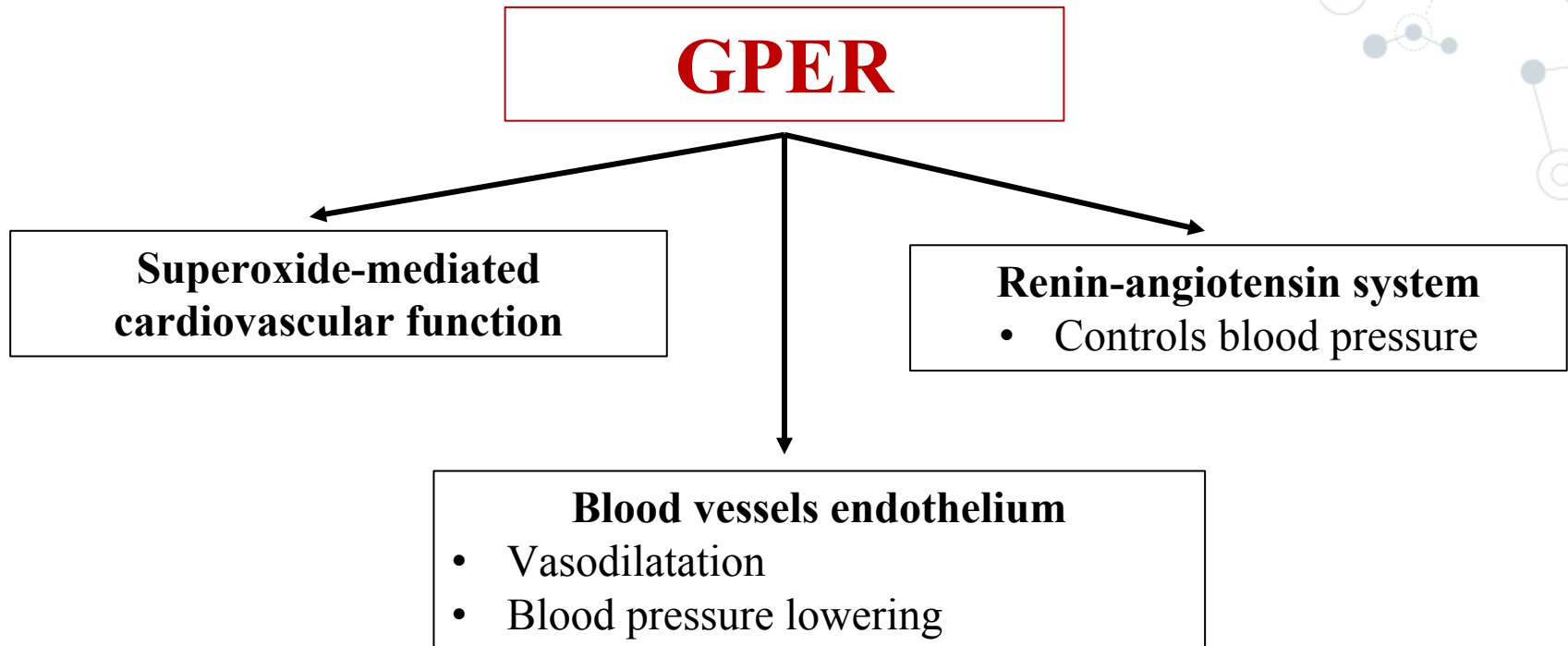


Role of Estrogens on Human Male Skeleton

Elderly men with late onset hypogonadism		
Estrogenic status	Relative estrogen deficiency (less functioning aromatase)	Normal circulating estrogens (normal functioning aromatase)
Clinical phenotype	Low serum E ₂	Normal serum E ₂
	Normal E ₂ /T ratio	Impaired E ₂ /T ratio
	Highest gonadotropins	Less increased gonadotropins
	Severely impaired BMD	Normal to moderate BMD decrease
	Osteoporosis	Osteopenia Risk of developing gynecomastia
Fracture risk	High	Low

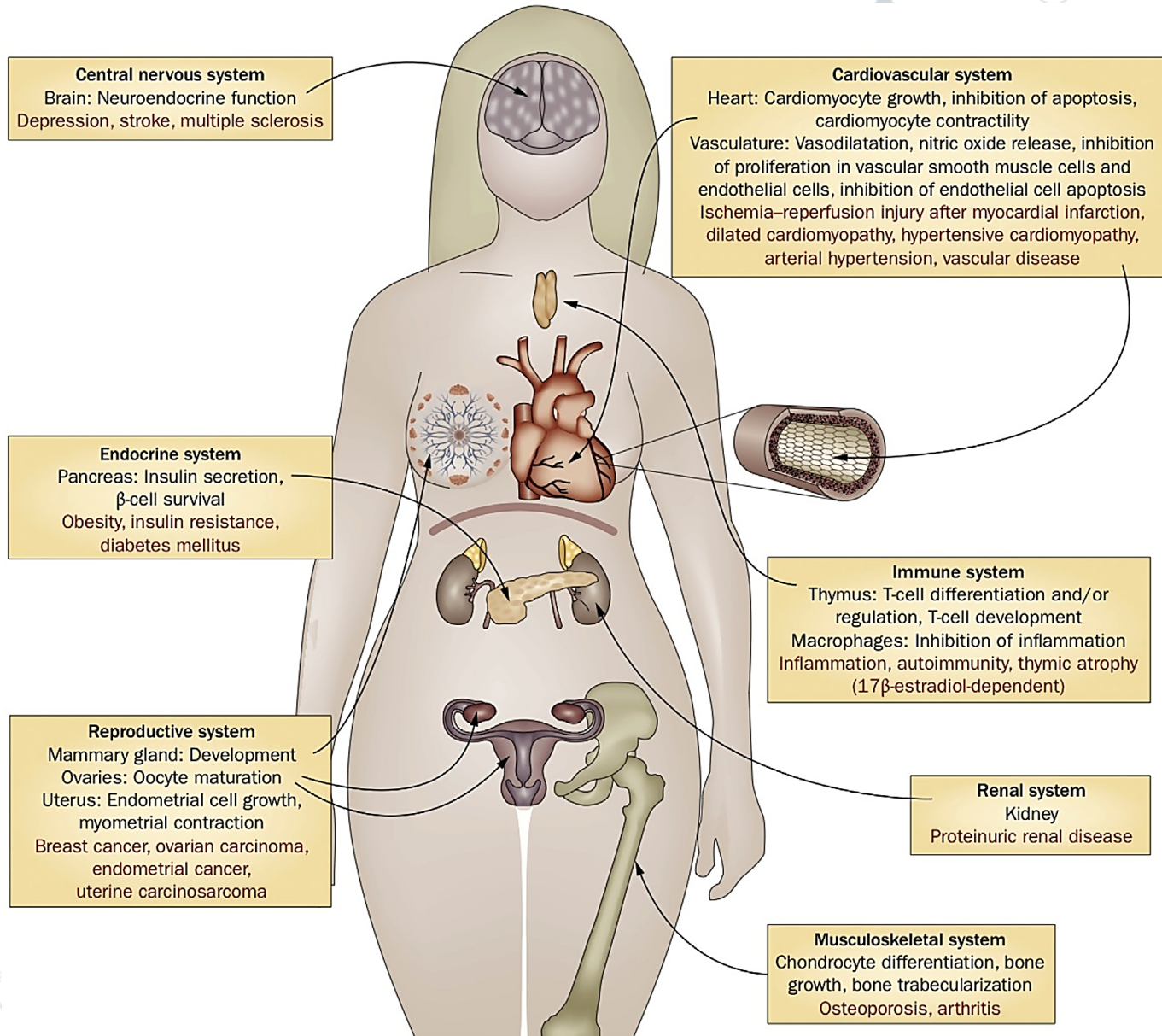
E₂: estradiol; T: testosterone; BMD: bone mineral density.

Role of estrogens in cardiovascular system



lower risk of cardiovascular disease

Role of estrogens in women



Conclusions

1. In men we are only at the beginning in our understanding of the estrogenic activities.
2. Many aspects of genomic and non-genomic effects of estrogen have not been fully elucidated to this date.
3. Estrogens synthesized within extragonadal sites are most probably biologically active only at the local tissue level in a paracrine or intracrine fashion. Thus these sources of estrogens play an important, but hitherto largely unrecognised, physiological and pathophysiological role.
4. Probably the androgen/estrogen ratio may prove to be more important than the individual actions of each hormone, in a tissue- and gender-specific manner.



THANK YOU!