PHYSIOLOGY OF REPRODUCTION

Life is a dynamic system with focused behavior, with

autoreproduction, *characterized by flow of substrates,*

energies and information.

Reproduction in mammals (humans):

1) Sexual reproduction
2) Selection of partners
3) Internal fertilization
4) Viviparity
5) Eggs, resp. embryos – smaller, less, slow development, placenta
6) Low number of offspring, intensive parental care

High investment, low-volume reproduction strategy !

Reproduction in humans – gender comparison:

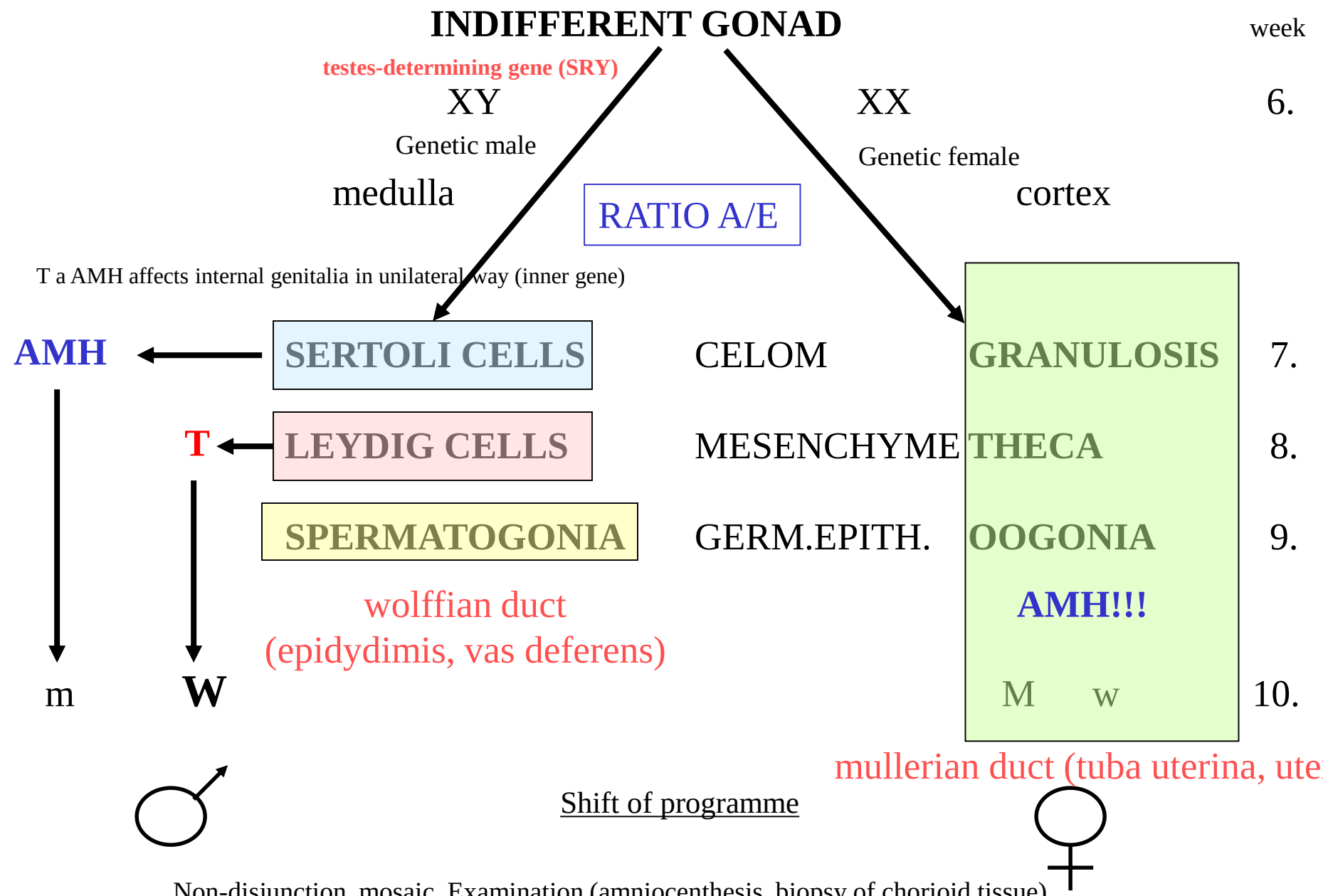
1) Both male and female are born immature (physically and sexually)

2) Sex hormones are produced in men also during prenatal and perinatal periods, not in women!

3) Reproduction period significantly differs – puberty, climacterical

4) Character of hormonal changes significantly differs – cyclic vs. non-cyclic

SEX DIFFERENTIATION



Non-disjunction, mosaic. Examination (amniocenthesis, biopsy of chorioid.tissue).

- Meiosis occurs only in germ cells and gives rise to male and female **GAMETES**
- Fertilization of an oocyte by an X- or Y-bearing sperm establishes the zygote´s **GENOTYPIC SEX**
- Genotypic sex determines differentiation of the indifferent gonad into either an OVARY or a TESTIS
- The testis-determining gene is located on the Y chromosome (testis-determining factor, sex-determining region Y)
- Genotypic sex determines the **GONADAL SEX**, which in turn determines **PHENOTYPIC SEX** (fully established at puberty)
- Phenotypic differentiation is modified by endocrine and paracrine signals (testosteron, DHT, AMH)

AMH (MIH, MIF, MIS, MRF) – ANTIMŰLLERIAN HORMONE

1940, TGF-β, receptor with internal TK activity

Source: Sertoli cells (**5th** prenatal week) or embryonal ovary (**36th** prenatal week)

In adult women – granulosa cells of small follicles (NO in antral – under influence of FSH - and atretic follicles)

Role in men: **TUMOUR MARKER**

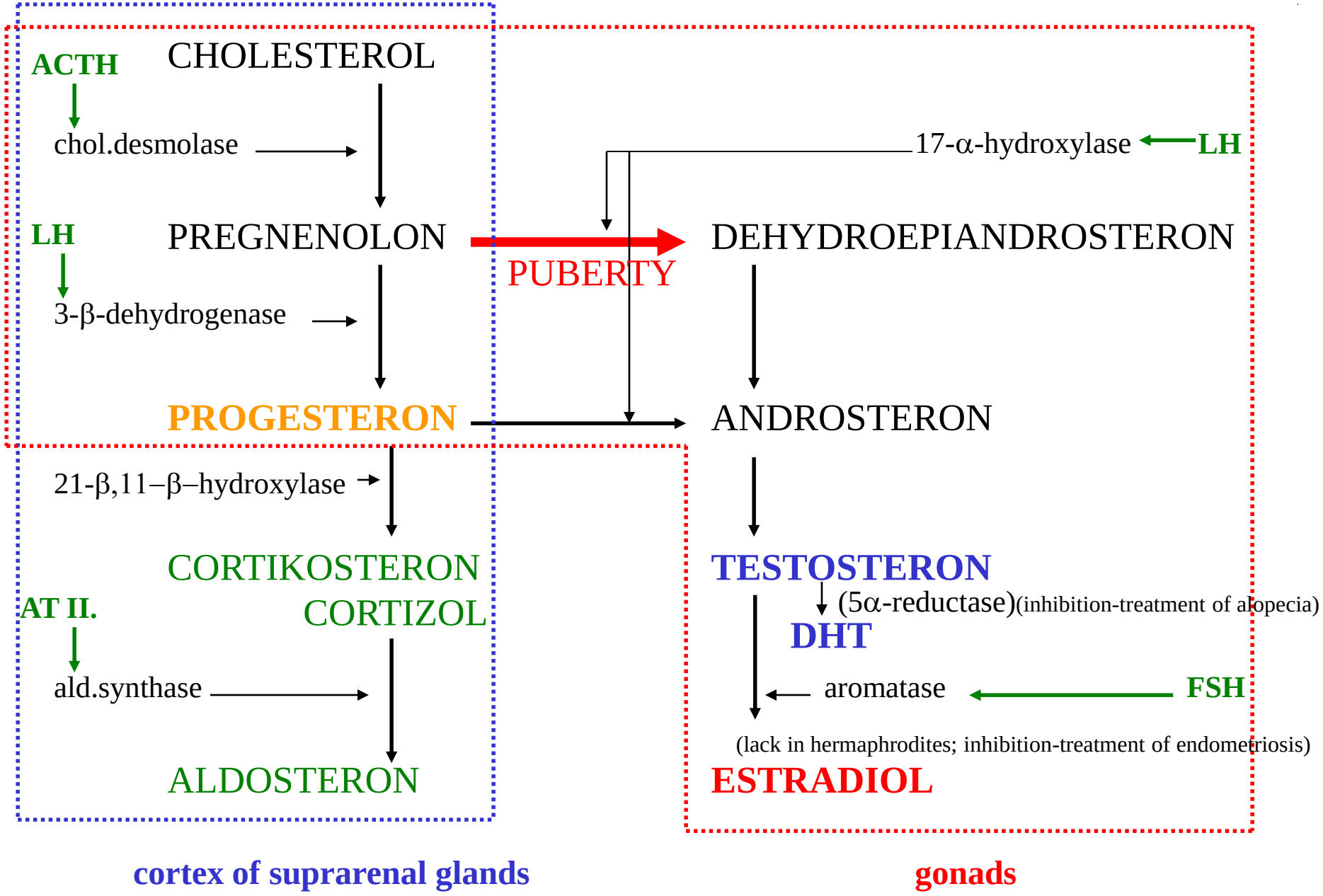
- Regression of müllerian duct
- Marker of central hypogonadism

Role in women:

- Lower plasmatic levels (by one order), till climacterical
- Estimation of ovarian reserve (AMH level corresponds to pool of pre-antral follicles)
- Marker of ovarian functions loss (premature climacterical)
- Diagnosing of polycystic ovaria syndrome

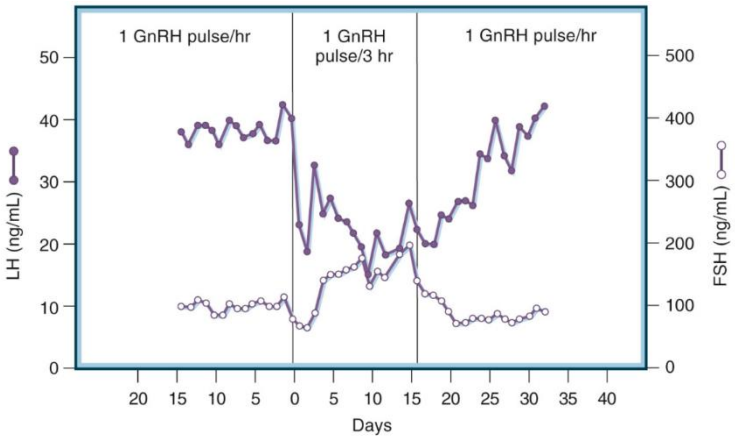
BIOSYNTHESIS OF STEROID HORMONES

Impact of androgens on CNS.



GONADOLIBERIN (GnRH, GONADOTROPIN-RELEASING HORMONE)

Characteristics
- Specific origin of GnRH neurons out of CNS
- GnRH-I, GnRH-II, (GnRH-III) – $G_{q/11}$ (PKC, MAPK)
- Important up and down regulation (steroidal hormones, gonadotrophs)
- **Down regulation** – malnutrition, lactation, seasonal effects, aging, continual GnRH
- **Up-regulation** – effect of GnRH on gonadotrophs (menstrual cycle)
- *GNRH1* – hypothalamus; *GNRH2* – other CNS areas



Hypothalamo-hypophyseal axis
- FSH, LH
- Significance of GnRH pulse frequency (glycosylation)
- Menstrual cycle, puberty and its onset

Clinical consequences
Continuously administered GnRH analogues – treatment of oestrogen/steroid-dependent tumours of reproduction system
- Treatment of premature puberty (leuprorelin – agonist!)

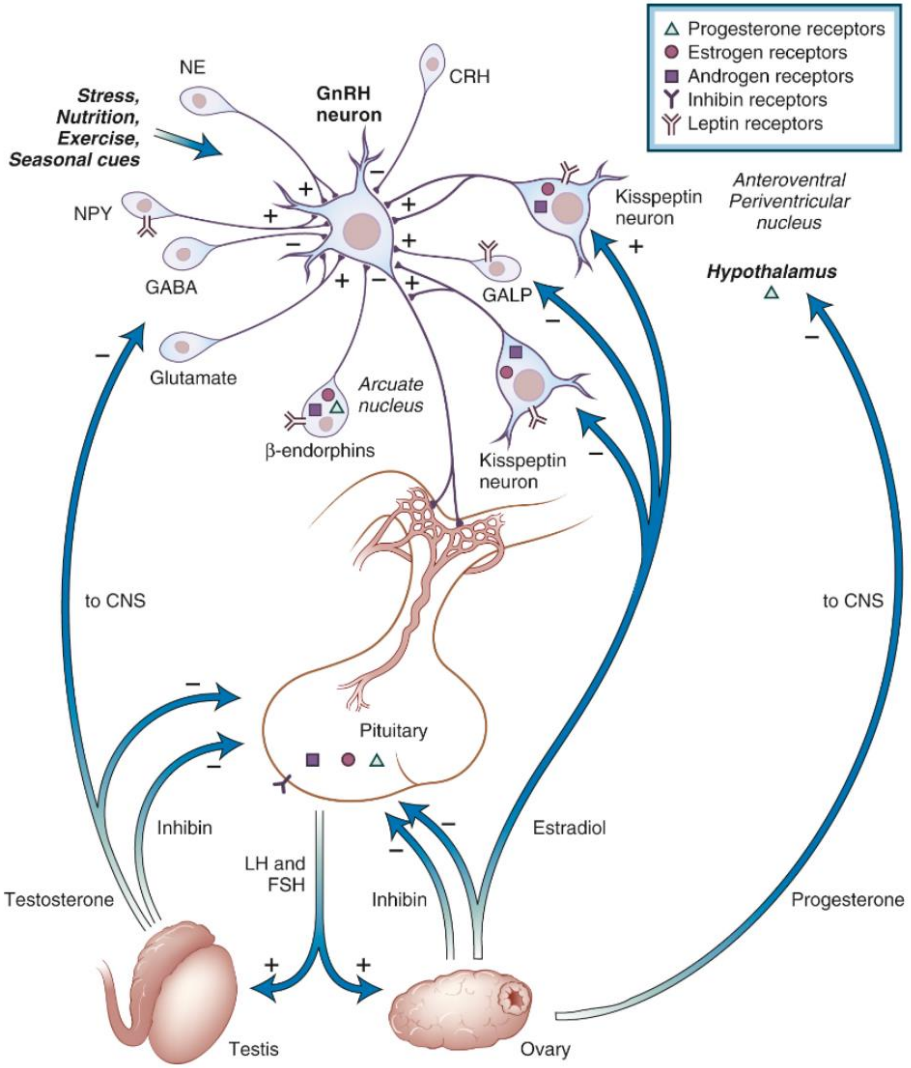
Other functions and places of production
- CNS – neurotransmitter (area preoptica)
- Placenta
- Gonads
- Tumours (prostate, endometrium)

} - Unknown function

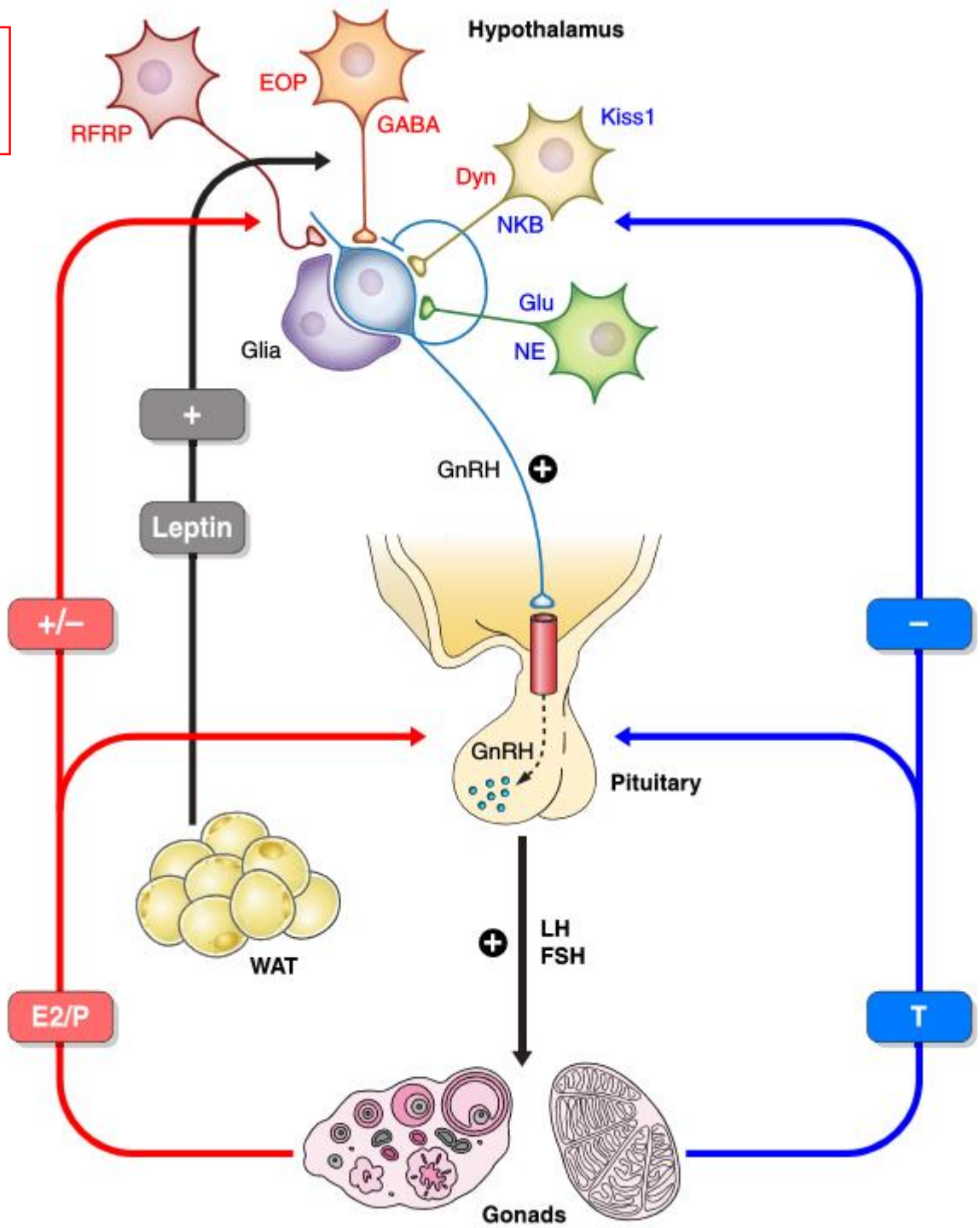
GONADOLIBERIN – REGULATION OF SECRETION

- Inputs from various CNS areas (pons, limbic system)
- Dominating inhibitory effect of sex hormones with exception of estradiol (**negative-positive feedback**)
- Kisspeptin in women
- Inhibitory effect of PRL
- Effect of circulating substrates (FA, Glu)
- Leptin (NPY, kisspeptin)

- Stress of various origin
  - Acute – MC impairment without effect on fertility
  - Chronic – impairment of fertility, decreased levels of circulating sex hormones

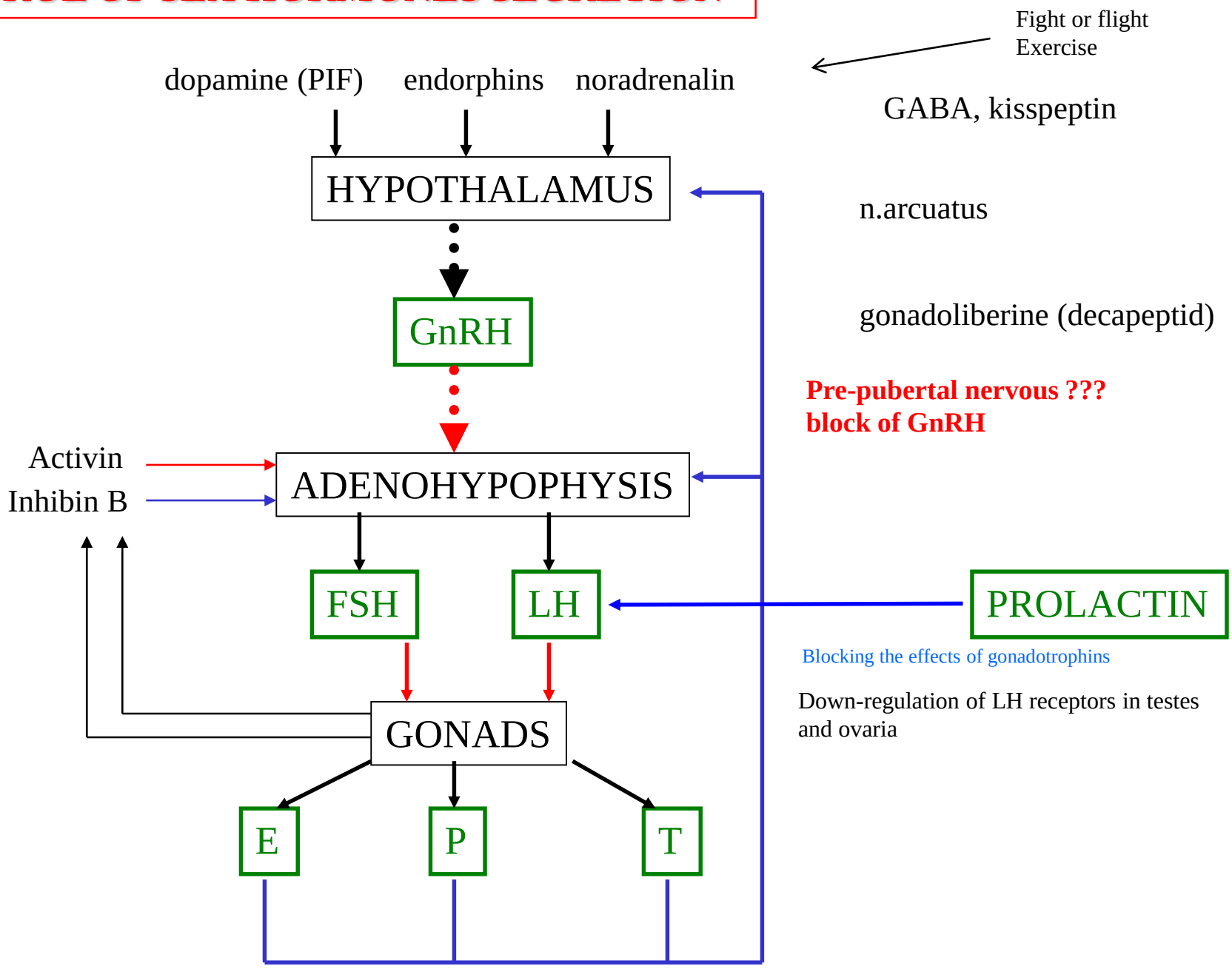


CONTROL OF SEX HORMONES SECRETION



Pinilla et al., Phys Rev 92: 1235- 1316, 2012

CONTROL OF SEX HORMONES SECRETION



LEPTIN A REPRODUCTION

Activation of reproductive system does not depend on age, but on nutritional state of organism.

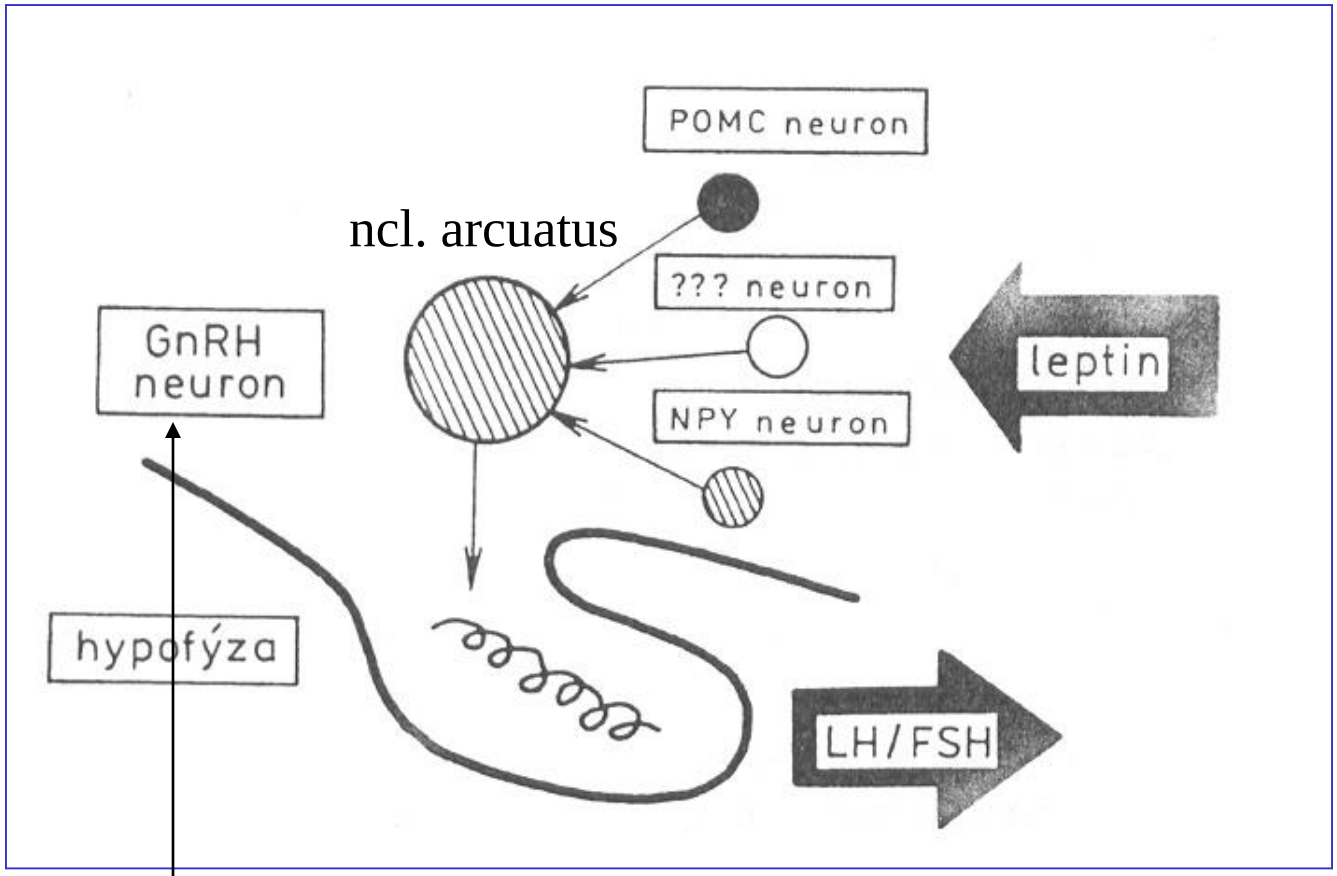
LEPTIN: ob-protein, ob-gen, 7.chromosome
„λεπτοσ“ = thin, slim
polypeptide, 176 AA

Bound in **hypothalamus**: n.paraventricularis, suprachiasmaticus, arcuatus a dorsomedialis

Produced in: adipocytes, placenta, stomach, mammal epithelium (???)
Leptin plasmatic levels are sex-dependent (less in males) and do not depend on nutritional state

Leptin receptor: gene on 4.chromosome, 5 types of receptor, A-E
Receptor B – effect in **gonads and hypophysis**

Leptin is not only a factor of body fat amount, but affects also the regulation of neuroendocrine functions including hypothalamo-hypophyseo-gonadal axis.



area preoptica - reproduction

???Critical amount of adipose tissue – leptin – hypothalamus – LHRH - puberty

Effects of leptin on testes are not fully elucidated yet.

Testosterone and dihydrotestosterone suppress production of leptin in adipocytes!

REGULATION OF PUBERTY ONSET BY LEPTIN

Critical body mass.

Leptin plasmatic levels in pre-pubertal children are sex-independent.

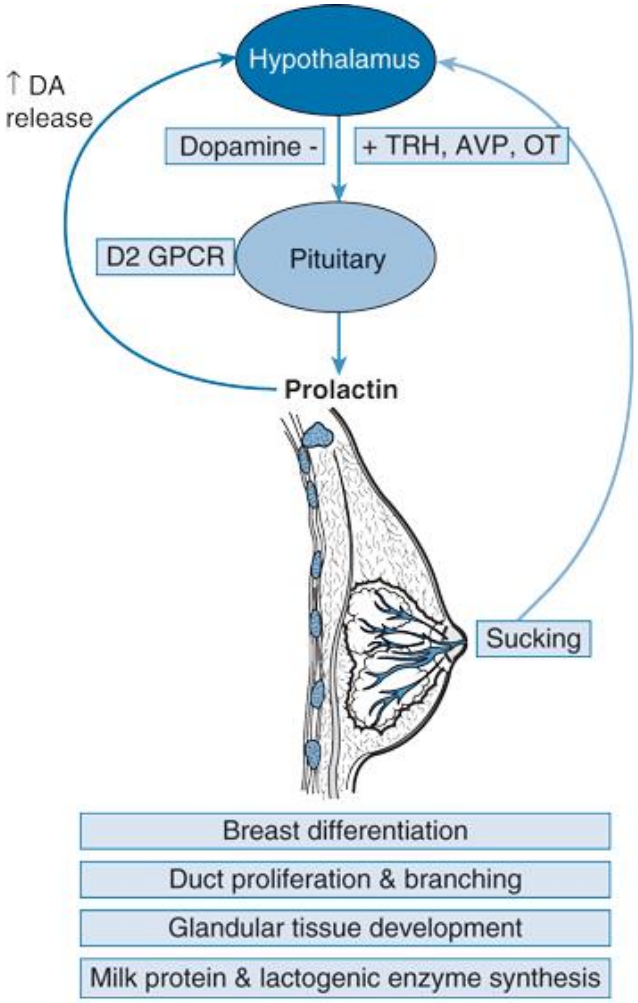
Pre-pubertal „leptin resistance“ (relative).

In puberty, girls produce 2x more leptin per 1kg of adipose tissue than boys.

PROLACTIN - PRL

Co-hormone

Characteristics
- Protein
- Lactotropic cells (only PRL)
- Mammosomatotrophic cells (PRL and GH)
- Hyperplasia – pregnancy and lactation
- Expression regulated by oestrogens, dopamine, TRH and thyroid gland hormones
- Polypeptide, circulating in 3 forms (mono-, di-, polymer)
- Monomeric PRL – highest biological activity
- Monomeric PRL further cleaved (8/16 kDA)
- 16 kDA PRL – anti-angiogenic function
- PRLR – mamma, adenohypophysis, suprarenal gland, liver, prostate, ovary, testis, small intestine, lungs, myocardium, SNS, lymphocytes



Regulation of secretion
- Pulsatile secretion: 4 – 14 pulses/day
- Highest levels during sleep (REM, nonREM)
- Lowest levels between 10:00 and 12:00
- Gradual decrease of secretion during aging
- TIDA cells – dopamine (-, D2R)
- Paracrine – endothelin-1, TGF-β1, calcitonin, histamine (-)
- FGF, EGF (+)
- TRH, oestrogens, VIP, serotonin, GHRH at higher concentrations (+)
- CCK - ?

PROLACTIN - FUNCTIONS

Milk production during pregnancy and lactation = „survival“ function

Other functions – metabolic, synthesis of melanin, maternal behaviour

Reproductive function of PRL

- Lactation = amenorrhea and secondary infertility
- Inhibition of GnRH secretion
- Significance of kisspeptin neurons (PRLR)
- Putative role of metabolic factors

Breast development a lactation

- Puberty – mamma development under the effects of GH a IGF-1
- Effect of oestrogens and progesterone
- Age of 8 – 13
- During pregnancy – proliferation of alveoli and proteosynthesis (proteins of milk and colostrum)
- During the 3rd trimester – production of colostrum (PRL, oestrogens, progesterone, GH, IGF-1, placental hormones)
- Lactation – increase in PRL post-partum, without sucking drop after approx. 7 days
- Milk accumulation prevents further PRL secretion
- Role of oxytocin

Immune function of PRL

- Anti-inflammatory effects ?

Clinical consequences

- Hyperprolactinemia – some antihypertensive drugs, chronic renal failure
- Macroprolactinemia
- Galactorrhoea – role of GH (acromegaly)
- PRL deficiency

CRITICAL DEVELOPMENTAL PERIODS

1) Birth
2) Weaning
3) Puberty (adolescence)
4) Climacterical (menopause)

Critical body mass (critical amount of adipose tissue)

Puberty

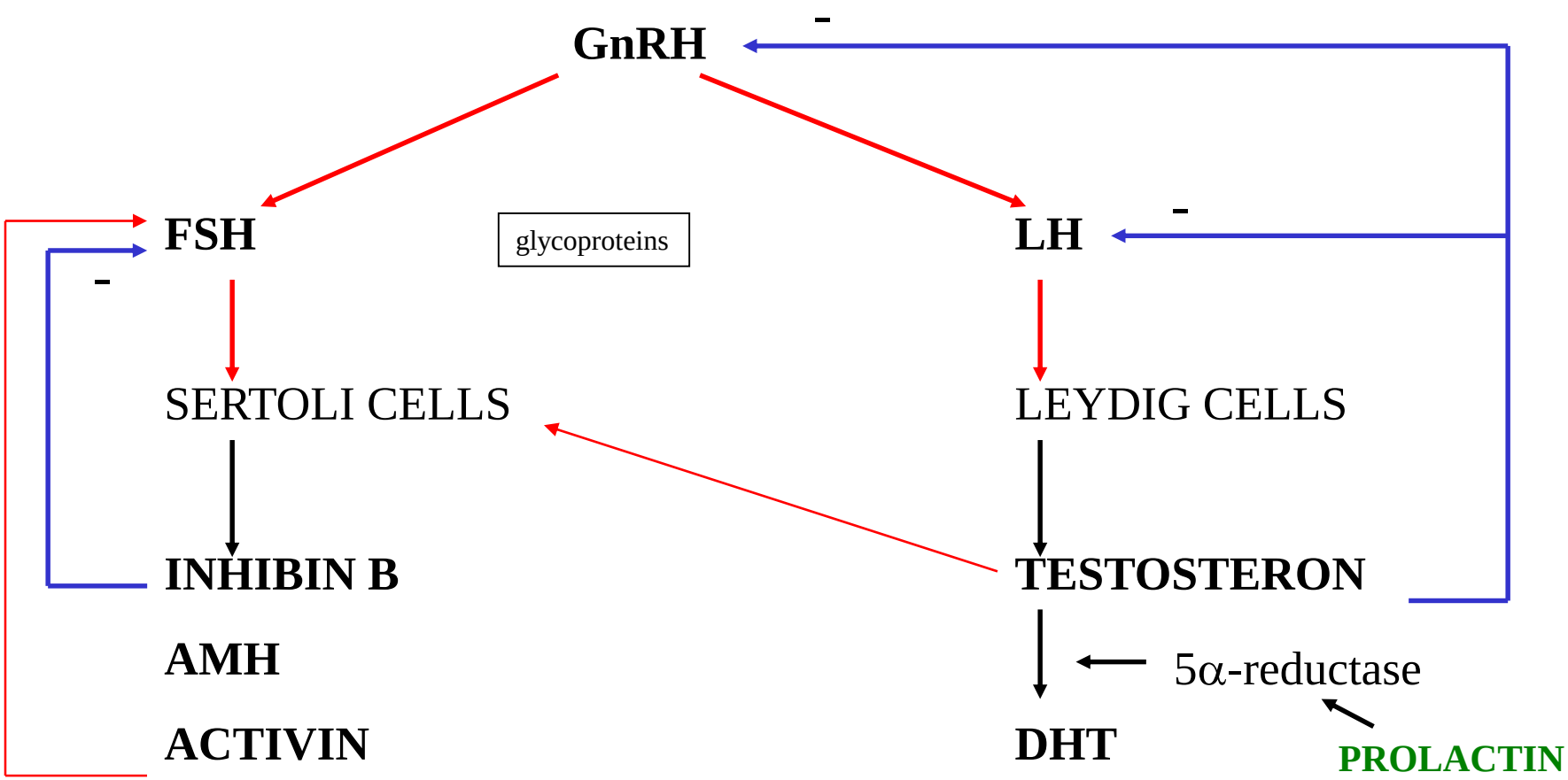
- *Adrenarche*
- *Pubarche*
- *Menarche*
- *Telarche*

Pubertas praecox (central)
Pseudopubertas praecox (peripheral)

Late puberty

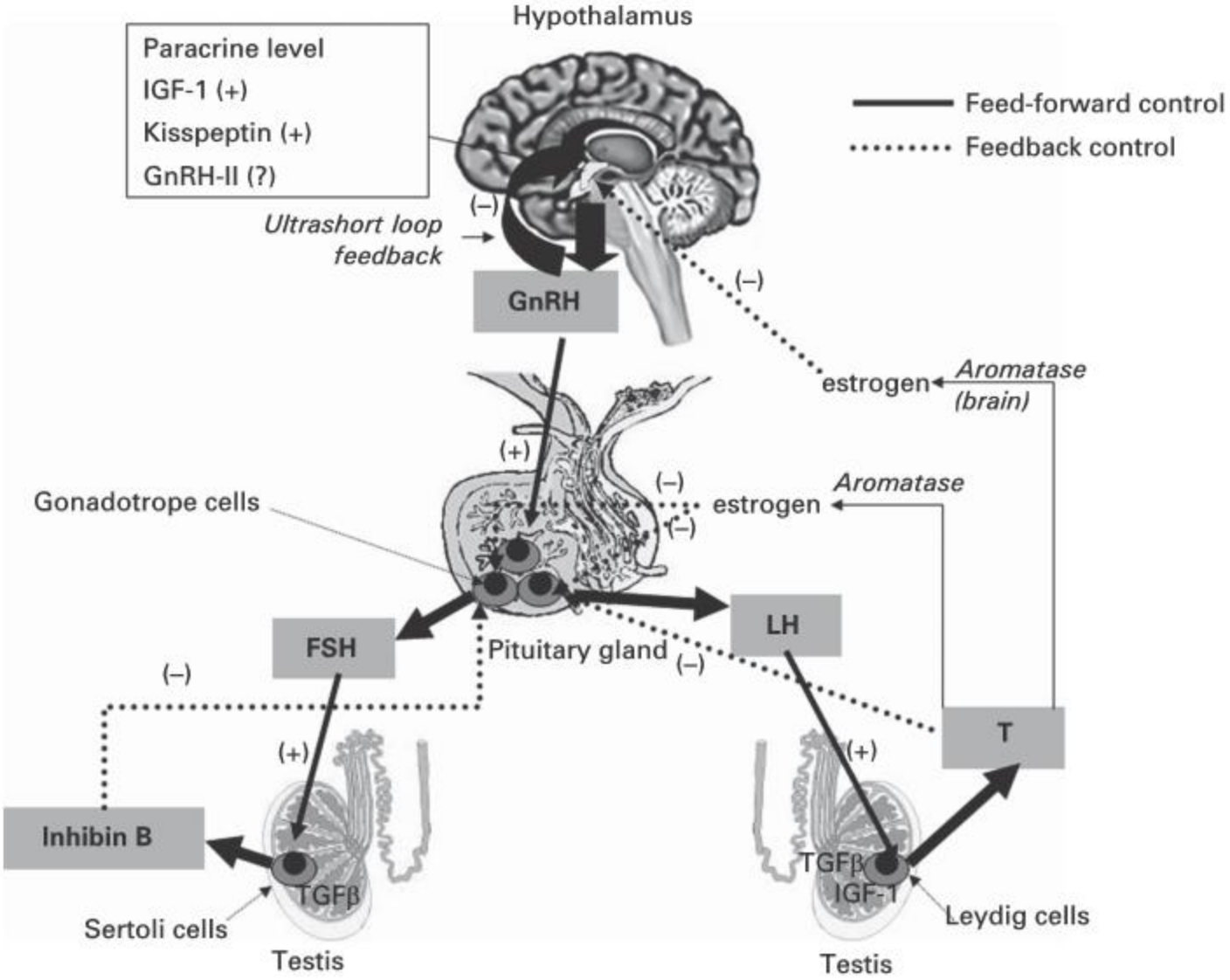
MALE REPRODUCTION SYSTEM

HUMOURAL CONTROL OF REPRODUCTIVE FUNCTIONS IN MAN



TESTOSTERON PRODUCTION:

- Embryonic – sex differentiation, development of generative organs
- Perinatal – descensus testis (?)
- Fertile period – LH pulsation
- After 50.year – decrease of sensitivity to LH



An Introduction to Male Reproductive Medicine

Edited by Craig Niederberger

Table 1.1 Regulation of hypothalamic–pituitary–gonadal axis hormone release

Hormone	Autocrine regulation	Paracrine regulation	Endocrine regulation
GnRH	GnRH itself (−)	GnRH II (+), IGF-1 (+), kisspeptin (+)	Testosterone (−), estrogens (−), neurotensin (+), norepinephrine (+)
FSH	–	Activin (+), follistatin (−)	GnRH (+), estrogens (−), inhibin B (−)
LH		Activin (+), follistatin (−)	GnRH (+), testosterone (−)
Testosterone	–	IGF-1 (+), GH(+), CRH (−), TGF-β (−), IL-1α (±)	LH (+)

+ Stimulatory effect, – Inhibitory effect. Transforming growth factor-β (TGF-β), corticotropin-releasing hormone (CRH), interleukin 1α (IL-1α), growth hormone (GH), insulin-like growth factor 1 (IGF-1).

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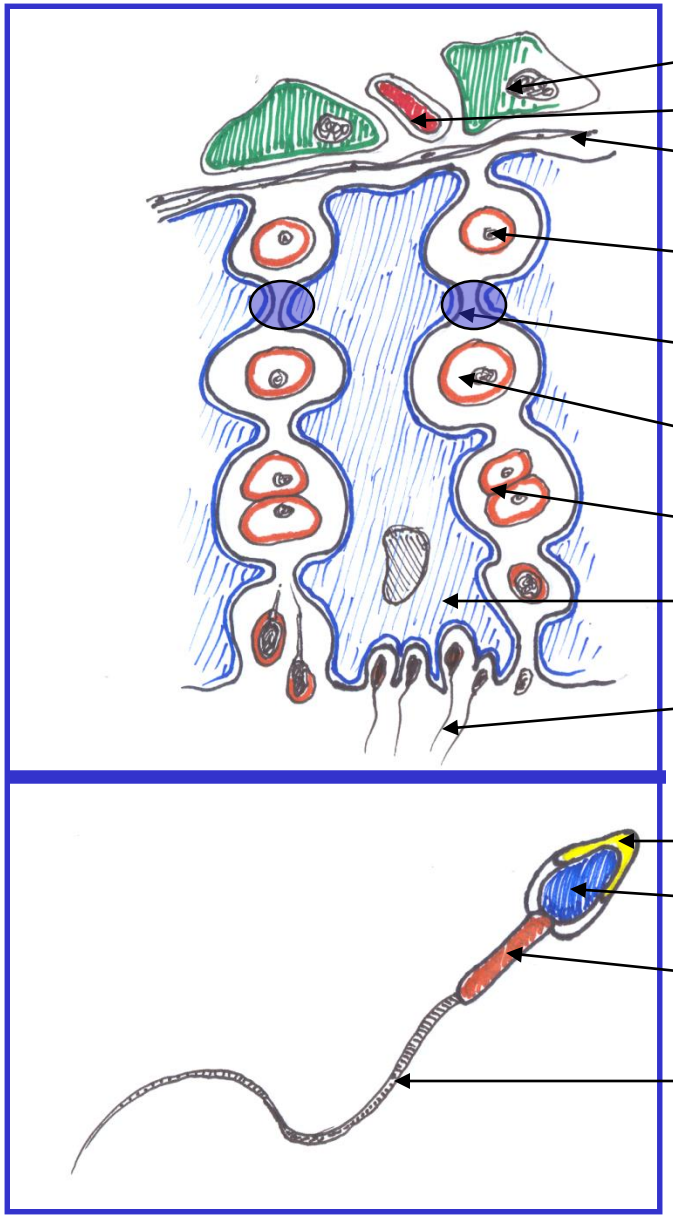
SPERMATOGENESIS



Leydig cell
Capillary
Basal membrane
Spermatogonium
Tight junction
Spermatocyte
Spermatide (haploid)
Sertoli cell (contraction)
Spermia

70 days

1-64 (6 divisions)

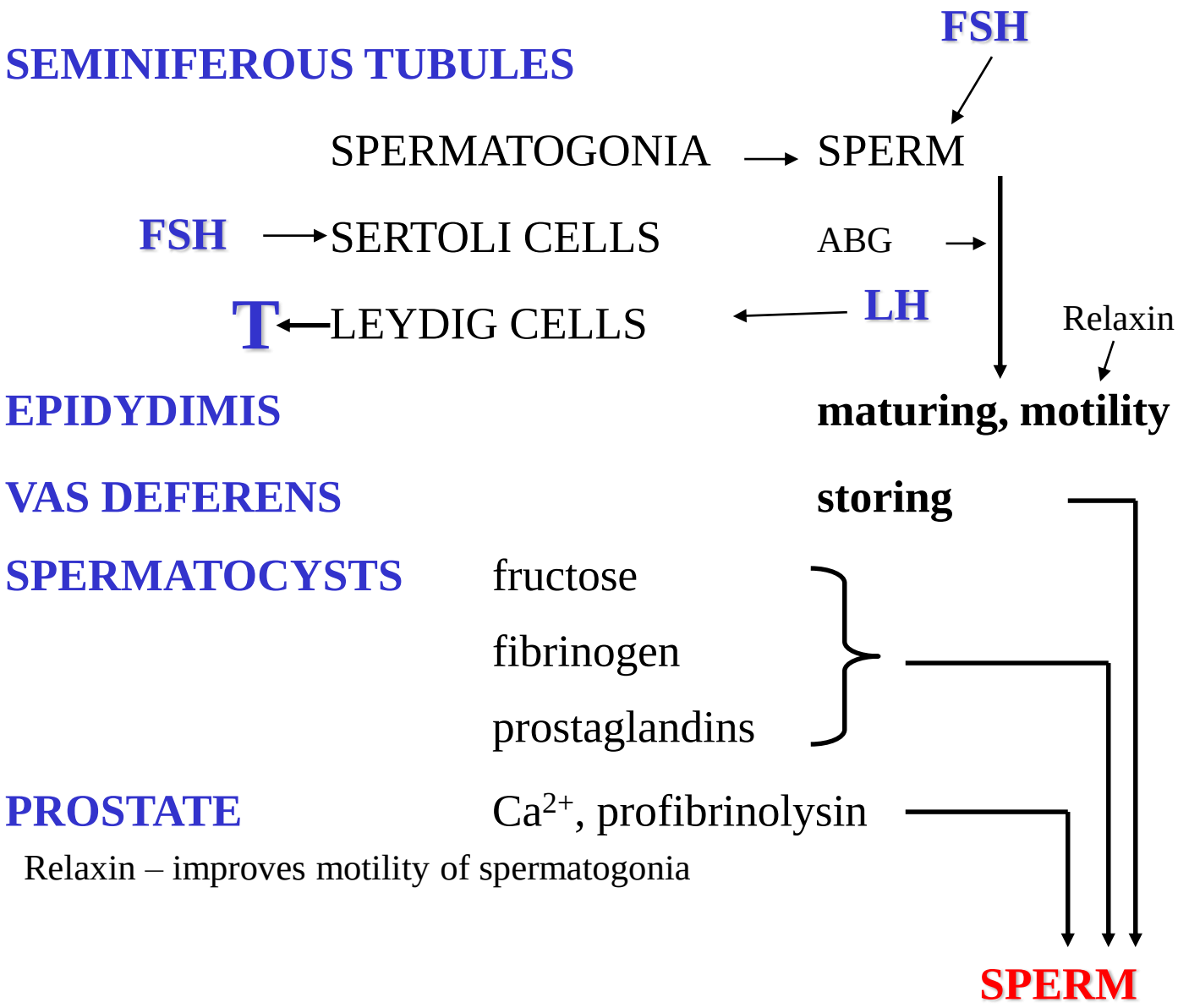
Temperature<35°C

Acrosom (enzymes)
Head (nucleus, DNA)
Body (mitochondria)
Flagella (microtubules, 9+2)

Lumen:

androg., estrog.
K^+
glutamate, aspartate
inositol

PRODUCTION OF SPERM



Relaxin – improves motility of spermatogonia

2 months

temperature

radiation

14-21 days

months

Ejaculation:

3-4 ml

10^8 sp / ml (season)

pH = 7.5

motility (3mm/min)

SPERMIOGRAM

Volume	1,5 - 2,0
pH	7,2 - 8,0
Concentration of sperm	20 mil/ml
Total number of sperm	40 mil and more
Motility	50% and more in category A+B, above 25% in A
Morphology	30% and more of normal forms
Vitality	75% and more of living sperm
Leukocytes	up to l mil/ml
Autoaglutination	< 2 (scale 0 - 3)

Vyšetření plodnosti muže

Jméno:
Datum vyšetření :
Sexuální abstinence:
Anamnéza:
Klinické vyšetření: varlata, tuhá, pružná nebol,
podélná osa pravého varlete mm:
podélná osa levého varlete mm:

Makroskopické vyšetření:

Vzhled:
Zkapalnění:
Viskozita:

Objem ejakulátu (2,0 - 5 ml)
pH vzorku (7,2 – 7,8)

Mikroskopické vyšetření:

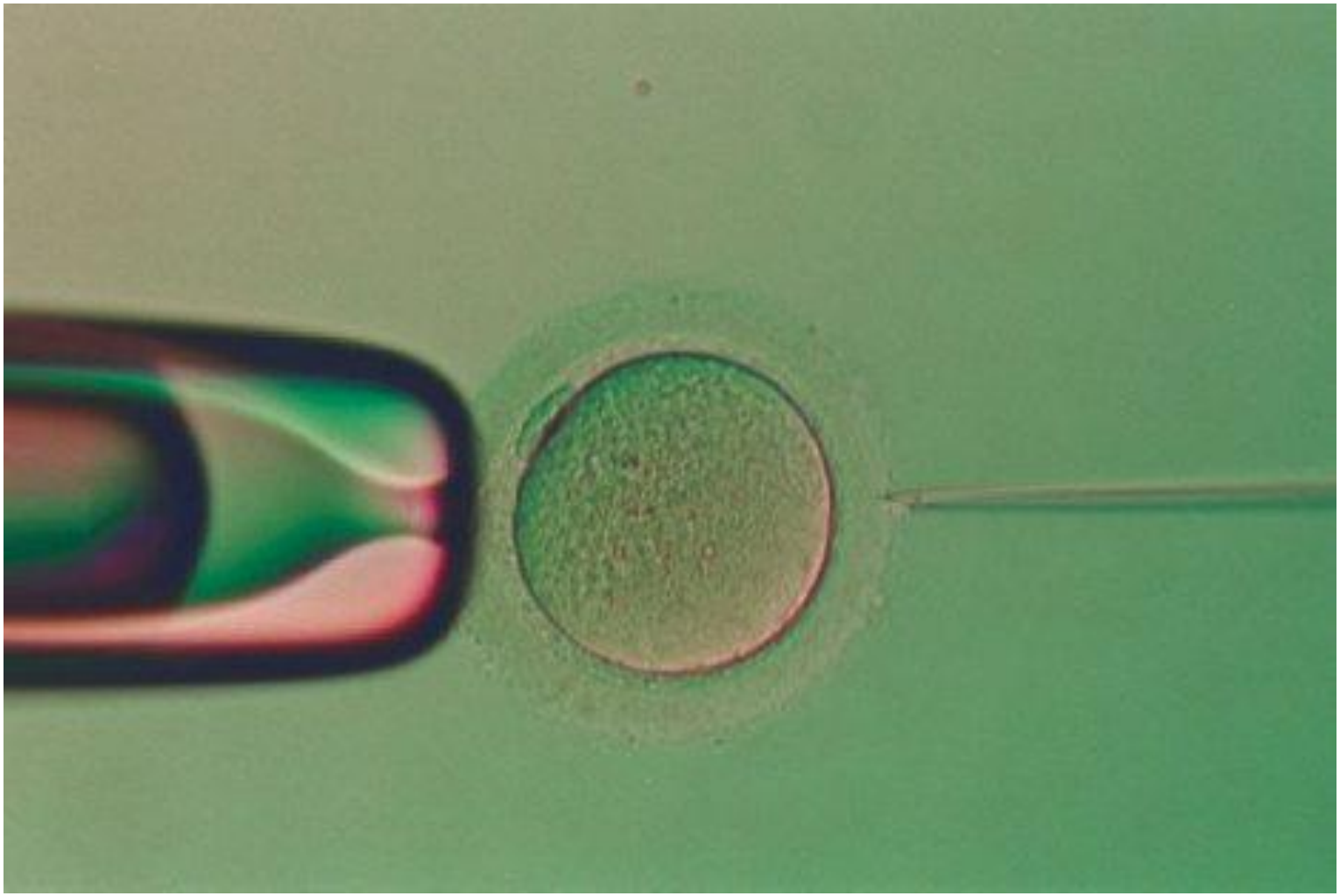
(spermiogram proveden v Makler counting chamber®, v závorkách normální referenční hodnoty)

Koncentrace spermií(nad 2O mil./ml):
Celkový počet spermií v ejakulátu(nad 4O mil./ml):
Pohyblivost spermií(minimálně 5O% kategorie A+B, 25% a více kategorie A):

A+B	C	D	
			mil/ml
			%

Vitalita (75% a více živých spermií):
Morfologie (30% a více normálních forem):
Leukocyty (do 1 mil/ml):
Přídatné buňky (do 5 mil/ml):
Aglutinace (< 2, stupnice 0 – 3):

Závěr:
Doporučení:
Vyšetřil:



SEXUAL REFLEXES