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PHYSIOLOGY OF REPRODUCTION

Life is a dynamic system with focused behavior, with ***autoreproduction****,*

characterized by flow of substrates, energies and information.

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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

Pregnancy (days)	
Mouse	20
Rat	23
Rabbit	31
Dog	63
Cat	65
Lion	107
Pig	114
Sheep	149
Human	**260 - 275**
Cow	285
Rorqual	360
Elephant (Indian)	609

High investment, low-volume reproduction strategy !

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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

- 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:

- Regression of müllerian duct
- Marker of central hypogonadism

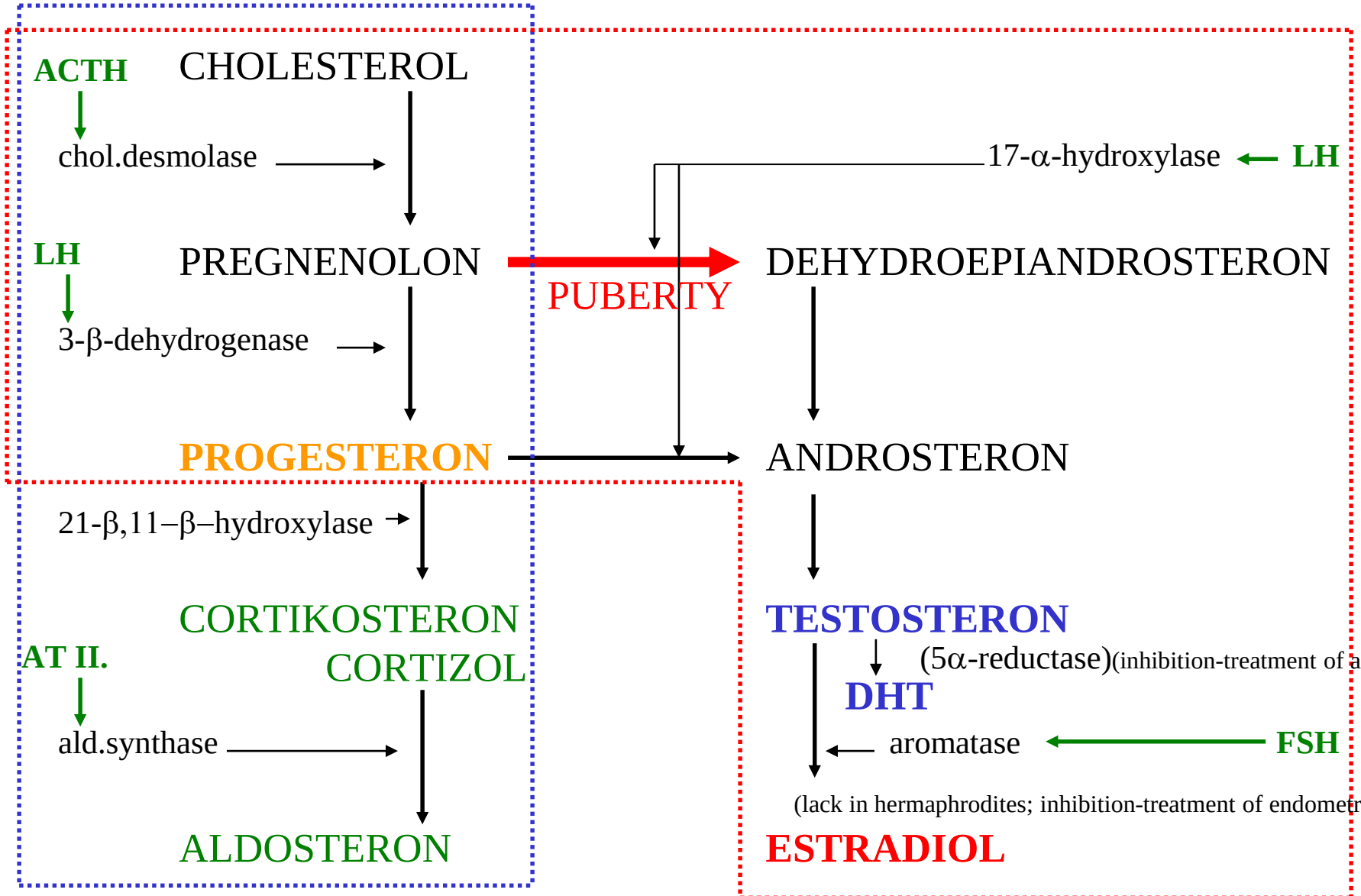
TUMOUR MARKER

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!



cortex of suprarenal glands

gonads

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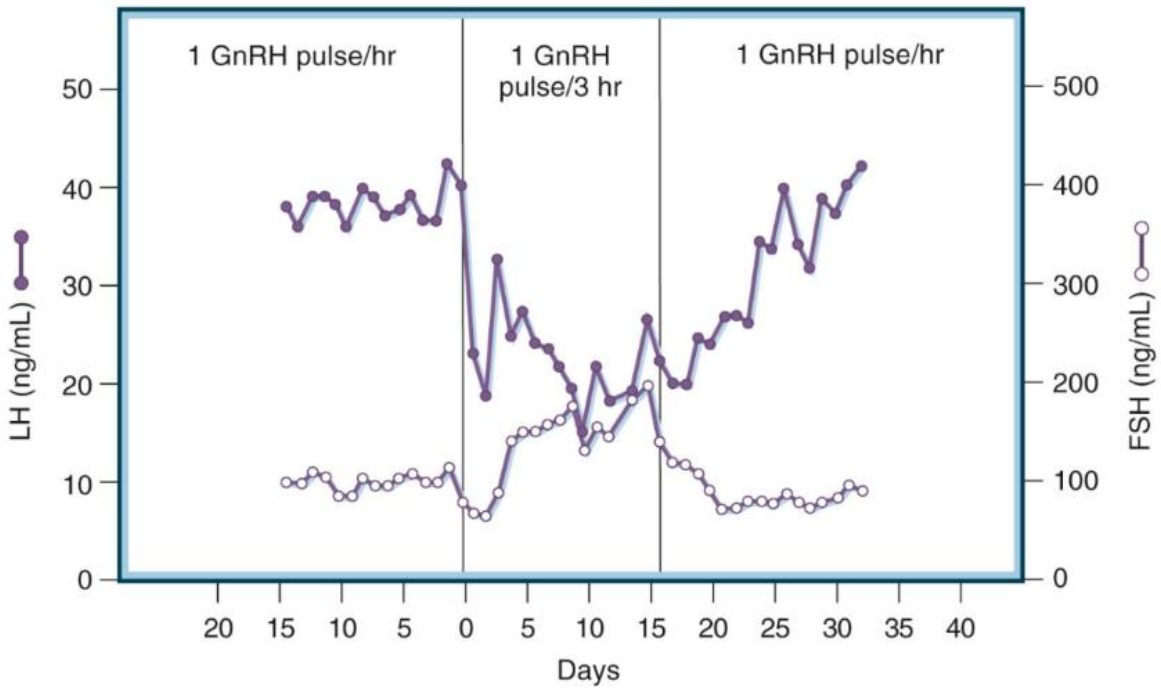
GONADOLIBERIN (GnRH, GONADOTROPIN-RELEASING HORMONE)

- Specific origin of GnRH neurons out of CNS
- GnRH-I, GnRH-II, (GnRH-III)
- 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)

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



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

} Unknown function

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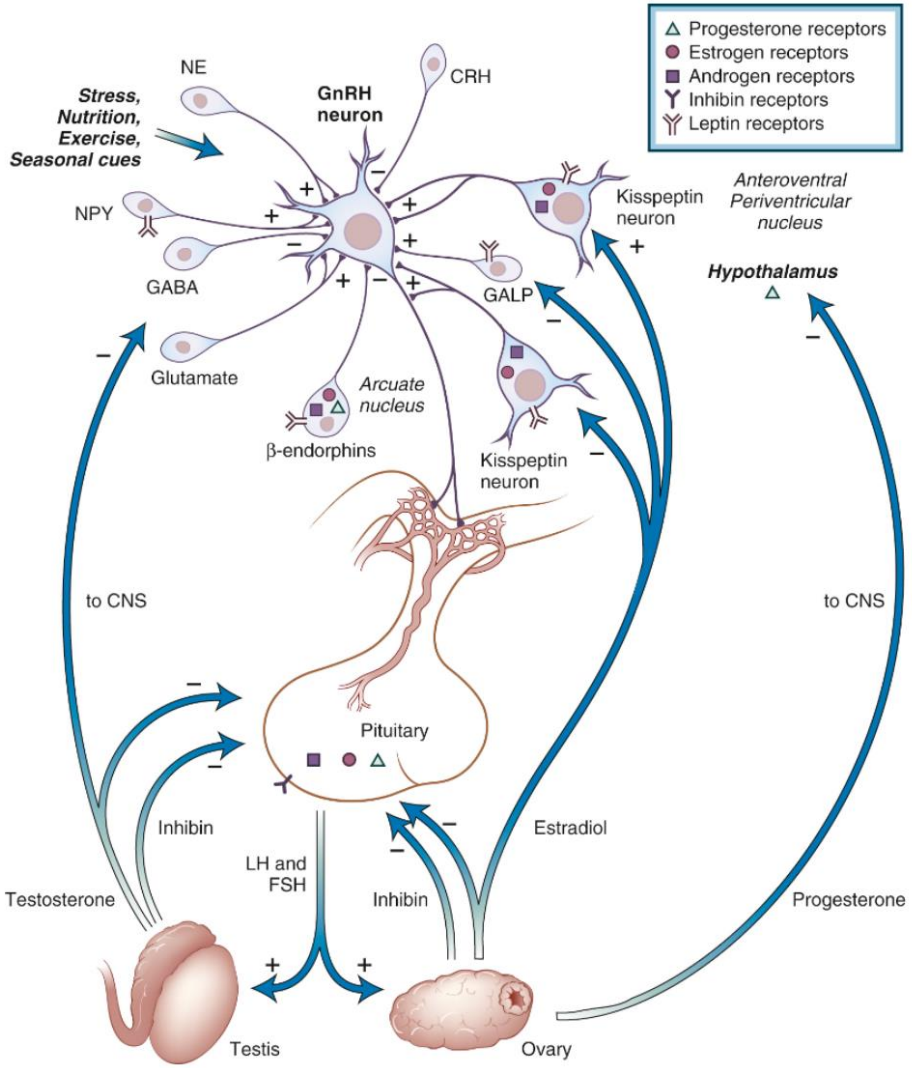
GONADOLIBERIN – REGULATION OF SECRETION

- Inputs from various CNS areas (pons, limbic system)
- Dominating inhibitory effect of sex hormones with exception of **estradiol** (**negative-positive-negative 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 – impaired fertility, decreased levels of circulating sex hormones



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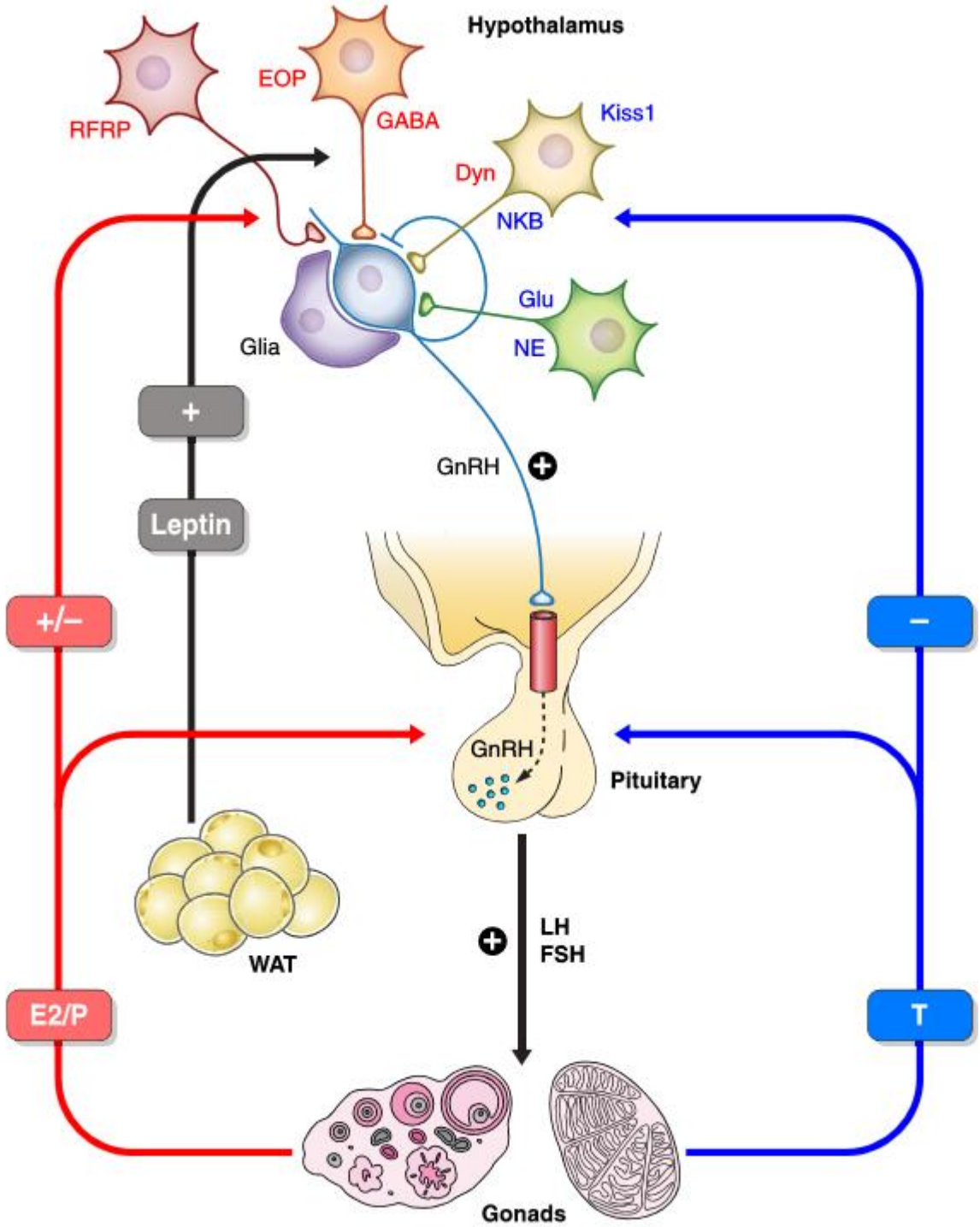
CONTROL OF SEX HORMONES SECRETION



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

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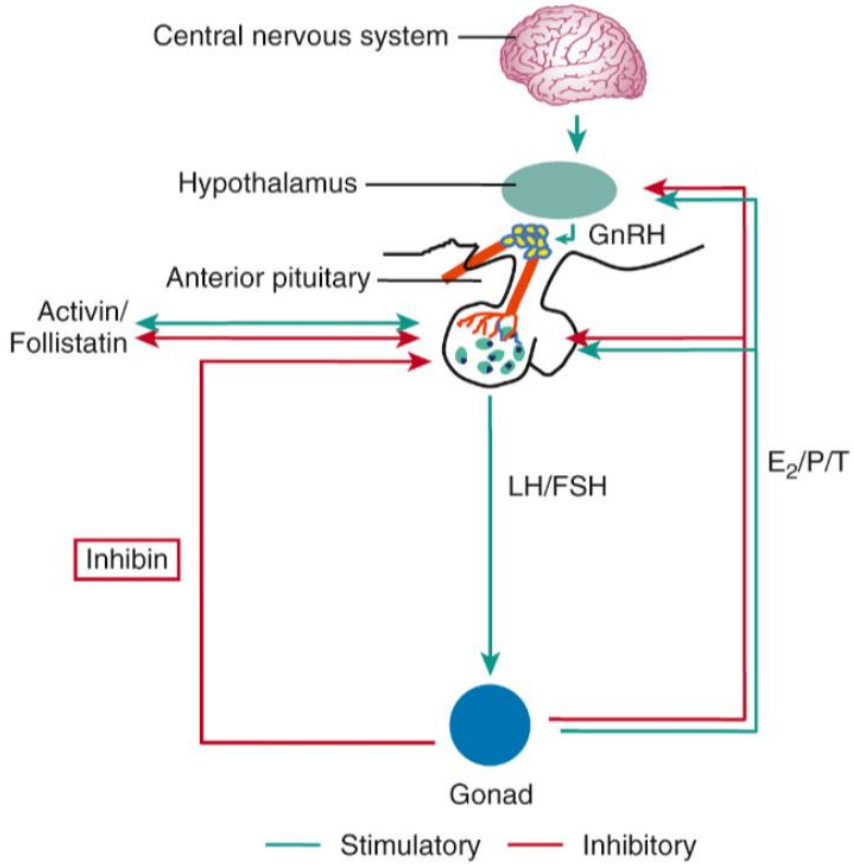
GONADOTROPHINS - FSH and LH

- Glycoproteins
- Heterodimer, different expression of subunits, glycosylation
- Structurally close to **hCG** (placenta)

Regulation of secretion
- sex hormones, local factors – paracrine (activins, inhibins, follistatin)
- (+) – glutamate, noradrenaline, leptin
- (-) – GABA, opioids
- Key role of kisspeptin, neurokinin B and substance P in GnRH secretion – FSH/LH
- Estrogens, progesterone, androgens – direct influence on gonadotrophs, indirect influence through GnRH
  - Estrogens (-) – inhibition of transcription (α), kisspeptin – NEG
  - Estrogens (+) shift
  - Progesterone (-) – influences pulsatile secretion of GnRH
  - Testosterone, estradiol (-) – males, kisspeptin neurons and AR
- Different half-life for circulating LH and FSH



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ACTIVINS and INHIBINS

Inhibins

– dimeric peptides (α + 1 or two β_A or β_B)
– circulating hormones produced by gonads
– inhibin A – dominant follicle, corpus luteum
– inhibin B – testes, luteal and early follicular phase of ovarian cycle

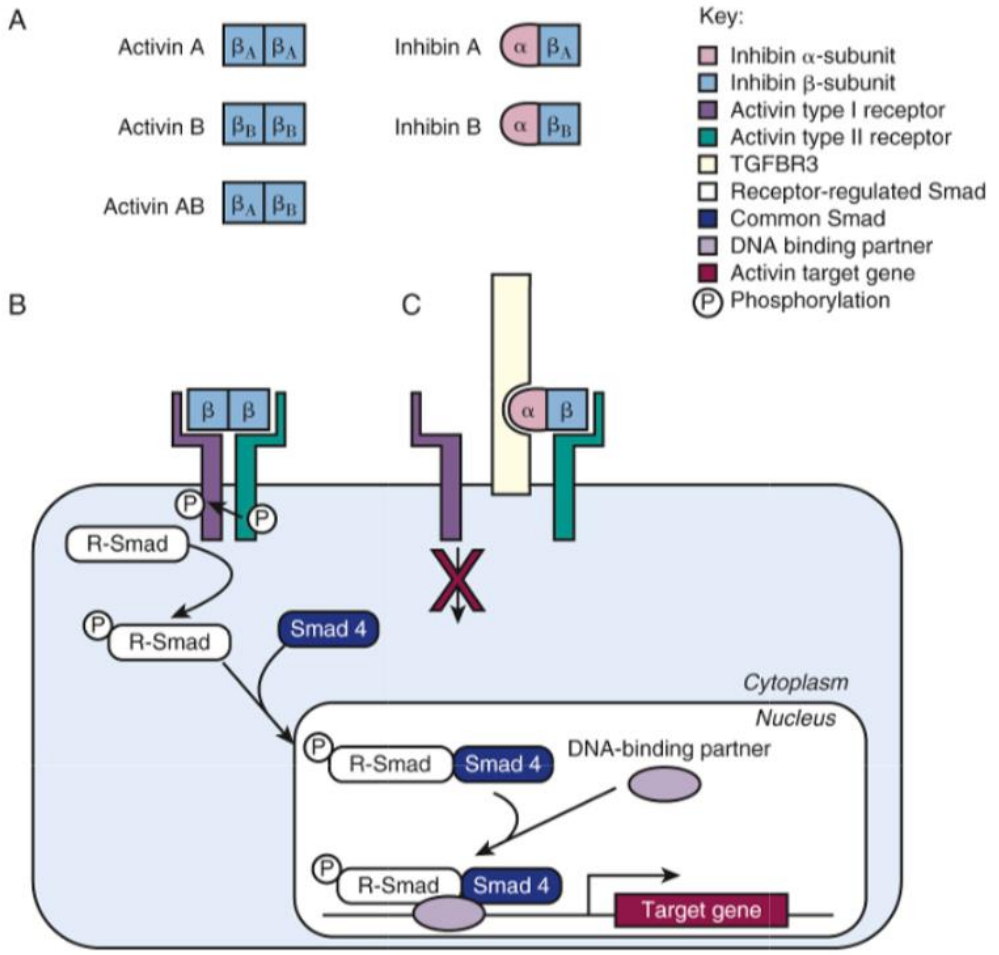
Activins

– dimeric peptides – dimers of β subunits
– FSH stimulation
– autocrine/paracrine factors
– other tissues – growth and differentiation

Follistatin

– monomeric polypeptide
– FSH inhibition

- „supplementary “ regulation of FSH and LH secretion
- activins = regulation of transcription, follistatin and inhibins = inhibition of activins through appropriate activin-receptor binding



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FSH and LH - functions

FEMALES

FSH

- Growth and development of follicular cell (maturation)
- Biosynthesis of estradiol
- Regulation of inhibin synthesis during follicular phase
- Upregulation of LH receptors (preovulatory follicles)
- Selection of dominant follicle
- Recruitment of follicles for next cycle

LH

- Stimulation of estrogen synthesis at various levels (theca)
- Oocyte maturation (preovulatory follicle)
- Rupture of ovulatory follicle, ovulation
- Conversion of follicle wall to corpus luteum

MALES

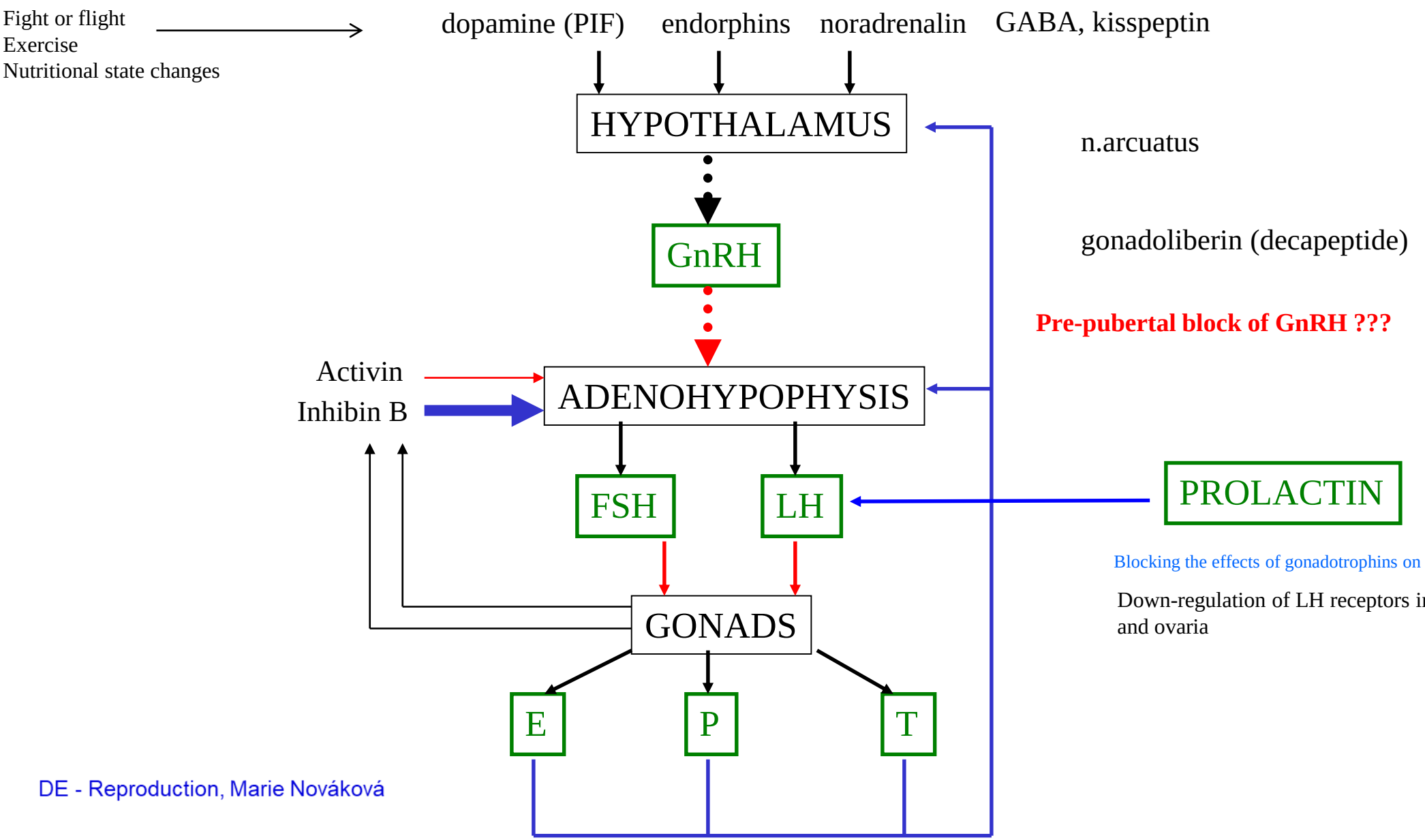
LH

Intratesticular synthesis of testosterone (Leydig cells)

FSH

Spermatogenesis (Sertoli cells)

REGULATION OF SEX HORMONES SECRETION – simplified scheme



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LEPTIN A REPRODUCTION

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

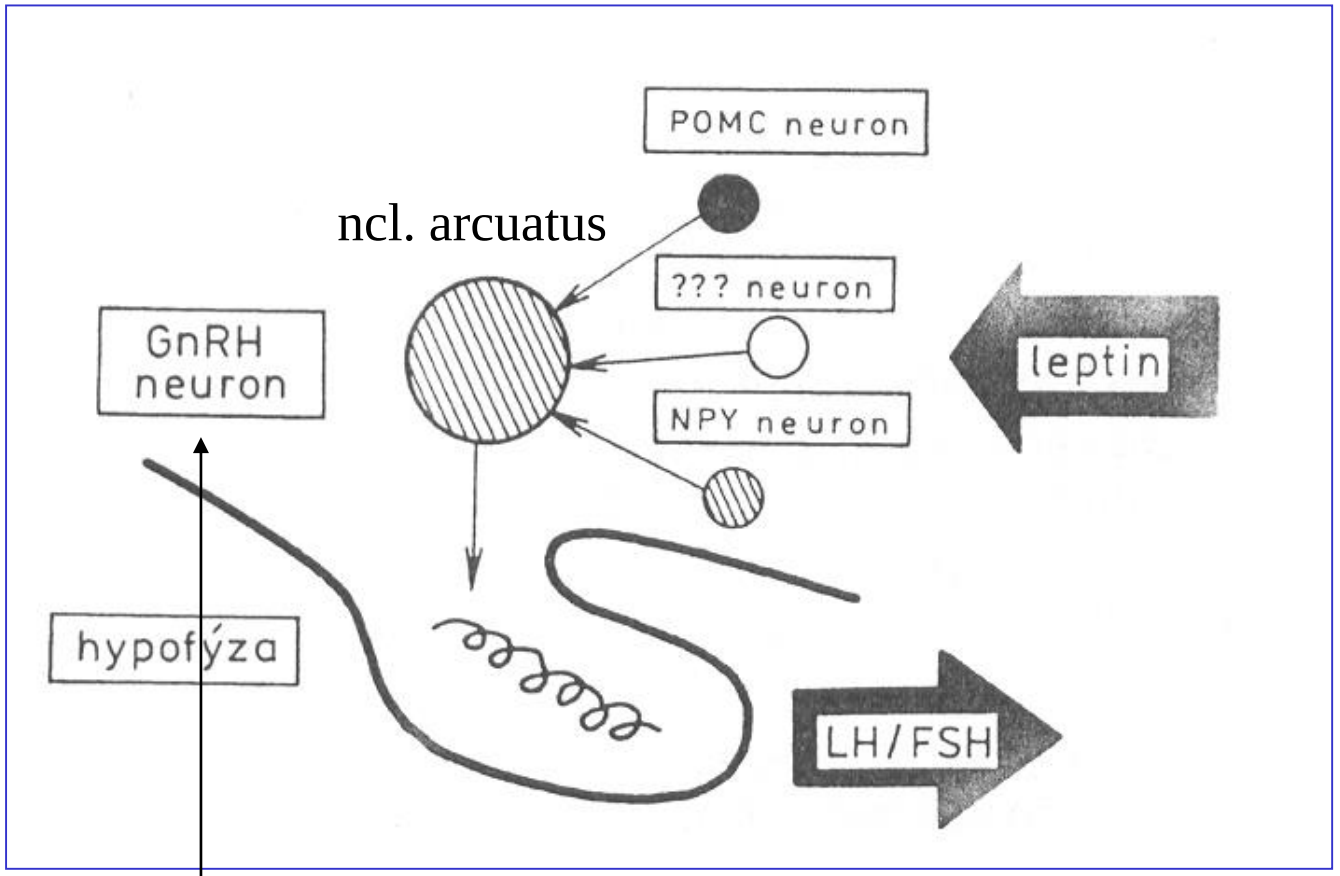
LEPTIN: ob-protein, ob-gen, 7.chromosome
„λεπτοσ“ = thin, slim
polypeptide, 176 AA

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

Produced in: **adipocytes**, stomach, placenta, 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 ???

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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 (critical nutritional state).

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

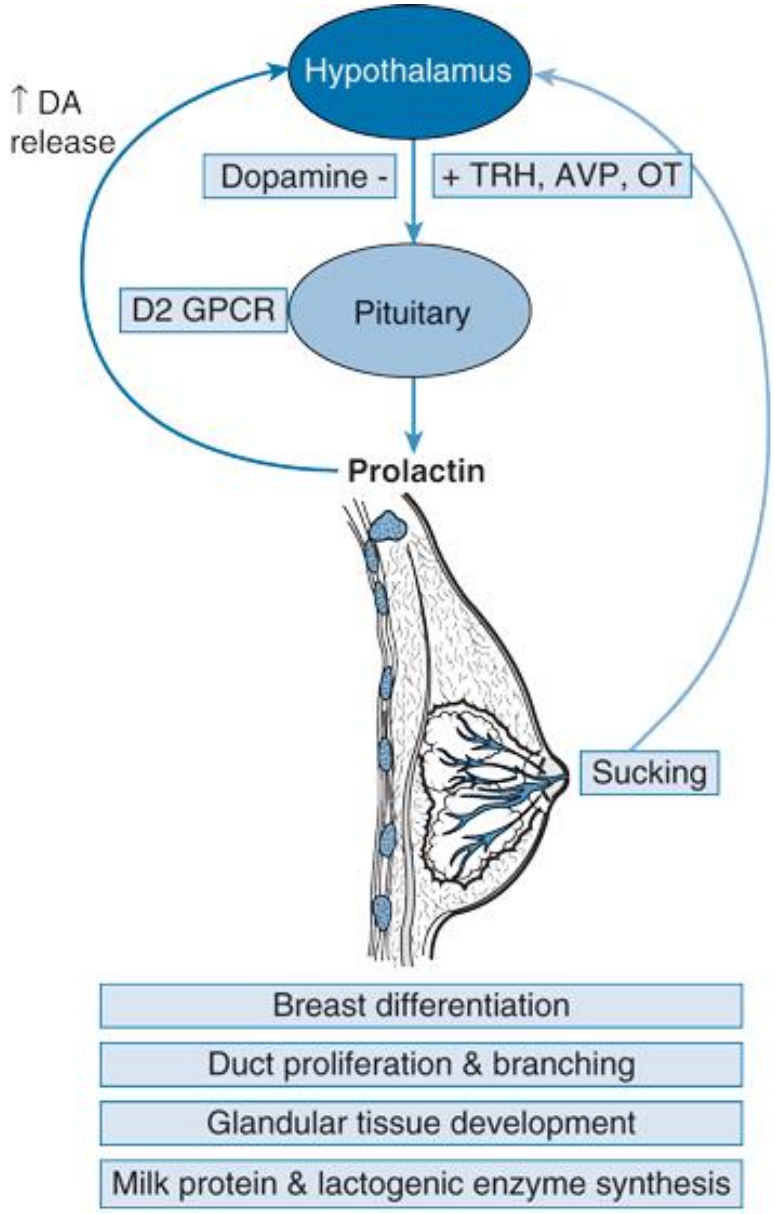
Pre-pubertal „leptin resistance“ (relative).

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

PROLACTIN - PRL (Co-hormone)

- 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)
- 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
- 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 (-)
- TRH, oestrogens, VIP, serotonin, GHRH at higher concentrations (+)



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PROLACTIN - functions

MAIN FUNCTION: Milk production during pregnancy and lactation = „survival“ function

Other functions – metabolic, synthesis of melanin, maternal behaviour

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

Reproductive function of PRL

- Lactation = amenorrhea and secondary infertility
- Inhibition of GnRH secretion

DOPAMINE (PIH, prolactin-inhibiting hormone)

Characteristics

- D2R (G protein inhibition, AC, cAMP decrease, inhibition of shaker type K^+ channels, MAPK, PAK – proliferation!)
- D1R (activation)

Hypothalamo-hypophyseal axis

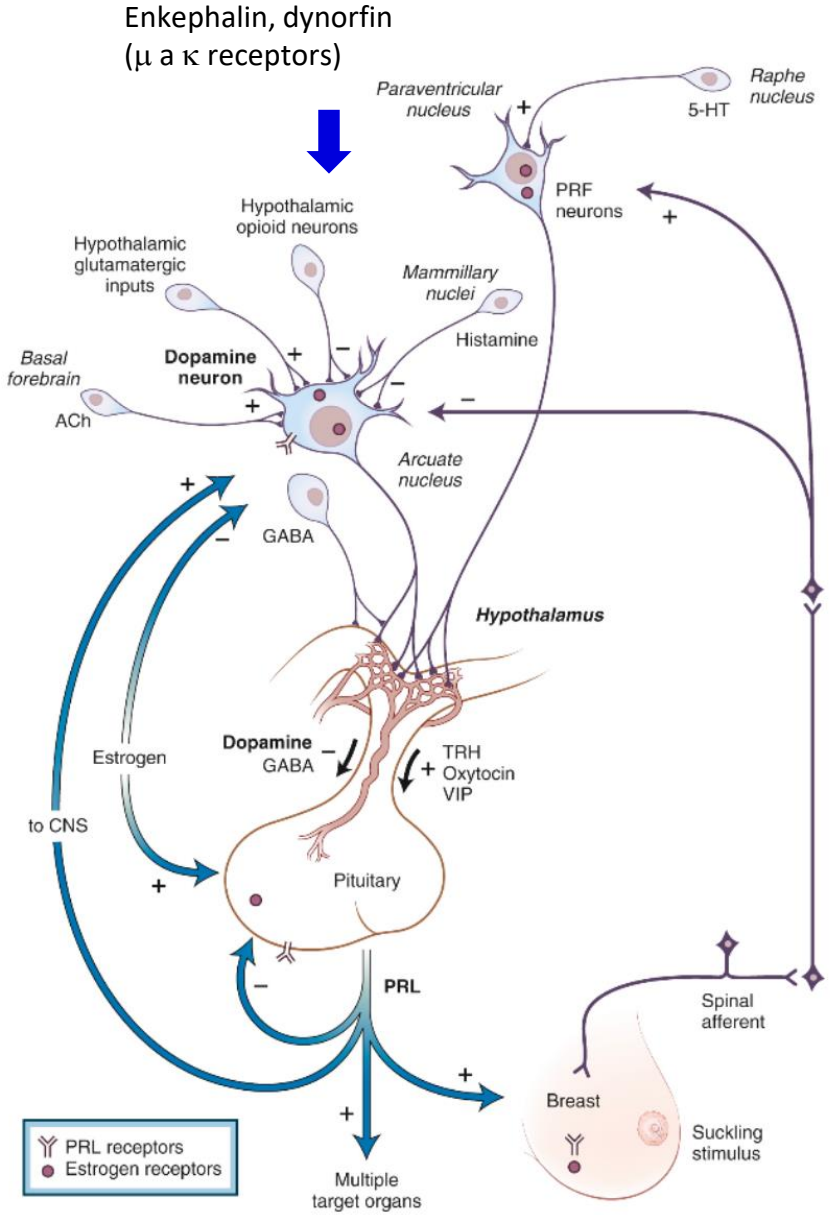
- Inhibition of PRL (D2R) secretion – lactotropic cells
- ! Lactotrophs with continual high PRL production
- PRL secretion regulated also at adenohypophysis level (paracrine, autocrine)
- Neuroendocrine regulation of PRL secretion – pregnancy, lactation, menstrual cycle, sensory inputs

DOPAMINE – REGULATION OF SECRETION

PROLACTIN-RELEASING FACTORS (PRF)

- TRH, oxytocin, VIP
- under specific conditions ADH, ATII, NPY, galanin, substance P, GRP, neurotensin
- *prolactin-releasing peptide* (PrRP) – stress, satiety (other parts of CNS)

- Important feedback mechanism (short loop) of PRL secretion regulation
  - Circadian rhythm (maximum in the morning)
  - Nipple stimulation (1-3 min, peak 10 – 20 min)



CRITICAL DEVELOPMENTAL PERIODS

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

Critical body mass (critical amount of adipose tissue/nutritional state)

Puberty

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

Pubertas praecox (central)
Pseudopubertas praecox (peripheral)

Late puberty

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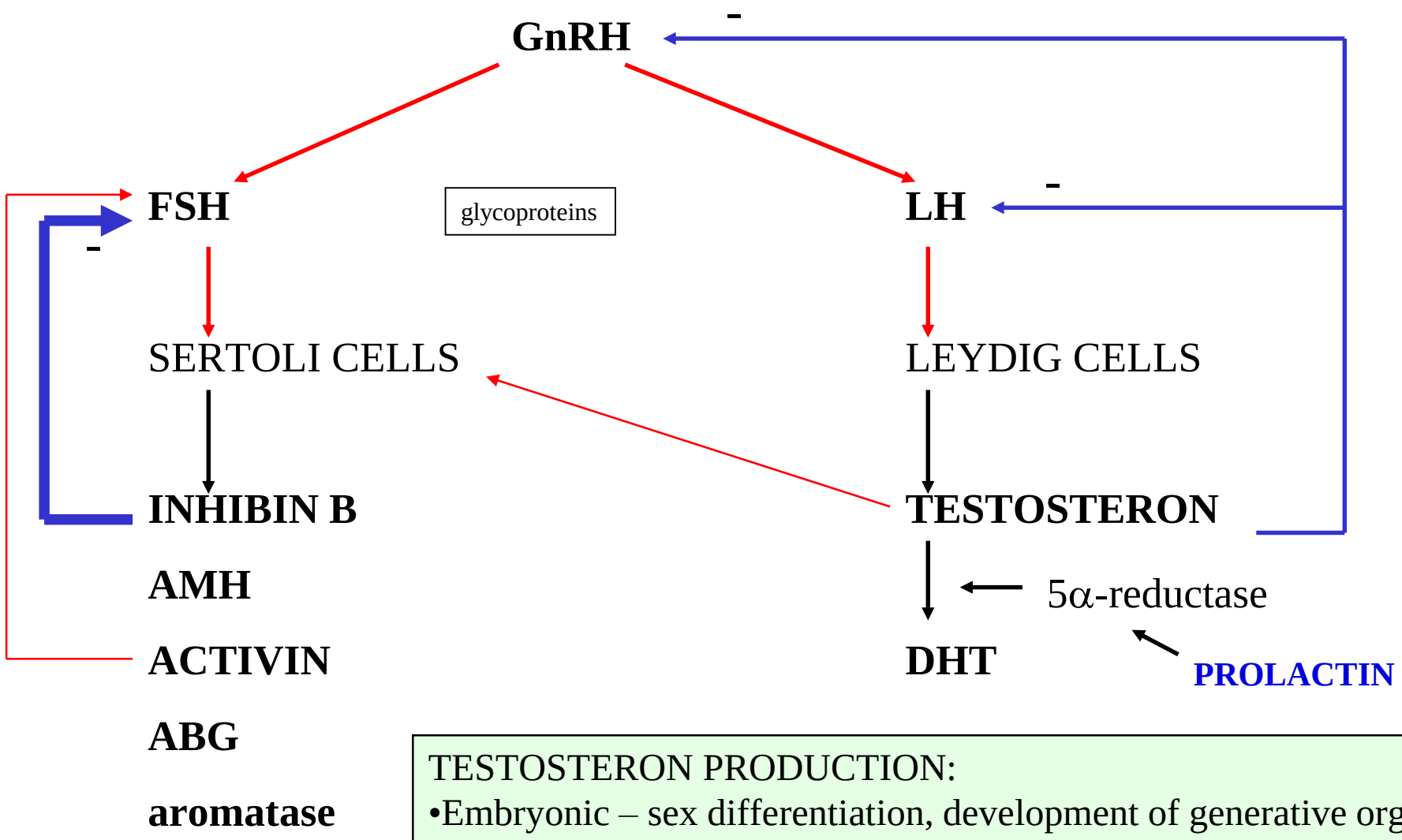
MALE REPRODUCTION SYSTEM

ENDOCRINE REGULATION OF REPRODUCTION FUNCTIONS IN MAN



TESTOSTERON PRODUCTION:
- Embryonic – sex differentiation, development of generative organs
- Perinatal – descensus testis (?)
- Fertile period – LH pulsation
- Ageing – decrease of sensitivity to LH

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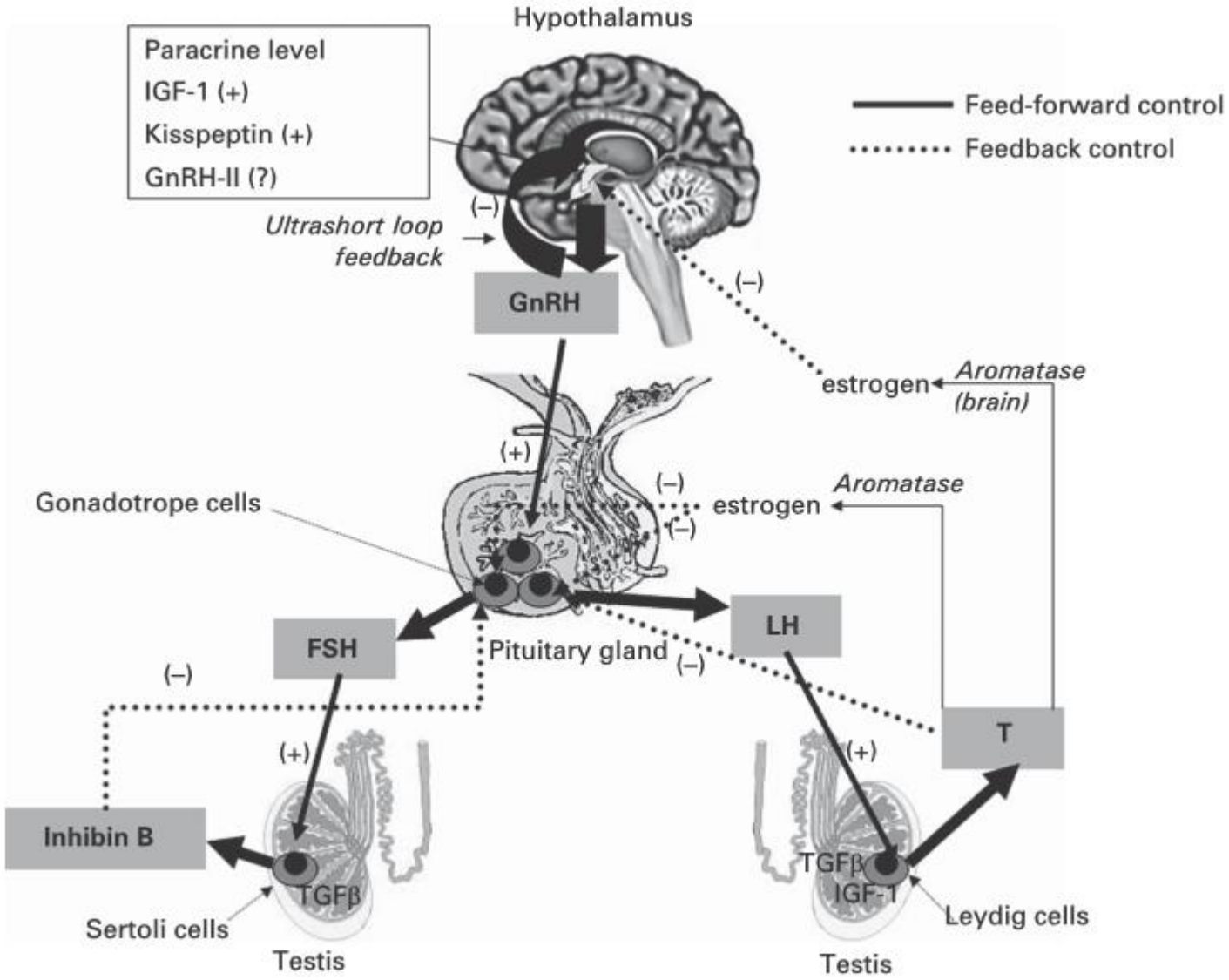

An Introduction to Male Reproductive Medicine

Edited by Craig Niederberger

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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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FEMALE REPRODUCTION SYSTEM

OOGENESIS

DEVELOPMENT:		6-8 weeks	GERMINAL EPITH.
hormonally independent		OOGONIA mitotic division	**FOLLICLE** PRIMORDIAL
	24 weeks	OOCYTES I.	7×10^6
		1. meiosis	
	birth	prophase	2×10^6
hormonally dependent (cyclic)	**puberty**	OOCYTES II. haploid 2. meiosis metaphase OVUM	3×10^5 DOMINANT (GRAAF) ATRETIC **OVULATION**
		2. meiosis – end	
	climacterical		0

CYCLIC CHANGES

ovarian

uterine

+ vagina/cervix uteri

+ mamma

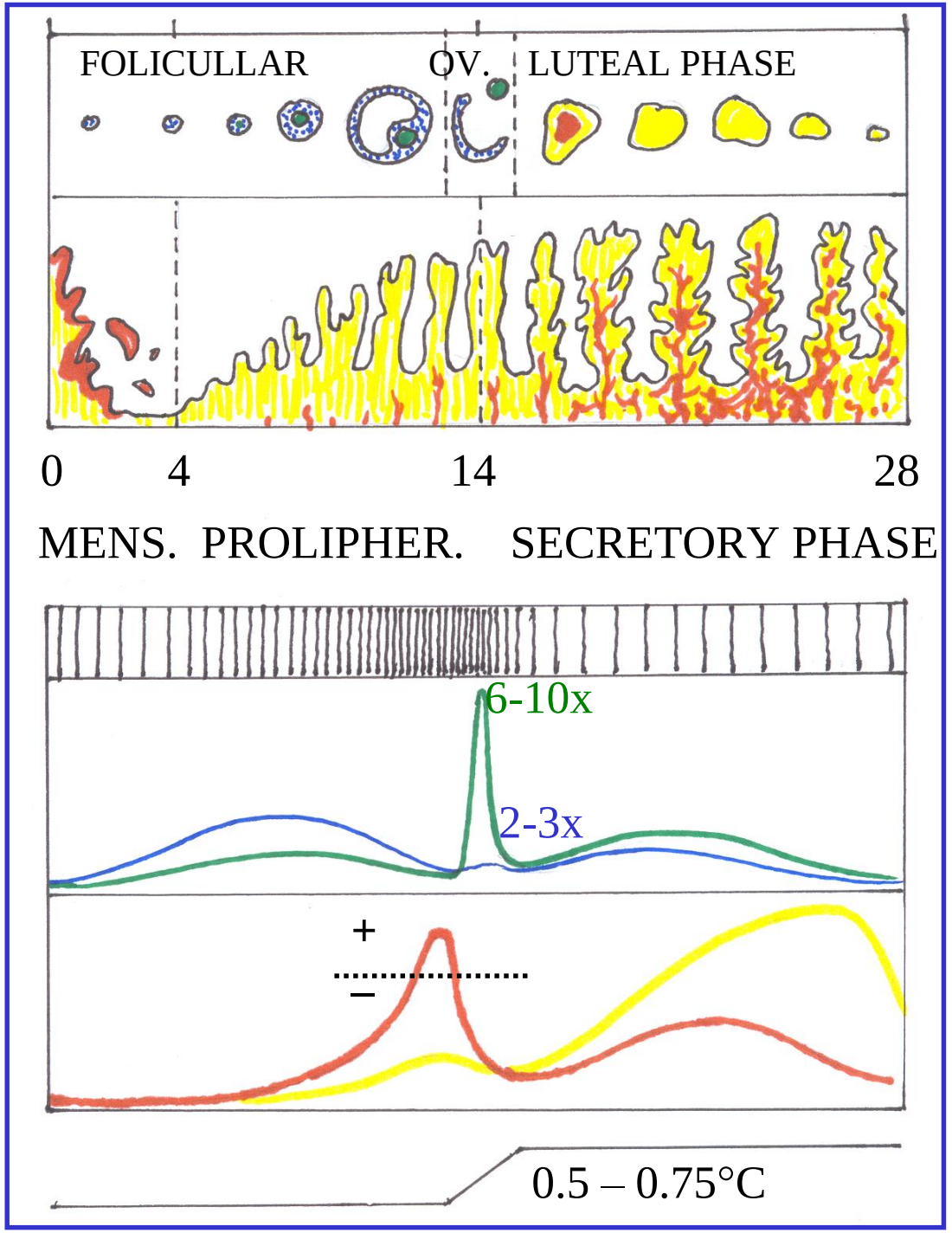
GnRH

FSH, LH

estradiol

progesteron

basal temper.



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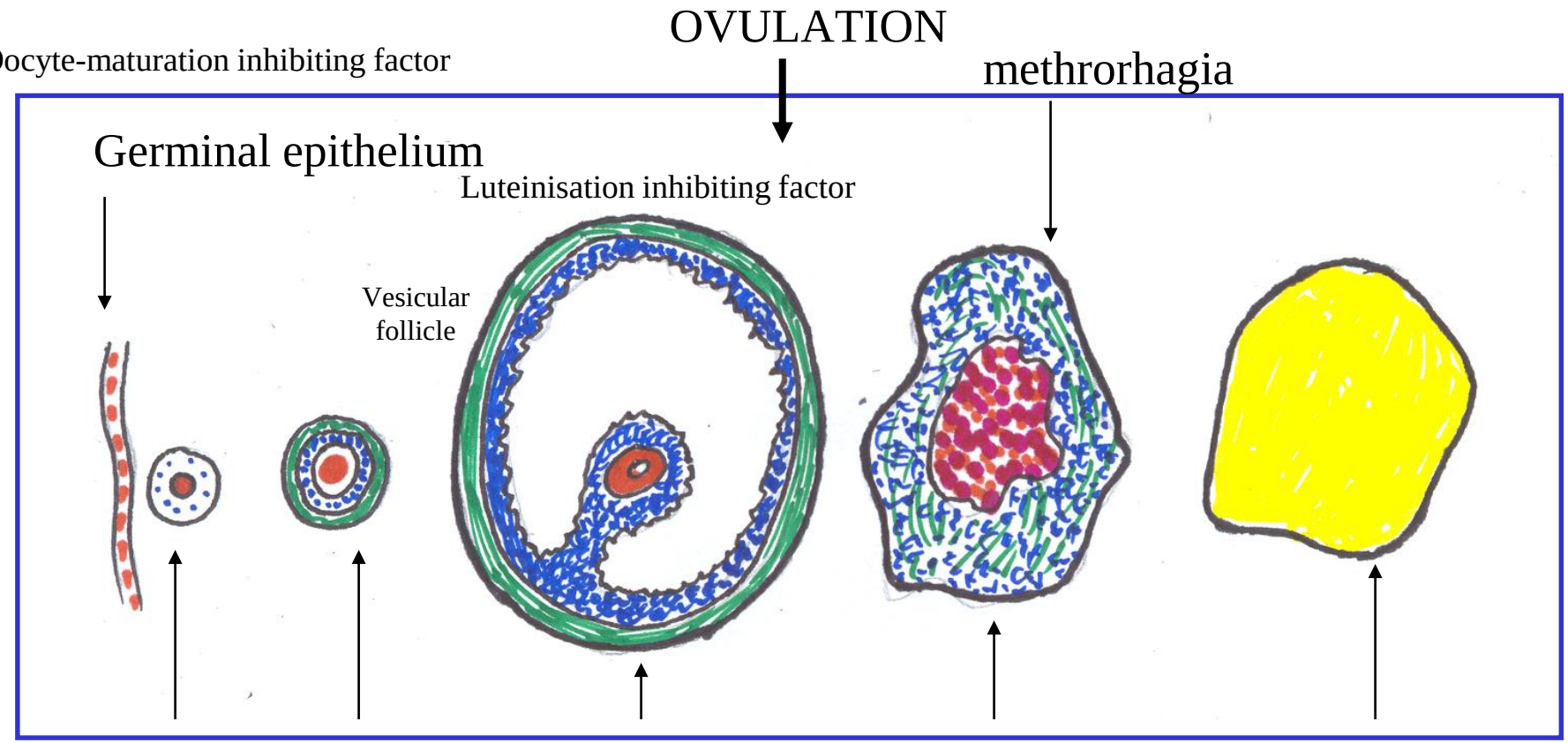
OVARIAN CYCLE



estradiol (estrogens)

progesterone (progestins)

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VESICULAR FOLLICLE

PRIMARY FOLLICLE - FSH

Growth acceleration of primary follicle – change into vesicular follicle:

1) estrogens released into follicle stimulate granul. cells

↓

UP REGULATION of **FSH** receptors and **intrinsic positive feedback** (higher sensitivity for FSH!!!)

2) **UP REGULATION** of LH receptors (estrogens and FSH) – another acceleration of growth due to „higher sensitivity“ to LH (**positive feedback**)

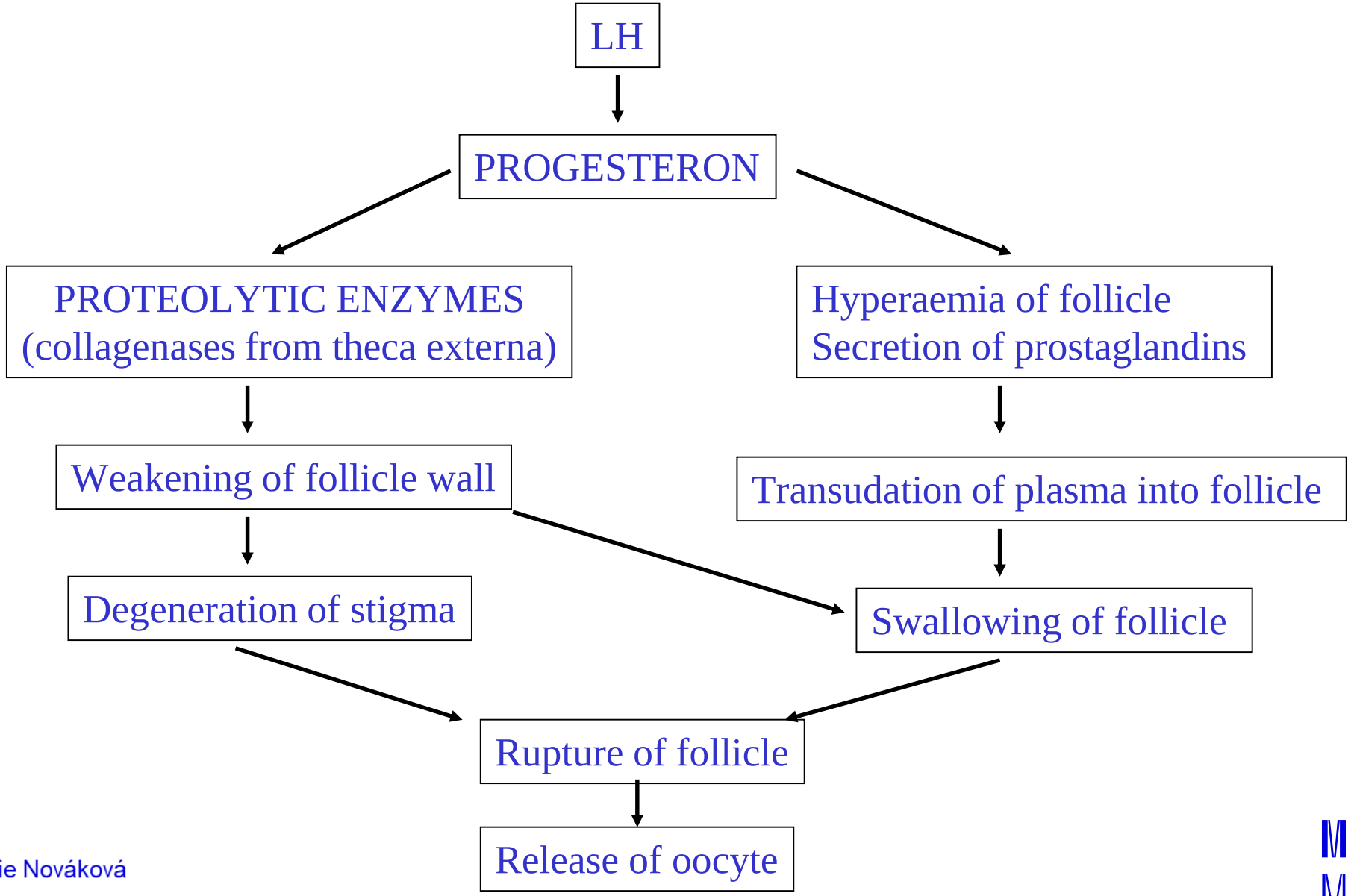
3) Increased estrogens and LH secretion accelerates growth of theca cells, secretion is increased

→ explosive growth of follicle

DOMINANT FOLLICLE

1. High levels of oestrogens from the fastest-growing follicle
2. Negative feedback on FSH production from adenohypophysis
3. Gradual decrease in FSH secretion
4. „Dominant follicle“ continues in growing due to intrinsic positive feedback
5. Other follicles grow slowly and subsequently become atretic

MECHANISMS OF OVULATION



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EFFECTS OF OVARIAN HORMONES

	E	P
Secondary sexual signs	+	-
Adipose tissue:	store (predilection), (critical amount)	-
Bone tissue:	absorption	-
	closure of fissures	-
	development of pelvis	-
Total water retention:	+	+
Sexual behaviour:	+	-

Ovaries:	**maturation of follicles**	
Hysterosalpinx:	motility	motility
Uterus:	proteosynthesis	proteosynthesis
	vascularisation and proliferation of endom.	**secretion of endom. glands**
	motility	glycogen
		motility
Cervix:	**colliquation of „plug“**	**creation of „plug“**
Vagina:	cornification of epithelium	proliferation of epithelium
Mamma:	growth of terminals	growth of acines

CONTRACEPTION (BIRTH CONTROL)

- RHYTHM METHOD
- SPERMICIDE SUBSTANCES
- COITUS INTERRUPTUS
- CONDOM, PESSARY
- IUD
- **HORMONAL CONTRACEPTIVES** – risk of failure less than 1%
- VASECTOMY AND LIGATION OF HYSTEROSALPINX

Hormonal curettage (excochleation). Substitution therapy in climacterium.

HORMONAL CONTRACEPTION

- block of ovulation by suppression of hypothalamic releasing hormones (block of preovulatory surge of LH)
- changes of character of cervical plug (progestin thickens mucus)
- changes of endometrium (suppression of its growth)
- changes of hysterosalpinx motility

PREGNANCY, PARTURITION, LACTATION

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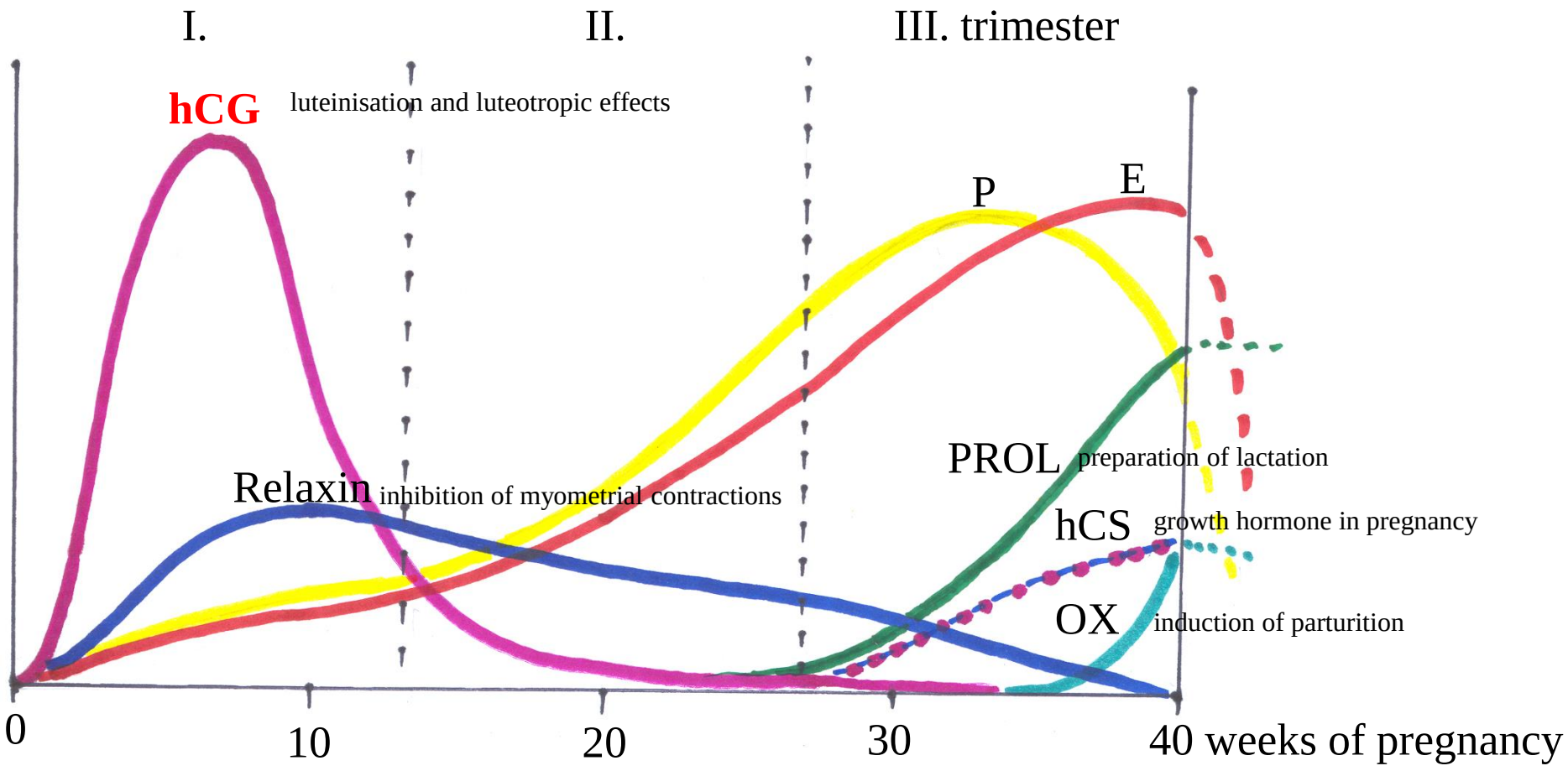
HORMONAL PROFILE OF PREGNANCY

(8th week!!!)

Corpus luteum graviditatis → E, P, Relaxin

Placenta → hCG, hCS, E, P



STH
TSH
ACTH
INS
KORT
ALD
T_4
PTH

Placental – maternal – foetal source of hormones

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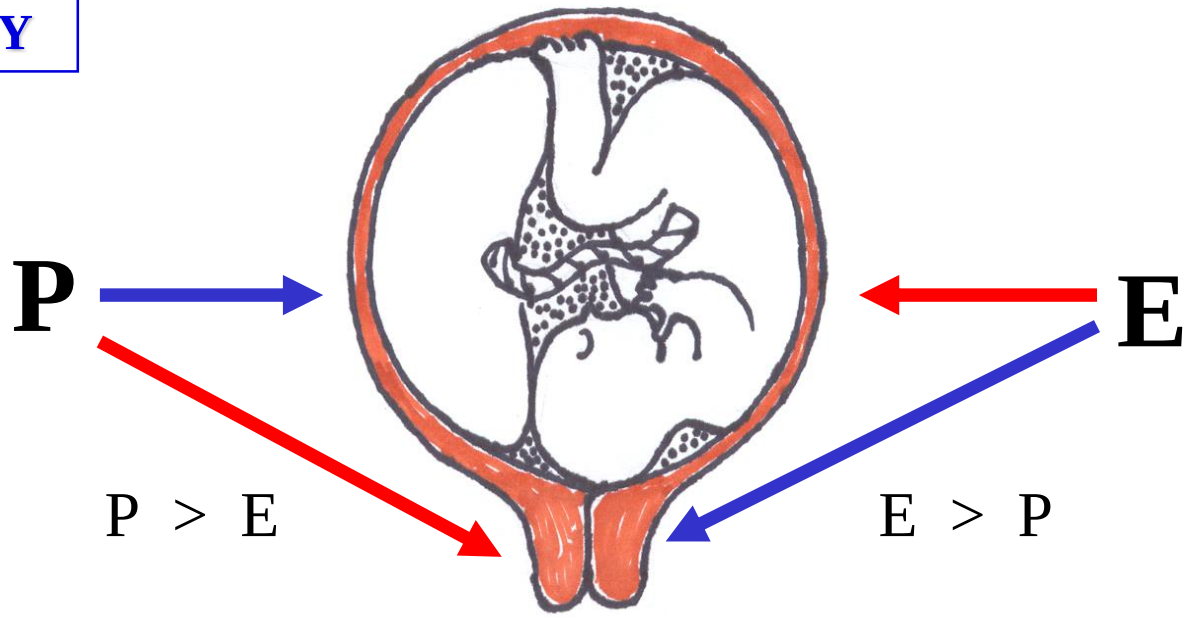
RELATIONSHIP BETWEEN P:E IN PREGNANCY



Foetoplacental unit

MOTHER	PLACENTA	FOETUS
cholesterol →	pregnenolone →	DHEAS 16OH-DHEAS
←	progesterone →	cortisol aldosterone
DHEAS →	estradiol Estriol	

Excretion of estriol in urine
– index of foetal status

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PHYSIOLOGICAL CHANGES DURING PREGNANCY

Changes of reproductive organs

- **Uterus**
  - Growth (from 60 g to 1000 g), change of position
  - Hyperaemia
  - Functional differentiation of myometrium
- **Cervix**
  - Changes of colour, consistency; shortening
  - Hypertrophy a hyperplasia of glandules – mucus plug
- **Vagina**
  - Changes of colour, increase of secretion
- **External genitals**
  - Vascularization, vasocongestion (changes of colour)

Somatic changes

- **Breasts**
  - Growth – alveolar as well as ductal part
  - Enlargement and hyperpigmentation of mammillae and areolas
- **Skin**
  - Increase in subcutaneous fat
  - Changes in connective tissue
  - Hyperpigmentation

Endocrine and metabolic changes

Immunological changes

Psychic changes

ENDOCRINE and METABOLIC CHANGES DURING PREGNANCY

Endocrine glands

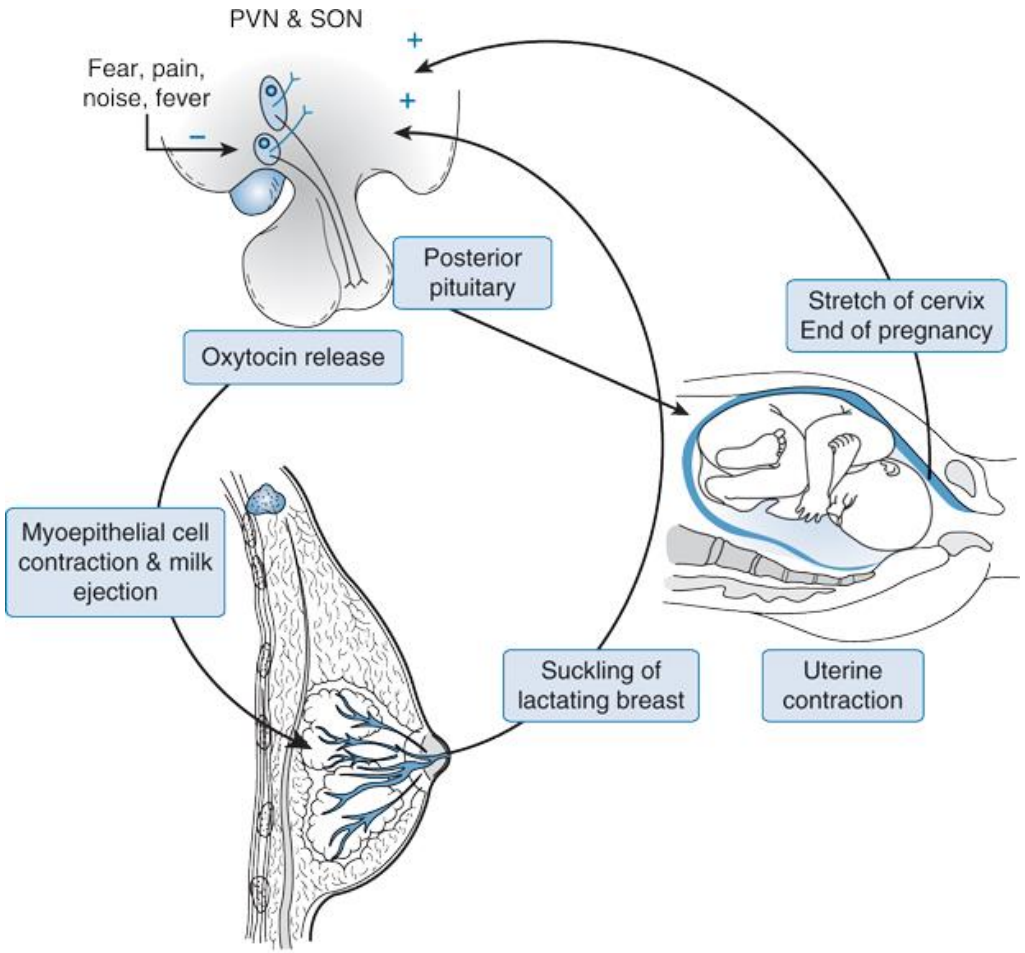
- **Thyroid gland**
  - Slight hypertrophy (E), increase in thyroxine production, in III. trimester BEE +25%
- **Parathyroid glands**
  - Increase in production of parathormone
- **Adrenal glands**
  - Increase in production of aldosterone
- **Pancreas**
  - Hyperplasia of Langerhans islets

Anterior pituitary gland

Metabolism

- **Weight gain**: 12-15 kg
- **Glycaemia**
  - Glc – main energetic source for foetus
  - Prohyperglycemic state
  - Decrease of renal glucose reabsorption, increase in glomerular filtration - glycosuria
  - Gestational diabetes
- Increased demand for **Ca** (1300 mg), P (1200 g) and Fe (18 mg/day)
- **Water** retention: + 6.5 l

OXYTOCIN



- Mechanoreceptors/tactile receptors
- Magnocellular neurons (PVN, SON)
  - inhibition by endogenous opioids, NO, GABA
  - Autocrine (+ ZV)
  - Prolactin, relaxin (-), Estrogens (+)
- OXT receptors ($G_{q/11}$) – effect of up/down regulation
- Acts together with prolactin and sex hormones

Functions

- Lactation (under 1 min)
- Parturition
  - rhythmical contractions of smooth muscles (gap-junction, stimulation of prostaglandin synthesis – extracellular matrix)
  - postpartum bleeding
  - uterus involution
- Ejaculation (males)
- Behavior

Other functions and places of synthesis

- CNS
  - Stimulation of ACTH secretion through CRH
  - Stimulation of ADH/induced vasoconstriction
  - Stimulation of prolactin secretion
  - Memory traces recollection inhibition
  - Maternal behavior

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OXYTOCIN

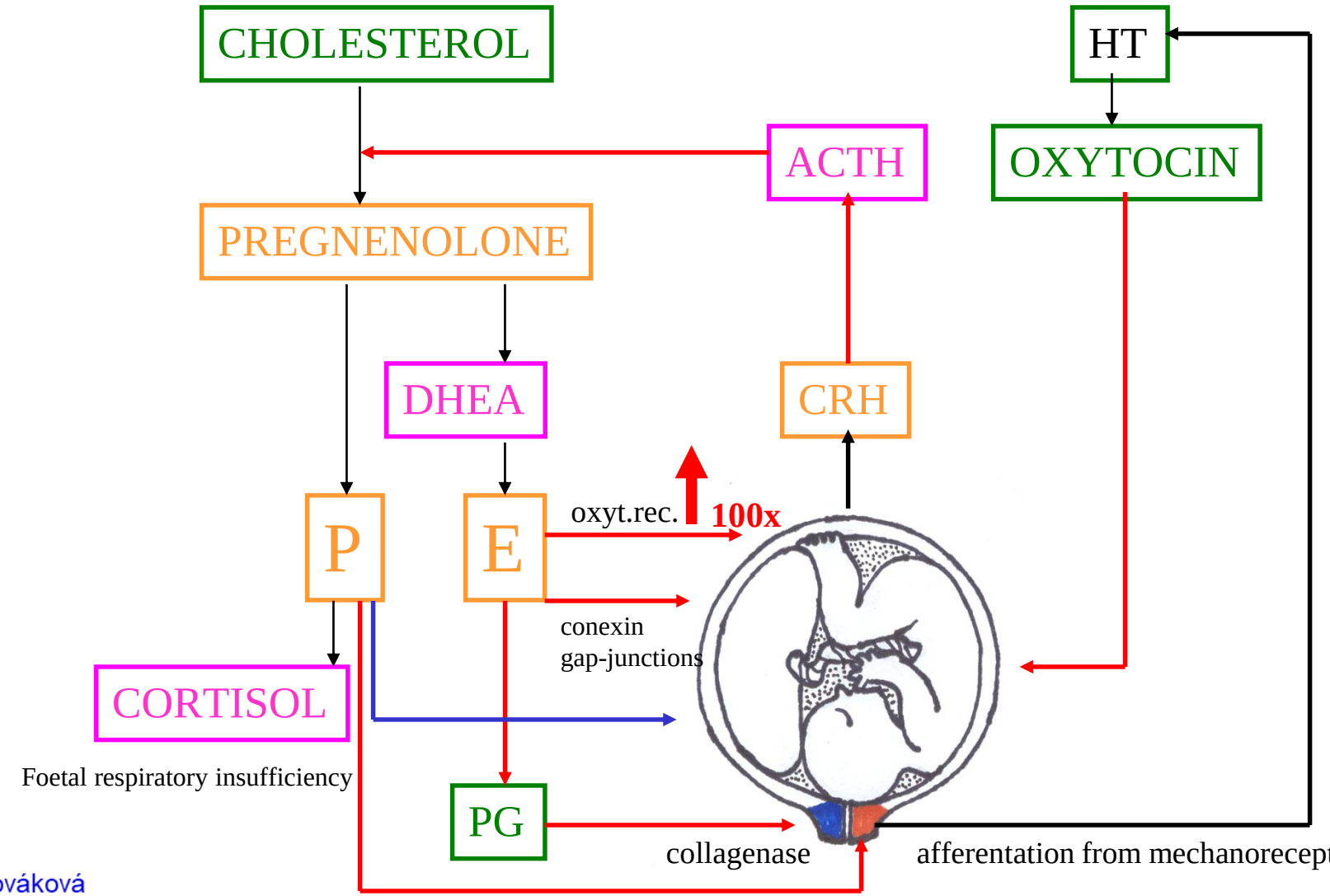
- 9 AA, differs from ADH in 3. a 8. AA
- Precursor molecule is synthetized in the same location as ADH (*nucleus paraventricularis*)
- Stimulus for synthesis: dilatation of birth path caused by pressure of foetus and stimulation of mechanoreceptors at breast nipple
- Reflex release: during breast-feeding, orgasm
- Main effects – on reproduction system:
  - **Uterokinetic effects** (induction of parturition), milk ejection, involution of uterus
  - In men: probably increases contractions of smooth muscle in *ductus deferens*
- Regulation of water and mineral metabolism – natriuretic effect, potentiation of ADH effect
- **Effect on memory**: opposite to ADH effect – inhibits forming of memory and its recollection

- Note: Melanocytes inhibiting factor – from oxytocin, modulates certain types of receptors, modulation of melatonin effects (melatonin – epiphysis, together with glomerulotrophin and DMT, circadian/circannual biorhythms, controlled by hypothalamus, information from retina)

INDUCTION OF BIRTH

maternal
placental
foetal

P > E ⟶ E > P



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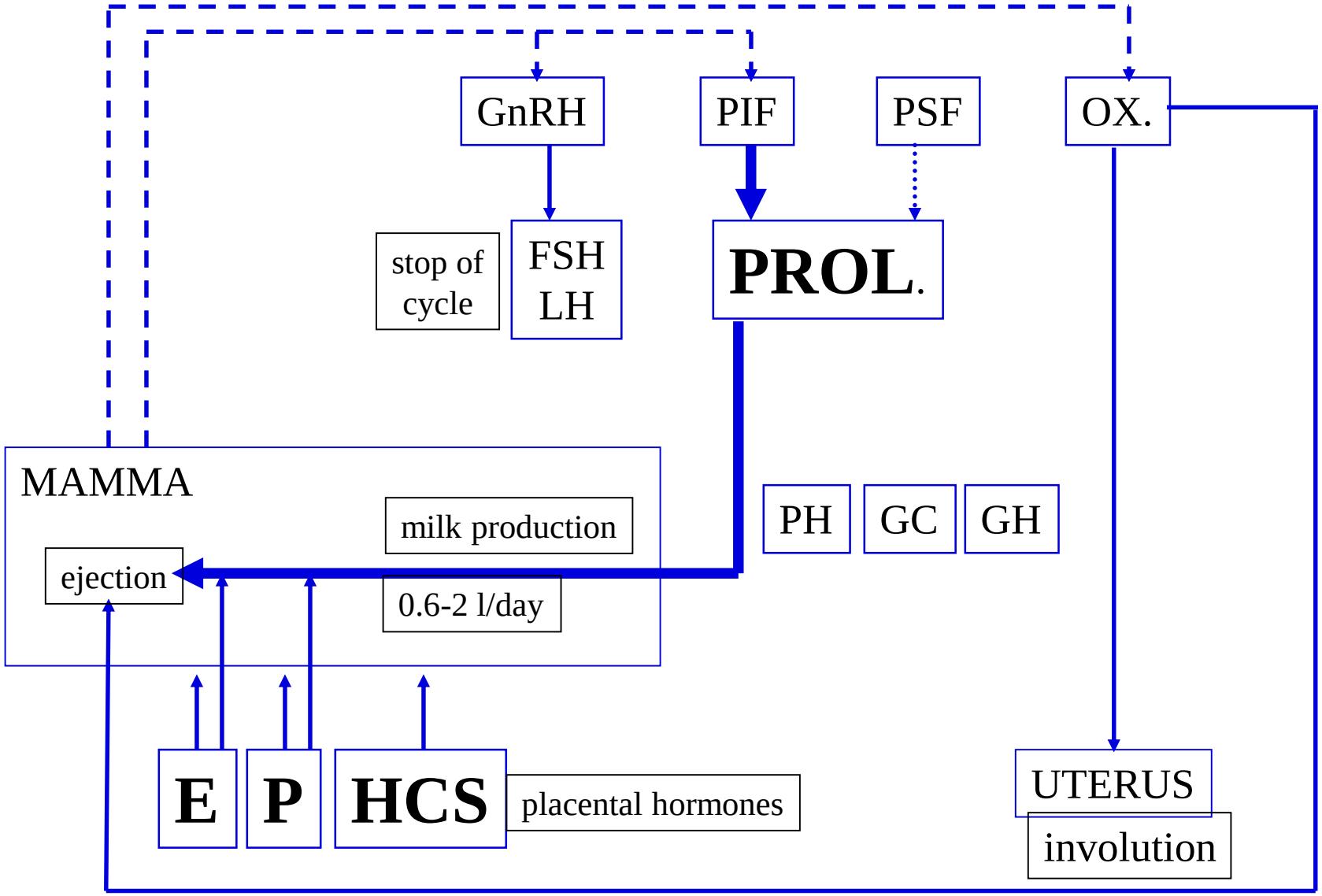
LACTATION

1 – 3 days after birth; initiated by decrease of oestrogens´ concentrations *post partum*



Composition of milk: water (88%), fat (3,5%), lactose (7%), proteins (1%)
trace minerals (Ca), vitamins, antibodies

(hyperprolactinaemia)

MUNI MED