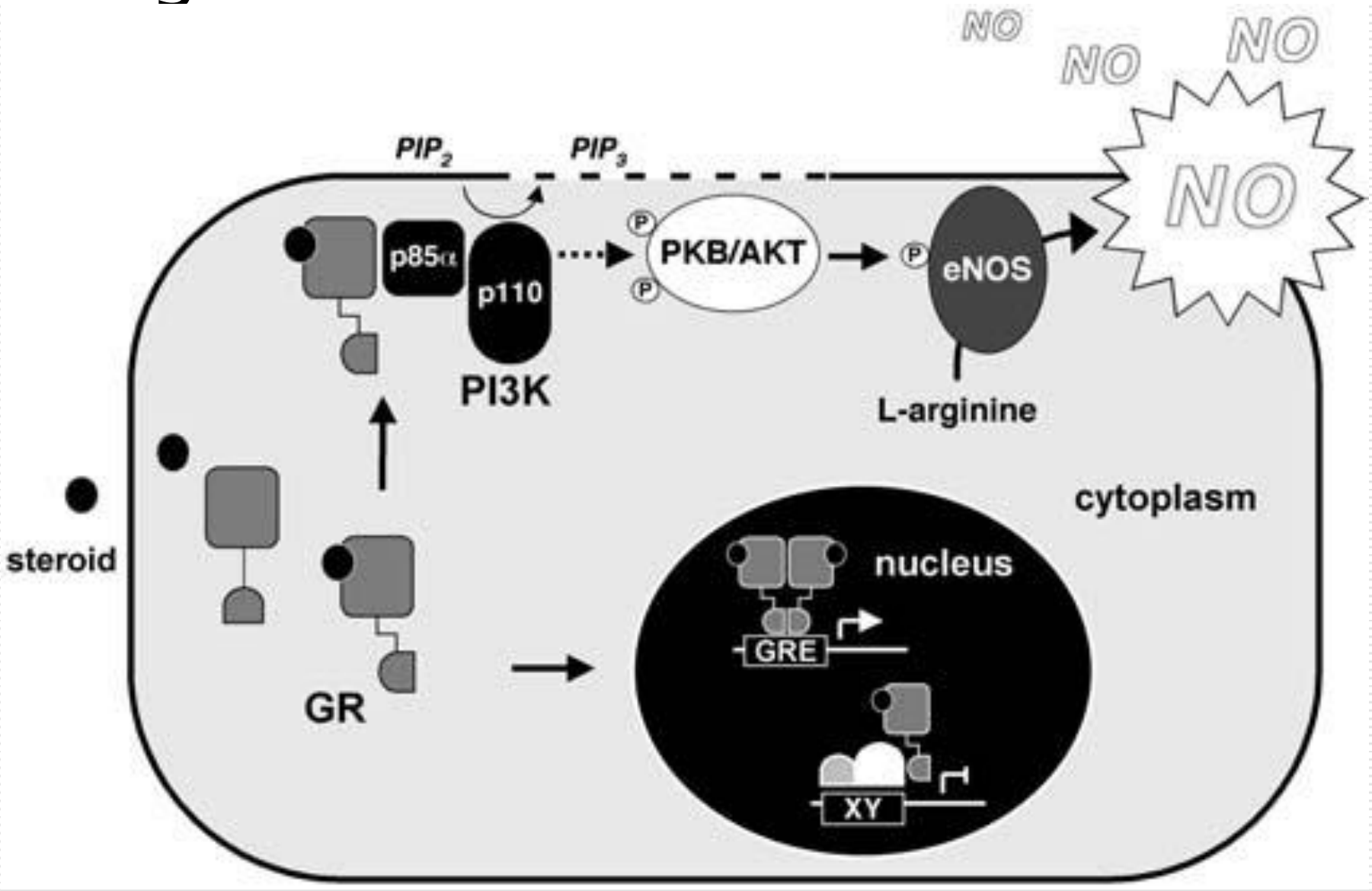
Special pathophysiology of endocrine system

March 20, 2018

Nuclear and non nuclear actions of glucocorticoids



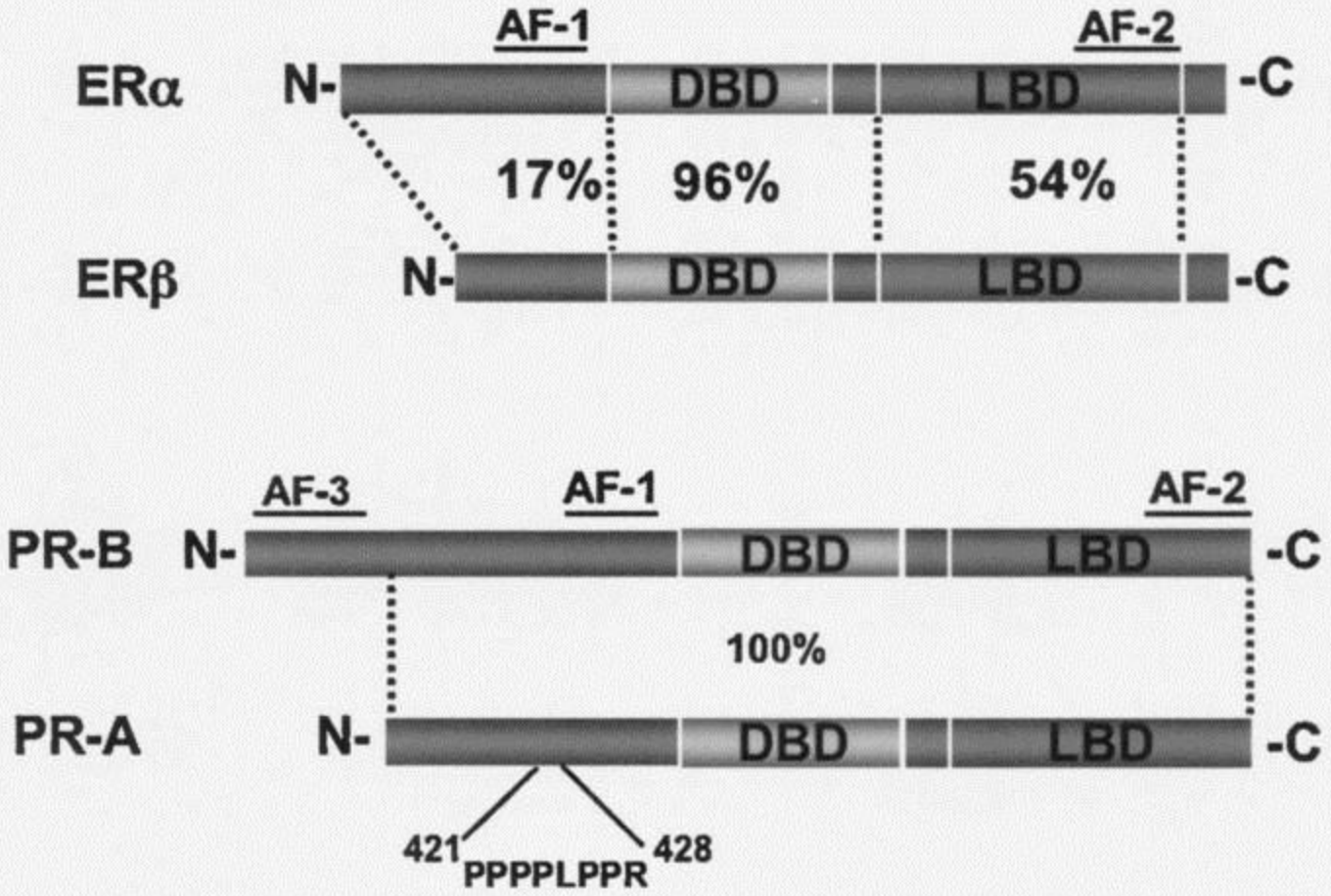


Figure 1 Domain structures of estrogen (ER) and progesterone (PR) receptors. LBD, ligand binding domain; DBD, DNA binding domain; AF, transcription activation domain (AF-1, AF-2, AF-3). The percentages indicate the amino acid identity between domains of ERα and ERβ and between A and B forms of PR. The N-terminal domain of PR contains a polyproline sequence motif that interacts with the SH3 domain of Src.

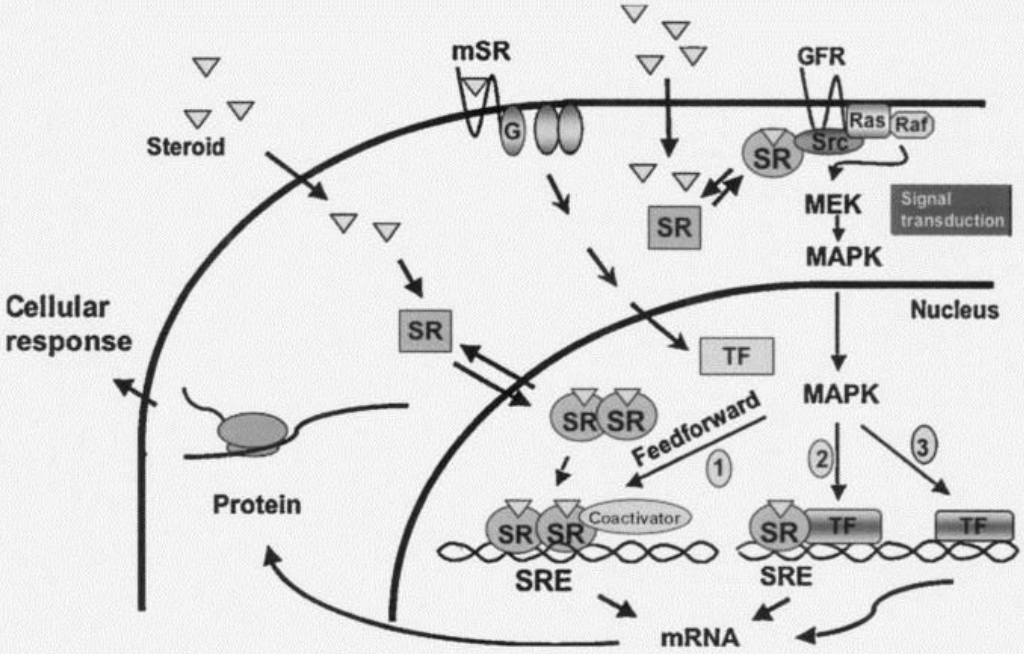


Figure 3 Nuclear transcription and extranuclear signaling pathways regulated by conventional steroid receptors. In the nuclear transcription pathway, steroid hormones activate steroid receptors (SR) by inducing conformational changes that lead to nuclear translocation, dimerization, and binding to steroid response elements (SREs) of target genes. Activated receptor bound to target DNA recruits coactivators that are essential for assembly of a productive transcription complex and for production of new RNA and protein that characterizes the cellular response to the hormone. Subpopulations of steroid receptors (ER and PR) can associate in a hormone-dependent manner with cytoplasmic or cell membrane signaling molecules including the tyrosine kinase Src. This interaction leads to an activation of Src and the downstream Ras, raf, MAP kinase protein phosphorylation cascade. A consequence of steroid-induced activation of MAP kinase is to ultimately influence gene transcription by three potential mechanisms: (1) A feed-forward pathway where activated MAPK increases the direct nuclear transcriptional activity of steroid receptors by phosphorylation of the receptor itself or a receptor interacting coactivator; (2) an activated MAPK phosphorylates and activates other transcription factors (TF) that cooperate with steroid receptors on composite SRE promoters; (3) or a mediated transactivation of genes that lack steroid response elements. Novel membrane receptors (mSR) unrelated to conventional receptors have been identified that mediate rapid steroid-induced activation of signaling pathways.

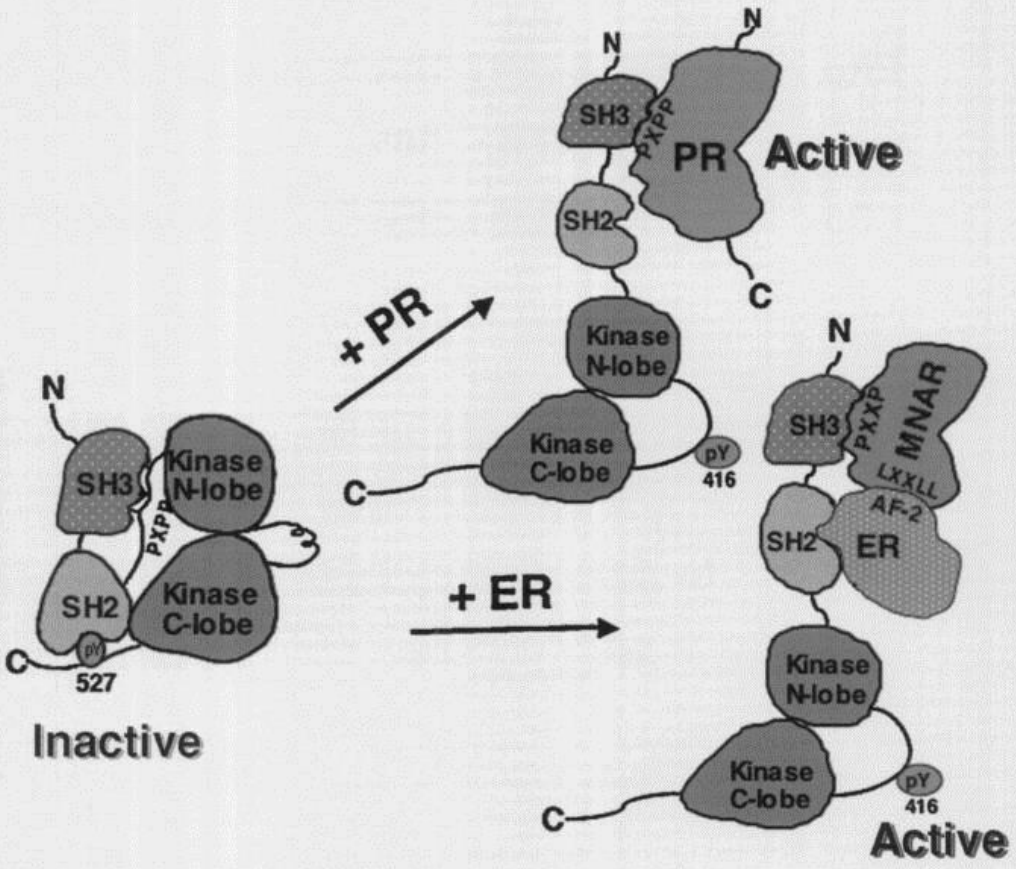
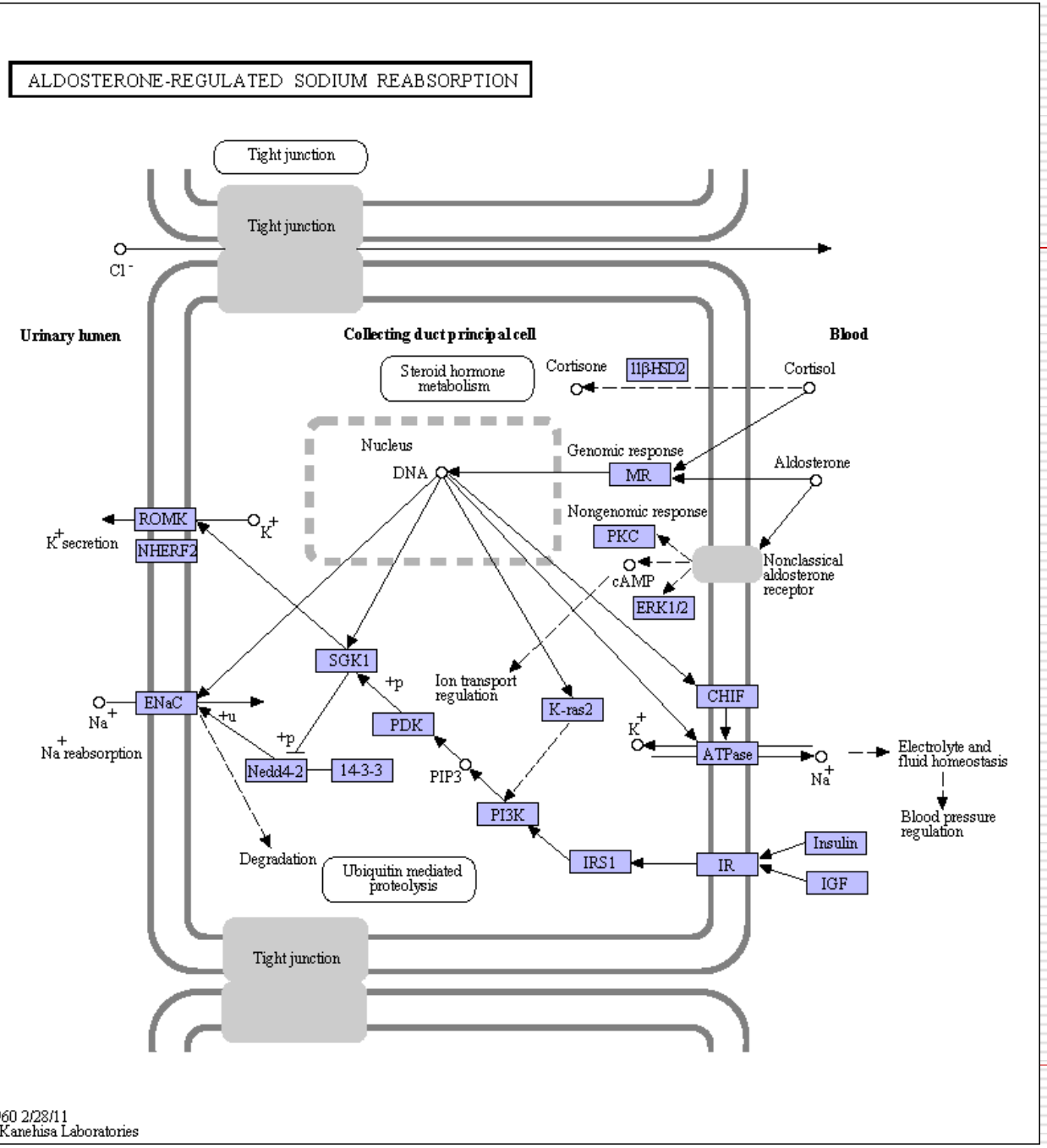


Figure 2 Mechanism of ER and PR activation of Src. PR interacts directly with the SH3 domain of Src through a PXXPXR motif located in the N-terminal domain. This interaction converts Src from an inactive closed conformation to an active open conformation by an SH3 domain displacement mechanism. A direct interaction of ER with the SH2 domain of Src is mediated by a tyrosine phosphorylation site (Y537) in the LBD. However, this interaction is not sufficient to activate Src. Additional interaction surfaces are provided by the adaptor protein MNAR, including an interaction with ER mediated by LXXLL motifs and an interaction with the SH3 domain of Src mediated by a PXXP motif. These additional interaction surfaces provided by MNAR are required for efficient activation of Src, presumably through stabilizing the complex and through interactions with the SH3 domain.

TABLE 1 Variant forms of ER and PR associated with the cell membrane

Receptor	Cell type	Rapid response	References
62–63-kDa ER-X (related to ERα LBD)	Neo-cortex	E-activation of MAPK	(79, 85)
46-kDa ERα (N-terminal truncation ERα)	Endothelial cells	E-activation of eNOS	(166)
45-kDa ERα (N-terminal truncation ERα)	Osteoblasts	Activation PKCα and Src	(167, 168)
46-kDa ERα (related to ERα LBD)	MCF-7 cells	E-activation MAPK and Akt	(169)
50–52-kDA PR (related to PR LBD)	Spermatozoa	P-initiated acrosome reaction	(123)
54–57-kDa PR (related to PR LBD)	Spermatozoa	P-initiated acrosome reaction	(118, 122)
60-kDa PR (related to PR LBD)	Ovarian granulosa cells	P-induced Ca^{2+} flux and activation of MAPK	(154–156)


ALDOSTERONE-REGULATED SODIUM REABSORPTION
Tight junction
Tight junction
Cl-
Urinary lumen
Collecting duct principal cell
Blood
Steroid hormone metabolism
Cortisone
11βHSD2
Cortisol
Nucleus
DNA
Genomic response
MR
Aldosterone
Nongenomic response
PKC
cAMP
ERK1/2
Nonclassical aldosterone receptor
ROMK
K+ secretion
NHERF2
K+
SGK1
+p
Ion transport regulation
K-ras2
CHIF
ENaC
Na+
+u
Na+ reabsorption
+p
PDK
Nedd4-2
14-3-3
PIP3
K+
ATPase
Na+
Electrolyte and fluid homeostasis
Blood pressure regulation
PI3K
Degradation
Ubiquitin mediated proteolysis
IRS1
IR
Insulin
IGF
Tight junction
04960 2/28/11
(c) Kanehisa Laboratories

Hormonal activity

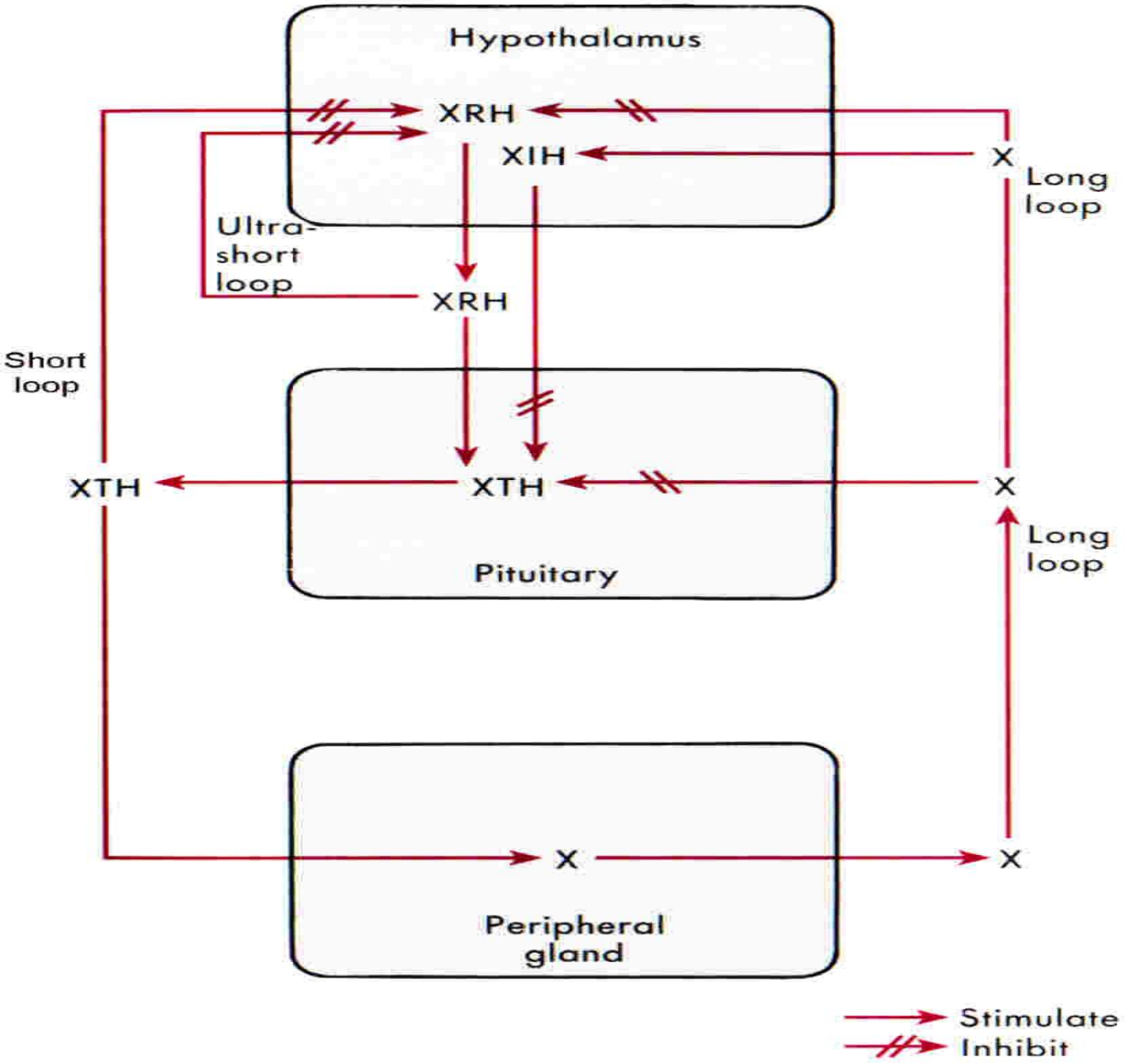
- At the molecular level there is little difference in the way how cellular activity is regulated between classical neurotransmitters that act across synaptic clefts, intercellular factors acting across gap junctions, classic endocrine and paracrine activity and a variety of other chemical messengers involved in cell regulation - such as cytokines, growth factors and interleukins;
- Progress in basic cell biology has revealed the biochemical similarities in the messengers, receptors and intracellular post-receptor mechanisms underlying all these aspects of cell function.

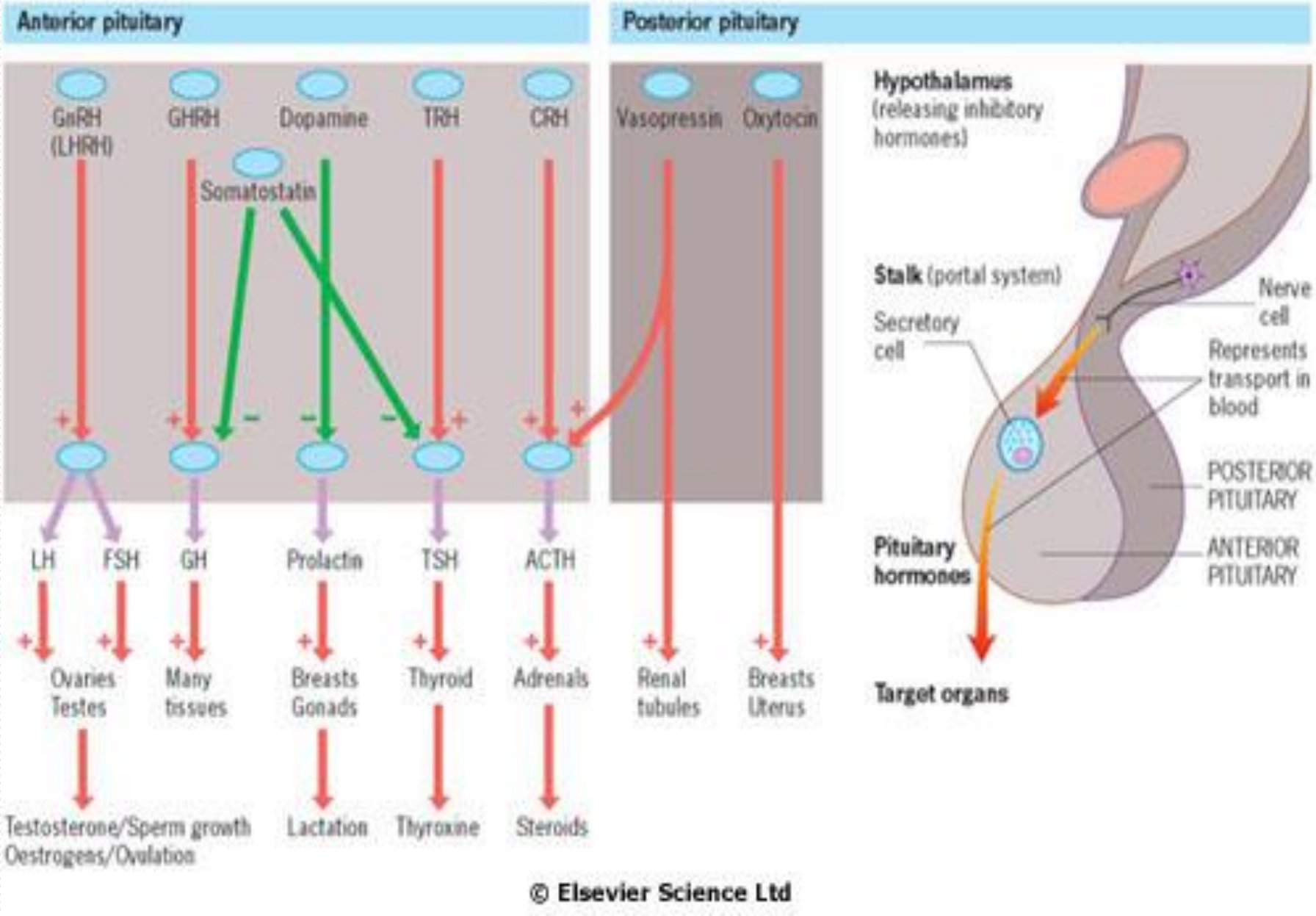
Table 18.5

Nomenclature and biochemistry of hypothalamic, pituitary and peripheral hormones

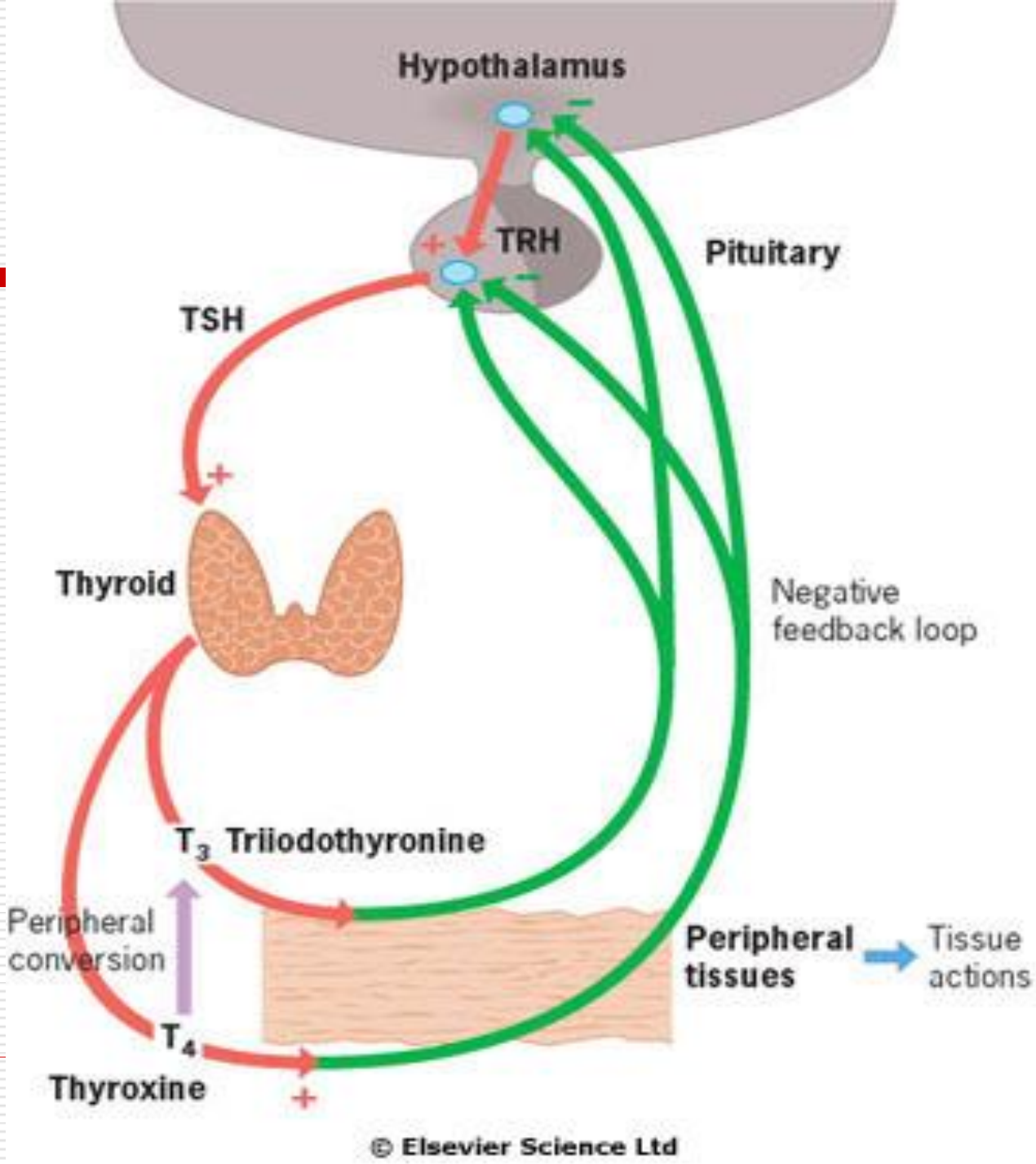
Hypothalamic hormones	Pituitary hormones	Peripheral hormones
Gonadotrophin-releasing hormone (GnRH, LHRH) (*Decapeptide*)	Luteinizing hormone (LH) Follicle-stimulating hormone (FSH) (*Two-chain α, β peptides*)	Oestrogens/androgens (*Steroid ring*)
Prolactin inhibiting factor (PIF – dopamine) (*Amine*)	Prolactin (PRL) (*Single chain peptide*)	–
Growth hormone-releasing hormone (GHRH) (*Peptide*) Somatostatin (GHRIH) (*Cyclic peptide*)	Growth hormone (GH) (*Peptide*)	Insulin-like growth factor-I (IGF-1) (*Peptide*)
Thyrotrophin-releasing hormone (TRH) (*Tripeptide*)	Thyroid-stimulating hormone (TSH) (*Two-chain α, β peptide*)	Thyroxine (T_4), triiodothyronine (T_3) (*Thyronines*)
Corticotropin-releasing hormone (CRH) (*Single-chain peptide*)	Adrenocorticotrophic hormone (ACTH) (*Single-chain peptide*)	Cortisol (*Steroid ring*)
Vasopressin (antidiuretic hormone; ADH) (*Nonapeptide*)	–	–
Oxytocin (*Nonapeptide*)	–	–

NB: The α chains of LH, FSH and TSH are identical
GHRIH, growth hormone release inhibitory hormone


Hypothalamus
XRH
XIH
X
Long loop
Ultra-short loop
XRH
Short loop
XTH
XTH
X
Pituitary
Long loop
X
X
Peripheral gland
Stimulate
Inhibit



Hypothalamic releasing hormones and the pituitary trophic hormones.


Hypothalamus
TRH
Pituitary
TSH
Thyroid
Negative
feedback loop
T_3 Triiodothyronine
Peripheral
conversion
Peripheral
tissues
Tissue
actions
T_4
Thyroxine
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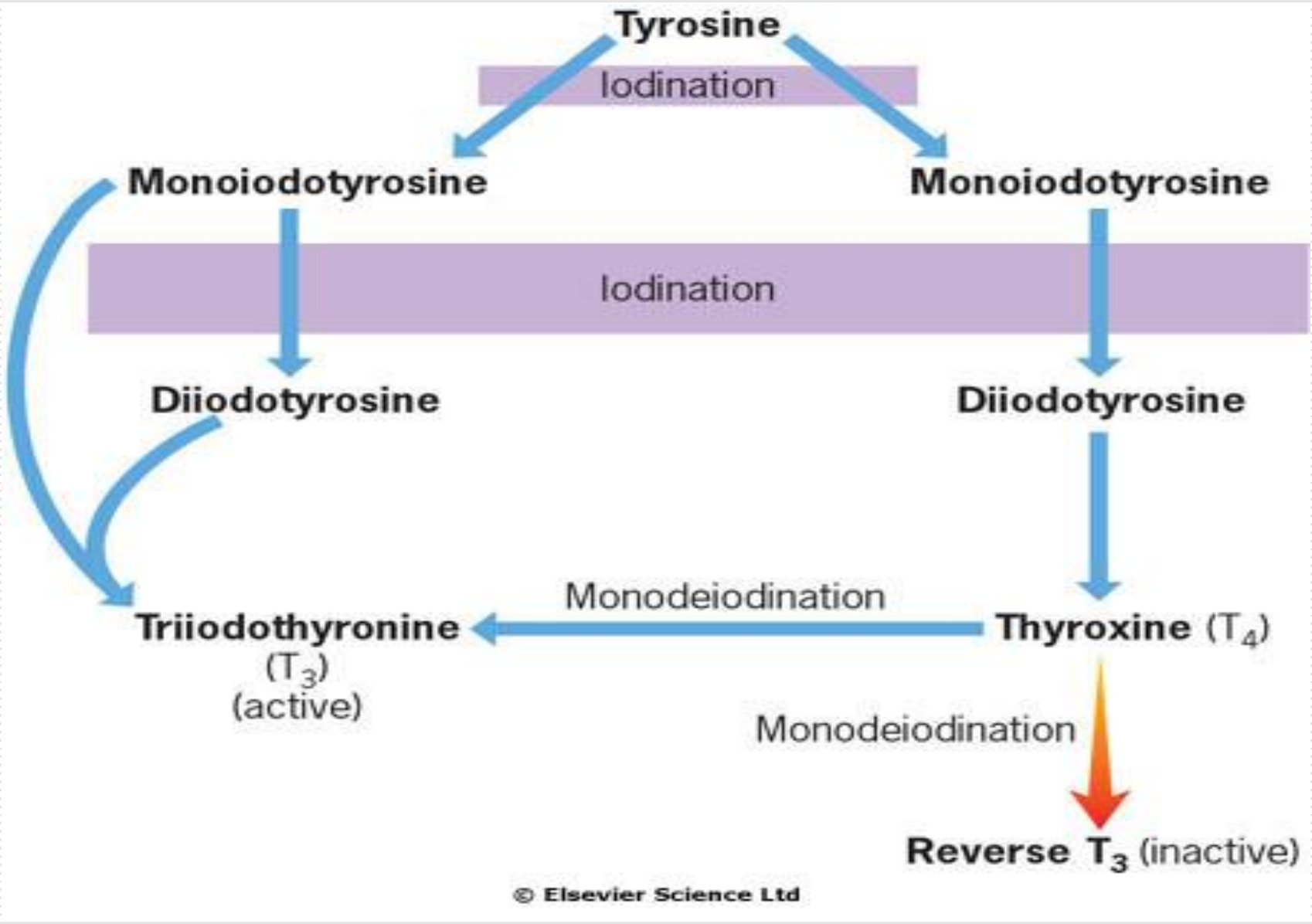
Tyrosine
Iodination
Monoiodotyrosine
Monoiodotyrosine
Iodination
Diiodotyrosine
Diiodotyrosine
Monodeiodination
Triiodothyronine
(T3)
(active)
Thyroxine (T4)
Monodeiodination
Reverse T3 (inactive)
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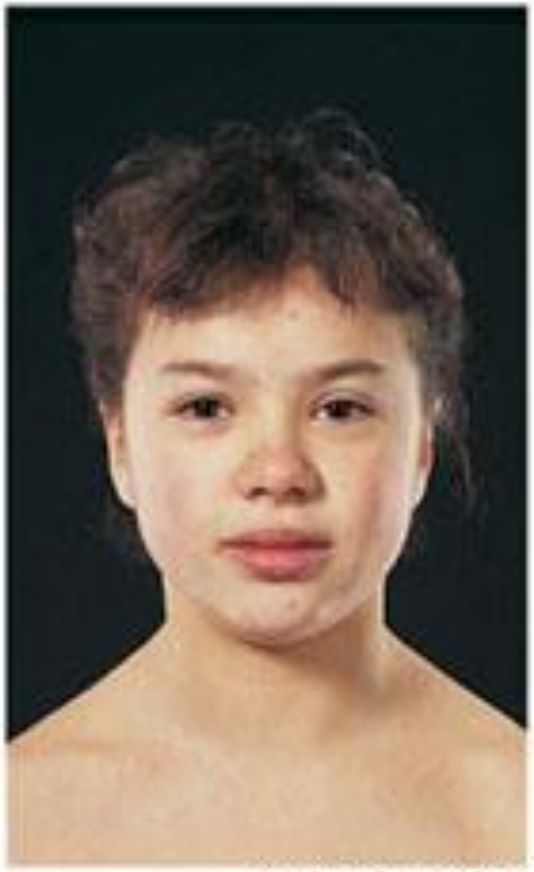
Symptoms

Tiredness/malaise
Weight gain
Anorexia
Cold intolerance
Poor memory
Change in appearance
Depression
Poor libido
Goitre
Puffy eyes
Dry, brittle unmanageable hair
Dry, coarse skin
Arthralgia
Myalgia
Muscle weakness/Stiffness
Constipation
Menorrhagia or oligomenorrhoea in women
Psychosis
Coma
Deafness



Signs

Mental slowness
Ataxia
Poverty of movement
Deafness
Psychosis/dementia (rare)

'Peaches and cream' complexion
Dry thin hair
Loss of eyebrows

Hypertension
Hypothermia
Heart failure
Bradycardia
Pericardial effusion

Cold peripheries
Carpal tunnel syndrome
Oedema

Periorbital oedema
Deep voice
Goitre

Dry skin
Overweight/obesity

Myotonia
Muscular hypertrophy
Proximal myopathy
Slow-relaxing reflexes

Anaemia

Table 18.22
Causes of hypothyroidism

PRIMARY

Congenital

Agenesis

Ectopic thyroid remnants

Defects of hormone synthesis

Iodine deficiency

Dyshormonogenesis

Antithyroid drugs

Other drugs (e.g. lithium, amiodarone, interferon)

Autoimmune

Atrophic thyroiditis

Hashimoto's thyroiditis

Postpartum thyroiditis

Infective

Post-subacute thyroiditis

Post-surgery

Post-irradiation

Radioactive iodine therapy

External neck irradiation

Infiltration

Tumour

SECONDARY

Hypopituitarism

Isolated TSH deficiency

Peripheral resistance to thyroid hormone

Symptoms

Weight loss
Increased appetite
Irritability/behaviour change
Restlessness
Malaise
Stiffness
Muscle weakness
Tremor
Choreoathetosis
Breathlessness
Palpitation
Heat intolerance
Itching
Thirst
Vomiting
Diarrhoea
Eye complaints*
Goitre
Oligomenorrhoea
Loss of libido
Gynaecomastia
Onycholysis
Tall stature (in children)
Sweating

*Only in Graves' disease

Signs

Tremor
Hyperkinesis
Irritability
Psychosis

Tachycardia or atrial fibrillation
Full pulse
Warm vasodilated peripheries
Systolic hypertension
Cardiac failure

Exophthalmos*
Lid lag and 'stare'
Conjunctival oedema
Ophthalmoplegia*
Periorbital oedema
Goitre, bruit
Weight loss

Proximal myopathy
Proximal muscle wasting
Onycholysis
Palmar erythema

Graves' dermopathy*
Thyroid acropachy
Pretibial myxoedema

*Only in Graves' disease

Table 18.23
Causes of hyperthyroidism

Common

Graves' disease (autoimmune)
Toxic multinodular goitre
Solitary toxic nodule/adenoma

Uncommon

Acute thyroiditis
- viral (e.g. De Quervain's)
- autoimmune
- post-irradiation
- post-partum

Gestational thyrotoxicosis (hCG stimulated)
Exogenous iodine
Drugs – amiodarone
Thyrotoxicosis factitia (secret T_4 consumption)

Rare

TSH-secreting pituitary tumours
Metastatic differentiated thyroid carcinoma
hCG-producing tumours
Hyperfunctioning ovarian teratoma (struma ovarii)

Table 18.21

Characteristics of thyroid function tests in common thyroid disorders (the clinically most informative tests in each situation are shown in bold)

	TSH (0.3–3.5 mU/L)	Total T_4 (50–150 mmol/L)	Free T_4 (10–25 pmol/L)	T_3 (1.2–3.1 nmol/L)
Thyrotoxicosis	**Suppressed (< 0.05 mU/L)**	Increased	**Increased**	**Increased**
Primary hypothyroidism	**Increased (> 10 mU/L)**	Low/low-normal	Low/low-normal	Normal or low
TSH deficiency	Low-normal or subnormal	Low/low-normal	**Low/low-normal**	Normal or low
T_3 toxicosis	Suppressed (< 0.05 mU/L)	Normal	Normal	**Increased**
Compensated euthyroidism	**Slightly increased (5–10 mU/L)**	Normal	**Normal**	Normal

Primary aldosteronism (PA),

- characterized by autonomous aldosterone overproduction by the adrenal glands, affects 6% of the general hypertensive population and can be either sporadic or familial.
- Aldosterone-producing adenoma (APA) and bilateral adrenal hyperplasia (BAH) are the two most frequent subtypes of sporadic PA and 4 forms of familial hyperaldosteronism (FH-I to FH-IV) have been identified.

Primary aldosteronism (PA),

- Germline mutations in *KCNJ5* and *CACNA1H* cause FH-III and FH-IV, respectively, while germline mutations in *CACNA1D* cause the rare PASNA syndrome, featuring primary aldosteronism seizures and neurological abnormalities.

Primary aldosteronism (PA),

- Somatic mutations in four genes (*KCNJ5, ATP1A1, ATP2B3* and *CACNA1D*), differently implicated in intracellular ion homeostasis, have been identified in nearly 60% of the sporadic APAs.

Addison's disease

- is a primary adrenocortical insufficiency with a deficiency in corticosteroids and mineralocorticoids. The most common cause for a primary adrenocortical insufficiency in Western populations is an autoimmune process (80 %). Further causes are cancer metastases, especially bronchial carcinoma, malignant melanoma or renal cell carcinoma.

Addison disease

- is an acquired primary adrenal insufficiency, which is a rare but potentially life-threatening endocrine disorder that results from bilateral adrenal cortex destruction leading to decreased production of adrenocortical hormones including cortisol, aldosterone, and/or adrenal.

Addison's disease

- In developing countries, kidney tuberculosis is still the most common cause of primary adrenocortical insufficiencies.

Addison's disease

- The symptoms manifest in a rather diffuse clinical pattern with unspecific general symptoms like fatigue, myalgia, nausea, and weight loss.

Addison's disease

- In case of inadequate substitution of adrenocortical hormones, there is a risk of an Addisonian crisis.
- Triggers of Addisonian crises are stress situations with an increased demand for cortisol, e.g. infections or severe physical stress. The therapy of an Addisonian crisis is substitution with high-dose hydrocortisone. Long-term therapy consists of hydrocortisone und fludrocortisone.

Addison disease

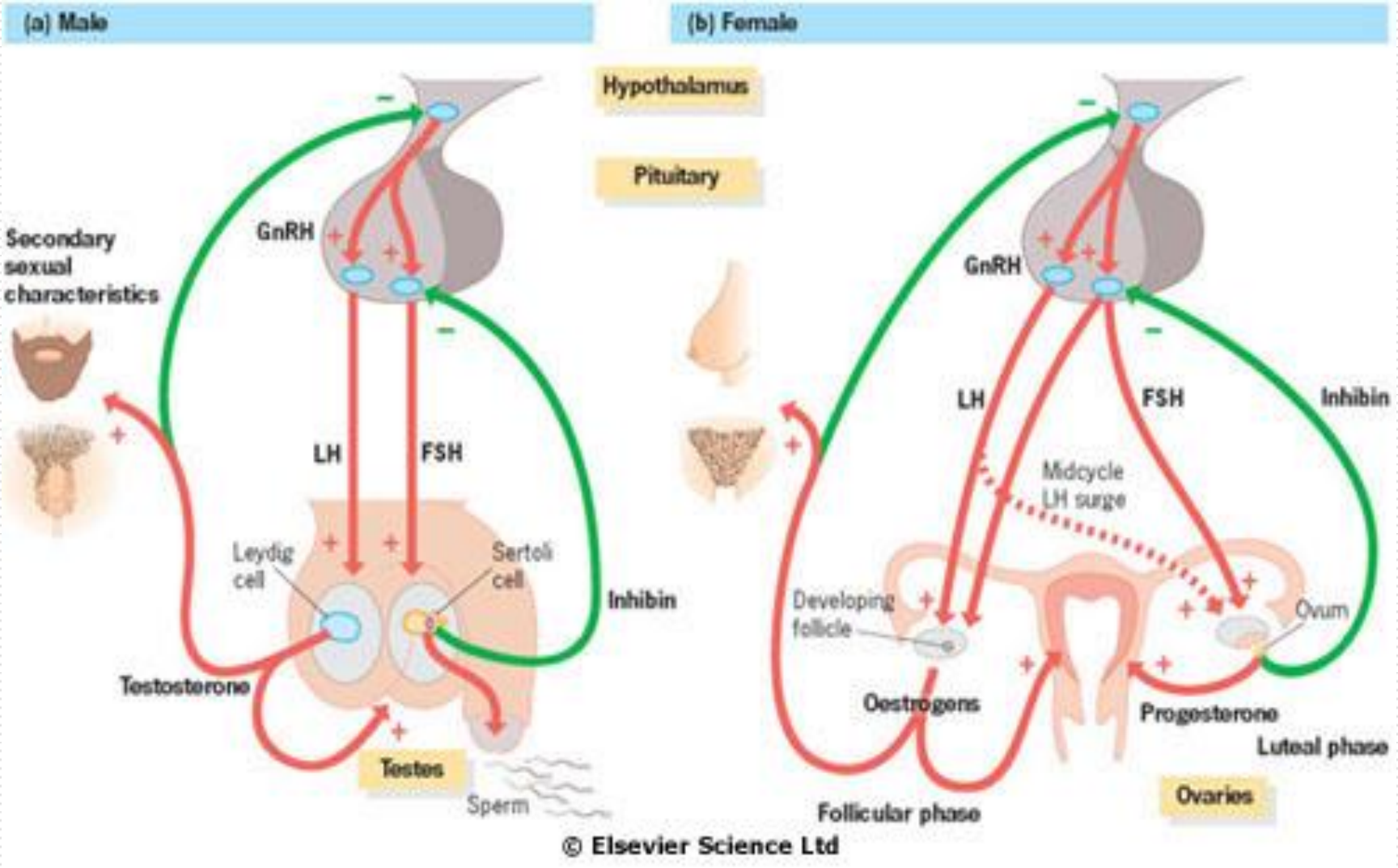
- insidious course of action usually presents with glucocorticoid deficiency followed by mineralocorticoid; however, it can present acutely, especially with inter-current illness, with adrenal crisis.
- The most common cause of primary adrenal insufficiency is autoimmune adrenalitis (Addison disease) which is associated with increased levels of 21-hydroxylase antibodies.

Embryology of reproduction

- Up to 8 weeks of gestation the sexes share a common development, with a primitive genital tract including the Wolffian and Müllerian ducts. There are additionally a primitive perineum and primitive gonads.
- In the presence of a Y chromosome the potential testis develops while the ovary regresses.
- In the absence of a Y chromosome, the potential ovary develops and related ducts form a uterus and the upper vagina.

Embryology

- Production of Müllerian inhibitory factor from the early 'testis' produces atrophy of the Müllerian duct, while, under the influence of testosterone and dihydrotestosterone, the Wolffian duct differentiates into an epididymis, vas deferens, seminal vesicles and prostate. Androgens induce transformation of the perineum to include a penis, penile urethra and scrotum containing the testes, which descend in response to androgenic stimulation. At birth, testicular volume is 0.5-1 mL.



Male and female hypothalamic-pituitary-gonadal axes. Note the close parallels. The green lines indicate negative feedback

Hypothalamic-pituitary-testicular axis

- Pulses of GnRH (LHRH) are released from the hypothalamus and stimulate LH and FSH release from the pituitary.
- LH stimulates testosterone production from Leydig cells of the testis.
- Testosterone acts systemically to produce male secondary sexual characteristics, anabolism and the maintenance of libido. It also acts locally within the testis to aid spermatogenesis. Testosterone circulates largely bound to sex hormone-binding globulin (SHBG). Testosterone feeds back on the hypothalamus/pituitary to inhibit GnRH secretion.
- FSH stimulates the Sertoli cells in the seminiferous tubules to produce mature sperm and the inhibins A and B.
- Inhibin causes feedback on the pituitary to decrease FSH secretion.
- The secondary sexual characteristics of the male for which testosterone is necessary are the growth of pubic, axillary and facial hair, enlargement of the external genitalia, deepening of the voice, sebum secretion, muscle growth and frontal balding.

The female

- In the adult female, higher brain centres impose a menstrual cycle of 28 days upon the activity of hypothalamic GnRH.
- Pulses of GnRH, at about 2-hour intervals, stimulate release of pituitary LH and FSH.
- LH stimulates ovarian androgen production by the ovarian theca cells.

The female

- FSH stimulates follicular development and aromatase activity (an enzyme required to convert ovarian androgens to oestrogens) in the ovarian granulosa cells. FSH also stimulates release of inhibin from ovarian stromal cells which inhibits FSH release.
- Although many follicles are 'recruited' for development in early folliculogenesis, by day 8-10 a 'leading' (or 'dominant') follicle is selected for development into a mature Graafian follicle.

The female

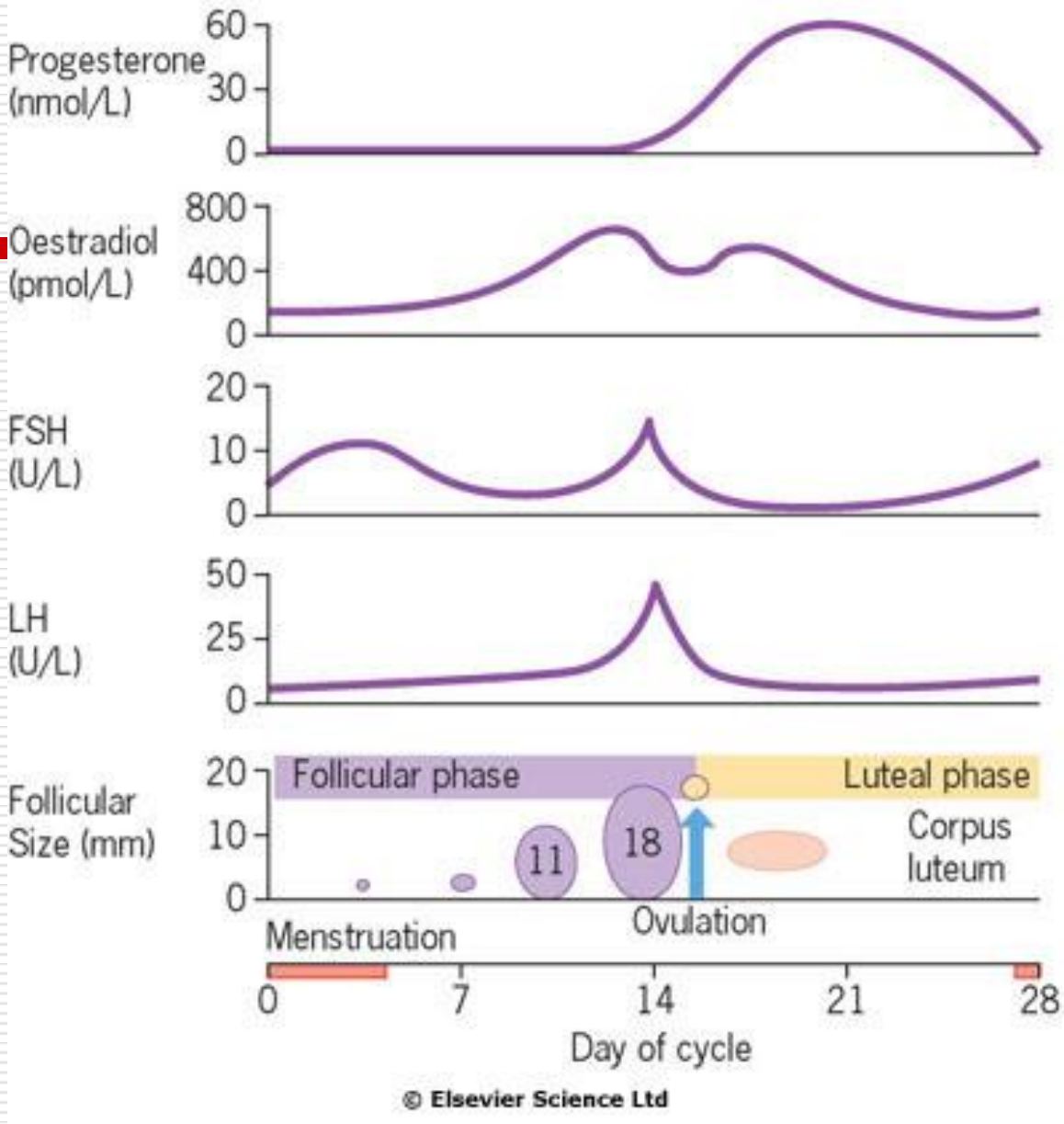
- Oestrogens show a double feedback action on the pituitary, initially inhibiting gonadotrophin secretion (negative feedback), but later high-level exposure results in increased GnRH secretion and increased LH sensitivity to GnRH (positive feedback), which leads to the mid-cycle LH surge inducing ovulation from the leading follicle.
- The follicle then differentiates into a corpus luteum, which secretes both progesterone and estradiol during the second half of the cycle (luteal phase).

The female

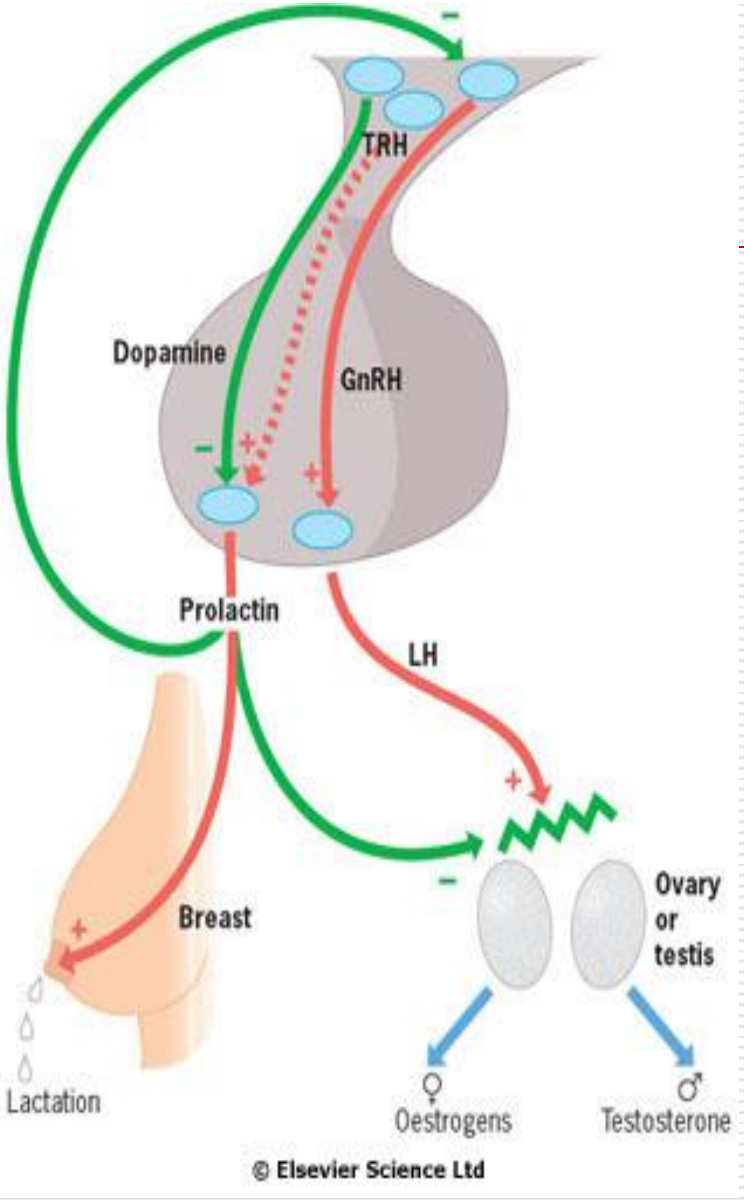
- Oestrogen initially and then progesterone cause uterine endometrial proliferation in preparation for possible implantation; if implantation does not occur, the corpus luteum regresses and progesterone secretion and inhibin levels fall so that the endometrium is shed (menstruation) allowing increased GnRH and FSH secretion.
- If implantation and pregnancy follow, human chorionic gonadotrophin (HCG) production from the corpus luteum maintains corpus luteum function until 10-12 weeks of gestation, by which time the placenta will be making sufficient oestrogen and progesterone to support itself.

The female

- Oestrogens also induce secondary sexual characteristics, especially development of the breast and nipples, vaginal and vulval growth and pubic hair development.
- They also induce growth and maturation of the uterus and Fallopian tubes.
- They circulate largely bound to sex hormone-binding globulin (SHBG).



Hormonal and follicular changes during the normal menstrual cycle.



The control of prolactin secretion.

Physiology of prolactin secretion

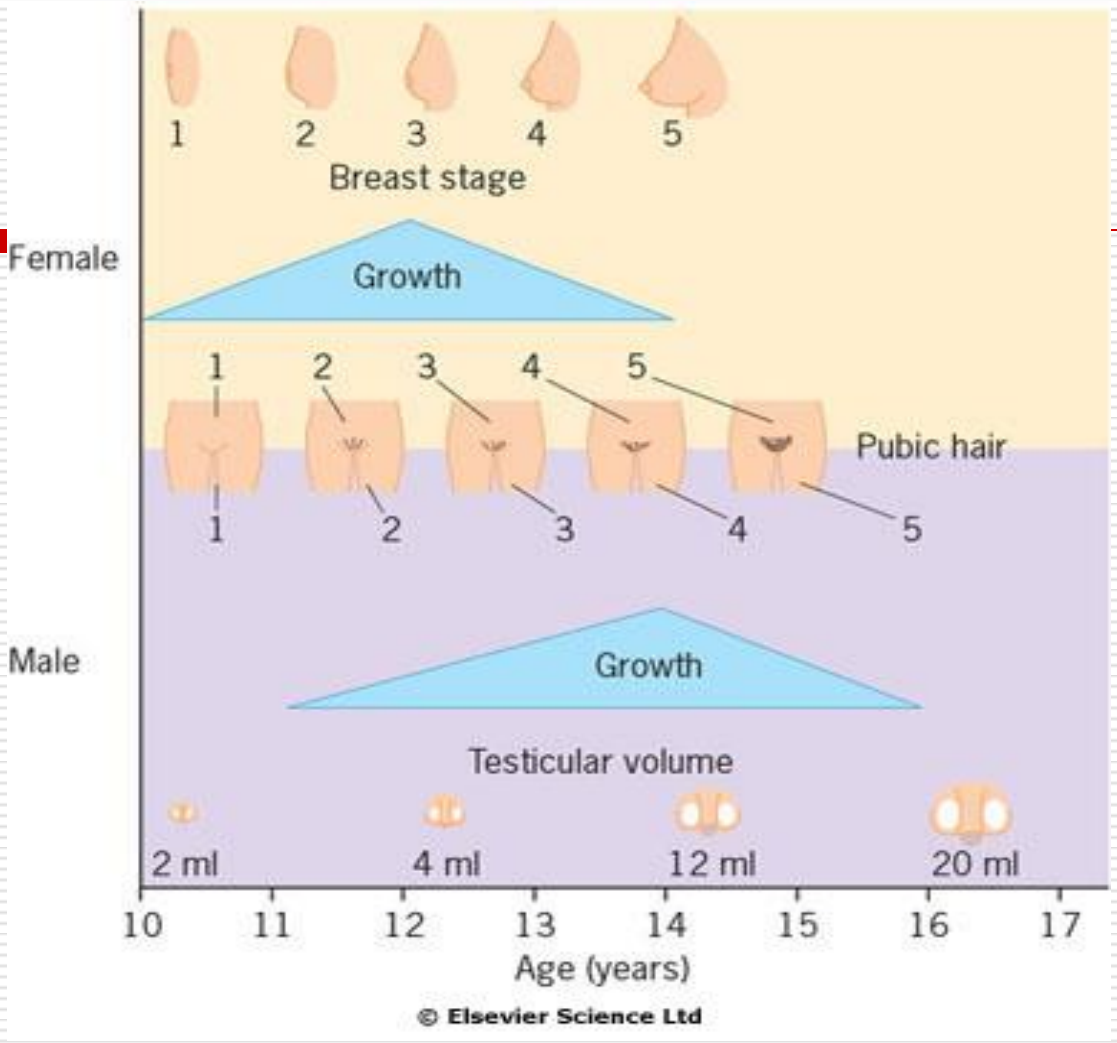
- Prolactin is under tonic dopamine inhibition (=PIH-prolactin inhibitory hormon), while other factors known to increase prolactin secretion (e.g. TRH) are probably of less importance.
- Function:
- ✓ Stimulation of milk secretion
- ✓ Reduction of gonadal activity. It decreases GnRH pulsatility at the hypothalamic level and, to a lesser extent, blocks the action of LH on the ovary or testis, producing hypogonadism. These actions may be clinically relevant.

Puberty

- The mechanisms initiating puberty are poorly understood but are thought to result from withdrawal of central inhibition of GnRH release. LH and FSH are both low in the prepubertal child. In early puberty, FSH begins to rise first, initially in nocturnal pulses; this is followed by a rise in LH with a subsequent increase in testosterone/oestrogen levels.

Puberty

- *In boys*, pubertal changes begin at between 10 and 14 years and are complete at between 15 and 17 years.
- ✓ The genitalia develop, testes enlarge and the area of pubic hair increases.
- ✓ Peak height velocity is reached between ages 12 and 17 years during stage 4 of testicular development.
- ✓ Full spermatogenesis occurs comparatively late.



The age of development of features of puberty. Stages and testicular size show mean ages, and all vary considerably between individuals. The same is true of height spurt, shown here in relation to other data. Numbers 2 to 5 indicate stages of development

Puberty

- *In girls*, events start a year earlier.
- ✓ Breast bud enlargement begins at ages 9-13 years and continues to 12-18 years.
- ✓ Pubic hair growth commences at ages 9-14 years and is completed at 12-16 years.
- ✓ Menarche occurs relatively late (age 11-15 years)
- ✓ Peak height velocity is reached earlier (at age 10-13 years)
- ✓ Growth is completed much earlier than in boys.

Precocious puberty

- Development of secondary sexual characteristics, or menarche in girls, at or before the age of 9 years is premature. All cases require specialist assessment by a paediatric endocrinologist.
- *Idiopathic (true) precocity* is most common in girls and very rare in boys. This is a diagnosis of exclusion. With no apparent cause for premature breast or pubic hair development, and an early growth spurt, it may be normal and may run in families.

The following are other forms of precocity:

- *Cerebral precocity.* Many causes of hypothalamic disease, especially tumours, may present in this way. In boys this must be rigorously excluded.
- *McCune-Albright syndrome.* This is usually in girls, with precocity, polyostotic fibrous dysplasia and skin pigmentation (café-au-lait).
- *Premature thelarche.* This is early breast development alone, usually transient, at age 2-4 years. It may regress or persist until puberty. There is no evidence of follicular development.
- *Premature adrenarche.* This is early development of pubic hair without significant other changes, usually after age 5 years and more commonly in girls.

Delayed puberty

- Over 95% of children show signs of pubertal development by age 14 years. In its absence, investigation should begin by age 15 years. Causes of hypogonadism (see below) are clearly relevant but most cases represent constitutional delay.
- *In constitutional delay*, pubertal development, bone age and stature are in parallel. A family history may confirm that other family members experienced the same delayed development, which is common in boys but very rare in girls.

Delayed puberty

- ✓ In boys, a testicular volume > 5 mL indicates the onset of puberty. A rising serum testosterone is an earlier clue.
- ✓ In girls, the breast bud is the first sign. Ultrasound allows accurate assessment of ovarian and uterine development. Basal LH/FSH levels may identify the site of a defect, and GnRH (LHRH) tests can indicate the stage of early puberty. If any progression into puberty is evident clinically, investigations are not required. When delay is great and problems are serious (e.g. severe teasing at school), low-dose short-term sex hormone therapy is used. Specialist assessment is advisable.

The menopause

- The menopause, or cessation of periods, naturally occurs about the age of 45-55 years. During the late forties, FSH initially, and then LH concentrations begin to rise, probably as follicle supply diminishes. Oestrogen levels fall and the cycle becomes disrupted. Most women notice irregular scanty periods coming on over a variable period, though in some sudden amenorrhoea or menorrhagia occur.
- Eventually the menopausal pattern of low estradiol levels with grossly elevated LH and FSH levels (usually > 50 and > 25 U/L, respectively) is established.
- Menopause may also occur surgically, with radiotherapy to the ovaries and with ovarian disease (e.g. premature menopause).

Premature menopause

- The most common cause of premature menopause in women (before age 40) is ***ovarian failure***, which may be autoimmune or of unknown aetiology.
- HRT should be given, as the risk of osteoporosis and premature ischaemic heart disease far outweigh the risks (?).

The ageing male

- In the male there is no sudden 'change of life'. However, there is a progressive loss in sexual function with reduction in morning erections and frequency of intercourse.
- The age of onset varies widely, but overall testicular volume diminishes and sex hormone-binding globulin (SHBG) and gonadotrophin levels gradually rise.
- If premature hypogonadism is present for any reason, replacement testosterone therapy should be given to prevent osteoporosis.
- Lowering of androgens forms part of the therapy of prostate hypertrophy and prostate cancer. Finasteride, an inhibitor of 5α-reductase, is used in benign prostatic hypertrophy. It prevents the conversion of testosterone to dihydrotestosterone, which causes prostatic hypertrophy.

Table 18.11
Tests of gonadal function

Test	Uses/comments
Male	
Basal testosterone	Normal levels exclude hypogonadism
Sperm count	Normal count excludes deficiency Motility and abnormal sperm forms should be noted
Female	
Basal estradiol	Normal levels exclude hypogonadism
Luteal phase progesterone (days 18–24 of cycle)	If >30 nmol/L, suggests ovulation
Ultrasound of ovaries	To confirm ovulation
Both sexes	
Basal LH/FSH	Demonstrates state of feedback system for hormone production (LH) and germ cell production (FSH)
HCG test (testosterone or estradiol measured)	Response shows potential of ovary or testis; failure demonstrates primary gonadal problem
Clomifene test (LH and FSH measured)	Tests hypothalamic negative feedback system; clomifene is oestrogen antagonist
Post-coital test	Demonstrates state of sperm and sperm–mucus interaction
LHRH test (now rarely used)	Shows adequacy (or otherwise) of LH and FSH stores in pituitary

Hypogonadism

- **Cryptorchidism** By the age of 5 years both testes should be in the scrotum. After that age the germinal epithelium is increasingly at risk, and lack of descent by puberty is associated with subfertility. Surgical exploration and orchidopexy are usually undertaken but a short trial of HCG occasionally induces descent: an HCG test with a testosterone response 72 hours later excludes anorchia. Intra-abdominal testes have an increased risk of developing malignancy; if presentation is after puberty, orchidectomy is advised.

Hypogonadism

- **Klinefelter's syndrome** Klinefelter's syndrome (seminiferous tubule dysgenesis), a chromosomal disorder (47XXY) affecting 1 in 1000 males, involves both loss of Leydig cells and seminiferous tubular dysgenesis. Patients usually present with
- ✓ poor sexual development
- ✓ small or undescended testes
- ✓ gynaecomastia
- ✓ or infertility.
- ✓ They are occasionally mentally retarded.
- ✓ Confirmation is by chromosomal analysis. Treatment is androgen replacement therapy unless testosterone levels are normal. No treatment is possible for the abnormal seminiferous tubules and infertility.

Hypogonadism

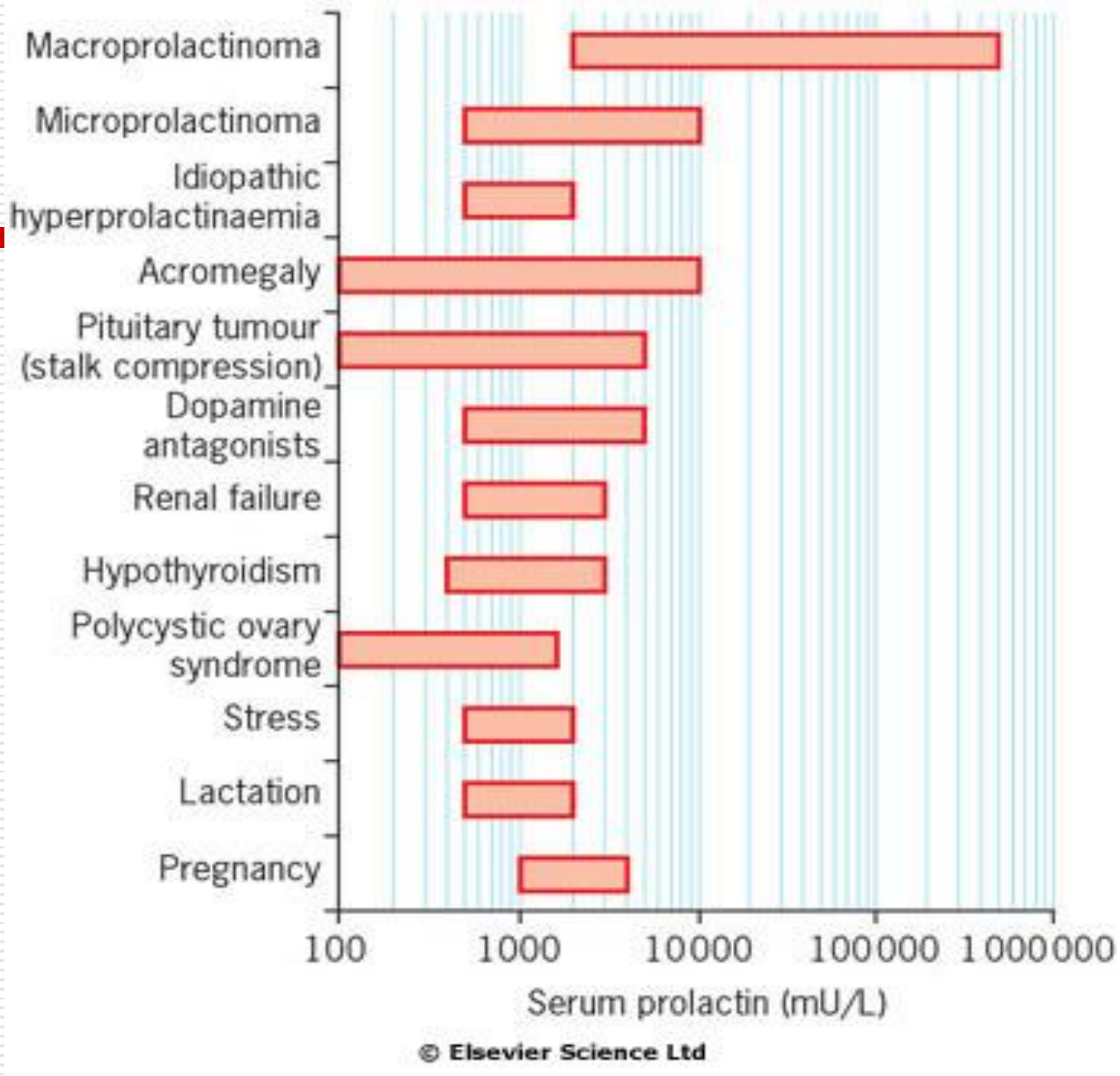
- **Kallmann's syndrome** This is due to isolated GnRH deficiency. It is often associated with decreased or absent sense of smell (anosmia), and sometimes with other bony (cleft-palate), renal and cerebral abnormalities (e.g. colour blindness). It is often familial and is usually X-linked; one sex-linked form is due to an abnormality of a cell adhesion molecule. Fertility is possible.
- **Oligospermia or azoospermia** These may be secondary to androgen deficiency and can be corrected by androgen replacement. More often they result from primary testicular diseases, in which case they are rarely treatable. Azoospermia with normal testicular size and low FSH levels suggests a vas deferens block, which is sometimes reversible by surgical intervention.

Gynaecomastia

- Gynaecomastia is development of breast tissue in the male.
- Pubertal gynaecomastia occurs in perhaps 50% of normal boys, often asymmetrically. It usually resolves spontaneously within 6-18 months, but after this duration may require surgical removal, as fibrous tissue will have been laid down. The cause is thought to be relative oestrogen excess.

Gynaecomastia

- *In the older male*, gynaecomastia requires a full assessment to exclude potentially serious underlying disease, such as bronchial carcinoma and testicular tumours (e.g. Leydig cell tumour).
- Drug effects are common (especially digoxin and spironolactone), and once these and significant liver disease are excluded most cases have no definable cause. Surgical removal is occasionally necessary.



Range of serum prolactin seen in common causes of hyperprolactinaemia.

Hypogonadism in female

- Impaired ovarian function, whether primary or secondary, will lead both to **oestrogen deficiency** and abnormalities of the menstrual cycle. The latter is very sensitive to disruption, cycles becoming anovulatory and irregular before disappearing altogether. Symptoms will depend on the age at which the failure develops. **Amenorrhoea :** Absence of periods or markedly irregular infrequent periods (oligomenorrhoea) are the commonest presentation of female gonadal disease.

Hypogonadism in female

- **Polycystic ovary syndrome** Polycystic ovary syndrome is the most common cause of oligomenorrhoea and amenorrhoea in clinical practice and should always be considered in the context of menstrual dysfunction.
- **Weight-related amenorrhoea** A minimum bodyweight is necessary for regular menstruation. While anorexia nervosa is the extreme form, this condition is common and may be seen at weights within the 'normal' range. The biochemistry is indistinguishable from gonadotrophin deficiency and some patients have additional mild endocrine disease (e.g. polycystic ovarian disease). Restoration of bodyweight is usually effective in restoring menstruation, but in the many cases where this cannot be achieved then oestrogen replacement must be considered. Similar problems occur with intensive physical training in athletes and dancers.

Hypogonadism in female

- **Hypothalamic amenorrhoea** Amenorrhoea with low oestrogen and gonadotrophins in the absence of organic pituitary disease, weight loss or excessive exercise is described as hypothalamic amenorrhoea. This may be related to 'stress', to previous weight loss or stopping the contraceptive pill, but some patients appear to have defective cycling mechanisms without apparent explanation.
- **Hypothyroidism** Oligomenorrhoea and amenorrhoea are frequent findings in severe hypothyroidism in young women.

Hypogonadism in female

- **Other** Pregnancy must always be considered as a possible cause. The possibility of genital tract abnormalities, such as an imperforate hymen, should also be remembered, especially in primary amenorrhoea. Severe illness, even in the absence of weight loss, can lead to amenorrhoea, as can stopping the contraceptive pill.

Table 18.17
Amenorrhoea – differential diagnosis and investigation

Diagnosis	Biochemical markers	Secondary tests
Polycystic ovarian syndrome*		
	Normal/slightly high testosterone	Serum androgens
	Normal/high LH	SHBG
	Normal FSH	Ultrasound of ovary
	Normal/high prolactin	Progesterone challenge
	Variable estradiol	
Ovarian failure		
Ovarian dysgenesis*	High FSH	Repeat FSH
Premature ovarian failure*	High LH	Karyotype
Steroid biosynthetic defect*	Low estradiol	Ultrasound of ovary/uterus
(Oophorectomy)	Normal prolactin	Laparoscopy/biopsy of ovary
(Chemotherapy)		HCG stimulation
Resistant ovary syndrome		
Gonadotrophin failure (see also hypothalamic causes below)		
Hypothalamic–pituitary disease*	Low LH	Pituitary MRI if diagnosis unclear
Kallmann's syndrome*	Low FSH	Clomifene test
Anorexia*	Low estradiol	Possibly LHRH test
Weight loss*	Normal/low prolactin	Serum thyroxine
General illness*		
Possible hypothalamic causes		
Hypothalamic amenorrhoea*	Variable LH	Serum thyroxine
Weight gain/loss*	Variable FSH	Serum testosterone, SHBG
Exercise-induced amenorrhoea	Normal prolactin	
Post-pill amenorrhoea	Low/normal estradiol	Pituitary MRI unless diagnosis clear

Hirsutism and polycystic ovary syndrome

- Hair in the beard, moustache, breast, chest, axilla, abdominal midline, pubic and thigh areas is sex-hormone dependent.
- Any excess in the latter regions is thus usually a marker of increased ovarian or adrenal androgen production.
- Some authorities divide patients with hirsutism into those with no elevation of serum androgen levels and no other clinical features (usually labelled 'idiopathic hirsutism') and those with an identifiable endocrine imbalance (most commonly polycystic ovary syndrome (PCOS), or rarely other causes).

Polycystic ovary syndrome (PCOS)

- PCOS, originally known in its severe form as the *Stein-Leventhal syndrome*, is characterized by multiple small cysts within the ovary and by excess androgen production from the ovaries and to a lesser extent from the adrenals, although whether the basic defect is in the ovary, adrenal or pituitary remains unknown.
- The precise levels of androgens in blood vary widely from patient to patient. In addition, oestrogens are converted to androgens in adipose tissue, which represents a further source of androgen excess in obese patients. The response of the hair follicle to circulating androgens also seems to vary between individuals with otherwise identical clinical and biochemical features, and the reason for this variation in end-organ response remains poorly understood.

Polycystic ovary syndrome (PCOS

- The ovarian 'cysts' represent arrested follicular development. Studies have shown an association of polycystic ovarian syndrome with anovulation and insulin resistance, which may also be associated with hypertension, hyperlipidaemia and increased cardiovascular disease prevalence.
- *Familial or idiopathic hirsutism* does occur, but usually involves a distribution of hair growth which is not typically androgenic. Similarly, non-androgen-dependent hair growth occurs with drugs such as phenytoin, diazoxide, minoxidil and ciclosporin. Iatrogenic hirsutism also occurs after treatment with androgens, or more weakly androgenic drugs such as progestagens or danazol. *Rarer, and more serious, endocrine causes* of hirsutism and virilization include congenital adrenal hyperplasia, Cushing's syndrome and virilizing tumours of the ovary and adrenal. All these conditions should be considered in any patient with hirsutism - as this may be their only presenting complaint.

Disorders of sexual differentiation

- Disorders of sexual differentiation are rare but may affect chromosomal, gonadal, endocrine and phenotypic development. Such cases always require extensive, multidisciplinary clinical management. An individual's sex can be defined in several ways:
- *Chromosomal sex.* The normal female is 46XX, the normal male 46XY. The Y chromosome confers male sex; if it is not present, development follows female lines.
- *Gonadal sex.* This is obviously determined predominantly by chromosomal sex, but requires normal embryological development.

Biosynthetic pathway of steroid hormones in vertebrates

- The relevant sex-steroids are in the squares with the red borders. Both males and females produce androgens and estrogens. The difference does no not reside in their types of sex steroids but in their titres in the blood. Females convert more testosterone into estradiol. Hence the testosterone titre is higher in males, while the opposite is true for estradiol.

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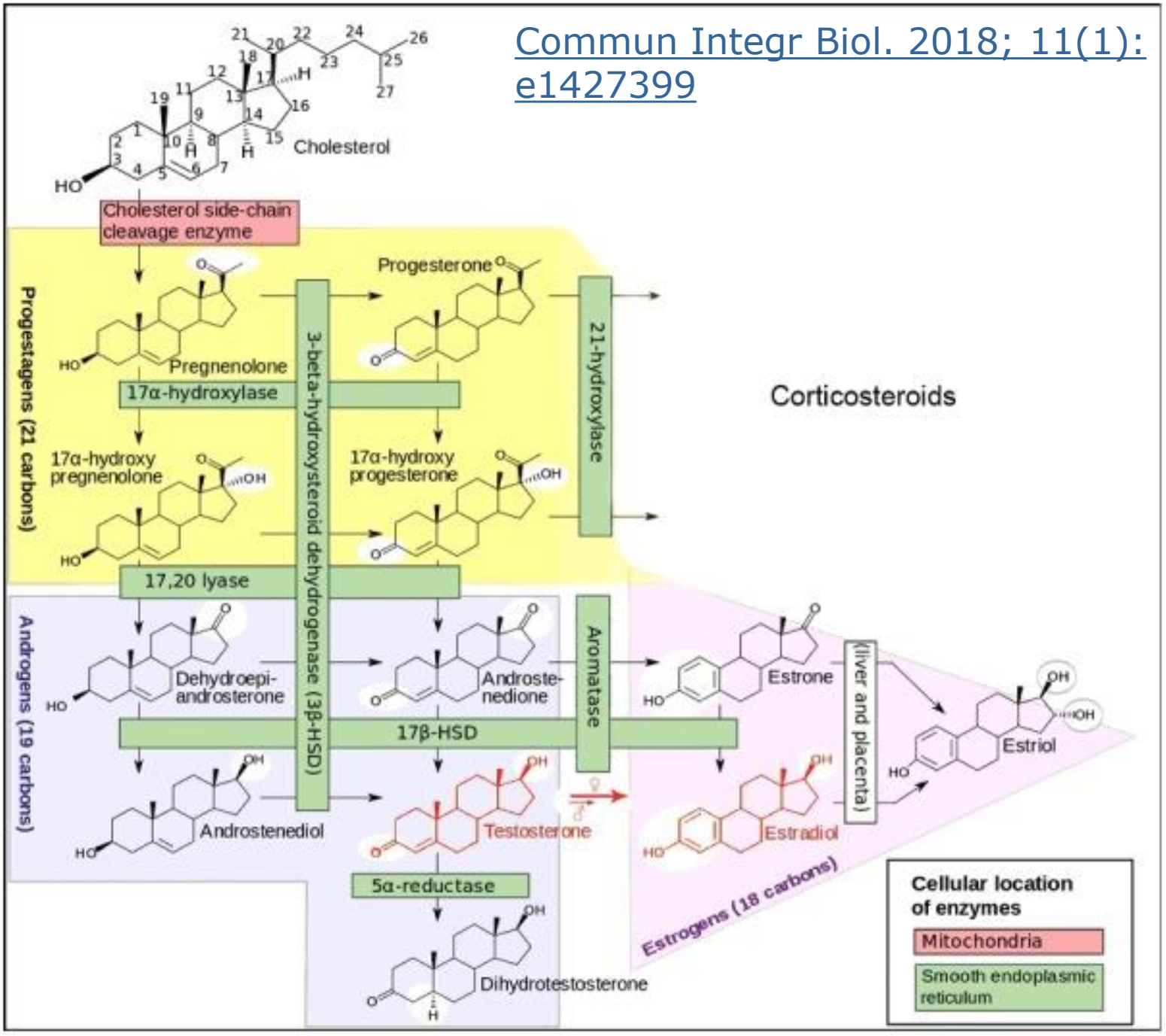
Commun Integr Biol. 2018; 11(1): e1427399
Cholesterol
Cholesterol side-chain cleavage enzyme
Progestagens (21 carbons)
Pregnenolone
Progesterone
17α-hydroxylase
3-beta-hydroxysteroid dehydrogenase (3β-HSD)
21-hydroxylase
Corticosteroids
17α-hydroxy pregnenolone
17α-hydroxy progesterone
17,20 lyase
Androgens (19 carbons)
Dehydroepi-androsterone
Androste-nedione
17β-HSD
Aromatase
Androstenediol
Testosterone
5α-reductase
Dihydrotestosterone
Estrone
Estradiol
Estriol
(liver and placenta)
Estrogens (18 carbons)
Cellular location of enzymes
Mitochondria
Smooth endoplasmic reticulum

Disorders of sexual differentiation

- *Phenotypic sex.* This describes the normal physical appearance and characteristics of male and female body shape. This in turn is a manifestation of gonadal sex and subsequent sex hormone production.
- *Social sex (gender).* This is heavily dependent on phenotypic sex and normally assigned on appearance of the external genitalia at birth.
- *Sexual orientation* - heterosexual, homosexual or bisexual. Some studies suggest that there may be some element of genetic determination of homosexuality.

Table 18.18
Disorders of sexual differentiation

Condition	Chromosomes	Gonads	Phenotype	Remarks
Turner's syndrome	45X	Streak	Female	Often morphological features (e.g. short stature, web neck, coarctation of aorta)
Gonadal dysgenesis	46XY	Streak or minimal testes*	Immature female	
Congenital adrenal hyperplasia	46XX	Ovary	Female with variable virilization	Obvious androgen excess
Virilizing tumour	46XX	Ovary	Female with variable virilization	Obvious androgen excess
True hermaphroditism	46XX/XY or mosaic	Testis and ovary	Male or ambiguous	
Klinefelter's syndrome	47XXY	Small testes	Male, often with gynaecomastia	Many are hypogonadal
Testicular feminization	46XY	Testes*	Ambiguous or infantile female	Androgen receptor defective
Testicular synthetic defects	46XY	Testes*	Cryptorchid, ambiguous	
5α-Reductase deficiency	46XY	Testes	Cryptorchid, ambiguous	Impaired conversion of testosterone to dihydrotestosterone
Anorchia	46XY	Absent	Immature female	

*Gonadectomy advised because of high risk of malignancy

Děkuji za pozornost