Lec # 3

Estrogens and Androgens

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Objectives

1. Description of sex hormones produced by gonads.
2. Role of sex hormones in conception, embryonic maturation, and development of primary and secondary sexual characteristics at puberty.
3. Therapeutic uses of steroid hormones

Overview:

The gonadal hormones are used therapeutically in

- replacement therapy,
- for contraception, and in management of menopausal symptoms.
- Several antagonists are effective in cancer chemotherapy.

Estrogens

- ***Estradiol***, also known as 17β-estradiol, is the most potent estrogen produced and secreted by the ovary. It is the principal estrogen in premenopausal women.
- ***Estrone*** is a metabolite of estradiol that has approximately one-third the estrogenic potency of estradiol. Estrone is the primary circulating estrogen after menopause.
- ***Estriol***, another metabolite of estradiol, is significantly less potent than is estradiol. It is present in significant amounts during pregnancy, because it is the principal estrogen produced by the placenta.
- Synthetic estrogen analogs: These compounds, such as ethinyl estradiol, mestranol, and estradiol valerate, are well absorbed after oral administration. Mestranol is metabolized more slowly than the naturally occurring estrogens by the liver and peripheral tissues. synthetic estrogen analogs have a prolonged action and a higher potency compared to those of natural estrogens.

Estrogens : Mechanism of action:

- After dissociation from their binding sites on sex hormone–binding globulin or albumin in the plasma, steroid hormones diffuse across the cell membrane and bind with high affinity to specific nuclear receptor proteins. The activated steroid–receptor complex interacts with nuclear chromatin to initiate hormone-specific RNA synthesis. This results in the synthesis of specific proteins that mediate a number of physiologic functions.

- [Note: The steroid hormones may elicit the synthesis of different RNA species in diverse target tissues and, therefore, are both receptor and tissue specific.] Other pathways that require these hormones have been identified that lead to more rapid actions. For example, activation of an estrogen receptor in the membranes of hypothalamic cells has been shown to couple to a G protein, thereby initiating a second-messenger cascade.
- In addition, estrogen-mediated dilation of coronary arteries occurs by the increased formation and release of nitric oxide and prostacyclin in endothelial cells.

Therapeutic uses:

Estrogen deficiency can be due to inadequate functioning of the ovaries (hypogonadism), premature menopause, or surgical menopause.

1. **Postmenopausal hormone therapy (HT):** The primary indication for estrogen therapy in postmenopausal women is menopausal symptoms, such as vasomotor instability (for example, “hot flashes” or “hot flushes”) and vaginal atrophy.

- For women who have an intact uterus, a progestogen is always included with the estrogen therapy, because the combination reduces the risk of endometrial carcinoma associated with unopposed estrogen.
- For women who have undergone a hysterectomy, unopposed estrogen therapy is recommended because progestins may unfavorably alter the beneficial effects of estrogen on lipid parameters.

- Delivery of estradiol by transdermal patch or gel is also effective in treating postmenopausal symptoms. Due to concerns over the risks of HT (increased risk of cardiovascular events and breast cancer), HT should be prescribed at the lowest effective dose for the shortest possible time to relieve menopausal symptoms.

- Women who only have urogenital symptoms, such as vaginal atrophy, should be treated with vaginal rather than systemic estrogen.

2. Contraception: The combination of an estrogen and progestogen provides effective contraception via the oral, transdermal, or vaginal route.

3. Other uses: Estrogen therapy mimicking the natural cyclic pattern, and usually in combination with a progestogen, is instituted to stimulate development of secondary sex characteristics in young women with primary hypogonadism. Continued treatment is required after growth is completed.

- Similarly, estrogen and progestogen replacement therapy is used for women who have premature menopause or premature ovarian failure.

Metabolism:

- Estrogens are transported in the blood bound to serum albumin or sex hormone–binding globulin. Bioavailability of estrogen taken orally is low due to first pass metabolism. To reduce first-pass metabolism, the drugs may be administered via the transdermal route (patch, topical gel, topical emulsion, or spray), intravaginally (tablet, cream, or ring), or by injection.

Adverse effects

- Nausea and breast tenderness are among the most common adverse effects of estrogen therapy. In addition, the risk of thromboembolic events, myocardial infarction, and breast and endometrial cancer is increased with use of estrogen therapy.

The increased risk of endometrial cancer can be offset by including a progestogen along with the estrogen therapy.

Selective Estrogen Receptor Modulators (SERMs)

- SERMs are a class of estrogen-related compounds that display selective agonism or antagonism for estrogen receptors depending on the tissue type.

- This category includes ***tamoxifen, toremifene, raloxifene(evista), clomiphene (clomide), and ospemifene***.

- **Mechanism of action:** **Tamoxifen, toremifene, and raloxifene** compete with estrogen for binding to the estrogen receptor in breast tissue.

- In addition, **raloxifene** acts as an estrogen agonist in bone, leading to decreased bone resorption, increased bone density, and decreased vertebral fractures.

- Unlike estrogen and tamoxifen, **raloxifene** does not have appreciable estrogen receptor agonist activity in the endometrium and, therefore, does not predispose to endometrial cancer.

- **Raloxifene** also lowers serum total cholesterol and low-density lipoprotein (LDL).

Selective Estrogen Receptor Modulators (SERMs)

- ***Clomiphene*** acts as a partial estrogen agonist and interferes with the negative feedback of estrogens on the hypothalamus. This effect increases the secretion of gonadotropin-releasing hormone and gonadotropins, thereby leading to stimulation of ovulation.

- **Therapeutic uses:** Tamoxifen is currently used in the treatment of metastatic breast cancer, or as adjuvant therapy following mastectomy or radiation for breast cancer. Both tamoxifen and raloxifene can be used as prophylactic therapy to reduce the risk of breast cancer in high-risk patients.

- Raloxifene is also approved for the prevention and treatment of osteoporosis in postmenopausal women.

- Clomiphene is useful for the treatment of infertility associated with anovulatory cycles. Ospemifene is indicated for the treatment of dyspareunia (painful sexual intercourse) related to menopause.

Adverse effects

The most frequent adverse effects of *tamoxifen* and *toremifene* are hot flashes and nausea.

Due to its estrogenic activity in the endometrium, endometrial hyperplasia and malignancies have been reported with *tamoxifen* therapy. This has led to recommendations for limiting the length of time on the drug for some indications.

Tamoxifen is also an inhibitor of CYP3A4 and P-glycoprotein.] Some CYP450 inhibitors may prevent the formation of active metabolites of *tamoxifen* and possibly reduce the efficacy (for example, *amiodarone*, *haloperidol*, *risperidone*).

In addition, there is an increased risk of deep vein thrombosis, pulmonary embolism, and retinal vein thrombosis. Women who have a past or active history of venous thromboembolic events should not take the drug.

Use of *clomiphene* increases the risk of multiple births (twins or triplets).

Progestogens

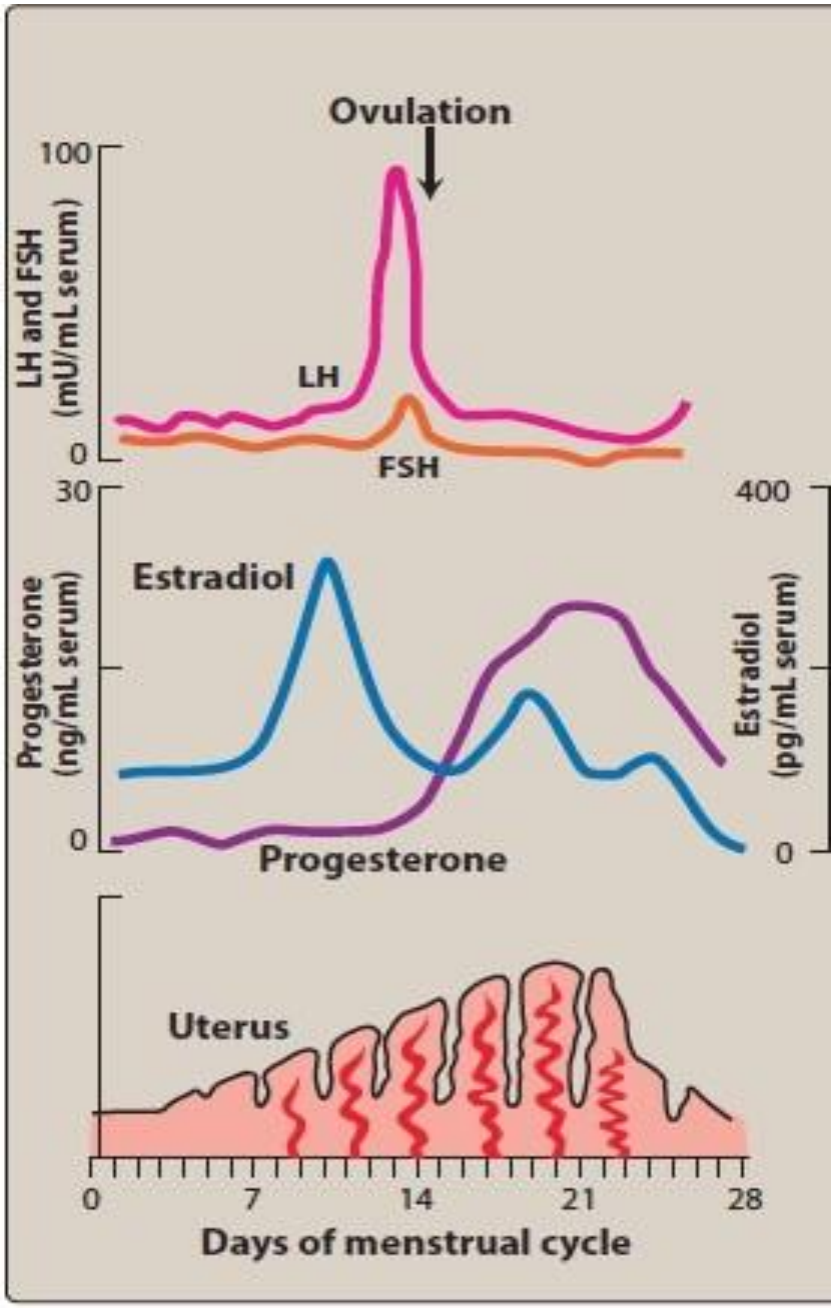
- Progesterone, the natural progestogen, is produced in response to luteinizing hormone (LH) by both females (secreted by the corpus luteum, primarily during the second half of the menstrual cycle, and by the placenta) and by males (secreted by the testes). It is also synthesized by the adrenal cortex in both sexes.

- **Mechanism of action:** Progestogens exert their mechanism of action in a manner analogous to that of the other steroid hormones. In females, progesterone promotes the development of a secretory endometrium that can accommodate implantation of a newly forming embryo.
- The high levels of progesterone that are released during the second half of the menstrual cycle (the luteal phase) inhibit the production of gonadotropin and, therefore, prevent further ovulation. If conception takes place, progesterone continues to be secreted, maintaining the endometrium in a favorable state for the continuation of the pregnancy and reducing uterine contractions.

If conception does not take place, the release of progesterone from the corpus luteum ceases abruptly. This decline stimulates the onset of menstruation.

- Therapeutic uses: The major clinical uses of progestogens are for postmenopausal HT, contraception and the treatment of hormone deficiency.

- For contraception, they are often used in combination with estrogens. Progesterone by itself is not used widely as a contraceptive therapy because of its rapid metabolism, resulting in low bioavailability.



Progestogens

Synthetic progestogens (that is, progestins) used in contraception are more stable to firstpass metabolism, allowing lower doses when administered orally.

- These agents include ***desogestrel, levonorgestrel, norgestrel, drospirenone, norethindrone, norethindrone acetate, norgestimate, and dienogest***.
- ***Medroxyprogesterone acetate*** is an injectable contraceptive, and the oral form is a common progestin component of postmenopausal HT.

- Progestins are also used for the control of dysfunctional uterine bleeding, treatment of dysmenorrhea, and management of endometriosis and infertility.

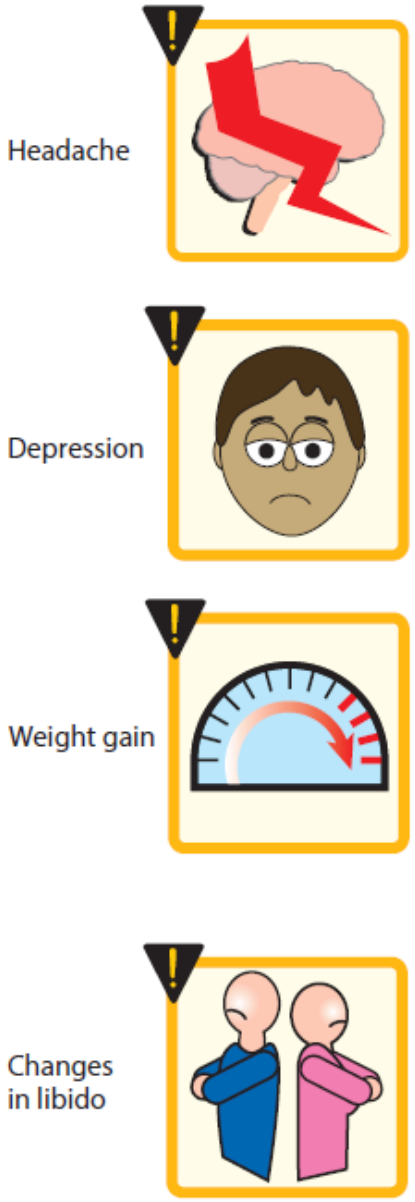


Figure 26.7
Some adverse effects associated with progestin therapy.

Adverse effects

•The major adverse effects associated with the use of progestins are headache, depression, weight gain, and changes in libido (Figure)

•Norethindrone, norethindrone acetate, norgestrel, levonorgestrel possess some androgenic activity because of their structural similarity to testosterone and can cause acne and hirsutism.

•Less androgenic progestins, such as norgestimate and drospirenone, may be preferred in women with acne. Drospirenone may raise serum potassium due to antimineralocorticoid effects, and concurrent use with other drugs that increase potassium (for example, angiotensin-converting enzyme inhibitors) may increase the risk of hyperkalemia.

Antiprogestin:

- ***Mifepristone*** is a progesterone antagonist with partial agonist activity.
- Administration of this drug to females early in pregnancy usually results in abortion of the fetus due to interference with the progesterone needed to maintain pregnancy. Mifepristone is often combined with the prostaglandin analog misoprostol (administered orally or intravaginally) to induce uterine contractions. The major adverse effects are significant uterine bleeding and the possibility of an incomplete abortion.

Contraceptives : Major classes of contraceptives

1. **Combination oral contraceptives:** Products containing a combination of an estrogen and a progestin are the most common type of oral contraceptives. Monophasic combination pills contain a constant dose of estrogen and progestin given over 21 to 24 days.

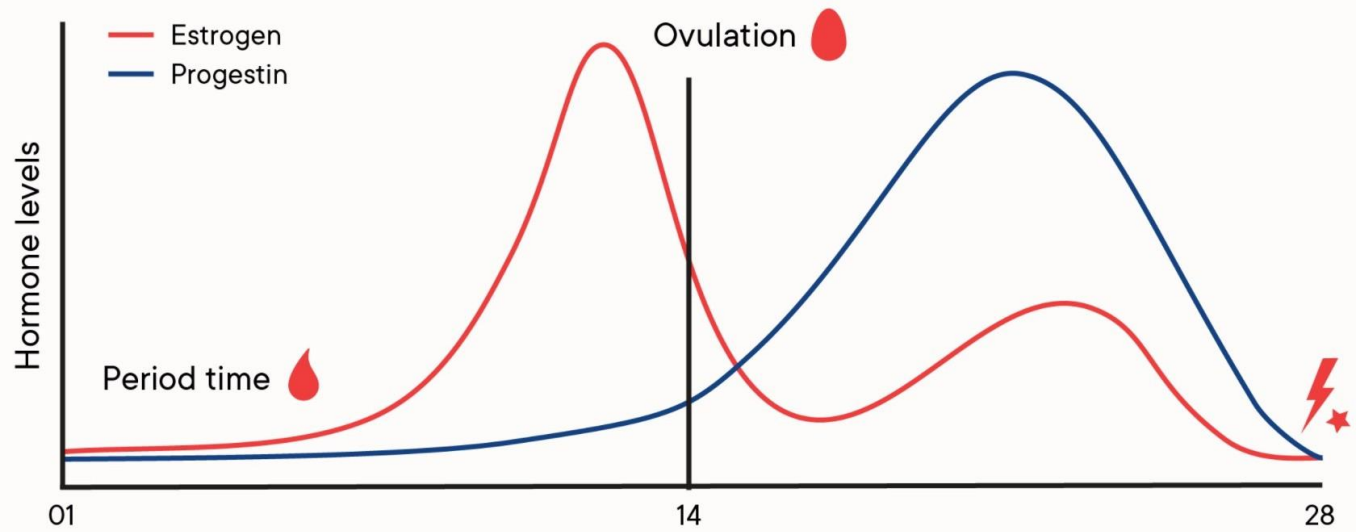
- With most oral contraceptives, active pills are taken for 21 to 24 days, followed by 4 to 7 days of placebo, for a total regimen of 28 days. Withdrawal bleeding occurs during the hormone-free (placebo) interval.

- The most common estrogen in the combination pills is **ethinyl estradiol**.

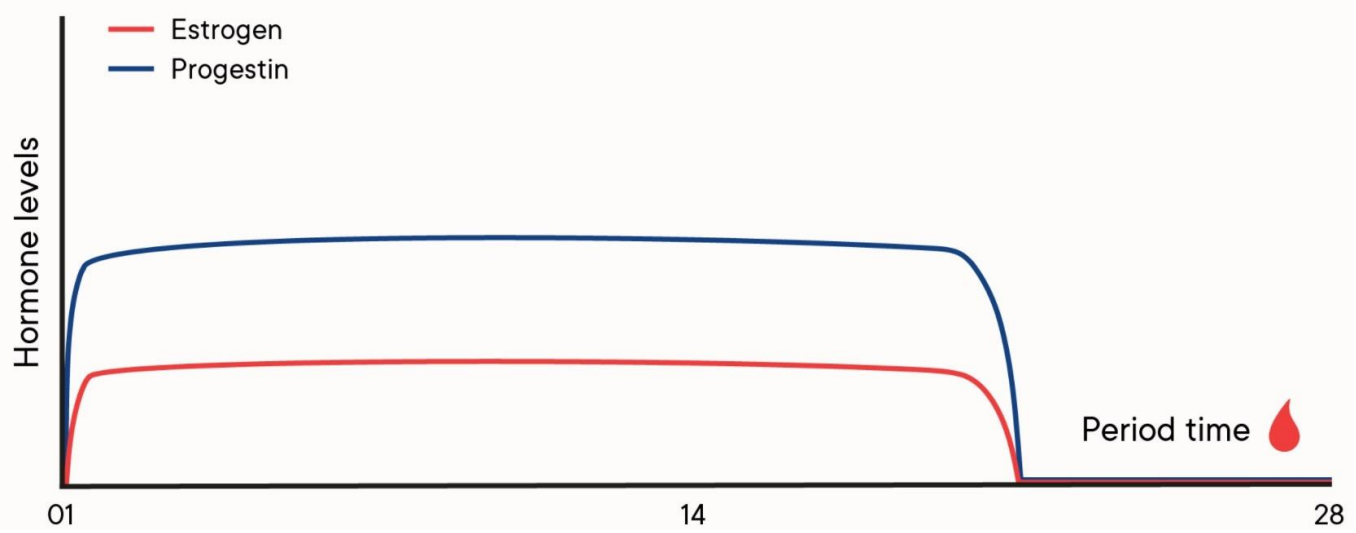
- The most common progestins are **norethindrone, norethindrone acetate, levonorgestrel, desogestrel, norgestimate, and drospirenone.**

- Triphasic oral contraceptive products attempt to mimic the natural female cycle and most contain a constant dose of estrogen with increasing doses of progestin given over three successive 7-day periods.

•Note: The combination of estradiol valerate and dienogest is available as a four-phasic oral contraceptive.



Hormone changes in an average cycle



Hormones levels for people using combination pill of contraceptive

Contraceptives

- Use of extended-cycle contraception (84 active pills followed by 7 days of placebo) results in less frequent withdrawal bleeding. A continuous oral contraceptive product (active pills taken every day) is also available.

2. Transdermal patch: An alternative to combination oral contraceptives is a transdermal patch containing **ethinyl estradiol and the progestin norelgestromin**.

- One contraceptive patch is applied each week for 3 weeks to the abdomen, upper torso, or buttock. No patch is worn during the 4th week, and withdrawal bleeding occurs.
- The transdermal patch has efficacy comparable to that of the oral contraceptives, but it is less effective in women weighing greater than 90 kg. Contraindications and adverse effects for the patch are similar to those of oral contraceptives.

3. Vaginal ring: contains **ethinyl estradiol and etonogestrel**. The ring is inserted into the vagina and is left in place for 3 weeks and then removed. No ring is used during the fourth week, and withdrawal bleeding occurs.

Contraceptives

4. Progestin-only pills: Products containing a progestin only, usually **norethindrone** (called a "mini- pill"), are taken daily on a continuous schedule.

- Progestin-only pills deliver a low, continuous dosage of drug. These preparations are less effective than combination products, and they may produce irregular menstrual cycles more frequently.
- The progestin-only pill may be used for patients who are breast-feeding (unlike estrogen, progestins do not have an effect on milk production), are intolerant to estrogen, are smokers, or have other contraindications to estrogen-containing products.

5. Injectable progestin: ***Medroxyprogesterone acetate*** is a contraceptive that is administered via intramuscular or subcutaneous injection every 3 months. Weight gain is a common adverse effect.

6. Progestin implants: After subdermal placement, the **etonogestrel** implant offers contraception for approximately 3 years. The implant is nearly as reliable as sterilization, and the effect is totally reversible when surgically removed.

Contraceptives

7. Progestin intrauterine device: A **levonorgestrel-releasing intrauterine system** offers a highly effective method of contraception for 3 to 5 years depending on the system. It is a suitable method of contraception for women who desire long-term contraception and those who have contraindications to estrogen therapy. It should be avoided in patients with pelvic inflammatory disease or a history of ectopic pregnancy.

8. Postcoital or emergency contraception: it reduces the probability of pregnancy after an episode of coitus without effective contraception to between 0.2% and 3%.

- Emergency contraception uses high doses of **levonorgestrel** (preferred) or high doses of **ethinyl estradiol plus levonorgestrel**.
- Formaximum effectiveness, emergency contraception should be taken as soon as possible after unprotected intercourse and preferably within 72 hours.

Contraceptives

- An alternative emergency contraceptive is the progesterone agonist/antagonist ***ulipristal***. It is indicated for emergency contraception within 5 days of unprotected intercourse.

- **Mechanism of action:** Estrogen provides a negative feedback on the release of LH and follicle-stimulating hormone (FSH) by the pituitary gland, thus preventing ovulation. Progestin also thickens the cervical mucus, thus hampering the transport of sperm. Withdrawal of the progestin stimulates menstrual bleeding during the placebo week.

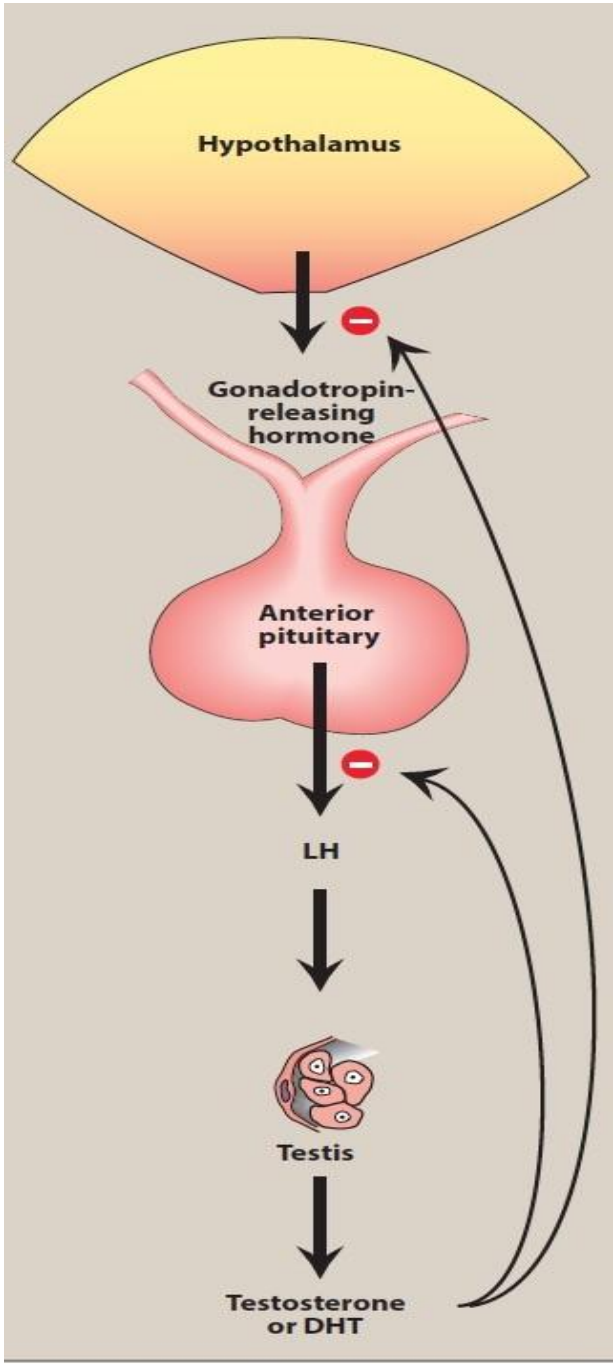
- Note: Drugs that induce the CYP3A4 isoenzyme (for example, rifampin and bosentan) may significantly reduce the efficacy of oral contraceptives. Antibiotics that alter the normal gastrointestinal flora may reduce enterohepatic recycling of the estrogen component of oral contraceptives, thereby diminishing the effectiveness.

Androgens

- The androgens are a group of steroids that have anabolic and/or masculinizing effects in both males and females.

- **Testosterone**, the most important androgen in humans, is synthesized by Leydig cells in the testes and, in smaller amounts, by thecal cells in the ovaries and by the adrenal gland in both sexes.
- Other androgens secreted by the testes are **5α-dihydrotestosterone (DHT), androstenedione, and dehydroepiandrosterone (DHEA)** in small amounts.

- In adult males, testosterone secretion by Leydig cells is controlled by gonadotropin- releasing hormone from the hypothalamus, which stimulates the anterior pituitary gland to secrete FSH and LH. Testosterone or its active metabolite, DHT, inhibits production of these specific trophic hormones through a negative feedback loop and, thus, regulates testosterone production.



- The androgens are required for 1) normal maturation in the male, 2) sperm production, 3) increased synthesis of muscle proteins and hemoglobin, and 4) decreased bone resorption.

- **Mechanism of action:** Like the estrogens and progestins, androgens bind to a specific nuclear receptor in a target cell. Although testosterone itself is the active ligand in muscle and liver, in other tissues it must be metabolized to derivatives, such as DHT.

- **Therapeutic uses:** Androgenic steroids are used for males with primary hypogonadism (caused by testicular dysfunction) or secondary hypogonadism (due to failure of the hypothalamus or pituitary). Anabolic steroids can be used to treat chronic wasting associated with human immunodeficiency virus or cancer.

- An unapproved use of anabolic steroids is to increase lean body mass, muscle strength, and endurance in athletes and body builders

- ***DHEA*** (a precursor of testosterone and estrogen) has been touted as an antiaging hormone as well as a "performance enhancer." There is no definitive evidence that it slows aging, however, or that it improves performance at normal therapeutic doses.

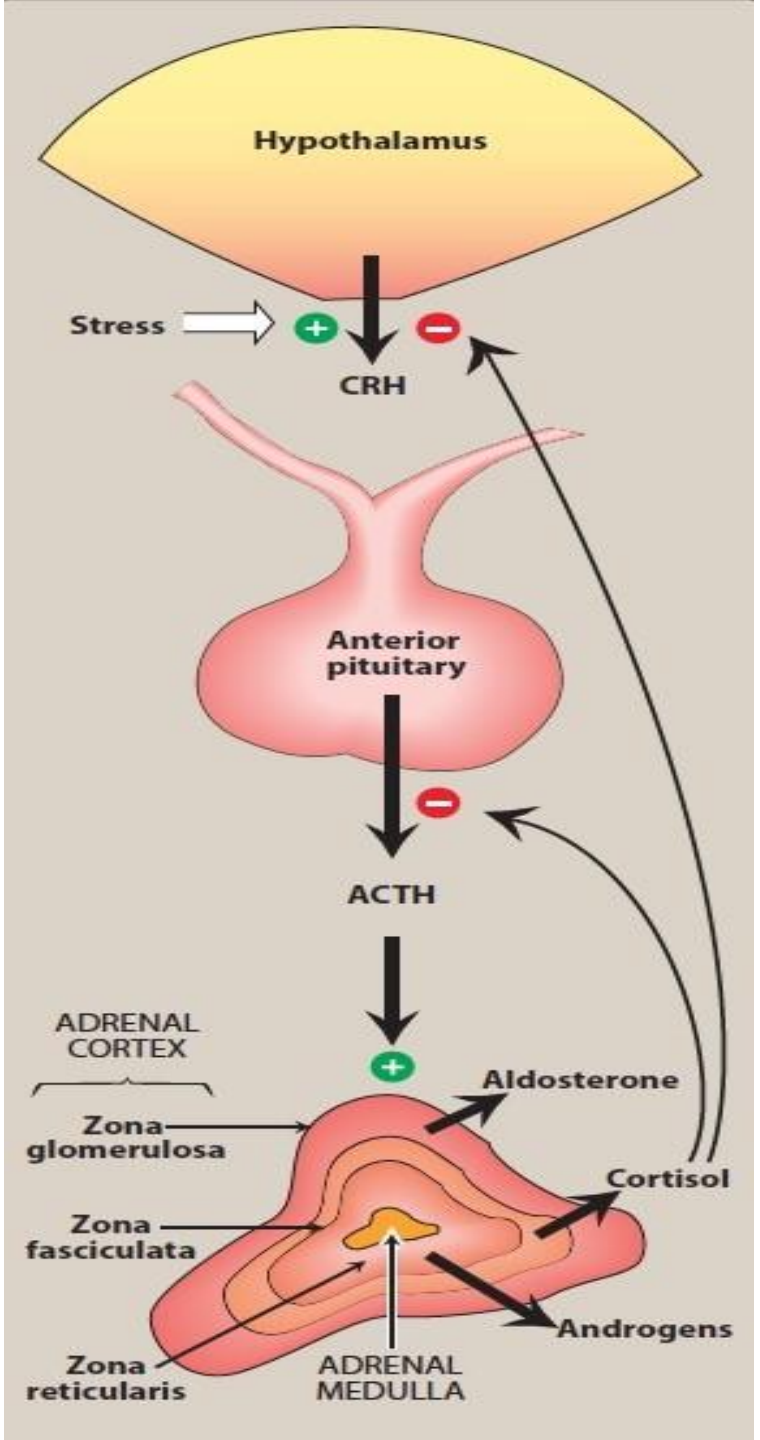
- ***Danazol***, a weak androgen, is used in the treatment of endometriosis (ectopic growth of the endometrium) and fibrocystic breast disease. Weight gain, acne, decreased breast size, deepening voice, increased libido, and increased hair growth are among the adverse effects. Note: Danazol also possesses antiestrogenic activity.

Antiandrogens:

- Antiandrogens counter male hormonal action by interfering with the synthesis of androgens or by blocking their receptors. **Finasteride and dutasteride** inhibit 5α-reductase resulting in decreased formation of dihydrotestosterone. These agents are used for the treatment of benign prostatic hyperplasia.

- Antiandrogens, such as ***flutamide, bicalutamide, enzalutamide, and nilutamide***, act as competitive inhibitors of androgens at the target cell and are effective orally for the treatment of prostate cancer.

Adrenal Hormones



Mechanism of action

The corticosteroids bind to specific intracellular cytoplasmic receptors in target tissues. After dimerizing, the receptor– hormone complex recruits coactivator (or corepressor) proteins and translocates into the nucleus, where it attaches to gene promoter elements. There it acts as a transcription factor to turn genes on (when complexed with coactivators) or off (when complexed with corepressors), depending on the tissue. This mechanism requires time to produce an effect.

However, other glucocorticoid effects are immediate, such as the interaction with catecholamines to mediate relaxation of bronchial musculature.

Corticosteroids (glucocorticoids and mineralocorticoids)

- **Cortisol** is the principal human glucocorticoid. Normally, its production is diurnal, with a peak early in the morning followed by a decline and then a secondary, smaller peak in the late afternoon.

- Factors such as stress and levels of the circulating steroid influence secretion. The effects of cortisol are many and diverse.

- In general, all glucocorticoids:

1. **Promote normal intermediary metabolism:** Glucocorticoids favor gluconeogenesis through increasing amino acid uptake by the liver and kidney and elevating activities of gluconeogenic enzymes. They stimulate protein catabolism (except in the liver) and lipolysis, thereby providing the building blocks and energy that are needed for glucose synthesis.

2. **Increase resistance to stress:** By raising plasma glucose levels, glucocorticoids provide the body with energy to combat stress caused by trauma, fright, infection, bleeding, or debilitating disease.

2. **Alter blood cell levels in plasma:** Glucocorticoids cause a decrease in eosinophils, basophils, monocytes, and lymphocytes by redistributing them from the circulation to lymphoid tissue. Glucocorticoids also increase hemoglobin, erythrocytes, platelets, and polymorphonuclear leukocytes.

4. **Have anti-inflammatory action:** The most important therapeutic properties of the glucocorticoids are their potent anti-inflammatory and immunosuppressive activities.

- These therapeutic effects of glucocorticoids are the result of a number of actions. The lowering of circulating lymphocytes is known to play a role. In addition, these agents inhibit the ability of leukocytes and macrophages to respond to mitogens and antigens.

Corticosteroids

- Glucocorticoids also decrease the production and release of proinflammatory cytokines. They inhibit phospholipase A2, which blocks the release of arachidonic acid (the precursor of the prostaglandins and leukotrienes) from membrane-bound phospholipid. The decreased production of prostaglandins and leukotrienes is believed to be central to the anti-inflammatory action.

- Lastly, these agents influence the inflammatory response by stabilizing mast cell and basophil membranes, resulting in decreased histamine release.

5. **Affect other systems:** High levels of glucocorticoids serve as feedback inhibitors of ACTH production and affect the endocrine system by suppressing further synthesis of glucocorticoids and thyroid-stimulating hormone.

- In addition, adequate cortisol levels are essential for normal glomerular filtration.

Mineralocorticoids

- Mineralocorticoids help to control fluid status and concentration of electrolytes, especially sodium and potassium.

- ***Aldosterone*** acts on distal tubules and collecting ducts in the kidney, causing reabsorption of sodium, bicarbonate, and water. Conversely, aldosterone decreases reabsorption of potassium, which, with H^+, is then lost in the urine. Enhancement of sodium reabsorption by aldosterone also occurs in gastrointestinal mucosa and in sweat and salivary glands.

- [Note: Elevated aldosterone levels may cause alkalosis and hypokalemia, retention of sodium and water, and increased blood volume and blood pressure. Hyperaldosteronism is treated with spironolactone.]
- MOA the same as glucocorticoids.

Therapeutic uses of the corticosteroids

1. **Replacement therapy for primary adrenocortical insufficiency (Addison disease):** Addison disease is caused by adrenal cortex dysfunction (as diagnosed by the lack of response to ACTH administration).

- ***Hydrocortisone***, which is identical to natural cortisol, is given to correct the deficiency.

- The dosage of hydrocortisone is divided so that two-thirds of the daily dose is given in the morning and one-third is given in the afternoon.

- Administrationof ***fludrocortisone***, a potent synthetic mineralocorticoid with some glucocorticoid activity, may also be necessary to supplement mineralocorticoid deficiency.

2. **Replacement therapy for secondary or tertiary adrenocortical insufficiency:** These disorders are caused by a defect in CRH production by the hypothalamus or in ACTH production by the pituitary. Note: Under these conditions, the synthesis of mineralocorticoids in the adrenal cortex is less impaired than that of glucocorticoids.

- Hydrocortisone is used for treatment of these deficiencies.

Therapeutic uses of the corticosteroids

3. **Diagnosis of Cushing syndrome:** Cushing syndrome is caused by hypersecretion of glucocorticoids (hypercortisolism) that results from excessive release of ACTH by the anterior pituitary or an adrenal tumor.

- Cortisol levels (urine, plasma, and saliva) and the ***dexamethasone*** suppression test are used to diagnose Cushing syndrome. The synthetic glucocorticoid dexamethasone suppresses cortisol release in normal individuals, but not those with Cushing syndrome.

4. **Replacement therapy for congenital adrenal hyperplasia (CAH):** CAH is a group of diseases resulting from an enzyme defect in the synthesis of one or more of the adrenal steroid hormones.

- Treatment of the condition requires administration of sufficient corticosteroids to normalize hormone levels by suppressing release of CRH and ACTH. This decreases production of adrenal androgens.

5. **Relief of inflammatory symptoms:** Corticosteroids significantly reduce the manifestations of inflammation associated with rheumatoid arthritis and inflammatory skin conditions, including redness, swelling, heat, and tenderness that may be present at the site of inflammation.

Therapeutic uses of the corticosteroids

- These agents are also important for maintenance of symptom control in persistent asthma, as well as management of asthma exacerbations and active inflammatory bowel disease.

6. **Treatment of allergies:** Corticosteroids are beneficial in the treatment of allergic rhinitis, as well as drug, serum, and transfusion allergic reactions.

7. **Acceleration of lung maturation:** Respiratory distress syndrome is a problem in premature infants.

- Fetal cortisol is a regulator of lung maturation. Consequently, a regimen of betamethasone or dexamethasone administered intramuscularly to the mother within the 48 hours proceeding premature delivery can accelerate lung maturation in the fetus.

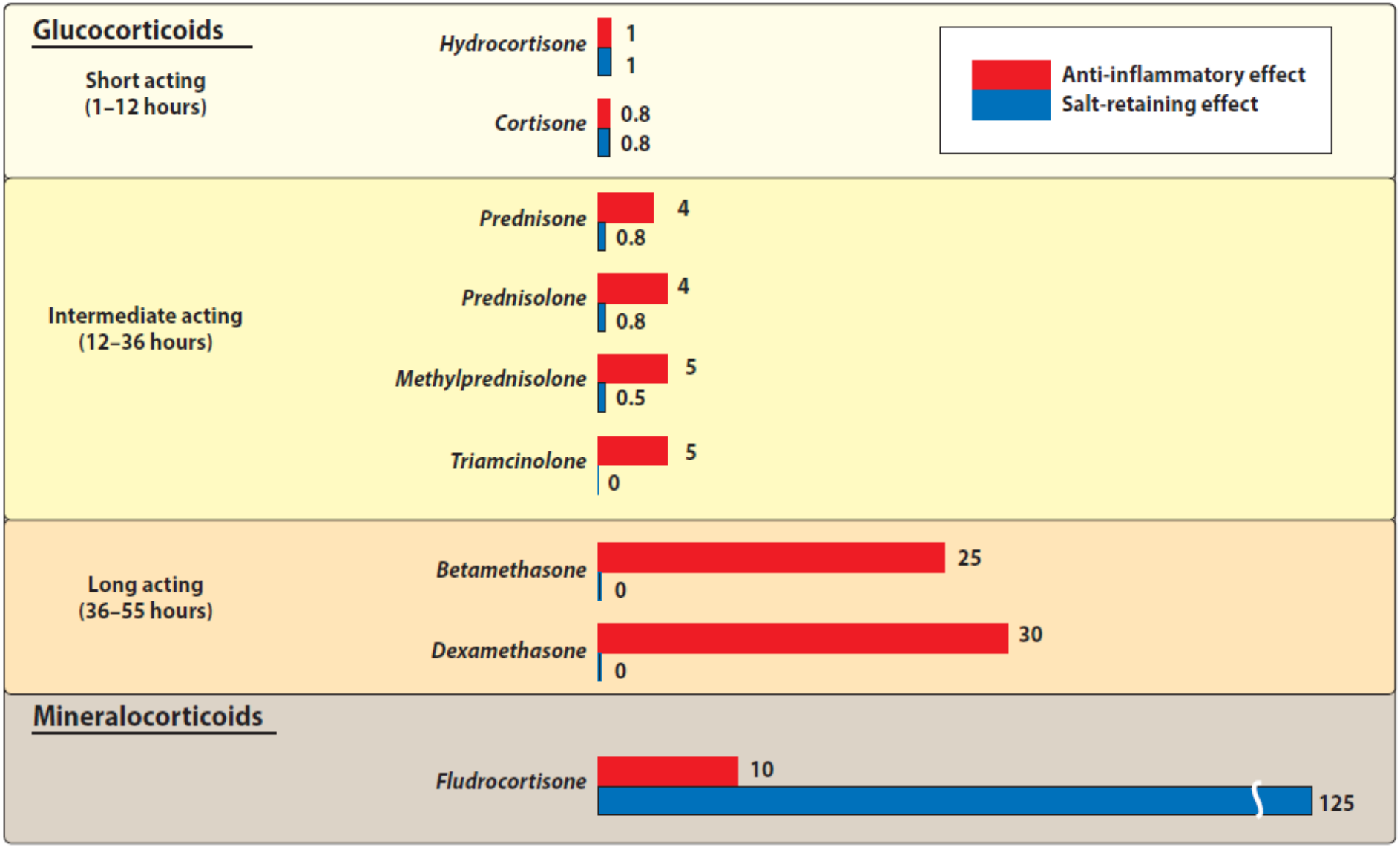


Figure 27.4

Pharmacologic effects and duration of action of some commonly used natural and synthetic corticosteroids. Activities are all relative to that of *hydrocortisone*, which is considered to be 1.

Pharmacokinetics

- Corticosteroids are metabolized by the liver microsomal oxidizing enzymes. The metabolites are conjugated to glucuronic acid or sulfate, and the products are excreted by the kidney.

- [Note: The half-life of corticosteroids may increase substantially in hepatic dysfunction.]
- *Prednisone* is preferred in pregnancy because it minimizes steroid effects on the fetus. It is a prodrug that is not converted to the active compound, *prednisolone*, in the fetal liver. Any *prednisolone* formed in the mother is biotransformed to *prednisone* by placental enzymes.

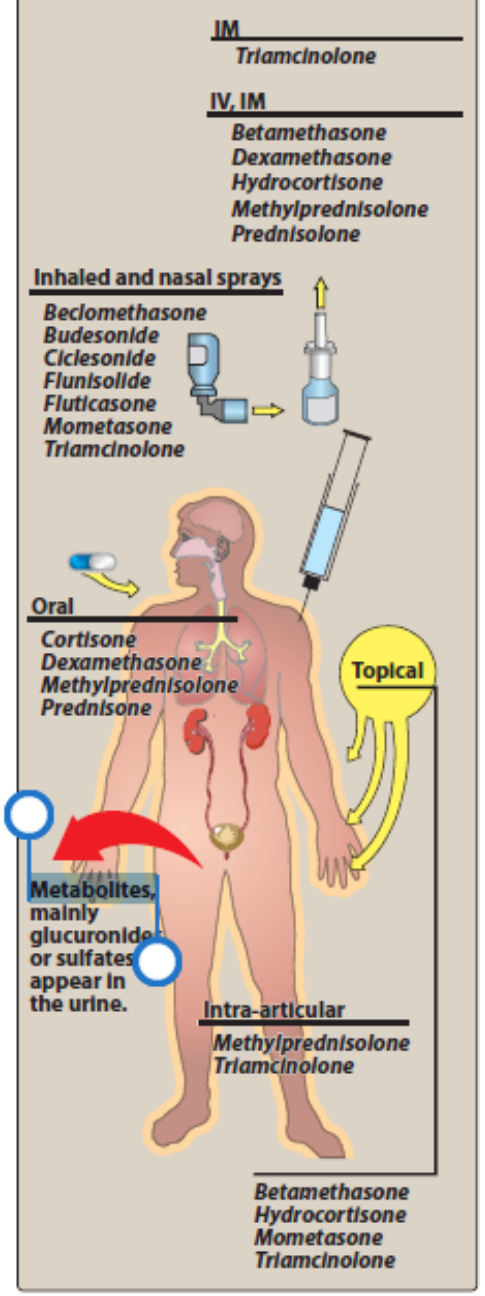
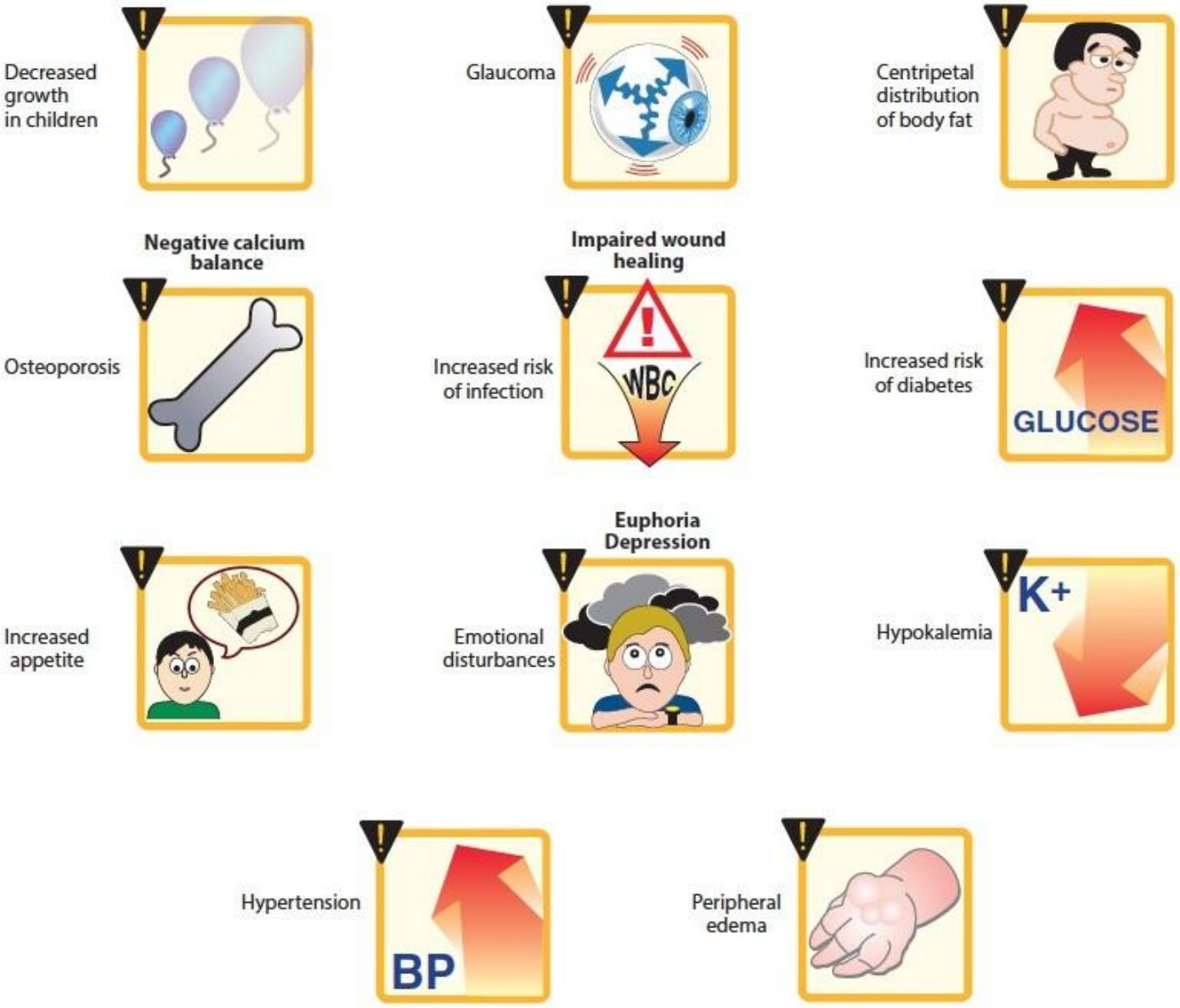


Figure 27.5
Routes of administration and elimination of corticosteroids.

Adverse effects : Adverse effects are often dose related.



- **Discontinuation:** Sudden discontinuation of these drugs can be a serious problem if the patient has suppression of the HPA axis.

- In this case, abrupt removal of corticosteroids causes acute adrenal insufficiency that can be fatal. This risk, coupled with the possibility that withdrawal might cause an exacerbation of the disease, means that the dose must be tapered slowly according to individual tolerance.

- **Inhibitors of adrenocorticoid biosynthesis or function:** Several substances have proven to be useful as inhibitors of the synthesis or function of adrenal steroids:

1. ***Ketoconazole:*** is an antifungal agent that strongly inhibits all gonadal and adrenal steroid hormone synthesis. It is used in the treatment of patients with Cushing syndrome.

2. ***Spironolactone:*** This antihypertensive drug competes for the mineralocorticoid receptor and, thus, inhibits sodium reabsorption in the kidney. It can also antagonize aldosterone and testosterone synthesis.

- It is effective for hyperaldosteronism and is used along with other standard therapies for the treatment of heart failure with reduced ejection fraction.

- Spironolactone is also useful in the treatment of hirsutism in women, probably due to interference at the androgen receptor of the hair follicle. Adverse effects include hyperkalemia, gynecomastia, menstrual irregularities, and skin rashes.

3. ***Eplerenone:*** specifically binds to the mineralocorticoid receptor, where it acts as an aldosterone antagonist. This specificity avoids the side effect of gynecomastia that is associated with the use of spironolactone.

- It is approved for the treatment of hypertension and also for heart failure with reduced ejection fraction.


Thank You!