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Basic Therapeutics

Adrenocortical Steroids

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Adrenocortical Steroids

- The adrenal cortex synthesizes two classes of steroids: the *corticosteroids* (glucocorticoids and mineralocorticoids).
- The actions of corticosteroids historically were described as glucocorticoid (carbohydrate metabolism-regulating) and mineralocorticoid (electrolyte balance-regulating), reflecting their preferential activities.

- In humans, *cortisol* (*hydrocortisone*) is the main glucocorticoid and aldosterone is the main mineralocorticoid.

Physiological Functions and Pharmacological Effects:

- The effects of corticosteroids are numerous and widespread, and include alterations in carbohydrate, protein, and lipid metabolism; maintenance of fluid and electrolyte balance; and preservation of normal function of the cardiovascular system, the immune system, the kidney, skeletal muscle, the endocrine system, and the nervous system.

- Corticosteroids are grouped according to their relative potencies in Na^+ retention, effects on carbohydrate metabolism (*i.e.*, hepatic deposition of glycogen and gluconeogenesis), and anti-inflammatory effects.
- Based on these differential potencies, the corticosteroids traditionally are divided into mineralocorticoids and glucocorticoids.

- Some steroids that are classified predominantly as glucocorticoids (*e.g.*, cortisol) also possess modest but significant mineralocorticoid activity and thus may affect fluid and electrolyte handling in the clinical setting.

General Mechanisms for Corticosteroid Effects:

- Corticosteroids interact with specific receptor proteins in target tissues to regulate the expression of corticosteroid-responsive genes, thereby changing the levels and array of proteins synthesized by the various target tissues.

- The receptors for corticosteroids are members of the nuclear receptor family of transcription factors that transduce the effects of a diverse array of small, hydrophobic ligands, including the steroid hormones, thyroid hormone, vitamin D, and retinoids.

- The GR resides predominantly in the cytoplasm in an inactive form until it binds glucocorticoids.
- Steroid binding results in receptor activation and translocation to the nucleus.
- After ligand binding, the GR dissociates from its associated proteins and translocates to the nucleus.

- There, it interacts with specific DNA sequences within the regulatory regions of affected genes.

Regulation of Gene Expression by Mineralocorticoids:

- Aldosterone exerts its effects on Na^+ and K^+ homeostasis primarily via its actions on the principal cells of the distal renal tubules and collecting ducts, while the effects on H^+ secretion largely are exerted in the intercalated cells.

1. Carbohydrate and Protein Metabolism:

- Corticosteroids profoundly affect carbohydrate and protein metabolism.
- These effects of glucocorticoids on intermediary metabolism can be viewed as protecting glucose-dependent tissues (*e.g.*, the brain and heart) from starvation.
- They stimulate the liver to form glucose from amino acids and glycerol and to store glucose as liver glycogen.

- In the periphery, glucocorticoids diminish glucose utilization, increase protein breakdown and the synthesis of glutamine, and activate lipolysis, thereby providing amino acids and glycerol for gluconeogenesis.
- The net result is to increase blood glucose levels.

- Because of their effects on glucose metabolism, glucocorticoids can worsen glycemic control in patients with overt diabetes and can precipitate the onset of hyperglycemia in patients who are otherwise predisposed.

- Glucocorticoids decrease glucose uptake in adipose tissue, skin, fibroblasts, thymocytes, and polymorphonuclear leukocytes; these effects are postulated to result from translocation of the glucose transporters from the plasma membrane to an intracellular location.

- These peripheral effects are associated with a number of catabolic actions, including atrophy of lymphoid tissue, decreased muscle mass, negative nitrogen balance, and thinning of the skin.

- Amino acids mobilized from a number of tissues in response to glucocorticoids reach the liver and provide substrate for the production of glucose and glycogen.

- In the liver, glucocorticoids induce the transcription of a number of enzymes involved in gluconeogenesis and amino acid metabolism, including phosphoenolpyruvate carboxykinase (PEPCK), glucose-6-phosphatase, and the bi-functional enzyme fructose-2,6-bisphosphatase.

2. Lipid Metabolism:

- Two effects of corticosteroids on lipid metabolism are firmly established.
- The first is the dramatic redistribution of body fat that occurs in settings of endogenous or pharmacologically induced hypercorticism, such as Cushing's syndrome.

- The other is the permissive facilitation of the lipolytic effect of other agents, such as growth hormone and b adrenergic receptor agonists, resulting in an increase in free fatty acids after glucocorticoid administration.
- With respect to fat distribution, there is increased fat in the back of the neck ("buffalo hump"), face ("moon facies"), and supraclavicular area, coupled with a loss of fat in the extremities.

3. Electrolyte and Water Balance:

- Aldosterone is by far the most potent endogenous corticosteroid with respect to fluid and electrolyte balance.
- Thus, electrolyte balance is relatively normal in patients with adrenal insufficiency due to pituitary disease, despite the loss of glucocorticoid production by the inner cortical zones.

- Mineralocorticoids act on the distal tubules and collecting ducts of the kidney to enhance reabsorption of Na^+ from the tubular fluid; they also increase the urinary excretion of K^+ and H^+.
- These actions on electrolyte transport, in the kidney and in other tissues (*e.g.*, colon, salivary glands, and sweat glands), appear to account for the physiological and pharmacological activities that are characteristic of mineralocorticoids.

- The primary features of hyperaldosteronism are positive Na^+ balance with consequent expansion of extracellular fluid volume, normal or slight increases in plasma Na^+ concentration, hypokalemia, and alkalosis.
- Mineralocorticoid deficiency leads to Na^+ wasting and contraction of the extracellular fluid volume, hyponatremia, hyperkalemia, and acidosis.

- Chronically, hyperaldosteronism can cause hypertension, whereas aldosterone deficiency can lead to hypotension and vascular collapse.
- Glucocorticoids also exert effects on fluid and electrolyte balance, largely due to permissive effects on tubular function and actions that maintain glomerular filtration rate.

- Glucocorticoids play a permissive role in the renal excretion of free water; the ability to excrete a water challenge was used at one time to diagnose adrenal insufficiency.
- In addition to their effects on monovalent cations and water, glucocorticoids also exert multiple effects on Ca^{2+} metabolism.
- Steroids interfere with Ca^{2+} uptake in the gut and increase Ca^{2+} excretion by the kidney.
- These effects collectively lead to decreased total body Ca^{2+} stores.

4. Cardiovascular System:

- Effects of corticosteroids on the cardiovascular system result from mineralocorticoid-induced changes in renal Na^+ excretion, as is evident in primary aldosteronism.
- The resultant hypertension can lead to a diverse group of adverse effects on the cardiovascular system, including increased atherosclerosis, cerebral hemorrhage, stroke, and hypertensive cardiomyopathy.

- The second major action of corticosteroids on the cardiovascular system is to enhance vascular reactivity to other vasoactive substances.
- Hypoadrenalism is associated with reduced response to vasoconstrictors such as norepinephrine and angiotensin II, perhaps due to decreased expression of adrenergic receptors in the vascular wall.

5. Skeletal Muscle:

- In patients with Addison's disease, weakness and fatigue are frequent symptoms that may reflect an inadequacy of the circulatory system.
- Excessive amounts of either glucocorticoids or mineralocorticoids also impair muscle function.
- In primary aldosteronism, muscle weakness results primarily from hypokalemia rather than from direct effects of mineralocorticoids on skeletal muscle.

- In contrast, glucocorticoid excess over prolonged periods, either secondary to glucocorticoid therapy or endogenous hypercorticism, causes skeletal muscle wasting.
- This effect, termed *steroid myopathy,* accounts in part for weakness and fatigue in patients with glucocorticoid excess.

6. Central Nervous System:

- Corticosteroids exert a number of indirect effects on the CNS, through maintenance of blood pressure, plasma glucose concentrations, and electrolyte concentrations.
- Increasingly, direct effects of corticosteroids on the CNS have been recognized, including effects on mood, behavior, and brain excitability.
  - Patients with adrenal insufficiency exhibit a diverse array of psychiatric manifestations, including apathy, depression, and irritability; some patients are frankly psychotic.

- Appropriate replacement therapy corrects these abnormalities.
- Conversely, glucocorticoid administration can induce multiple CNS reactions.
- The mechanisms by which corticosteroids affect neuronal activity are unknown, but it has been proposed that steroids produced locally in the brain (termed *neurosteroids*) may regulate neuronal excitability.

7. Formed Elements of Blood:

- Glucocorticoids exert minor effects on hemoglobin and erythrocyte content of blood, as evidenced by the frequent occurrence of polycythemia in Cushing's syndrome and of normochromic, normocytic anemia in adrenal insufficiency.
- Corticosteroids also affect circulating white blood cells.
- Addison's disease is associated with an increased mass of lymphoid tissue and lymphocytosis.

- In contrast, Cushing's syndrome is characterized by lymphocytopenia and decreased mass of lymphoid tissue.
- The administration of glucocorticoids leads to a decreased number of circulating lymphocytes, eosinophils, monocytes, and basophils.

- A single dose of hydrocortisone leads to a decline of these circulating cells within 4 to 6 hours; this effect persists for 24 hours and results from the redistribution of cells away from the periphery rather than from increased destruction.
- In contrast, glucocorticoids increase circulating polymorphonuclear leukocytes as a result of increased release from the marrow, diminished rate of removal from the circulation, and increased demargination from vascular walls.

8. Anti-inflammatory and Immunosuppressive Actions:

- In addition to their effects on lymphocyte number, corticosteroids profoundly alter the immune responses of lymphocytes.
- These effects are an important facet of the antiinflammatory and immunosuppressive actions of the glucocorticoids.

- Glucocorticoids can prevent or suppress inflammation in response to multiple inciting events, including radiant, mechanical, chemical, infectious, and immunological stimuli.
- The immunosuppressive and antiinflammatory actions of glucocorticoids are inextricably linked, perhaps because they both involve inhibition of leukocyte functions.

- Multiple mechanisms are involved in the suppression of inflammation by glucocorticoids.
- It is now clear that glucocorticoids inhibit the production by multiple cells of factors that are critical in generating the inflammatory response.
- As a result, there is decreased release of vasoactive and chemoattractive factors, diminished secretion of lipolytic and proteolytic enzymes, decreased extravasation of leukocytes to areas of injury, and ultimately, decreased fibrosis.

- Glucocorticoids can also reduce expression of pro-inflammatory cytokines, such as COX-2.
- The net effect of these actions on various cell types is to diminish markedly the inflammatory response.

Absorption, Transport, Metabolism, and Excretion:

Absorption:

- Hydrocortisone and numerous congeners, including the synthetic analogs, are orally effective.
- Certain water-soluble esters of hydrocortisone and its synthetic congeners are administered intravenously to achieve high concentrations of drug rapidly in body fluids.

- More prolonged effects are obtained by intramuscular injection of suspensions of hydrocortisone, its esters, and congeners.
- Minor changes in chemical structure may markedly alter the rate of absorption, time of onset of effect, and duration of action.

Transport, Metabolism, and Excretion:

- After absorption, 90% or more of cortisol in plasma is reversibly bound to protein under normal circumstances.
- Only the fraction of corticosteroid that is unbound can enter cells to mediate corticosteroid effects.

- Two plasma proteins account for almost all of the steroid-binding capacity: corticosteroid-binding globulin (CBG; also called transcortin), and albumin.
- As a general rule, the metabolism of steroid hormones involves sequential additions of oxygen or hydrogen atoms, followed by conjugation to form water-soluble derivatives.

Toxicity of Adrenocortical Steroids

Two categories of toxic effects result from the therapeutic use of corticosteroids:

1. Those resulting from withdrawal of steroid therapy
2. Those resulting from continued use at supraphysiological doses.

- The side effects from both categories are potentially life-threatening and mandate a careful assessment of the risks and benefits in each patient.

Withdrawal of Therapy:

- A characteristic glucocorticoid withdrawal syndrome consists of fever, myalgias, arthralgias, and malaise, which may be difficult to differentiate from some of the underlying diseases for which steroid therapy was instituted.

- Finally, *pseudotumor cerebri,* a clinical syndrome that includes increased intracranial pressure with papilledema, is a rare condition that sometimes is associated with reduction or withdrawal of corticosteroid therapy.

Continued Use of Supraphysiological Glucocorticoid Doses:

- There are a number of other complications that result from prolonged therapy with corticosteroids.

- These include fluid and electrolyte abnormalities, hypertension, hyperglycemia, increased susceptibility to infection, osteoporosis, myopathy, behavioral disturbances, cataracts, growth arrest, and the characteristic habitus of steroid overdose, including fat redistribution, striae, and ecchymoses.

Therapeutic Uses:

- Except in patients receiving replacement therapy, glucocorticoids are neither specific nor curative; rather, they are palliative by virtue of their anti-inflammatory and immunosuppressive actions.
- Finally, abrupt cessation of glucocorticoids after prolonged therapy is associated with the risk of adrenal insufficiency, which may be fatal.

1. **Replacement Therapy:**
   - Adrenal insufficiency can result from structural or functional lesions of the adrenal cortex (primary adrenal insufficiency or Addison's disease) or from structural or functional lesions of the anterior pituitary or hypothalamus (secondary adrenal insufficiency).

- In developed countries, primary adrenal insufficiency most frequently is secondary to autoimmune adrenal disease, whereas tuberculous adrenalitis is the most frequent etiology in underdeveloped countries.
- Other causes include adrenalectomy, bilateral adrenal hemorrhage, neoplastic infiltration of the adrenal glands, acquired immunodeficiency syndrome, inherited disorders of the steroidogenic enzymes, and X-linked adrenoleukodystrophy.

- Secondary adrenal insufficiency resulting from pituitary or hypothalamic dysfunction generally presents in a more insidious manner than does the primary disorder, probably because mineralocorticoid biosynthesis is preserved.

a. Acute Adrenal Insufficiency:

- This life-threatening disease is characterized by gastrointestinal symptoms (nausea, vomiting, and abdominal pain), dehydration, hyponatremia, hyperkalemia, weakness, lethargy, and hypotension.
- It usually is associated with disorders of the adrenal rather than the pituitary or hypothalamus, and sometimes follows abrupt withdrawal of glucocorticoids used at high doses or for prolonged periods.

- The immediate management of patients with acute adrenal insufficiency includes intravenous therapy with isotonic sodium chloride solution supplemented with 5% glucose and corticosteroids and appropriate therapy for precipitating causes such as infection, trauma, or hemorrhage.

- Because cardiovascular function often is reduced in the setting of adrenocortical insufficiency, the patient should be monitored for evidence of volume overload such as rising central venous pressure or pulmonary edema.

- After an initial intravenous bolus of 100 mg, hydrocortisone (cortisol) should be given by continuous infusion at a rate of 50 to 100 mg every 8 hours.
- At this dose, which approximates the maximum daily rate of cortisol secretion in response to stress, hydrocortisone alone has sufficient mineralocorticoid activity to meet all requirements.

- As the patient stabilizes, the hydrocortisone dose may be decreased to 25 mg every 6 to 8 hours.
- Thereafter, patients are treated in the same fashion as those with chronic adrenal insufficiency.

b. Chronic Adrenal Insufficiency:

- Patients with chronic adrenal insufficiency present with many of the same manifestations seen in adrenal crisis, but with lesser severity.
- These patients require daily treatment with corticosteroids, traditional replacement regimens have used hydrocortisone in doses of 20 to 30 mg/day.

- *Cortisone acetate,* which is inactive until converted to cortisol, also has been used in doses ranging from 25 to 37.5 mg/day.
- In an effort to mimic the normal diurnal rhythm of cortisol secretion, these glucocorticoids generally have been given in divided doses, with two-thirds of the dose given in the morning and one-third given in the afternoon.

2. Congenital Adrenal Hyperplasia:

- This term denotes a group of genetic disorders in which the activity of one of the several enzymes required for the biosynthesis of glucocorticoids is deficient.
- The impaired production of cortisol and the consequent lack of negative feedback inhibition lead to increased release of ACTH.

- Congenital adrenal hyperplasia (CAH) includes a spectrum of disorders whose precise clinical presentation, laboratory findings and treatment depend on which of the steroidogenic enzymes is deficient.
- Such patients are unable to conserve Na^+ normally and thus are called "salt wasters."
- These patients can present with cardiovascular collapse secondary to volume depletion.

- All patients with classical CAH require replacement therapy with hydrocortisone or a suitable congener, and those with salt wasting also require mineralocorticoid replacement.
- The goals of therapy are to restore levels of physiological steroid hormones to the normal range and to suppress ACTH and thereby abrogate the effects of overproduction of adrenal androgens.

- The typical oral dose of hydrocortisone is approximately 0.6 mg/kg daily in two or three divided doses.
- The mineralocorticoid used is fludrocortisone acetate (0.05 to 0.2 mg/day).

3. Therapeutic Uses in Nonendocrine Diseases:

a. Rheumatic Disorders:

- Glucocorticoids are used widely in the treatment of a variety of rheumatic disorders and are a mainstay in the treatment of the more serious inflammatory rheumatic diseases, such as systemic lupus erythematosus, and a variety of vasculitic disorders.

- For these more serious disorders, the starting dose of glucocorticoids should be sufficient to suppress the disease rapidly and minimize resultant tissue damage.
- Initially, prednisone (1 mg/kg per day in divided doses) often is used, generally followed by consolidation to a single daily dose, with subsequent tapering to a minimal effective dose as determined by clinical variables.

- While they are an important component of treatment of rheumatic diseases, glucocorticoids are often used in conjunction with other immunosuppressive agents such as *cyclophosphamide* and *methotrexate,* which offer better long-term control than steroids alone.

- In rheumatoid arthritis, because of the serious and debilitating side effects associated with chronic use, glucocorticoids are used as temporizing agents for progressive disease that fails to respond to first-line treatments such as physiotherapy and non-steroidal anti-inflammatory agents.

- In this case, glucocorticoids provide relief until other, slower-acting anti-rheumatic drugs, such as methotrexate or newer agents targeted at tumor necrosis factor take effect.
- In noninflammatory degenerative joint diseases (*e.g.,* osteoarthritis) or in a variety of regional pain syndromes (*e.g.,* tendinitis or bursitis), glucocorticoids may be administered by local injection for the treatment of episodic disease flare-up.

b. Renal Diseases:

- Patients with nephrotic syndrome secondary to minimal change disease generally respond well to steroid therapy, and glucocorticoids clearly are the first-line treatment in both adults and children.
- Initial daily doses of prednisone are 1 to 2 mg/kg for 6 weeks, followed by a gradual tapering of the dose over 6 to 8 weeks.

c. Allergic Disease:

- The onset of action of glucocorticoids in allergic diseases is delayed, and patients with severe allergic reactions such as anaphylaxis require immediate therapy with epinephrine: for adults, 0.3 to 0.5 ml of a 1:1000 solution intramuscularly or subcutaneously (repeated as often as every 15 minutes for up to three additional doses if necessary).

- The manifestations of allergic diseases of limited duration such as hay fever, serum sickness, urticaria, contact dermatitis, drug reactions, bee stings, and angioneurotic edema can be suppressed by adequate doses of glucocorticoids given as supplements to the primary therapy.

- In severe disease, intravenous glucocorticoids (methylprednisolone 125 mg intravenously every 6 hours, or equivalent) are appropriate.
- In less severe disease, antihistamines are the drugs of first choice.
- In allergic rhinitis, intranasal steroids are now viewed as the drug of choice by many experts.

d. Bronchial Asthma and Other Pulmonary Conditions:

- Corticosteroids frequently are used in bronchial asthma and chronic obstructive pulmonary disease (COPD).
- In severe asthma attacks requiring hospitalization, aggressive treatment with parenteral glucocorticoids is considered essential, even though their onset of action is delayed for 6 to 12 hours.

- Intravenous administration of 60 to 120 mg of methylprednisolone (or equivalent) every 6 hours is used initially, followed by daily oral doses of prednisone (30 to 60 mg) as the acute attack resolves.
- The dose then is tapered gradually, with withdrawal planned for 10 days to 2 weeks after initiation of steroid therapy.

- In many patients, inhaled steroids (*e.g.*, *beclomethasone dipropionate,* triamcinolone acetonide, *fluticasone* or *budesonide* can either reduce the need for oral corticosteroids or replace them entirely.
- Dysphonia or oropharyngeal candidiasis may develop, but the incidence of such side effects can be reduced substantially by maneuvers that reduce drug deposition in the oral cavity, such as spacers and mouth rinsing.

e. Infectious Diseases:

- One example of beneficial effects of Glucocorticoids is seen in AIDS patients with *Pneumocystis carinii* pneumonia and moderate to severe hypoxia; addition of glucocorticoids to the antibiotic regimen increases oxygenation and lowers the incidence of respiratory failure and mortality.

- Similarly, glucocorticoids clearly decrease the incidence of long term neurological impairment associated with *Haemophilus influenzae* type b meningitis in infants and children 2 months of age or older.

f. Ocular Disease:

- Glucocorticoids frequently are used to suppress inflammation in the eye and can preserve sight when used properly.
- They are administered topically for diseases of the outer eye and anterior segment and attain therapeutic concentrations in the aqueous humor after instillation into the conjunctival sac.

- A typical prescription is 0.1% dexamethasone sodium phosphate solution (ophthalmic), 2 drops in the conjunctival sac every 4 hours while awake, and 0.05% dexamethasone sodium phosphate ointment (ophthalmic) at bedtime.
- For inflammation of the posterior segment, typical doses are 30 mg of prednisone or equivalent per day, administered orally in divided doses.

g. Skin Diseases:

- Glucocorticoids are remarkably efficacious in the treatment of a wide variety of inflammatory dermatoses.
- A typical regimen for an eczematous eruption is 1% hydrocortisone ointment applied locally twice daily.
- Glucocorticoids are administered systemically for severe episodes of acute dermatologic disorders and for exacerbations of chronic disorders.
- The dose in these settings is usually 40 mg/day of prednisone.

h. Gastrointestinal Diseases:

- Glucocorticoid therapy is indicated in selected patients with inflammatory bowel disease (chronic ulcerative colitis and Crohn's disease).
- In mild ulcerative colitis, hydrocortisone (100 mg) can be administered as a retention enema with beneficial effects.

- In more severe acute exacerbations, oral prednisone (10 to 30 mg/day) frequently is employed.
- For severely ill patients-with fever, anorexia, anemia, and impaired nutritional status-larger doses should be used (40 to 60 mg prednisone per day).

i. Hepatic Disease:

- Glucocorticoids clearly are of benefit in autoimmune hepatitis, where as many as 80% of patients show histological remission when treated with prednisone (40 to 60 mg daily initially, with tapering to a maintenance dose of 7.5 to 10 mg daily after serum transaminase levels fall).

j. Cerebral Edema:

- Corticosteroids are of value in the reduction or prevention of cerebral edema associated with parasites and neoplasms, especially those that are metastatic although can be used in the treatment of cerebral edema caused by trauma or cerebrovascular accidents.

k. Miscellaneous Diseases and Conditions:

- In thrombocytopenia, prednisone (0.5 mg/kg) is used to decrease the bleeding tendency.
- In more severe cases, and for initiation of treatment of idiopathic thrombocytopenia, daily doses of prednisone (1 to 1.5 mg/kg) are employed.
- Patients with refractory idiopathic thrombocytopenia may respond to pulsed, high-dose glucocorticoid therapy.

- Autoimmune Destruction of Erythrocytes Patients with autoimmune destruction of erythrocytes (*i.e.,* hemolytic anemia) are treated with prednisone (1 mg/kg per day).
- In the setting of severe hemolysis, higher doses may be used, with tapering as the anemia improves.
- Small maintenance doses may be required for several months in patients who respond.

- In organ transplantation, high doses of prednisone (50 to 100 mg) are given at the time of transplant surgery, in conjunction with other immunosuppressive agents, and most patients are kept on a maintenance regimen that includes lower doses of glucocorticoids.