

Corticosteroid

I. Structure and Function

Corticosteroids are made in the adrenal cortex. There are two types: glucocorticoids and mineralocorticoids. The adrenal cortex has three glandular regions made up mostly of adrenocortical cells; two of these regions secrete glucocorticoids and DHEA (a precursor for androgens and estrogens), and the other secretes mineralocorticoids. They are lipophilic, like estrogen and thyroid hormones. Corticosteroid structure consists of a 21 carbon steroid ring. (Carr and Norris, p.65)

Glucocorticoids (corticosterone and cortisol are common ones) control glucose metabolism, and have anti-inflammatory effects. They are also involved in stress responses in organisms. Stress responses are controlled through the hypothalamus-pituitary-adrenal (HPA) axis. Corticotropin-releasing hormone (CRH) and corticotropin (ACTH) from the pituitary gland directly stimulates glucocorticoid and DHEA secretion, which controls metabolism and ionic regulation to lessen and/or neutralize stressors. An increase in cortisol can also stimulate the conversion of $T_4$ to $T_3$, an example of cross-talk between intracellular hormone actions.

Mineralocorticoids (aldosterone is a major mineralocorticoid) are largely involved in regulation of electrolyte and water levels. They do this by affecting sodium and potassium transport mechanisms in nephrons of the kidney.

Prednisone in a common medication that has corticosteroid properties and is used to promote anti-inflammatory processes in the body.

Addison’s disease is a commonly known disease that is caused by adrenal insufficiency. This causes insufficient amounts of corticosteroids (made in the adrenal cortex), and sex hormones like estrogen (made in the adrenal medulla).

![Chemical Structures of Common Corticosteroids](Fig1.png)
Biosynthesis and Regulation

Corticosteroids are synthesized in the hydrophobic region of the smooth E.R. of cells (like all steroids) from cholesterol. They are synthesized by enzyme action on other molecules, unlike protein hormones which are coded for by genes. Cholesterol (LDL) is taken into the cell by receptor mediated endocytosis. Progesterone is made from cholesterol, and then corticosteroid hormones are made from the progesterone. DHEA and testosterone/estrogen are also made from progesterone. P450 cytochromes (a class of membrane bound enzymes) play very important roles in the synthesis of corticosteroids. Important synthesis enzymes are listed in the table below (Carr and Norris, p.69-72, 265):

<table>
<thead>
<tr>
<th>Enzyme</th>
<th>Gene for Enzyme</th>
<th>Action</th>
</tr>
</thead>
<tbody>
<tr>
<td>P450\text{acc}</td>
<td>CYP11A</td>
<td>Side chain cleaving enzyme that works on cholesterol. (Need StAR to bring cholesterol into membrane where these enzymes are located)</td>
</tr>
<tr>
<td>3\beta-HSD</td>
<td>HSD3B2</td>
<td>(hydroxysteroid dehydrogenase) Converts the $\beta$-OH on carbon 3 of progesterone to a ketone to make progesterone. The drug cyanoketone can bind the enzyme and block progesterone access to prevent production of progesterone.</td>
</tr>
<tr>
<td>P450\text{c21}</td>
<td>CYP21</td>
<td>21-hydroxylase is involved in the production of corticosteroids from progesterone</td>
</tr>
<tr>
<td>P450\text{c11}</td>
<td>CYP11B1</td>
<td>11\beta-hydroxylase is involved in the production of corticosteroids from progesterone. The drug metyrapone selectively inhibits this enzyme.</td>
</tr>
<tr>
<td>P450\text{aldo}</td>
<td>CYP11B2</td>
<td>Aldosterone synthase converts corticosterone to aldosterone.</td>
</tr>
</tbody>
</table>
FIGURE 3-22 Synthesis pathway for progesterone.

1. Cholesterol → 22α-Hydroxycholesterol
2. 20α-Hydroxycholesterol → Dihydroxycholesterol
3. Dihydroxycholesterol → Progesterone

Chemical reactions:
- P450 enzyme system
- 3β-HSD enzyme system
**Fig. 2** Corticosteroid biosynthetic pathway
Corticosteroids are produced and released according to stress response (as previously described) and circadian rhythms. The most is produced in the morning, and less as the day goes on. During the human lifespan, adrenal function is elevated between puberty into the mid-20s, and after that it declines. Some corticosteroid is stored in membranes, but it is mostly released into the bloodstream as it is made. 90% of glucocorticoids bind a plasma transport protein in the blood called corticosteroid binding globulin (transcortin). Transcortin is a serine protease inhibitor. It binds the target cell, and the glucocorticoid dissociates and enters the target cell. Aldosterone is present in a free state in the blood without binding proteins (present at much lower levels in the blood than glucocorticoids). Since they lack binging proteins in the blood, they are metabolized faster.

Corticosteroids are mostly metabolized in the liver where they are conjugated with sulfates or other glucoronides to increase their solubility in water. They are then excreted via urine, bile, or feces. (Carr and Norris, p.266-267)

III. Receptors and Gene Transcription in Target Cell

Corticosteroid receptors belong to the nuclear receptor superfamily like PPAR, ecdysone and estrogen. Corticosteroid receptors are cytoplasmic, instead of in membranes like other hormone receptors that are not lipophilic and cannot move through the membrane on their own (G-protein coupled). Unoccupied receptors have chaperone proteins (or heat shock proteins) bound to them that inhibit a cellular response. Once the hormone binds the receptor, it moves into the nucleus where it homodimerizes with another occupied receptor (like estrogen and all other vertebrate steroids). The chaperone proteins are released and the homodimer complex becomes a ligand-activated transcription factor that interacts with DNA to initiate transcription of proteins (like anti-inflammatory proteins). When chaperone proteins are released, loops called zinc fingers are exposed, which bind to the gene promotors on DNA that they are specific to (hormone response elements). Different corticosteroids bind receptors specific to them with different zinc fingers that have their own specific promotor region. This is how specific corticosteroid molecules cause the transcription of specific proteins. (Carr and Norris, p. 76, 271) Signal transduction does not occur because the receptor-ligand homodimer directly binds DNA to regulate synthesis of proteins.

Ecdysone uses an ancestral invertebrate nuclear receptor in which it binds its receptor and heterodimerizes with RXR. Corticosteroids and estrogen form a homodimer (vertebrate).
FIGURE 3-26  Genomic mechanism of activation by steroids. The interaction of steroids with different genes in a target cell may direct the synthesis of structural proteins such as cytoskeletal elements or receptors as well as enzymes. These enzymes may produce a variety of effects within the cell. The genomic mechanism of action for thyroid hormones is very similar, with the emphasis more on nuclear location of unoccupied receptors. Additionally, occupied thyroid hormone receptors form heterodimers with RXR receptors (see Figure 3-33).

Fig. 3 Receptor and Gene Transcription
There is also evidence that a histone deacetylase complex is involved in turning off gene expression of the corticosteroid receptor. It doesn’t allow the DNA out of nucleosomes to interact with the transcription factors. (Ito, et. al.)

**Fig. 4**

Gene repression and activation are regulated by acetylation of core histones. In the resting state, DNA is tightly coiled around histones, forming a dense nucleosomal structure due to electrostatic attraction between negatively charged DNA and positively charged lysine residues. Acetylation of histones removes this charge, allowing loosening of the nucleosomal structure. Histone acetylation is mediated by transcriptional coactivators, which have intrinsic histone acetyltransferase (HAT) activity, whereas repression is induced by histone deacetylases (HDACs), which reverse this acetylation, allowing repackaging of the nucleosomes. (Hayashi, et.al.)
References

