Steroidogenesis

In this video, we're going to discuss steroidogenesis, which is the process or pathway by which some cells can manufacture steroids such as aldosterone, estradiol, and testosterone from the parent steroid, which is known as cholesterol. Now, cholesterol has a variety of other functions, which we've mentioned periodically in other videos, such as it's involved in stabilizing cell membranes over a wide range. It's also used to manufacture bile acids, which are used in the emulsification of fats. But arguably, one of the most important functions of cholesterol is its conversion into all of these steroids that are shown in. this diagram and that's what we're going to discuss in detail in this video. So there's a couple of nice things about this diagram. First of all, it's divided into the various types or classes of steroids.

For example, in yellow right here, we have the progestogens; down here in blue, we have the androgens; these are the masculinizing hormones. Over here on the right, in pink, we have the estrogens, or typically feminizing hormones, and then in green, the glucocorticoids or corticosteroids, and then up here in purple, the one general mineralocorticoid, which is aldosterone. The other thing is some of these enzymes are actually going. to be in different cellular compartments. The ones in red are going to be mitochondrial enzymes, and then all the others for the most part in green, these are going to be microsomal enzymes, meaning they're embedded in the membrane of the smooth endoplasmic reticulum. Make sure you understand it's smooth, not rough. Alright, so let's go into the pathway.

So here's our parent steroid, cholesterol, and pay attention to the numbering system because some of these enzymes are going to be named based on the numbering system of cholesterol. For example, they're going to act on certain carbon atoms or hydroxyl groups. So here's our parent steroid cholesterol. Notice its numbering system: we have 1, 2, 3, 4, and so on and so forth. These numbers are going to be important because any of these enzymes out here that have a number beside them, such as 21 hydroxylase, this numbering system is based on the numbering system of cholesterol. And so this number in front of this enzyme name, 21 hydroxylase, gives you an indication of which atom it's acting on. Okay, based on the cholesterol numbering system.

So first, the tail of cholesterol, beginning at carbon number 22 and going through 27, this tail is going to be removed. And this is done so by the mitochondrial enzyme cholesterol. side chain cleavage enzyme. Now, some of these enzymes, which are P450 enzymes, are typically going to be referred to by their gene name. So, for example, cholesterol side chain cleavage enzyme is a P450 enzyme; it's encoded by the gene CYP11A1. And so, typically, in most textbooks, you'll either see this name or the gene name CYP11A1. And so, when side chain cleavage enzyme or CYP11A1 acts on cholesterol, this 22 through 27 carbon tail is going to be removed as isocapraldehyde, not shown here, and we get this ketone molecule, which is going to be pregnenolone.

So, in some sources, you may see pregnenolone as the parent steroid, but that's only because pregnenolone is the first steroid that we see where the tail has been, for the most part, removed. Now, pregnenolone can go one of two directions; we're gonna go to the right here first and see the development of the glucocorticoids and aldosterone. So first of all, pregnenolone can be hydroxylated into 17 alpha hydroxypregnenolone. Notice at the 17 position right here, which is on the five-membered ring, it's gonna get hydroxylated by this enzyme, and that gives us 17 alpha hydroxypregnenolone. Now, both pregnenolone and 17 alpha hydroxypregnenolone can go to the right here and form corticosteroids. So, for example let's look at this first enzyme, 3 beta-hydroxysteroid dehydrogenase. So this enzyme is going to oxidize this hydroxyl group at the 3 position, thus the name 3.

So this hydroxyl group is going to become a ketone, as shown right here. The other thing is we see a net isomerization of this double bond between positions 5 and 6. It's eventually going to be here, between positions 4 and 5, and this is the case for both of these two reactions. So pregnenolone will be oxidized into progesterone, and progesterone is actually going to be a progestogen or progestin that we can recognize as a functional mammalian hormone. And then 17 alpha. hydroxypregnenolone is going to be oxidized down here into 17 alpha hydroxyprogesterone. Now, in general, this progesterone right here can act independently, or the progesterone can be processed into aldosterone. Down here, the 17 alpha hydroxyprogesterone is going to be processed into cortisol.

Now, the next enzyme in this pathway, regardless of which pathway you're taking, whether it's progesterone or this hydroxylated version, the enzyme is going to be 21 hydroxylase. So, this position right up here on the ketone right here, this carbon, which actually is going to be position number 21, as noted by this enzyme, is going. to be hydroxylated by 21 hydroxylase. 21 hydroxylase is another P450 enzyme. This is actually going to be encoded by CYP21A2 typically. There's another version of this enzyme as well. In any case, progesterone will be hydroxylated into deoxycorticosterone. And then, 17 alpha hydroxyprogesterone will be hydroxylated into 11 deoxycortisol. Okay, now both of these enzymes, the 21 hydroxylase and the 3 beta hydroxysteroid dehydrogenase, are microsomal enzymes. The next enzyme we're going to see is actually going to be a mitochondrial enzyme.

So, deoxycorticosterone and 11 deoxycortisol must be transported into the mitochondria. and they can just move mostly by a simple diffusion into the mitochondria because they're hydrophobic molecules. Now, 11 beta hydroxylase, what it's going to do is it's going to hydroxylate the 11 position right here. Okay, this is on the highest up six-membered ring on the corner right here of my mouses. So, 11 beta hydroxylase is going to hydroxylate deoxycorticosterone into corticosterone, as shown right here. We'll come back to that in a And then, 11 deoxycortisol will be hydroxylated into cortisol. Now, cortisol is hopefully what we know from an anatomy course and so forth, the primary glucocorticoid or corticosteroid. that's present in humans. So this is going to be the chronic stress hormone that we see in many mammals, such as.

And so cortisol can act independently. However, the corticosterone that's formed up here is present in humans and does possess some of the glucocorticoid activity that cortisol does. But corticosterone is going to be a minor corticosteroid in humans. There are some organisms, however, such as mice and rats, where corticosterone becomes a primary glucocorticoid; cortisol, more or less, becomes a minor one. But in general, these are both glucocorticoids. Now corticosterone can be processed further into the one general mineralocorticoid known as aldosterone, which is going to be involved in salt and water retention. So, this is going to be another mitochondrial enzyme, aldosterone synthase. And what this enzyme is going to do is going to do two things. Not shown here, it's actually first going to hydroxylate this position right here.

This is actually position number 18. And so, sometimes this enzyme is actually called CYP18B2 because it hydroxylates initially at the 18 position. But then, there's another activity of this enzyme which will oxidize the hydroxyl group right here that's put here into an aldehyde that's shown right. here in aldosterone. And the reason aldosterone gets its name is because it's an aldehyde, aldosterone. So, aldosterone synthase generally is going to have these two activities: a hydroxylase activity, which is the CYP18B2, and then an 18-hydroxysteroid dehydrogenase to convert that hydroxyl into the aldehyde shown here. Now, in general, unless we're talking about some minor degradation pathways, which will be involved in the aldosterone and cortisol, they are going to be sort of ends of the pathway. They're dead ends.

Because these two hormones are going to have one of two things they're going to do: They're either going to act. independently at their corresponding receptors throughout the, or they're just going to be metabolized, as I said, in the liver. So we're done with this part of the pathway. Let's go back to the progestogens for a because now we're going to see how androgens and estrogens are made. So actually, in order to make androgens, you have to first make two progestogens. And these progestogens are the hydroxylated versions of pregnenolone and progesterone. Respectively, they are 17 alpha hydroxypregnenolone and 17 alpha hydroxyprogesterone. Now we have another enzyme right here. This is called 1720 lyase. Now, actually 1720 lyase is the same enzyme as 17 alpha hydroxylase.

So it actually does the first activity right here of the 17 alpha hydroxylation, which we see right here. But sometimes the steroid can be released from the enzyme prematurely, and that's okay because that gives us the 17 alpha hydroxypregnenolone and the 17 alpha hydroxyprogesterone, which we know now are going to be processed to aldosterone and cortisol, respectively. And so if 17,20 lyase performs its second activity on pregnenolone and progesterone, it's actually going to use the hydroxyl group it just added to induce the removal of this ketone. And so what you see here are the two first androgens, dehydroepiandrosterone or DHEA, and androstenedione. These are two first recognizable androgens, and notice the difference between the androgens and the progestogens.

The main difference is that the tail here, which was really just a smaller version of the tail, this ketone, has been completely removed in all of the androgens. And notice in all the estrogens, it's completely removed as well. That's a characteristic feature of both of these sex hormones. Now there's another enzyme at play here, and it's one that we've seen before. It's actually this 3 beta hydroxysteroid dehydrogenase. What we can also do is oxidize this 3 beta hydroxy group into a ketone. And notice again, just as we saw up here in the progestogens, we have a net isomerization of this double bond, which is initially between positions 5 and 6. It gets isomerized between positions 4 and 5. And so what we can have is this 3 beta hydroxysteroid dehydrogenase oxidizes DHEA into androstenedione.

That can also occur. And then, if we've already reduced DHEA into androstenediol, then 3 beta hydroxysteroid dehydrogenase can then reoxidize this hydroxyl group into testosterone. And so what we see here are two general pathways from DHEA to get to testosterone. We can either first react with the 3 beta hydroxysteroid dehydrogenase and then the 17 beta hydroxysteroid dehydrogenase, or we can do it the other way around. But in any case, from these four androgens, the goal really is to get to testosterone because out of these four, testosterone is the most potent of those four androgens. Now, testosterone is out of these four the most potent androgen, but it is not the most potent androgen. The most potent androgen, at least shown here, is dihydrotestosterone.

And it's formed from testosterone by the action of this enzyme, 5 alpha reductase, which uses the reducing power of NADPH to reduce. this 4 5 double bond right here. Notice in dihydrotestosterone that double bond is gone. And a simple removal of that double bond actually increases the androgenic power of this hormone by about 20 to 100 fold. So this is a very, very strong androgen. Now back to these two androgens, androstenedione and testosterone. Both of these androgens can be processed directly into estrogens. And so that brings up a really important point. If you want to actually synthesize estrogens, you have to first make progestogens, then convert them into androgens, and then finally into your estrogens. The enzyme that's going to be involved in This conversion is going to be called aromatase.

So, notice what aromatase's action on androstenedione does. This ketone has a net reduction into an alcohol, and then the A ring becomes completely aromatic. So, one of the defining features of all the estrogens is the A ring. And that's actually what gives this enzyme, encoded by CYP19A1, its name, aromatase, because it aromatizes the A ring. So, that's what this enzyme does to androstenedione. It converts it into estrone, which is actually going to be the less active estrogen. But testosterone can also be aromatized in the same manner: net reduction of this ketone into an alcohol. and aromatization. And that gives us this molecule which is going to be generally the primary estrogen in pretty much every mammalian species, and that is estradiol.

Now both of these, estrone and estradiol, can be metabolized in the liver and placenta to produce this molecule which is called estriol. I won't go into its function here. That'll be a separate video. But in any case, the conversion of estradiol to estriol is a one-step process. It involves a hydroxylation at this position right here on the corner of the five-membered ring, the D ring. And then estrone, it's going to be a two-step process. First, this ketone is going to have to be. That's going to be ultimately by 17 hydroxysteroid dehydrogenase, and then the same hydroxylation at this position, which happens to be the 16 position. That's going to be catalyzed by another P450 hydroxylase, okay? A 16 hydroxylase, as it would be. All right, so this hopefully gives you a really good idea of the steroidogenic pathway.

We have really three of these enzymes are going to be located in the mitochondria. The vast majority of these are going to be embedded in the membrane of the smooth endoplasmic reticulum. Therefore, they're a microsomal. And hopefully what you see is that really, even though cholesterol. is the parent steroid; the progestogens, in general, could also be considered a parent because to get mineralocorticoids you have to first synthesize glucocorticoids, which come from progestogens. On top of that, in order to make estrogens, you have to first make androgens, which clearly come from progestogens. Okay. And so that's going to become important when you're learning this pathway and making some sense of it. One thing we're going to talk about in the next video is that some of these steroids, particularly ones that have a 3 beta hydroxy group, such as cholesterol, DHEA, and estrone, can actually be sulfated. And it turns out that sulfation is a good way to, first of all, inactivate a steroid, but also it prepares it for excretion in the urinary system, which is actually how these steroids are going to be. That's actually going to be part of phase 2 metabolism in the