pep Pharmacology Education Partnership

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Steroids and athletes: Genes work overtime

6

A Project Funded by a NIDA Science Education Drug Abuse Partnership Award

Module 6: Steroids and athletes: Genes work overtime

Description of the module

The use of steroids by athletes (and body builders) is common and it presents serious health risks. Despite the potential disqualification of athletes for using steroids before or during competition, athletes continue to use them. They must feel that the advantage of enhanced performance is worth the risk of being disqualified. In this module we explore the mechanism by which steroids promote muscle growth. They are notorious regulators of gene transcription, resulting in the synthesis of muscle proteins. Athletes who use steroids try to outwit the drug-testing "police," but, often, they fail the drug test. In this module, we highlight why steroids can persist in the body long after the person stops using the drug.

Learning objectives

1. Understand what is a steroid
2. Understand the definition of 'anabolic' and 'androgenic'
3. Understand the concept of a lipophilic molecule
4. Understand the difference between passive and facilitated diffusion
5. Understand the concept of hormone receptors and where in a cell they are located
6. Understand how proteins pass through a nuclear membrane
7. Be able to describe the structure of DNA
8. Understand the process of gene transcription, how it can be "turned on"
9. Understand the process of protein synthesis
10. Be able to identify parts of a muscle cell; understand how muscle contraction occurs
11. Understand the role of the liver and the kidney in eliminating compounds from the body

This module integrates information from the following areas:

cell biology, endocrinology, chemistry, physiology, sociology, sports

Student Handout

It's fairly common knowledge that exercising a muscle makes the muscle grow and become stronger. However, athletes in the US as well as in many other countries try to enhance their muscle performance even more by using steroids. Similarly, body builders use steroids to make their muscles grow beyond the size that would be produced naturally by lifting weights. How does this actually happen, and what are the consequences?

Let's explore the biology of steroids. Steroids are compounds that are synthesized in the body from the precursor, cholesterol. Some steroids are made in the adrenal glands (near the kidney) and some are made in the sex glands of both males and females.

1. Give an example of a steroid found in the adrenal glands and in the male and female sex glands.

2. Which of these steroids is used by athletes and by body builders?

3. What is an anabolic steroid?

Although anabolic steroids are used to increase muscle growth (and enhance performance), they do a lot of other things in the body as well. In fact, all anabolic steroids have androgenic properties, despite claims to the contrary. For this reason, they are termed anabolic-androgenic steroids or AAS, although most people just say "anabolic steroids" as a shortcut.

4. What is an androgen?

5. List 3 common androgenic effects of anabolic steroids in the body.

When athletes use anabolic steroids to enhance their performance, they don't just take a pill or an injection before the race or before the game. They must use the drug over a period of time in order to obtain the muscle growth. To understand why this is the case, we need to know how steroids actually make the muscles grow. First, after taking an anabolic steroid (by mouth or by injection), the steroid enters the bloodstream and travels to all tissues in the body (see Module 1). Most anabolic steroids are very lipophilic, and therefore, they can cross cell membranes easily to reach the inside of all cells.

6. Define "lipophilic." What characteristic of the steroid structure makes it lipophilic?

7. Why can a lipophilic steroid cross cell membranes so easily?

Once inside the cell, the steroid binds to a special protein called a steroid receptor. In this case we are referring to the "androgen receptor." The complex containing the anabolic-androgenic steroid and its receptor then travels through the cytoplasm and crosses the nuclear membrane to enter the nucleus.

8. How does a big, bulky molecule consisting of a steroid and a protein get across a nuclear membrane?

Once in the nucleus, the steroid receptor complex comes into contact with the DNA. The steroid receptor binds to a specific site on the DNA molecule, causing the DNA to start the process of gene transcription. This leads to the synthesis of certain proteins, depending on the cell-type and the part of the DNA to which the steroid receptor complex binds. All of these events take time, and a sustained use of the steroid is required to continually instruct the genes to synthesize more protein.

9. What kind of molecule is DNA? Describe its essential features.

10. What is gene transcription?

11. How is the protein synthesized?

The cell-type that contains the androgen receptor will define the kind of protein that is synthesized. For example, in the case of the muscle cell, the anabolic steroid will stimulate the synthesis of certain types of muscle fiber proteins.

12. In what type of cells would anabolic-androgenic steroids act to cause:
    - the growth of chest hair
    - acne
    - emotional disturbances such as aggression

As more muscle fiber proteins are produced, the muscle gets bigger and more powerful. But once the athlete or body builder stops taking the steroids, their muscles slowly revert to their normal size.

13. Draw a muscle cell. Label the essential structures in the muscle cell that help it to contract. Which muscle proteins constitute the muscle fibers?

The use of the steroids provides an unfair advantage over non-drug using athletes. So steroids have been banned from use in local, national and international competition. Despite this rule, many athletes continue to use steroids until shortly before a competition, when they hope that a drug test will not detect it. In many cases, this plan doesn't work. The drug is still present in their bodies long after the athlete stops taking it. This is due to the lipophilic character of the steroid.

Lipophilic compounds are difficult to eliminate from the body (the same is true for THC, found in marijuana). Normally, drugs are eliminated by the liver and the kidney. Enzymes in the liver convert (metabolize) drugs into a more water-soluble (polar) form. Once the drug is in a more water-soluble form, it travels through the bloodstream to the kidney, where it is collected in the urine and eliminated from the body. But in the case of highly lipophilic drugs such as anabolic steroids, they are metabolized very slowly so that only small amounts of drug are eliminated over time.

14. Why is it so difficult for an anabolic steroid to be metabolized by the liver enzymes?

15. Why is it so difficult for an anabolic steroid to be retained by the kidney where it would be eliminated in the urine?

If the lipophilic steroid can't be metabolized easily nor retained by the kidney, then it re-enters the bloodsteam to circulate throughout the body. However, it does like to "hide" in cells that contain a lot of lipids, such as fat cells. With continued use, the anabolic steroid starts to accumulate in the fat cells.

16. If the athlete stops using the steroid, the amount of steroid in the blood starts to decrease. What would account for the initial decrease of steroid in the blood?

17. Although the steroid decreases in the blood, it doesn't disappear right away. Instead, there is a steady low-level amount of steroid that is present in the blood over a long period of time (and thus the positive drug test). Where is the steroid coming from? What is the major force moving it into the bloodstream?

The ban on steroid use in sports is not based solely on the unfairness issue. There are serious health consequences that can occur from long-term steroid use.

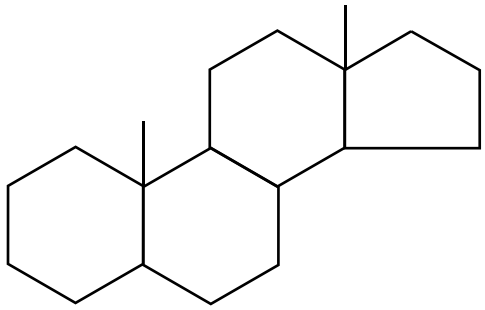
18. List 3 additional health consequences from the repeated use of anabolic steroids.

Teacher's Instructional Guide

The biochemistry of steroids

Steroids are a class of **hormones** that are synthesized by specific cells or tissues in the body and released into the bloodstream. Steroids are **non-polar** molecules produced from the precursor cholesterol. Four interconnected rings of carbon atoms form the skeleton of all steroids (**Figure 1**). The type of steroid formed is dependent upon the **polar** hydroxyl groups (OH) attached to the interconnected rings and the synthesizing tissue. Examples of synthesizing tissues, the corresponding steroids and some of their many functions are listed below.

Adrenal gland	glucocorticoids (cortisol)	maintain blood glucose during stress, anti-inflammatory
	mineralocorticoids (aldosterone)	regulate kidney function (water retention)
Ovaries	estrogen	promotes endometrial cell (uterine) proliferation
	progesterone	promotes endometrial cell differentiation
Testes	testosterone	stimulates sperm production promotes muscle growth



General steroid structure

Figure 1. The general structure of a steroid molecule is shown. Different steroids are defined by the location of polar hydroxyl groups (OH) attached to the C atoms within the rings.

Most steroids are used for medicinal purposes, especially the glucocorticoids, which are powerful anti-inflammatory agents. However, due to very serious side effects from long-term use (such as weight gain, bone density loss, increase in blood cholesterol levels, and liver disorders), they are only used as a last resort. Estrogen and progesterone are used in birth control pills and also in post-menopausal women to replace what is lost during aging (this is controversial). Testosterone (**Figure 2**) is an **anabolic steroid**, which promotes growth of muscle tissue. “Anabolic” literally means to build up tissue and it refers to the retention of nitrogen atoms in the body reflecting an increase in protein synthesis and/or a decrease in protein breakdown. While testosterone may be used in some clinical situations (e.g. testosterone-deficient men), it (or synthetic versions) is used mainly by body builders to increase muscle growth and by athletes to increase muscle growth and performance. Testosterone, like other steroids, has multiple effects in the body. It not only promotes muscle growth, it is also an **androgen.** It causes the development of male sexual characteristics such as growth of chest and facial hair, growth of the testes and deepening of the voice (Figure 2). Other effects of testosterone include acne, fluid retention, increased libido, aggression and other psychological disturbances.

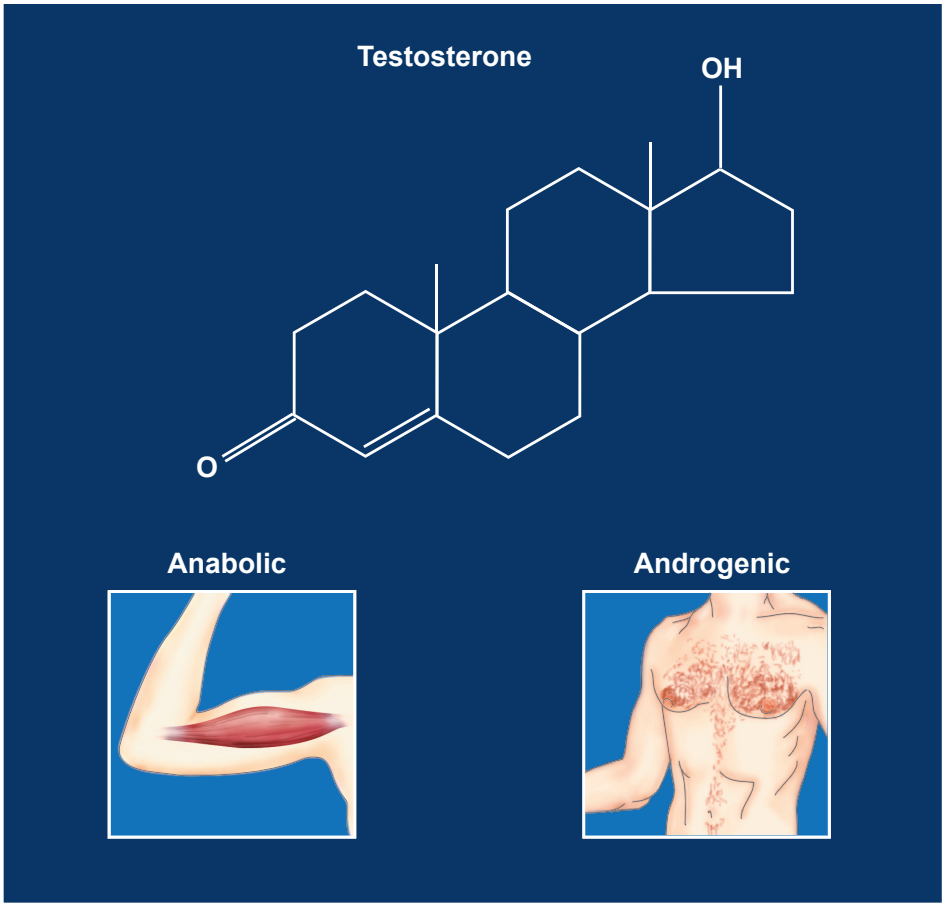


Figure 2. The structure of testosterone is shown. This steroid, synthesized in the testes, has both anabolic and androgenic properties.

Synthetic anabolic steroids

There are several problems with the use of testosterone. Since it has both androgenic effects (development of male sexual characteristics) and anabolic effects (promotion of muscle growth), both males and females may appear to be more "masculine." Athletes have tried to get around this issue by using synthetic forms of testosterone that have a chemical structure modified slightly from the original testosterone. These synthetic versions are called **anabolic steroids** and the manufacturers claim that they are more selective in their ability to produce anabolic effects compared to androgenic effects. However, despite these claims, anabolic steroids do have androgenic (masculinizing) effects, and thus a new terminology has emerged—anabolic-androgenic steroids, or AAS. The androgenic effects of anabolic steroids are a big problem for females who can develop facial hair, male pattern baldness and deepening of the voice (some of these effects are irreversible!). Another problem with taking the natural form of testosterone is that it is not very effective when given orally. After oral administration, testosterone is absorbed from the intestine into the bloodstream, which takes it to the liver (see Module 1), where it is immediately metabolized (inactivated). Thus, relatively little testosterone circulates throughout the bloodstream to reach its target. To address this problem, the chemists have chemically modified the testosterone structure to make it more difficult for the liver to metabolize it. The major chemical modification is the addition of C and H atoms (alkyl group) on the 5-membered ring at carbon #17 (**Figure 2**). Thus, this modification allows more testosterone to be available in the general circulation. However, there is a problem. The addition of an alkyl group at the 17th C atom not only enables the testosterone to be more slowly metabolized by the liver, but it also causes the liver to work harder to get rid of it, eventually resulting in liver damage or cancer.

How does an anabolic steroid reach its target?

Once in the bloodstream, the anabolic steroid travels to all tissues in the body, where it enters the cells to reach its target. In order to get into a muscle cell for example, the steroid must leave the capillary and then enter the muscle cell. This means that the steroid must cross two different types of membranes, the capillary membrane and the muscle cell membrane. To cross the capillary membrane, there are numerous pores or **fenestrae**, which allow small molecules to squeeze through (**Figure 3** and see Module 1). However the muscle cell membrane (like most cells in the body) does not have these small pores and therefore the steroid can only cross the membrane by diffusing across or by transport via a carrier protein. Steroids cross the muscle cell membrane by **passive diffusion**, which occurs in the direction of the concentration gradient— this does not require energy. Passive diffusion depends on the physiochemical characteristics of the membrane and the drug. The cell membrane, like all cell membranes in the body, is a lipid bilayer (**Figure 4**). It consists of lipids arranged with their polar head

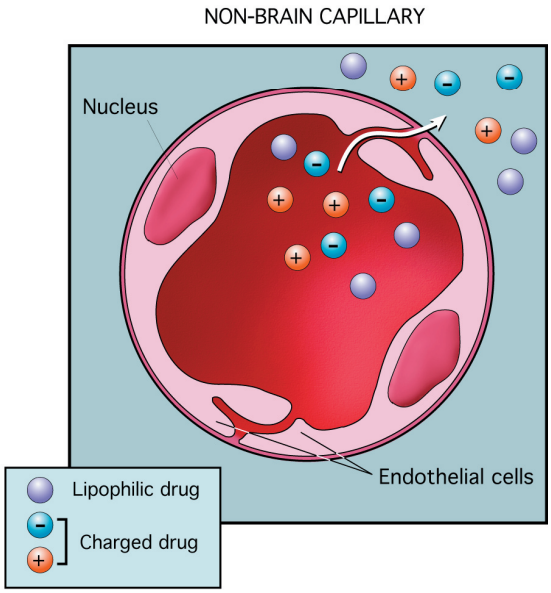


Figure 3. A capillary is composed of endothelial cells that connect together loosely. Small pores or *fenestrae* are also present, allowing solutes to move in and out of the capillaries.

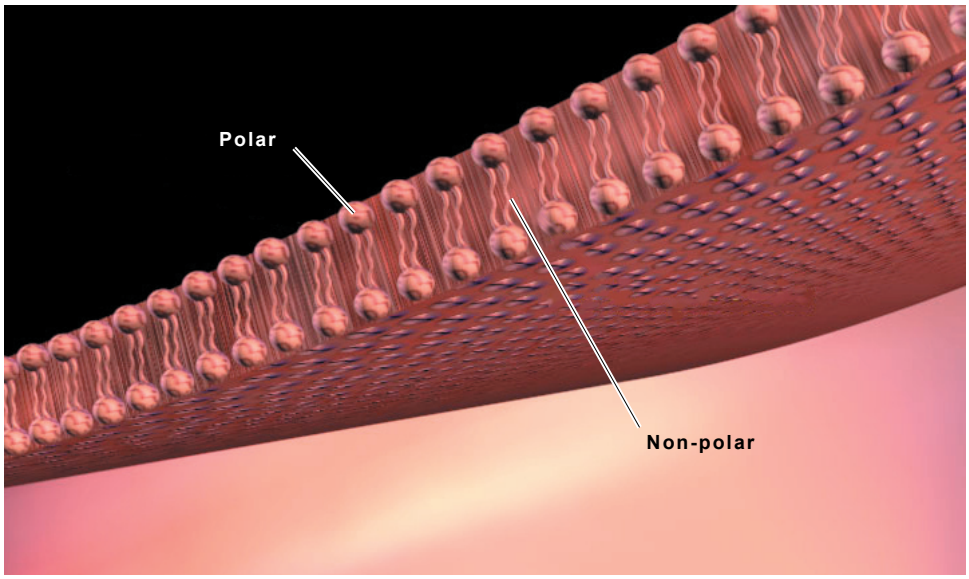


Figure 4. Schematic view of a cell membrane. Lipids are arranged with polar head-groups facing the outside and inside of the cell, while the fatty acid chains form the non-polar (hydrophobic) membrane interior.

groups facing the outside and inside of the cell. The chains of fatty acids face each other, forming the **hydrophobic** (water-fearing) or non-polar interior. Because anabolic steroids are very **lipophilic** (lipid-loving), they diffuse easily into the hydrophobic membrane interior. As they concentrate within the hydrophobic membrane interior, a new driving force is generated, pushing the steroid into the cytoplasmic side of the cell membrane. Once the anabolic steroid diffuses into the cytoplasm of the cell**,** it binds to the androgen receptor (**Figure 5**). [Receptors for other steroids are found in the nucleus instead of the cytoplasm.] This complex of steroid and protein then crosses the nuclear membrane to enter the nucleus of the cell, where it exerts its effects. In this case, passive diffusion can't occur because the protein is too large and not lipophilic. Instead, the steroid-receptor complex moves through small pores in the nuclear membrane to enter the nucleus. Although scientists are still elucidating exactly how this occurs, it is possible that the complex interacts with transport proteins that line the nuclear pores. This is an example of **facilitated diffusion,** which occurs in the direction of the concentration gradient. Therefore, no energy is required. This is unlike **active transport**, which occurs against the concentration gradient, and requires energy.

Steroids alter genetic function

Once inside the nucleus, the steroid-receptor complex binds to specific areas within the DNA (regulatory sites) to induce **gene transcription**, which directs the synthesis of specific proteins (**Figure 5**). A brief review of protein synthesis follows so we can understand how this happens.

DNA (deoxyribonucleic acid) is a large molecule containing the genes that code instructions for the synthesis of proteins. The code consists of a sequence of repeating subunits, or **nucleotides**. Each nucleotide has three parts: 1) a phosphate group (an acid), 2) a sugar (in the case of DNA, deoxyribose), and 3) a ring of carbon and nitrogen atoms (the nitrogen can form a bond with hydrogen so the nucleotide is basic) (**Figure 6**). A chain of nucleotides (**nucleic acids**) is formed by linking the phosphate group of one nucleotide to the sugar of an adjacent nucleotide. The bases stick out from the side of the phosphate-sugar backbone. The 3rd component described above, the base consisting of a ring of carbon and nitrogen atoms, occurs in 4 forms for DNA. These bases can be divided into two classes: the **purine bases** (adenine and guanine), which have double rings of nitrogen and carbon atoms, and the **pyrimidine bases** (cytosine and thymine), which have only a single ring. A molecule of DNA consists of two polynucleotide chains coiled around each other in the form of a double helix (**Figure 6**). The chains are held together by hydrogen bonds (see Module 5) between purine and pyrimidine bases – specifically, adenine is paired with thymine and guanine is paired with cytosine. Thus, one chain in the double helix is complementary to the other.

DNA is "read" by using three-base sequences to form "words" that direct the production of specific amino acids. These three-base sequences, known as triplets, are arranged in a linear sequence along the DNA. Each triplet codes for the synthesis of an amino acid and the specific chain of amino acids builds a specific protein. Most of the DNA is contained in the nucleus of the cell (a small amount is in the mitochondria), yet most protein synthesis occurs in the cytoplasm of the cell. Since DNA molecules are too large to pass through the nuclear membrane into the cytoplasm, a message must carry the genetic information from the nucleus into the cytoplasm. This message is carried by **messenger RNA** (mRNA; ribonucleic acid) molecules (Figure 5). The passage of information from DNA to mRNA in the nucleus is called **transcription** because the DNA sequence is actually transcribed into a corresponding RNA sequence. Once the mRNA passes through the nuclear membrane into the cytoplasm, it directs the assembly of a specific sequence of amino acids to form a protein – this process is **translation** (Figure 5). This occurs on ribosomes or in the rough endoplasmic reticulum (not shown in the figure). Thus, the synthesis of a protein is governed by the information in the DNA – mRNA simply serves as the messenger (and thus its name)! In the case of anabolic steroids, the steroid-receptor complex induces genes

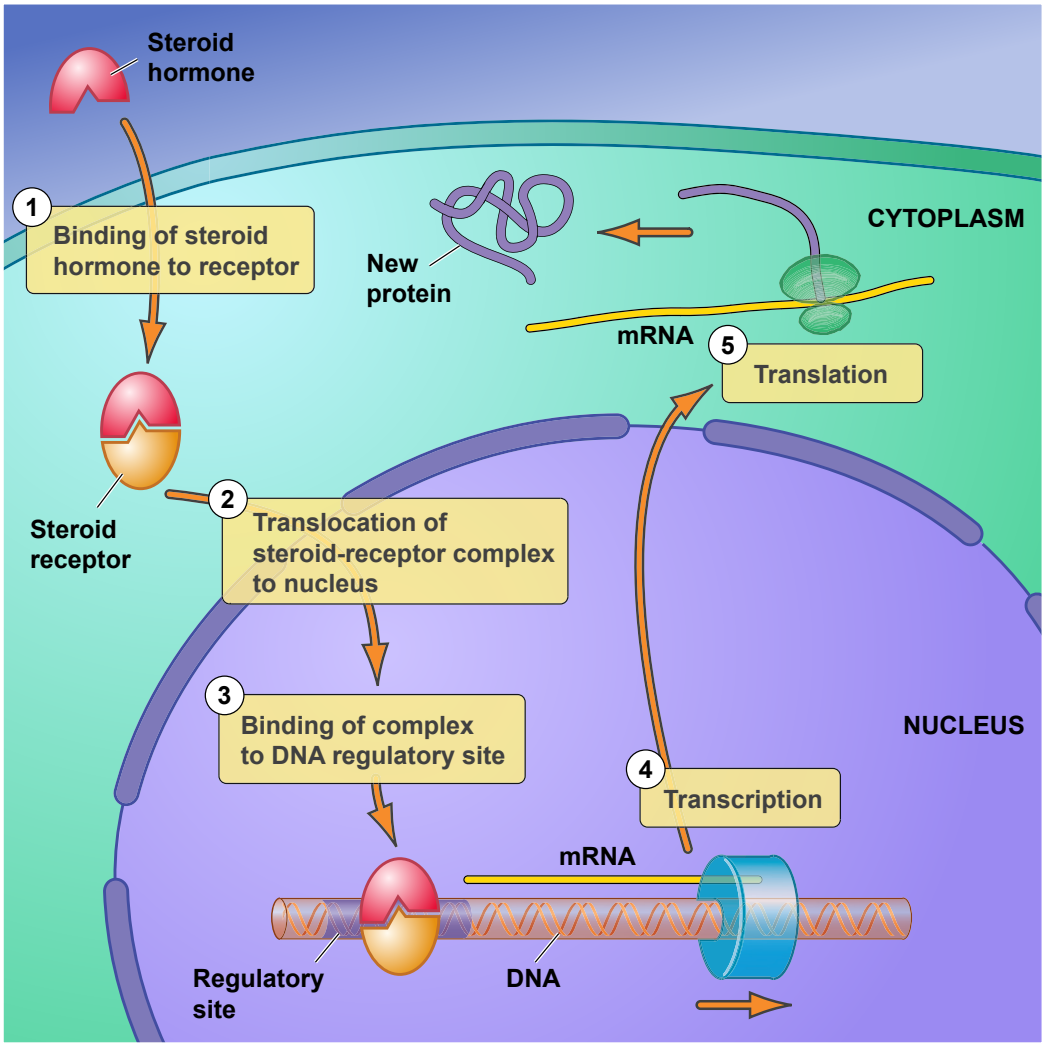


Figure 5. Testosterone (or anabolic-androgenic steroids) binds to the androgen receptor in the cytoplasm and the complex moves into the nucleus where it interacts with DNA to initiate protein synthesis.

to make specific proteins within muscle cells that help them to become larger and more powerful (discussed below). However, increased muscle growth is not the only action of anabolic steroids. Like testosterone, anabolic steroids can stimulate chest hair growth and cause acne and emotional problems (i.e., depression and hostility). The ability of anabolic steroids to produce these side effects is due to the cell type in which the steroid receptors are found and the specific DNA sequence that is transcribed. Thus, androgen receptors must be plentiful in cells of chest hair follicles (see Module 2), in secretory cells of sebaceous glands, and on neurons within the limbic system (important in mood) of the brain.

How does the alteration of genetic function by anabolic steroids increase muscle mass?

Consider the swimmer or weight-lifter who might use anabolic steroids (in fact both swimmers and weight-lifters in the 2000 Olympics were disqualified for steroid use). They have larger, more powerful arm muscles due to an increased production of specific proteins contained within skeletal muscle. A review of muscle structure will help us understand how this happens.

There are three main types of muscle in the body – skeletal, smooth, and cardiovascular. Steroids work predominantly on skeletal muscles, which account for approximately 40% of the 630 muscles in the human body!! Skeletal muscle cells contain a contractile mechanism that is activated by an electrical impulse generated when the neurotransmitter, acetylcholine, binds to acetylcholine receptors on the

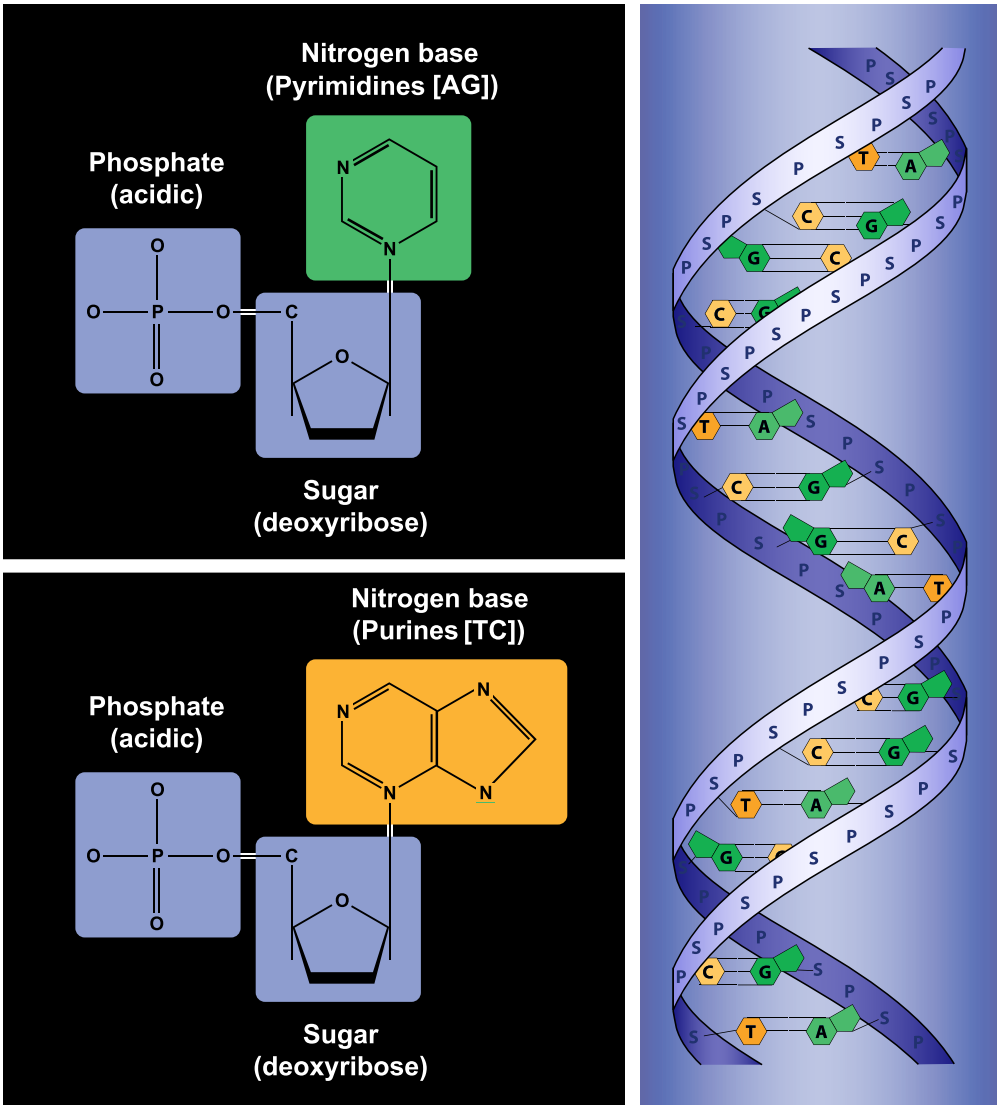


Figure 6. The generic structure of a nucleotide is shown. Nucleotides are joined together in a chain (phosphate groups of one nucleotide are linked with the sugar moiety of an adjacent nucleotide). The bases in one chain bind to complementary bases in another chain to form the double helical structure of DNA.

muscle (see Module 4). A single skeletal muscle cell is known as a muscle fiber (**Figure 7**). The term muscle refers to a number of muscle fibers bound together by connective tissue known as tendons, which are located at each end of the muscle. Skeletal muscle fibers (cells) appear striated because of an organized arrangement of thick and thin protein filaments (**myofibrils**) within cylindrical bundles in the cytoplasm--these myofibrils fill up most of the cytoplasm and extend from one end of a fiber to the other end. Each myofibril contains a repeating pattern of the thick and thin filaments surrounded by the sarcoplasmic reticulum and the sarcoplasm (cytoplasm). One unit of this repeating pattern is called a **sarcomere** (**Figure 8**). The thick filaments are composed of the contractile protein **myosin** and the thin filaments are composed of the contractile protein **actin**. Contraction occurs when the sarcomeres shorten by the action of the myosin filaments sliding over the actin filaments. The sliding of the myosin filaments is initiated when acetylcholine binds to its receptor in the muscle cell, generating an electrical signal to release calcium from the sarcoplasmic reticulum (where it is sequestered) into the sarcoplasm. The muscle relaxes when the calcium is removed from the sarcoplasm back into the sarcoplasmic reticulum by the enzyme calcium-ATPase.

For advanced students:

The cellular mechanism for muscle contraction
Actin contains active sites to which myosin binds during contraction. When the muscle is relaxed, the active sites are covered by another protein called tropomyosin, preventing any contraction. Troponin molecules are located along the actin-tropomyosin filaments and they help position the tropomyosin filaments over the active sites on the actin filaments. When calcium enters the sarcoplasm, troponin undergoes a conformational change that results in the movement of tropomyosin off the active sites, allowing myosin and actin to interact. The uncovering of the active sites allows myosin heads to bind to the actin active sites, initiating a movement of the myosin head toward the center of the sacromere. This pulls the actin along and shortens the sarcomere, thus causing the contraction. Each of the myosin heads operates independently of the others, each attaching and pulling in a continuous alternating ratchet cycle. This cycle stops when the calcium is removed from the sarcoplasm (as described above), causing troponin to change its conformation back to the resting state. The tropomyosin can then "cover up" (rebind to) the active sites causing the muscle to relax.

Anabolic steroids will induce the genetic machinery (as discussed above) in muscle cells to synthesize more muscle proteins. More contractile proteins make the muscle cell bigger, and therefore, the whole muscle gets bigger. Muscle growth is aided by another important action of anabolic steroids. Anabolic steroids can also bind to glucocorticoid receptors (there is some similarity in the structure of androgen and glucocorticoid receptors), preventing glucocorticoids from carrying out their normal **catabolic** or muscle-breakdown activity. Athletic performance improves as the muscles grow. The performance-enhancing effects of anabolic steroids do not occur in people who are not exercising unless large doses are used. Athletes tend to believe that the more steroids they take, the bigger their muscles will become. However, this doesn't happen. There are only a finite number of steroid receptors in the muscle cell. Thus, when all of the receptors are bound to the steroid (i.e., the receptors become saturated), any additional steroid molecules remain in the bloodstream, where they travel to the liver and kidneys. The high levels of steroids presented to the liver and kidneys can cause damage. High doses of anabolic steroids can have other adverse effects too. They can actually increase protein breakdown during the muscular stress that occurs with intense athletic training, increase fluid and electrolyte retention, or produce an increase in body weight.

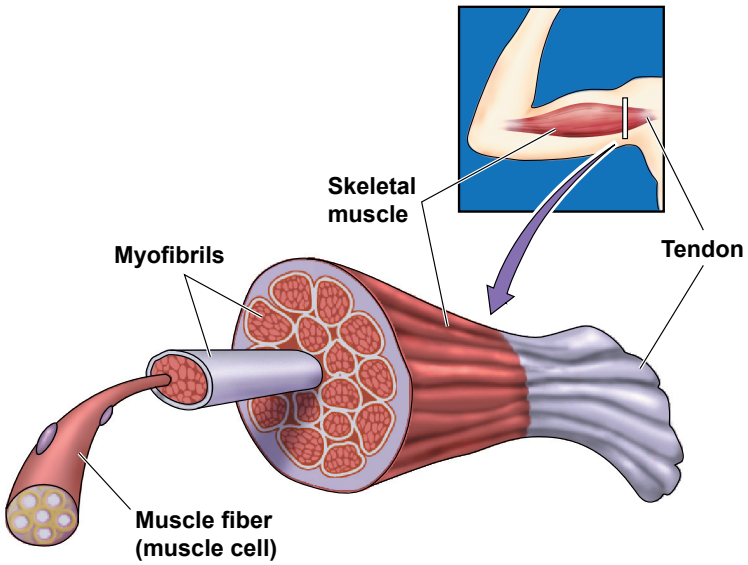


Figure 7. A skeletal muscle cell (also called a muscle fiber) is shown containing several myofibrils. These protein filaments are important in muscle contraction.

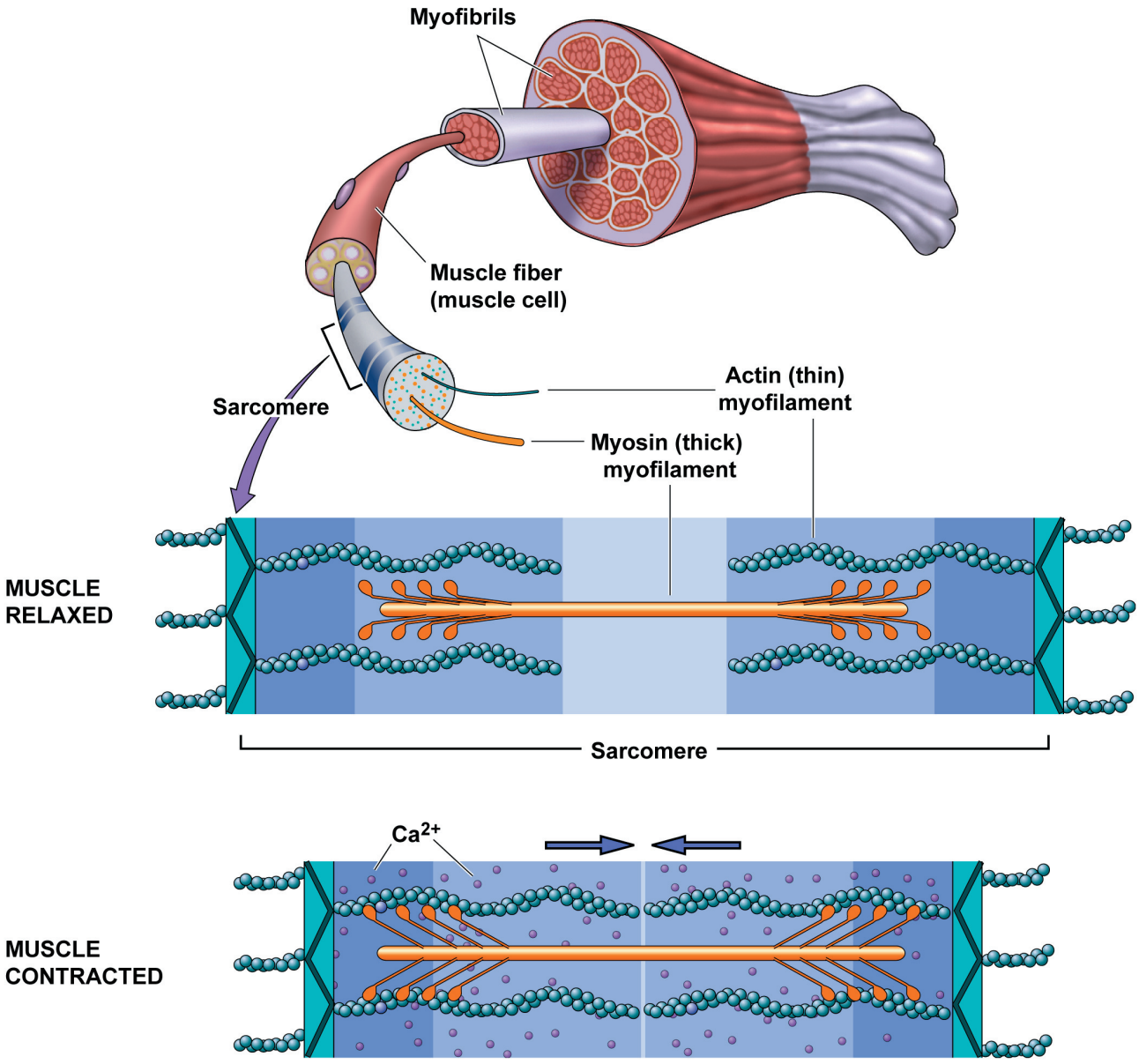


Figure 8. The repeating pattern of thick and thin filaments is a sarcomere. The presence of calcium causes sarcomeres to shorten when actin filaments slide over the myosin filaments. This produces muscle contraction. (After Seeley, et. al. Essentials of Anatomy and Physiology. Boston, MA: Mc-Graw-Hill, 1999.)

Why can anabolic steroids be detected in the body for long periods of time?

Every athlete knows that his/her urine will be tested for drug use when they enter an important competition. To avoid detection of steroids in their urine, athletes will stop using the drugs well before the competition. Yet, in many cases, steroids can still be detected long after the athlete stops using them (even weeks later!). The reason for this lies in the chemical structure of the anabolic steroid. As discussed above, anabolic steroids are very lipophilic molecules. This property makes it very difficult for the drug to remain long enough in the liver to be metabolized (inactivated) or in the kidney to be excreted in the urine (**Figure 9**). The lipophilic drug moves with its concentration gradient from the liver or the kidney cells right back into the bloodstream. Thus, it doesn't get eliminated very well. Instead,

it seeks out fat cells that exist in the athlete (these are much smaller than those found in the average couch potato!). The lipophilic steroid likes to enter fat cells, and with repeated use, the steroid accumulates there. When the user stops taking the steroid, the blood levels decline rather quickly in the absence of the drug. But now, the steroid concentration inside the fat cell becomes greater than that in the blood, so the concentration gradient reverses in the direction of fat cell-to-blood capillary. The fat cells are like a storage depot, releasing small amounts of steroid into the blood over time (via passive diffusion). Eventually the steroid gets metabolized and makes its way to the kidney to be excreted in the urine. This explains why it is possible to detect small amounts of the steroid in the urine at competition weeks after the athlete stops using it.

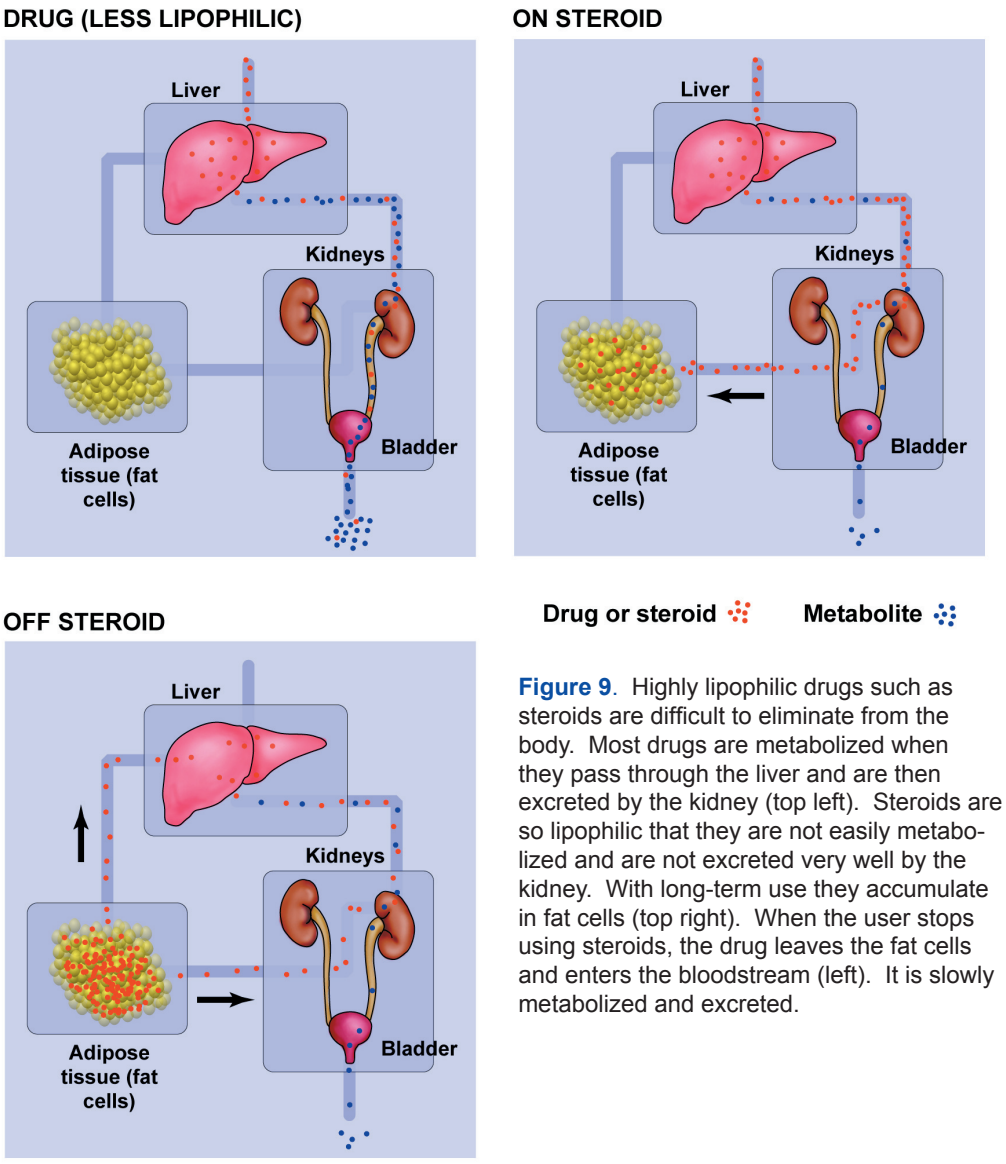


Figure 9. Highly lipophilic drugs such as steroids are difficult to eliminate from the body. Most drugs are metabolized when they pass through the liver and are then excreted by the kidney (top left). Steroids are so lipophilic that they are not easily metabolized and are not excreted very well by the kidney. With long-term use they accumulate in fat cells (top right). When the user stops using steroids, the drug leaves the fat cells and enters the bloodstream (left). It is slowly metabolized and excreted.

Why can't users stop taking steroids abruptly? Is it an addiction?

The answer is "not really." An **addiction** to a substance indicates that the person uses the drug compulsively, with a loss of control in their intake, despite negative consequences. Most athletes are not compulsive users of steroids (although there may be a few out there!)—if they were, they would not be able to stop taking the steroids prior to competition. However, chronic users can become dependent on steroids. A **dependence** means that the athlete's body adapts to the presence of the steroid, and if the steroid is withdrawn suddenly, physiologic symptoms emerge. Withdrawal symptoms include

nausea, headaches, dizziness, increased blood pressure, decreased libido (sex drive), depression and craving. The basis for this dependence involves the brain and the gonads. More specifically, the hypothalamus, found at the base of the brain, releases hormones that direct other tissues in the body to produce steroids (**Figure 10**). In the case of the sex steroids, the hypothalamus produces a hormone called "gonadotropin releasing factor" or GNRH. This hormone binds to GNRH receptors on the pituitary gland (located near the hypothalamus, but not actually part of the brain), where it activates the release of lutenizing hormone (LH) and follicular stimulating hormone (FSH). These pituitary hormones travel throughout the bloodstream and when they reach the gonads (i.e., testes and ovaries), they bind to LH and FSH receptors in gonadal cells to cause the release of testosterone and estrogen. The body attempts to keep the steroid levels in balance using "feedback regulation." When the sex steroid levels in the blood become elevated, the hypothalamus reduces its production of GNRH, the pituitary reduces production of LH and FSH, and the gonads reduce production of testosterone and estrogen. [In women taking birth control pills, this is the basis for the contraceptive activity—without enough LH and FSH, they can't ovulate.] So, when the athlete takes the steroids chronically, his/her hypothalamus stops producing GNRH and the gonadal tissues stop producing testosterone or estrogen due to this negative feedback. Now, if athletes stop taking the steroids abruptly, they won't have enough testosterone or estrogen. It takes some time (it can take 6 months!) for their hypothalamus, pituitary, and gonads to recover normal activity and start producing these hormones again. Therefore, all people who use steroids, even for therapeutic purposes, must taper off the drug slowly to give their hypothalamus, pituitary and gonads time to recover normal hormone production.

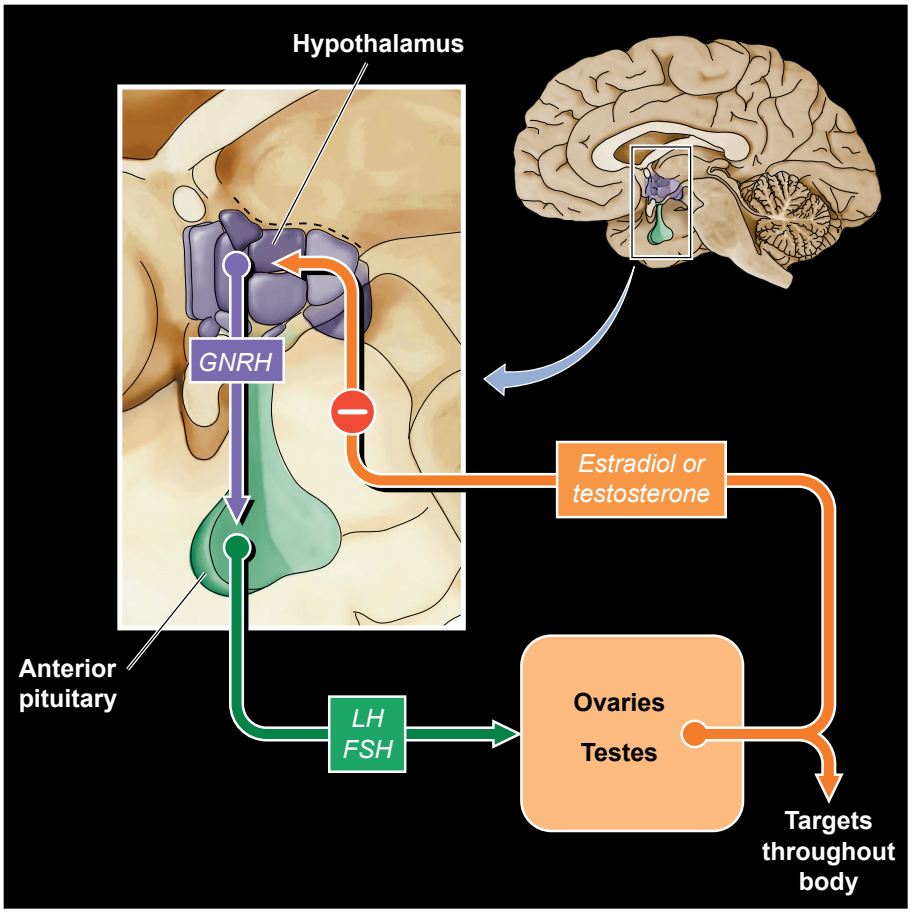


Figure 10. The hypothalamus-pituitary-gonadal "axis" is shown. GNRH is released by the hypothalamus, signaling the pituitary gland to release LH and FSH into the blood. In males, the testis synthesizes and releases testosterone in response to the LH and FSH. Circulating testosterone signals the hypothalamus to shut down GNRH release ("feedback inhibition").

Glossary

actin – contractile protein that is present in the thin filaments of the myofibrils.

active transport – the movement of molecules against the concentration gradient with the help of a transport protein. This transport requires energy in the form of ATP.

addiction – a behavior pattern that occurs when a person uses drugs compulsively, with a loss of control of their intake, despite negative consequences.

anabolic steroids – synthetic versions of testosterone designed to promote muscle growth without producing androgenic effects. The better term is anabolic-androgenic steroid.

androgen – a steroid hormone such as testosterone that is masculinizing (deepens voice, produces facial & chest hair, sperm production)

catabolic – a compound that causes the breakdown of muscle resulting in the net loss of nitrogen from the body. Glucocorticoids are catabolic in skeletal muscle.

dependence – the body functions normally in the presence of the drug. When the drug is present, the body has adapted physiologically to its presence. When the drug is removed, withdrawal symptoms are produced, usually in opposition to the effects produced by the drug's presence.

DNA (deoxyribonucleic acid) – a large molecule containing the genes that provide the instructional code for the synthesis of proteins. DNA consists of two complementary polynucleotide chains coiled around each other in the form of a double helix.

facilitated diffusion – the movement of molecules across a membrane with the concentration gradient. No energy is required, but transport proteins can become saturated, limiting the diffusion process.

fenestrae – small spaces or pores between endothelial cells that form the capillary membrane. These pores allow charged drugs or larger drugs to pass through the capillaries.

hormones – chemicals in the body that are synthesized in one tissue and secreted into the bloodstream for actions in tissues some distance away. They regulate many physiologic functions.

hydrophobic – "water-fearing"; a compound that is soluble in fat but not water. This is typical of compounds with chains of C atoms.

lipophilic – high lipid solubility. Lipophilic compounds dissolve readily in oil or organic solvent. They exist in an uncharged or non-polar form and cross biological membranes very easily.

messenger RNA – also known as mRNA or ribonucleic acid; it is transcribed from DNA and moves to the cytoplasm to direct protein synthesis.

myofibrils – a repeating pattern of thick (myosin) and thin (actin) protein filaments that are organized in cylindrical bundles within the sarcoplasm. The myofibrils extend from one end of a muscle fiber to the other end.

myosin – contractile protein that is present in the thick filaments of the myofibrils.

non-polar - a chemical property of a substance that indicates an even distribution of charge within the molecule. A non-polar or non-charged compound mixes well with organic solvents and lipids but not with water.

nucleic acid – a chain of repeating subunits of nucleotides.

nucleotides – the hydrolysis product of nucleic acids comprising 3 parts: 1) a phosphate group (an acid), 2) a sugar (deoxyribose for DNA and ribose for RNA), and 3) a ring of carbon and nitrogen atoms (nucleosides; purines and pyrimidines).

passive diffusion – the net movement of molecules from higher to lower concentrations. This form of diffusion does not require an energy source to occur.

polar compound – a chemical property of a substance that indicates an uneven distribution of charge within the molecule. A polar substance or drug mixes well with water but not with organic solvents and lipids. Polar or charged compounds do not cross cell membranes (lipid) very easily.

purine base – a type of nucleotide present in DNA that consists of double rings of carbon and nitrogen atoms. The two purine bases present in DNA are adenine and guanine.

pyrimidine base – a type of nucleotide present in DNA that consists of a single ring of carbon and nitrogen atoms. The two pyrimidine bases present in DNA are cytosine and thymine.

ribosomes – structures within the cytoplasm consisting of proteins and a different form of RNA (rRNA) that support the process of protein translation

sarcomere – one unit of a repeating pattern of actin and myosin present in a myofibril.

steroids – a class of hormones synthesized from cholesterol by specific cells in the body. They are powerful compounds that alter genetic function, causing numerous effects in the body.

transcription – the passage of information from DNA to mRNA in the nucleus; this is directed by several enzymes.

translation – the process of assembling a specific sequence of amino acids (based on the instructional code provided by mRNA) to form a protein. It occurs in the cytoplasm on ribosomes or in the rough endoplasmic reticulum.

Module 6: Supplementary Classroom Activities

"Steroid Use: THE GOOD, BAD, and UGLY"

***Objectives*:**

1. To understand the interaction of various steroids with biological targets within the human body.
2. To demonstrate the understanding of lipophilic drug storage in fat and slow diffusion into the bloodstream
3. To understand the positive impacts steroids have had in the lives of many individuals who otherwise would die.
4. To understand the negative impacts steroids have had in the lives of people who otherwise would have fewer health problems.
5. To understand how a single chemical can have both a strong positive impact on the body, as well as hazardous actions.
6. To understand that steroids are not only used in the popular world of sports, but in the everyday world by people they know.

***Standards and Skills*:**

CA24, CA25, CB23, CB25, CB34, CC12, CE13, CE14, CE20, CF10, CF12, CF13, CF14, CF16, CG21, AA1, AB11, AB14, AC2, AE1, TB2, TE4

***Science Concepts*:**

The role of steroids in our society is important, as it impacts various genres of life from athletics to respiratory ailments. For this reason, there are multiple areas of science incorporated into this investigation. Several of the major concepts will include the following:

- *The various types of steroids and their chemical structures.*
- *The interaction of steroids on biological targets within the body.*
- *The interaction of steroids with DNA and consequently on individual cell function*
- *How the use of these steroids can affect multiple targets including those not intended to be affected.*
- *The short term benefits of steroids*
- *The long-term benefits of steroids*
- *The short and long-term problems of steroid use.*
- *Why different steroid types are used*
- *Why different routes of administration are use..*
- *How scientific data are used to make hiring decisions.*

***Materials needed*:**

PEP Module 6--content
Internet access
Books and journals with information about steroids

***Procedure*:**

This activity involves students working in groups to prepare a skit that will be presented to the whole class. The class should be divided into groups of approximately 3 students each. Each group will be assigned a “scenario” that describes a particular type of steroid use.

1. Arrange students into groups of approximately 3 students each.
2. Give each group one of the scenarios below.
3. Arrange time for students to do research using the internet and other resources.
4. Encourage students to discover how these steroids work at a molecular/cellular level.

5. Allow students time to prepare a skit that will teach the other students about the steroid in question, how it affects the body, the positive and negative effects, and the dilemma faced by the person that is using the steroid.
6. Evaluate the skits as they are presented. See assessment rubric.

As students prepare their skits, they may need more participants. Allow students to enlist people from other groups to play minor roles in their skits. The skits should be creative but, equally important, they should reveal all of the important information about the particular steroid that is being highlighted by that scenario. Each scenario is provided with guiding questions to encourage in-depth research.

It is suggested that the rubric be handed out to students before they plan their role-plays so that they can clearly see what is expected.

***Assessment strategies*:**
Use the provided rubric to assess the skits as they are presented.

SCENARIOS

A. Mr. and Mrs. Brookstone have a two-year-old son who has just been diagnosed with autism. The doctor has recommended special schools and programs that can help the family work with this young child. Mrs. Brookstone goes onto the Internet and discovers families who have experienced "miracles" with autistic children who are prescribed a particular steroid. She wants to begin this treatment on her son.

    1. What is this steroid and why is it being used with autistic children?
    2. How does this steroid usually work?
    3. What are the positives of using this steroid for autism?
    4. What are the side effects of using this steroid?
    5. Is the use of this steroid for autism warranted or not?

B. Mr. and Mrs. Nordstrom have just given birth to a baby girl who is 2.5 months premature. The doctor is recommending steroids to help prevent the lung problems that are common with infants who are so premature. Mr. Nordstrom remembers taking steroids for asthma and he knows they have side effects. He is very concerned about giving them to his baby.

    1. What is the steroid that the doctor is recommending?
    2. What does this steroid do for premature lung development?
    3. What are the positives of using this steroid for lung development?
    4. What are the side effects of this steroid?
    5. Is the use of this steroid for premature lungs warranted or not?

C. Major League Baseball has never tested for steroids. However, the new labor agreement states that the league will begin steroid testing. Major League Baseball is big business. Millions of dollars in business as well as athletes' careers are at stake. You are a doctor on the medical review board for Major League Baseball. You and your colleagues have conducted random steroid testing and are reviewing the results. In your group, review the test results and determine whether the player (see list below) should be suspended from play, put on probation, or not charged. You need to defend your decision with an explanation of the scientific evidence on which it was based.

Base your decision on the following criteria.

Suspension from play = the player is currently using steroids
Probation = signs of past steroid use
Not charged = no (or not enough) evidence of current or past steroid use

1. Player 1 is a member of the Yankee organization. The male hormone testosterone has been detected in his bloodstream. The player shows no sign of liver or kidney damage.

2. Player #2, from the Red Sox, shows signs of liver damage. He has normal kidney function. His LH and FSH levels are low. He has high blood pressure. The player also complains of frequent headaches and dizziness.

3. Player # 3, from the Blue Jays, shows signs of kidney damage. Liver function is normal. Blood pressure is normal. The player has gained weight recently. Electrolyte levels are high. LH and FSH levels are low.

4. Player #4 is a member of the Padres organization. No signs of kidney damage. Slight liver damage was found. Electrolytes are normal. LH and FSH levels are normal.

5. Player #5, from the Mariners, has slight liver and kidney damage. Electrolytes are normal. LH and FSH levels are normal. Blood pressure is normal. Trace amounts of steroid were detected in the blood.

D. Mr. and Mrs. Dubey have a beloved Golden Retriever who is continually losing fur by scratching and chewing at its skin. The veterinarian has diagnosed a flea allergy. As well as treating the dog for fleas, the doctor wants to give the dog steroids.

1. What kind of steroids would the vet be likely to prescribe and for what reason?
2. What do these steroids do for flea allergies?
3. What are the positives of using these steroids for flea allergies?
4. What are the side effects of using these steroids?
5. Is the use of these steroids for flea allergies warranted or not?

E. Mrs. Hematocrit has been diagnosed with anemia. She is not producing enough red blood cells. Her doctor wants to treat her with steroids. She has heard a lot of negative things about using steroids and is very reluctant to use them.

1. Which steroid is the doctor likely to prescribe?
2. What do these steroids do for this type of anemia?
3. What are the positive of using these steroids for anemia?
4. What are the side effects of these steroids?
5. Is the use of these steroids for anemia warranted or not?

F. Mr. Achoo went into the hospital when he was having great difficulty breathing. He was diagnosed with asthma. His doctor is eager to treat him with steroids in an inhaler form. But Mr. Achoo was reluctant to take steroids because he had heard about all the side effects.

1. Which steroid is the doctor likely recommending?
2. How do steroids affect the symptoms of asthma?
3. What are the positives of using the steroid inhaler for asthma?
4. What are the side effects of using the steroid inhaler for asthma?
5. Is a steroid inhaler warranted in this case?

G. Ms. Fleetfoot is a serious runner who has a chance to make the Olympic team. She is concerned that she will have a hard time competing with the strongest runners and she is having a hard time increasing her stamina. A friend tells her that steroids will greatly improve her strength and stamina.

1. Which steroids are Ms. Fleetfoot considering using?
2. What effects do these steroids have on Ms. Fleetfoot's athletic ability?
3. What are the positives of using these steroids for strength and stamina?
4. What are the side effects of using these steroids?
5. Is steroid use warranted in this case?

H. Mr. Jones is a 17 year old teenager who has not developed typical male secondary sex characteristics. His doctor diagnosed him with a chromosomal condition called Klinefelter Syndrome and prescribed a steroid as well as other treatments.

1. Which steroid is the doctor likely prescribing for Mr. Jones?
2. What effect would this steroid have on the physical symptoms that Mr. Jones is experiencing?
3. What are the positives of using this steroid for Klinefelter Syndrome?
4. What are the side effects of using this steroid?
5. Is steroid use warranted in this case?

I. Mr. Boone went to his doctor with a raging case of poison ivy. His doctor recommended a particular steroid treatment. Mr. Boone is reluctant to take this steroid because he took them one other time for back pain and he did not like the side effects.

1. Which steroid is the doctor likely prescribing for Mr. Boone?
2. What effect does this steroid have on poison ivy exposure?
3. What are the positives of using this steroid for poison ivy exposure?
4. What are the side effects of using this steroid?
5. Is steroid use warranted in this case?

J. Ms. Spears has been diagnosed with CLL – chronic lymphocytic leukemia. Her doctor has prescribed chemotherapy for a period of time and has also prescribed steroid use along with the chemotherapy.

1. Which steroid is the doctor likely prescribing for Ms. Spears?
2. What effect does this steroid have on cancer patients such as Ms. Spears?
3. What are the positives of using this steroid along with chemotherapy?
4. What are the side effects of using this steroid?
5. Is steroid use warranted in this case?

Rubric for Role Play Presentations - Module 6

Criterion	INADEQUATE	ADEQUATE	COMPETENT	OUTSTANDING
Introduction The presenters "set the stage" for the role play. This is where the presenters "engage" the audience by connecting the role play to the experiences or interests of the class.	- no introduction - introduction weak	- introduction present - introduction not particularly inspiring	- introduction leads directly to body of presentation	- introduction piques interest - leads directly to body of presentation
Role Play This is the most important part of presentation. This is where the presenters help the class understand the content through the role play. The presenters must have a deep understanding of the content in order to present a meaningful role play.	- understanding of concepts is weak - role play does not explain concepts well	- understanding of concepts is adequate - role play is clear but not connected	- understanding of concepts is good - connections between concepts is strong - role play of content and issues is strong	- understanding of concepts is excellent - connections between concepts is strong - content, principles, and connections well presented
Summary At the end of the role play, the presenters help the class by summarizing the content. This can be done through the role play or more traditionally. It could also involve the class through asking questions or "quizzing" them.	- no summary - summary very weak - truncated summary	- summary present - summary connected to body of presentation	- summary present - summary connected to body of presentation - summary connected to larger concepts	- summary connects well to body of presentation and to larger concepts - summary proposed new areas of thinking and research
Use of Visuals Good presenters use appropriate visuals to help the class understand the concepts being presented. The visuals are designed to make concepts much more clear and are used by the presenters to explain difficult ideas.	- no visuals used - visuals don't increase understanding of concepts	- visuals are useful to improve learning most of the time	- visuals are useful and consistently appropriate - visuals are strategically placed to improve learning	- visuals are useful, well-explained and inherently connected to concepts - use and/or preparation of visuals shows creativity
Creativity A good role play will not only be accurate and present content well, it will also show creativity and will evoke interest from the audience.	- No creativity evident - Creativity is not directed toward better understanding	- Role play shows some creativity - Creativity is not directly related to content	- Role play shows creativity - Creativity is connected to the content	- Role play is extremely creative - Role play is inherently connected to the content
Shared Participation Good presenters make sure that each person is involved in the presentation and that the total presentation is connected.	- very unequal participation of presenters - one or more persons does not participate	- participation is not equal but each person participates at least 20% of the time	- participation is equal but each person's part is not well connected to the other presenter(s).	- participation is interactive and equal - each person's presentation enhances the other presentations

Resources

The following resources provide supplemental information that pertains to the topic in this module.

RR Levine, CA Walsh and RD Schwartz-Bloom. Pharmacology: Drug Actions and Reactions , Parthenon Publishing Group, New York, 2000.

C Kuhn, S Swartzwelder and W Wilson. Pumped. WW Norton & Co., New York, 2000.

C Kuhn. Anabolic steroids. Recent Progress in Hormone Research. 57:411-34, 2002.

NIDA Research Report; Anabolic Steroid Abuse, April, 2000
http://www.drugabuse.gov/ResearchReports/Steroids/AnabolicSteroids.html

CE Yesalis and MS Bahrke. Anabolic-Androgenic Steroids: Current Issues. Sports Medicine, 19: 326-340, 1995. or http://www.naturalstrength.com/steroids/detail.asp?ArticleID=382

JM Hoberman and CE Yesalis. The history of synthetic testosterone. Scientific American. 272: 76-81, 1995.