

# The Pharmacology Of Anabolic Steroids

Contributed by By Dan Gwartney, MD  
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Anabolic-androgenic steroids (AAS) are immensely popular with athletes and individuals interested in building muscle mass because they are reliable and effective.<sup>1</sup> Much like any other drug, licit or illicit, patients or users can easily administer the drug(s) and readily predict the body's response with the slightest degree of experience. Sadly, because AAS are so simple, most users fail to even attempt to understand how the drugs work and why different AAS provide different results. Further, safety is rarely considered until a problem occurs.

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Pharmacology is the study of the factors involved with how a drug enters and works in the body, the various ways the cells and systems regulate the processes affected and how the body clears the drug. Despite the fact that AAS are based upon an endogenous hormone (testosterone) and have been utilized as a pharmaceutical product for over 50 years, the complete pharmacology of AAS remains undetermined, even though a significant number of men suffer from symptoms of androgen deficiency, with associated health consequences including cardiovascular disease and earlier mortality.<sup>2-4</sup> Fortunately, there is a substantial body of published research in the field, nicely reviewed by Dr. Andrew Kicman of the Department of Forensic Science and Drug Monitoring at King's College London (England) in the *British Journal of Pharmacology*.<sup>5</sup> While the collective knowledge in the field of AAS is incomplete (as it is with every other drug, such being the nature of science), it is sufficient to develop a working understanding of AAS and suggest potential research to improve safety and efficacy.

Kicman's review is organized in excellent fashion and comprehensively referenced. Those truly interested in learning about AAS, which should include anyone using or prescribing such drugs (licitly or illicitly), would be well-served to read the review. The *British Journal of Pharmacology* has provided free access to the article at their website: <http://www.nature.com/bjp/journal/v154/n3/pdf/bjp2008165a.pdf>.

As has been stated repeatedly, AAS contain or are derivatives of the natural male sex hormone, testosterone. Knowing this, it is not surprising that AAS affect a myriad of tissues which respond to testosterone, including: reproductive tissues,

muscle, bone, hair follicles, liver, kidneys, brain, white and red blood cells. These effects are usually divided into androgenic (referring to masculinization) and anabolic (primarily protein building in muscle and bone). As the effects of AAS on fetal development, pre-adolescents and females add greatly to the complexity of the topic, this article is restricted to the effects of AAS on post-pubescent males.

### Skeletal Muscle, Testosterone And Hypertrophy

The effects of AAS on specific tissue-types (fat cells versus muscle versus brain, etc.) depend in part on how that tissue enzymatically processes androgens and whether a particular AAS is protected against such enzyme "attacks."<sup>6</sup> In tissue related to the reproductive system, testosterone acts as a prohormone, being converted to the more androgenic DHT by the enzyme 5-alpha-reductase, as happens in the prostate; similarly, testosterone is converted to estradiol (an estrogen) in breast tissue and fat cells by the enzyme aromatase. Many tissues convert testosterone into both DHT and estradiol (i.e., brain, bone).

However, the primary tissue of interest, relative to AAS use for physique or performance improvement, is skeletal muscle. Skeletal muscle includes the familiar biceps, pecs, quads and other muscles that aid in movement. Two other classes of muscle include smooth muscle, which is present in the gut and blood vessels, the second being cardiac (heart) muscle. AAS may affect these other two types, particularly the heart, but these effects are outside the scope of this article. Skeletal muscle does not contain detectable levels of 5a-reductase, but does have significant aromatase activity.<sup>7,8</sup> Thus, testosterone is the primary androgen responsible for muscle hypertrophy; the role of estrogen in skeletal muscle remains unknown at this time.

Testosterone affects the muscle cell by activating genomic and non-genomic targets. The genomic effects of testosterone involve the classically understood mechanism of testosterone entering the cytoplasm (the inside of the cell), binding with an androgen receptor (AR) and traveling together into the nucleus of the cell. Once in the nucleus, the testosterone-AR complex turns on or off specific genes (segments of DNA), resulting in muscle cell hypertrophy (growth). However, the genomic signaling is not so simple. Every cell contains varying concentrations of co-regulators which can promote or inhibit the ability of the testosterone-AR complex to activate genes.<sup>9</sup> Unfortunately, this is an area that is poorly understood, so until further research emerges, the relative importance of these co-regulators remains unclear.

Testosterone can also affect receptors and enzymes directly. Receptors imbedded in the membrane or in the cytoplasm can be activated by testosterone and have a near-immediate effect on cell function and behavior.<sup>10,11</sup> This is most evident in mating-related or risk-taking behaviors. Researchers at Lehigh University recently published a study demonstrating that the reflexive testosterone release of male mice in mating situations directly and rapidly increased arousal and mounting of a receptive female.<sup>12</sup> In other words, when a new, sexually receptive female was introduced into a male mouse's pen, his body produced a surge of testosterone that made him more quickly get aroused and mount the female. Additionally, reductions in anxiety and pain perception have been reported, as well as increases in behavior-reward association.<sup>13</sup> This effect has not been as directly measured in humans, but advertising executives have been aware of a similar phenomenon in men for centuries. Sociologists and neurologists have confirmed that men will take greater sexual and financial risks (i.e., failing to use a condom, gambling) when sexually aroused or even when simply presented with an erotic image.<sup>14,15</sup>

Clearly, the near-immediate response seen in such situations and replicated by injecting a rapidly available form of testosterone in mice, requires a much faster mechanism than the genomic effects of testosterone provide.<sup>16</sup> Genomic changes take hours to days to manifest, while non-genomic take seconds to minutes.

A third avenue by which AAS appear to promote muscle growth is by inhibiting the catabolism (muscle wasting) caused by cortisol and other glucocorticoids. The balance between anabolism (muscle building) and catabolism (muscle wasting) is generally attributed to the testosterone-cortisol ratio; of course, there are many other factors involved.<sup>17</sup> Testosterone is generally considered to promote anabolism, while cortisol promotes catabolism. However, there is some research supporting the idea that testosterone may also reduce catabolism, either by attaching to the glucocorticoid (cortisol) receptor and blocking the catabolic effect or reducing the concentration of glucocorticoid receptors by turning down the “manufacturing” signal from the nucleus (DNA).<sup>5</sup>

### Chemical Structure Of AAS

AAS differ from testosterone by minor changes in the chemical structure that can dramatically affect the absorption, androgenicity, metabolism, receptor affinity, conformation of the AAS-AR complex and potency of each specific AAS. Testosterone is not a drug that can be taken orally because it is rapidly degraded and eliminated by enzymes in the intestines and liver.<sup>18</sup> However, when the 17-carbon is bound to a small carbon chain (17 $\alpha$ -alkylation), the AAS is protected from these enzymes. Unfortunately, 17 $\alpha$ -alkylated AAS are associated with liver damage and potentially life-threatening tumors, as well as negative changes in (good) HDL cholesterol.<sup>19</sup> Certain AAS will place a double-bond at the 1-carbon which provides some, but less, protection from degradation. The prototypical oral AAS, Dianabol, combined with the use of 17 $\alpha$ -alkylation and a 1-carbon double bond; oral-turinabol, the AAS most commonly used by East Germany during their era of Olympic dominance, adds a chlorine to the 5-carbon, conferring further protection. Certainly, there are many other possible modifications but these represent the more commonly encountered oral AAS. The effects of oral AAS are short-lived, as they are cleared in a matter of hours.

Common injectable AAS are naturally produced androgens (testosterone, nortestosterone, boldenone) that are bound to a fatty acid by an ester bond at the 17-carbon. Rather than protecting against enzymes, as the 17 $\alpha$ -alkylated AAS are, the 17 $\beta$ -esters merely increase the time that the bound AAS remains in an oil globule, after injection, before it circulates through the body. Once an AAS-ester hits the bloodstream, the fatty acid is rapidly split off by enzymes called esterases. A long fatty acid makes the AAS more lipid-soluble and it will disperse from the injected oil depot more slowly (days to weeks). Without the addition of an ester, injected testosterone will clear the system in a matter of hours.

AAS can also be placed into gels or patches containing permeation-enhancers that allow the AAS to be absorbed across the skin or the gum/cheeks of the mouth.<sup>20</sup> Intranasal testosterone is also being developed, as the lining of the nose and airways is also an effective site for absorption.<sup>21</sup> AAS absorbed across skin or mucosa does not need to be modified. Transdermal and mucosal testosterone do not maintain elevated concentrations for long after the application (patch, gel or spray) has been removed. Thus, they are applied daily.

In the body, the various AAS do not provide identical responses to testosterone or each other. The major differences are generally believed to be due to whether the AAS used can be converted into estrogen via the aromatase pathway, DHT via 5 $\alpha$ -reductase, both or neither.<sup>6</sup> Even the non-steroidal SARMs (meaning they are not based upon testosterone) being developed by numerous pharmaceutical companies (still) seeking to dissociate anabolic from androgenic effects are believed to be less androgenic, because they are not affected by 5 $\alpha$ -reductase.<sup>6</sup> Drugs that 5 $\alpha$ -reductase can convert are typically changed into more androgenic metabolites, leading to hair loss, acne and prostate enlargement. 19-Nortestosterone (nandrolone, Deca) is the exception to this rule, as it actually converts to a less androgenic compound.<sup>22</sup> AAS that can be 5 $\alpha$ -reduced typically provide less dramatic mass and strength gains, may be associated with joint pain, but tend to result in "higher quality" gains, as there is little water retention and fat loss appears to be enhanced.

AAS that can be aromatized tend to provide greater mass and strength gains, but also predispose users to increased water retention and fat gain. These effects could logically be anticipated, as skeletal muscle does not contain 5 $\alpha$ -reductase but does produce aromatase, suggesting that the more androgenic DHT is not the preferred anabolic androgen, rather testosterone appears to be so. Also, the encoded production of estradiol in muscle suggests that aromatizable AAS provide supplementary stimuli, promoting growth that would not be generated by 5 $\alpha$ -reduced or poorly aromatizable AAS. In fact, the poorly aromatizable 19-nortestosterone (Deca) provides lesser mass and strength gains than testosterone despite having a much higher anabolic:androgenic ratio.

#### Nuclei: The "Foreman" Of Muscle Growth

It is also important to note the difference in effect of various AAS at non-skeletal muscle tissue. Satellite cells are stem-cell like in that they allow for the growth of muscle tissue. Rather than increasing cell number though, satellite cells enter existing skeletal muscle cells and add to the number of nuclei. This makes little sense at first, as one would think the addition of more muscle cells would be of greater benefit than cells with more than one nucleus, especially since nearly every other cell in the body has only one nucleus (the DNA center). However, it has been shown that skeletal muscle size is directly related to the number of nuclei present in a cell; more so, the nuclei function best if they are located in the center of the cell.<sup>23</sup> When satellite cells add nuclei to the skeletal muscle cell, the potential for growth is increased. Confusing as this is, consider each nucleus a foreman who can only manage 10 laborers; if a company wants to increase production, it cannot simply add more laborers but must also add foremen. Thus, for every additional foreman, the company can grow by 10 more laborers. Without adding foremen, the additional laborers would not know what jobs to perform and the company would not grow.

Satellite cells exist between muscle fibers, but do not migrate into muscle cells without being prompted by mechanical and hormonal signals, such as weight training and AAS. Satellite cells come from a pool of even more primitive cell types, referred to as pluripotent stem cells. This long term describes cells that can become more than one type of cell. In this specific case, these pluripotent stem cells can become skeletal muscle or fat cells. To no one's surprise, when exposed to threshold concentrations of testosterone or certain other AAS, pluripotent stem cells begin the process of becoming myogenic (meaning progressing toward becoming skeletal muscle) as opposed to adipogenic (or becoming fat cells). Thus, in an environment of higher androgen:estrogen presence, changes in the stem cell pool would promote muscle growth and reduce the predisposition toward gaining fat.<sup>24</sup>

Many people find it difficult to understand the relevance of AR (androgen receptor) binding, as AAS with a higher AR-affinity (meaning how tightly they connect with the androgen receptor) are not necessarily more potent at promoting anabolic or androgenic effects. DHT has a higher AR-affinity than testosterone, but is less effective at promoting muscle

growth; 19-nortestosterone has a higher affinity than testosterone, but is less effective in generating androgen-based changes in the prostate. In part, this may be due to the co-regulators mentioned earlier. Very few of these co-regulators have been identified and none are well understood. In each type of tissue (prostate, skeletal muscle, skin, heart, etc.), there are different co-regulators, accounting for many of the differences seen among various tissue types.<sup>25</sup> The co-regulators attach onto the AAS-AR complex and help or hinder the complex attaching onto and activating the androgen-sensitive genes in the DNA.<sup>26</sup> To attach onto the AAS-AR complex, the co-regulators look for a specific shift in the shape of the molecule, anticipating the openings that would be present if testosterone or DHT combined with the AR. When a synthetic AAS attaches, the AAS-AR may not shift completely, failing to generate the necessary opening for the co-regulators.

In the absence of a complete AAS-AR-co-regulator complex, the genes may not be stimulated to the same degree, if at all. As a number of genes are turned on by testosterone-AR, the possibility exists that changes may be seen in certain genes being activated while others proceed as if the AAS is a completely natural hormone. As stated, this is an area just beginning to be understood and will undoubtedly provide future advancements in this area.

### All AAS Are Not Created Equal

In summary, though the class of drugs is primarily based upon the male sex hormone testosterone, AAS cannot be viewed as simply substituting or even increasing the natural production of testosterone. Testosterone, which is regulated through a negative feedback system (meaning if too much is produced, the manufacturing signal from the brain is reduced), pulses throughout the day several times, giving a peak-and-valley rhythm, with highs being two to three times the lows.<sup>27</sup> Testosterone can be converted into metabolites with greater estrogenic or androgenic properties, depending upon the tissue the hormone reaches. Once the signal has been generated, the body deactivates and clears these hormones to ready the body for the next signal. These signals can be rapid, acting through non-genomic pathways, directly altering receptor sensitivity, enzymes or ion channeling; such actions occur in seconds to minutes and do not always require the androgen to enter the cell. Slower but more permanent responses are typically generated when testosterone (or a metabolite) combines with an androgen receptor, the pair then connecting co-regulators present in the cell before traveling to the cell nucleus (DNA center) where specific genes are activated or suppressed. Testosterone may also partially block the catabolic response to cortisol by competing with the glucocorticoid receptor or reducing a cell's production of glucocorticoid receptors.

When minor alterations are made to testosterone (or related steroids), these changes affect how the body processes and responded to the drug. AAS can be taken orally if protected against the "first-pass clearance" of the liver and intestines, provide elevated concentrations for weeks to months when injected as a long-chain ester, or absorb across the skin or mucosal membrane of the mouth or nose. AAS are reliably anabolic, but the effects vary depending upon the drug used. Some carry significant androgenic potential, possibly leading to hair loss or urinary retention; others are more estrogenic and may stimulate the growth of breast tissue in men or promote water retention and fat gain. Skeletal muscle is stimulated rapidly but the majority of anabolic processes are based upon the activation of growth-promoting genes in the cell nucleus.

AAS must bind with the androgen receptor and combine with co-regulators to generate this anabolic stimulation. However, if the chemical changes made to the AAS alter the shape of the androgen receptor significantly, then the co-regulators may not be able to effectively combine with the AAS-AR complex and gene stimulation may be reduced or fail. Maximal skeletal muscle growth cannot be achieved unless the cell incorporates additional nuclei, which are provided by satellite cells. Satellite cells are prompted to combine with muscle cells under the influence of androgens and other cell factors produced by exercise. Satellite cells arise from pluripotent stem cells, which can become either fat cells or muscle cells. In an androgen-rich environment, pluripotent stem cells are influenced toward muscle development and away from fat development. This may account for some of the "cutting" effect seen with non-aromatizable AAS.

Clearly, there is much to digest in this article, but also a recognition of much still to be learned. Unquestionably, all AAS

are not created equal and the tendency for regulators, researchers and the media to regard all AAS as the same is dangerous and misguided. As with any class of drug, simple molecular changes can result in drastically different responses and unanticipated benefits or risks. Science and athletes should each take heed of the lessons learned by the other to better direct future research. There are benefits and risks in using AAS. Until more specific information arises, the use of these agents should be monitored closely by health care professionals. Certainly, there are benefits to individuals and society in treating the relatively common androgen deficiency seen in adult males. Whereas testosterone replacement therapy will likely remain the cornerstone of such therapy, there is likely a place for the directed use of specific AAS, such as 19-nortestosterone. Recreational users and those involved in sports doping should approach the decision to use AAS with appropriate caution from a "health" point-of-view, recognizing also the social and legal consequences of illicit use.

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