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Review

The neurobiology and addiction potential of anabolic androgenic steroids and the effects of growth hormone

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ABSTRACT

Anabolic androgenic steroids (AAS) are substances that mimic the hormone testosterone, and primarily act via the androgen receptor. In addition to their physiological effect on muscle tissue and growth, research from the last decade has shown that AAS have a pronounced impact on the central nervous system. A large number of studies have demonstrated that AAS affect the mesolimbic reward system in the brain. However, whether the direct effects of AAS on endorphins, dopamine, serotonin and GABA *etc.* and on the corresponding and related systems lead to dependence needs to be further elucidated. According to recent studies, the prevalence of AAS dependence among AAS users has been estimated to be approximately 30%, and polysubstance use, of both pharmaceutical drugs and narcotics, within this group is common. The present review primarily discusses AAS in the context of addiction and dependence, and further addresses the issue of using multiple substances, *i.e.* stimulants and opiates in combination with AAS. In addition, aspects of the treatment of AAS dependence, the connection between AAS abuse and cognition, and AAS-induced neurotoxicity are presented. Currently, performance enhancing drugs are frequently used in combination with AAS. Therefore, a large section on growth hormone and insulin-like growth factor is also included.

Contents

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1. Introduction

Doping and the use of anabolic androgenic steroids (AAS) were previously associated with sports and athletes. However, in recent decades the use of AAS has also spread outside the area of competitive sports. Young adults, usually in their 20s (Cohen et al., 2007; Pope et al., 2014a, 2014b), use AAS for different reasons. The estimated use in society varies between 1 and 5% depending on the age-group studied (Pope et al., 2014a; Thiblin and Petersson, 2005). In certain sub-populations, such as body-builders or the prison population, the prevalence is reported to be much higher and accounts for approximately 10% (Korkia and Stimson, 1997; Korte et al., 1998). Overall, AAS users can be classified into three groups; athletes, aesthetes, and those who use AAS to improve self-esteem and become braver (Brower et al., 1989; Kindlundh et al., 1998). All three groups aim to increase strength and body size, however, the reasons for using AAS may differ. While athletes aim to perform better in their specific sport, the aesthetes are more focused on their appearance. The last group are more prone to aggressive behaviour, and are in many cases criminals using steroids. Using drugs to achieve certain goals has been suggested as a concept of "drug instrumentalization" (for a review see: (Muller and Schumann, 2011)). Similar instrumentalization goals can be found when studying non-addictive drug use of psychoactive drugs. For example, the goal may be to change a present mental state or to perform better at a certain task (Muller and Schumann, 2011).

There are several different ways to administer AAS. The most common method is to administer the steroids in cycles 2–3 times per year, each cycle lasting 6–18 weeks. The cycles are followed by recovery periods in order to restore the suppressed hypothalamic-pituitary-adrenal (HPA) axis. This may take weeks to months depending on the length of the cycles and the type of steroid used. Both orally administered steroids and intramuscular administration are common and are usually combined over a period of weeks. An average cycle may contain 2–3 different steroids (Pope and Katz, 1994), where the doses are increased each week, a method termed 'stacking'. The stacking usually involves one or two depot steroids, such as nandrolone decanoate together with orally administered AAS. Nandrolone decanoate, which is a prodrug of nandrolone, is one of the most common steroids used, together with testosterone, trenbolone, boldenone, methandrostenolone, and stanozolol (Eklof et al., 2003; Pope et al., 2014b), see Fig. 1. In addition to prodrugs of nandrolone, prodrugs of testosterone such as testosterone propionate, testosterone phenylpropionate, and testosterone undecanoate, are commonly used in different formulations, see Fig. 2.

In order to reduce AAS-associated side-effects and increase exercise efficiency, steroid users also combine AAS with other drugs. In fact, polysubstance use is common and has been reported in 50% of steroid users. In addition to drugs, many users take various pharmaceuticals (Skarberg et al., 2009). Some pharmaceuticals are applied to control the adverse effects of steroids, but others, such as growth hormones, are used as complements. Furthermore, stimulants are frequently used to increase the intensity of the exercise, increase endurance, and burn fat – thus maximizing the anabolic gains. These hard training programs can result in joint and muscle pain, which may lead to the use of opiate drugs. In fact, in the last decade, AAS have been reported to act as gateway drugs to opioid dependence (Arvary and Pope, 2000; Kanayama et al., 2003a).

2. Neurobiology

The classical genomic AAS signaling pathway involves binding to the androgen receptor (AR). In blood, approximately 98% of the testosterone is bound to the serum proteins, human sex hormone-binding globulin (hSHBG), and albumin, and only a small amount, 1–3%, is unbound (Dunn et al., 1981). The balance between unbound testosterone and protein-bound testosterone can be controlled by the levels of hSHBG. Albumin binds to testosterone with low affinity and the dissociation of the albumin-testosterone complex is fast, while testosterone binds strongly to hSHBG (Heinrich-Balard et al., 2015). Hence, unbound testosterone and albumin-bound testosterone, corresponding to approximately 40%, has been estimated to constitute a major source of the testosterone that is the physiologically active. As a lipid soluble substance, testosterone crosses cell membranes, including those forming the blood brain barrier, and is able to permeate neurons and other cells (Cornford et al., 1982). The AR is an intracellular receptor functioning as a ligand-activated transcription factor, and a member of the nuclear receptor family (Mangelsdorf et al., 1995). When AAS bind to the receptor, AR is transported from the cytoplasm to the cell nucleus, where it binds to a specific DNA element, *i.e.* the androgen response element, in target genes (Matsumoto et al., 2013). The AR is mainly expressed in androgen target tissues, such as skeletal muscle, male and female reproductive organs, the adrenal gland, liver, and the central nervous system (CNS). In the CNS, AR is widely expressed and is most abundant in regions such as the amygdala, hippocampus, and hypothalamus (Simerly et al., 1990). Another important aspect is that some AAS are aromatized to estrogens and these metabolites exert their effects via estrogen receptors. For example, the A-ring of testosterone is aromatized, delivering estradiol, a compound with estrogen activity, see Fig. 3. However, not all AAS are good aromatase substrates. Compared with testosterone, nandrolone, which lacks the 19-methyl group, is five times less prone to serve as a substrate to aromatase and to undergo aromatization. Consequently, the administration of nandrolone leads to fewer estrogen related side-effects. Hence, the steroid structure determines the degree of aromatization and eventually the level of the adverse physiological outcomes that are attributed to interactions with the estrogen receptors.

In addition to the slow-onset genomic effects, numerous studies have suggested that AAS can induce rapid, non-genomic effects (Matsumoto et al., 2013). AAS have been demonstrated to induce rapid increases in intracellular calcium concentrations in various cell types, such as skeletal muscle cells, cardiac myocytes, and neurons (Vicencio et al., 2011). A cell membrane-bound AR has been suggested as a mediator of transcription-independent AAS effects (Matsumoto et al., 2013), and experiments using membrane-impermeable AAS, *e.g.* bovine serum albumin (BSA)-conjugated AAS, have demonstrated that some AAS actions are restricted to cell-surface receptors (Sato et al., 2010). AAS have also been demonstrated to interact with other receptors. For example, studies have demonstrated the allosteric modulation of gamma-aminobutyric acid type A ($GABA_A$) receptors by AAS (Oberlander et al., 2012). In addition, G-protein coupled receptors have been suggested as pos-