Steroids 75 (2010) 377–389

Contents lists available at ScienceDirect

Steroids

journal homepage: www.elsevier.com/locate/steroids

Review

# Tissue selectivity and potential clinical applications of trenbolone (17β-hydroxyestra-4,9,11-trien-3-one): A potent anabolic steroid with reduced androgenic and estrogenic activity

Joshua F. Yarrow[a,b,*], Sean C. McCoy[a,b], Stephen E. Borst[a,b]

[a] Geriatric Research, Education & Clinical Center, VA Medical Center, Gainesville, FL 32608, United States
[b] Department of Applied Physiology & Kinesiology, University of Florida, Gainesville, FL 32611, United States

ARTICLE INFO

*Article history:*
Received 11 August 2009
Received in revised form 21 January 2010
Accepted 26 January 2010
Available online 4 February 2010

*Keywords:*
Androgen
Testosterone
SARM
Muscle
Bone
Adipose

ABSTRACT

Recently, the development of selective androgen receptor modulators (SARMs) has been suggested as a means of combating the deleterious catabolic effects of hypogonadism, especially in skeletal muscle and bone, without inducing the undesirable androgenic effects (e.g., prostate enlargement and polycythemia) associated with testosterone administration. 17β-Hydroxyestra-4,9,11-trien-3-one (trenbolone; 17β-TBOH), a synthetic analog of testosterone, may be capable of inducing SARM-like effects as it binds to androgen receptors (ARs) with approximately three times the affinity of testosterone and has been shown to augment skeletal muscle mass and bone growth and reduce adiposity in a variety of mammalian species. In addition to its direct actions through ARs, 17β-TBOH may also exert anabolic effects by altering the action of endogenous growth factors or inhibiting the action of glucocorticoids. Compared to testosterone, 17β-TBOH appears to induce less growth in androgen-sensitive organs which highly express the 5α reductase enzyme (e.g., prostate tissue and accessory sex organs). The reduced androgenic effects result from the fact that 17β-TBOH is metabolized to less potent androgens *in vivo*; while testosterone undergoes tissue-specific biotransformation to more potent steroids, dihydrotestosterone and 17β-estradiol, via the 5α-reductase and aromatase enzymes, respectively. Thus the metabolism of 17β-TBOH provides a basis for future research evaluating its safety and efficacy as a means of combating muscle and bone wasting conditions, obesity, and/or androgen insensitivity syndromes in humans, similar to that of other SARMs which are currently in development.

Published by Elsevier Inc.

**Contents**

1. Introduction ..... 378
2. Androgen receptor signaling ..... 378
3. Recent advances in SARMs ..... 379
4. 17β-TBOH metabolism ..... 379
   4.1. 17β-TBOH and 5α reductase ..... 380
   4.2. 17β-TBOH and aromatase ..... 380
5. Mechanisms of body growth ..... 380
   5.1. Effects of 17β-TBOH on skeletal muscle ..... 380
   5.2. Effects of 17β-TBOH on bone ..... 381

*Abbreviations:* 17 β-TBOH, trenbolone; 17 α-TBOH, epitrenbolone; 17β-$E_2$, estradiol; AR, androgen receptor; Akt, serine/threonine-specific kinase family; ACTH, adrenocorticotropic hormone; BMD, bone mineral density; $Ca^{2+}$, calcium; CSA, cross-sectional area; DHT, dihydrotestosterone; ER, estrogen receptors; ERK, extracellular signal regulated kinases; FZ, frizzled receptor; Frat-1, proto-oncogene protein of the GSK-3 family; FSH, follice stimulating hormone; GnRH, gonadotropin-releasing hormone; GNX, gonadectomized; GP, G-protein; GR, glucocorticoid receptors; GSK3, glycogen synthase kinase-3; HPG, hypothalamic-pituitary-gonadal axis; HRE, hormone responsive elements; IGF-1, insulin-like growth factor 1; IGF-1R, insulin-like growth factor 1 receptor; IR, ischemia reperfusion; LEF, lymphoid enhancer factor 1; LH, luteinizing hormone; MAPK, mitogen activated protein kinase; MEK, mitogen activated protein kinase or extracellular signal regulated kinases; PI3K, phosphatidylinositol 3-kinase; PLC, phospholipase C; Raf-1, family of protein kinases; SARM, selective androgen receptor modulator; SERM, selective estrogen receptor modulator; SR, sarcoplasmic reticulum; TBO, trendione; TCF, T-cell factor; VTG, vitellogenin.

* Corresponding author at: Malcolm Randall VA Medical Center, Research 151, Gainesville, FL 32608, United States. Tel.: +1 352 376 1611x6917; fax: +1 352 374 6142.
*E-mail address:* jfyarrow@ufl.edu (J.F. Yarrow).

0039-128X/$ – see front matter. Published by Elsevier Inc.
doi:10.1016/j.steroids.2010.01.019

5.3. Effects of 17β-TBOH on adipose tissue ..... 382
5.4. Erythropoiesis ..... 382
5.5. Potential adverse events associated with 17β-TBOH ..... 383
5.6. Potential androgen-mediated clinical side effects ..... 383
5.7. Disruption of hypothalamic-pituitary-gonadal axis ..... 383
5.8. Androgenization and teratogen activity ..... 383
5.9. Genotoxicity and cytotoxicity ..... 384
6. Conclusion – future research focus and potential therapeutic use of 17β-TBOH ..... 384
References ..... 384

## 1. Introduction

Testosterone, and its more potent metabolites, dihydrotestosterone (DHT) and estradiol (17β-$E_2$), are known to influence the development and maintenance of numerous tissues, including skeletal muscle [1], bone [2], adipose tissue [3], and sex-organs [4]. In males, reduced testosterone (i.e., hypogonadism) induces losses in skeletal muscle mass and bone mineral density (BMD) and increases adiposity [5]. However, administration of testosterone at replacement doses results in only minor improvements in skeletal muscle mass and strength in hypogonadal older men [6]. In contrast, administration of supraphysiological doses of testosterone results in robust increases in skeletal muscle mass and BMD and reductions in adiposity in both humans [7–18] and animals [19–21], but also results in a variety of adverse events, of which prostate enlargement and polycythemia appear to be most prevalent [22]. Alternative pharmacological treatments such as selective androgen receptor modulators (SARMs) [23] or combined treatment with high-dose testosterone plus 5α reductase inhibitors (e.g., finasteride or dutasteride) [7,19,20,24] have been proposed as a means of producing the desired anabolic effects with a lower incidence of adverse effects. Our main objective is to review current research related to the potent anabolic steroid 17β-hydroxyestra-4,9,11-trien-3-one (trenbolone; 17β-TBOH), especially its SARM-like properties that may make it beneficial for the treatment of several clinical conditions [25,26]. Additionally, we will offer brief overviews on androgen signaling and on the recent developments with SARMs.

## 2. Androgen receptor signaling

Classical, or genomic, androgen signaling begins with binding of testosterone or DHT to cytosolic androgen receptors (ARs) and ultimately results in altered gene expression. Most of the familiar effects of androgens on muscle, bone, and male sexual development are genomic effects which require the synthesis of new protein; thus, they may take days to months to manifest. More recently, rapid non-genomic testosterone signaling has been discovered [27] which is mediated by cell-surface, G-protein (GP) coupled receptors [28]. An example of non-genomic signaling is the rapid, testosterone-induced release of calcium ($Ca^{2+}$) from intracellular stores occurring in mouse IC-21 macrophages [28]. The non-genomic, actions of testosterone are not inhibited by classical androgen blockers such as cyproterone and flutamide, suggesting that the genomic and non-genomic effects of androgens may be quite different. For example, we [29] and others [30] have shown that long-term administration of testosterone to male rats confers cardioprotection against ischemia/reperfusion (IR) injury. However, when testosterone is added *in vitro* to the working heart preparation, it worsens IR injury [31].

The genomic effects of androgens occur through two distinct pathways. In the first pathway, binding of androgens to cytosolic ARs cause ARs to translocate to the nucleus and bind to chromosomal DNA as homodimers [32] (Fig. 1). The specific regions of DNA that bind ARs are called hormone response elements (HREs) and they regulate the transcription of specific genes, producing androgenic effects. In the second pathway, the actions of androgens are mediated by interaction of ARs with the Wnt/β-catenin pathway. Wnts are a family of secreted glycoproteins that regulate differentiation in a wide variety of tissues. Canonical Wnt/β-catenin signaling involves binding of Wnt to the cell-surface frizzled receptor (FZ), which through its interactions with Axin, Frat-1 and Dsh, results in the inhibition of glycogen synthase kinase-3 (GSK3). GSK3 phosphorylates β-catenin, marking it for proteasomal degradation. As a result, inhibition of GSK3 results in the accumulation of β-catenin in the cytosol and increased translocation of β-catenin into the nucleus, where it interacts with transcriptional regulators to alter gene expression [33]. It is hypothesized that androgen signaling bypasses the canonical Wnt pathway by interacting with downstream Wnt effectors [34] to stimulate the commitment of mesenchymal pluripotent cells to the myogenic line and to inhibit their commitment to the adipogenic line [3]. By this mechanism, androgens increase the number of muscle satellite cells [35]. In culture, androgens have been shown to induce translocation of β-catenin to the nucleus in mouse 3T3 preadipocytes and inhibit their differentiation into mature adipocytes [34]. Wnt/β-catenin signaling has also been implicated in androgen-induced masculinization of external genitalia [4].

The metabolism of testosterone also plays an important role in its actions. Testosterone may be converted to DHT by either 5α reductase isoenzyme [36] and to 17β-$E_2$ by aromatase [37]. Tissues expressing 5α reductase include the prostate, testes, accessory sex organs, beard and scalp, sebaceous glands, liver, brain, and skin [38] and in these tissues the effects of circulating testosterone are amplified by two known mechanisms. First, DHT has an approxi-

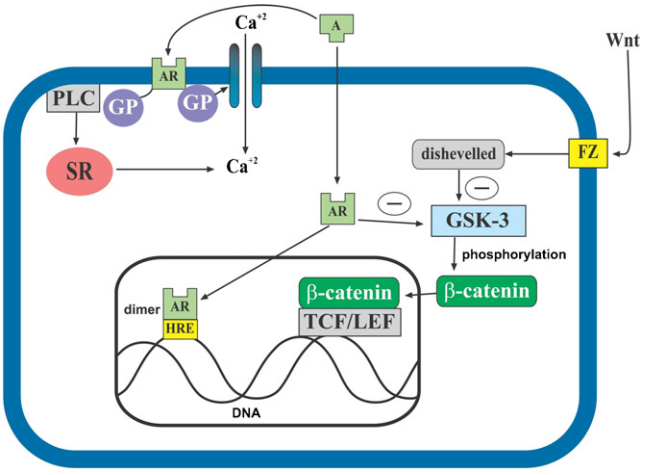


**Fig. 1.** Androgen receptor signaling pathways. A = androgen, AR = androgen receptor, $Ca^{2+}$ = calcium, FZ = frizzled receptor, GP = G protein, GSK-3 = glycogen synthase kinase 3, HRE = hormone response element, PLC = phospholipase C, SR = sarcoplasmic reticulum, TCF = T cell factor, LEF = lymphoid enhancer factor 1, Wnt = Wingless-Int.

Download English Version:

https://daneshyari.com/en/article/10847729

Download Persian Version:

https://daneshyari.com/article/10847729

Daneshyari.com