Renal Heat Shock Proteins Over-Expression Due to Anabolic Androgenic Steroids Abuse

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Abstract: Chronic use of anabolic adrogenic steroids (AAS) has been known to cause serious adverse effects. While the effects of AASs on cardiovascular system are well known, toxicity on other organs has received less attention. A dose-related nephrotoxic effect has been proposed and a wide variety of morpho-functional damages have been observed, but , the exact pathophysiological mechanism of action is still not well known. In the present minireview, we highlight the remaining issues through an analysis of the pertinent literature. As with HSPs toxic agents their overexpression could be considered a protective reaction against AAS abuse however, comprehensive studies concerning the whole range of Hsps/chaperones expressions in all organs after long term use of AAS are needed.

Keywords: Anabolic androgenic steroid, double contour membrane, fibrinogen, focal segmental glomerulosclerosis, heat shock protein, nephrotoxicity.

INTRODUCTION

Anabolic-androgenic steroids (AAS) are used as ergogenic aids by athlete and non-athletes to enhance performance by increasing muscular development and strength [1,2]. Their use began in 1950s with muscular exercise athletes and bodybuilders. Since then, structural and pharmacokinetic properties have been reviewed extensively. The mechanism of action of all AAS is similar to all other steroid hormones in that they bind, in target tissues, to an intracellular protein, known as androgen receptor, to form an androgen receptor complex in the cell nucleus. This steroid-receptor complex binds to palindromic DNA sequences, and specifically, to hormone response elements (HRE). This process initiates gene transcription and the consequent synthesis of mRNA from DNA in the cell nucleus, and synthesis of chaperone proteins. In addition, supraphysiologic doses of nandrolone decanoate enhance the production of the inflammatory cytokines interleukin-1beta (IL-1β) and tumor necrosis factor-α (TNF- α) in human peripheral blood lymphocytes cultures *in vitro* [3]. Chronic use of AASs has been known to cause serious adverse effects (virilization, feminization, liver disorders, neuropsychiatric disorders, adverse blood lipid profiles, cardiovascular complications) [4,5]. Damages to renal structures and function have received less attention.

AAS AND KYDNEYS

A dose-related nephrotoxic effect of AAS has been proposed and a wide variety of renal morpho-functional damages have been observed; however the exact pathophysiological mechanism of action is still not completely known.

Athletes who practice weightlifting or body building often experience an elevation in serum creatinine as a result of an increase in mass of skeletal muscle, as well as increased nitrogen and uric acid in blood and urine. Diets high in protein are often associated with AAS use and cause marked changes in renal hemodynamics, both acutely and chronically. Protein ingestion seems to cause an increase in renal blood flow and glomerular filtration rate by a variety of mechanisms. In all cases, improvements in renal conditions have been observed in patients after discontinuation of anabolic steroids [6,7].

Renal abnormalities related to the use of anabolic steroids in supra-physiologic dose are still not well described. Although the potential effects of AASs on renal function have not been well characterized in humans, several studies suggest that androgens may exert a direct toxic effect on glomerular cells, leading to mesangial matrix accumulation and podocyte depletion independent of structural functional adaptations.

Few animal model studies have been conducted in order to evaluate the impact of AAS supraphysiological doses on kidneys, and human studies still fail to clearly establish a direct cause-effect relationship between AAS abuse and renal injury [8,9,10].

Men are known to be at an overall increased risk for renal disease compared to women and prognosis in men is worse for various types of chronic kidney diseases; the basis for these sex-related differences are under investigation, and there is mounting evidence that androgen may play a central role in both normal and diseased kidney function and that estrogens are protective [11].

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Acute kidney injury (AKI) associated with anabolic steroid use is rare and only a few case are reported in the medical literature and the pathophysiology as well as clinical presentation are still not well known [12,13]. Rhabdomyolysis has also been linked to the possible pathophysiology of anabolic steroid abuse-induced acute kidney injury [14].

Focal segmental glomerulosclerosis (FSGS) has been associated with AAS long term use. The pattern of glomerular injury observed, involved scarring of the glomerules mediated by elevated glomerular filtration rate (hyperfiltration), glomerular pressure and other adaptive structural-functional responses within the kidneys [11]. It has been also reported that non-obese individuals with increased body mass index owing to elevated muscle mass are susceptible to developing secondary FSGS [15].

Severe nephritic alterations with nephrosclerosis, obstructive lesions of preglomerular vessels, glomerulosclerosis and diffuse tubule interstitial damages, in body builders abusing high doses of Deca-Durabolin have also been described [16]

Cholestasis and hyperbilirubinemia induced by the use of AAS has been proposed as a possible cause of acute renal failure in some cases [19,20,21]. Disorders in the liver, the major site for detoxification of steroids and other xenobiotics can hinder its performance and hence worsen the renal conditions due to elevated level of circulating toxins.

A case of severe nephritic syndrome with diffuse membrano-proliferative glomerulonephritis in an athlete who took creatine and AAS for prolonged periods has been reported [13].

Experimental model on rats proposed by Zeier *et al.* documented abnormal histological changes in the kidneys in the form of glomerular atrophy and dilatation of distal tubules after steroid abuse [10] while other authors reported abnormal dilatations of the proximal and distal convoluted tubules [8].

In our experimental model with trained mice treated with high doses of AAS, we observed focal cytoplasmic vacuolization of epithelial cells combined with the of presence of a PAS positive "double contour" membrane, as observed in case of type I membranoproliferative-glomerulonephritis or IgA nephropathy.

In regard to the mechanism of action, it has been proposed that the toxic effects induced by abusing anabolic drugs for long period on the target organs develop through the accumulation of certain toxic metabolites of testosterone (17alfa-19nortestosterone and 17alfa-testosterone) [22].

Furthermore it has been reported that some types of anabolic steroids are able to induce massive necrosis and damages in the target organs in the form of chromatin condensation, DNA strand breakage and cytoplasmic shrinkage [23].

Other investigators believe that abusing anabolic androgenic drugs cause cellular damages in the target organs such as the kidneys by damaging the DNA structure or mitochondria. Finally, a genetic correlation between use of anabolic androgenic steroids and renal disorders has been proposed [24,25,26].

HEAT SHOCK PROTEINS: AN OVERVIEW

Cells are exposed during their life to a number of stressors: chemical, physical, mechanical, biological, etc, from which they defend through a class of molecules, highly conserved during evolution, called Heat shock proteins (HSPs). These are classified in several groups, depending on their molecular weight (i.e. Hsp90: 90kDa; Hsp70: 70 kDa, etc), and each of these groups includes a number of different molecules. Moreover, they are ubiquitous in cells and tissues, being present in all compartments (nucleus, cytosol, reticulum, mitochondria, membrane, etc) as well as in intercellular *milieu*. Indeed, HSPs may be released actively from the cell, by conventional and unconventional mechanisms, thus reaching also the bloodstream. Outside cells, HSPs may be involved in modulating paracrine effects, as well as in eliciting immune responses by both direct and indirect mechanisms that include their recognition of membrane receptors present on cellular surfaces [27,28].

Many HSPs are able to protect cells from protein denaturation, defolding and precipitation; at the same time, they are involved in assessing the correct folding of nascent polypeptides and in protein traffic inside the cell. For these reasons, many HSPs belong also to the family of "molecular chaperones". In particular, there is a functional system, called "chaperoning system", that includes all chaperones of our body and that has a role in human cell and tissue homeostasis from embryo/foetal life through adult to old age, thus being involved in the mechanisms of cell senescence. Hence, chaperonology is nowadays an emerging area of science and the importance of this field of research lies in the fact that defective chaperones can contribute to the pathogenesis of a number of diseases, now referred as chaperonopathies. Particularly, chaperonopathies can be genetic or acquired, and both are quite common in humans [29].

Some sources of stress that induce their overexpression may also provoke a series of post-translational modifications that underlie their localisation in non-canonical cell compartments, as well as their extrusion outside cells. Finally, empirical evidence suggests that the appearance of defective chaperones may cause the initiation and progression of age-associated pathological manifestations affecting cellular processes, called "chaperonopathies of aging".

Hence, despite their protective roles in cells and tissues and their importance for cell survival, molecular chaperones are also involved in the pathogenesis of a number of disorders. A new challenge nowadays is to understand in which pathologies they are active players rather than innocent bystanders [30,31].

The nephrotoxicity of many agents is well known (intravenous contrast agents, nephrotoxic antibiotics, heavy metals, or a variety of chemotherapeutic agents). The mechanisms of cytotoxicity appear to differ for these insults and include: direct toxic effects to renal epithelial cells,

vasoconstriction leading to significant cellular ischemia, damage to mitochondria, protein denaturation, renal epithelial cell apoptosis and necrosis. Several studies also demonstrated that molecular chaperones increase cytoresistance to nephrotoxic injury.

The ability of Hsp72 to regulate cisplatin-induced apoptosis is well described [32,33,34]. An increase in Hsp70 content may alter the prognosis for renal cell carcinomas [35], perhaps by altering the sensitivity of cancer cells to chemotherapeutic drugs [36].

Exposure to gentamicin, a nephrotoxic antibiotic known to cause acute tubular necrosis, induces the expression of renal molecular chaperones. Increased expression of Hsp47 and Hsp73 was observed in rat kidneys after subcutaneous injection of gentamicin. Accumulation of Hsp47 was maximal at day 3, and developed several days after the appearance of acute tubular necrosis. In contrast, Hsp73 accumulated rapidly within lysosomes of damaged proximal tubular epithelial cells after gentamicin exposure, suggesting that this chaperone may facilitate lysosomal protein degradation [37].

Heavy metals such as mercuric or cadmium chloride cause marked toxicity to renal cells and also induce the synthesis of molecular chaperones. Although heavy metals cause protein denaturation, a potent stimulus for chaperone induction, it has been also observed as a response to either mitochondrial injury or the protein-damaging effects of hydrogen peroxide, and molecular chaperones. An increase in the de novo synthesis of both Hsp72 and Hsp90 was observed in slices of rat kidney after heavy metal exposure [38].

Stress proteins may be an important component of resistance to glomerular injury and, infact, the presence of constitutive and inducible stress proteins has been demonstrated in animal kidneys with experimental glomerulonephritis [39,40,41].

Mesangial cell proliferation is an important precursor of glomerular dysfunction. It has been proposed that mesangial cells produce only a trivial amount of Hsp70 under basal status but a marked increase in response to certain disease status such as puromycin aminonucleoside-induced nephrosis. It has been demonstrated that mesangial cells play a major role in the production of HSPs in response to certain stress.

In the presence of oxidative injury of mesangial cell, the protective role of Hsp70 include: prevention from protein degradation membrane lipid peroxidation or calcium intrusion from the extracellular milieu, maintenance of ATP levels, induction of classic scavengers such as superoxide dismutase (SOD) glutathione, inhibition of any of the multiple steps involved in oxidative injury-mediated cell death such as uncoupling of oxidative phosphorilation, a decrease in calcium ATPase activation, activation of phospholipase A_2 or maintenance of a normal cellular structure [42].

HEAT SHOCK PROTEINS AND AAS NEPHROTOXICITY

AASs related nephrotoxicity has been only recently investigated [11]. FSGS has been proposed as a peculiar damage to kidneys after long term use of anabolic androgenic steroids. Herlitz *et al.* indicated post-adaptive FSGS secondary to muscular hypertrophy in athletes abusing AASs (and creatine) as the mechanism for nephrotoxicity. Postadaptive forms of FSGS are usually due to structural-functional adaptations driven by increased hemodynamic stress on the glomerulus. Animal models suggest that podocyte depletion plays a key role in postadaptive models of FSGS [43]. Increased body mass requires an increase in glomerular filtration. In an attempt to meet these demands, individual glomeruli adapt to hyperfiltration through hypertrophy. Podocytes are terminally differentiated cells that cannot proliferate, and in conjunction with compensatory glomerular hypertrophy, podocyte connections to the glomerular basement membrane (GBM) become mechanically strained. If these conditions persist, the podocytes eventually detach from the GBM, leading to development of a segmental scar [44]. Chronic hyperfiltration due to a high-protein diet may accelerate progression to glomerulosclerosis. Anyway, the clinical features and biopsy findings in Herlitz in cohorts , with relatively high incidence of full nephrotic syndrome, presence of collapsing or cellular lesions of FSGS, advanced fibrosis and glomerulosclerosis and the high degree of foot process effacement, implicate androgens direct nephrotoxicity , leading to mesangial matrix accumulation and podocyte depletion independent of structural functional adaptations. It has been supposed that androgens may increase androgen receptor expression on glomerular and mesangial cells as well as mRNA levels of the profibrotic cytokine TGF-β1thus providing a potent proapoptotic stimulus to podocytes and promoting FSGS [45, 46]. Androgens are also known to induce oxidative stress and upregulate components of the renin-angiotensin system [47, 48] (Fig. **1**).

It is well know that environmental stress leads to proteotoxic damage. Damaged, misfolded proteins bind to chaperones, and liberate the heat shock factor (HSF) from its chaperone complexes. HSF is activated and transcription of chaperone genes takes place [49, 50]. Susceptibility to various proteotoxic damages is mainly increased due to dysfunction of mitochondrial oxidation. Our experimental studies have confirmed overexpression on mesangial cells of Hsp90, Hsp70 and Hsp 27 with intensive perinuclear reaction, in trained mice treated with high doses of AAS.

CONCLUSION AND PERSPECTIVES

Abusing high doses of an anabolic androgenic drug for long periods can cause wide spread peculiar histological modifications of the normal kidneys structure which may lead to serious renal disorders such as renal failure in late stages. Despite this, the molecular mechanism of AAS direct toxic effect on kidney is still not completely understood. A great contribution could be provided in the future if the mechanisms explaining the meaning for HSPs

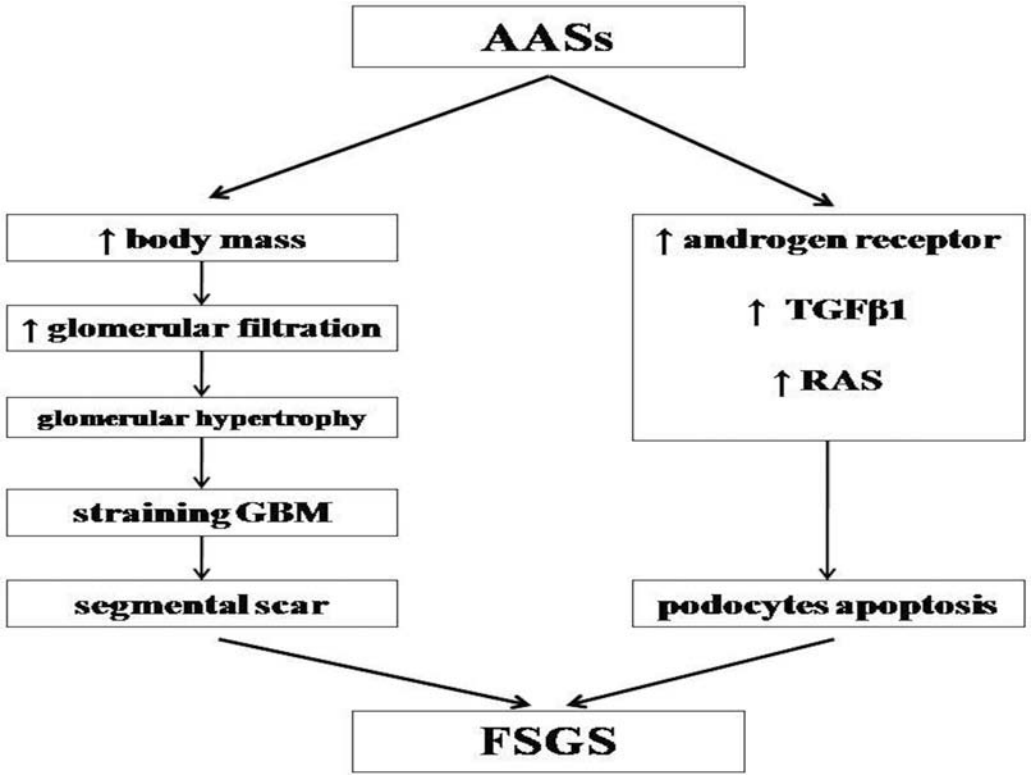

Fig. (1). AAS-related nephrotoxicity (FSGS). Postadaptive and direct renal damage. [FSGS. Focal segmental glomerulosclerosis. GBM. Glomerular basement membrane. RAS. Rennin-angiotensin system].

overexpression after acute and chronic administration of AAS could be elucidated. The correlation between AAS-induced kidney alterations and HSPs over expression which we have reported, is consistent with empirical data, and more investigations are needed to determine if these molecules may have role in preventing and or treatment of complications related to toxic insults induced by AAS.

ABBREVIATIONS

AAS = Anabolic androgenic steroid abuse

FSGS = Focal segmental glomerulosclerosis

GBM = Glomerular basement membrane

Hsp = Heat shock protein

HSF = Heat Shock Factor

RAS = Renin angiotensin system

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