Journal of Steroid Biochemistry & Molecular Biology 145 (2015) 200–205

Contents lists available at ScienceDirect

Journal of Steroid Biochemistry and Molecular Biology

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

Review

Exercise and sex steroid hormones in skeletal muscle

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ARTICLE INFO

Article history:
Received 5 March 2014
Accepted 16 March 2014
Available online 3 April 2014

Keywords:
Sex steroidogenesis
Glucose metabolism
Sarcopenia
Aerobic exercise
Resistance training
Aging

ABSTRACT

Sex steroid hormones are secreted mainly by the ovary and testis and regulate diverse physiological processes in target tissues. Recent studies have shown that sex steroidogenesis-related mRNA and protein expressions, such as for 17β-hydroxysteroid dehydrogenase (HSD), 3β-HSD, 5α-reductase and aromatase cytochrome P-450 (P450arom) enzymes, are detected in the skeletal muscle, while testosterone, estradiol, and 5α-dihydrotestosterone (DHT) were locally synthesized in skeletal muscle from dehydroepiandrosterone (DHEA). Moreover, in animal and human studies, the sex steroidogenesis enzymes and sex steroid hormone levels in skeletal muscle are upregulated by acute and chronic exercise stimulation. The enhanced muscle sex steroidgenesis is associated with glycemic control via upregulation of muscle glucose transporter-4 (GLUT-4) signaling in obese and diabetic rats and with muscle mass and strength in older men. Thus, an exercise-induced increase of sex steroid hormone in muscle may positively impact age-related concerns such as life-related diseases and sarcopenia.

Contents

1. Introduction

Dehydroepiandrosterone (DHEA) is a precursor of sex steroid hormones and is converted to testosterone by 17β-hydroxysteroid dehydrogenase (HSD) and 3β-HSD enzymes [1]. To exert physiological actions through binding to androgen receptors, testosterone can be converted to 5α-dihydrotestosterone (DHT) by 5α-reductase enzymes [2]. Additionally, estrogens are converted from androgens as catalyzed by aromatase cytochrome P-450 (P450arom). Although sex steroid hormones are mainly produced and secreted by the ovary and testis and affect diverse physiological processes in target organs or tissues such as bones, liver, kidney heart and brain, we found that 3β-HSD, 17β-HSD, P450arom and 5α-reductase enzymes are expressed in skeletal muscle, and steroid hormones including testosterone, estradiol, and DHT were locally synthesized in skeletal muscle from DHEA *in vitro* and *in vivo* [3,4]. Furthermore, the mRNAs encoding these steroidogenic enzymes in women and their protein expression in men were recently detected in human muscle [5,6]. Thus, skeletal

Abbreviations: DHEA, dehydroepiandrosterone; HSD, hydroxysteroid dehydrogenase; DHT, 5α-dihydrotestosterone; P45-arom, aromatase cytochrome P-450; GLUT-4, glucose transporter-4; Akt, protein kinase B; PKCλ/ζ, protein kinase λ and ζ; MRI, magnetic resonance imaging; CT, computerized tomography; CSA, cross sectional area.

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http://dx.doi.org/10.1016/j.jsbmb.2014.03.009
0960-0760/

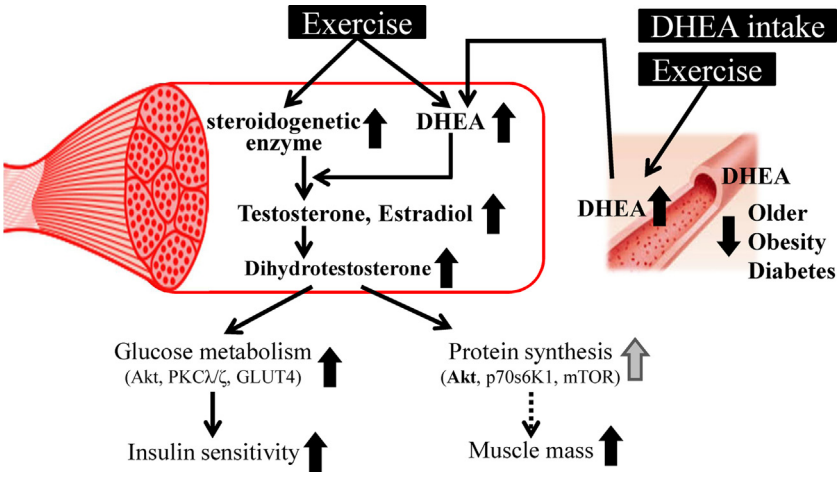

Fig. 1. Schematic illustration of the effect of exercise on muscle steroidogenesis, potentially resulting in prevention and treatment of life-related diseases.

muscle is capable of synthesizing and metabolizing testosterone and estradiol from DHEA, and DHT from testosterone.

Exercise prevents age-related concerns such as age-related diseases: diabetes, hypertension, hyperlipidemia and sarcopenia, resulting in improvement of the quality of life for individuals (Fig. 1). Sex steroid hormones generally decrease with aging [7], and it has been reported that a deficiency of sex steroid hormones in both men and women is a risk factor for the development of metabolic syndrome and sarcopenia [8]. The decline in circulating DHEA levels with aging and/or obesity has been correlated with the gradually increasing prevalence of diabetes [9]. Thus, generally, patients with obesity and type 2 diabetes show lower circulating DHEA levels [10].

It has been reported that both acute and chronic exercises induce a change in serum sex steroid hormone levels [11], whereas recent studies have investigated exercise as inducer of changes in muscular sex steroidogenesis [12–14]. Moreover, exercise induced increase in muscle sex steroid hormone levels and steroidogenic enzyme expression may contribute to the prevention and treatment of obesity, type 2 diabetes and sarcopenia. Therefore, this review addresses the new evidences of the effects of acute and chronic exercise on the response of muscle steroidogenesis, and the response to exercise of muscle sex steroidogenesis in obesity and type 2 diabetic model rats, as well as in young and older men.

2. The response of steroidogenesis and sex steroid hormone levels to exercise

2.1. The response to exercise of serum sex steroid levels

Acute and chronic exercise-induced changes in serum sex steroid hormone levels have so far been reported in many studies. For instance, serum level of testosterone were reduced during marathon running [15] and treadmill running using the Bruce protocol decreased serum testosterone levels in physically active men [15]. On the contrary, repeat sprint exercise (consisting of 10 repetitions of 30-s sprinting at a target load of 150% of the work capacity) increased serum total testosterone, free testosterone and DHT levels in healthy active young men [16]. Furthermore, progressive maximal intensity exercise on a cycle ergometer increased serum testosterone levels after 20 min from the beginning of exercise and returned to baseline within 10 min after exercise termination [17]. A 2 h subsequent prolonged exercise increased by 18–25% the concentration of serum testosterone [18]. Concerning the response of serum sex steroid hormone levels to chronic exercise reported in recent studies, we previously demonstrated that in high-sucrose induced obesity in rats and Zucker fatty rats, lower serum sex steroid hormone levels, such as DHEA and DHT. However, 6-week aerobic exercise training greatly increased these serum sex steroid hormone levels [12]. Thus, the response to acute exercise of serum sex steroid hormone levels is inconsistent. This difference may be affected by characteristics of subjects, exercise design as well as intensity and duration of the exercise. Furthermore, it may be important to focus on the effect of exercise on tissue levels of sex steroidogenesis rather than on the change of circulating sex steroid hormone levels, because both acute and chronic exercise-induced alteration of serum sex steroid hormone levels are systemic circulating sex steroid hormone levels and may not accurately reflect intracellular sex steroid hormone levels.

2.2. The response of muscular sex steroidogenesis to acute exercise

Several previous studies have shown that the responses of muscle sex steroid hormone levels and level of steroidogenic enzyme protein and mRNA expression were changes by a single bout of exercise stimulation. Muscle free testosterone and DHT levels were acutely elevated by exercise; treadmill running [13,14] and intense swimming [19]. Furthermore, our laboratory has demonstrated that protein and mRNA expression of steroidogenic enzymes in skeletal muscle were changed by a single bout of treadmill running in rats [13]. However, the responses to acute exercise of the muscle sex steroid hormones levels and steroidogenic enzyme expression were different between males and females in normal healthy rats. Muscle testosterone levels as well as 17β-HSD, 3β-HSD and 5α-reductase protein expression were increased by acute aerobic exercise in both sexes [14]. By comparison, muscle estradiol levels increased in males following exercise, but remained unchanged in females. Moreover, after acute exercise, the protein and mRNA expression of P450arom in the skeletal muscle increased in males, but decreased in females. In addition, 5α-reductase protein and mRNA expression significantly increased in both sexes even though the expression of 5α-reductase at rest (pre-exercise) was lower in females. Therefore, acute exercise may increase muscle estrogen synthesis in males, and may increase testosterone synthesis in females. In fact, muscle estrogen levels were increased in males, while muscle testosterone levels in females were increased by acute exercise (Fig. 2). Thus, the responses of muscle steroidogenesis were increased by acute exercise, and furthermore, sex differences in the regulation of P450arom by exercise may contribute to compensate for insufficient local levels of sex steroid hormones [13,14].