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Review Article

Synthesis of testosterone and its regulation; role of aldehyde oxidase and keto-reductase enzymes

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ABSTRACT

Retinoic acid (RA) is produced by the conversion of retinol to retinaldehyde by the enzyme aldehyde dehydrogenase. The mouse aldehyde oxidase AOX (aldehyde oxidase) is a molybdoflavoenzyme. Testosterone is a negative regulator of AOX in Harderian glands. Purified AOX oxidizes retinaldehyde into retinoic acid, while it is devoid of pyridoxal-oxidizing activity. *In* mice lacking the aldehyde oxidase, the first aldehyde oxidase knockout animals ever generated, are viable and fertile. In the rodents the Harderian gland's transcriptome of knockout demonstrates overall down regulation of direct retinoid-dependent genes as well as perturbations in pathways controlling lipid homeostasis and cellular secretion, particularly in sexually immature animals.Humans have been shown to have the AOX enzymes although little is known about their possible patho-physiological functions. This review article will discuss the role of aldehyde oxidase and aldehyde keto reductase enzymes in testosterone hormone synthesis and maintenance.

Keywords: Testosterone, aldehyde oxidase, keto reductase,enzymes,hormones

Introduction

Aldehyde is a carbonyl containing compound and is acted upon by the Aldehyde oxidases (AOXs) (EC 1.2.3.1) which are structurally conserved proteins belonging to the family of molybdoflavoenzymes along with xanthine oxidoreductase (XOR), the key enzyme in the catabolism of purines (1,2). In their catalytically active form, both AOXs and XORs are dimers of identical subunits characterized by three conserved domains separated by no conserved hinge regions (3). The amino-terminal 25-kDa domain contains two no identical 2Fe-2S redox centers. The flavin adenine dinucleotide binding region is located in the intermediate 45-kDa domain, while the substrate and the molybdopterin cofactor binding pocket reside in the carboxy-terminal 85-kDa domain (3). AOXs have broad substrate specificity, hydroxylating N-heterocyclic or oxidizing aliphatic as well as aromatic aldehydes into the corresponding acids (4,5). There is growing interest in the aldehyde oxidase and aldehyde keto reductase isozymes in their role in the synthesis and regulation of sex steroid hormones (6). The critical mediator in this process is the retinoic acid (RA).RA stimulates testosterone synthesis in cultures of Leydig cells.Testoterone levels has been shown to be altered under the influence of the peptide hormone atrial natriuretic peptide and appear to be also affected by the nitric oxide synthase enzyme and free radical nitric oxide (7-8). It appears that aldehyde oxidase and keto reductase contribute effectively to regulate the synthesis of sex steroid hormones and in particular testosterone hormone. This article discusses some of the recent advances in this area of science.

Aldehyde oxidase activity:

The aldehyde oxidase activity can be measured according to the method of Branzoli and Massey in 1974 (9). In brief, samples of the supernetant fraction (0.2ml) are incubated with 1.0 µmol of N-methylnicotinamide in 0.2ml of 0.075 M potassium phosphate buffer, pH 7.5 at 37^0 C with shaking. The reaction mixtures were routinely incubated for 30 minutes and the increase in optical density at 310 nm was evaluated spectrophotometrically.

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Lipid peroxidation test:

Malondialdeyde, a lipid peroxidation (LPO) product in samples of liver and kidneys was estimated following the method of Jordan and Schenkman (10).Microsomes were separated following the procedure of described earlier (11). The formation of thiobarbituric acid reactive substances (TBARS) was recorded at 530 nm using a spectrophotometer (Systronics, India).1, 1,3-tetramethoxy propane (Sigma) was used as the standard for the tests.

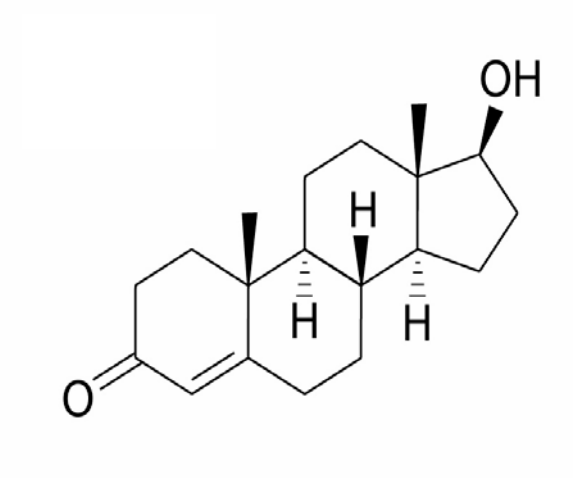

Figure 1: Chemical structure of the hormone Testosterone

Table 1: Effect of testosterone on rat liver lipid peroxidation

Concentration of Testosterone (M)	Malondialdehyde (nmoles/mg protein)
Control	2.57± 0.33
10^{-9}	2.47 ± 0.37
10^{-8}	1.99 ± 0.27
10^{-6}	1.52 ± 0.22^{+}

The values are means ± SE for 5 separate experiments. +Value significantly different from the control, P<0.01

Discussion:

Testosterone is an key hormone controlling male sexual characteristics, anabolic actions and physiological functions and oxidative stress (12-13) (Refer Table 1).It is also a metabolite in the synthesis of female sex hormone estrogen mediated by the aromatase enzymes.There is growing interest in aldehyde modulating enzymes like the AOX and dehydrogenase in affecting the levels, synthesis and maintenance of sex steroids. In this connection theAOXs oxidize aldehydes into carboxylic acids and hydroxylate aromatic heterocycles. The active form of AOXs is a 300 kDa homodimer. The number of mammalian AOX isoenzymes varies according to the species considered. Humans are characterized by a single enzyme, AOX1, while rodents synthesize four isoenzymes, AOX1, AOX2 (previously AOX3L1), AOX3 and AOX4.This indicates the arising peculiarities in the regulation of expression of genes of enzymes which catalyze the reductive pathway of endogenous aldehydes scavenging in the organism at certain stages of individual development (14). It is significant that compositions of blood aldo-keto reductases spectra are similar in early immature age from 3 weeks to aging i.e 26 months (15). It can be assumed that this is due to the peculiarities of the endocrine system functioning at these stages of ontogenesis, as hormones act as natural regulators of gene expression. It should be noted that unidirectional changes in endocrine regulation system arise in early postnatal development and in aging: children age is characterized by its functional immaturity, and late ontogenesis is characterized by manifestations of its involutionand effects of aldehyde metabolizing enzymes (16-18). Generally it is regarding production of sex steroids including testosterone. This suggests the involvement of testosterone in the regulation of gene expression of some aldo-keto reductases isozymes. AKR1C3 is a key steroidogenic enzyme to catalyze the conversion of low active androstenedione and androsterone hormone precursors to highly active testosterone and dihydrotestosterone in steroid synthesis pathway (19). Thus it can be concluded that these two enzymes contribute effectively in patho-physiological modulation of testosterone hormone levels and have implications for gender specificity and there appears to be a feedback interaction between the synthesis of the hormone and the two regulatory enzymes.

Conclusion:

This study suggests that the carbonyl containing metabolite aldehyde is important endogenous

chemical regulating sex steroid synthesis and maintenance of physiological levels as the two enzymes critical in its metabolism i.e the aldehyde oxidase and aldehyde keto reductase seem to play an important role and probably there is a interactive feedback relationship between the steroid synthesis and these enzymes. In this regard, association studies aimed at defining the relevance of AOX1 for the aetio-pathogenesis and progression of specific human diseases are also required, as they may give important insights into the functional significance of these enzymes. These studies will integrate the knowledge that is likely to be generated from the phenotypic analysis of the genetically engineered mice and which are already available or will be available in the near future. Thereby still comprehensive studies are required to ascertain this relationship.

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