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Influence of Testosterone Concentration on Activity of 5α-reductase and Aromatase

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Abstract

Objective: **To study the influence of testosterone concentration on activity of 5α-reductase and aromatase**

Material and Methods: **This experimental research was conducted on the testosterone-sensitive cell line of fibroblasts of male foreskin. The cell culture was incubated in mediums with various concentrations of testosterone.**

Results: **The investigation revealed that a minimal formation of 17β-oestradiol and 5α-dihydrotestosterone was observed in mediums that contain a concentration of the hormone close to the average physiological indices. Any deviation of the testosterone concentration both up and down was accompanied by an increase in the formation of 17β-oestradiol and 5α-dihydrotestosterone.**

Conclusions: **Any changes in the content of the testosterone in the medium (either an increase or decrease) lead to a consistent growth in the formation of 5α-dihydrotestosterone and 17β-estradiol and consequently, an increase in 5α-reductase activity and aromatase. An increase in the level of 5α-dihydrotestosterone and 17β-oestradiol contributes to the development of benign hyperplasia and cancer of the prostate. Conversely, rehabilitating the level of testosterone to its physiological level leads to a decrease in the production of 5α-dihydrotestosterone and 17β-oestradiol and leads to prevention of the above-mentioned diseases.**

Keywords: **fibroblasts, testosterone, 17β-oestradiol, 5α-dihydrotestosterone, 5α-reductase, aromatase**

Introduction

Based on the data of many studies, the volume of the prostate during benign hyperplasia depends on the levels of 5α-dihydrotestosterone and 17β-oestradiol. The stimulating effect of 5α-dihydrotestosterone is strongest on epithelial cells during the synergic influence of estrogens on the stroma. These factors are seen as the main factors in pathogenesis of the development of benign hyperplasia and prostate cancer.[1-5]

But despite the large number of publications dedicated to this topic, the reasons for the increase in the formation of 5α-dihydrotestosterone and 17β-oestradiol in men older than 40-50 years have still not been adequately researched to this day.

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Materials and Methods

Hormonal analysis

Research on the levels of 5α-dihydrotestosterone and 17β-oestradiol was measured using immuno-fermentation methods. A normal level of testosterone is 12-33 nmol/l.[6]

The concentration of 5α-dihydrotestosterone was measured using a test-system kit produced by "Alpha-Diagnostic" (San Antonio, Texas, USA). The normal level of 5α-dihydrotestosterone, according to the manufacturer of the test-system, is 1.0-2.9 nmol/l. The concentration of 17β-oestradiol was measured using a test-system kit produced by "Dia Metra S.R.I." (Italy). The normal level of 17β-oestradiol in the blood plasma in men is from 22-161 pmol/l.[7]

The sensitivity and the coefficients of variation were as follows: for 5α-dihydrotestosterone 0.07 nmol/l and 11.7 %; for 17β-oestradiol 3.0 pmol/l and 3.2 %.

Methods of experimental research on foreskin fibroblasts

Experimental work was conducted on testosterone-sensitive cell lines of foreskin fibroblasts (from a 14 year old child) of three parallel trials. In the experiment a qualitatively cross-sown culture of cells was incubated for two hours on a three-time duplicated incubation medium, containing testosterone in various concentrations. These concentrations corresponded to a reduction of the hormone: 1 ng/ml (3.47 nmol/l) and 3 ng/ml (10.4 nmol/l); a normal level of the hormone: 7 ng/ml (24.29 nmol/l); and to a high level of the hormone: 12 ng/ml (41.64 nmol/l), 24 ng/ml (83.3 nmol/l) and 600 ng/ml (2082.0 nmol/l). After two hours of incubation, an accumulation of 5α-dihydrotestosterone and 17β-oestradiol in the medium of biologically active products of the conversion testosterone was found. Both 5α-dihydrotestosterone and 17β-oestradiol affect the intensity of the flow in cells corresponding to 5α-reductase and aromatase reaction.[8]

Statistical analysis

An evaluation of the results was done on the basis of the statistical method of dispersal analysis of several groups. All data in the text and the tables are presented in the form of average values and standard deviations ($M \pm \sigma$).[9]

Results

The results of the experiment on the model of testosterone-sensitive cell lines of the foreskin are shown in Table 1. According to the results, the accumulation of biologically active metabolites of testosterone (5α-dihydrotestosterone and 17β-oestradiol) was minimal when the cells were incubated with a concentration of testosterone of 7.0 ng/mL (24.3 nmol/L), which is close to the average expression of testosterone content in the blood plasma of men. Any change in the level of testosterone in the incubation

Table 1 Dependence of the accumulation of 5-α-dihydrotestosterone and 17-β-oestradiol in the incubation milieu of cells of fibroblasts of the foreskin of a man on the concentration of testosterone in the medium

Characteristics of the breeding of testosterone in the medium	Concentration of testosterone in the medium (nmol/l)	Content of 5α-dihydrotestosterone in the medium after 2 hours of incubation (nmol/l)	Content of 17β-oestradiol in the medium after 2 hours of incubation (pmol/l)
Mediums with a concentration of testosterone lower than normal	3.5	5.0 ± 1.3*	58.3 ± 5. 8*
	10.4	2.8 ± 0.5*	55.4 ± 7.0 n.s.
Mediums with a normal concentration of testosterone	24.3	1.5 ± 0.4	45.9 ± 4.8
Mediums with a concentration of testosterone above normal	41.6	4.5 ± 1.1*	55.1 ± 5.8 n.s.
	83.3	7.6 ± 1.8*	62.0 ± 7.3*
	2082.0	16.0 ± 4.5*	67.9 ± 9.2*

**p <0.05; n.s. p >0.05 not significant in comparison to the content of the corresponding hormones in the incubation milieu with a breed of testosterone of 24.29 nmol/L (7.0 ng /ml)*

medium accompanied a rise in the production of 5α-dihydrotestosterone and 17β-oestradiol.

Discussion

A minimum accumulation of 5α-dihydrotestosterone and 17β-oestradiol is noted in mediums with a normal physiological level of testosterone in the blood plasma of men. Any changes in the content of the testosterone in the medium (either an increase or decrease) lead to a consistent growth in the formation of 5α-dihydrotestosterone and 17β-oestradiol and consequently, an increase in 5α-reductase activity and aromatase. Therefore, when the concentration of testosterone was reduced to 3 ng/ml (10.41 nmol/l) the level of 5α-dihydrotestosterone rose by 1.82 times ($p<0.05$). When the level of testosterone was reduced to 1 ng/ml (3.5 nmol/l), the level of 5α-dihydrotestosterone rose by 3.3 times ($p<0.05$). Where larger concentrations of testosterone were found, growth in the content of 5α-dihydrotestosterone was also noted: in a concentration of 12 ng/mL (41.6 nmol/l), a growth by 2.9 times ($p<0.05$); in a concentration of 24 ng/ml (83.3 nmol/l) a growth by 4.9 times ($p<0.05$); and in a concentration of 600 ng/ml (2082.0 nmol/l) a growth by 10.5 times ($p<0.05$). Similar results were found in the dynamics of the accumulation of 17β-oestradiol in the incubational medium.

The increase in the activity of 5α-reductase and aromatase is determined by the physiological role of testosterone, 5α-dihydrotestosterone and estrogens. Testosterone takes part in processes of growth and differentiation of cells.[5,10] Both testosterone and 5α-dihydrotestosterone, connecting with one and the same inner-cell receptor,[11] stimulate the proliferation activity of cells.[12] Estrogens induce an intensive metogenesis in tissues containing specific receptors.[13] The estrogen receptors are located both in the cells of the stroma and in the cells of the epithelial of the prostate gland, with a primary localization in the stroma. The stimulation of growth of stromal cells induces a proliferation of the epithelium.[5]

A reduction in the level of testosterone inhibits the natural cycle of development of cells with androgen receptors. This leads to a reduction of the intensity of reproduction of cells in a whole series of tissues based on measures of ageing.[14-16] The transition of androgen-independent transitory-proliferative cells into the androgen-dependent pool of transitory cells,[5] which demand the presence of the physiological level of testosterone in order to develop further, is accompanied by a breach in the process of these cells' differentiation. The risk of their neoplastic transformation goes up.[14-17] Difficulties, undergone by cells when the testosterone-dependent stage of the cells' development is overcome, hinder the beginning of the next (final) phase of the cell cycle-apoptosis.

An increase in the activity of aromatase and 5α-reductase is directed at compensating for the lack of mitogenic activity of testosterone.[18,19] An increase in the level of 5α-dihydrotestosterone and 17β-oestradiol in the future contributes to the development of benign hyperplasia and cancer of the prostate. Conversely, rehabilitating the level of testosterone to its physiological level leads to a decrease in the production of 5α-dihydrotestosterone and 17β-oestradiol and leads to prevention of the above-mentioned diseases.

When the level of testosterone goes up, the increase in the activity of aromatase and 5α-reductase also, apparently, has a compensatory character, since the main way to reduce the level of testosterone is to increase the intensity of testosterone's metabolism.[20] In this case some of the interim products include 5α-dihydrotestosterone and 17β-oestradiol become the reason for the development of cancer of the prostate in animals receiving large doses of androgens in experiments.[5,21]

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