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Effects of dietary fat on androgen secretion and metabolism

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SUMMARY

In humans and animals, food composition, especially dietary fat, affects androgen secretion and metabolism. On the other hand, disturbances of sex steroid metabolism play an important role in the etiology of hormone-related cancers. In this report the roles of dietary fat, its quantity, fatty acid composition and feeding period on androgens metabolism was described. In conclusion, it should be stated that the amount of dietary fat, and its composition, (i.e. the content of individual fatty acids and/or their groups), as well as the period during which the nutrient is fed to animals affect significantly the secretion and metabolism of androgens. *Reproductive Biology 2006* ***6*** *Suppl. 2:13–20.*
Key words: androgens, dietary fat, dietary fatty acids, prostate

INTRODUCTION

Epidemiological studies indicate that androgens and/or other factors including diet and dietary fat content play an important role in prostate carcinogenesis [1, 8, 12]. It is of interest that dietary fat seems to significantly influence

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the systemic turnover of androgens [10, 11]. In addition to the amount of fat in the diet, androgen secretion and metabolism are influenced by fat composition, especially the presence of some fatty acids in dietary fat.

DIETARY FAT QUANTITY

Results of *in vivo* and *in vitro* studies revealed that the amount of dietary fat is particularly important factor affecting androgen secretion. In men, a fat-rich meal results in a prolonged reduction in total and free testosterone (T) plasma levels [30]. In rats high fat food causes an increase in total and unbound plasma T levels [3], a decrease in sex hormone binding globulin (SHBG) level [14] and inhibition of aromatase activity in testes [5]. Conversely, restrictions of fat consumption in the latter species lead to a decrease in plasma level of T [10] and other androgens [31]. Results of our study (fig. 1) also showed that

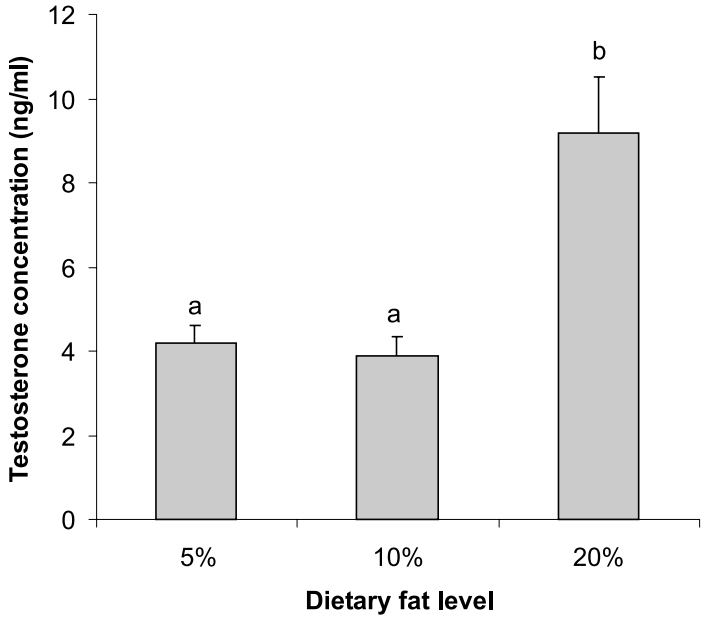

Figure 1. Plasma testosterone concentration in male rats (n=21) fed diet containing different levels of rapeseed oil during 6 weeks (mean ± SEM). The means were compared by one-way ANOVA followed by LSD test. Bars with different superscipts are significantly ($p \leq 0.05$) different.

the amount of dietary fat influences plasma T concentration in male rats fed a diet containing different levels of rapeseed oil for six weeks. Significantly higher T concentrations were observed in animals fed high fat diet (20% w/w) compared to those fed a lower fat diet (5 or 10%). These data confirmed results obtained by other authors. Moreover, Meikle et al. [17] demonstrated in mice that low fat containing meal reduces T concentration without affecting LH. This indicates that fatty acids may directly affect gonadal T production.

DIETARY FAT COMPOSITION

Fatty acids are components of the phospholipid layer of cell membranes and may affect the membrane property and interactions between membrane components [25]. Therefore, fatty acids may exert an effect on protein transport, membrane receptors and activities of membrane-related enzymes. Dietary fatty acids may influence the gonadal synthesis of T at the level of cell membrane. In rodents, changes in lipid composition of the cell membrane may affect the binding of LH to LH receptor, activation of the adenyl cyclase system [28] and steroidogenic enzyme activities in the testes [17].

Free fatty acids affect the binding of sex hormone by plasma proteins [24]. Therefore, they are important regulators of hormone bioavailability for tissues [19]. Saturated fatty acids (SFAs) with short-chain molecules (C8-C12) and polysaturated fatty acids (PUFAs) are more effective inhibitors of androgens binding by SHGB than long-chain saturated or monounsaturated fatty acids (MUFAs; [29]). The mechanism of such action is probably associated with the higher affinity of SFAs to the binding protein compared to that of steroids [32]. Moreover, contrary to the saturated acids (palmitic, stearic and arachidonic), the mono- and polyunsaturated fatty acids (oleic, linoleic and linolenic) increase the association constant of nonspecific T binding by plasma albumin [4].

The metabolism and synthesis of androgens seem to be particularly affected by the Ω-3 (α-linolenic, eicosapentanoic, docosahexaenoic fatty acids) and Ω-6 (γ-linolenic, linoleic, arachidonic, docosapentaenoic fatty

acids) families of PUFAs. The Ω-3 PUFAs reduce the number of androgen receptors (AR), decrease total T level in plasma [20, 22, 27] and inhibit 5α-reductase activity [15, 21] in men and rats. On the other hand, it was found that the Ω-6 PUFAs stimulate T synthesis in Leydig cells [26] and 17β-hydroxysteroid dehydrogenase (17βHSD) activity in rat testes [16] as well as increase the androgen-AR binding in the human prostate [2].

The influence of dietary fat composition on the gene expression and enzyme activity involved in the metabolism of androgens is not sufficiently elucidated. Arachidonic acid is known to inhibit the activity of 17βHSD [16]. Therefore, it may indirectly influence the rate of cellular synthesis of testosterone. Oleic acid inhibits the activity of cholesterol esterase [18], whereas γ-linolenic acid and eicosapentanoic acid metabolites inhibit the activity of 5α-reductase [21]. Changes in the activity of the complex of isoenzymes representing the 17βHSD group act probably as a "molecular switch" modulating the control of hormone-dependent prostate tumors. Results of the experimental studies have shown that dietary fat is one of the factors promoting the development of neoplastic lesions in the prostate [33, 34] by altering the metabolism of androgens and enhancing oxidative stress [8]. It has also been demonstrated that Ω-3 fatty acids present in fish oil reduce the binding of androgens by prostate receptors [27], with decosahexanoic acid being particularly active [2].

Oxidative stress is one of the main mechanisms that may cause carcinogenesis. Research results point to a close correlation between the oxidative stress level and the incidence of prostate cancer [6] as the reactive oxygen species (ROS) damage cellular DNA, lipids and proteins. Dietary fat (especially rich in PUFAs) is, in turn, one of the main substrates for oxidative stress [7, 27]. On the other hand, androgens may promote carcinogenesis by changing the activity of ARs and affecting regulatory genes and transcription factors [13], especially the nuclear factor kappa B [12]. Thus, it has been observed that changes in the expression of AR genes play an important role in proliferation of neoplastic cells in the prostate [35].

We found, that AR density in the prostate of rats fed with 20% grape-seed oil-diet, rich in linoleic acid (the Ω-6 PUFA), was higher than in animals fed high-lard diet rich in SFAs (fig. 2). This was true for prostate

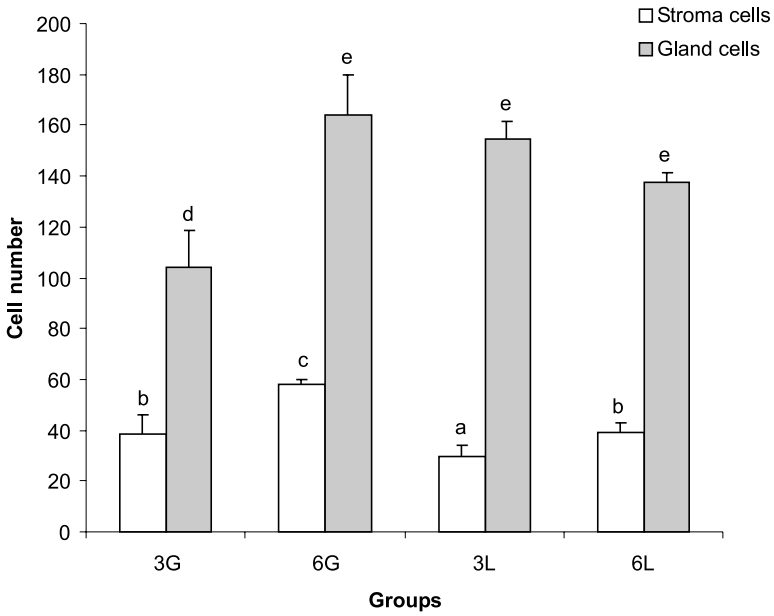

Figure 2. Androgen receptor density (number of cells with positive immunohistochemical reaction in estimated area) in the rat prostate (mean ± SEM). Rats were fed high-fat diet (20% w/w) with grape-seed oil (G; n=14 rats) or with lard (L; n=14 rats) for 3 or 6 weeks. The means were compared by one-way ANOVA followed by LSD test. Bars with different superscipts are significantly ($p \leq 0.05$) different.

stroma cells examined after 3 and 6 week-feeding periods as well as for prostate gland cells after six weeks of experimental diet feeding period. Conversely, in rats fed high-lard diet for three weeks, the AR density in prostate gland cells was higher than in rats fed a grape-seed oil diet. These observations indicate that a high-fat diet with high Ω-6 (substrates for peroxidation) level during the shorter feeding period can promote an increase in ARs density, and potentially, carcinogenesis, acting probably through the Ω-3 fatty acid influence on cell membrane fluidity.

DIETARY FAT FEEDING PERIOD

Our previous results indicated [9, 23] that the period of time during which the fat rich diet is applied may be another significant factor affecting androgen

secretion and metabolism. During a prolonged period of feeding a high-fat diet to rats, T plasma concentration initially increases and then decreases below the baseline values [22]. Additionally, a significant correlation was shown between the feeding time and the fat type and dietary fat level [22].

Realtionships between the effects of fat-feeding period and dietary fat type on plasma T level in male rats are shown in Figure 3. In this experiment, eight groups of male Wistar rats were fed four diets containing different fats

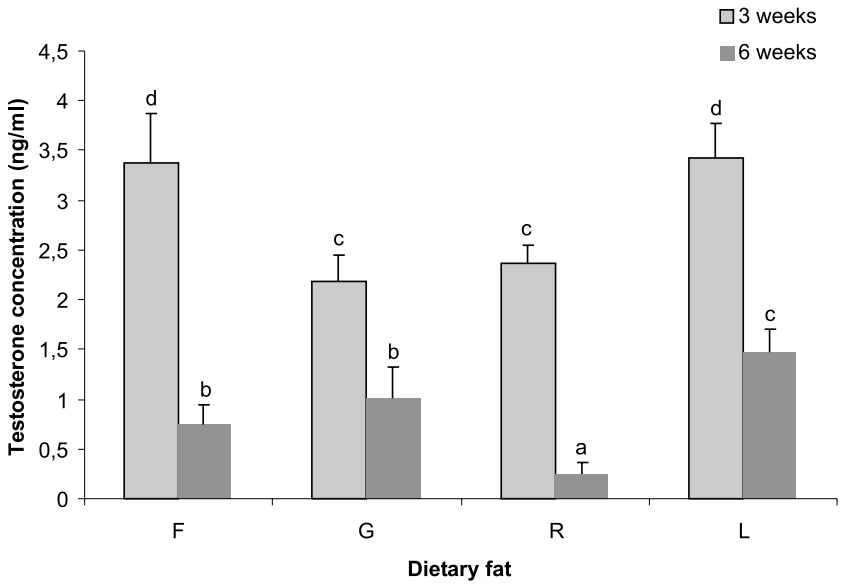

Figure 3. Effects of feeding period (3 or 6 weeks) and dietary fat type (F, G, R, L) on plasma testosterone level in male rats (mean ± SEM; n=56 rats). The means were compared by one-way ANOVA followed by LSD test. Bars with different superscipts are significantly different ($p \leq 0.05$). F: diet with fish oil; G: diet with grapeseed oil; R: diet with rapeseed oil; L: diet with lard.

(fish oil rich in Ω-3 PUFA docosahexaenoic acid, grape-seed oil rich in Ω-6 PUFA linoleic acid, rapeseed oil rich in MUFA oleic acid, and lard rich in SFA stearic acid) during three or six weeks. The results clearly showed that plasma T concentration is influenced by dietary fat type and feeding period with higher T level after three weeks of feeding found in all fat-type groups. On the other hand, significantly lower T concentration was observed in animals fed a diet with rapeseed oil during 6 weeks. Our data together with

those published previously [9, 22] indicate that there are some adaptation processes in these nutrient effects on androgens secretion.

In conclusion, it should be stated that the amount of dietary fat, and its composition, i.e. the content of individual fatty acids and/or fatty acid groups, as well as the period during which the nutrient is fed to animals significantly affect the secretion and metabolism of androgens.

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