Hormonal regulation of appetite and body mass in patients with advanced prostate cancer treated with combined androgen blockade

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ABSTRACT. Cachexia is rarely observed in patients with advanced prostate cancer treated with combined androgen blockade. Androgens play an important role in the regulation of body mass composition and influence the secretion of leptin, the appetite regulating hormone. The aim of the study was to assess the influence of a combined treatment with nonsteroidal antiandrogen and LH-RH analogue on the hormonal regulation of appetite and changes in body mass in patients with advanced prostate cancer (Whitmore-Jewett stage D1 or D2). Eighteen patients with prostate cancer and 17 healthy subjects matched for age and body mass index were included. In all patients serum concentrations of leptin, neuropeptide Y (NPY), insulin, testosterone and estradiol were measured before and after four and twelve weeks of androgen blockade. Pretreatment serum leptin levels were similar in patients with prostate cancer and in the controls. In a multiple regression analysis only body mass index and testosterone significantly contributed to the variation of plasma leptin. During the treatment body mass and plasma leptin significantly increased while NPY decreased. The change of plasma NPY was significant only after 4 weeks of therapy. This study shows that the afferent regulation of leptin secretion is unchanged in advanced prostate cancer. Androgen ablation significantly increases body mass and influences secretion of appetite regulating hormones. Testosterone appears to play a significant role in the regulation of leptin secretion.

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INTRODUCTION

Combined androgen blockade (CAB) is the treatment of choice in metastatic prostate cancer (1, 2). Its therapeutic value has been confirmed in the last decade in several prospective, randomized, multicenter trials (1, 3). Although survival advantage of androgen blockade appears to be modest (3), the treatment with LH-RH analogue combined with a nonsteroidal androgen results in an improvement of the quality of life and has high acceptance rate among patients (4).

Interestingly, cachexia is observed in less than 2% of patients with advanced prostate cancer treated with the CAB which is far less than in advanced stages of cancers of other organs (5). To our knowledge this phenomenon has not been investigated thoroughly. The discovery of leptin, a hormone which regulates appetite and thereby body mass and composition (6) may open the way to study the mechanisms which lead to cancer cachexia. Until now in several studies in patients with cancers of various organs, *i.e.* of lung (7), gastrointestinal tract (8) and breast (9), afferent regulation of leptin secretion was found to be unaffected, whereas a central resistance to the action of leptin was postulated (7). The production of leptin by fat cells is controlled by several mechanisms (10, 11). An important role is played by sex steroids which explains the well described gender difference of serum leptin levels (12). Estrogens both *in vivo* (13, 14) and *in vitro* (14) increase serum leptin whereas androgens may show the opposite effect (15, 16). However, the association between androgens and leptin has not been found in all studies (17, 18). Moreover the link between androgens and leptin has been observed mostly in cross-sectional studies in heteroge-

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nous populations and only limited data have come from intervention studies (19-21). The relation between sex steroids and the regulation of body mass and appetite is complex because, although leptin remains crucial in this respect, several other hormones are also involved, *e.g.* sex steroids, neuropeptide Y – a key mediator of a central action of leptin (22), and insulin (23).

The study aimed to examine the influence of a combined treatment with antiandrogen and LH-RH analogue on appetite-related hormones in patients with metastatic prostate cancer. It was expected that suppression of androgen secretion would increase plasma leptin levels providing the evidence that leptin production is under control of androgens.

PATIENTS AND METHODS

Eighteen patients with advanced prostate cancer in Whitmore-Jewett stage D1 or D2 were recruited. The control group comprised 17 healthy subjects matched for body mass and age who underwent general screening to exclude organic diseases and in whom a detailed medical history was available. The diagnosis of prostate cancer was confirmed in each case by histologic examination of the bioptate taken from the prostate gland. The presence of metastases was confirmed by ultrasound, X-ray and bone scintigraphy. The patients were qualified after the following conditions had been excluded, *i.e.* dementia, heart, liver or kidney failure, diabetes, arterial hypertension or obesity (BMI above 30 kg/m^2).

The study protocol was approved by the Local Ethics Committee and an informed consent was given by all participants.

Study design

Before the treatment started the following parameters had been measured in all patients: body mass, BMI and waist/hip ratio (WHR), serum concentrations of glucose, insulin, prostate specific antigen (PSA), acid phosphatase, testosterone, estradiol, leptin and neuropeptide Y (NPY). Appetite was self-assessed by patients in a 5-point scale. The volume of the prostate gland was measured by a standard ultrasound technique (Pederson formula). The blood for biochemistry was taken in the fasting state in subjects resting in a supine position. After all measurements had been completed all patients received the antiandrogen flutamide 750 mg per day and seven days later a first dose of goserelin, a LH-RH analogue. Goserelin was given subcutaneously in a dose of 3.6 mg once a month. All measurements were repeated 4 and 12 weeks from the beginning of CAB. Additionally to above-listed parameters liver function tests and serum levels of urea, uric acid and creatinine were monitored at each visit during the treatment.

Serum leptin concentrations were also corrected for the changes in body mass index (the results were multiplied by 10).

Laboratory methods

Plasma leptin was measured by radioimmunoassay (Linco Research, Inc, USA). Intra- and interassay coefficients of variation were 7.1% and 10.8%, respectively. Plasma neuropeptide Y was estimated by radioimmunoassay (Peninsula Laboratories) after extraction by Sep-Pac C18 catridges (Waters Associates, Milford, USA). Intra- and interassay coefficients of variations were 9.8% and 12%, respectively. Insulin was measured by radioimmunoassay and plasma testosterone and estradiol by ELISA (Enzymun-Test form Boehringer Mannheim Immunodiagnostics; intra- and interassay of variation were below 6.5 and 10%, respectively). All other biochemical parameters were measured with standard laboratory methods.

Statistical analysis

To analyse changes in serum leptin, NPY and insulin caused by the treatment analysis of variance was used with Mann-Whitney U test and matched-pairs Wilcoxon test for *post-hoc* analysis. In correlation studies both simple and multiple regression were used. *P* values of less than 0.05 were taken as significant. All results are expressed as mean±standard deviation.

RESULTS

The treatment was well-tolerated and all patients survived the observation period. The minor problem was a transient elevation of liver function tests in two patients which normalized at the end of the observation period.

The mean age was 67±9 years in patients with prostate cancer and 71±4 years in control subjects. The patients did not differ from control subjects with respect to body mass and BMI (70.4±12 *vs* 69.2±9 and 24.7±3.6 *vs* 24.9±3.1, respectively). Microscopic examination of bioptate of the prostate gland revealed adenocarcinoma in all cases with histologic grading (Mostofi scale) ranging from G1 (9 patients), G2 (7 patients) to G3 (2 patients). According to the Whitmore-Jewett scale 5 patients were in stage D1 and 13 in D2.

Table 1 shows the changes in body mass, BMI and

Table 1 - *Changes of body mass, body mass index (BMI) and waist hip ratio (WHR) in patients with prostate cancer treated with a complete androgen blockade.*

	Basal	4 weeks	12 weeks
Body mass (kg)	70.4±12.2	71.4±12.6*	73.1±12.5*
BMI (kg/m^2)	24.7±3.6	25.1±3.7*	25.7±3.5*
WHR (1/1)	0.97±0.05	0.98±0.05*	1.00±0.05*

*p<0.01 (*vs* baseline).

WHR observed during the treatment. As indicated a significant increase of all these parameters was observed. During the treatment total activity of acid phosphatase and PSA decreased significantly (from 30.6±45 to 13.9±22 U/l after 4 weeks and 11.6±22 after 12 weeks and 347±623 to 28±65 and 3.8±9.6 ng/ml, respectively). These changes occurred along with the decrease of the volume of the prostate gland (from 59±31 to 45±25 and 30±17 ml, after 4 and 12 weeks, respectively).

The patients reported an improvement of appetite and the mean score increased from 3.3±1.1 at baseline to 3.9±0.9 and 4.4±0.9 after 4 and 12 weeks, respectively, p<0.01).

During the treatment there was a trend for serum glucose to increase but its levels remained in the normal range in all subjects during the observation period. Serum insulin increased significantly (p<0.05) during CAB (from 39±27 to 77±52 and 90±71 pmol/l after 4 and 12 weeks, respectively).

Basal plasma testosterone was 13.2±6.2 nmol/l. During the treatment plasma testosterone concentrations decreased below castrate level (2.5 nmol/l) in all subjects (their respective values were 0.4±0.6 nmol/l after 4 weeks and 0.2±0.3 nmol/l after 12 weeks, p<0.001). Basal plasma estradiol was within normal range in all subjects (42±44 pmol/l). The treatment resulted in a significant decrease of plasma estradiol to 18±19 pmol/l after 4 weeks (p<0.05) and 7±9 pmol/l after 12 weeks (p<0.05) of CAB. As shown on Figure 1 plasma leptin increased during the 12-week therapy in all but one subjects (p<0.001 after 4 and 12-weeks). This relation remained significant when plasma leptin concentration was corrected for body mass (p<0.001 after 4 weeks and p<0.01 after 12 weeks) (Fig. 2). Plasma NPY decreased significantly after 4 weeks of CAB only (Fig. 3).

In a linear regression analysis the significant correlations were found between basal plasma leptin and body mass (r=0.57, p<0.01), BMI (r=0.62, p<0.001), WHR (r=0.58, p<0.05), testosterone (r=-0,24, p<0.01) and estradiol (r=0.60, p<0.05). In a multiple regression analysis only body mass index and testosterone contributed significantly to the variances of plasma leptin measured at baseline (β=0.85, p<0.005 and β=-0.44, p<0.05, respectively) and of change of plasma leptin during CAB (β=0.36, p<0,05 and β=-0.40, p<0.05, respectively).

DISCUSSION

The major result of this study is a finding of the influence of androgen blockade on the secretion of appetite regulating hormones. Since the discovery of leptin many studies examined the mechanisms of regulation of its secretion and as a result fat mass cannot be longer considered the single determinant of leptin production. In our study as in other studies [reviewed by Auwerx and Staels (10)]. BMI was the major determinant of plasma leptin. The important role which leptin plays in reproduction (24) prompt-

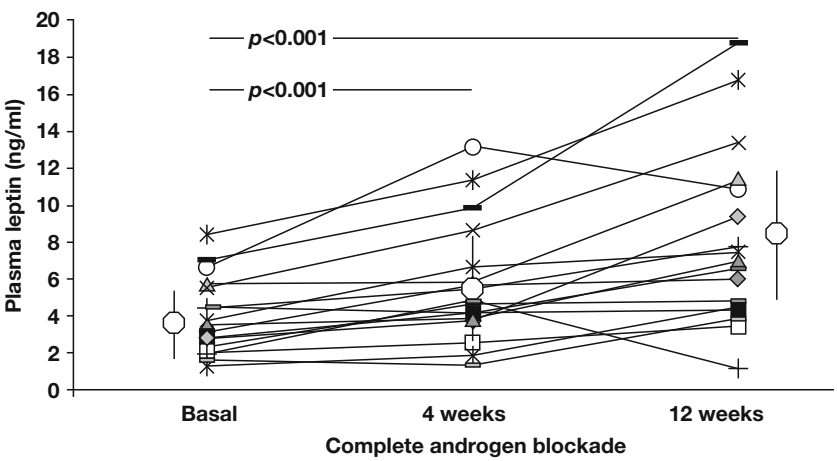

Fig. 1 - *Individual changes of plasma leptin observed during the complete androgen blockade in patients with prostate cancer.*

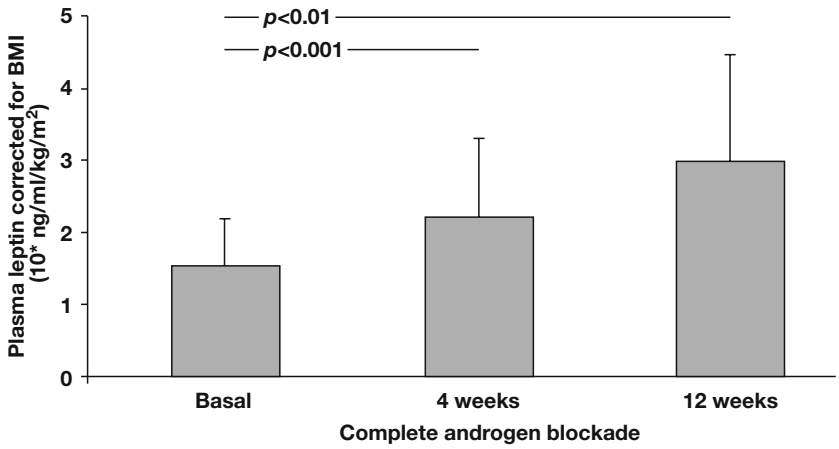

Fig. 2 - *Changes in plasma leptin corrected for body mass index (BMI) observed during the complete androgen blockade in a group of patients with prostate cancer.*

ed investigators to study the role of sex steroids in the control of leptin production. Both estrogens and androgens levels have been found to correlate with serum leptin but in some cross-sectional studies those associations were weaker or abolished when an adjustment for body mass was made (19, 23, 25). As stated above there is limited evidence for a link between androgens and leptin coming from intervention studies. In one recent study (19) in which testosterone was given to healthy men for contraceptive purposes a suppression of serum leptin was seen. In another study (20) in hypogonadal men elevated serum levels of leptin were normalized after administration of testosterone. In an interesting study an increase of serum leptin was found in male to female transsexuals in whom an antiandrogen was given with estrogen (21). In that study however the effects of antiandrogen were difficult to differentiate from that of estrogen because both drugs were combined. In experimental study in rats surgical castration increased serum leptin levels (14). In contrast, in another study orchiectomy in diabetic Otsuka-Long-Evans-Tokushima fatty rats significantly lowered plasma leptin (26). In a recently published study on rats the stimulating effect of orchidectomy on plasma leptin was attributed to fat mass changes but not to hormonal changes (27). To our knowledge, our study is the first which shows the effect of pharmacologic castration on plasma leptin in men. However, it should be mentioned that CAB protocol combines two drugs which block the androgen secretion and effects at different levels and therefore it is difficult to separate their effects. The interaction of leptin and gonadotropins has been postulated in a study of McCann *et al*. (28). Although that study showed that leptin controls the secretion of LH-RH and FSH-RH a bidirectional interaction cannot be excluded (24). The changes in estrogen production may be anoth-

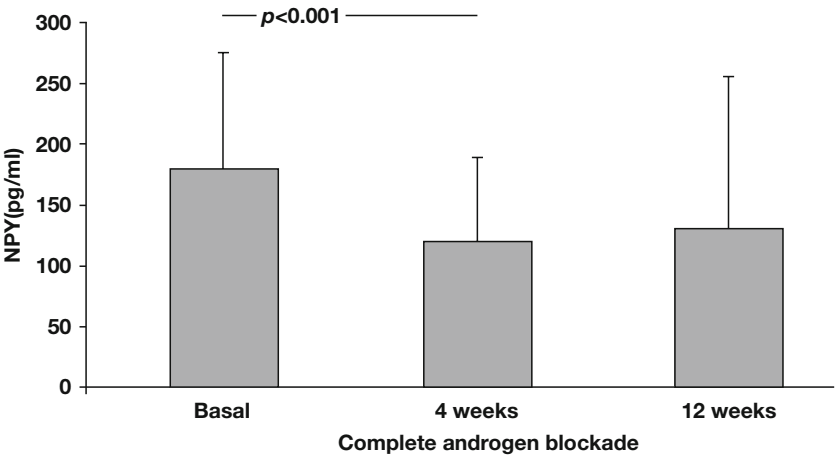

Fig. 3 - *Changes in plasma neuropeptide Y (NPY) observed during the complete androgen blockade in a group of patients with prostate cancer.*

er confounding factor when analysing the influence of CAB on plasma leptin. In our study the levels of estradiol were reduced (but to much lower extent than the level of testosterone) but this change should rather lower plasma leptin thus ameliorating the observed effect of CAB (13, 14).

As shown in our study, in subjects with prostate cancer the physiologic relation of leptin to body mass was preserved. Furthermore, plasma leptin levels in cancer patients at baseline were similar to those in the control group of elderly subjects matched for body mass. These results suggest that the regulation of leptin secretion is not affected by the presence of neoplasm. Such results are in agreement with other studies in patients with cancers of the gastrointestinal tract (8), breast (9) and lung (7). It should also be mentioned that leptin was not found to be involved in the pathogenesis of prostate diseases such as benign hypertrophy and cancer (29). In order to clarify whether a resistance to the action of leptin is present in our patients as was suggested in the study of patients with lung cancer (7) we also examined plasma levels of NPY, the main mediator of the anorectic action of leptin. As shown, a significant decrease of plasma NPY was found after 4 weeks of CAB. We were not able to show any correlation between the levels of leptin and NPY under basal conditions and between the changes in plasma leptin and NPY which occurred during the treatment. The lack of such correlation may be explained by the fact that NPY found in the plasma is released from peripheral sympathetic nerve endings and plasma levels of NPY may not correlate with its secretion in the hypothalamus where the interaction between leptin and NPY takes place. This concept is in accordance with the study of Dotsch *et al*. (30) who found a correlation between the levels of NPY and leptin in the cerebrovascular fluid but not in the plasma. Insulin is the "classic" hormone known to regulate body mass. There is a bidirectional interaction between leptin and insulin (23). It has been found that prolonged hyperinsulinemia stimulates leptin production (31). In our subjects insulin levels increased during CAB. Since no correlation was found between plasma leptin and insulin both at baseline and during the treatment, it is difficult to assess the possible contribution of the increase of serum insulin to the observed changes in plasma leptin.

As has been previously recognised (2) the significant increase of body mass, BMI and WHR during CAB was observed in our study. These results suggest indirectly that the fat mass increased in our subjects. Since we did not assess body composition and in particular fat mass by more objective methods to avoid the possible confounding effect of such changes on plasma leptin (25), those were corrected for body mass index. Since they did not change the statistical significance of the increase of plasma leptin during CAB, the observed changes could be most probably attributed to the therapy, *i.e.* to the suppression of androgen production. It should be however stated that the definite conclusion of the relation between androgens and leptin will require the direct measurement of body fat mass (to exclude that fat mass increased at the expense of muscle mass) which should be undertaken in the future studies.

In conclusion we showed that the afferent regulation of leptin production is not changed in advanced prostate cancer. Androgen blockade increases body mass and significantly influences the hormonal regulation of appetite. The study also confirms that androgens may play a role in the regulation of leptin secretion. The finding of the positive influence of androgen blockade on body mass may offer an interesting new option for treatment of cancer cachexia.

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