The effect of pheochromocytoma treatment on subclinical inflammation and endocrine function of adipose tissue

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Pheochromocytoma and adipokines

Summary

The aim of our study was to evaluate the influence of surgical removal of pheochromocytoma on the endocrine function of adipose tissue and subclinical inflammation as measured by circulating C-reactive protein (CRP) levels.

18 patients with newly diagnosed pheochromocytoma were included into study. Anthropometric measures, biochemical parameters, serum CRP, leptin, adiponectin and resistin levels were measured at the time of diagnosis and 6 months after surgical removal of pheochromocytoma, respectively. Surgical removal of pheochromocytoma significantly increased body weight, decreased both systolic and diastolic blood pressure, fasting blood glucose and glycated hemoglobin levels. Serum CRP levels were decreased by 50 % 6 months after surgical removal of pheochromocytoma (0.49 ± 0.12 mg/l vs. 0.23 ± 0.05 mg/l, $p < 0.05$) despite a significant increase in body weight. Serum leptin, adiponectin and resistin levels were not affected by the surgery. We conclude that increased body weight in patients after surgical removal of pheochromocytoma is accompanied by an attenuation of subclinical inflammation probably due to catecholamine normalization. We failed to demonstrate an involvement of the changes of circulating leptin, adiponectin or resistin levels in this process.

Key words: pheochromocytoma, body weight, inflammation, leptin, adiponectin, resistin

Introduction

Chronic low-grade inflammation appears to play an important role in the development of endothelial dysfunction, atherosclerotic plaque initiation, formation and later on in its instability that may result in a plaque rupture (Jialal *et al.* 2004; Kvasnicka *et al.* 1997; Raitakari *et al.* 2005). Recent studies have demonstrated that obesity is accompanied by markedly increased infiltration of adipose tissue by immunocompetent cells that in turn produce increased amount of proinflammatory factors such as tumor necrosis factor-α, interleukin-6, resistin and many others (Anderlova *et al.* 2007; Weisberg *et al.* 2003; Xu *et al.* 2003). It has been suggested that adipose tissue of obese individuals and, in particular, its visceral compartment, might be the primary site where the subclinical inflammation arises (Neels and Olefsky 2006). Both experimental and clinical studies have demonstrated that numerous hormones of adipose tissue such as adiponectin and resistin, may be directly or indirectly involved in the etiopathogenesis of atherosclerosis (Haluzik *et al.* 2004; Kawanami *et al.* 2004; Matsuda *et al.* 2002; Pischon *et al.* 2005; Reilly *et al.* 2005; Shimada *et al.* 2004). Patients with a catecholamine-secreting tumor (pheochromocytoma originating from adrenal medulla and functioning paraganglioma arising from sympathetic nervous system associated chromaffin tissue) (Pacak *et al.* 2005; Zelinka *et al.* 2007a) represent another group of patients that may suffer from early progression of atherosclerosis and higher risk of cardiovascular diseases (Daub 2007; Khorram-Manesh *et al.* 2005). The exact mechanism of accelerated atherosclerosis in these patients is only partially understood. It very likely includes increased blood pressure with increased variability or diminished diurnal variation (Zelinka *et al.* 2004), disturbances in glucose metabolism and possibly other factors such as increased inflammation markers relative to both healthy subjects and patients with primary aldosteronism (Zelinka *et al.* 2007b). Previous *in vitro* studies have demonstrated that

increased catecholamine levels can markedly modulate the endocrine function of adipose tissue (Bottner *et al.* 1999; Cong *et al.* 2007).

Here we tested the hypothesis that catecholamine-induced perturbations in endocrine function of adipose tissue may contribute to disturbed metabolic profile in patients with pheochromocytoma and assessed the influence of operational removal of pheochromocytoma on the metabolic parameters and on the endocrine function of adipose tissue.

Patients and methods

Patients

Eighteen patients, 11 men and 7 women, with pheochromocytoma were included into study. All patients were examined during hospitalization in the 3rd Department of Medicine, 1st Faculty of Medicine, Charles University and General University Hospital, Prague. The baseline examination was performed at the time of diagnosis of pheochomocytoma. The diagnosis of pheochomocytoma was based on elevated 24-hour urine catecholamines or metanephrines (analysis performed by means of high-performance liquid chromatography on Agilent 1100, Agilent Technologies, Santa Clara, CA, USA) and positive imaging study with computed tomography or magnetic resonance. All subjects underwent surgical removal of the tumor and the diagnosis was confirmed on histopathology.

The second examination of subjects free of disease recurrence was performed at least 6 months after adrenalectomy. No hypolipidemic, hormonal treatment or treatment affecting food intake was given. Patients with coronary heart disease, stroke, renal failure or acute infectious diseases were excluded from the study. All patients were informed about the purpose of the study and provided their informed consent to participate. The study was approved by the Human Ethical Review Committee, 1st Faculty of Medicine and General

University Hospital, Prague, Czech Republic, and was performed in accordance with the guidelines proposed in the Declaration of Helsinki.

Anthropometric examination and blood sampling

All patients were measured and weighed and the body mass index (BMI) was calculated. Casual blood pressure (BP) values were obtained in the sitting position using a standard sphygmomanometer. Twenty four hours blood pressure monitoring was performed by means of an oscillometric device SpaceLabs 90207 (SpaceLabs Medical, Richmond, Washington, USA) which was set to measure blood pressure every 20 min during the day (from 6:00 to 22:00 h) and every 30 min during the night (from 22:00 to 6:00 h).

Blood samples were withdrawn from all patients after an overnight fasting. Serum was obtained by centrifugation and the samples were subsequently stored in aliquots at -70 °C until further analysis.

Hormonal and biochemical assays

Plasma insulin concentrations were measured by commercial radioimmunoassay kit (CIS Bio International, Gif-sur-Yvette, France). Serum leptin concentrations were determined by commercial double sandwich ELISA kit (BioVendor, Brno, Czech Republic). Serum adiponectin concentrations were measured by commercial RIA kit (Linco Research, Inc., St. Charles, Missouri, USA). Serum resistin concentrations were measured by commercial ELISA kit (BioVendor, Brno, Czech Republic). CRP levels were measured by Ultra-Sensitive C-Reactive Protein ELISA kit (DSL, Oxon, UK). Biochemical parameters were measured by standard laboratory methods in the Department of Clinical Biochemistry of the General University Hospital.

Statistical analysis

For the statistical analysis the SigmaStat software (Jandel Scientific, San Rafael, CA USA) was used. Results are expressed as means ± standard error of means (SEM). Paired *t*-test was used to compare the values of patients before and after treatment. Unpaired *t*-test or Mann-Whitney Rank Sum Test was used to calculate gender-related differences. The relationships between the data were calculated by Pearson or Spearman correlation test.

Results

Anthropometry, biochemical parameters and blood pressure in patients with pheochromocytoma before and after treatment

Baseline and postoperational parameters of patients with pheochromocytoma are shown in Table 1. At baseline, systolic and diastolic blood pressure, serum total cholesterol, fasting blood glucose and serum glycated hemoglobin were above the normal limits of our laboratory. Surgical removal of pheochromocytoma significantly increased BMI, decreased average systolic and average diastolic blood pressure as measured by 24-hour monitoring. The total cholesterol, HDL cholesterol and triglyceride levels did not change after treatment. The removal of pheochromocytoma significantly decreased fasting glucose levels and the glycated hemoglobin levels. Insulin levels tended to decrease after operation, but the difference did not reach the statistical significance.

Serum CRP, leptin, adiponectin and resistin levels in patients with pheochromocytoma before and after treatment

The surgical removal of pheochromocytoma significantly decreased C-reactive protein (CRP) levels (Table 2). On the contrary, no significant changes in serum leptin, adiponectin and resistin levels after surgical treatment were found despite a significant increase in BMI (Table 2). When comparing leptin levels according to gender, there were higher leptin levels in women than in men (12.4 ± 3.6 vs. 3.2 ± 0.8 ng/ml before surgery, $p = 0.046$). The same tendency on the borderline of statistical significance was found after the surgery (16.7 ± 6.4 vs. 3.7 ± 0.8 ng/ml, $p = 0.052$).

The relationship of adipokines to anthropometric parameters, blood pressure, CRP and biochemical variables

In patients before the operation, serum leptin levels significantly positively correlated with age ($r = 0.7$, $p = 0.001$), BMI ($r = 0.50$, $p = 0.01$), triglycerides ($r = 0.59$, $p = 0.01$) and insulin levels ($r = 0.54$, $p = 0.02$). After the operation serum leptin levels positively significantly correlated with age ($r = 0.67$, $p = 0.02$), BMI ($r = 0.60$, $p = 0.01$) and triglyceride levels ($r = 0.5$, $p = 0.04$). Serum leptin levels negatively correlated with 24-hour diastolic blood pressure before surgery ($r = - 0.59$, $p = 0.011$). No other significant relationships of leptin with other parameters were found including the lack of correlation of leptin with urine epinephrine and norepinephrine levels. Serum resistin levels after operation positively correlated with total cholesterol levels ($r = 0.61$, $p = 0.007$). No significant correlations between CRP and the adipokines were found. CRP levels positively correlated with both systolic and diastolic blood pressure ($r = 0.51$, $p = 0.04$ and $r = 0.53$, $p = 0.04$, respectively; Figure 1), with total cholesterol ($r = 0.65$, $p = 0.01$), triglyceride levels ($r = 0.55$, $p = 0.03$) and

24-hour urine epinephrine levels ($r = 0.56$, $p = 0.02$) in patients after surgery. No other significant relationships between CRP, adipokines, catecholamines and other parameters studied were found.

Discussion

Our study showed that successful treatment of pheochromocytoma led to a significant weight gain accompanied by decreased blood glucose, glycated hemoglobin levels together with attenuation of subclinical inflammation as measured by C-reactive protein levels. The most important finding of this study, however, is the dissociation between subclinical inflammatory reaction, weight gain and the endocrine function of adipose tissue in patients with pheochromocytoma after surgical removal of the tumor. Overproduction of catecholamines in patients with pheochromocytoma is accompanied by a higher basal metabolic rate (Gifford *et al.* 1964), therefore its successful removal leads to a body weight gain probably due to an increase of body fat content resulting from the shift of energy balance. Here we show that increase in body weight was accompanied by attenuated subclinical inflammatory response as measured by circulating CRP levels. This finding is rather surprising since numerous studies have linked increased CRP levels to increased BMI in obesity (Haffner 2003a; Haffner 2003b; Stoll and Bendszus 2006). On the contrary, low BMI in malnourished patients such as those with anorexia nervosa is accompanied by lower CRP relative to normal weight subjects (Dolezalova *et al.* 2007). Based on the previous studies, it could have been expected that the increase in body weight would rather promote the production of proinflammatory factors in adipose tissue (Anderlova *et al.* 2006; Cancello *et al.* 2005). On the other hand the increase in BMI in our study was rather mild and it still remained within the normal or slightly overweight limits. Therefore its influence on the subclinical inflammation could have been

relatively small. More likely explanation of the dissociation of body weight gain and simultaneous decrease in CRP levels probably lies in the direct effect of increased catecholamines on CRP and/or the possible influence of increased blood pressure on CRP levels. The possible direct influence of catecholamines on CRP is further supported by a positive correlation between CRP and 24-hour urine epinephrine levels after surgery.

To assess directly the changes of endocrine function of adipose tissue, we measured serum concentrations of three adipose tissue-derived hormones known to affect body weight and/or systemic inflammation – leptin, adiponectin and resistin both before and after surgical treatment of pheochromocytoma. Decreased adiponectin levels have been previously linked to increased risk of insulin resistance and atherosclerosis (Shimada *et al.* 2004; Yamauchi *et al.* 2003; Yang *et al.* 2001), while the opposite was found for circulating resistin levels (Degawa-Yamauchi *et al.* 2003; Pischon *et al.* 2005; Reilly *et al.* 2005; Ukkola 2002). Serum leptin levels appear to most closely correlate with body fat content being increased in patients with obesity relative to lean subjects (Maffei *et al.* 1995; Tartaglia *et al.* 1995). Surprisingly, none of the three adipose tissue-derived hormones measured was significantly affected by surgical removal of pheochromocytoma. This finding argues against the direct involvement of these hormones in the suppression of systemic inflammatory reaction in patients with pheochromocytoma.

In contrast to catecholamine inhibitory effects on leptin production in experimental (Kosaki *et al.* 1996; Trayhurn *et al.* 1996) and also some clinical studies (Wocial *et al.* 2002) we did not observe significant effect of pheochromocytoma removal on serum leptin levels. This lack of effect might be due to downregulation of functional adrenergic receptors and development of tolerance of adipose tissue to catecholamines regulatory action (Bottner *et al.* 1999) or due other yet unknown mechanism.

In conclusion, our study demonstrated that the weight gain in patients after surgical removal of pheochromocytoma was accompanied by a significant decrease of CRP levels. The drop of CRP thus may reflect positive effects of pheochromocytoma removal on atherosclerosis progression and cardiovascular risk or rather the discontinuation of the effect of increased catecholamine levels on CRP production. Finally, we failed to demonstrate a direct involvement of the changes in serum leptin, adiponectin or resistin levels in this process.

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Table 1

Characteristics of patients with pheochromocytoma before and after treatment. Values are means ± SEM.

	Before treatment n = 18	**After treatment n = 18**	
Gender (woman/man)	7/11	7/11	
Age (years)	45.7 ± 2.9	46.5 ± 2.7	
BMI (kg/m^2)	24.3 ± 0.8	25.5 ± 0.9 **	** p < 0.001
Systolic blood pressure (mmHg)	137 ± 4	126 ± 3 *	* p < 0.05
Diastolic blood pressure (mmHg)	84 ± 4	82 ± 2	NS
Average systolic blood pressure during 24 hour monitoring (mmHg)	134 ± 4	118 ± 2 **	** p < 0.001
Average diastolic blood pressure during 24 hour monitoring (mmHg)	83 ± 3	74 ± 1 *	* p < 0.01
Total cholesterol (mmol/l)	5.7 ± 0.3	5.5 ± 0.3	NS
Triglyceride levels (mmol/l)	1.5 ± 0.2	1.4 ± 0.2	NS
HDL cholesterol (mmol/l)	1.6 ± 0.06	1.4 ± 0.06	NS
Fasting blood glucose (mmol/l)	7.0 ± 0.4	4.7 ± 0.1 **	** p < 0.001
Glycated hemoglobin (%)	4.5 ± 0.3	3.8 ± 0.2 *	* p = 0.01
Insulin levels (μIU/ml)	19.2 ± 2.1	15.5 ± 1.5	NS
Epinephrine levels (nmol/g creat)	377.9 ± 155	19.1 ± 2.8 *	* p < 0.05
Norepinephrine levels (nmol/g creat)	2676 ± 438	176.9 ± 15.3 **	** p < 0.001

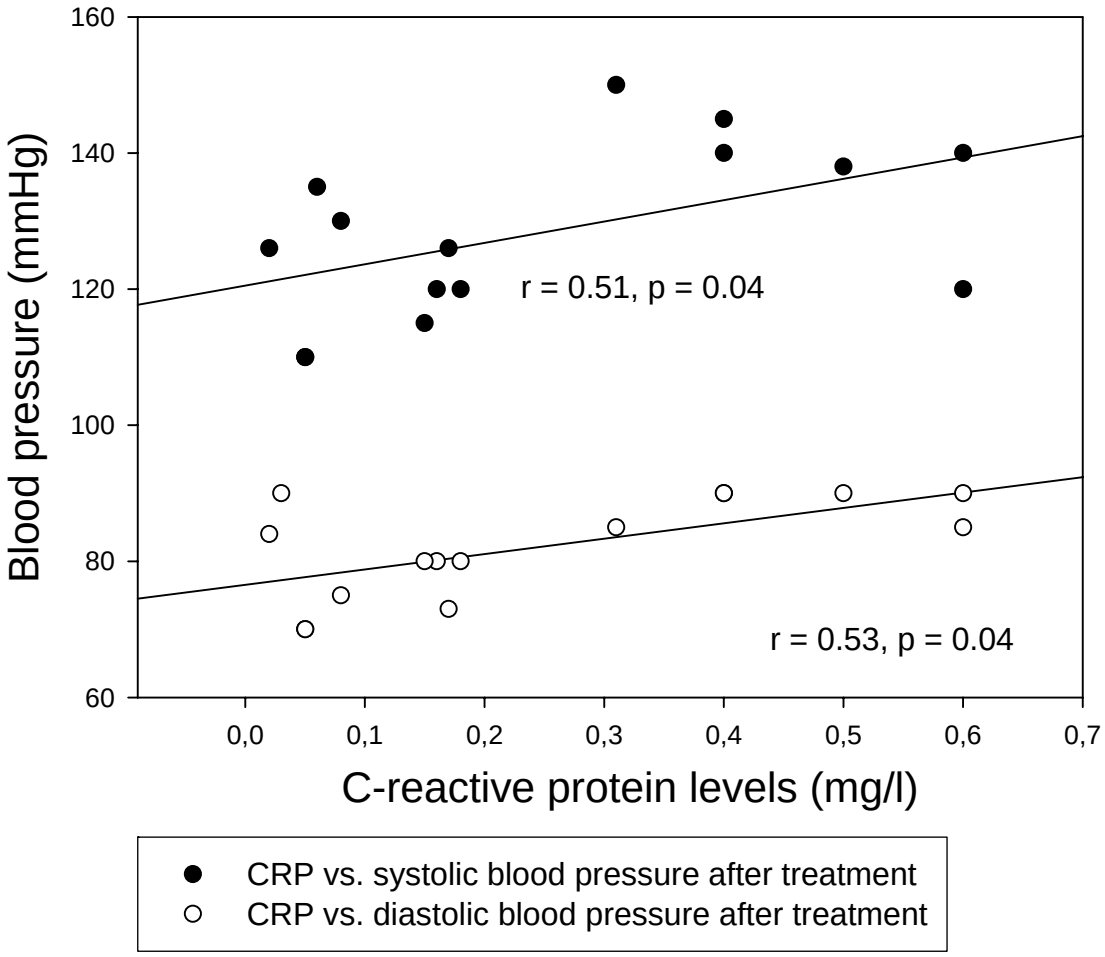
Table 2.

Serum levels of C-reactive protein, leptin, adiponectin and resistin in patients with pheochromocytoma before and after treatment. Values are means ± SEM.

	Before treatment n = 18	**After treatment n = 18**	
CRP (mg/l)	0.492 ± 0.123	0.235 ± 0.051 *	* p < 0.05
Leptin (ng/ml)	6.76 ±1.78	8.79 ±2.86	NS
Adiponectin (ug/ml)	20.01 ± 2.49	18.34 ± 2.49	NS
Resistin (ng/ml)	5.34 ± 0.5	5.56 ± 0.55	NS

Figure 1

Correlation of serum CRP levels with systolic (black circles) and diastolic (open circles) blood pressure in patients with pheochromocytoma after the operation.



Bosanska et al, Figure 1