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ORIGINAL ARTICLE

Sibutramine therapy in obese women – effects on plasma neuropeptide Y (NPY), insulin, leptin and β-endorphin concentrations

Bogusława Baranowska[1], Ewa Wolińska-Witort[1], Lidia Martyńska[1], Magdalena Chmielowska[1], Teresa Mazurczak-Pluta[2], Anna Boguradzka[2], Agnieszka Baranowska-Bik[1]

[1] Department of Neuroendocrinology, Marymoncka 99, 01-813 Warsaw, Poland.
[2] Training Centre for Family Medicine, Medical Centre of Postgraduate Education

Correspondence to: Bogusława Baranowska MD, PhD
Department of Clinical Neuroendocrinology,
Medical Centre of Postgraduate Education,
Marymoncka 99, 01-813 Warsaw, POLAND
TEL: +48 22 569 3850
FAX: +48 22 569 3859
EMAIL: zncmkp@op.pl

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Abstract

OBJECTIVE: Some neuropeptides and monoaminergic neurotransmitters may affect hypothalamic feeding centres, sympathetic activity and thermogenesis. Sibutramine (BTS54524; N – [1-[1(4-chloro phenyl) cyclobutyl] -3methyl N,N – dimethylamine hydrochloride monohydrate) is a new 5-HT serotonin and noradrenaline reuptake inhibitor (SNRI), antiobesity drug. The aim of this study was to evaluate the effects of the sibutramine therapy on plasma neuropeptide Y (NPY), insulin, leptin and β-endorphin concentrations in obese patients.

METHODS: Sibutramine, serotonin and noradrenaline reuptake antiobesity drug was administered for 6 months in a dose of 10 mg daily in 60 obese women (BMI 30–40 kg/m^2) (mean 34 kg/m^2). Plasma NPY, leptin, β-endorphin and insulin concentrations were measured with RIA methods using commercial kits (Peninsula Lab, Linco, Peninsula Lab, Świerk respectively). The above neuropeptides levels were evaluated before and after the 6 month sibutramine therapy in 60 obese women as well as in 30 obese women on low caloric diet and in 30 of the control group.

RESULTS: In 85% obese patients a decrease of body weight was found after 6 month therapy with sibutramine. A decrease in total cholesterol, LDL and triglicerides and an increase in HDL were observed after the sibutramine treatment. We have demonstrated that the sibutramine therapy leads to the decrease of plasma NPY, β-endorphin, insulin and leptin concentrations in obese patients. After low diet therapy we have observed a decrease in plasma leptin levels, however we did not find significant changes in plasma leptin, NPY, β-endorphin and insulin concentrations.

CONCLUSIONS: We suggest that the effects on the disturbed activity of NPY, β-endorphin, insulin and leptin may be involved in the mechanism of sibutramine action.

Introduction

Some neuropeptides and monoaminergic neurotransmitters such as adrenaline, noradrenaline, dopamine and serotonin may affect hypothalamic feeding centres, sympathetic activity and thermogenesis [1, 2, 3, 4].

Sibutramine (BTS54524; N – [1-[1(4-chloro phenyl) cyclobutyl] -3methyl N,N – dimethylamine hydrochloride monohydrate) is a new 5-HT serotonin and noradrenaline reuptake inhibitor (SNRI), antiobesity drug [5, 6]. Sibutramine enhances monoamine function by reuptake inhibition rather than by monoamine release [7].

Sibutramine reduces the food intake in rodents and this effect is reversed by pretreating with 5-HT or noradrenaline antagonist [8]. Sibutramine also increases thermogenesis in rats and in humans [7, 9, 10]. This effect is mediated via stimulation of β3 adrenoreceptors in brown adipose tissue [9]. Sibutramine increases central 5-HT function via its secondary and primary amine metabolites through 5-HT uptake inhibition like that of fluoxetine, however, fenfluramine and amphetamine enhances 5-HT release [5].

Chronic administration of sibutramine decreases food intake and body weight in obese rats [7,11, 12, 13].

Kelly et al demonstrated [14] that sibutramine caused the weight loss in depressed patients. Sibutramine produces the dose related weight loss, and in humans it is well tolerated [15].

The serotoninergic agents (fenfluramine, dexfenfluramine) were effective weight loss drugs but were withdrawn because of cardiovascular and pulmonary complications.

The combination of noradrenergic/serotoninergic agent, sibutramine is indicated for the pharmacological treatment of obesity [16].

In patients receiving sibutramine, the reduction in triglycerides, uric acid, total cholesterol, low-density lipoprotein (LDL), and an increase in high-density lipoprotein (HDL) were observed [17].

Despite effects on brain monoamine metabolism and thermogenesis, sibutramine attenuated the increased ARC (arcuate nucleus) neuropeptide Y (NPY) mRNA and decreased proopiomelanocortin (POMC) expression in obese rats [11].

The aim of this study was to evaluate the effects of the sibutramine therapy on plasma NPY, leptin, insulin and β-endorphin concentrations in obese patients.

Material and methods

Material consisted of 90 obese women aged 18–45 years (mean 33 years), BMI 30–40 kg/m^2 (mean 34 kg/m^2), WHR< 0.8, and 30 lean women aged 19–44 (mean 32 years), BMI 22–24 kg/m^2 (mean 23 kg/m^2) as the control group. Among 90 investigated obese women 60 were treated with sibutramine and 30 were on low caloric diet (1000 kcal – daily).

All endocrine diseases known to cause obesity were excluded.

Blood samples for NPY, leptin and β-endorphin assays were taken at 8 am from fasting subjects.

Plasma NPY, leptin, β-endorphin and insulin concentrations were measured with RIA methods using commercial kits (Peninsula Lab, Linco, Peninsula Lab, Świerk respectively).

The above neuropeptides levels were evaluated in obese women before and after the 6-month sibutramine therapy or after low caloric diet therapy.

Sibutramine (Meridia-Abbott) was administrated for 6 months in a dose of 10 mg daily.

The statistical analysis was performed with the unpaired t-test and ANOVA as appropriate.

Results

The data are presented as the mean ± SEM.

In 85% obese women a decrease in body weight was observed. After 6 month therapy with sibutramine their mean BMI markedly decreased from 34 kg/m^2 to 26 kg/m^2.

In these patients total cholesterol, triglicerydes and LDL were lowered, and increase in HDL was found. In five patients sibutramine was withdrawn because of hypertension and tachyarrhythmia. We observed a decrease of mean BMI from 33 kg/m^2 to 27 kg/m^2 in group being on low caloric diet.

Plasma NPY, leptin, β-endorphin and insulin concentrations before and after the sibutramine therapy or diet therapy are shown in Figs. 1, 2, 3, 4.

Plasma NPY, leptin, β-endorphin and insulin levels in obese women were significantly higher as compared with the control group ($p<0.001$), $p<0.001$, $p<0.01$, $p<0.001$, respectively.

A significant decrease in plasma NPY after the sibutramine therapy was found ($p<0.001$) (Fig. 1), however we did not observe significant changes in plasma NPY in patients after diet therapy.

Plasma leptin concentrations, increased in obese patients compared to controls, significantly lowered after the sibutramine therapy ($p<0.01$)(Fig. 2). Plasma leptin levels after low caloric diet were lower but the decrease was not significant.

Plasma insulin levels were decreased after sibutramine therapy ($p<0.01$), but not in group being on low caloric diet (Fig. 3).

Plasma β-endorphin concentrations are presented in Fig. 4.

The sibutramine therapy did not change plasma β-endorphin concentrations significantly in obese patients, although β-endorphin levels were lowered after sibutramine treatment. β-endorphin release did not change after six months of low caloric diet therapy.

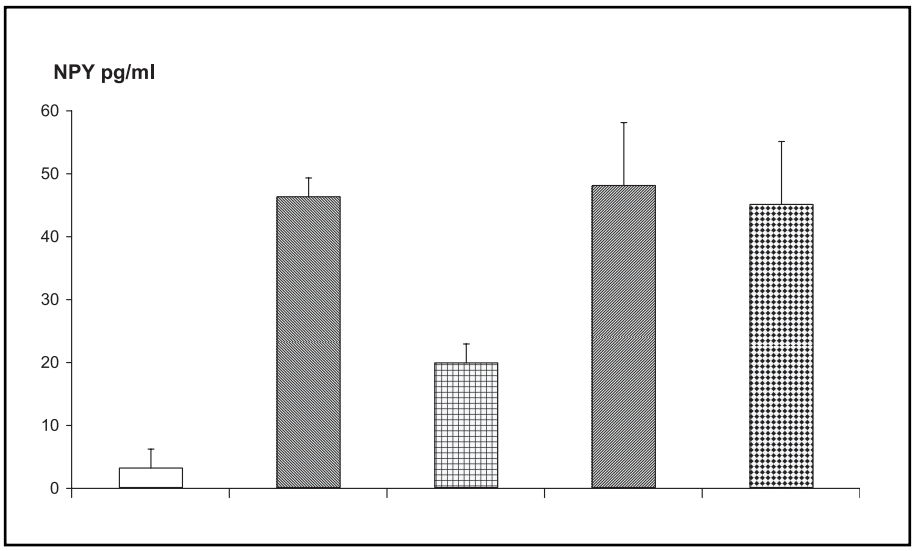

Figure 1. Plasma neuropeptide Y (NPY) concentrations in obese women before and after the sibutramine therapy.

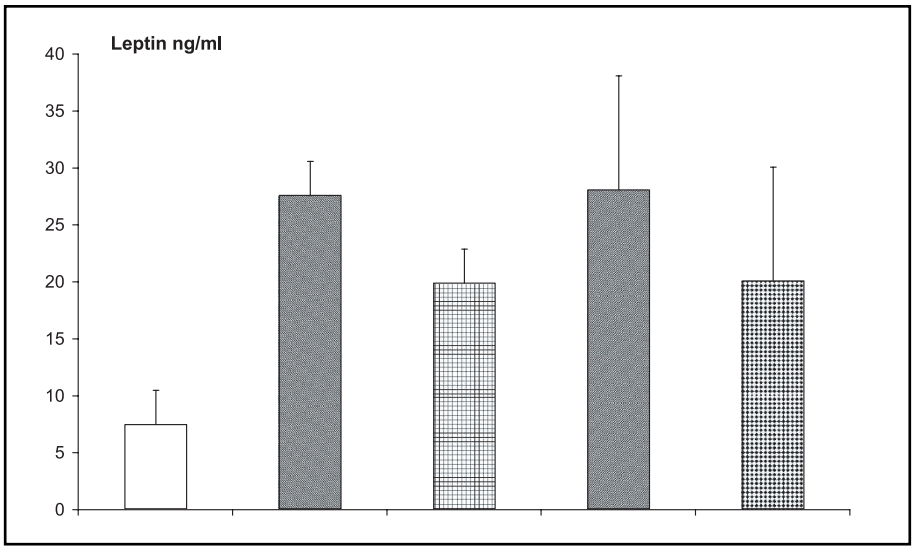

Figure 2. Plasma leptin concentrations in obese women before and after the sibutramine therapy.

Discussion

It has been reported that many neuropeptides are involved in the mechanism of feeding behaviour [18, 19, 20, 21]. Neuropeptide Y (NPY) and β-endorphin (β-E) are strong orexigenic peptides [18, 22, 23, 24, 25].

NPY is widely distributed in the central and peripheral nervous systems. In the periphery NPY is found in the adrenal medulla and it is costored in catecholaminergic nerves [26]. Moreover, the interaction of NPY with serotonin, opioids, CRH, MSH, CART, orexines and other peptides is established [27, 28, 29, 30].

The interaction between central and peripheral signals is probably due to leptin – a peptide secreted mainly by adipocytes [31].

In our previous paper we demonstrated that plasma NPY and leptin concentrations are increased in obese patients with the increase of BMI [3]. The highest levels of NPY were found in hypertensive and diabetic obese patients [4].

We also observed a marked increase of NPY and β-E, insulin after the carbohydrate administration (OGTT) [4]. Our present data show for the first time a marked decrease in plasma NPY after the sibutramine therapy. We did not observe a significant decrease in plasma NPY in patients being on low caloric diet despite a decrease of BMI.

We also found a significant decrease of plasma insulin after the sibutramine treatment but not after diet treatment. Previously we observed the significant positive correlation between NPY and insulin in obese patients [4].

It has been reported that NPY produces not only an increase of basal insulinemia and an increase of insulin–stimulated glucose uptake by adipose tissue but

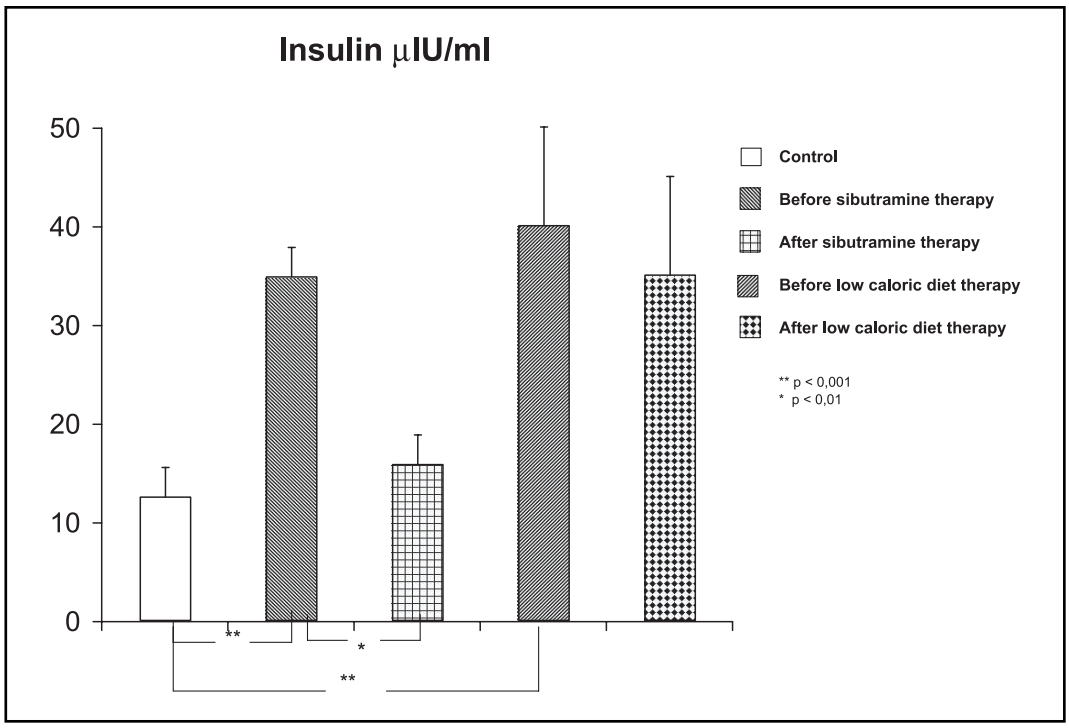

Figure 3. Plasma insulin concentrations in obese women before and after the sibutramine therapy.

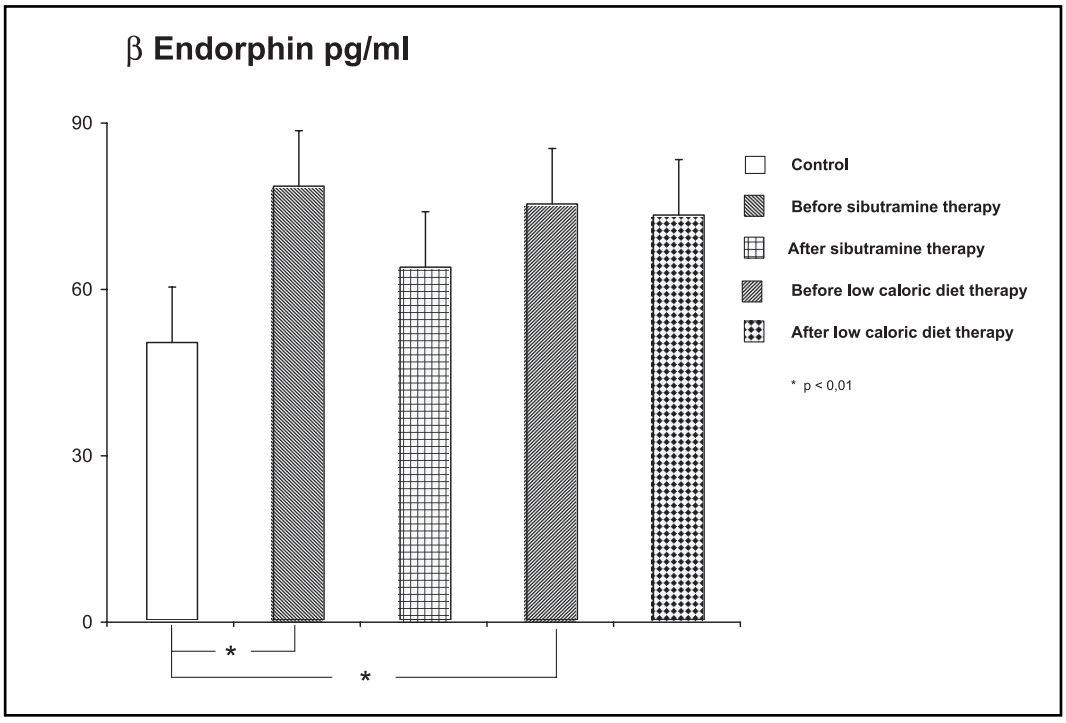

Figure 4. Plasma β-endorphin concentrations in obese women before and after the sibutramine therapy.

also a marked decrease in glucose uptake by the muscle [32].

A decrease of plasma leptin levels after sibutramine in our studies may be connected with the decrease of BMI, because plasma leptin concentrations were also lowered in patients after low caloric diet.

Plasma β-endorphin levels were enhanced in obese patients [33]. β-endorphin levels were decreased in patients treated with sibutramine but we did not observe significant changes. In women treated with low caloric diet plasma β-endorphin did not change.

It has been published that leptin, NPY and other peptides may penetrate through the brain – blood barrier [34].

Some authors have reported that NPY, CRH and β-endorphin concentrations in the cerebrospinal fluid (CSF) in obese patients are low [35].

An increase of plasma NPY, β-endorphin and insulin after GOTT [33] in obese patients may suggest that

NPY and β-endorphin may originate from the pancreas or other sites of gut rather than from brain. On the other hand it can be postulated that permeability of the brain – blood barrier is changed in eating disorders.

Conclusions

1. The therapy with sibutramine exerts beneficial effects on metabolic and neuroendocrine balance in obese patients.

2. The effects of sibutramine on the disturbed release of NPY, β-endorphin and insulin in obesity indicate that the regulation of neuropeptides activity may play an important role in the mechanism of this drugs action.

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