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GHRELIN AS A POTENTIAL FACTOR THAT REDUCES BLOOD PRESSURE DURING WEIGHT LOSS TREATMENT

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RESEARCH ARTICLE

ABSTRACT. A CLOSE RELATION between obesity and hypertension has been reported in epidemiological studies. The present paper presents data on ghrelin, a peptide whose involvement in the regulation of appetite, metabolic processes, and cardiovascular system seems to be of considerable importance in the pathophysiology of hypertension. By sympathetic suppression, improvement of baroreflex control, and, probably, peripheral vasodilatation, the peptide can exert positive hemodynamic action. Some other ghrelin-related mechanisms such as antiinflammatory and antioxidant role, modulation of insulin-resistance as well as contra-regulatory role in food intake are also significant. However, ghrelin constitutes a part of a complex network; it both influences and is influenced by several factors. All neurotransmitters – such as leptin, ghrelin, NPY, AGRP – might as well participate in sympathetic and arterial pressure regulation.

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1. INTRODUCTION

A close relation between obesity and hypertension has been reported in epidemiological studies. Excess fat mass is accompanied by increase in blood volume, heart rate, cardiac output and systemic blood pressure. Obesity is associated with high circulating levels of free fatty acids and hyperinsulinemia. Activation of the sympathetic nervous system, renin-angiotensin-aldosteron system, and changes in sodium balance and adipocyte-derived factors may directly contribute to obesity-related hypertension. Also, leptin, an adipocyte-derived hormone, might stimulate obesity-associated cardiovascular sympathoactivation.

Several recent studies showed that also obesity related peptides, i.e., neuropeptide Y, corticotrophin-releasing factor (CRF), alpha-melanocyte stimulating hormone (alpha-MSH), and cocaine- and amphetamine-regulated transcript (CART) peptides might play an important role in cardiovascular regulations, and lead to obesity-related hypertension [1].

The continuing search for mechanisms regulating energy homeostasis could help understand the pathophysiology of obesity-related hypertension. In this review, we discuss the potential role of ghrelin.

2. BIOLOGICAL ACTIVITY OF GHRELIN

In 1999 Kojima at al. [2] first identified an endogenous GHS-receptor ligand, i.e. ghrelin, from the stomach of rat. The peptide consists of 28 aminoacids, and includes a unique structure with an n-octanoyl ester at third serine residue that is essential for its biological activity [3].

The human ghrelin gene is located on chromosome 3, and is composed of 4 exons and 3 introns [4]. The principal site of ghrelin synthesis is the stomach. However, its expression has been also demonstrated in the bowel, pancreas, kidneys, placenta, gonads, pituitary, hypothalamus, and adipose tissue [5-7]. Normal range of mean serum ghrelin concentration in humans is 117 ± 37 fmol/mL [8]. It was observed that, in human plasma, the concentration of des-acyl ghrelin is higher than that of its acylated form. Des-acyl form of ghrelin can bind to high density lipoproteins, and may be involved in lipid transport and metabolism [9].

Ghrelin is a potent appetite stimulant. Plasma levels of ghrelin increase before meals and during fasting and fall shortly after meals [10].

The orexant activity of ghrelin may be mediated partially by overexpression of genes coding neuropeptide Y (NPY) and agouti-related protein (AGRP) [11]; according to some authors also by the vagal nerve, which stimulates stomach contraction, secretion and filling [12].

Ghrelin is best known for its potent GH-releasing action. However, recent studies suggest that ghrelin could also be involved in wide regulation of the endocrine system. Intravenous ghrelin administration in humans resulted in an increase of not only GH, but also LH levels, and corticotropin secretion [13]. Ghrelin and its receptors were found in human gonads, both testes and ovaries. In the testes ghrelin may be linked to the control of testicular function and inhibit testosterone secretion [5]; in the ovaries ghrelin may inhibit androgens secretion and action [M-29]. Arvat et al. [13] showed that, in humans, administration of ghrelin caused increased cortisol levels. Kanamoto et al. [15] observed ghrelin production in human thyroid gland. They hypothesized that thyroid hormones may have an effect on ghrelin expression.

3. GHRELIN AND INSULIN RESISTANCE

The recent data on insulin resistance further clarify the role of ghrelin in obesity development. There are studies supporting the concept of basal ghrelin levels being directly related to insulin sensitivity; in obesity the levels get supressed, which is generally associated with increased insulin resistance [16]. Greenman et al. found that low ghrelin was independently associated with type 2

diabetes, insulin concentration, insulin resistance, and elevated blood pressure [16]. In subjects with insulin-resistance obesity, ghrelin serum levels were decreased in comparison to obese insulin-sensitive control [17]. According to Poykko et al. [18], ghrelin was inversely related to both fasting insulin levels and WHR, a useful index of central obesity.

4. GHRELIN AND WEIGHT GAIN/LOSS

Tischop and al. [19] reported that circulating ghrelin levels were reduced in obesity. Parallel to studies on obesity, those on anorexia nervosa revealed increased serum ghrelin levels. Shiiya et al. [20] found elevated ghrelin in anorectic patients, i.e., with negative energy balance, when compared to that of healthy subjects. The above-mentioned reports seem to confirm the hypothesis that ghrelin secretion is regulated by energy balance. This, in turn, is in accordance with our observations that weight loss in obese subjects results in an increase of ghrelin levels [21]. Considering the fact that the activation of the ghrelin - GH axis exerts anabolic effects, we suggest that the elevation of ghrelin levels following weight loss might constitute a secondary, counter-regulatory mechanism preventing further weight loss.

Although obesity is generally associated with decreased ghrelin levels, elevated concentrations have been found in some forms of obesity, such as in Prader Willi syndrome, suggesting its role in etiology of at least some forms of obesity [22].

5. GHRELIN AND HEART FAILURE

Interesting findings were reported in patients with heart failure and cardiac cachexia. Nagaya et al. [23,24] found significant correlations between ghrelin, GH, and Tumor Necrosis Factor α (positive correlation), and BMI (negative correlation). Changes of ghrelin concentrations were related to body mass in cachectic patients, and an increase of ghrelin levels was observed following cachexia development. The results suggest that not only the absolute value of fat mass, but also the progressive weight loss may influence plasma ghrelin levels.

Investigations on the role of ghrelin in chronic circulatory insufficiency have shown that its intravenous administration not only diminishes cardiac cachexia, but also significantly affects haemodynamic parameters. The following have been observed: increase of cardiac index and left ventricular stroke volume, and decrease of peripheral resistance and mean blood pressure (no effect on HR). No significant IGF-1 changes were found, which was suggestive of ghrelin directly influencing NO synthesis and exerting vasodilatory effect independent of GH/IGF-1 [25].

Recent studies of Nagaya et al. [26] also revealed positive effect of ghrelin administration on left ventricular function, exercise capacity, and muscle wasting in patients with chronic heart failure. Nagaya [26] investigated the results of three-week intravenous ghrelin administration. A significant decrease in plasma norepinephine was also noted – the index of sympathetic activity suppression. Ghrelin-induced improvement of baroreflex control also seems important in heart failure (see below). Furthermore, it has been shown that ghrelin inhibits apoptosis of cardiomyocytes and endothelial cells [27] by a receptor different than GHSR-1a. According to some authors, ghrelin might be soon developed into a therapeutic agent for the treatment of congestive heart failure [28]. Recently some data were published on the role of ghrelin in induced pulmonary hypertension and right heart failure. Animal models revealed that endogenous ghrelin production was abolished in healthy rats treated with ghrelin. In induced pulmonary hypertension, pulmonary expression of ghrelin was maintained, and right ventricle expression was increased more than 20 times; exogenous ghrelin administration attenuated pulmonary hypertension, and caused a decrease in right ventricle hypertrophy, thickening of pulmonary arteries, and right ventricle diastolic disturbances, without affecting the endogenous production of the ghrelin – hormon. Authors concluded that ghrelin might modulate pulmonary

hypertension by changes in pulmonary arteries and right ventricle hypertrophy [29].

6. GHRELIN AND INFLAMMATION

Interesting data on antiinflammatory role of ghrelin were published recently [30]. The study was based on two facts: (i) the growth hormone secretagogue receptor was identified in blood vessels, and (ii) cytokine-induced inflammation seen both in cachexia and cancer was alleviated by ghrelin administration. The authors revealed that ghrelin inhibited both basal and TNFα-induced cytokine release in human vascular endothelial cells and mononuclear cell binding; it also inhibited basal and TNFα–induced nuclear translocation of NF-kB. It should be pointed that NF-kB plays a critical role in inflammatory response to a variety of stimuli. Therefore, a potential mechanism of ghrelin modulating inflammatory response by blocking NF-kB might be of importance. Antiinflammatory effects of ghrelin required interaction with endothelial growth hormone secretagogue receptor.

These data are in accordance with a study of Chang et al. [31], who documented ghrelin-induced correction of the hemodynamic and metabolic abnormalities in endotoxic shock in rats. This might account for the beneficial effects of ghrelin administration in myocardial reperfusion injury, cardiac cachexia and septic shock.

Another novel hypothesis is associated with antiinflammatory role of ghrelin in atherosclerosis. Obesity is associated with proinflammatory activation, that is thought to increase risk for cardiovascular disease. The reduced concentration of ghrelin levels observed in obesity could potentially contribute to this proinflammatory state, and could explain increased frequency of atherosclerosis development. In summary, activation of the ghrelin signalling pathway seems to represent a novel approach in the prevention and treatment of atherosclerosis.

Furthermore, ghrelin does not act as antioxidant per se, however, it interferes with redox signalling to inhibit cytokine release. Ghrelin could probably modulate redox signalling by stimulating the production of NO. In a recent report of Sibilia et al. [32] suggested that ghrelin might induce the release of endogenous NO. On the other hand, ghrelin action on vascular bed may also be associated with IGF-1 activation, which is an atherogenic factor. IGF-1 involvement has been demonstrated in the pathogenesis of hypertension, atheroclerosis, post-PCI restenosis, angiogenesis, and postinfarctional remodelling.

7. GHRELIN AND SYSTEMIC HYPERTENSION

7.1. ARTERIAL BAROREFLEX CONTROL AND RENAL SYMPATHETIC NERVE ACTIVITY

When discussing the role of ghrelin in obesity-related hypertension, the role of arterial baroreflex control of renal sympathetic nerve activity should be emphasized.

Dysfunction of arterial baroreflex in hypertensive individuals results in sustained stimulation of sympathetic system, including renal sympathetic nerve activity (RSNA) and increase in arterial pressure. RSNA alterations in response to arterial baroreceptors are sustained in both short- and long-term regulation of arterial pressure. Nitric oxide is a mediator of this regulation [33,34].

Increased RSNA stimulates tubular sodium reabsorption, and contributes to renal vasoconstriction, decreased blood flow, and diminished glomerular filtration. The decrease of renal excretory function leads to body fluid and sodium retention, and, ultimately, to systemic hypertension. The fact that bilateral renal denervation prevents the development of hypertension in obese patients [35] seems to confirm the above data.

7.2. POTENTIAL MECHANISM OF THE HYPOTENSIVE ACTIONS OF GHRELIN

Various evidence seems to suggest that ghrelin participates not only in feeding behaviour but also in cardiovascular and sympathetic regulations. It is likely that ghrelin decreases blood pressure by

TABLE 1. THE CHARACTERISTICS OF PATIENTS.

	PRE-TREATMENT	POST-TREATMENT	P
BODY WEIGHT (KG)	96.7 ± 17.2	87.9 ± 15.7	<0.001
BMI (KG/M^2)	36.5 ± 5.4	33.4 ± 5.2	<0.001
FFM (KG)	53.8 ± 6.9	51.5 ± 6.8	<0.05
FFM (%)	56.4 ± 7.9	59.3 ± 5.9	<0.01
FAT TISSUE (KG)	42.2 ± 13.6	35.6 ± 10.6	<0.001
FAT TISSUE (%)	43.2 ± 7.9	40.3 ± 6.0	<0.01
HR (BPM)	76.6 ± 3.0	71.2 ± 2.4	P = 0.036
SBP (MMHG)	119.6 ± 13.3	114.8 ± 13.8	<0.01
DBP (MMHG)	80.0 ± 11.9	77.4 ± 9.7	No significance
GHRELIN (PG/ML)	66.9 ± 13.7	73.9 ± 15.4	0.005
INSULIN (μUI/ML)	15.7 ± 7.2	14.4 ± 10.5	no significance

BMI, Body Mass Index; FFM, Fat-Free Mass; HR, Heart Rate; SBP, Systolic Blood Pressure; DBP, Diastolic Blood Pressure.

central suppression sympathetic activity. It also probably modulates heart rate and baroreflex control of renal sympathetic nerve activity [36].

In animal model a decrease of arterial pressure without a change in heart rate has been observed following intracerebroventricular ghrelin administration [37]. Ghrelin suppressed the renal sympathetic activity (RSNA) and augmented baroreflex control of RSNA and HR. The intravenous injection of high ghrelin doses decreased arterial pressure and HR without causing a significant change in RSNA.

Since the depressor response to intravenous ghrelin injection was not accompanied by tachycardia, a mechanism other than that of direct vasodilatation is involved in the response. The above data suggest that systemic administration of ghrelin causes suppression of central sympathetic activity thus contributing to decrease in arterial pressure and HR.

Both intravenous and intracerebral ghrelin infusion increased plasma GH concentrations. Moreover, ghrelin has been demonstrated to exert a vasodilatory effect in humans [38], namely, intravenous injections of human ghrelin seem to decrease blood pressure without increasing HR. Ghrelin increases the stroke volume and cardiac index not only in patients with congestive heart failure [25], but also in healthy men [39].

Until now, all studies on the location of central ghrelin action have been performed in animal models. Their authors have shown that ghrelin acts at the nucleus of the solitary tract to suppress sympathetic activity and to decrease arterial pressure in rats [38].

The nucleus of solitary tract constitutes the region where baroreceptors and chemoreceptors afferents terminate; thus, the brain region plays an important role in the regulation of blood pressure and sympathetic activation. Activation of the nucleus of solitary tract by L-glutamate, an excitatory neurotransmitter in the brain, decreases arterial pressure and inhibits RSNA [40]. Other regions of central ghrelin action are also located at the medulla oblongata — in the dorsomotor nucleus of the vagus, and the arcuate hypothalamic nucleus. Mechanisms of action are the same, i.e., modulation of the sympathetic nervous system and

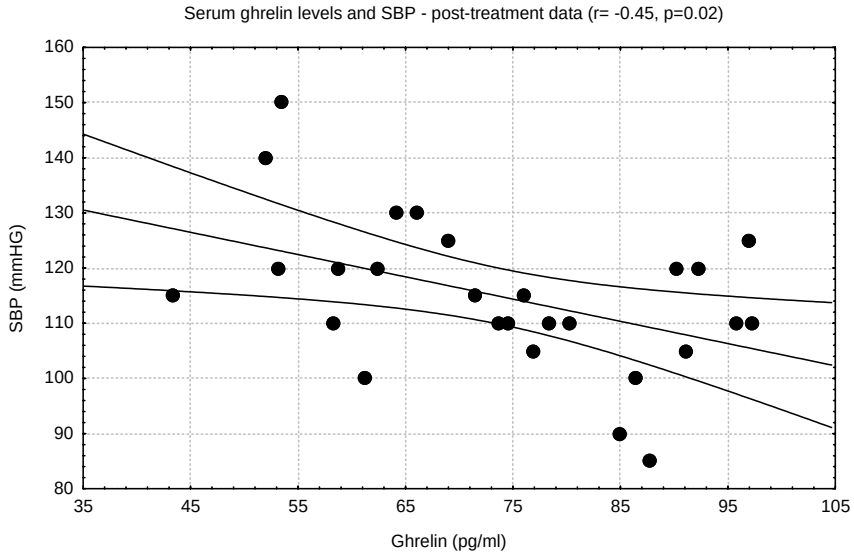

FIGURE 1. THE POST-WEIGHT REDUCING TREATMENT DATA ABOUT SERUM GHRELIN LEVELS AND SBP ($r = -0.45$; $P = 0.02$).

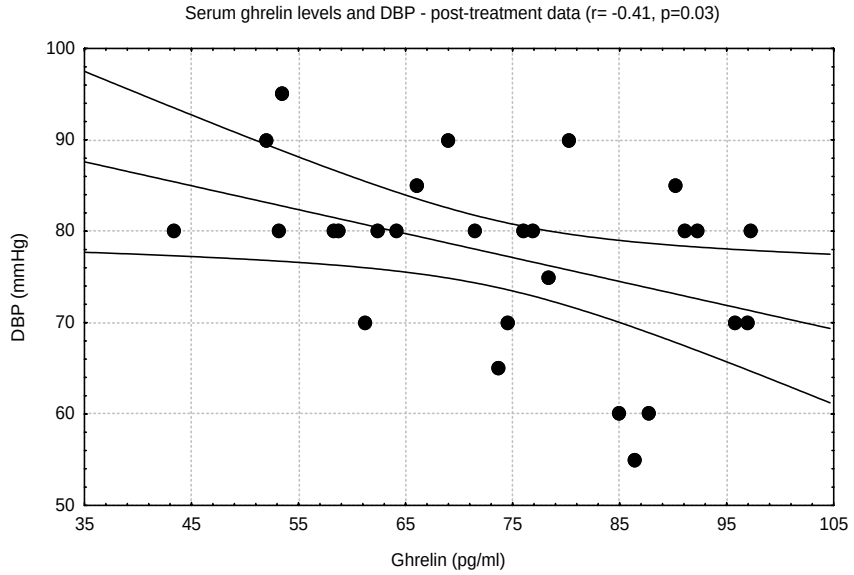

FIGURE 2. THE POST-WEIGHT REDUCING TREATMENT DATA ABOUT SERUM GHRELIN LEVELS AND DBP ($r = -0.41$; $P = 0.03$).

baroreflex control.

Prolonged central administration of ghrelin increases both neuropeptide Y and agouti-related protein (AGRP) mRNA levels in the arcuate nucleus [41]. AGRP is an endogenous melanocortin-3 and -4 receptor (MC4-R) antagonist. Thus, central effects of ghrelin injection may be mediated by neuropeptide Y activation, and AGRP MC3-R and MC4-R suppression. The data are based mainly on animal studies; intracerebroventricular injections

contained high doses of ghrelin – probably exceeding physiological range. Indirect conclusion might be that physiological levels of central ghrelin modulate NPY and AGRP action. The effects of prolonged small-dose ghrelin administration on cardiovascular system remain to be investigated.

When we analyse the potential mechanisms of the hypotensive actions of ghrelin, its metabolic, antiinflammatory, antioxidant, and genetic mechanisms should also be taken into account. Ghrelin serum levels correlate negatively with insulin-resistance – another pathomechanism in obesity-induced hypertension [17]. However, only sympathetic-activity-increasing hyperinsulinemia contributes to systemic hypertension. The lack of this correlation in Pima Indians might account for low prevalence of hypertension in this population [42].

Antiinflammatory and antioxidant ghrelin action contributes to suppression of atherosclerosis and vascular remodelling, and, secondarily, to delayed increase of total peripheral resistance. Ghrelin-stimulated increase in NO synthesis may also be of some importance for hypertension development.

Ghrelin Arg51Gln mutation is a risk factor for type 2 diabetes and hypertension; additionally, 51Gln carriers have lower IGF-1 concentrations and higher IGFBP-1 levels compared to non-carriers. The data suggest that the mechanism might be associated with low GH production [43].

7.3. GHRELIN VS LEPTIN IN CARDIOVASCULAR SYSTEM

Currently, ghrelin is studied very thoroughly and novel mechanisms of its action are being discovered. However, the available data are yet limited, and especially in comparison to data on leptin, which exerts effects inverse to those of ghrelin.

Both leptin and ghrelin are secreted by peripheral tissue, however, they reach the brain to transmit peripheral metabolic information. Both substances engage central neural pathways involved in regulating energy homeostasis, especially by modulation of central sympathetic activation.

Leptin increases sympathetic activity and blood pressure by activation of neurons containing alpha-melanocyte stimulating hormone, and cocaine- and amphetamine-regulated transcript peptides [44,45]. Cardiovascular action of alpha-melanocyte stimulating hormone is mediated through melanocortin-4 receptor; agouti-related protein constitutes an endogenous melanocortin-4 receptor antagonist. As explained above ghrelin acts in opposite direction, it constitutes a natural leptin antagonist not only in metabolic processes but in central cardiovascular homeostasis, too.

In obesity, leptin levels are increased because of leptin resistance. The concept of selective leptin resistance with maintenance of its renal sympathoactivation, might explain the role of leptin in sympathetic overactivity in obesity. Currently it is not known whether it is ghrelin resistance or selective resistance that plays a role in obesity.

7.4. GHRELIN AS A POTENTIAL FACTOR REDUCING BLOOD PRESSURE – OUR EXPERIENCE

Literature data and our previous observations suggested that ghrelin might be regarded as a new challenge in clinical research into metabolic syndrome [20,21,46,47]. Thus we designed a study to evaluate a potential relationship between weight loss treatment, blood pressure and serum ghrelin concentrations in obese women.

The examinations were carried out in 37 premenopausal women with simple obesity without previous history of hypertension (mean age 40.7 ± 11.0 years; mean body weight 96.7 ± 17.2 kg; mean body mass index – 36.5 ± 5 kg/m^2). Possible secondary causes for obesity were ruled out based on case history, physical examination, and laboratory tests (e.g., determinations of glucose and hormones levels). Mean values of blood pressure ranged: SBP 119.6 ± 13.3 mmHg, DBP 80 ± 11.9 mmHg.

The examination (i.e, blood pressure, body composition, ghrelin and insulin serum concentrations) was carried out twice: before and after an

effective, three-month weight reduction treatment, which comprised a low calorie diet (1000 kcal) with water and vitamin supplementation, constant daily sodium and potassium intake, and physical exercises. Additionally, group instruction in behavioural and dietary methods of weight control was presented out every two weeks.

The exclusion criteria included: evidence of present or recent (preceding 3 months) infectious disease, fever, and drug therapy.

8. RESULTS

A 3-month weight reduction treatment, which allowed for 8.9 ± 4.8 kg weight loss, resulted in a significant decrease of body mass index values (36.5 ± 5.4 kg/m^2, 33.4 ± 5.2 kg/m^2, respectively) and changes in body composition as assessed by impedance method (TABLE 1). The heart rate slowed down compared to baseline values (76.6 ± 3.0 vs 71.2 ± 2.4 bpm, P = 0.036). The post-treatment SBP was significantly lower in comparison to pre-treatment values (120 ± 13 vs 115 ± 14 mmHg, P = 0.01). There were not any differences between baseline and post-treatment DBP values (TABLE 1). Mean serum ghrelin concentration significantly increased after 3-month weight reduction treatment (66.9 vs 73.9 pg/mL; P = 0.005). Serum insulin concentrations were comparable before and after follow up (TABLE 1).

PRE-TREATMENT CORRELATIONS. The statistical analysis of baseline parameters did not reveal any correlation between ghrelin levels and assessed clinical data. Insulin levels correlated positively with weight (r = 0.43, P = 0.02), and BMI (r = 0.42, P = 0.03). The baseline SBP correlated with age (r = 0.47, P = 0.01), BMI (r = 0.55, P = 0.003), and body composition indexes. The baseline DBP correlated with both BMI (r = 0.45, P = 0.02) and body composition indexes.

POST-TREATMENT CORRELATIONS. The analysis of post-treatment data revealed that SBP correlated negatively with ghrelin levels (r = -0.45, P = 0.02) (FIG. 1), and positively with insulin levels (r = 0.44, P = 0.02). Similar to the baseline findings, the post-treatment SBP also correlated with age (r = 0.48, P = 0.01), BMI (r = 0.52, P = 0.005) and indexes of body composition.

There were also significant correlations between DBP and ghrelin (r = -0.45, P = 0.02) (FIG. 2) and insulin levels (r = 0.44, P = 0.02). Additionally, DBP correlated with BMI (r = 0.49, P = 0.01) and FFM (r = -0.46, P = 0.02).

There were significant correlations between: post-weight loss values of ghrelin levels and SBP (r = -0.450, P = 0.018), DBP (r = -0.415, P = 0.031); and Δghrelin levels and ΔSBP (r = 0.516, P = 0.006), ΔDBP (r = 0.529, P = 0.005). There was positive correlation between increase of ghrelin and decrease of body fat % during weight loss (P = 0.002).

8. DISCUSSION

The present study evaluated potential relationships between the concentrations of ghrelin and blood pressure values in obese women undergoing complex management for obesity. At the enrolment we did not observe any correlations between the above-discussed parameters. However, following weight-loss treatment, significant negative correlations were noted between ghrelin serum levels and SBP, DBP values. We did not find similar reports in literature.

It should be pointed out that the remaining correlations, e.g. between insulin and BMI, have been well-documented in the literature [48]. This confirms that our study used optimum methods and protocol.

It is unclear what mechanism – vascular, myocardial or both may be responsible for the observed hemodynamic effects of ghrelin. However, the decrease in systolic pressure and heart rate seems to confirm the role of sympathetic activity suppression, probably mediated by ghrelin in the central nervous system. The observed decrease of blood pressure after weight loss may

have also resulted from increased ghrelin and/or increased insulin sensitivity. It should be emphasized that we assessed insulin levels only, and did not find any differences between the baseline and post-weight loss measurements. Our study seems to confirm the hypothesis that weight loss-associated blood pressure decrease in obese patients might be an effect of some ghrelin-dependent mechanism.

9. MORE QUESTIONS OR ANSWERS?

As several metabolic, neuroendocrine and hemodynamic factors affect blood pressure, the identification of a primary causative mechanism underlying hypertension development would hardly be possible. However, new data on hypertension pathophysiology might help establish novel targets for hypotensive therapy. Ghrelin seems to be promising as such a target, and especially, because modifications of its activity result in sympathetic suppression.

The guidelines of hypertension management do not recommend high doses of one medicine, but a complex therapy. Ghrelin mechanism might become incorporated into such management, and possibly exert beneficial effects in the treatment of both heart failure and systemic hypertension. Further research into similar mechanisms is definitely necessary.

10. SUMMARY

Presently available data on ghrelin, which is a new peptide involved in the regulation of appetite, metabolism and cardiovascular system, seem to be quite promising for explanation of pathophysiology of hypertension. Through sympathetic suppression, improvement of baroreflex control, and probably also peripheral vasodilatation, ghrelin can exert positive hemodynamic effects. Some other ghrelin-related mechanisms such as antiinflammatory and antioxidant action, insulin-resistance modulation, as well as contra-regulation of food intake might also be of importance. However, ghrelin constitutes a part of network, i.e., it both influences and is influenced by several factors. At present it is still unknown whether changes of ghrelin axis in obesity and hypertension should be classified as alterations or adaptations. It is probable that neurotransmitters, such as leptin, ghrelin, NPY and AGRP, all participate in arterial pressure and sympathetic regulation. These peptides, and especially ghrelin, are considered to be the most promising targets for the development of both novel anti-obesity and hypotensive drugs.

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