Original Article

An α_1 -Receptor Blocker Reduces Plasma Leptin Levels in Hypertensive Patients with Obesity and Hyperleptinemia

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Obesity is often complicated by hypertension, and both conditions are risk factors for atherosclerosis. Leptin has attracted attention as a possible cause of hypertension in obese persons. We investigated the effect of a slow-release α_1 -receptor blocker, bunazosin hydrochloride, on leptin levels and insulin resistance in obese hypertensive patients with hyperleptinemia. The subjects were 17 patients (12 men and 5 women aged 56.1 ± 12.2 years) with essential hypertension who were not receiving α_1 -receptor blockers. They had a body mass index (BMI) ≥ 25 kg/m² and a plasma leptin concentration ≥ 5 ng/ml. They received oral therapy with bunazosin hydrochloride at doses of up to 9 mg/day. The plasma leptin concentration, body weight, blood pressure, heart rate, fasting blood glucose, plasma insulin concentration, and free fatty acid level were compared between before and after treatment. Although there was no significant change of BMI, there was a significant decrease of plasma leptin after treatment (10.6 ± 5.4 ng/ml vs. 8.7 ± 3.4 ng/ml, $p=0.0128$), as well as a significant decrease of plasma insulin (9.8 ± 4.8 μ U/ml vs. 8.1 ± 4.6 μ U/ml, $p=0.0494$) and HOMA-R (2.9 ± 2.1 vs. 2.2 ± 1.5 , $p=0.0237$). In conclusion, bunazosin hydrochloride reduced the plasma leptin level and improved insulin resistance in hypertensive patients with obesity and hyperleptinemia. (*Hypertens Res* 2006; 29: 805–811)

Key Words: leptin, hypertension, obesity, α_1 -receptor blocker

Introduction

Obesity is commonly complicated by other lifestyle-related diseases such as hypertension, diabetes, and hyperlipidemia, which are risk factors for arteriosclerosis, associated with coronary artery disease. Hypertension is often associated with obesity (1), but many points remain unclear regarding the mechanism of this association.

In recent years, leptin has received much attention as one of the possible causes of hypertension associated with obesity. Leptin is a hormone produced by adipocytes (2) that chiefly acts on leptin receptors in the hypothalamus. In addition to suppressing food intake (3–5), leptin promotes weight loss by

enhancing sympathetic nerve activity (6) to increase thermogenesis in brown adipose tissue (7, 8), which results in considerable energy consumption (9–11). Presumably, this action also causes the release of catecholamines from sympathetic nerve terminals and leads to vasoconstriction that increases the blood pressure (12–14).

Transgenic mice with overexpression of leptin have persistently high plasma leptin concentrations and their blood pressure is significantly increased compared with that of control mice (15–17). In addition, the daily urinary excretion of catecholamines is increased by 2.5-fold in these mice and sympathetic activity is persistently enhanced. When low doses (that did not affect blood pressure in control mice) of an α_1 -receptor blocker (bunazosin hydrochloride) and a β -receptor

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Table 1. Effects of Bunazosin Therapy on Clinical Variables (n=17)

	Baseline	2 months of treatment
Age	56.1±12.2	
Sex (male:female)	12:5	
BMI	29.3±3.9	29.1±4.1
SBP (mmHg)	139.1±13.6	129.1±15.2*
DBP (mmHg)	83.5±12.7	78.6±11.1
Heart rate (bpm)	63.6±10.6	65.0±10.3
Leptin (ng/ml)	10.6±5.4	8.7±3.4*
IRI (μU/ml)	9.8±4.8	8.1±4.6*
Glucose (mg/dl)	111.7±28.1	106.4±20.7
HOMA-R	2.9±2.1 (1.0–9.3)	2.2±1.5* (0.4–6.4)
Medications (n)		
Calcium antagonists	10	
ACE inhibitors	7	
ARB	2	
β-Blockers	8	
Statins	6	

* $p < 0.05$ vs. baseline. BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; IRI, immunoreactive insulin; HOMA-R, homeostasis model assessment of insulin resistance; ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker.

blocker (propranolol) or a sympathetic blocker (hexamethonium) were administered intraperitoneally to such transgenic mice, there was a significant decrease of blood pressure. These findings suggest that leptin may increase blood pressure through enhancement of sympathetic activity (18, 19).

Clinically, the plasma leptin concentration shows a positive correlation with the percent body fat (6, 20), and leptin levels are significantly increased in obese patients. There is also a positive correlation between the plasma leptin concentration and the blood pressure (21, 22), indicating that hyperleptinemia due to an increase of body fat is involved in the mechanism of hypertension associated with obesity.

In obese persons, leptin is secreted by adipocytes after the ingestion of food, but there is resistance to the suppression of food intake by this hormone and weight loss does not occur, so the lack of negative feedback due to weight adjustment means that the production of leptin is promoted, resulting in hyperleptinemia (23, 24). Because there is no mechanism to limit the effect of leptin on the sympathetic nervous system (25), blood pressure is also increased.

Although leptin resistance in obese persons results in the impaired suppression of food intake, leptin still influences the sympathetic nervous system, so these people have selective leptin resistance (26). Hyperleptinemia due to such selective leptin resistance has been reported to be a risk factor for cardiovascular disease and hypertension (27–32).

Despite the known association between leptin and high

Fig. 1. Body mass index (BMI) before and after bunazosin treatment. There was no change of the BMI after treatment.

blood pressure, there have been few investigations of the changes of blood pressure and leptin levels when patients are treated for hypertension complicated by hyperleptinemia. Accordingly, we investigated the changes of leptin levels and insulin resistance in obese patients who had hypertension and hyperleptinemia during treatment with a slow-release α_1 -receptor blocker, which has already demonstrated efficacy for hypertension in patients with abnormal glucose/lipid metabolism (33–36).

Methods

We enrolled patients with essential hypertension, a body mass index (BMI) ≥ 25 kg/m², and a plasma leptin concentration ≥ 5 ng/ml who were seen at the Institute of Geriatrics or the Aoyama Hospital of Tokyo Women's Medical University from April 2004 to April 2005. The patients were either untreated (blood pressure $> 140/90$ mmHg) or were being treated with antihypertensive agents other than α_1 -receptor blockers. The present study was conducted in accordance with the Declaration of Helsinki and the patients gave informed consent after receiving a written explanation. We enrolled a total of 17 patients, or 12 men and 5 women with a mean age of 56.1 ± 12.2 years. Five of the patients also had diabetes, among whom 2 were receiving treatment with sulphonylureas or α -glucosidase inhibitors. None of the patients were taking medications to improve insulin resistance. The concomitant drugs were calcium antagonists, ACE inhibitors, angiotensin II receptor antagonists, β -blockers, and statins in 10, 7, 2, 8, and 6 patients, respectively (Table 1). During the study, these concomitant therapies were not changed and new drugs that were likely to influence the blood pressure were not administered. Patients were reviewed at monthly intervals during treatment, with the plasma leptin concentration, body weight, and blood pressure being measured. Blood pressure was measured at the arm twice with a 1-min interval between measurements after the patient had been seated for at least 5 min. The heart rate, fasting plasma glucose level, and plasma

Fig. 2. Blood pressure before and after bunazosin treatment. Systolic blood pressure (SBP) decreased significantly after treatment (A), but diastolic blood pressure (DBP) did not (B).

insulin concentration were also measured. Blood samples were obtained after the patient had been seated for at least 5 min in the morning following a 10-h fast. It was confirmed that there was no rapid weight gain, weight loss, or sudden change of the plasma leptin level. A slow-release α_1 -receptor blocker, bunazosin hydrochloride (Detantol®, Eisai Co., Ltd., Bunkyo-ku, Tokyo, Japan), was administered orally from a starting dose of 3 mg once a day in the morning, and the dose was increased up to 9 mg if adequate blood pressure control was not obtained. The plasma leptin concentration, body weight, blood pressure, heart rate, fasting plasma glucose, plasma insulin, and free fatty acid levels were measured after 2 months of bunazosin treatment and were compared with the baseline values before treatment. Homeostasis model assessment of insulin resistance (HOMA-R) was employed to investigate insulin resistance.

Student's paired *t*-test was used to compare values obtained before and after treatment. Results are expressed as the mean $\pm$ SD. For all analyses, the level of significance was set at $p < 0.05$.

Fig. 3. Heart rate before and after bunazosin treatment. There was no change of the heart rate after treatment.

Results

Body Mass Index

Figure 1 shows the BMI before and after the start of treatment with slow-release bunazosin hydrochloride. The BMI values were 29.3 ± 3.9 kg/m² and 29.1 ± 4.1 kg/m² before and after administration, respectively, showing no significant change.

Blood Pressure

Systolic blood pressure decreased significantly ($p=0.0025$) from 139.1 ± 13.6 mmHg before treatment to 129.1 ± 15.2 mmHg after the administration of bunazosin (Fig. 2A). The diastolic blood pressure also decreased, from 83.5 ± 12.7 mmHg before treatment to 78.6 ± 11.1 mmHg after administration, but the change was not significant (Fig. 2B).

Heart Rate

Figure 3 shows the heart rates before and after the start of treatment with slow-release bunazosin hydrochloride. The heart rates were 63.6 ± 10.6 bpm and 65.0 ± 10.3 bpm before and after administration, respectively, showing no significant change.

Plasma Leptin Concentration

Figure 4 shows the plasma leptin concentration before and after the start of treatment with bunazosin hydrochloride. Plasma leptin decreased significantly from 10.6 ± 5.4 ng/ml before administration to 8.7 ± 3.4 ng/ml after administration ($p=0.0128$). Even after excluding two subjects with extremely high leptin levels, a significant difference was still recognized after the start of administration (9.0 ± 3.1 ng/ml vs. 7.9 ± 2.8 ng/ml, $p=0.0140$).

Fig. 4. Changes of plasma leptin levels with bunazosin treatment. The plasma leptin level was decreased significantly after treatment.

Insulin Resistance

As shown in Fig. 5A, plasma insulin decreased significantly from 9.8 ± 4.8 $\mu\text{U/ml}$ before administration of bunazosin to 8.1 ± 4.6 $\mu\text{U/ml}$ after the start of treatment ($p=0.0494$). Fasting plasma glucose showed a slight decrease from 111.7 ± 28.1 mg/dl before administration to 106.4 ± 20.7 mg/dl after administration, but this change was not significant (Fig. 5B). HOMA-R decreased significantly from 2.9 ± 2.1 before administration to 2.2 ± 1.5 after administration ($p=0.0237$), indicating an improvement of insulin resistance (Fig. 5C). Even after excluding two patients with extremely high immunoreactive insulin (IRI) and HOMA-R values, HOMA-R still decreased significantly with bunazosin treatment (2.6 ± 2.1 vs. 2.0 ± 1.5 , $p=0.0476$).

Free Fatty Acids

Free fatty acids showed a slight decrease from 0.80 ± 0.37 mEq/l before bunazosin administration to 0.69 ± 0.34 mg/dl after administration ($p=0.0697$), but this change did not reach the level of statistical significance (Fig. 6) because the number of patients was small.

Discussion

Because α_1 -receptor blockers can improve glucose and lipid metabolism (33–36), these agents are presently positioned as first-line drugs for the treatment of hypertension associated with abnormal glucose/lipid metabolism in the guidelines for management of hypertension issued by the Japanese Society of Hypertension. However, there have been no investigations into the effect of these drugs on plasma leptin levels in obese patients with hypertension. In the present study, we administered slow-release bunazosin hydrochloride, an α_1 -receptor blocker, to obese patients with hypertension and hyperleptinemia and observed a significant decrease of the plasma lep-

Fig. 5. Changes of plasma insulin, fasting plasma glucose, and insulin resistance with bunazosin treatment. Plasma insulin decreased significantly after treatment (A), but fasting plasma glucose did not change significantly (B). HOMA-R also decreased significantly after treatment, indicating an improvement of insulin resistance (C).

tin concentration.

Leptin is a hormone that adjusts body weight, so changes of

Fig. 6. Changes of free fatty acids with bunazosin treatment. The free fatty acid level decreased slightly after treatment, but this change was not significant.

the plasma leptin level are usually related to increases and decreases of weight. However, plasma leptin levels decreased significantly after administration of bunazosin in this study, even though BMI did not change significantly. These findings indicate that bunazosin therapy itself caused a decrease of plasma leptin. There was also a significant decrease of the plasma insulin concentration and a decrease of fasting plasma glucose after administration of bunazosin, indicating the improvement of insulin resistance.

While the mechanism by which α_1 -adrenoreceptor blockade improves insulin resistance is unknown, it has been proposed that systemic arteriolar dilatation may increase tissue blood flow and the responsiveness to glucose (37). Improvement of insulin sensitivity accompanied by an increase of lipoprotein lipase activity and decreased very low-density lipoprotein (VLDL) production are the most likely mechanisms responsible for the influence of α_1 -receptor blocker therapy on lipid metabolism (38).

There are still many uncertainties regarding the exact relationship between insulin resistance and leptin resistance, but several studies have shown a close correlation (39–44). The plasma leptin concentration also shows a positive correlation with HOMA-R, which is an index of insulin resistance (45). Accordingly, hyperleptinemia and insulin resistance are commonly associated, suggesting that bunazosin hydrochloride may have decreased the plasma leptin concentration because improvement of insulin resistance (40, 41) decreased the plasma insulin level and led to a secondary decrease of leptin. It is also likely that a decrease of the leptin level would lead to further improvement of insulin resistance. We examined the relationship between changes of leptin and insulin resistance, but we did not find a significant correlation because the number of patients studied was small. Free fatty acids have been reported to show a close relationship with leptin (46–50), so another possible mechanism to explain our findings is that a decrease of plasma free fatty acids due to administration of bunazosin hydrochloride (35, 36) may have reduced leptin

secretion by adipocytes.

Although we observed a relationship between α_1 -receptor mediated signaling and the plasma leptin level, the number of patients in this study was small, so larger studies are needed to confirm our findings, particularly the potential of α_1 -receptor blocker therapy for improving leptin resistance.

In conclusion, our study showed that slow-release bunazosin hydrochloride, an α_1 -receptor blocker, can improve insulin resistance and decrease the plasma leptin level in hypertensive patients with hyperleptinemia. Such effects may help to improve lifestyle diseases that accompany obesity, such as diabetes and hypertension, and thus decrease the risk of cardiovascular disease. Similar effects have been reported for another α_1 -blocker, suggesting that the action of α_1 -blockers is special in this regard (51).

Accordingly, slow-release bunazosin hydrochloride seems to be a useful drug for obese patients with hypertension and hyperleptinemia.

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