Positive Effect of Baclofen on Body Weight Reduction in Obese Subjects: A Pilot Study

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Abstract

Background and objective We previously reported that baclofen, a GABA_B agonist, reduces body weight in obese mice. In this clinical study, we examined the possibility that baclofen might serve as an effective therapeutic agent for obesity in humans.

Methods Seven women and three men ranging from 25-51 years of age and 31.3-41.0 kg/m² body mass index were included in the study. Baclofen, which was started at a dose of 15 mg/day and increased to 30 mg/day in 10 days, was administered for 12 weeks.

Results Administration of baclofen for 12 weeks significantly decreased both body weight (baseline: 93.30 ± 9.80 kg, 12 weeks: 91.70 ± 10.30 kg) and waist circumference (baseline: 107.9 ± 9.0 cm, 12 weeks: 105.6 ± 10.0 cm). Serum leptin levels, which possibly reflect the amount of adipose stores, were also decreased significantly by the treatment. On the other hand, there were no significant changes in the blood pressure or metabolism of glucose and lipid. No adverse effects were observed.

Conclusion Although the anti-obesity effects of baclofen in the present study were mild, this pilot study suggests the possibility that baclofen might serve as a new anti-obesity drug in humans.

Key words: baclofen, obesity, leptin

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Introduction

The prevalence of obesity, which is associated with a higher risk of mortality (1), is growing rapidly worldwide (2). While pharmacological treatment for obesity has been explored, the drugs approved for long-term (>12 months) management of obesity by the United States Food and Drug Administration are only sibutramine and orlistat, a serotonin and norepinephrine reuptake inhibitor and a gastrointestinal lipase inhibitor, respectively (3). These drugs have significant side effects such as hypertension and insomnia for sibutramine and diarrhea and flatus for orlistat (3).

Baclofen, a GABA_B agonist, has been used clinically for many years to treat patients with muscle stiffness due to multiple sclerosis and cerebral palsy (4). The signaling of GABA_B receptors in the central nervous system has been implicated in the regulation of energy balance (5); our previ-

ous study (6) showed that baclofen reduces body weight (BW) in diet-induced obesity (DIO) mice as well as *db/db* mice which genetically lack leptin receptors (7). The effects of baclofen on BW and food intake are unique in that baclofen does not affect energy balance in lean control mice (6).

In order to examine the hypothesis that baclofen might work as an anti-obesity drug in humans, we administered baclofen to obese subjects in this clinical study.

Patients and Methods

Design and subjects

This study was performed during the period from November 2008 to February 2010 at the Nagoya University Medical Hospital. The protocol was approved by the institutional review board of the Nagoya University Hospital. All patients gave their written informed consent.

Table 1. Profiles of Subjects

Pt	Gender	age (years)	height (cm)	BW (kg)	BMI (kg/m ²)	waist (cm)	DM	HT	DL
1	M	36	175.0	108.55	35.4	116.5	Yes	Yes*	No
2	F	39	161.2	106.45	41.0	115.0	No	No	Yes
3	F	43	161.3	82.30	31.6	110.0	Yes	No	Yes
4	F	32	169.4	89.65	31.3	93.5	No	No	No
5	F	51	166.9	94.30	33.9	120.0	No	No	Yes
6	F	40	156.0	96.00	39.4	110.5	Yes*	No	No
7	F	37	154.8	83.50	34.8	97.0	No	Yes	No
8	M	25	167.0	96.50	34.6	114.0	Yes	No	No
9	M	38	167.7	92.05	32.7	102.5	Yes*	Yes*	Yes*
10	F	26	155.8	80.40	33.1	100.0	Yes	No	No

DM=diabetes mellitus; HT=hypertension; DL=dyslipidemia; M=male; F=female; *: medications (Patient 1=amlodipine besilate 5 mg/day, candesartan cilexetil 8 mg/day, imidapril hydrochloride 5 mg/day; Patient 6=metformin hydrochloride 750 mg/day, pioglitazone hydrochloride 30 mg/day; Patient 9=metformin hydrochloride 750 mg/day, voglibose 0.9 mg/day, losartan potassium 25 mg/day, furosemide 40 mg/day, spironolactone 25 mg/day, atorvastatin calcium hydrate 10 mg/day).

While eleven subjects were enrolled in the study, the data of one subject were excluded from analyses because she discontinued baclofen for a week due to a cold. As a result, this study involved 7 women and 3 men 25-51 years of age and 31.3-41.0 kg/m² body mass index (BMI) as shown in Table 1. Among 10 subjects, six had diabetes mellitus, three had hypertension, and four had dyslipidemia. Three patients were receiving medications as shown in Table 1. While all subjects had been encouraged to reduce BW by improving lifestyle under the guidance of a physician or a nutritionist before the study, none of them had a BW loss of more than 2% in the preceding 3 months. During the first 3 days of the study, subjects were given a total daily dose of 15 mg racemic baclofen (Novartis, 5 mg after each meal), and the dose was increased to 20 mg on day 4, 25 mg/day on day 7 and 30 mg on day 10. The patients briefly visited the clinic at 4-week intervals (20 minutes at week 0, and each 10 minutes at weeks 4-12), when BW with light clothing, waist circumference and blood pressure were measured along with blood sampling. General encouragement of an appropriate diet was given by the physician at each visit. Changes in appetite and desire to take sweets were assessed every 4 weeks with visual analogue scales using 100 mm lines anchored with a description at each end (0 mm="not at all" and 100 mm="extremely"). The subjects were requested to make a vertical mark on the lines in response to the following questions: "How strong is your appetite?" and "How strong is your desire to take sweets?". For the statistical analyses, the values at baseline were expressed as 100%. The primary endpoint was the changes in BW and waist circumference at 12 weeks in comparison with the baseline values (UMIN 000001573).

Biochemical assays

Blood sampling for fasting blood glucose (FBS), HbA1c and lipid profile was performed at each visit. The serum levels of leptin, adiponectin and insulin were measured by a radioimmunoassay, an enzyme immunoassay and a chemiluminescent immunoassay, respectively, at baseline as well as the end of the study in all subjects. Homeostasis model assessment-insulin resistance (HOMA-IR) was calculated by the following formula: fasting serum insulin (μU/mL) × FBS (mg/dL)/405.

Statistics

The values of all parameters are presented as the mean ± standard deviation. Post-treatment values were compared to those at baseline using paired *t*-test. *p*<0.05 indicated statistical significance.

Results

BW and waist circumference

Administration of baclofen significantly decreased BW (baseline: 93.30 ± 9.80 kg, 12 weeks: 91.70 ± 10.30 kg, *p*<0.05) and waist circumference (baseline: 107.9 ± 9.0 cm, 12 weeks: 105.6 ± 10.0 cm, *p*<0.05). As shown in Fig. 1, BW decreased more than 2% and the waist circumference decreased more than 2 cm in five out of ten subjects. The changes in BW during 12 weeks in these five patients (patient numbers 2, 6, 7, 9 and 10 in Table 1) are shown Fig. 2.

Figure 1. Histogram of changes in BW and waist circumference. Changes in BW (A) and waist circumference (B) after administration of baclofen for 12 weeks are shown.

Figure 2. Time course changes in BW in 5 subjects who lost more than 2% BW after baclofen administration for 12 weeks.

Serum leptin, serum adiponectin, glucose and lipid metabolism and blood pressure

Administration of baclofen decreased serum leptin levels in all patients and the difference was statistically significant (Table 2). On the other hand, there were no significant changes in the levels of adiponectin, FBS, HbA1c, serum insulin, HOMA-IR, serum lipid and blood pressure (Table 2).

Appetite and desire for sweets

Appetite as well as the desire for sweets was significantly decreased by the administration of baclofen (Fig. 3).

Adverse effects

There were no apparent adverse effects throughout the study.

Figure 3. Changes in appetite and desire for sweets. Visual analogue scales were used to monitor changes. Values at baseline (week 0) are expressed as 100%. *, $p < 0.05$ versus values at baseline.

Discussion

In this pilot study, we examined the anti-obesity effects of baclofen in obese subjects. Our data demonstrated that baclofen significantly decreased BW, waist circumference as well as serum leptin levels, which could reflect the amount of adipose tissues (7, 8). As there were no apparent adverse effects throughout the study, it is suggested that baclofen might be used as an anti-obesity drug in humans.

Decreases in BW in obese patients could lead to improvement in hypertension, diabetes and dyslipidemia. In the present study, however, there were no significant changes in blood pressure and metabolism of glucose and lipid. This might be explained by the fact that the anti-obesity effects of baclofen were mild and the subjects of this study were heterogeneous (six had diabetes mellitus, three had hypertension, and four had dyslipidemia). Although the anti-obesity effects of baclofen during the 12-week treatment were mild, further BW decreases might be expected with longer treatment as the BW in the five subjects in whom baclofen was effective still showed a tendency to decrease at 12 weeks. It should be also noted that only one dose of baclofen was examined in this study and that further studies are required to determine the optimal dose as an anti-obesity drug. On the other hand, the fact that five out of 10 patients lost more than 2% BW suggests that some factors affect the anti-obesity effects of baclofen. Although it is not possible to point out the responsible factors due to the relatively

Table 2. Changes in Glucose, Lipid Profiles and Blood Pressure

	week 0	week 12
FBS (mg/dL)	114 ± 20	107 ± 15
HbA1c (%)	5.8 ± 1.0	5.7 ± 1.0
Insulin (μU/mL)	19.0 ± 7.2	17.2 ± 8.5
HOMA-IR	5.4 ± 2.4	4.7 ± 2.7
Leptin (ng/mL)	19.8 ± 7.6	16.0 ± 8.2*
Adiponectin (μg/mL)	8.9 ± 5.4	8.6 ± 4.5
Cholesterol (mg/dL)		
Total	192 ± 32	189 ± 27
LDL	119 ± 29	121 ± 28
HDL	50 ± 10	47 ± 8
Triglyceride (mg/dL)	141 ± 83	142 ± 58
Blood pressure (mmHg)		
Systolic	124 ± 12	122 ± 12
Diastolic	81 ± 11	79 ± 12

*, p<0.05 versus values at baseline (week 0).

small number of subjects involved in this study, it is noteworthy that two patients who had been taking metformin lost BW more than 2%, as metformin itself reportedly decreases BW in obese patients with type 2 diabetes (9). Since there were no apparent changes in BW in these two patients during the three months before the study, it is possible that baclofen and meformin manifested synergic anti-obesity effects in these subjects.

In a previous study, we reported that baclofen reduces BW by decreasing food intake in obese mice (6). Baclofen reportedly penetrates the blood brain barrier (10) and decreases the expression of neuropeptide Y (NPY), one of the most potent orexygenic peptides in the brain (11), in the arcuate nucleus in rodents (5, 6). Thus, the NPY neurons in the arcuate nucleus could be one of the possible sites of action for baclofen. In this study, baclofen decreased appetite, which was evaluated by a visual analogue scale. While these data suggest that baclofen could reduce food intake in obese humans as well, future studies such as a double blinded test or the evaluation of food consumption using a buffet-style meal would be required to confirm this.

GABA_B agonists reportedly reduced self-administration of some drugs such as cocaine, nicotine, alcohol and heroin (12, 13), suggesting they may be useful in the treatment of addictive disorders. Recent studies also reported that baclofen was effective to treat binge-eating of fat in animals (14) as well as binge-eating in humans (15), the mechanisms of which have been postulated to be similar to drug abuse (14). While we have not examined changes in the desire for fat exclusively, the desire to take sweets evaluated by a visual analogue scale was decreased by baclofen in this study. Given the common mechanisms involved in obesity and drug addiction (16), it is possible that baclofen might act as well on the mesocorticolimbic system such as the nucleus accumbens, which has been implicated in reward (17).

The anti-obesity effects of sibutramine and orlistat were enhanced when they were administered in combination with a diet therapy (3). Given that baclofen reduced appetite as well as the desire for sweets in the present study, its anti-obesity effects might also be enhanced by diet therapy. In addition, while racemic baclofen was used in the present study, the effects of R-baclofen on body weight in obese humans are worth examining as R-baclofen was shown to be more effective than S-baclofen in reducing BW in obese mice (6).

In conclusion, we demonstrated that baclofen reduced BW and waist circumference without any apparent adverse effects in obese subjects. Future studies with a placebo group to examine various doses of baclofen for longer periods in a greater number of obese patients are warranted to prove that baclofen could be a new therapeutic agent for obesity.

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