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Failure of Clonidine to Stimulate Feeding in Healthy Humans

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CROW, S., W. MELLER, B. PRAUS, S. RAATZ AND J. MITCHELL. *Failure of clonidine to stimulate feeding in health humans.* PHARMACOL BIOCHEM BEHAV **61**(3) 317–321, 1998.—The α_2-adrenergic system is involved in the regulation of food intake in animals but its effects on feeding in humans are unknown. We hypothesized that clonidine administration would stimulate food intake in healthy human subjects. Ten men and 4 women, all physically and psychiatrically healthy, received clonidine 3 μg/kg or placebo, orally, in blinded, balanced, randomized order. Consumption of a liquid test meal was measured; also, serum growth hormone levels were used as a secondary measure of clonidine effects. Visual analog scale ratings of hunger, satiety, and sedation were obtained before, during, and after the test meal. A subset of five subjects also received 1.5 μg/kg clonidine, in addition to the two trials described above. Test meal consumption was greater following placebo than following clonidine. Sedation ratings were substantially higher at all time points after clonidine and correlated with meal consumption (correlation coefficient $r = -0.584$; $p = 0.028$). Hunger and satiety ratings did not differ. The 1.5 μg/kg dose did not provide different effects on feeding from that seen with placebo. Contrary to our hypothesis, clonidine did not stimulate food intake in humans. Sedation associated with clonidine administration may have suppressed any effects on feeding. © 1998 Elsevier Science Inc.

Clonidine α-Adrenergic system Feeding behavior Satiety

THE α_2-adrenergic system is known to exert a regulatory effect on feeding behavior in animals. Administration of the centrally acting α_2-adrenergic agonist, clonidine, has been shown to promote feeding behavior in numerous animal species, including mice (7), rats (1,2,14–23), rabbits (11), and monkeys (20); this effect appears to hold true whether clonidine is administered peripherally, intraperitoneally, or centrally into either the periventricular nucleus of the hypothalamus or sulcal prefrontal cortex.

Little is known about the effects of clonidine on feeding behavior in humans. However, clonidine administration has been shown to diminish the thermic effect of feeding in humans (21,28). Also, based on its effect in animal models, clonidine has been used in the treatment of anorexia nervosa in one small controlled trial, with negative results (3). However, its effects on food intake in healthy humans have not been reported.

Clonidine is used clinically to treat hypertension in humans; both oral and transdermal patch administration are possible. This drug has also been used as a research tool to examine the function of the α_2-adrenergic system in psychiatric illness. In healthy controls, clonidine administration via the intravenous (12) or oral (13) routes leads to elevation of circulating growth hormone levels. A characteristic blunting of this response in depression provides some of the strongest evidence for involvement of the α_2-adrenergic system in that illness (24). Similar abnormalities in cortisol response and REM sleep patterns also occur (22,25).

The aim of this study was to investigate the effects of clonidine administration on feeding in humans. We hypothesized that, similar to the effects seen in animal systems, oral administration of clonidine would result in acutely increased food consumption.

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METHOD

Subjects

Fourteen healthy, weight-stable individuals between the ages of 18–50 (average 24.9, range 21–30 years old, 10 women and 4 men) were invited to participate in the study. All subjects were within 15% of ideal body weight as determined by the Metropolitan Height and Weight tables (1973). A clinical interview was used to obtain prior health history and exclude any subjects with gastrointestinal and other significant medical illnesses. Subjects completed the Structured Clinical Interview for DSM-III-R-Patient Version (SCID-P) (26) and the Hamilton Depression Inventory to rule out current or lifetime psychiatric illnesses. We chose this exclusionary criterion based on substantial evidence of α_2-adrenergic dysregulation in mood disorders (22,24,25). All subjects were instructed, by a registered dietitian, in the completion of 3-day dietary records that were completed for the 3 consecutive days prior to each CRC visit. Also, at the time of initial evaluation, electrolytes, complete blood count, and thyroid function tests were drawn, to help exclude active medical illnesses.

Approval was obtained from the Institutional Review Board prior to initiating the study, and informed consent was obtained from each subject at the time of initial evaluation.

Subjects completed 3-day dietary records immediately prior to each CRC admission.

Procedures

Subjects were admitted to the Clinical Research Center by 1600 h on day 1. An intravenous line was placed in the forearm to provide subsequent easy and painless access for blood draws so as not to interfere with growth hormone levels. Also, this provided easy access for IV fluid administration for any subjects developing significant hypotension (which was never required). A standardized meal was consumed at 1700 h, consisting of 900 kcal (46% carbohydrate, 19% protein, 35% fat). A standard snack was then provided at 2000 h consisting of 302 kcal (60% carbohydrate, 10% protein, 30% fat). Thereafter, patients were NPO until morning.

In the morning of day 2, growth hormone levels were drawn hourly beginning at 0600 h until noon. At 0700 h, the blinded study medication was given as described below. At 0800 h a test meal was given again as described below. The medication used was oral clonidine in a dose of 3 μg/kg. The medication or placebo was administered in a blinded fashion, and a balanced randomization for order of administration was used.

The test meal, presented at 0800 h, consisted of vanilla-flavored Carnation Instant Breakfast prepared in whole milk. The mixture was consumed, through a straw, from a container hidden in wooden box approximately 15 × 18 × 24″; this design was chosen to eliminate visual cues as an influence on the amount of liquid meal consumed. An analytical balance interfaced with a laptop computer using Mettler Balance Link software (Mettler-Toledo AG, Switzerland, 1993) was used to provide real time measurements of food consumption. Approximately 2 liters of liquid test meal were available to insure that no subject ran out of test meal.

Subjects completed 100-mm visual analog scales for hunger, satiety, and sedation just prior to receiving the test medication and every 5 min during the test meal through 30 min following its completion. Rating scales were completed for meal palatability upon completion of the test meal. Vital signs, including blood pressure and pulse, were obtained every 30 min between 0600 h and 1200 h on day 2.

When the last growth hormone level had been obtained and the subject was deemed medically stable, the subject was discharged from the research center. Subjects returned at least 3, and no more than 7 days later to complete the second stay. This visit was identical to the first except that the alternate condition, either clonidine or placebo, was given. As before, subjects filled out 3-day dietary record prior to the time of admission.

Because the clinical experience during the study suggested sedation from clonidine in this dosage, a second experiment was instituted. This revised protocol included experimental sessions during which subjects received 1.5 μg/kg, and 3 μg/kg of clonidine in addition to placebo. The three trials were completed as outpatients, with patients arriving at 0600 h on the day of medication administration but were otherwise identical to the procedures above.

Analysis

Meal intake was analyzed using matched-paired *t*-tests. Visual analog scale measures scores were collapsed into premeal, during meal, and postmeal composite averages; these ratings were then analyzed by the use of a repeated measures MANOVA, examining dose (placebo vs. 3.0 μg/kg) by time interactions. Repeated measures MANOVA was also used to examine changes in growth hormone response between the two groups (placebo vs. 3.0 μg/kg) across six time points. Matched-pair *t*-tests were then used to compare groups at specific time points, and to calculate aras under curve.

RESULTS

Complete dietary records were received from 12–14 subjects participating in this study. All records were analyzed with commercially available nutrient analysis software (Nutritionist III, Version 4.0) (18). The records were evaluated for energy and macronutrient intake. Table 1 illustrates the consumption of subjects for the 3 consecutive days prior to each admission to the research center. No statistically significant differences were noted in energy or macronutrient consumption between subjects.

TABLE 1

BASELINE ENERGY AND MACRONUTRIENT INTAKE (MEAN ± SE)

Nutrient	Placebo (n = 12)	Clonidine 1.5 μg/kg (n = 4)	Clonidine 3.0 μg/kg (n = 12)
Energy (kcal)	2144.5 (73.8)	2173 (184)	2070 (140)
Carbohydrate (g)	311.1 (15.4)	270.0 (41.7)	283.1 (25.4)
Protein (g)	67.42 (3.97)	73.2 (13.5)	72.09 (6.53)
Fat (g)	73.67 (4.88)	92.43 (7.18)	72.76 (7.99)

No statistically significant differences were determined between groups.

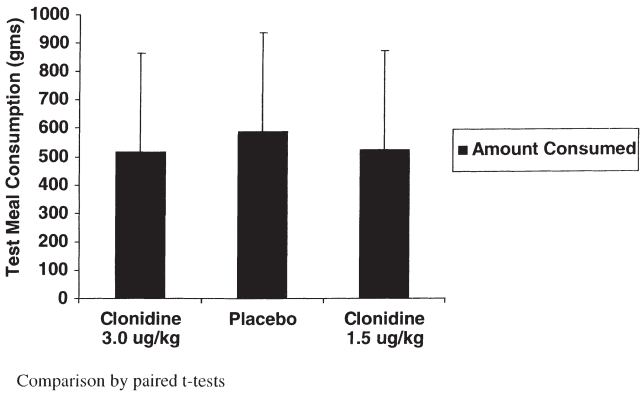

FIG. 1. Test meal consumption.

The amounts of liquid test meal consumed following clonidine and placebo are shown in Fig. 1. Mean meal consumption was lower after 3.0 μg/kg clonidine than with placebo (514.9 ± 331.9 g vs. 586.1 ± 342.0; $p = 0.001$). Visual analog ratings of hunger and satiety are shown in Figs. 2 and 3; no significant differences were seen. Sedation ratings, shown in Fig. 4, did differ between clonidine and placebo, however, with higher ratings of sedation after clonidine at all time points ($p < 0.001$).

Sedation ratings were inversely correlated with meal consumption for subjects receiving clonidine 3.0 μg/kg but not for placebo (Figs. 5 and 6; for clonidine 3.0 μg/kg, correlation coefficient $r = -0.584$, $p = 0.028$; for placebo, correlation coefficient $r = 0.101$, $p = 0.730$).

Body mass index was not correlated with consumption; for clonidine 3.0 μg/kg, correlation coefficient $r = 0.337$, $p = 0.239$; for placebo, correlation coefficient $r = 0.044$, $p = 0.881$).

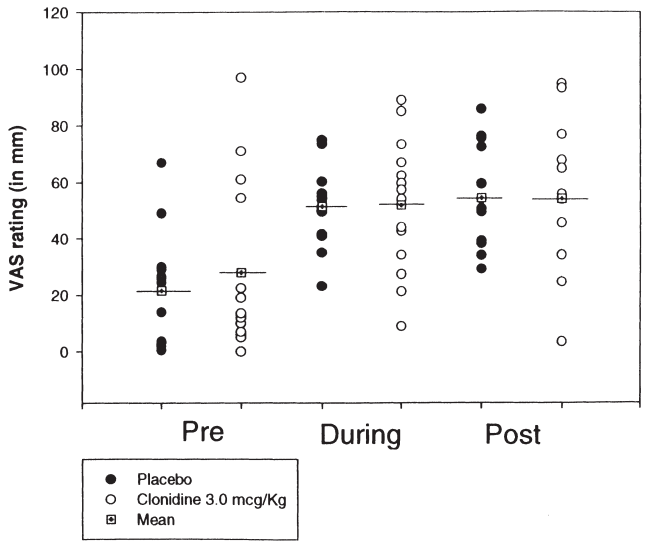

FIG. 3. Satiety rating.

Serum growth hormone measurements are shown in Fig. 7. As expected, growth hormone levels were higher following administration of clonidine 3.0 μg/kg than following placebo (AUC for clonidine 1080.64, SEM 339.67; AUC for placebo 771.85, SEM 198.03; clonidine–placebo = 308.79, SEM 153.04; $p = 0.065$).

In subjects receiving the 1.5 μg/kg dose, growth hormone levels did not differ significantly from those seen in the same subjects with placebo (1.5μg/kg: 1.10 ± 0.54 vs. placebo: 1.84 ± 1.18). In the subjects receiving 1.5 μg/kg clonidine, meal consumption was again lower than following placebo administration although this failed to reach statistical significance (522.0 ± 379.2; $p = 0.087$).

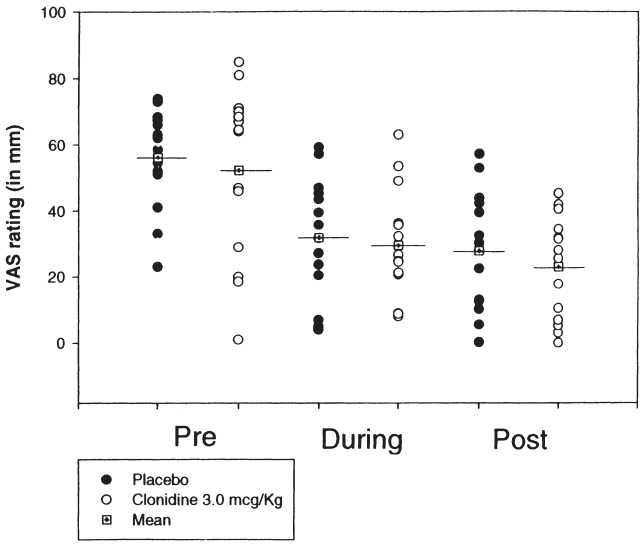

FIG. 2. Hunger rating.

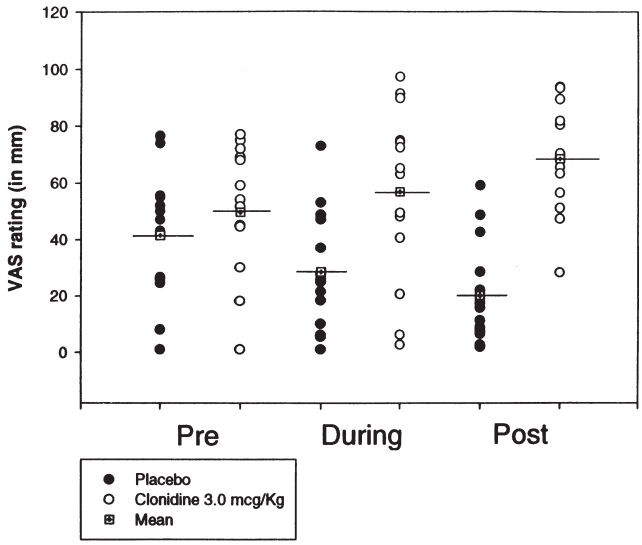

FIG. 4. Sedation rating.

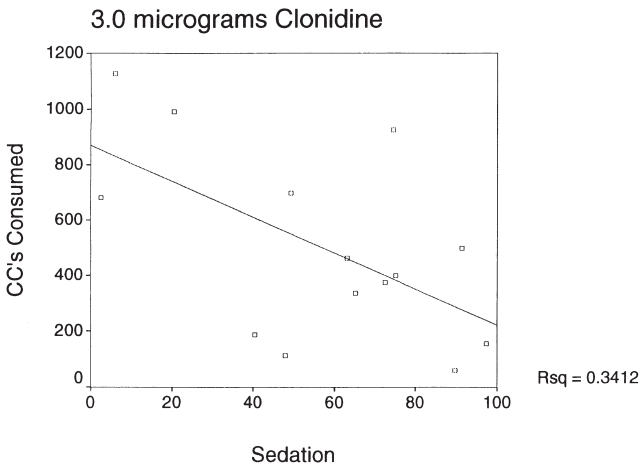

FIG. 5. Consumption and sedation.

DISCUSSION

In this study, clonidine did not stimulate feeding in healthy controls. In fact, lower intake occurred following clonidine administration. There was a wide variability in response to the clonidine with some subjects having a substantial increase but most having little change or a substantial decrement in feeding after the administration of clonidine. Pre- and postmeal ratings of hunger and satiety were very similar between clonidine and placebo days. Sedation ratings, however, were substantially higher in the clonidine condition and were statistically correlated with test meal consumption. It appeared clinically that subjects were substantially sedated on some study days but not on others. It may be that the potential impact of clonidine on feeding was negated by sedation; a similar effect has been described with escalating doses of clonidine used in a rat model (7).

Previous work has defined the pharmacokinetic properties of both oral and intravenous clonidine (8,9). The dose of clonidine used in the current study was based on oral doses that would be expected to yield similar serum levels to prior studies involving intravenous administration. One might hypothesize that a lower dose would have had a greater impact on feeding with less sedation, but the results of the 1.5 μ/kg trial do not support this. In fact, the growth hormone levels from this small sample suggest that 1.5 μ/kg is inadequate to produce the expected increase in growth hormone levels, although a larger sample is clearly required to confirm this. Alternatively, in some animal models of feeding, higher doses have been used. However, the sedation seen in the current study suggests higher doses would not have had a greater effect using this paradigm.

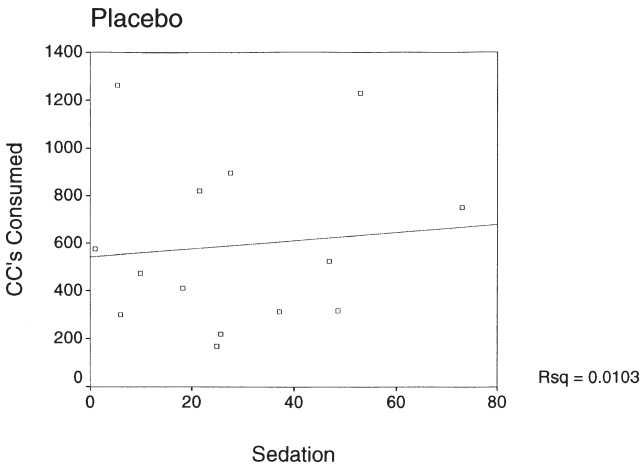

FIG. 6. Consumption and sedation.

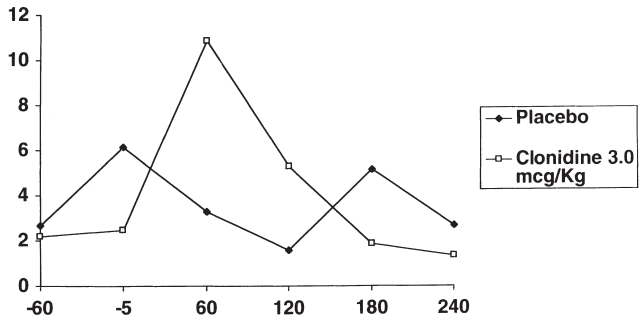

FIG. 7. Growth hormone response.

There was a significant difference in growth hormone levels between the placebo and 3.0 μ/kg conditions. Although this does not in itself ensure that sufficient clonidine was given to achieve any possible effects on feeding, it does suggest that the dose utilized was sufficient to produce the expected central nervous system effects.

Although animal models are exceedingly useful in understanding the mechanisms controlling feeding in humans, some findings may not generalize. This is perhaps most clearly true for social, interpersonal, and especially cultural issues that exert greater impact on eating behavior in humans than in animal models. However, biochemical and neuroendocrine differences exist as well. An excellent current example is leptin. Defects of leptin production or of its receptor have profound effects on weight in some animal models (4,10,23,27,29). However, it has proven difficult thus far to demonstrate these defects as a major cause of human obesity (5,6,16,19). A more complex role may also exist for the α_2-adrenergic system in human vs animal models.

In conclusion, oral clonidine administration did not increase liquid meal intake in healthy adult subjects; sedation appears to have reduced meal intake after clonidine administration. It appears that the α_2-adrenergic system may exert a more complex influence on feeding behavior in humans than in other animal species that have been examined.

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REFERENCES

1. Atkinson, J.; Kirchertz, E. J.; Peters-Haefeli, L.: Effect of peripheral clonidine on ingestive behavior. Physiol. Behav. 21:73–77; 1978.
2. Broekkamp, C.; van Rossum, J. M.: Clonidine induced intrahypothalamic stimulation of eating in rats. Psychopharmacologia 25:162–168; 1972.
3. Casper, R. C.; Schlemmer, R. F.; Javaid, J. I.: A placebo-controlled crossover study of oral clonidine in acute anorexia nervosa. Psychiatr. Res. 20:249–260; 1987.
4. Chua, S. C., Jr.; Chung, W. K.; Wu-Peng, X. S.; et al.: Phenotypes of mouse diabetes and rat fatty due to mutations in the OB (leptin) receptor. Science 271:994–996; 1996.
5. Clement, K.; Garner, C.; Hager, J.; et al.: Indication for linkage of the human OB gene region with extreme obesity. Diabetes 45:687–690; 1996.
6. Considine, R. V.; Considine, E. L.; Williams, C. J.; et al.: Evidence against either a premature stop codon or the absence of obese gene mRNA in human obesity. J. Clin. Invest. 92:2986–2988; 1995.
7. Currie, P. J.; Wilson, L. M.: Bidirectional effects of clonidine on carbohydrate intake in genetically obese (ob/ob) mice. Pharmacol. Biochem. Behav. 38:177–184; 1991.
8. Davies, D. S.; Wing, L.M. H.; Reid, J. L.; Neill, E.; Tippett, P.; Dollery, C. T.: Pharmacokinetics and concentration–effect relationships of intravenous and oral clonidine. Clin. Pharmacol. Ther. 21:593–601;1976.
9. Dollery, C. T.; Davies, D. S.; Draffan, G. H.; Dargie, H. J.; Dean, C. R.; Reid, J. L.; Clare, R. A.; Murray, S.: Clinical pharmacology and pharmacokinetics of clonidine. Clin. Pharmacol. Ther. 19:11–17; 1975.
10. Halaas, J. L.; Gajiwala, K. S.; Maffei, M.; et al.: Weight-reducing effects of the plasma protein encoded by the obese gene. Science 269:543–546; 1995.
11. Katz, N. L.; Schlemmer, R. F., Jr.; Waller, D. P.: Stereospecific reduction by narcotic antagonists of clonidine-induced food intake. Pharmacol. Biochem. Behav. 22:649–651; 1985.
12. Lal, S.; Tolis, G.; Martin, J. B.: Effect of clonidine on growth hormone, prolactin, luteinizing hormone, follicle-stimulating hormone, and thyroid-stimulating hormone in the serum of normal men. J. Clin. Endocrinol. Metab. 41:827; 1975.
13. Lancranjan, I.; Marbach, P.: New evidence for growth hormone modulation by the α-adrenergic system in man. Metabolism 26:1225–1230; 1977.
14. Leibowitz, S. F.; Brown, O.; Tretter, J. R.; Kirschgessner, A.: Norepinephrine, clonidine and tricyclic antidepressants selectively stimulate carbohydrate ingestion through noradrenergic system of the paraventricular nucleus. Pharmacol. Biochem. Behav. 23:541–550; 1985.
15. Mauron, C.; Wurtman, J. J.; Wurtman, R. J.: Clonidine increases food and protein consumption in rats. Life Sci. 27:781–791; 1980.
16. McGregor, G. P.; Desaga, J. F.; Ehlenz, K.; et al.: Radioimmunologic measurement of leptin in plasma of obese and diabetic human subjects. Endocrinology 137:1501–1504; 1996.
17. McGregor, I. S.; Menéndez, J. A.; Atrens, D. M.; Lin, H. Q.: Prefrontal cortex α_2-adrenoceptors and energy balance. Brain Res. Bull. 26:683–691; 1991.
18. Nutritionist III, Version 4.0, First Data Bank, The Hearst Corporation, 1111 Bayhill Dr., San Bruno, CA.
19. Rosenbaum, M.; Nicolson, M.; Hirsch, J.; et al.: Effects of gender, body composition, and menopause on plasma concentrations of leptin. J. Clin. Endocrinol. Metab. 81:3424–3427; 1996.
20. Schlemmer, R. F.; Casper, R. C.; Narasimhachari, N.; Davis, J. M.: Clonidine induced hyperphagia and weight gain in monkeys. Psychopharmacology (Berlin) 61:233–234;1979.
21. Schwartz, R. S.; Jaeger, L. F.; Veith, R. C.: Effect of clonidine on the thermic effect of feeding in humans. Am. J. Physiol. 254:R90–R94; 1988.
22. Shittecatte, M.; Charles, G.; Machowski, R.; Garcia-Valentin, J.; Mendlewicz, J.; Wilmotte, J.: Reduced clonidine rapid eye movement sleep suppression in patients with primary major affective illness. Arch. Gen. Psychiatry 49:637–642;1992.
23. Shor-Posner, G.; Azar, A. P.; Volpe, M.; Grinker, J. A.; Leibowitz, S. F.: Clonidine hyperphagia: Neuroanatomic substrates and specific function. Pharmacol. Biochem. Behav. 30:925–932; 1988.
24. Siever, L. J.; Uhde, T. W.: New studies and perspectives on the noradrenergic receptor system in depression. Effects of the α_2-adrenergic agonist clonidine. Biol. Psychiatry 19:131–156; 1984.
25. Siever, L. J.; Uhde, T. W.; Jimerson, D. C.; Post, R. M.; Lake, R.; Murphy, D. L.: Plasma cortisol responses to clonidine in depressed patients and controls. Evidence for a possible alteration in noradrenergic-neuroendocrine relationships. Arch. Gen. Psychiatry 41:63–68;1984.
26. Spitzer, R. L.; Williams, J. B. W.; Gibbon, M.; First, M. B.: Structured clinical interview for DSM-III-R-patient version (SCID-P, 6/1/88), Biometrics Research Department, New York State Psychiatric Institute, 722 West 168th Street, New York, New York, 10032.
27. Tartaglia, L. A.; Dembski, M.; Weng, X.; et al.: Identification and expression cloning of a leptin receptor, OB-R. Cell 83:1263–1271; 1995.
28. Thompson, D. A.; Pénicaud, L.; Welle, S. L.: α_2-adrenoreceptor stimulation inhibits thermogenesis and food intake during glucoprivation in humans. Am. J. Physiol. 247:R560–R566; 1984.
29. Zhang, Y.; Proenca, R.; Maffei, M.; Barone, M.; Leopold, L.; Friedman, J. M.: Positional cloning of the mouse obese gene and its human homologue. Nature 372:425–432; 1994.