Systemic Administration of the Long-Acting GLP-1 Derivative NN2211 Induces Lasting and Reversible Weight Loss in Both Normal and Obese Rats

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Postprandial release of the incretin glucagon-like peptide-1 (GLP-1) has been suggested to act as an endogenous satiety factor in humans. In rats, however, the evidence for this is equivocal probably because of very high endogenous activity of the GLP-1 degrading enzyme dipeptidyl peptidase-IV. In the present study, we show that intravenously administered GLP-1 (100 and 500 μg/kg) decreases food intake for 60 min in hungry rats. This effect is pharmacologically specific as it is inhibited by previous administration of 100 μg/kg exendin(9-39), and biologically inactive GLP-1(1-37) had no effect on food intake when administered alone (500 μg/kg). Acute intravenous administration of GLP-1 also caused dose-dependent inhibition of water intake, and this effect was equally well abolished by previous administration of exendin(9-39). A profound increase in diuresis was observed after intravenous administration of both 100 and 500 μg/kg GLP-1. Using a novel long-acting injectable GLP-1 derivative, NN2211, the acute and subchronic anorectic potentials of GLP-1 and derivatives were studied in both normal rats and rats made obese by neonatal monosodium glutamate treatment (MSG). We showed previously that MSG-treated animals are insensitive to the anorectic effects of centrally administered GLP-1(7-37). Both normal and MSG-lesioned rats were randomly assigned to groups to receive NN2211 or vehicle. A single bolus injection of NN2211 caused profound dose-dependent inhibition of overnight food and water intake and increased diuresis in both normal and MSG-treated rats. Subchronic multiple dosing of NN2211 (200 μg/kg) twice daily for 10 days to normal and MSG-treated rats caused profound inhibition of food intake. The marked decrease in food intake was accompanied by reduced body weight in both groups, which at its lowest stabilized at ~85% of initial body weight. Initial excursions in water intake and diuresis were transient as they were normalized within a few days of treatment. Lowered plasma levels of triglycerides and leptin were observed during NN2211 treatment in both normal and MSG-treated obese rats. In a subsequent study, a 7-day NN2211 treatment period of normal rats ended with measurement of energy expenditure (EE) and body composition determined by indirect calorimetry and dual energy X-ray absorptiometry, respectively. Compared with vehicle-treated rats, NN2211 and pair-fed rats decreased their total EE corresponding to the observed weight loss, such that EE per weight unit of lean body mass was unaffected. Despite its initial impact on body fluid balance, NN2211 had no debilitating effects on body water homeostasis as confirmed by analysis of body composition, plasma electrolytes, and hematocrit. This is in contrast to pair-fed animals, which displayed hemoconcentration and tendency toward increased percentage of fat mass. The present series of experiments show that GLP-1 is fully capable of inhibiting food intake in rats via a peripherally accessible site. The loss in body weight is accompanied by decreased levels of circulating leptin indicative of loss of body fat. The profound weight loss caused by NN2211 treatment was without detrimental effects on body water homeostasis. Thus, long-acting GLP-1 derivatives may prove efficient as weight-reducing therapeutic agents for overweight patients with type 2 diabetes.
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Peripheral administration of glucagon-like peptide-1 (GLP-1) acutely affects food intake in humans, but the underlying mechanisms that decrease food intake concomitant with earlier onset of subjective sensation of fullness are not fully understood (1–4). The anorectic effects of continuous intravenous administration of GLP-1 are present in individuals who are lean or obese or have type 2 diabetes (1,3,4), suggesting that the observed effects are part of a physiologically relevant meal-terminating system. Results from similar experiments in rats have been ambiguous, probably because of high activity of GLP-1 degrading enzyme dipeptidyl peptidase-IV (DPP-IV) (5,6). Thus, early experiments were unable to demonstrate peripheral effects of intraperitoneal GLP-1 injections on feeding behavior (7,8), whereas later experiments have shown significant but short-lasting anorectic effects of subcutaneous administration of GLP-1 (9). Anorexia induced by peripheral administration of GLP-1 involves vagal control of gastric motility (10,11).

Central administration of 1–3 μg of GLP-1 specifically inhibits food intake in rats via a hypothalamic site that is sensitive to neonatal monosodium glutamate (MSG) lesioning (12). However, central administration of slightly

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ANOVA, analysis of variance; DEXA, dual energy X-ray absorptiometry; DPP-IV, dipeptidyl peptidase-IV; EE, energy expenditure; FFA, free fatty acids; GLP-1, glucagon-like peptide-1; MSG, monosodium glutamate; RER, respiratory exchange ratio; TG, triacylglycerol.

higher doses of GLP-1 leads to taste aversion, but because this latter effect is unaffected by MSG treatment, it further stresses the specificity of the central GLP-1–induced anorexia (12). In addition, it is possible to elicit anorexia without concomitant taste aversion if GLP-1 is injected directly into the hypothalamic paraventricular nucleus (13). Acute injections of both GLP-1 and NN2211 exerts profound adipsia and diuresis. These effects on body water homeostasis could potentially hamper long-term treatment of patients with type 2 diabetes with GLP-1 agonists, and the potential anorectic effects of these agonists may be accompanied with debilitating affects on body water homeostasis.

Given that peripheral administration of GLP-1 affects food intake in humans, we decided to study further the anorectic potential of this peptide in the laboratory rat. Dose-response studies investigating the effect of intravenously administered GLP-1(7-37) or a novel long-acting acylated GLP-1 derivative NN2211 (14) on food intake were performed. In continuation of acute pharmacological studies, we examined the effect on food intake and body weight of twice daily subcutaneous administration of NN2211 for 10 days followed by a 5-day recovery period. To study the impact of 7 days of NN2211 treatment on energy expenditure (EE) and body composition, we studied normal rats by indirect calorimetry and subsequently subjected them to dual energy X-ray absorptiometry (DEXA) scanning. Before, during, and after treatment, blood biochemical markers of energy and fluid homeostasis metabolic state were monitored.

RESEARCH DESIGN AND METHODS

Animals. All experiments were carried out on male Wistar rats. Normal male rats arrived at the animal facilities 2 weeks before experimentation, and until use, animals were housed three to four per cage under standard laboratory conditions (12:12 light:dark cycle, lights on 6:00 A.M.). Before experimentation, animals had free access to a standard rat diet (Altromin 1324) and water ad libitum. Hypothalamically obese rats were obtained by treating neonatal rats with MSG. Pregnant Wistar rats (Møllegården, Ll; Skensved, Denmark) arrived at the animal unit 1 day before timed labor (E21). Neonatal Wistar pups received a number of subcutaneous injections with MSG (L-glutamic acid, G-1626; 4 mg/g body wt; Sigma, Vallensbaek Strand, Denmark) dissolved in sterile distilled H_2O. Injections were given at days P1, P3, P5, P7, and P9 according to a previously published method (12). After weaning, pups were separated by sex and allowed to grow to the age of 12–14 weeks before experiments were initiated. Neonatal MSG treatment is accompanied by adult obesity and a number of neuroendocrine dysfunctions (hypothalamic hypogonadism, low fertility, stunted growth, chronic HPA-axis activation), and currently used MSG-treated rats all displayed characteristic stunted growth, adiposity, short tail caused by self-mutilation, and apparent blindness. All experiments were carried out in accordance with guidelines provided by the Danish Justice Department and approved by a personal license to P.J.L.

Formulation of GLP-1(7-37), GLP-1(1-37), exendin(9-39), and NN2211. GLP-1(7-37) and GLP-1(1-37) were obtained from L. Thim (Novo Nordisk); exendin(9-39) was purchased from Bachem (Bissendorf Biochemicals, Hamburg, Germany). High-performance liquid chromatography analyses of all peptides claim >90% purity. Peptides were dissolved in sterile isotonic saline to which 1% bovine serum albumin (BSA) was added (Fraction V, #735 086; Boehringer Mannheim, Mannheim, Germany). The GLP-1 derivative NN2211 (Arg34, Lys26-[N-ε(γ-Glu[N-α-hexadecanoyl])]-GLP-1[7-37]) was synthesized according to a previously described procedure (14). The compound NN2211 is a member of a group of pharmacologically active GLP-1 derivatives that have long plasma half-lives (14). Thus, NN2211 is an acylated GLP-1 derivative with a plasma half-life of ~14 h in pigs. Pharmacokinetic data from rats show that $t_{1/2}$ = 4 h probably as a result of considerably higher endogenous DPP-IV activity in this species (L.B.K., unpublished observations). NN2211 was dissolved in sterile phosphate-buffered saline (50 mmol/l, pH 7.4) to a final concentration of either 0.1 or 1.0 mg/ml. Solutions were always made fresh ~1 of NN2211 was used, and corrections for impurity were always performed. Subcutaneous injections were administered using standard 1-ml syringes equipped with 25-G needles.

Experiment 1: single dose of GLP-1. Sixteen adult male Wistar rats were equipped with jugular intravenous catheters (Department of Pharmacology, The Panum Institute, University of Copenhagen). Catheters were implanted under Avertin (tribromoethanol, 200 mg/kg) anesthesia in the right jugular vein with the tip aiming at the right atrium. After placement, the catheter was externalized via subcutaneous tunneling to the interscapular area. Catheter patency was secured by instillation of heparinized (1,000 IU/l) isotonic sterile saline into the catheter before closure with a metal rod. After 7 days of postoperative recovery, animals were housed individually in standard metabolic cages (Techniplast, Gazzoda, Italy) and acclimatized over a period of 7 days to a 5-h restricted feeding scheme with access to food from 8:00 A.M. to 1 P.M. and water ad libitum.

Seven days after initiation of the restricted feeding scheme, animals were assigned to a random crossover dosing paradigm. Five minutes before presentation of food, animals received an intravenous injection of GLP-1 (5, 100, or 500 μg/animal). Statistical analysis of intergroup treatment variation was carried out using factorial analysis of variance (ANOVA) followed by Scheffe post hoc analysis.

Experiment 2: single dose of NN2211. Normal adult male Wistar rats (n = 16) and MSG-treated rats (n = 16) were housed individually in metabolic cages with free access to a rat diet and water for at least 1 week before experimentation. Animals were kept in a 12:12 light:dark cycle, and the effect of NN2211 on nighttime food intake was assessed by injecting animals subcutaneously 2–3 h before lights out. Animals were left without food and water in the period from dosing to the onset of darkness. Three doses of NN2211 and vehicle were tested in a random crossover experiment (10, 50, and 200 μg/kg). Food and water intake and diuresis were monitored every 30 min for the first 2 h after onset of nighttime (lights out) and finally 12 h later at lights on (t_{720}). All measurements were done in complete darkness with the assistance of night vision goggles (Bausch and Lomb, Rochester, NY). The minimum interval between experiments was 48 h. Statistical analysis of intergroup treatment variation was carried out using factorial ANOVA followed by Scheffe post hoc analysis.

Experiment 3: continuous administration of NN2211. Beginning 1 week before the first dose was administered, normal adult male Wistar rats (n = 16) and MSG-treated rats (n = 16) were housed individually in metabolic cages with free access to a rat diet and water. Animals were kept on a 12:12 light:dark cycle, and the subchronic effect of two daily subcutaneous injections of NN2211 or vehicle on body weight, food and water intake, diuresis, and feces excretion was monitored. All parameters were measured between 9 and 11 A.M. while animals received their morning dose. On the basis of daily food intake, animals were stratified to different treatment groups ensuring comparable baseline values for food and water intake. Animals received two daily injections of NN2211 (100 or 200 μg/kg b.i.d.) at 8:00 A.M. and 7:00 P.M. throughout a 10-day period followed by a 5-day drug-free recovery period.

Animals were weighed every morning (between 9 and 11 A.M.) together with measurement of daily food and water intake as well as diuresis and feces excretion. At day 0, orbital blood samples were taken from all animals before the first dose was administered. Further orbital blood samples were taken at day 7 and 14 (i.e., during and after treatment with NN2211). At the final day of experimentation, animals were decapitated and trunk blood was collected as described. Different dose administrations were conducted in two separate experiments, each with its own vehicle-treated control groups. Data from these control groups were pooled.

Statistical analysis of effect of treatment on body weight, food and water intake, diuresis, and feces excretion was carried out using factorial ANOVA followed by Bonferroni correction for multiple comparison. Biochemical data from plasma samples were analyzed using factorial ANOVA followed by Fisher's or Scheffe's post hoc analysis.

Experiment 4: effect of subchronic NN2211 treatment on energy expenditure and body composition. Twenty-four 12-week-old male rats were used in this study. The rats were housed individually in a temperature- (20°C) and light-controlled environment (12:12 light:dark cycle; lights on from 7:00 A.M.) with free access to food and water for at least 7 days before experimentation. The rats were stratified into three groups (G1, G2, and G3) according to weight 3 days before study start (n = 7 per group). The rats in G1 and G3 were treated with vehicle, and the rats in G2 were treated with NN2211 (200 μg/kg b.i.d.). The rats in G1 and G2 had free access to food and water during the 7-day treatment period, whereas the rats in G3 were "single" pair fed after the rats in G2. Body weight and food and water intake were recorded daily. By the end of the study (day 7), oxygen consumption and body composition were determined by indirect calorimetry and DEXA, respectively. Likewise, blood

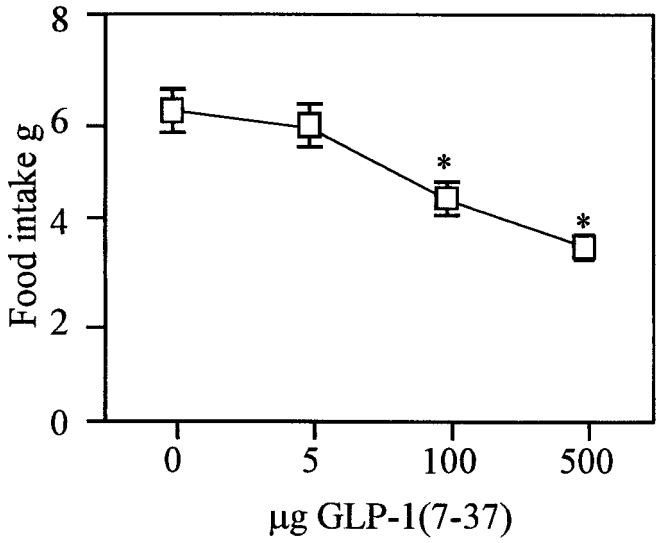

FIG. 1. Single intravenous infusions of GLP-1(7-37) cause dose-dependent anorexia in rats that are kept on a restricted feeding schedule. Food intake over the initial 30 min of the feeding session was recorded for all doses tested (5, 100, and 500 μg/rat). *, statistically significant differences from vehicle-treated animals ($P < 0.05$ as determined by ANOVA followed by Scheffe's post hoc analysis).

levels of triacylglycerol (TG), glycerol, free fatty acids (FFAs), and total cholesterol.

DEXA. Body composition was determined by DEXA (pDEXA Sabre, Stratec Medizintechnic; Norland Medical Systems, Phörzheim, Germany). The instrument settings used were as follows: a scan speed of 40 mm/s, a resolution of 1.0 × 1.0 mm, and automatic/manual histogram width estimation. The coefficient of variation as assessed by 10 repeated measurements (with repositioning of the rat between each measurement) was 3.48, 3.17, and 3.73% for bone mineral content, lean tissue mass, and fat tissue mass, respectively. By the end of the study (day 7), the rats were killed. The carcasses were stored in plastic bags at −20°C before determination of body composition; which was determined on defrosted carcasses.

Indirect calorimetry. Oxygen consumption, CO_2 production, EE, and the respiratory exchange ratio (RER) were determined by indirect calorimetry (Oxymax System; Columbus Instruments, Columbus, OH). The rats ($n = 1$ per chamber) were placed in airtight acrylic chambers (10.5 l). Oxygen and CO_2 concentrations in the chamber in- and outlet gas were determined simultaneously every 20.25 min over a period of 4.4 h. Instrument settings used were as follows: a gas flow rate of 1.86 l/min, settle time of 90 s; measure time of 40 s, and system recalibration for each eight-chamber measuring cycle. By the end of the study (day 7), the nonfasted rats were subjected to indirect calorimetry (from 8:00 A.M. 1:00 P.M.). In contrast to the previous 6 days, the nonfasted rats did not receive NN2211 between 7:30 and 8:30 before indirect calorimetry. On the day of indirect calorimetry, the rats received treatment at 9:30—after four pretreatment measurements. The rats had no access to food or water during their stay in the acrylic chamber. The indirect calorimetric measurements were performed over 3 days. As a "positive" instrument control, every day included a reference animal "treated" with the EE increasing compound 2,4-dinitrophenol (DNP, Sigma). On the basis of the measurements of O_2 and CO_2 in the chamber in- and outlet gas, estimates of O_2 consumption, CO_2 production, EE, and RER were calculated.

Blood sampling and biochemical assays

Blood sampling. Orbital blood samples were obtained by puncture of the orbital venous plexus with glass capillary tubes. Samples were taken in standard heparinized EDTA (0.18 mol/l) glass tubes (Vacutainer) to which aprotinin (1,500 KIE/ml) and bacitracin (3%) were added. After sampling, tubes were kept on ice before being centrifuged (4°C at 5,000*g* for 10 min), and the resulting plasma was stored at −80°C before being analyzed. Trunk blood was obtained by decapitating animals and sampling into heparinized (~500 IU/tube) glass tubes to which aprotinin (1,500 KIE/ml) and bacitracin (3%) were added. Glycerol and FFA concentrations were determined in EDTA (0.18 mol/l) plasma containing 1% NaF (wt/vol).

Plasma glucose. Plasma glucose was measured on a standard COBAS analyzer (Toxicology Projects & Planning, Novo Nordisk, Copenhagen, Denmark).

mouse leptin enzyme-linked immunosorbent assay kit (Crystal Chemical, Chicago, IL), showing >95% cross-reactivity to rat leptin.

Plasma biochemistry. Orbital blood samples (days 0, 7, and 14) were taken from rats that were receiving 100 μg/kg b.i.d. NN2211 and a set of corresponding vehicle-treated animals. Plasma values of sodium, TG, cholesterol, creatinine, carbamide, and total protein were measured on a standard COBAS analyzer. FFA and glycerol were measured on a standard Hitachi Automatic analyzer.

Plasma potassium. Orbital blood samples (days 0, 7, and 14) were taken from rats that were receiving 200 μg/kg b.i.d. NN2211 and a set of corresponding vehicle-treated animals. Blood was collected in heparinized glass tubes (Vacutainer), and the potassium content in resulting plasma was measured potentiometrically with an ion selective probe on a standard COBAS analyzer.

RESULTS

Experiment 1

Effects of a single dose of GLP-1 on feeding behavior. Acute intravenous administration of high doses of GLP-1 (100 and 500 μg/animal) decreased food intake at 30 and 60 min after onset of feeding period in rats that were kept on a restricted feeding scheme (Fig. 1). The anorectic effect of the highest dose of GLP-1 (500 μg/animal) was completely abolished by previous administration of 100 μg of exendin(9-39) (6.1 ± 0.4 vs. 5.9 ± 0.3 g). Also, the biologically inactive peptide GLP-1(1-37) (500 μg/animal) had no acute effect on food intake (6.1 ± 0.4 vs. 6.2 ± 0.3 g). Water intake was similarly decreased in rats that were receiving an intravenous injection of GLP-1, and the pharmacological characteristics of water consumption mirrored that of feeding.

Intravenous administration of GLP-1 also affected diuresis. Water excretion was markedly and dose-dependently increased in rats that were receiving intravenous bolus injections of GLP-1 (100 and 500 μg/animal; Fig. 2). The effect displayed pharmacological specificity in as much it was not elicited by 500 μg/animal GLP-1(1-37). However, an attempt to antagonize the diuretic effect of 500 μg of GLP-1 with exendin(9-39) (100 μg/animal) was only partially successful. Thus, exendin(9-39) completely abolished anorectic GLP-1 actions, whereas the diuretic actions of 500 μg GLP-1 were only partially abolished (Fig. 2).

Experiment 2

Effects of a single dose of NN2211 on feeding behavior in rats. The acute effects of three doses of NN2211 on nighttime feeding were tested in a random crossover experiment (10, 50, and 200 μg/kg). The dose dependence of NN2211 on overnight food intake in normal rats is illustrated in Fig. 3. Two hours after onset of the feeding

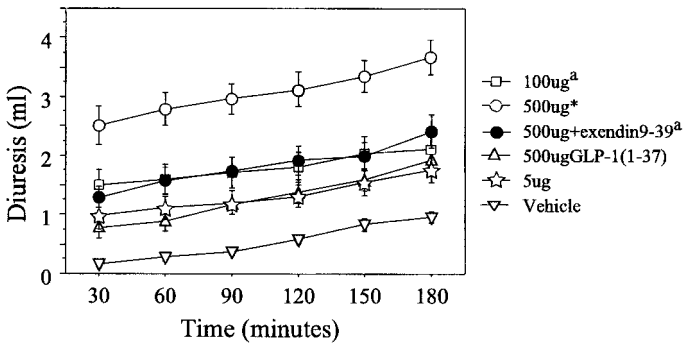

FIG. 2. Acute intravenous administration of GLP-1 causes profound diuresis. *, statistically significant difference from all other groups; a, statistically significant differences from vehicle-treated animals ($P <$

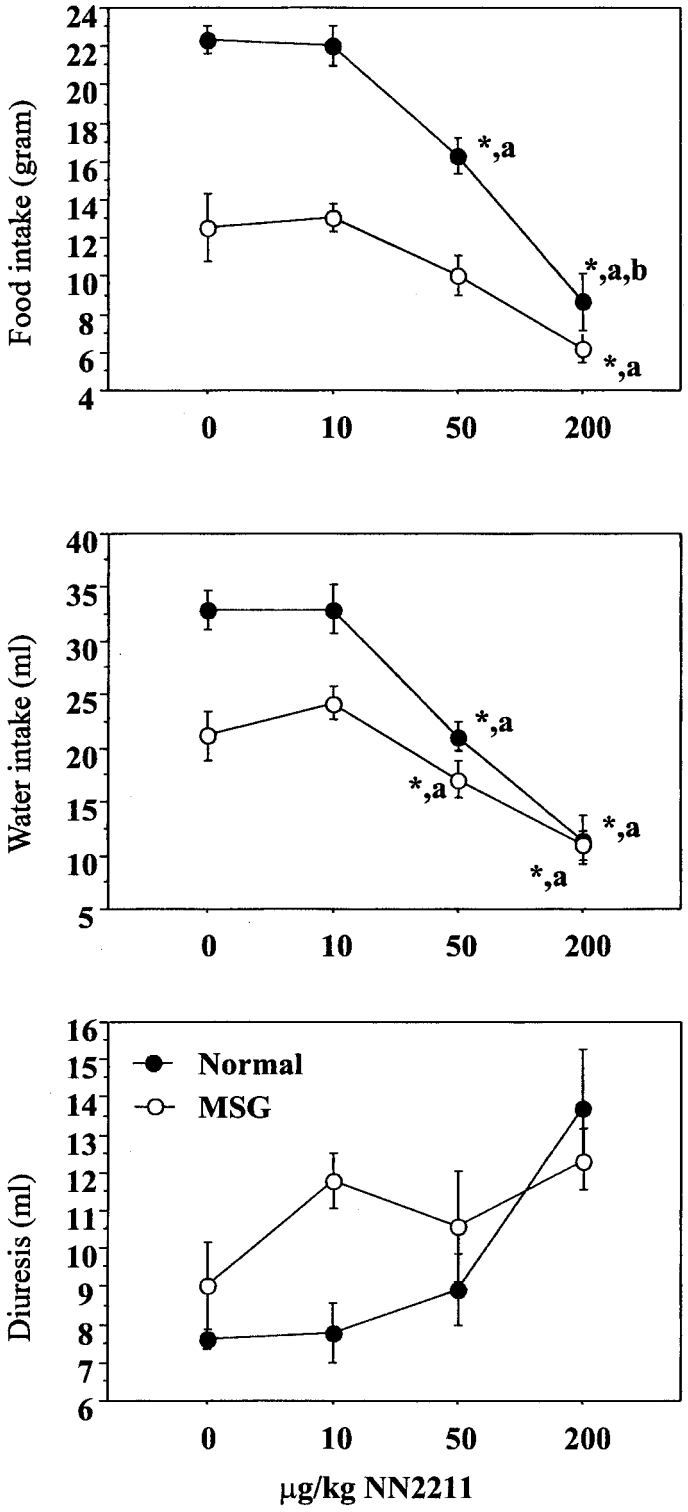

FIG. 3. Single subcutaneous injections of NN2211 dose-dependently inhibit food and water in both normal and MSG-treated rats. Dose-response curves for 720 min of food and water intake as well as diuresis in normal and MSG-treated rats receiving a single subcutaneous dose of NN2211. *$P < 0.05$ versus vehicle (ANOVA followed by Scheffe's post hoc analysis); [a]$P < 0.05$ versus 10 µg/kg NN2211 (ANOVA followed by Scheffe's post hoc analysis); [b]$P < 0.05$ versus 50 mg/kg NN2211 followed by Scheffe's post hoc analysis).

session, 200 µg/kg NN2211 significantly inhibited food intake (3.8 ± 0.3 vs. 5.2 ± 0.3 g of food). The following

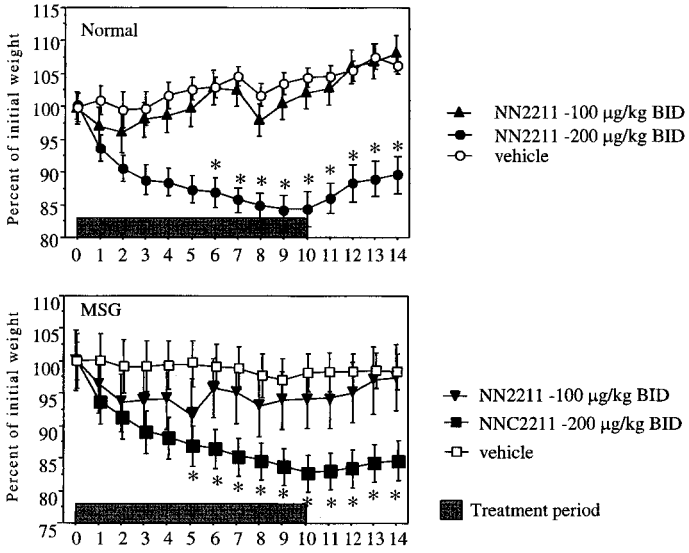

FIG. 4. Subchronic administration of NN2211 dose-dependently decreases body weight in both normal adult male Wistar rats and MSG-treated rats. Animals received two daily subcutaneous injections of NN2211 (100 or 200 µg/kg) or vehicle for 10 days followed by a 5-day recovery period. Body weight was monitored each morning. Values are mean ± SE (n = 5–8). *, significant difference from relevant vehicle-treated control as determined by ANOVA followed by Bonferroni multiple comparison post hoc analysis.

ited food intake in normal rats (control: 22.4 ± 0.7; 50 µg/kg: 16.3 ± 0.7; 200 µg/kg: 8.7 ± 1.3 g of food) as well as in MSG-treated rats (control: 12.5 ± 1.9; 50 µg/kg: 10.0 ± 1.0; 200 µg/kg: 5.8 ± 0.7 g of food).

Effects of a single dose of NN2211 on water intake and diuresis. In the same experiment, water intake and diuresis was monitored (Fig. 3). Both 50 and 200 µg/kg NN2211 significantly inhibited overnight (t_{720}) water intake in normal and MSG-treated rats (vehicle: 32.8 ± 2.0; 50 µg/kg: 21.1 ± 1.1; 200 mg/kg: 11.5 ± 2.5 g; vehicle-MSG: 21.2 ± 2.5; MSG-50 µg/kg: 17.1 ± 1.9; MSG-200 µg/kg: 11.5 ± 1.3 ml; $P < 0.05$ as determined by ANOVA followed by post hoc Scheffe's analysis). In contrast, the highest dose of NN2211 (200 µg/kg) significantly increased diuresis in both normal and MSG-treated rats (vehicle: 7.6 ± 0.3; 200 µg/kg: 13.7 ± 1.7; vehicle-MSG: 9.0 ± 1.2; MSG-200 µg/kg: 12.3 ± 0.9 ml; $P < 0.05$ as determined by ANOVA followed by post hoc Scheffe's analysis).

Experiment 3

Effect of subchronic administration of NN2211 on food intake and body weight. Two daily injections of NN2211 to adult male Wistar rats dose-dependently decreased body weight over the entire 10-day treatment period with significant differences obtained with the 200 µg/kg b.i.d. dosing regimen between treatment days 7 and 14 (Fig. 4). Loss in body weight was preceded by decreased food and water intake and increased diuresis (Fig. 5). Food intake was significantly lower during the initial 3 days of treatment for normal animals that were treated with 100 µg/kg b.i.d. (data not shown). Thereafter, the anorectic effect of this low dose was no longer statistically significant. In animals that were treated with 200 µg/kg b.i.d., food intake was significantly lower throughout the 10-day treatment period. After cessation of the treatment,

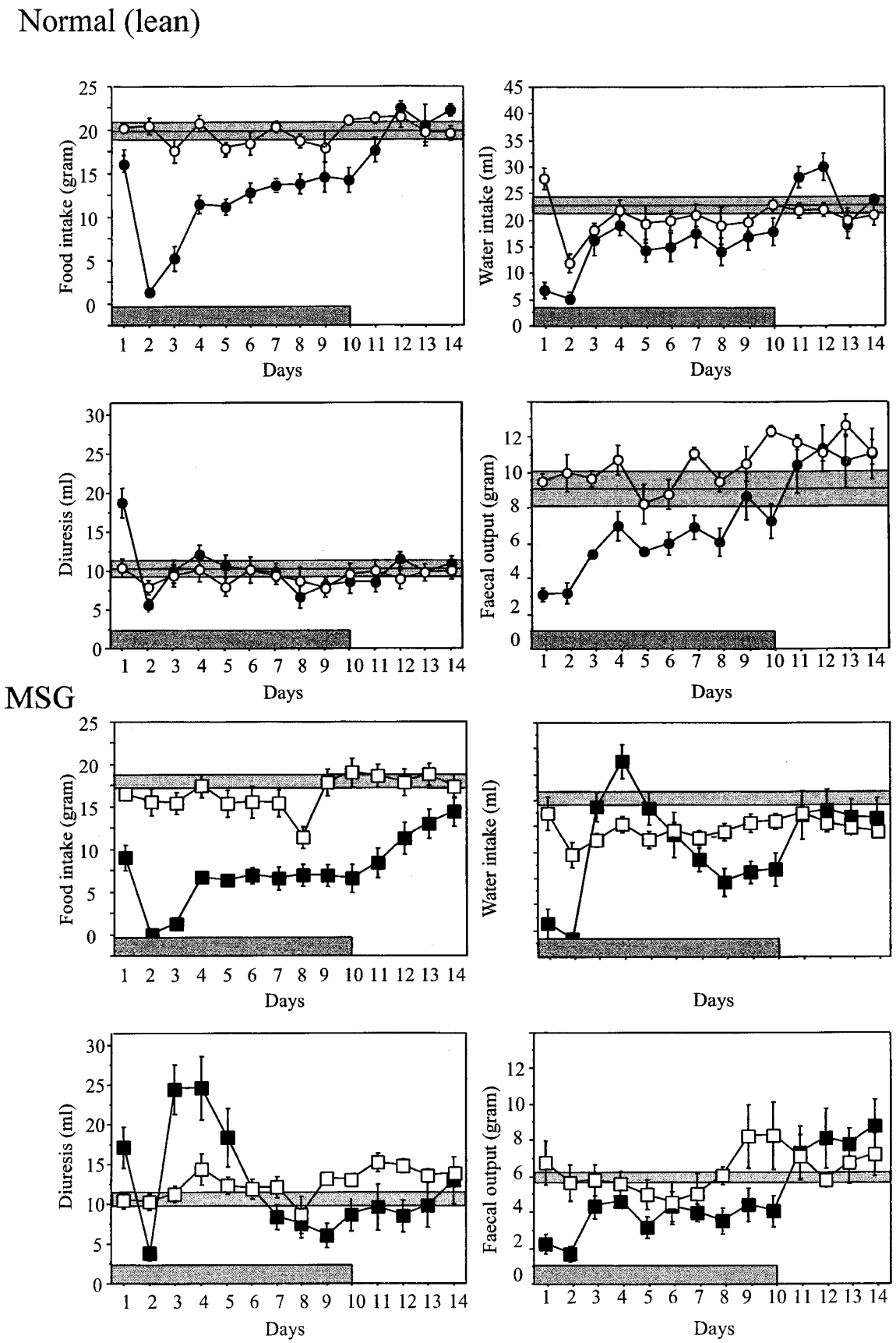

FIG. 5. The effect of subchronic administration of 200 μg/kg NN2211 to normal male Wistar rats (circles) or MSG-treated rats (boxes) on food and water intake as well as diuresis and feces excretion. Open symbols represent vehicle-treated animals; closed symbols represent NN2211-treated animals. Shaded areas reflect baseline values obtained from all animals in the group throughout the week before onset of

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