



Research report

Intraventricular GLP-1 reduces short- but not long-term food intake or body weight in lean and obese rats

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Abstract

Glucagon-like-peptide-1 (7–36) amide (GLP-1), when infused into the third ventricle (IVT), reduces short-term food intake. In the present experiments, we assessed whether IVT administration of GLP-1 could influence long-term food intake and body weight of lean Long Evans rats and of fatty Zucker (*fa/fa*) rats. In Experiment 1, we replicated the observation that 10 μg GLP-1, given IVT, reduces one and 2 h food intake, and extended the observation to fatty Zucker rats. However, in both rat strains, 24 h food intake and body weight were unchanged by this acute treatment. In Experiment 2, GLP-1 (30 $\mu\text{g}/\text{day}$) was infused IVT continuously for 4 days via an osmotic mini-pump. This treatment also had no effect on food intake or body weight in either Long–Evans or fatty Zucker rats. A control experiment verified that the GLP-1 remained biologically active over the duration of the infusion period. In a final experiment, Long-Evans rats were restricted to two 2 h periods of access to food each day for 6 days. Prior to each of these access periods, rats received either 15 μg of GLP-1 IVT or a vehicle control injection. While GLP-1 significantly reduced food intake on the first day of treatment, this effect of GLP-1 rapidly disappeared such that it was reduced on the second day and absent on the third day; and there was no effect on body weight at any time. Collectively, the present experiments do not support the hypothesis that GLP-1, acting in the CNS, is an important regulator of long-term food intake and body weight. © 1998 Elsevier Science B.V.

Keywords: Obesity; Zucker rat; Third ventricle; Food intake

1. Introduction

The accurate regulation of food intake and body weight depends on the complex interaction of several regulatory systems. Some of these systems appear to act primarily at the level of individual bouts of ingestion or meals. The prototypical compound for such a short-term satiety signal is the gut peptide cholecystokinin (CCK) which is secreted in response to food in the upper intestine. When administered intraperitoneally or directly into the central nervous system (CNS), CCK causes a potent reduction in the size of the subsequent meal [16]. After such treatment, however, total daily food intake is not different from that of controls [22]. This implies that the effect of CCK is short-lived, and that animals eat more in subsequent meals in order to compensate for the lost calories from the reduced first meal in order to maintain daily caloric intake

and body weight constant [22]. When CCK is administered at the onset of each spontaneous meal in non-deprived and freely feeding rats, it reliably reduces the size of each meal compared to the meal size of control animals, but daily caloric intake and body weight are unchanged because animals receiving CCK compensate by increasing the number of individual meals they take [22]. Hence, satiety factors such as CCK, if given alone, are unlikely to provide effective therapeutic tools for obesity.

A second category of peptides, including insulin and leptin, act in a fundamentally different manner. When administered continuously into the CNS over days, insulin or leptin produces persistent reductions in daily caloric intake and body weight at doses that have no effect when administered into the periphery [15,23] suggesting that the CNS is the likely target for this action. Since both insulin and leptin are secreted in proportion to body adiposity, each has been considered a likely factor that interacts with meal-generated satiety factors in the long-term control of body adiposity [13,24]. Consistent with this, there is evi-

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dence that the administration of small amounts of insulin (and possibly leptin) potentiates the action of meal-generated satiety factors such as CCK [14]. Hence, when an animal loses weight, it secretes less insulin and leptin, and satiety factors such as CCK are rendered less effective. One result is larger meals until weight is restored. The opposite occurs if an animal gains weight. In this way adiposity factors act in concert with satiety factors to coordinate food intake with the maintenance of total body adiposity.

Turton and colleagues have proposed that glucagon-like-peptide-1 (7–36) amide (GLP-1), acting at receptors in the CNS, is an endogenous factor important in the regulation of food intake [17,19]. GLP-1 is secreted from the distal gut in response to the presence of mixed nutrients in the gastrointestinal tract [3,8]. In the periphery, GLP-1 influences glucose homeostasis after ingestion of carbohydrate meals via modulation of gastric emptying and alteration of the secretion of insulin and glucagon from the pancreas [2]. The precursor for GLP-1 (preproglucagon) is also synthesized in the CNS in the nucleus of the solitary tract (NTS) [4,7,10]. Receptors for GLP-1 are concentrated in the paraventricular nucleus of the hypothalamus (PVN), the amygdala, and several regions of the brainstem including the area postrema and the NTS [5]. In their report, Turton et al. [19] observed that bolus administration of GLP-1 into the third ventricle of lean rats produced a potent and dose-dependent reduction of 2 h food intake, and they further reported that this reduction could be blocked by pretreatment with the specific GLP-1 receptor antagonist, exendin. Based on these findings, they proposed GLP-1 as a natural regulator of food intake and possibly adiposity as well. The purpose of the present experiments was to determine whether central administration of GLP-1 alters long-term food intake and body weight in lean Long–Evans rats and in genetically obese (*fa/fa*) Zucker rats. We therefore sought to determine whether GLP-1 acts in the CNS as a short-term regulator of food intake, as occurs with CCK, or as a long-term adiposity-type signal such as leptin or insulin.

2. Materials and methods

2.1. Animals

Male Long–Evans rats were obtained from the vivarium maintained by the Department of Psychology at the University of Washington; and female fatty Zucker rats (*fa/fa*) were obtained from Harlan Inc. Rats were individually housed in stainless steel hanging cages (Long Evans) or plexiglass tubs with shavings on the floor (Zuckers). The rooms were maintained on 12:12 h light:dark cycle in a temperature-controlled room. Except where noted, animals were maintained on ad lib water and pelleted chow.

2.2. Surgical preparation

Under ketamine (9 mg/kg; i.p.) and xylazine (1.5 mg/kg; i.p.) anesthesia, rats were implanted with 21-gauge stainless steel cannulae (Plastics One, Roanoke, VA) aimed at the third cerebral ventricle as described previously [1]. Stereotaxic techniques were used to implant a guide sleeve directly on the midline, 2.2 mm posterior to bregma, with its tip 7.5 mm ventral to dura. The cannula was secured to the skull with screws and dental acrylic, and following implantation was fitted with a removable obturator which extended 0.5 mm beyond the tip of the guide sleeve. Following surgery, all animals were prophylactically injected with 0.15 ml of both Chloromycetin (100 mg/ml; s.c.) and Gentamycin (40 mg/ml; i.m.), and then were allowed at least one week to recover before an experiment began. Rats were also injected with Chloromycetin (100 mg/ml; s.c.) on any day that infusions were made into the cannulae. Cannula patency was confirmed by administration of angiotensin-II (10 ng in 1 μ l saline). Animals which failed to consume 5 ml water in 60 min following injection were not included.

2.3. Drugs

Glucagon-like-peptide-1 (7–36) amide was purchased from American Peptide Co., Sunnyvale, CA. Sterile saline served as vehicle for GLP-1 injections.

2.3.1. Experiment 1

2.3.1.1. Animals. Twelve Long–Evans (306 to 368 g) and 16 fatty Zucker rats (403 to 546 g) were maintained and surgically prepared as described above.

2.3.1.2. Procedure. Two hours before lights out, food hoppers were removed and weighed. One hour later, each rat was removed from its cage and weighed, the obturator was removed and a 26-gauge infusion cannula extending 1.0 mm beyond the tip of the guide cannula was inserted. The infusion cannula was connected to a Hamilton syringe via PE-50 tubing, and solutions (3 μ l) were infused manually over 60 s. Half of the rats received GLP-1 (10 μ g), and the other half received sterile saline. At lights out, the food hoppers were replaced on the cages and intake was determined after 1, 2 and 24 h (Long Evans) and after 2 and 24 h (fatty Zuckers). Rats were weighed 24 h after the injections.

2.3.2. Experiment 2

2.3.2.1. Animals. Eleven Long–Evans (280 to 388 g) and 13 fatty Zucker rats (432 to 614 g) that had been used in Experiment 1 served as subjects in Experiment 2. For this experiment, no chow was available and rats were placed

on a regimen in which they had access to the nutritionally complete liquid diet, Ensure (Ross Labs), for 17 h daily starting 2 h before lights out. Animals were adapted to this schedule prior to the start of the experiment.

2.3.2.2. Procedure. On Day 1, rats were briefly anesthetized with ketamine/xylazine and implanted subcutaneously with an osmotic minipump (Alzet, 2002) that infused at a rate of 0.5 $\mu\text{l/h}$. The minipump was filled with sterile saline and was connected to tubing which contained > 60 μl of either GLP-1 (30 $\mu\text{g}/12 \mu\text{l/day}$; $n = 6$ Long-Evans and $n = 6$ fatty Zuckers) or sterile saline (12 $\mu\text{l/day}$; $n = 5$ Long-Evans and $n = 7$ fatty Zuckers). An air bubble separated the solution in the pump from that in the tubing. The other end of the tubing was connected to a 26-gauge infusion cannula, which was inserted into the guide sleeve and extended 1.0 mm beyond its tip. Over four days following implantation, intake of Ensure, and body weight, were measured daily. At the end of the fourth day, animals were sacrificed and both the presence of the bubble and its movement along the tubing were verified to ensure that experimental solutions remained separate and had infused properly.

2.3.3. Experiment 3

2.3.3.1. Animals. Twelve Long-Evans rats weighing from 409 to 555 g with third ventricle cannulas were used for Experiment 3. These animals had been used in a previous, unrelated experiment.

2.3.3.2. Procedure. GLP-1 (150 $\mu\text{g}/60 \mu\text{l}$ saline) and saline were placed in the same tubing used for mini-pump infusions, sealed and left in a temperature controlled water bath at 38°C for 4 days. Then the solutions were removed from tubing and half the animals received an ICV injection of GLP-1 (10 $\mu\text{g}/3 \mu\text{l}$) or saline (3 μl) and food intake was measured as in Experiment 1.

2.3.4. Experiment 4

2.3.4.1. Animals. Fourteen Long-Evans rats (292 to 350 g) were surgically prepared as described above. Following recovery from surgery, rats were adapted to a meal-feeding schedule on which they had access to pelleted chow during two 2 h periods per day. Meal 1 began 2 h after lights on, and meal 2 began 8 h after lights on. The subjects were able to maintain their ad lib fed body weights on this schedule.

2.3.4.2. Procedure. On five consecutive days, rats received bolus IVT injections of either GLP-1 (15 $\mu\text{g}/3 \mu\text{l}$; $n = 6$) or sterile saline (3 μl ; $n = 8$) 1 h before each meal. Food hoppers were weighed before and after each meal, and body weights were recorded before the first meal each day.

On Day 6, rats were maintained on the same feeding schedule, but did not receive any injections.

3. Results

3.1. Experiment 1

The purpose of this experiment was to determine if single intraventricular (ivt) injections of GLP-1 reduce food intake of Long Evans and of fatty Zucker rats. Data were analyzed with the Student's *t*-test, with $p < 0.05$ (two-tailed) indicating significance.

In the first hour following injection, Long Evans rats receiving GLP-1 consumed significantly less chow than saline controls (0.7 vs. 2.6 g, $p < 0.001$; Fig. 1, top panel). After 2 and 24 h, intake of the two groups did not differ reliably (2 h: 2.1 vs. 3.6 g, $p = 0.074$; 24 h: 11.1 vs. 13.2 g, $p = 0.71$). Change in body weight over the 24 h following injection also did not differ reliably between groups ($p = 0.75$).

In the first 2 h following injection, fatty Zucker rats receiving GLP-1 consumed significantly less chow than their saline controls (1.6 vs. 4.1 g, $p < 0.001$; Fig. 1, bottom panel). After 24 h, the difference was no longer reliable (12.7 vs. 12.6 g, $p = 0.98$). Change in body weight over the 24 h following injection also did not differ reliably between the two groups of fatty rats ($p = 0.54$).

Whereas GLP-1 initially and robustly reduced food intake in both strains of rat (i.e., over the first 1 to 2 h), this reduction was completely compensated by the end of the 24 h period. These findings therefore replicate and extend the observations of Turton et al. [19]. Consistent with that report, GLP-1 is highly efficacious in the short term, but the effects of a single injection are short-lived. One new observation is that obese Zucker rats are comparably sensitive to this anorexic effect of GLP-1.

3.2. Experiment 2

The purpose of this experiment was to determine whether chronic administration of GLP-1, lasting several days, would reduce food intake and body weight. Results were analyzed by a repeated measures ANOVA followed by additional ANOVAs. Condition (saline vs. GLP-1) served as the between-groups variable, while Day of measurement served as the within-group variable.

Daily food intake of Long-Evans rats receiving either chronic infusions of saline or GLP-1 is depicted in Fig. 2, top panel. ANOVA revealed no effect of Condition ($F[1,8] = 0.18$, $p = 0.68$) on food intake, but a significant effect of Day ($F[4,32] = 18.91$, $p < 0.001$) and a significant interaction between Condition and Day ($F[4,32] = 3.05$, $p < 0.05$). Follow-up ANOVA comparison of baseline intake vs. intake on Days 1 through 4 revealed a significant

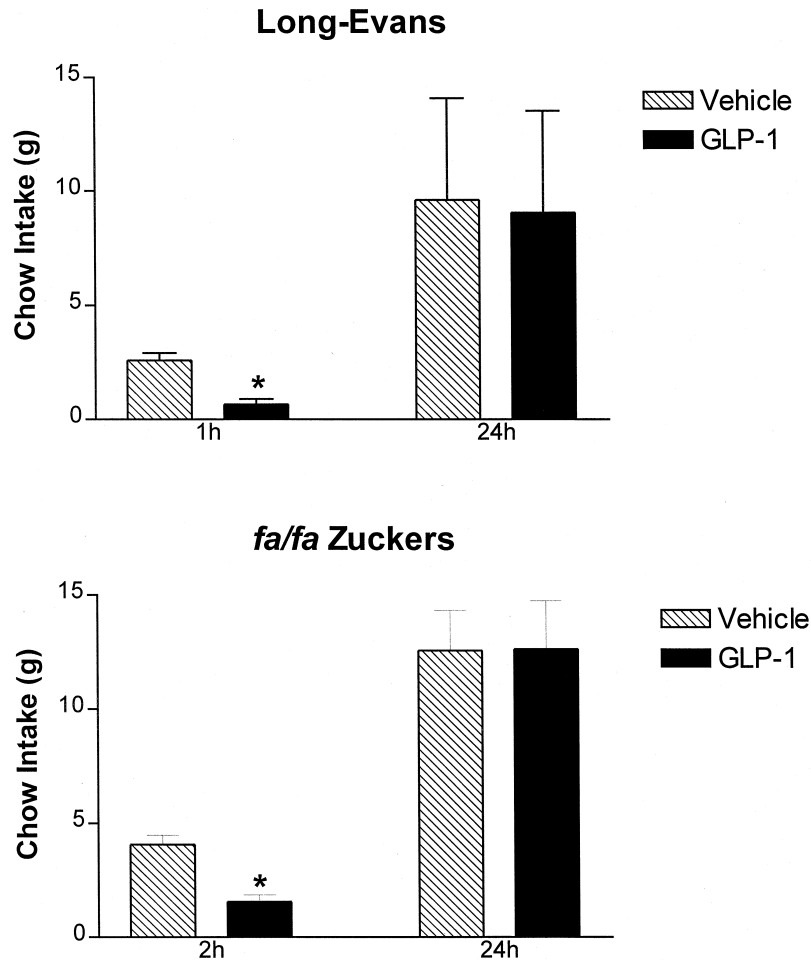


Fig. 1. The effect of a bolus ICV injection of GLP-1 (10 μ g) on chow intake in Long-Evans (top panel) and *fa/fa* Zucker rats (bottom panel). Data are represented as mean \pm S.E.M. and * indicates statistically different from vehicle at $p < 0.05$.

effect of Day on Days 1 and 2 ($F[1,9] = 98.99$, $p < 0.001$, and $F[1,8] = 12.50$, $p < 0.01$, respectively), but no interactions of Condition and Day.

Body weights of Long-Evans receiving infusions of saline or GLP-1 are depicted in Fig. 2, bottom panel. ANOVA revealed no significant effects of either Condition ($F[1,9] = 1.92$, $p = 0.199$), Day ($F[4,36] = 0.28$, $p = 0.891$), or the interaction between the variables ($F[4,36] = 1.12$, $p = 0.363$).

Food intake of fatty Zucker rats receiving infusions of saline or GLP-1 is depicted in Fig. 3, top panel. ANOVA revealed no significant effect of Condition ($F[1,11] = 0.04$, $p = 0.853$). The effect of Day was significant ($F[4,44] = 45.67$, $p < 0.001$), and the interaction was not significant ($F[4,44] = 0.84$, $p = 0.51$). Follow-up ANOVA comparing pre-surgical intake with Days 1 through 4 revealed a significant effect of Day for each comparison ($F[1,11] = 150.11$, $p < 0.001$; $F[1,11] = 43.48$, $p < 0.001$; $F[1,11] = 28.24$, $p < 0.001$; and $F[1,11] = 34.07$, $p < 0.001$, for Days 1 through 4, respectively), but no effect of Condition and no significant interactions.

Body weights of fatty Zucker rats are depicted in Fig. 3 bottom panel. ANOVA revealed no overall effect of Condition ($F[1,10] = 0.04$, $p = 0.849$). Similar to the observations with food intake, there was a significant overall effect of Day on body weight ($F[4,40] = 14.62$, $p < 0.001$), but no interaction between Condition and Day ($F[4,40] = 0.21$, $p < 0.93$). Follow-up ANOVA comparing pre-surgical body weight with weight on experimental days 1 through 4 revealed a significant effect of Day for each comparison ($F[1,11] = 44.43$, $p < 0.001$; $F[1,10] = 23.01$, $p < 0.01$; $F[1,11] = 24.95$, $p < 0.001$; and $F[1,11] = 13.32$, $p < 0.01$, for Days 1 through 4, respectively). There were no significant effects of Condition and no significant interactions for any of the comparisons of individual days to pre-surgical weight.

In this experiment, GLP-1 infusion failed to effect food intake or body weight over a several-day interval relative to a saline infusion. The treatment paradigm per se resulted in a non-specific reduction of food intake from baseline (likely do to the stress of anesthesia and surgical manipulation at the time of mini-pump placement) over the course

of the infusion in both Long Evans and fatty Zucker rats, but the magnitude of the effect was comparable for saline and GLP-1 treatments. The non-specific reduction of food intake was insufficient to reduce the body weight in the Long Evans rats but did do so, albeit slightly in the fatty Zucker rats. Such non-specific reductions in food intake do present an interpretive difficulty. It is possible that this reduction masked an effect of GLP-1 to reduce food intake over the long term. It is important to note, however, that the lack of a drug effect on body weight in both groups fail to provide evidence that GLP-1 can cause long-term reductions in body weight in this paradigm.

3.3. Experiment 3

The lack of effect of GLP-1 in Experiment 2 could have resulted from the method of administration. It is possible, for example, that when kept in solution in a small-diameter

tube at body temperature for several days, GLP-1 loses its potency. The purpose of this experiment was to assess this possibility. Data were analyzed using a Student's *t*-test.

GLP-1 produced a significant reduction in food intake at 1 and 2 h ($p < 0.001$, see Fig. 4) but not after 24 h after the exposure to the tubing and body temperatures for 4 days that was comparable to Experiment 2 using the osmotic mini-pump. The results of this experiment suggest that the GLP-1 in Experiment 2 had maintained its potency throughout the time of the infusion. Hence, the lack of effect of GLP-1 on food intake or body weight cannot be attributed to a loss of biological activity of the GLP-1 *per se*.

3.4. Experiment 4

Another possible interpretation of the lack of effect of GLP-1 in Experiment 2 is that the chronic pattern of

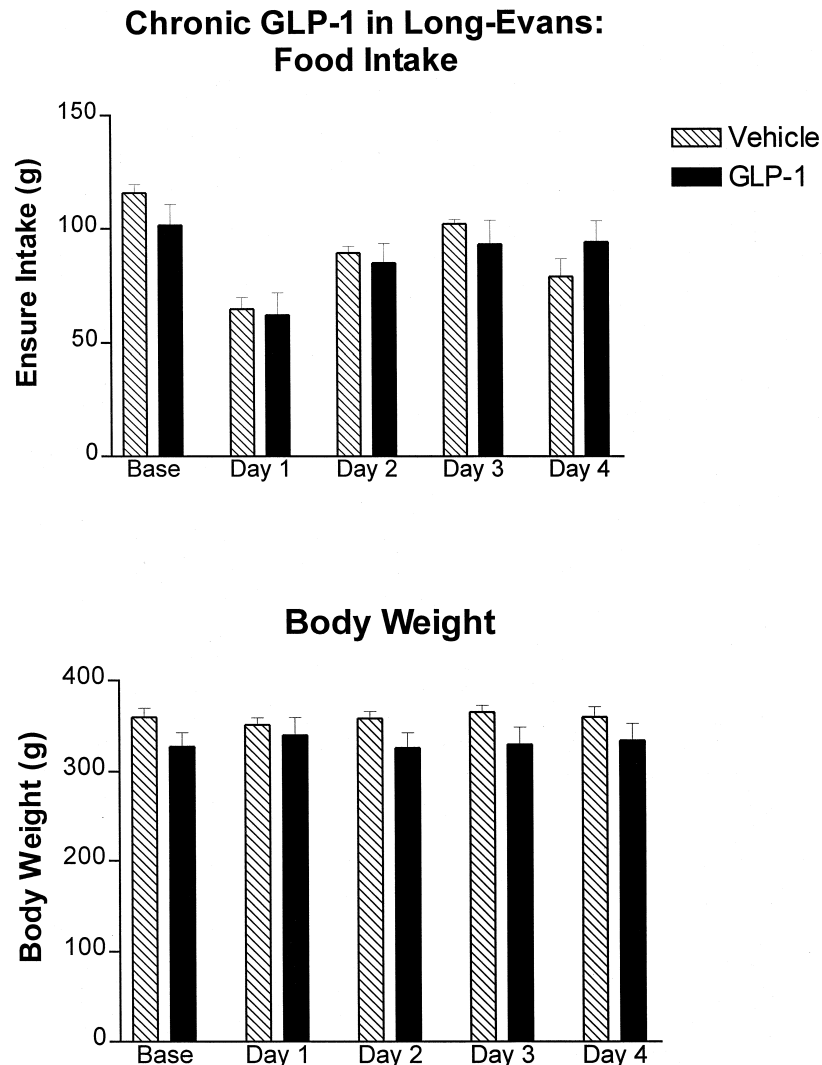


Fig. 2. The effect of continuous 4-day ICV infusion of GLP-1 (30 μ g/day) on ensure intake (top panel) and body weight (bottom panel) in Long-Evans rats. Data are represented as mean \pm S.E.M.

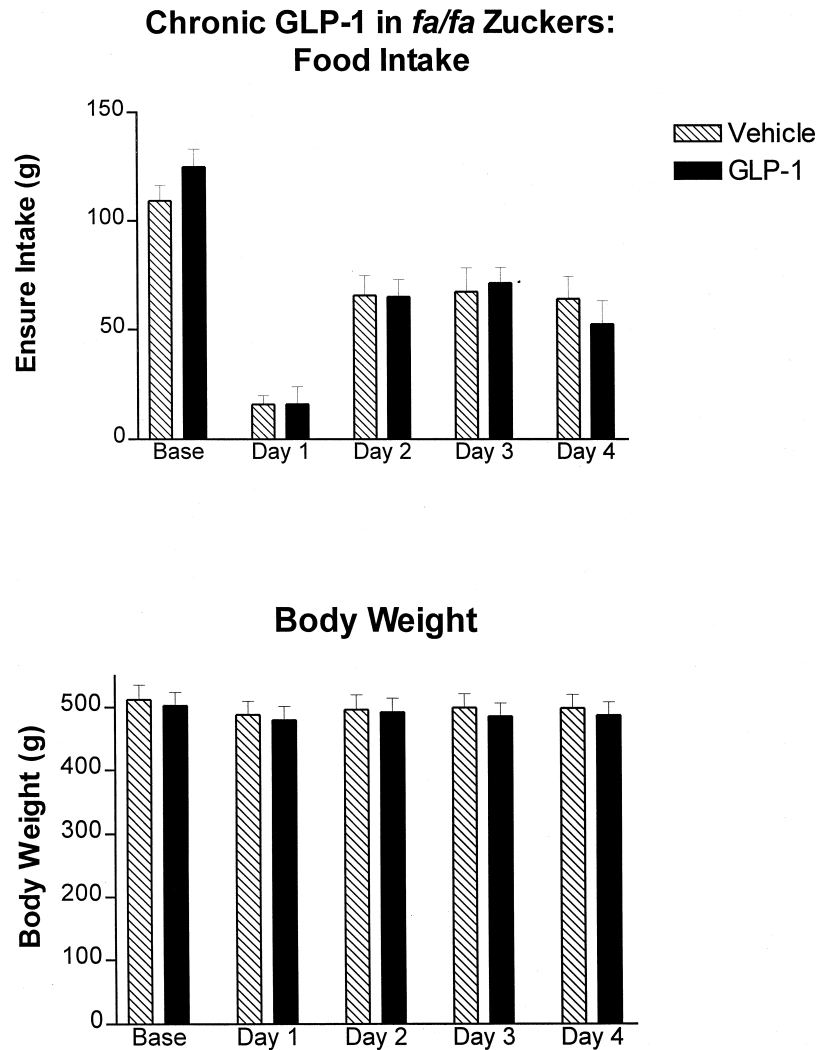


Fig. 3. The effect of continuous 4-day ICV infusion of GLP-1 (30 $\mu\text{g}/\text{day}$) on ensure intake (top panel) and body weight (bottom panel) in Long-Evans rats. Data are represented as mean \pm S.E.M.

administration failed to mimic a physiological pattern of secretion. In the present experiment, we therefore administered the same daily dose of GLP-1 that was used in Experiment 2, but as a bolus just prior to each bout of feeding. These bouts of feeding were 2 h in duration, a duration over which we and others have reported reduced feeding for GLP-1. Results were analyzed by a repeated measures ANOVA. Condition (saline vs. GLP-1) served as the between-groups variable, while Day of measurement served as the within-group variable.

The effect of repeated bolus injections of saline or GLP-1 on food intake are depicted in Fig. 5A. ANOVA revealed no significant overall effect of Condition ($F[1,12] = 2.48$, $p = 0.141$). There was a significant effect of Day ($F[6,72] = 10.23$, $p < 0.001$) and a significant interaction between Condition and Day ($F[6,72] = 4.04$, $p < 0.01$).

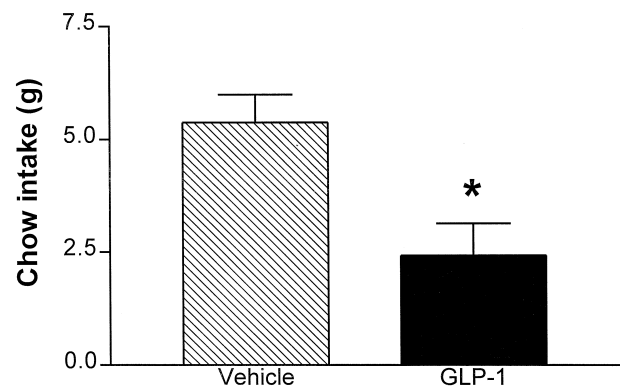


Fig. 4. The effect of a bolus ICV injection of GLP-1 (10 μg) on chow intake in Long-Evans rats after that GLP-1 had been held in osmotic mini-pump tubing and kept at body temperature for 4 days. Data are represented as mean \pm S.E.M. and * indicates statistically different from vehicle at $p < 0.05$.

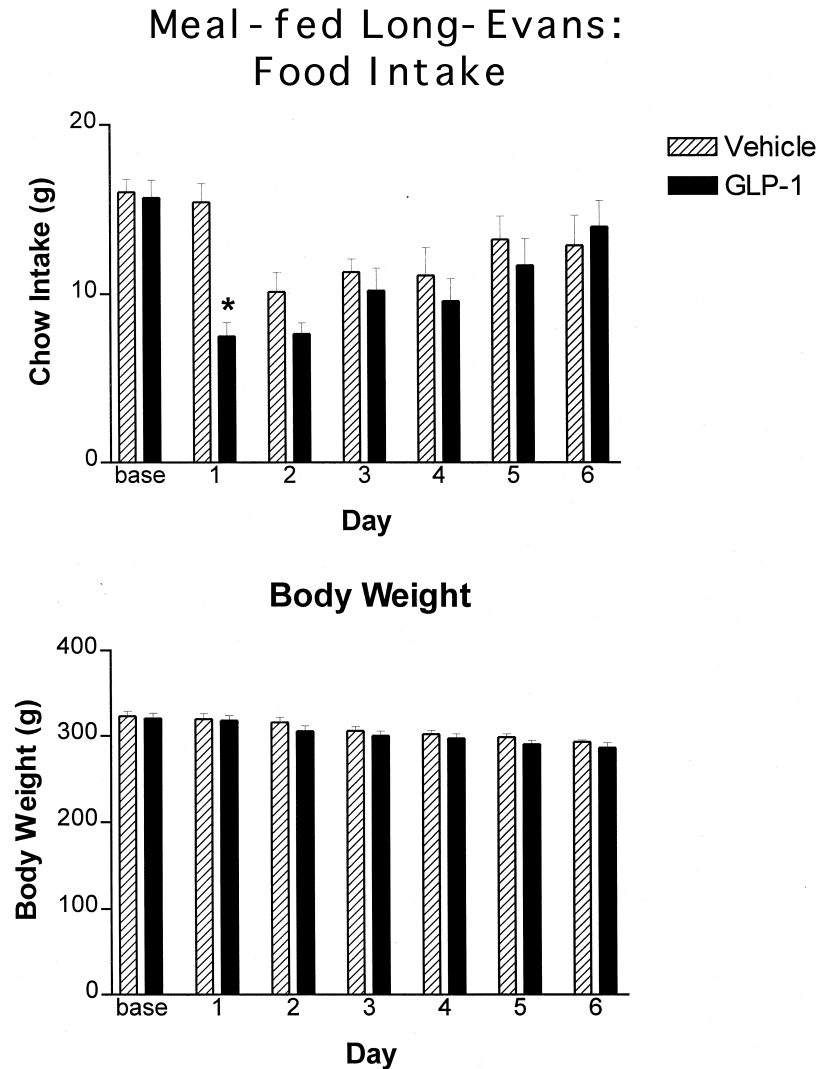


Fig. 5. The effect of two daily bolus ICV injections of GLP-1 (30 μ g/day) on chow intake in Long-Evans rats that were constrained to two 2 h periods of access to food per day on total daily food intake (top panel) and body weight (bottom panel). Data are represented as mean \pm S.E.M. and * indicates statistically different from vehicle at $p < 0.05$.

To analyze this interaction, follow-up ANOVA's were performed. Comparing baseline intake with Day 1 of treatment revealed a significant effect of Condition ($F[1,12] = 13.56$, $p < 0.01$), Day ($F[1,12] = 30.09$, $p < 0.001$) and the interaction between Condition and Day ($F[1,12] = 22.61$, $p < 0.001$). By Day 2, the comparison with baseline intake revealed no effect of Condition ($F[1,12] = 1.82$, $p = 0.202$), and no interaction ($F[1,12] = 1.82$, $p = 0.202$), but a significant effect of Day ($F[1,12] = 30.09$, $p < 0.001$).

The effect of repeated bolus injections of saline or GLP-1 on body weight is depicted in Fig. 5B. ANOVA revealed a significant overall effect of Day on body weight ($F[7, 84] = 26.16$, $p < 0.001$), but no effect of Condition ($F[1,12] = 0.88$, $p = 0.367$) and no interaction ($F[7,84] = 0.83$, $p = 0.566$). In comparison to baseline body weight, on Days 1 through 6, all rats' body weights were significantly reduced, regardless of condition ($F[1,12] = 7.32$,

$p < 0.05$; $F[1,12] = 38.32$, $p < 0.001$; $F[1,12] = 237.84$, $p < 0.001$; $F[1,12] = 121.63$, $p < 0.001$; $F[1,12] = 121.88$, $p < 0.001$; and $F[1,12] = 95.42$, $p < 0.001$, for Days 1 through 6, respectively). By day 7, all rats had returned to their pre-treatment weight ($F[1,12] = 3.32$, $p = 0.93$). Over the course of the six days of the experiment, change in body weight did not differ as a function of GLP-1 treatment. In fact, even when food intake was suppressed by GLP-1, body weight was not reduced relative to that of the saline controls.

These results replicate and extend the results of Experiment 1. On the first day of treatment the bolus injections of GLP-1 suppressed food intake when the animals only were allowed short-term feeding bouts of 2 h each. However, from Day 2 until the end of the experiment, food intake of rats receiving GLP-1 was no longer suppressed relative to that of saline-injected controls. Therefore, the rats receiving GLP-1 quickly compensated for the initial

reduction in food intake. The fact that food intake was initially reduced indicates that the GLP-1 was effective. As in experiment 2, food access restriction combined with multiple third ventricle injections produced a non-specific reduction in food intake and a small reduction in body weight. The possibility that these non-specific effects of the control condition masked a small effect of GLP-1 can not be eliminated. As in the previous experiments, however, the inability of GLP-1 to produce an effect over and above the appropriate control conditions do not support a role for GLP-1 in the regulation of long-term food intake and body weight.

4. General discussion

The current results replicate those of Turton et al. [19] demonstrating that when administered into the third ventricle, GLP-1 potently reduces food intake, and that the effect lasts for up to 2 h in lean Long–Evans rats. The current experiments extend the findings of Turton et al. in several important ways. First, when food intake is assessed over longer intervals following bolus injections, the effect of GLP-1 on food intake is found to be short-lived and essentially non-existent after 24 h. Second, comparably to what is seen in Long–Evans rats, IVT administration of GLP-1 to fatty Zucker rats reduces 2 h but not 24 h food intake. Hence, GLP-1 has a short functional time constant, and the lack of a longer effect could be due to its short half-life and/or to compensation by other factors later in the day. Finally, GLP-1 is comparably effective in fatty Zucker rats as it is in lean Long Evans rats. All of these actions fit a profile of a short-acting, meal-related satiety factor.

To assess whether GLP-1 would be more efficacious if given over a longer interval, we administered GLP-1 as a continuous infusion into the third ventricle via osmotic mini-pumps. Despite using a daily dose that is 10 times the effective bolus dose, continuous infusion of GLP-1 had no effect on food intake or body weight in either Long–Evans or fatty Zucker rats. While there are always caveats associated with interpreting negative data especially when the control conditions appear to have effects on food intake and body weight, these data suggest that providing continuous stimulation of central GLP-1 receptors does not produce changes in daily food intake or body weight. The results of Experiment 3 further suggest that the GLP-1 remained potent throughout the infusion interval, such that the animals evidently became refractory to its anorexic actions.

In the final experiment, animals were restricted to two 2 h intervals of feeding each day, a schedule on which they were able to maintain their free-feeding body weights. GLP-1 could thus be administered immediately prior to each feeding bout, with the food being available for a duration over which IVT administration of GLP-1 effec-

tively reduces intake (cf. Fig. 1). And whereas GLP-1 did reliably reduce intake early in the paradigm, its anorexic effect was reduced by the second day of treatment and completely gone by the third day. Importantly, at no point did GLP-1 reduce body weight, suggesting that infused animals might have had reduced energy expenditure during the periods when food intake is being reduced. Again, caveats apply to such negative data. The control conditions in this experiment (repeated i3vt vehicle administration in animals with only 4 h access to food per day) appeared to have an effect to reduce food intake. It is possible that this effect of the control condition obscured a small effect of GLP-1 to continue to reduce food intake and body weight. Collectively, however, the present experiments provide no evidence that central administration of GLP-1 can influence long-term food intake or body weight.

The results with GLP-1 therefore contrast with those of other peptides hypothesized to be long-term regulators of food intake and body weight via actions in the CNS. When either the pancreatic hormone insulin or the adipocyte hormone leptin are infused into the third ventricle in multiple boluses or continuously via osmotic mini-pumps, they produce dose-dependent reductions of daily caloric and, if continued, loss of body weight as well [1,15]. In further contrast to the effects of GLP-1, fatty Zucker rats are resistant to the food and body weight suppressive effects of both insulin and leptin infused into the third ventricle [9,15].

Finally, the pattern of neuronal activation as assessed by *c-fos* immunohistochemistry is different for GLP-1 and leptin. Leptin produces significant increases in *c-fos*-like-immunohistochemistry (c-FLI) in several hypothalamic nuclei and in the central nucleus of the amygdala. In addition to activation in these same brain regions, a dose of GLP-1 that produces similar reductions short-term food intake also produces increased in c-FLI in several brainstem nuclei, including the area postrema, the parabrachial nucleus and the NTS [20]. Finally, at doses that produce significant reductions in food intake and body weight, neither insulin nor leptin [1,18] produce conditioned taste aversions. Doses of GLP-1 that reduce food intake, however, cause the formation of robust conditioned taste aversions [18,21]. Thus, the available data on the effects of central administration of GLP-1 on food intake and body weight do not support the hypothesis that GLP-1 has a role in the regulation of long-term food intake and body weight.

The actions of GLP-1 in the CNS are seemingly more analogous to those of CCK. Exogenous administration of GLP-1 (IVT) or CCK (i.p. or IVT) reduces short-term food intake in both lean and *fa/fa* Zucker rats without changing daily caloric intake or body weight [12]. CCK receptor antagonists, when administered alone, produce reliable increases of meal size [16], and Turton et al. have evidence that this is also true for a GLP-1 antagonist [19]. GLP-1 and CCK also produce overlapping patterns of neuronal activation in the brainstem as measured by c-FLI [11,20].

Thus, if GLP-1 in the CNS does have a role as a homeostatic regulator of food intake, it would appear to be as a short-term satiety signal and not a long-term regulator of caloric intake and body weight. On the other hand, unlike GLP-1, CCK reduces meal size at doses that do not cause conditioned taste aversions; and CCK does not cause a generalized depression as has recently been reported for GLP-1 [6]. Hence, GLP-1 may act in a different manner to effect food intake than satiety agents such as CCK.

The growing prevalence of obesity has produced a pressing need (and a lucrative market) for pharmacological treatments that could produce reductions in food intake leading to reductions in body adiposity. The initial observation that GLP-1 administered into the third ventricle produced a potent reduction of food intake made central GLP-1 receptors attractive targets for developing pharmacological interventions. However, an agonist for the GLP-1 receptor administered into the CNS produces aversive side effects (as indicated by its ability to support robust conditioned taste aversions [18,21]). Further, the present data support the hypothesis that producing reductions of long-term food intake and body weight with a GLP-1 agonist is unlikely.

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