There is evidence that central infusion of brain-derived neurotrophic factor (BDNF) induces weight loss in rats. We have begun to investigate the physiological basis for BDNF-induced weight loss by assessing its relationship to (a) appetite, (b) serum indices of metabolic and renal toxicity, and (c) brain monoamine activity in areas associated with feeding or motor function. BDNF (0-6 μg/day) was infused into the lateral ventricle (LV) of male Long-Evans rats for 14 days. Body weight and food intake were monitored throughout infusion and recovery periods. BDNF induced severe, dose-dependent appetite suppression and weight loss. Although appetite began to recover after the 10th infusion day, body weight had not returned to control values at the end of the recovery period. The weight loss observed in BDNF-infused rats was related to appetite suppression, since uninfused rats that were pair-fed to high dose BDNF-treated rats showed comparable weight loss. Despite severe weight loss, serum BUN, creatinine, thyroxine, glucose, and total protein were not affected by BDNF infusion. Striatal DOPAC/DA was similarly unaffected by BDNF. In contrast, BDNF-infused rats showed a dose-dependent increase in hypothalamic 5-HIAA/5-HT that was not observed in pair-fed rats, suggesting that the observed increase in hypothalamic 5-HIAA/5-HT was a direct effect of BDNF infusion rather than a secondary effect of food restriction. These data suggest that BDNF may induce appetite suppression and weight loss through a central mechanism.

INTRODUCTION

Although the role of brain-derived neurotrophic factor (BDNF) in the adult central nervous system (CNS) is unclear, there is a rapidly growing body of evidence implicating BDNF in neuronal degeneration/regeneration mechanisms. Hippocampal BDNF mRNA levels are increased after seizure activity (9), kainic acid injection (3), and CA1 induction of LTP (21). Further, hippocampal BDNF mRNA is decreased after partial or complete fimbria-fornix transections (11) and in the hippocampal formation of Alzheimer’s victims (24). Finally, both intraventricular and intraseptal infusion of BDNF can protect the hippocampus from cholinergic cell loss after unilateral fimbria-fornix transections (10, 19, 35).

The above evidence suggests that BDNF, like NGF, may be clinically useful in the treatment of diseases that involve neuronal degeneration. There are however, very few published data on the central or systemic effects of BDNF in animal models. Aside from evidence that unilateral nigral infusion of BDNF can augment rotational behavior (1, 16), and induce analgesia (30), the only other report of central BDNF effects has been that central infusion of BDNF can attenuate weight gain (12). The effect on body weight is consistent with the fact that other growth factors (including NGF) have also been reported to either attenuate weight gain or induce weight loss (25, 36). The fact that intraventricular BDNF infusion can affect body weight could be viewed as an indication of toxicity or as evidence for a specific role of BDNF in CNS function. An understanding of this mechanism would be important for either view. To date, the mechanism for BDNF-induced attenuation of weight gain is unknown.

The following report summarizes experiments that were designed to explore the mechanism by which BDNF affects body weight. In order to understand this mechanism, we examined several issues: (i) the importance of hypophagia in BDNF-induced weight loss, (ii) the role of general toxicity in BDNF-induced weight loss, and (iii) the possibility that BDNF might affect appetite through a central mechanism. These issues were examined by (i) measuring body weight and food intake during the ventricular infusion of several doses of BDNF along with assessing weight loss in uninfused rats pair-fed to rats receiving the highest dose of BDNF, (ii) assessing the rate of recovery from hypophagia/weight loss along with examination of general serum indices of toxicity and metabolism, and (iii) assessing the effects of increasing doses of BDNF on brain biogenic amines that have been associated with appetite suppression.

MATERIALS AND METHODS

Subjects

All subjects were male Long-Evans rats (290–315 g) that were housed singly in Amgen’s vivarium, where
temperature was held constant at 25°C and a 12-h light cycle (7 AM–7 PM) was in effect. All rats were allowed food and water ad lib, except for those involved in the pair-feeding study. During the 28 days of feeding measurements, animals were given liquid diets (Dyets, Inc.).

Forty-eight rats were used in the initial experiment that assessed body weight, food intake, and recovery in rats infused with one of four BDNF doses, a PBS vehicle, or a high dose of NGF. A second set of 40 rats was used to assess the dose-dependent effects of BDNF on plasma variables and brain amines on the 7th day of BDNF infusion. NGF-treated rats were not included in this set because of its minimal effects on feeding and body weight. A third set of 16 uninfused rats was pair-fed with the high-dose group of BDNF-infused rats to assess the effects of hypophagia itself on weight loss and recovery, serum insulin, and brain monoamines.

Surgery

All rats were habituated to the liquid diet and showed comparable food intake and body weights at the time of pump implantation. Prior to surgery, rats were assigned to one of five dose groups, with body weights equalized across groups. Eight rats were assigned to each dose group. All rats were implanted with the osmotic pumps under sodium pentobarbital anesthesia (55 mg/kg, ip). Stainless steel osmotic pump connectors (28 g) (Plastics One, Roanoke, VA) were implanted into either the left or the right lateral ventricle, using the stereotaxic coordinates (flat skull): AP: −0.3 from bregma; ML: ±1.4 from the midline; DV: −3.4 (22). The DV coordinate was measured from the skull surface. Following implantation, cannulae were secured to the skull surface with dental cement. The pump itself was then placed into a subcutaneous "pocket" in the subscapular area of the neck and connected to the ventricular cannula with polyethylene tubing (PE 50). The pumps had been filled immediately prior to implant with either phosphate-buffered saline (PBS) or BDNF diluted in PBS so that the pump would deliver 0.375, 1.5, 3.0, or 6.0 μg BDNF/day. The osmotic minipumps (Alza Corp., Palo Alto, CA; Model 2002) used in these studies delivered 0.5 μl/h for a period of 2 weeks. Two sets of rats were implanted with the above doses of BDNF or PBS. Pumps were removed from one set on the 15th day after implantation using inhalation anesthesia (Metafane) so that recovery from hypophagia could be assessed. The second set was sacrificed on the 7th day of infusion so that serum variables and brain monoamines could be measured during a period of maximal appetite suppression.

The BDNF used in this report was the recombinant product of the human BDNF gene sequence, which was produced in Chinese hamster ovary (CHO) cells grown in serum-free media at Amgen, Inc. The production, purification, and formulation of BDNF have been described elsewhere (7). The recombinant BDNF used in these experiments showed activity (3 to 3+ at 5–10 ng/well) similar to BDNF isolated from pig brain using bioassays of cultured dorsal root ganglion explants (7).

Weight and Food Intake Measurements

Body weight and food intake were measured for 5 days prior to pump implantation to obtain baseline data, to allow habituation to the liquid diet, and to allow an equal distribution of body weights for each dose group. Body weight and food intake were then measured every day of the infusion period, as well as 2 weeks after the pumps had been removed for the long-term survival groups. Measurements were always taken at the same time of day (3:00 PM). Food intake was measured using a liquid diet (Dyets, Inc.) that was calorically and nutritionally similar to solid rat chow. This liquid diet consisted of 19.3% protein (derived primarily from casein), 68.8% carbohydrate (maltose), and 11.9% fat (corn oil), with a caloric density of 1.0 kcal/ml. (Standard solid rat chow has a caloric density of 3.04 kcal/gm.) A liquid diet was chosen to increase the accuracy and efficiency of daily food intake measurements. Food intake was measured at the same time as body weight every day. Bottle weights for water were also measured each day.

Pair-Feeding

To determine if changes in serum and brain monoamine variables were the direct result of BDNF infusion or the result of appetite suppression, the food intake of 16 intact controls was matched to that of rats in the 6.0-μg BDNF group for a period of 28 days. After the 7th day, 8 of these rats were sacrificed, and serum insulin and brain monoamines were measured. The remaining rats were allowed to survive for the full 28-day period to assess the effects of appetite suppression alone on body weight.

Serum Measurements

Blood from the tail vein was collected in untreated tubes and centrifuged at room temperature at 5000 rpm for 15 min on the 7th day of infusion. Serum was collected as the supernatant and frozen at −20°C until the time of assay. Glucose, blood urea nitrogen (BUN), creatinine (CRE), and total protein were measured from plasma using a Synchron Astra 8 Clinical System (Beckman, Inc.). BUN, creatinine, and total protein were measured to assess renal function, while insulin, blood glucose, and thyroxine were measured as a rough assessment of metabolic parameters. Insulin and thyroxine (T4) were measured using radioenzymatic assay kits from Incstar, Inc. Briefly, the T4 assay is based upon the competition of serum T4 with iodinated T4 for the binding sites of a monoclonal mouse T4 antibody that is immobilized on a coated assay tube. The insulin RIA is based upon the competition between iodinated porcine insulin and serum insulin for guinea pig insulin anti-
body. The bound insulin/antibody complex is separated from free iodinated insulin by precipitation with goat anti-guinea pig serum and centrifugation.

**Neurochemical Assays of Brain Tissue**

Hypothalami and striata were all rapidly dissected from the brains of rats that were sacrificed on Day 7 of infusion. Hypothalamus and striatum were chosen as representative of brain areas involved in feeding and motor components of feeding. Tissue was immediately frozen on dry ice, and stored at -80°C until the time of analysis. Hypothalami and striata were analyzed for biogenic amines using HPLC with electrochemical detection. Tissue was homogenized in 14% methanol (HPLC grade), 0.75 mM heptane sulfonic acid (Na salt), 0.1 M sodium citrate, and 0.075 M sodium phosphate dibasic (heptahydrate). This buffer (pH 3.8) also served as the mobile phase for subsequent HPLC analysis. Homogenates were centrifuged at 12,000 rpm for 20 min at 4°C. The supernatant was filtered through a 0.2-μm nylon syringe filter. Dihydroxybenzylamine (DBA) (1 ng) and ascorbic acid oxidase (1.4 units) were added to 200 μL of the filtrate; 20 μL of this filtrate was injected onto the column, which was a 3-μm, reverse-phase, ODS-II column. Oxidation potential was set at 0.75 nA. Peak area was integrated using software developed by BAS, Inc., and sample catecholamine concentrations were based upon a standard curve that ranged from 0.5 to 10 ng, where DBA served as the internal standard.

**Statistical Analyses**

Body weight and food intake were analyzed using a two-way repeated measures ANOVA where difference from presurgical weight or food intake was the within-groups variable and dose was the between-groups variable. There were five levels for the dose variable, including four BDNF doses and the PBS control. Separate repeated measures ANOVAs were used to (i) compare food intake and body weight for the high-dose NGF group with the other BDNF doses for a 9-day period and (ii) to analyze weight and food intake during infusion and recovery periods. Simple effects analysis and the Neuman-Keuls test were used for post hoc analyses. Plasma variables and brain neurochemical variables were analyzed using one-way between-groups ANOVAs for each measure. The Neuman-Keuls test was then used to compare group means. Finally, a repeated measures ANOVA was used to assess the results of the pair-feeding study, where body weights of untreated pair-fed rats were placed into the same ANOVA used to assess body weight changes in BDNF-treated rats. This was done to determine which dose of BDNF produced a change in body weight comparable to that observed in rats pair-fed to the high-dose BDNF group. A similar analysis using a simple one-way ANOVA was used to assess the effects of pair-feeding on serum insulin and hypothalamic 5-HIAA/5-HT.

**RESULTS**

**Lateral Ventricular Infusion of BDNF and Recovery**

**Body weight.** Intraventricular infusion of BDNF decreased body weight in a statistically significant, dose-[F(4, 377) = 60.02; P < 0.001] and time- [F(13, 377) = 28.18; P < 0.001] dependent manner, as can be observed by inspection of Fig. 1a. There was a significant interaction between dose and time [F(52, 377) = 24.52; P < 0.001]. Simple effects analysis of this interaction revealed that while weight change was similar in all dose groups the first 2 days after pump implantation, these groups began to separate by dose from the 3rd through the 14th day of infusion (P < 0.01). Weight loss in the 3.0- and 6.0-μg dose groups was greater than any other dose group (P < 0.01). Further, the 1.5-μg dose group lost more weight than those in the PBS or 0.375-μg groups and less than animals in the 3.0- and 6.0-μg groups (P < 0.01). A separate ANOVA comparing BDNF doses with NGF (6 μg/day) for a 9-day period showed that weight loss in the NGF group was equivalent to the 1.5 μg/day BDNF dose, and different from all of the BDNF doses (P < 0.05). Preinfusion (baseline) body weight was similar across groups (range = 295–315 g; average SEM = 6.5).

Weight change continued to differ across groups in a dose- and time-dependent manner during the 2-week recovery period, despite the fact that BDNF was no longer being infused [F(4, 377) = 38.67; P < 0.001] (dose), and [F(13, 377) = 223.65; P < 0.001] (time). Although all rats showed weight gain over time, weight gain varied with dose, resulting in a significant interaction between dose and time [F(52, 377) = 7.39; P < 0.001]. Post hoc analysis of group means revealed a pattern similar to that of the dose effect observed during infusion. Weight gain after pump removal was the most rapid in the 1.5-, 3.0-, and 6.0-μg doses (P < 0.01), with weight gain slower in the 1.5-μg group than in the 3.0- or 6.0-μg groups (P < 0.01). Further, although the 1.5-, 3.0-, and 6.0-μg groups showed a significant weight increase over time, they weighed significantly less than the 0.375 or PBS group at the end of the recovery period (P < 0.01). Extrapolation from the slopes of the recovery curves for the PBS, 3.0-, and 6.0-μg groups suggested that BDNF groups would reach the weights of the PBS group 32 days after pump removal.

**Food intake.** Similar to body weight, food intake was significantly decreased in a dose- [F(4, 377) = 37.6; P < 0.001] and time- [F(13, 377) = 6.35; P < 0.001] dependent manner, as can be observed in Fig. 1b. There was also a significant interaction between time and dose variables [F(52, 377) = 2.82; P < 0.001], indicating that the magnitude of the dose-related differences in food intake varied with time. Simple effects analysis of this interaction showed a significant effect of dose at all time points (P < 0.001), while there was a significant effect of time only at the 0.375- and 6.0-μg doses (P < 0.001).
Animals that received the 6.0-μg dose demonstrated a "rebound" effect in feeding over the 3.0- and 1.5-μg BDNF dose groups, which is reflected in the above simple effects analysis. There were no significant group differences in baseline food intake prior to pump implantation (see Fig. 1b).

Similar to the results of the body weight analysis, a separate ANOVA for the first 9 days was conducted to compare the effects of a 6.0-μg dose of NGF with all doses of BDNF on feeding. Animals infused with the 6.0-μg NGF dose ate significantly less than the PBS group (P < 0.05), and significantly more than rats...
infused with the 3.0- and 6.0-μg doses of BDNF ($P < 0.01$).

There were no significant dose differences during the 14-day recovery period, although there was a significant interaction between dose and time [$F(52, 377) = 2.34; P < 0.0011$]. Simple effects analysis of this interaction revealed that a dose effect remained during the first 2 days after the pumps were removed ($P < 0.058; 0.009$), after which all rats consumed as much as controls. Therefore, recovery for the food intake measure preceded recovery for the body weight measure. Animals infused with BDNF did not show a “rebound” effect over food intake values for controls at any point during the infusion or recovery period. Although there were no significant group differences in water consumption as measured by water bottle weights, it must be emphasized that the observed suppression of food intake using the liquid diet necessarily inferred a reduction in water consumption as well (data not shown).

**Effects of BDNF on Plasma Variables 7 Days after Pump Implantation**

There were no significant differences in any of the plasma variables except for insulin. Insulin was decreased in a dose-dependent manner in BDNF-treated rats [$F(4, 28) = 10.6; P < 0.0011$]. Insulin levels in the 1.5-, 3.0-, and 6.0-μg groups were significantly lower than those in the PBS group ($P < 0.01$). These results are illustrated in Fig. 2a. Serum total protein, glucose, BUN/creatinine, and T4 were all unaffected by increasing doses of BDNF. Table 1 summarizes the effects of BDNF on these serum variables.

**Effects of Ventricular BDNF Infusion on Brain Monoamines 7 Days after Pump Implantation**

Hypothalamic 5-HIAA/5-HT was significantly increased by BDNF in a dose-dependent manner [$F(4, 23) = 3.46; P < 0.0241$]. Hypothalamic 5-HIAA/5-HT was significantly elevated in the 1.5-, 3.0-, and 6.0-μg groups relative to the 0.375-μg and PBS groups ($P < 0.05$). Striatal DOPAC/DA was not significantly altered by BDNF infusion. Other monoamine/metabolite ratios (hypothalamic MHPG/NE and striatal 5-HIAA/5-HT) were not uniformly detectable in our system. Figures 3a and 3b summarize these results.

**Effects of Pair-Feeding on Body Weight, Serum Insulin, and Hypothalamic 5-HIAA/5-HT**

When body weights from pair-fed animals were included in the overall repeated measures ANOVA with BDNF dose groups, main effects and interaction effects were essentially unchanged (see Fig. 4). Post hoc tests comparing group means over time revealed that pair-fed body weights were similar to the 3.0- and 6.0-μg BDNF groups, but lower than the PBS, 0.375-, and 1.5-μg dose groups ($P < 0.01$). During the recovery phase, a similar analysis revealed that again, the main effects and interaction effects were essentially unchanged from the ANOVA conducted on BDNF dose groups alone. Post hoc group comparisons, however, showed that body weights of pair-fed rats during the recovery period were similar to the 1.5-μg BDNF group, rather than to the 6.0-μg BDNF group to which they were pair-fed. Body

![Graph](image-url)
weights of pair-fed rats were significantly higher than the 6.0-μg group ($P < 0.01$) during the recovery period, suggesting that the recovery curve for pair-fed rats was steeper (more rapid) than that of the 6-μg BDNF group.

An ANOVA comparing serum insulin in the pair-fed group with that of PBS, free-fed, and all BDNF dose groups revealed a similar overall $F$ ratio as in the comparison with BDNF or PBS groups alone [$F(6, 36) = 9.69; P < 0.001$]. Post hoc comparison of group means showed that serum insulin in the pair-fed group was significantly less than in the free-fed or PBS groups ($P < 0.01$), but was not significantly different than any of the BDNF dose groups. These results can be observed in Fig. 2b. A similar ANOVA comparing hypothalamic 5-HIAA/5-HT in the pair-fed group with that of PBS, free-fed, or BDNF dose groups revealed a similar overall $F$ ratio as in the comparison with BDNF or PBS groups alone [$F(6, 31) = 8.7; P < 0.001$]. In contrast to the case of insulin in pair-fed rats, hypothalamic 5-HIAA/5-HT in pair-fed rats was similar to that of either free-fed or PBS-treated rats, but was significantly different from that of rats given either 1.5, 3.0, or 6.0 μg/day of BDNF ($P < 0.05$). These results can be observed in Fig. 3a.

DISCUSSION

Intraventricular administration of BDNF resulted in a severe, dose-dependent weight loss that continued throughout the infusion period, although all rats began to show weight gain by the 10th or 11th day of infusion. Despite the trend to gain weight after BDNF had been discontinued, rats that had received the 1.5-μg dose or higher weighed significantly less than controls 14 days after termination of BDNF infusion. Extrapolation from the weight loss curves, however, would suggest that all rats would be as heavy as controls by the 32nd day of the recovery period. The weight loss we observed after icv

### TABLE 1

<table>
<thead>
<tr>
<th>Dose</th>
<th>BUN/CRE (mg/dl)</th>
<th>Glucose (mg/dl)</th>
<th>Total protein (g/dl)</th>
<th>T4 (μg/dl)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PBS</td>
<td>38.42 ± 2.39</td>
<td>176 ± 9.48</td>
<td>5.19 ± 0.2</td>
<td>2.55 ± 0.59</td>
</tr>
<tr>
<td>0.37 μg/day</td>
<td>36.7 ± 4.06</td>
<td>183.6 ± 4.14</td>
<td>5.32 ± 0.17</td>
<td>3.12 ± 0.32</td>
</tr>
<tr>
<td>1.5 μg/day</td>
<td>41.57 ± 5.4</td>
<td>164.86 ± 3.8</td>
<td>4.87 ± 0.19</td>
<td>2.59 ± 0.38</td>
</tr>
<tr>
<td>3 μg/day</td>
<td>34.86 ± 3.7</td>
<td>160 ± 9.9</td>
<td>4.84 ± 0.25</td>
<td>2.29 ± 0.17</td>
</tr>
<tr>
<td>6 μg/day</td>
<td>36.7 ± 4.09</td>
<td>177.43 ± 10.2</td>
<td>4.65 ± 0.13</td>
<td>2.08 ± 0.19</td>
</tr>
</tbody>
</table>

*Note.* All of the above serum variables were measured on the 7th day of ventricular BDNF infusion at the same time of day that feeding measures were normally taken (3:00 PM). There were no significant differences between BDNF treatment and PBS in any of the illustrated parameters. BUN and CRE levels are expressed as a ratio to provide an "index" of dehydration. Neither BUN nor CRE alone was altered by increasing BDNF dose. Six or seven rats/group are represented in this table.

### FIG. 3

Hypothalamic 5-HIAA/5-HT and striatal DOPAC/DA during BDNF infusion into the lateral ventricle. (a) Brain monoamines were measured on the 7th day of BDNF infusion. A significant, dose-dependent increase in hypothalamic 5-HIAA/5-HT was observed in rats infused intraventricularly with BDNF ($P < 0.02$). Hypothalamic 5-HIAA/5-HT was not altered in rats that were pair-fed to the high dose BDNF group. (b) Striatal DOPAC/DA was not significantly altered by lateral ventricle infusion of BDNF. There were six or seven rats/group for the above experiments.

BDNF infusion was accompanied by an equally severe and dose-dependent appetite suppression that continued for approximately half of the infusion period. Most of the animals that had demonstrated appetite suppression dramatically increased their food intake during the 2nd week of infusion, so that their food intake was
comparable to controls by the end of the infusion period. These feeding data, along with the fact that rats pair-fed to high-dose BDNF-treated rats lost a comparable amount of weight at a similar rate, suggest that the weight loss induced by BDNF can be explained by hypophagia.

Interestingly, recovery of body weight after pump removal did not proceed at the same rate as recovery in rats that were pair-fed to the high-dose BDNF group. Recovery in the pair-fed rats was more rapid than for their BDNF-treated counterparts, and began as soon as food intake increased. In contrast, body weight gain in BDNF-treated rats was delayed, but then proceeded at a rate similar to pair-fed rats. All of this suggests that recovery from BDNF-induced weight loss is somewhat different than recovery from weight loss due to food restriction. While the reason for these differences in body weight recovery is unclear, it is possible that the slow recovery in body weight from appetite suppression observed in high-dose BDNF rats might reflect some general toxicity.

It seems improbable that toxicity completely explains BDNF-induced appetite suppression, however, for the following reasons: (i) Other commonly used indices of renal/metabolic toxicity, such as serum BUN, creatinine, total serum protein, t-thyroxine (T4), and blood glucose were all unchanged by BDNF infusion, despite the fact that they were measured during the period of peak appetite suppression. Although we did not directly measure markers for liver toxicity such as SGOT or SGPT with ventricular administration, these measures have been conducted in animals given chronic high doses of BDNF peripherally which have also resulted in appetite suppression. These markers were unchanged even after 3 months of administration of very high (70 mg/kg and up) doses of BDNF (4).

Although insulin levels were decreased significantly in a dose-dependent manner during BDNF infusion, it is doubtful that this was a direct result of BDNF. Insulin levels were also decreased in rats that were pair-fed to high-dose BDNF counterparts, suggesting that food restriction itself resulted in decreased serum insulin. The latter is in general agreement with several reports (5, 26) that have described decreased serum insulin in states of food restriction. It is somewhat surprising, however, that hypoglycemia did not accompany hypoinsulinemia in BDNF-treated rats, and may suggest a more complex role for BDNF in insulin regulation than is indicated by the results of the pair-feeding study. (ii) General observation of animals that received BDNF indicated that despite severe appetite suppression and weight loss, they continued to groom normally, were slightly hyperactive (which could be attributed to hypophagia itself), and appeared healthy.

It is possible that these animals appeared to show appetite suppression because BDNF induced changes in motor activities that would compete with feeding behavior. There is evidence that intranigral or striatal BDNF...
infusion can moderately increase open field locomotor activity (27) and can enhance amphetamine-induced rotation on the side controversial to the infusion site (1, 16). Intranigral infusion of BDNF, however, does not increase locomotor activity or stereotypic behavior above the levels of free-feeding controls when measured in the home cage (16). Therefore, it is doubtful that the presence of competing behaviors could explain the appetite suppression that we observed after intraventricular BDNF infusion. Further, our failure to find any changes in striatal dopamine activity during icv BDNF infusion (as indicated by the ratio of DOPAC/DA) does not support a motor dysfunction hypothesis for the effects of BDNF on feeding.

Several lines of evidence suggest that BDNF-induced appetite suppression and weight loss could be mediated through CNS pathways that play a role in feeding. First of all, centrally administered BDNF induced appetite suppression. Although it is always possible that BDNF “leaked” into the periphery via the venous system, its peripheral distribution and elimination half-lives are so rapid (6 min and 2 h, respectively) that a dose as small as 6 μg/day could not affect circulatory system parameters involved in feeding (4). Further, the dose of peripherally injected BDNF that is required to show any effect at all on feeding is 500–8000 times greater than the dose that induced appetite suppression centrally (4).

Second, our data showed that lateral ventricular infusion of BDNF resulted in a fairly specific central neurochemical response, in that hypothalamic 5-HIAA/5-HT was increased in a dose-dependent manner, while striatal DOPAC/DA was unchanged. It is possible that the increase in hypothalamic 5-HIAA/5-HT during BDNF infusion could have been secondary to food restriction. This is doubtful, however, since hypothalamic 5-HIAA/5-HT was not altered in rats pair-fed to those receiving the highest dose of BDNF, suggesting that the effects of BDNF on serotonin activity may have preceded its effects on appetite. It should be emphasized, however, that the pair-feeding data only partially rule out an effect on hypothalamic 5-HIAA/5-HT that is secondary to food restriction. A more complete resolution to the above issue (as well as the insulin effects) would have been provided by assessing the effects of BDNF infusion on hypothalamic 5-HIAA/5-HT and serum insulin in force-fed animals. In our hands, however, this was technically impossible because of the presence of the minipumps in the subscapular area.

There is an established body of evidence implicating hypothalamic serotonin in several forms of appetite suppression. Hypothalamic injection of serotonin has been shown to suppress appetite, particularly for carbohydrate macronutrients (13, 28, 31, 33). Further, a variety of serotonin agonists induce appetite suppression, which in some cases can be blocked by coadministration of serotonergic antagonists (8). There is even evidence to suggest that the anorectic effects of some dopaminergic agonists may be mediated by serotonergic mechanisms (37).

BDNF has been shown to alter central serotonergic transmission. Intraventricular BDNF infusion increases striatal 5-HIAA/5-HT (16), and BDNF infusion into the midbrain increases serotonergic activity in the raphe and spinal cord (30). Further, intracortical infusion of BDNF has been shown to prevent the parachloroamphetamine-induced loss of cortical serotonergic neurons (15). Interestingly, the latter effects on serotonergic neurons appear specific to BDNF, since NGF and NT3 did not have significant protective effects on cortical serotonergic neurons in the same study (15). The above data, along with evidence that BDNF and NGF have very different effects on central CCK and NPY expression (6, 20), may also help to explain the dissimilar effects of BDNF and NGF on the magnitude of appetite suppression and weight loss.

A serotonergic mechanism for BDNF-induced appetite suppression may be more compelling than mechanisms involving other transmitters with documented effects on appetite. For example, central injection of cholecystokinin (CCK) has also been shown to decrease food intake, and has been characterized as a “satiety” factor (18). A recent report, however, has shown that ventricular injection of BDNF does not alter hypothalamic CCK levels (6, 20). Feeding behavior has also been attributed to hypothalamic norepinephrine (NE) and neuropeptide Y (NPY) mechanisms (14, 29, 32, 34). Direct infusion of either NE or NPY results in increased feeding (14, 29, 32, 34). Therefore, it would be reasonable to suggest that BDNF would act to suppress appetite by decreasing the levels of NE or NPY. Recent work, however, has shown that BDNF infusion does not alter hypothalamic NPY (6, 20). Unfortunately, the effects of BDNF on hypothalamic NE are not clear at this time.

Finally, there is evidence that BDNF could play a role in hypothalamic function. BDNF and its receptor, trkB, are expressed in the adult hypothalamus in moderate to high density (3, 9). Further, direct infusion of BDNF into the hypothalamus has been shown to markedly suppress appetite (23), suggesting that BDNF may interact with hypothalamic systems that are involved in appetite suppression.

In conclusion, our data are consistent with and extend the results of an earlier report that BDNF attenuated weight gain (12). Further, our data support the idea that BDNF-induced weight loss can be explained by appetite suppression, and that the appetite suppression observed during icv BDNF infusion may be centrally mediated, perhaps through a hypothalamic serotonergic mechanism. These data, however, still do not rule out other central appetite suppression mechanisms or the possibility that BDNF-induced appetite suppression is at least
partly a reflection of some form of CNS toxicity that is not reflected in the serum measures we used. Studies are in progress to further investigate the importance of the hypothalamic serotonergic system as a mediator of BDNF-induced appetite suppression.

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