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Fibroblast growth factor inhibits locomotor activity as well as feeding behavior of rats

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Abstract

The effects of acute and chronic intracerebroventricular (i.c.v.) administration of basic fibroblast growth factor (bFGF) on behavior were examined in free-feeding rats. An i.c.v. injection of bFGF induced behavioral changes, such as an increase in resting and decreases in grooming, moving, and food intake at a dose of 20 or 50 ng. These effects appeared at 4–5 h and lasted at least 11 h after the injection. These changes, as well as inhibition of body weight gain, were also found during a 6-day period of chronic i.c.v. infusion of bFGF at a dose of 20 ng/h. These results indicate that bFGF as both bolus i.c.v. injection and chronic i.c.v. infusion inhibits not only feeding behavior but also locomotor activity in rats. It is suggested that the inhibitory effect of bFGF on food intake may be in part ascribed to the suppression of behavior by bFGF.

Keywords: FGF (fibroblast growth factor); Locomotor activity; Feeding behavior; Intracerebroventricular injection; Osmotic pump

1. Introduction

Acidic and basic fibroblast growth factors (aFGF and bFGF) are present throughout the central nervous system (Baird and Walicke, 1989; Gospodarowicz et al., 1986). They are known to affect the growth, function, and survival of neural cells in vitro and in vivo (Anderson et al., 1988; Gospodarowicz et al., 1986; Morrison et al., 1986; Otto et al., 1989; Walicke et al., 1986). Besides these neurotropic effects, FGFs have an inhibitory action on feeding behavior in rats (Hanai et al., 1989; Oomura et al., 1992; Plata-Salamán, 1988) and mice (Denton et al., 1995) when injected intracerebroventricularly (i.c.v.). The levels of aFGF and bFGF in cerebrospinal fluid increase postprandially and reach their peaks in 2 h after the start of eating in rats (Hanai et al., 1989; Oomura et al., 1992; Sasaki et al., 1991). Cell bodies of the lateral hypothalamic area, an appetite-controlling center, but not the ventromedial hypothalamus are labeled with ^{125}I-aFGF or ^{125}I-bFGF infused i.c.v. in rats (Ferguson and Johnson, 1991). In addition, FGF receptor 1, to which both FGFs bind, has been immunohistochemically demonstrated in lateral hypothalamic area neurons of the rat (Ferguson and Johnson, 1991; Matsuo et al., 1994), and FGFs electrophoretically applied suppress the activity of glucose-sensitive neurons in the lateral hypothalamic area with long latency and long duration (Hanai et al., 1989). Furthermore, injection of antibodies against FGFs into the lateral hypothalamic area increases food intake in rats (Sasaki et al., 1991). These findings suggest that FGFs in the lateral hypothalamic area play a role in the regulatory mechanism of feeding behavior.

In addition to FGFs, various peptides are known to affect feeding behavior, influencing or not locomotor activity as described below. Corticotropin-releasing factor (CRF) inhibits food intake and increases the locomotor activity of rats in their home cages when administered i.c.v.(Morley and Levine, 1982). Cholecystokinin, an inhibitor of feeding behavior, reduces locomotor activity when injected intraperitoneally (Rojas-Ramirez et al., 1982). Neuropeptide Y increases food intake without af-

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Table 1
Behavioral changes induced by i.c.v. injection of 20 ng or 50 ng bFGF in rats

		Resting	Grooming	Rearing	Moving
1–2 h	Vehicle	41.3±2.9	3.0±0.7	1.6±1.1	12.6±4.1
	FGF 20 ng	37.6±3.1	4.3±1.9	0	17.6±4.5
	FGF 50 ng	42.2±2.4	2.0±1.0	0	15.3±5.2
2–3 h	Vehicle	56.4±0.8	1.2±0.5	0	2.4±1.2
	FGF 20 ng	53.6±2.6	2.0±2.0	0	4.4±1.0
	FGF 50 ng	54.0±2.2	1.4±2.0	0	4.6±2.3
3–4 h	Vehicle	50.0±3.2	2.0±0.6	0	7.2±3.0
	FGF 20 ng	52.0±2.8	1.2±0.5	0	5.6±2.4
	FGF 50 ng	56.8±3.0	0	0	3.2±1.0
4–5 h	Vehicle	45.6±3.5	3.7±1.2	0.3±0.1	11.2±1.7
	FGF 20 ng	53.2±2.4[a]	1.2±0.5[a]	0	5.2±1.7[b]
	FGF 50 ng	58.0±2.0[a]	1.0±0.8[a]	0	1.0±0.5[b]
6–7 h	Vehicle	50.2±3.3	2.9±1.3	0.1±0.1	6.0±2.1
	FGF 20 ng	58.5±0.5[a]	0.3±0.3[a]	0	1.0±0.4[a]
	FGF 50 ng	58.5±0.5[a]	0.7±0.5	0	0.7±0.4[a]
8–9 h	Vehicle	46.8±1.6	4.2±1.4	0	4.6±1.1
	FGF 20 ng	51.7±1.4[a]	1.7±1.3	0.1±0.1	1.5±0.8[b]
	FGF 50 ng	52.7±0.8[b]	1.0±0.7[a]	0	0.3±0.3[b]
10–11 h	Vehicle	50.6±1.4	3.6±0.6	0.2±0.1	5.8±1.3
	FGF 20 ng	56.5±1.1[b]	1.5±0.8[a]	0	1.7±0.7[b]
	FGF 50 ng	55.0±1.4[a]	2.2±1.0[a]	0	2.5±1.0[b]
24–25 h	Vehicle	53.7±1.3	2.9±0.5	0.2±0.1	4.4±0.6
	FGF 20 ng	53.3±2.5	1.7±0.9	0	5.0±1.9
	FGF 50 ng	53.7±1.6	2.0±0.7	0	4.2±1.1

The number of rats in each group was seven. Data are expressed as means ± S.E.M.
[a] $P < 0.05$ vs. vehicle.
[b] $P < 0.01$ vs. vehicle.

fecting locomotor activity when administered i.c.v. (Clark et al., 1985; Levine and Morley, 1984; Yamada et al., 1996). These findings indicate that neuropeptides affect feeding behavior and locomotor activity in different ways.

It has been reported that FGFs decrease locomotor activity of rats when injected subcutaneously in a novel environment (Guaza et al., 1996). However, the effect of i.c.v. injection of FGF on locomotor activity of rats in a familiar environment has not been tested. Furthermore, the effects of chronic i.c.v. infusion of FGF on locomotor activity, food intake, and body weight gain have not been studied in rats. Therefore, in the present study, we tested the effects of bFGF on locomotor activity and feeding behavior when injected i.c.v. as a bolus or infused i.c.v. for 6 days in free-feeding rats in a familiar environment to clarify whether the inhibitory effect of FGF on feeding behavior is accompanied by the effect on locomotor activity and how long the effects of FGF on feeding behavior and locomotor activity last.

2. Materials and methods

2.1. Animals and drug

Male Wistar rats weighing 180–200 g were housed individually in cages 30(L)× 20(W)×18(H) cm on a 12:12-h light cycle (lights on at 0800) and were allowed ad libitum access to food (Oriental Lab Chow, Tokyo, Japan) and tap water. The number of rats in each treated group was seven and the total number of rats used in this study was 56. Five days before the experiment, a polyethylene guide cannula (SP-45 polyethylene tube, Natsume, Tokyo, Japan) for i.c.v. injection or infusion of samples was implanted into the right lateral ventricle under sodium pentobarbital anesthesia (50 mg/kg body weight, intraperitoneally) as previously described (Yamada et al., 1996). Human bFGF, provided by Takeda Chemical Industries (Osaka, Japan), was expressed in *Escherichia coli*, purified to homogeneity, and shown to be endotoxin-free as described previously (Seno et al., 1988)]. bFGF was diluted in 0.9% saline.

2.2. I.C.V. injection of bFGF

To investigate the effects of a bolus injection of bFGF (20 or 50 ng) on locomotor activity and feeding behavior in a familiar environment, free-feeding rats were used. At 0900, 10 μl of bFGF solution or vehicle as control was administered into the lateral ventricle via an injection cannula connected to a 10-μl microsyringe (Hamilton, NV, USA) and inserted into the guide cannula for approximately 1 min. The injection cannula was left in place for another minute to prevent backflow of the solution. The behavior of the rats was observed in their home cages through a mirror every minute for 60 min 1, 2, 3, 4, 6, 8, 10 and 24 h after the injection of samples. The sum of all behavioral scores for 60 min is 60. The behavior of the rats was classified into one of the following categories: resting, grooming, rearing and moving. Resting includes pausing posture and sleeping. Moving means turning, walking, and stretching. The amount of lab chow eaten in 25 h after the i.c.v. injection of sample solution was measured using rats other than those used for the behavior study.

2.3. Chronic i.c.v. infusion of bFGF

To investigate the effects of chronic infusion of bFGF on locomotor activity, food intake and body weight gain, the guide cannula implanted into the ventricle was connected to an Alzet osmotic pump (model 2001, Alza, Palo

Table 2
Effects of i.c.v. injection of bFGF on food intake and increase of body weight in free-feeding rats

Treatment	*n*	Food intake (g) 0–25 h	Increase of body weight (g)
Vehicle	7	17.9±2.4	7.7±1.9
bFGF 20 ng	7	9.2±2.1[a]	−5.1±4.3[b]
bFGF 50 ng	7	3.9±1.4[b]	−7.6±3.8[b]

Data are expressed as means ± S.E.M.
[a] $P < 0.05$ vs. vehicle.
[b] $P < 0.01$ vs. vehicle.

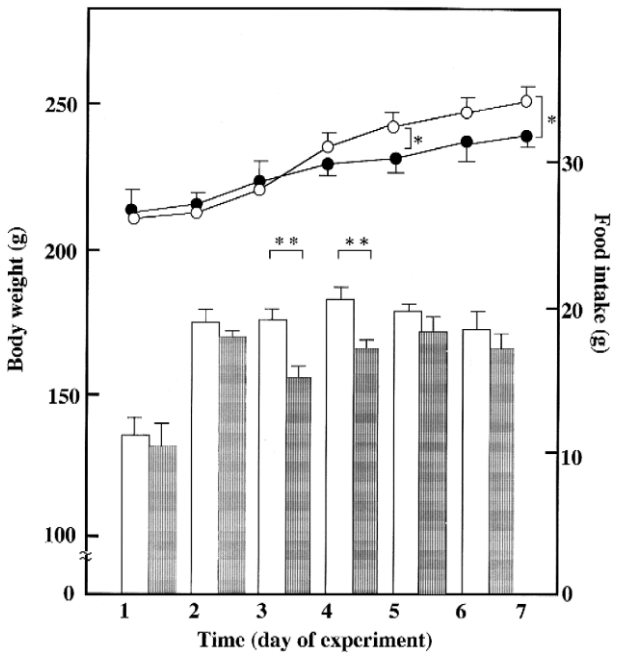

Fig. 1. Effects of chronic i.c.v. infusion of bFGF (20 ng/h) on daily food intake and body weight gain in rats. Body weight of vehicle-infused group (open circles) and bFGF-infused group (solid circles) and food intake of vehicle-infused group (open bars) and bFGF-infused group (solid bars). The number of rats in each group was seven. Data are expressed as means ± S.E.M. $^{*}P < 0.05$ $^{**}P < 0.01$.

Alto, CA, USA) containing bFGF solution (20 ng/μl) or vehicle, and the osmotic pump was then settled in the subcutaneous space of the dorsal region of the rats under sodium pentobarbital anesthesia (50 mg/kg body weight, intraperitoneally) on day 1. The pump had been filled with bFGF solution or vehicle and then placed in 0.9% saline at room temperature overnight before the start of the experiments as described previously (Hotta et al., 1991). After recovery from anesthesia, rats were put back in their home cages. Food intake and body weight were measured daily at 0900 for 6 days. The behavioral changes of rats in their home cages were observed at 1600 to 1700 on days 3 and 6 of the experiment.

2.4. Statistical analysis

All results are expressed as means ± S.E.M. Data were subjected to analysis of variance and group comparisons were performed using the Mann–Whitney's *U*-test with a Bonferroni correction. Statistical significance was established at the $P < 0.05$ level.

3. Results

3.1. I.C.V. injection of bFGF

No significant difference in locomotor activity was found between vehicle-administered and bFGF-administered rats until 4 h after the i.c.v. injection (Table 1). The i.c.v. administration of bFGF at doses of both 20 and 50 ng significantly increased the frequency of resting and decreased the frequency of grooming or moving at 4–5 h after the injection (Table 1). These effects of bFGF on locomotor activity lasted for at least 11 h after the injection, and the changes in behavior induced by bFGF were

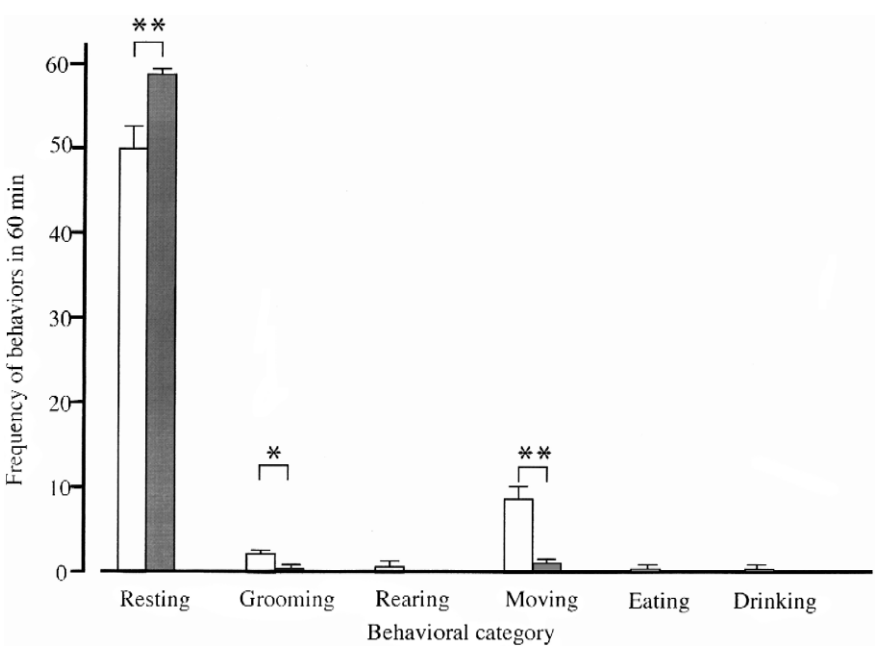

Fig. 2. Behavioral changes induced by chronic i.c.v. infusion of bFGF (20 ng/h) for 60 min in their home cages on day 6 after the start of infusion. Vehicle-infused group (open bars) and bFGF-infused group (solid bars). The number of rats in each group was seven. Data are expressed as means ± S.E.M. $^{*}P < 0.05$ $^{**}P < 0.01$.

not observed for more than 24 h after the injection (Table 1). No significant change in rearing was noted in animals injected with bFGF during the period of observation.

The mean amount of food intake in 25 h after the i.c.v. injection of bFGF was significantly suppressed at a dose of 20 or 50 ng (Table 2). The mean increase in body weight of rats injected with bFGF at a dose of 20 or 50 ng was significantly less than that of the control rats (Table 2).

3.2. Chronic i.c.v. infusion of bFGF

The daily food intake of rats chronically infused with bFGF at a rate of 20 ng/h was significantly suppressed on days 3 and 4 as shown in Fig. 1. The total amount of food eaten for 6 days by the rats chronically infused with bFGF (98.2 ± 4.9 g) was significantly smaller than that of control rats (109.4 ± 3.2 g) ($P < 0.05$). The body weight of the rats chronically infused with bFGF was significantly lower than that of control rats on days 5 and 7 (Fig. 1).

The locomotor activity of the rats was analyzed on days 3 and 6 in their home cages. As shown in Fig. 2, the frequency of resting increased, and the frequency of grooming and moving decreased, in bFGF-infused rats on day 6. Similar changes were also found on day 3 (data not shown).

4. Discussion

The present study is the first to show that an i.c.v. injection of bFGF at a dose of 20 or 50 ng significantly decreases locomotor activity in rats. A bolus i.c.v. injection of bFGF induced an increase in resting and a decrease in locomotor activity as well as a decrease in food intake in a familiar environment. The results of the present study confirmed previously reported findings that bFGF decreases the amount of food intake of rats when injected i.c.v. as a bolus (Hanai et al., 1989; Oomura et al., 1992; Plata-Salamán, 1988; Sasaki et al., 1991). However, in these reports, only feeding behavior was examined and changes in locomotor activity were not described.

It has been reported that subcutaneous injection of FGFs decreases locomotor activity (Guaza et al., 1996). In these latter experiments, locomotor activity of rats was evaluated in a novel environment every 5 min only for 30 min through a Digiscan animal activity monitor system, and locomotor activity was found to be decreased by aFGF or bFGF at a dose of 1, 10, or 100 μg/kg body weight (Guaza et al., 1996). The results of the present study revealed that the effects of bFGF on locomotor activity last for at least 11 h after the injection. It is unclear whether FGFs injected subcutaneously exerted the suppressive effect on locomotor activity by reaching the central nervous system. However, since the dose of bFGF which was injected i.c.v. and showed the suppressive effect on locomotor activity in the present study was about a tenth of the dose injected subcutaneously in the earlier experiments, it is likely that FGFs injected subcutaneously cross the blood–brain barrier and show the suppressive effect. Thus, FGFs decrease locomotor activity in both familiar and novel environments when administered i.c.v. or peripherally.

The suppressive effect of other peptides such as CRF and Neuropeptide Y on food intake appears in 30 min when they are administered i.c.v. as a bolus (Clark et al., 1985; Morley and Levine, 1982). In contrast, the suppressive effect of bFGF on food intake was not significant within 1 h after the injection (data not shown). Similarly, the inhibitory effect of bFGF on locomotor activity became apparent 4–5 h after the injection in the present study. This difference in latency of effect between bFGF and other peptides such as CRF and Neuropeptide Y may be partially explainable by a difference in the latency of their actions on neurons, as both aFGF and bFGF inhibit glucose-sensitive neurons of the lateral hypothalamic area with a long latency, approximately 8 min, on electrophoretic application (Sasaki et al., 1991). This is much longer than the few seconds other peptides such as CRF take to act on neurons (Eberly et al., 1983). Furthermore, the long latency of the effect of bFGF may also be explained by a finding that ^{125}I-FGFs injected i.c.v. is internalized at the terminals and retrogradely transported to the neuronal cell bodies in various brain regions of rats including the lateral hypothalamic area several hours after the injection (Ferguson and Johnson, 1991).

We also found that continuous i.c.v. infusion of bFGF for 6 days also decreases locomotor activity as well as food intake and body weight gain. The suppressive effect of bFGF on locomotor activity seemed to last the duration of the i.c.v. infusion, since changes in locomotor activity were observed on both days 3 and 6 when they were tested. The daily food intake during a 6-day i.c.v. infusion of FGF at 50 ng/h in mice was reported to be significantly smaller than that during the pre-FGF-infusion period when vehicle was infused i.c.v. (Denton et al., 1995). In the present study, the daily food intake was significantly suppressed on days 3 and 4 during the 6-day period of the chronic i.c.v. infusion of bFGF at a rate of 20 ng/h, and the total amount of food intake for 6 days of the rats infused with bFGF was significantly suppressed. The food intake of both the control and bFGF-infused rats was smaller on day 1 than on other days. This decrease in food intake on day 1 seems to have been induced by anesthesia and surgical treatment for placement of the osmotic pump in the subcutaneous space of the dorsal region. There was no significant difference in food intake between the control and bFGF-treated rats on day 2. The suppressive effect of bFGF on food intake might have been overcome by compensatory mechanism for the decrease in food intake on day 1.

The presence of binding sites of ^{125}I-FGFs (Ferguson and Johnson, 1991) and FGF receptor 1 in the lateral

hypothalamic area (Matsuo et al., 1994), the suppressive effect of bFGF on the activity of glucose-sensitive neurons in the lateral hypothalamic area (Hanai et al., 1989), and the induction of food intake by injection of anti-FGFs antibodies into the lateral hypothalamic area of rats (Sasaki et al., 1991) suggest that FGFs in the lateral hypothalamic area play a role in the regulatory mechanism of feeding behavior, although bFGF-positive fibers have not yet been demonstrated in the lateral hypothalamic area (Iwata et al., 1991). Therefore, the site of action of bFGF to inhibit feeding behavior seems to be the neurons in the lateral hypothalamic area. The site of the inhibitory action of bFGF on locomotor activity remains unknown. However, since FGF receptor mRNA has been identified in specific neuronal subpopulations, such as the striatum and substantia nigra (Wanaka et al., 1990), associated with locomotor activity (Alexander et al., 1986; Gulley et al., 1999; Haracz et al., 1989), these areas may be the sites of action of FGF to inhibit locomotor activity.

The decrease in locomotor activity in bFGF-treated rats may reflect generalized suppression of behavior by bFGF, and the inhibitory effect of bFGF on food intake may be partially ascribed to the suppression of behavior. CRF inhibits food intake and increases locomotor activity of rats in a familiar environment when it is injected i.c.v. (Morley and Levine, 1982). In contrast, as shown in the present study, bFGF decreases both food intake and locomotor activity. Therefore, bFGF appears to keep rats from losing energy by decreasing locomotor activity while CRF lets rats consume energy by increasing locomotor activity, although both peptides inhibit food intake.

In conclusion, bFGF inhibits locomotor activity as well as feeding behavior both when injected i.c.v. as a bolus and when chronically infused i.c.v. in rats. These results suggest that the inhibitory effect of bFGF on food intake may be in part ascribed to the suppression of behavior by bFGF.

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