

Requirement of Endogenous Basic Fibroblast Growth Factor for Sensitization to Amphetamine

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Repeated exposure to amphetamine produces long-lasting increases in sensitivity to its effects. We reported previously that repeated amphetamine treatment results in increased astrocytic expression of basic fibroblast growth factor (bFGF) in the ventral tegmental area (VTA) and substantia nigra compacta (SNc) and that this effect is prevented by coadministration of a nonspecific glutamate receptor antagonist. Here we show that the development of sensitization to amphetamine is prevented when amphetamine injections are preceded by infusions of a neutralizing antibody to bFGF into the VTA. In addition, we show that astrocytic bFGF expression is increased in the VTA and SNc of animals that exhibit behavioral sensitization and

that the number of bFGF-immunoreactive astrocytes in these regions is strongly and positively correlated with the magnitude of sensitization. Cotreatment with an NMDA glutamate receptor antagonist blocks both the development of behavioral sensitization and bFGF induction. These results show that endogenous bFGF is necessary for the development of sensitization to amphetamine and suggest that bFGF mediates the glutamatergic-dopaminergic interaction that initiates the long-term consequences of repeated drug use.

Key words: basic fibroblast growth factor; bFGF; FGF-2; neurotrophic factors; amphetamine; sensitization; dopamine; glutamate; NMDA

Repeated exposure to the stimulant drug amphetamine results in enduring increases in its effects on behavioral activation, dopaminergic function (Robinson and Becker, 1986; Kalivas and Stewart, 1991), and reward (Lett, 1989; Piazza et al., 1989; Mendrek et al., 1998; Vezina et al., 1999; Lorrain et al., 2000). Sensitization to the effects of amphetamine develops gradually (Kolta et al., 1985; Paulson et al., 1991; Paulson and Robinson, 1995) and is persistent (Paulson et al., 1991; Castner and Goldman-Rakic, 1999). The development of sensitization is initiated by actions of amphetamine in the cell body region of midbrain dopaminergic neurons (Kalivas and Weber, 1988; Vezina and Stewart, 1990; Vezina, 1993, 1996; Cador et al., 1995) and depends on glutamatergic activity (Wolf, 1998).

The long-lasting, perhaps permanent, nature of the changes induced by repeated administration of stimulant drugs suggests that sensitization may involve structural modifications in neuronal circuitry. Changes in dopaminergic cell size, neurofilament proteins, and glial fibrillary acidic protein have all been observed in the ventral tegmental area (VTA) after repeated injections of cocaine and morphine (Beitner-Johnson et al., 1992, 1993; Sklair-Tavron et al., 1996). Furthermore, enduring structural changes in neurons in the nucleus accumbens (NAcc) and prefrontal cortex have been observed after repeated exposure to amphetamine and cocaine (Robinson and Kolb, 1997, 1999). This evidence suggests the involvement of neurotrophic factors, which are known to play

a critical role in the survival, maintenance, and morphological plasticity of adult neurons (Hefti et al., 1993). Recently, we showed (Flores et al., 1998) that as few as three injections of amphetamine induce increased expression of the neurotrophic and neuroprotective substance basic fibroblast growth factor (bFGF) in astrocytes in the VTA and substantia nigra pars compacta (SNc). Increased bFGF immunoreactivity (IR) in these regions is evident 24 hr after the last amphetamine injection and remains elevated for at least 1 month. Coadministration of a nonspecific glutamate receptor antagonist prevents the effects of amphetamine on bFGF. Subsequently, we found that a 2 week escalating-dose amphetamine treatment induces increases in bFGF in NAcc (Flores and Stewart, 1999).

After injections of amphetamine there are increases in both extracellular dopamine and glutamate in the VTA (Wolf, 1998; Kalivas et al., 1989; Wolf and Xue, 1999). Repeated exposure to these effects may place excessive demands on dopaminergic neurons and lead to the recruitment of bFGF. The actions of bFGF in turn may initiate processes leading to persistent changes in dopaminergic function and behavior [see for example Takayama et al. (1995)]. Here, we tested directly whether bFGF is necessary for the development of enduring changes in the effectiveness of

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amphetamine. We infused a neutralizing antibody to bFGF into the VTA during the induction phase and examined its effects on the development of behavioral sensitization to amphetamine. In a second experiment, we assessed the relation between glutamate, bFGF expression, and the magnitude of behavioral sensitization.

MATERIALS AND METHODS

Subjects and surgery

Male Wistar rats (Charles River, Quebec, Canada; 325–350 gm), housed in a colony room on a normal light/dark schedule with free access to food and water, served as subjects. In the first experiment, rats were anesthetized (65 mg/kg sodium pentobarbital, i.p.) and given atropine (0.25 mg/kg, s.c.) to reduce bronchial secretions. With stereotaxic arms angled at 15° off the sagittal plane, 22-gauge guide cannulae were bilaterally implanted into the VTA, 5.3 mm posterior from bregma, 2.8 mm lateral from the midsagittal sinus, and 6 mm below the dura (Paxinos and Watson, 1997). Stainless-steel obturators (28-gauge) were inserted into the guide cannulae, extending 2 mm beyond the tip. Rats were allowed to recover for 2 weeks before experiments began. Intra-VTA microinfusions were performed by inserting into the guide cannulae 28-gauge injector cannulae that extended 2 mm beyond the tip and that were connected via polyethylene tubing to 1 μ l Hamilton syringes.

Antibodies and drugs

The bFGF antibody that was used was a mouse monoclonal antibody known to specifically recognize the biologically active conformation of bFGF (a gift from Dr. K. Nishikawa, Kanazawa Medical University, Japan) and to be an effective immunoneutralization reagent both *in vitro* and *in vivo* (Matsuzaki et al., 1989; Tao et al., 1997). Mouse IgG (Jackson ImmunoResearch Laboratories) was used as control. Antibodies were administered to unrestrained rats (0.5 mg/ml in 0.9% saline, 0.5 μ l/side, over 60 sec). The dose used was based on pilot work, on previous *in vivo* studies with bFGF antibodies (Tao et al., 1997), and on the advice of Dr. Nishikawa. No obvious behavioral alterations were detected after intra-VTA infusions with either of the protein solutions, nor were there any effects on body weight. Both 3-(2-carboxypiperazine-4-yl)propyl-1-phosphonic acid (CPP; Tocris Cookson) and D-amphetamine sulfate (SmithKline Beecham Pharma) were dissolved in saline and injected intraperitoneally.

Immunocytochemistry

Perfusions, immunoreactivity, and qualitative analysis were conducted as described previously (Flores et al., 1998). For detection of the intracranially administered antibody in brain tissue, incubation with primary antibody was omitted. When both primary and secondary antibody incubations were omitted, no labeling was obtained.

Procedures

bFGF immunoneutralization. In this and the following experiment, 1 d before the start of the induction phase of sensitization, all rats were tested for 2 hr in an activity monitoring apparatus [described previously (Stewart and Druhan, 1993)] and then assigned to treatment groups matched on the basis of the scores on this test. On day 1 of the induction phase, to assess any possible adverse effects of the antibodies, rats received bilateral VTA microinfusions of the bFGF antibody or mouse IgG while they were in the colony room and then were placed back in their home cages. On days 3, 5, 7, and 9, rats were given similar intra-VTA infusions of either bFGF antibody or mouse IgG, and 1 hr later they were taken to the activity monitoring room where they were injected intraperitoneally with either saline or amphetamine (1.5 mg/kg) and placed immediately in the activity boxes for 2 hr. To determine whether pretreatment with neutralizing antibody to bFGF blocked the development of sensitization to amphetamine, tests were conducted 1 and 2 weeks after the last day of the induction phase. For these tests, all animals, whether exposed previously to amphetamine or saline, were given a single intraperitoneal injection of 0.75 mg/kg amphetamine and placed immediately in activity boxes for 2 hr. For these tests, no infusions of antibodies were given. The dose of amphetamine given during the induction phase is one that increases locomotion and, after repeated administration, stereotypy. For the test phase, therefore, the dose was halved to reveal primarily locomotion.

Effects of CPP on both behavioral sensitization and bFGF expression. On days 1, 3, 5, and 7 of the induction phase of this experiment, CPP (4.0

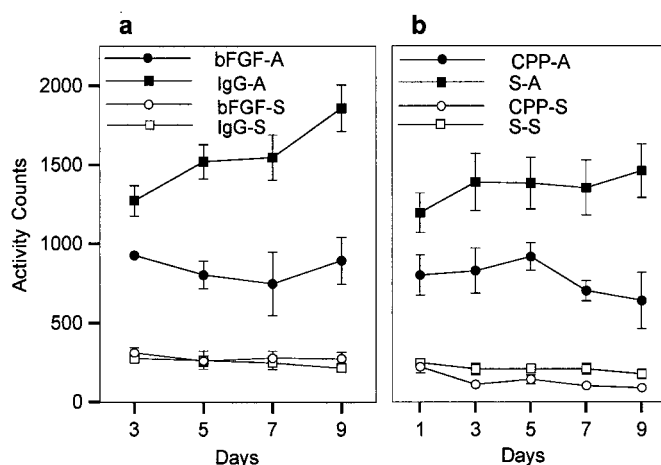


Figure 1. Mean \pm SEM activity counts during the induction phases of the bFGF antibody and CPP experiments. *a*, Animals were infused intra-VTA with bFGF antibody or mouse IgG before each amphetamine (A, $n = 4$ per group) or saline (S, $n = 6$ per group) injection. ANOVA: amphetamine treatment ($F_{(1,48)} = 287.6, p = 0.0001$); amphetamine by antibody interaction ($F_{(1,48)} = 45.1, p = 0.0001$). *b*, Animals were injected intraperitoneally with CPP or saline before each amphetamine (A) or saline (S) injection ($n = 6$ per group). ANOVA: amphetamine treatment ($F_{(1,80)} = 107.9, p = 0.0001$); amphetamine by CPP interaction ($F_{(1,80)} = 8.4, p = 0.008$).

mg/kg, i.p.) or saline was administered to animals in the colony room 30 min before they were taken to the activity room where they received injections of either saline or amphetamine (1.5 mg/kg, i.p.) and were placed in the activity boxes for 2 hr. The test for sensitization was given 1 week later, during which all animals were injected intraperitoneally with 0.75 mg/kg amphetamine only. Immediately after the sensitization test, animals were perfused and brains were processed for bFGF-IR using the same bFGF antibody (Matsuzaki et al., 1989) that was used in our former study (Flores et al., 1998) and in the present study to block bFGF activity.

Statistical analyses

Data were analyzed by two- and one-way ANOVAs as required. *Post hoc* comparisons were made using one-way ANOVAs or Fisher's protected LSD test ($p \leq .05$).

RESULTS

Blockade of bFGF prevents the development of behavioral sensitization to amphetamine

Immunoneutralization of bFGF during the induction phase blocked completely the development of sensitization to amphetamine (see Fig. 2, right panel). On the test day, animals that had been exposed to amphetamine in the presence of VTA infusions of the bFGF antibody during the induction phase (Fig. 1a) responded to amphetamine challenge in a manner similar to that of animals previously exposed to saline. In contrast, animals that had been exposed to amphetamine, in the presence of the control infusions of mouse IgG during the induction phase, showed sensitized responding on the test day (Fig. 2, left panel). Locomotor activity in these animals, in response to the single injection of amphetamine, was significantly greater than that seen in animals given amphetamine for the first time. Similar effects were seen in a second test given 1 week later (data not shown).

To rule out the possibility that the lack of sensitization observed on the test days resulted from residual antibody in the VTA at the time of test, we used immunohistochemistry to determine whether the bFGF antibody was present in the VTA of animals that had been infused either 1 hr or 1 week before

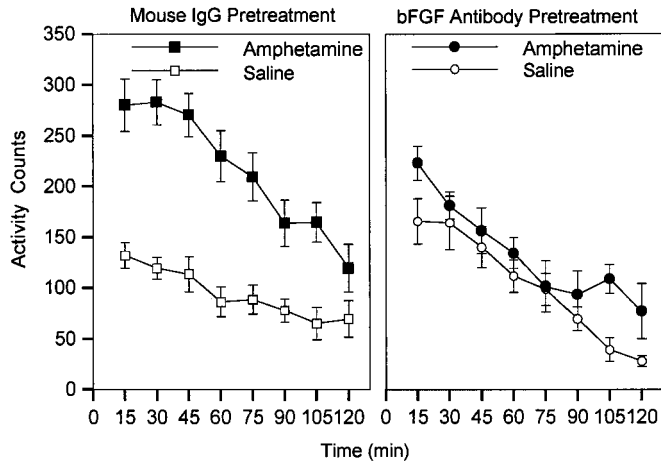


Figure 2. Test for sensitization: bFGF antibody experiment. All animals received amphetamine (0.75 mg/kg, i.p.) before being placed in the activity boxes. *Left panel*, Mean \pm SEM activity counts in animals exposed during the induction phase to amphetamine or saline in the presence of control intra-VTA infusions of mouse IgG. *Right panel*, Activity counts in animals exposed during induction to amphetamine or saline in the presence of the bFGF antibody. ANOVA for pretreatment (bFGF antibody vs IgG) by drug (amphetamine vs saline) revealed significant main effects ($F_{(1,16)} = 6.0, p = 0.02$; $F_{(1,16)} = 26.5, p = 0.0001$) and a significant interaction ($F_{(1,16)} = 8.9, p = 0.008$). There were significant differences between amphetamine and saline groups that were pretreated with mouse IgG during the induction phase ($F_{(1,8)} = 41.6, p = 0.0002$) and between the two groups previously exposed to amphetamine ($F_{(1,6)} = 11.3, p = 0.01$). The two saline groups did not differ ($F_{(1,10)} = 0.20, ns$). Amphetamine: $n = 4$ per group; saline: $n = 6$ per group.

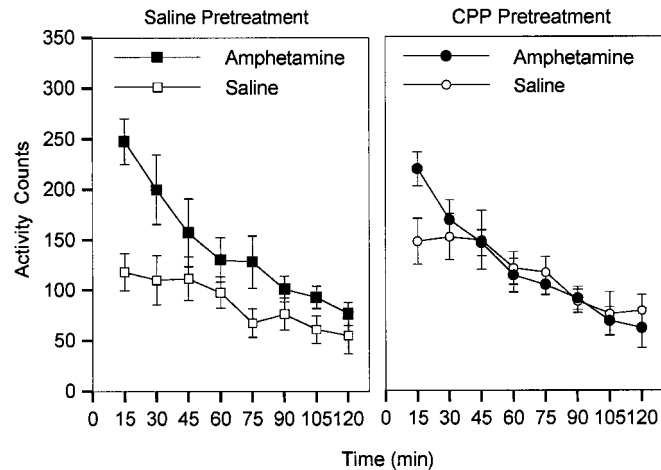


Figure 3. Test for sensitization: CPP experiment. All animals received amphetamine (0.75 mg/kg, i.p.) before being placed in the activity boxes. *Left panel*, Mean \pm SEM activity counts in animals exposed during the induction phase to amphetamine or saline after saline pretreatment ($F_{(1,10)} = 4.9, p = 0.05$); *right panel*, activity counts in animals exposed during induction to amphetamine or saline after CPP ($F_{(1,10)} = 0.07, ns$). $n = 6$ per group.

perfusion ($n = 2$ per time point). Immunoreactivity for the bFGF antibody was evident and localized in the VTA 1 hr after infusion but was undetectable in animals that had received infusions 1 week earlier; similar results were found after IgG infusions. Nissl staining confirmed that all microinfusions were made into the VTA, and no detectable differences were found in tissue damage (glial scar) between brain sections of rats given mouse IgG or anti-bFGF antibody.

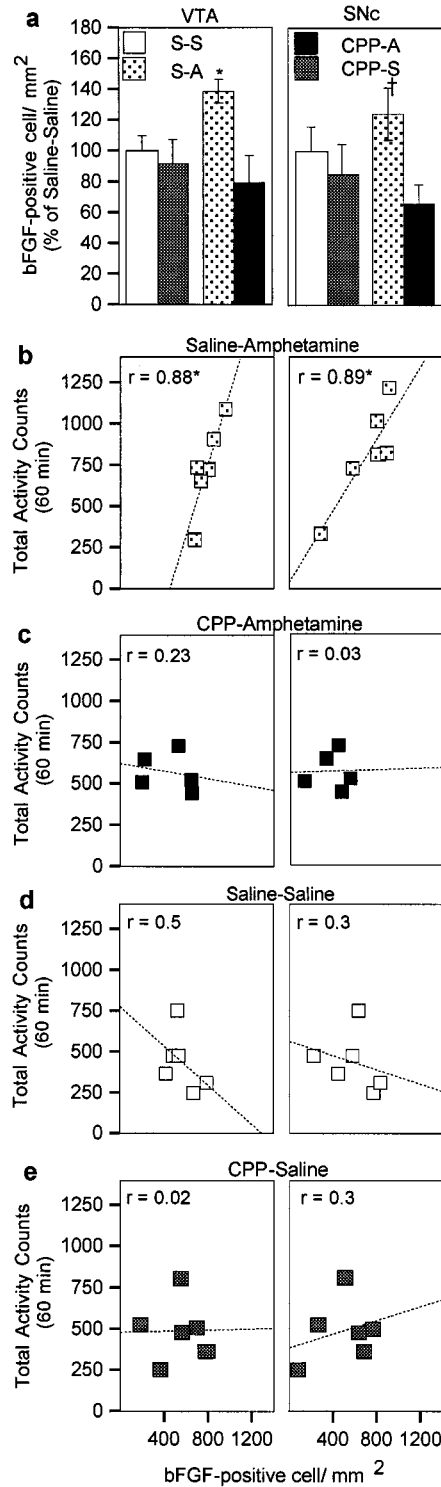


Figure 4. Effects of NMDA antagonist on bFGF expression. *a*, Mean \pm SEM bFGF-labeled cells in each group as a percentage of the saline-saline group. ANOVAs were performed on raw scores: VTA, $F_{(3,19)} = 3.9, p = 0.02$; SNc, $F_{(3,19)} = 2.1, p = 0.13$. In VTA, * indicates significantly different from all other groups; in SNc, † indicates significant difference between CPP-amphetamine and saline-amphetamine (p values < 0.05). No effects of treatment on bFGF-IR were observed in NAcc or striatum (data not shown). bFGF-IR was confined to astrocytes (Flores et al., 1998, 1999). *b-c*, Correlations between activity counts during the first 60 min of the sensitization test (see Fig. 3) and number of bFGF-labeled cells in each of the groups. * p values < 0.05 .

Blockade of both the development of sensitization and bFGF expression by CPP cotreatment

There was a remarkable similarity between the effects of blocking bFGF activity in the VTA and the effects of the NMDA receptor antagonist CPP. Coadministration of CPP during induction blocked the development of sensitization (Fig. 3, *right panel*). Animals given CPP injections and either amphetamine or saline during the induction phase (Fig. 1*b*) did not differ in their response to amphetamine on the test day. In contrast, those animals that had been exposed only to amphetamine during the induction phase showed sensitized responding compared to saline control animals when challenged with amphetamine on the test day (Fig. 3, *left panel*). As shown in Figure 4*a*, expression of astrocytic bFGF in the VTA and SNc was elevated in animals showing behavioral sensitization on the test day. CPP coadministration during the induction phase prevented this effect.

bFGF expression correlates with behavioral sensitization

As shown in Figure 4*b*, in the group of animals that received amphetamine alone during the induction phase, highly significant positive correlations were found between locomotor activity induced by the amphetamine challenge during the sensitization test and the number of bFGF-immunoreactive astrocytes in the VTA and SNc. No significant correlations were found between locomotor activity and bFGF expression in the other groups (Fig. 4*c–e*).

DISCUSSION

Blockade of bFGF activity in the VTA during the period of repeated exposure to amphetamine (the induction phase) was sufficient to prevent the development of sensitized responding to amphetamine. On the tests for sensitization, given 1 and 2 weeks after the induction phase, animals previously exposed to amphetamine in the presence of the bFGF antibody showed no evidence of sensitized responding to amphetamine. These findings show that bFGF in the VTA plays a critical role in the development of sensitization to amphetamine.

The effects of the bFGF antibody on the development of sensitization paralleled those observed in the CPP study. Animals exposed during the induction phase to amphetamine in the presence of CPP did not show sensitization to amphetamine on the test day. Furthermore, these animals did not show the increased bFGF expression in the VTA and SNc seen in animals previously exposed to amphetamine alone. Most importantly, in animals showing sensitized responding to amphetamine on the test day, there was a highly significant positive correlation between locomotor activity and bFGF expression in both VTA and SNc. These findings suggest that glutamate participates in the development of sensitization to amphetamine by increasing astrocytic bFGF expression in dopaminergic cell body regions. This idea receives support from evidence showing that repeated injections of amphetamine into the VTA are sufficient to induce sensitization (Vezina, 1993; Cador et al., 1995), that systemic and intra-VTA amphetamine increase glutamate release in the VTA, and that intra-VTA injections of NMDA antagonists block the development of sensitization to amphetamine (Wolf, 1998).

Here we show that an endogenous neurotrophic factor, bFGF, which is known to promote growth and survival of midbrain dopaminergic cells (Takayama et al., 1995; Hou et al., 1997), is directly involved in the development of sensitization of the locomotor effects of amphetamine. We propose that in response to

amphetamine, increased extracellular glutamate activates astrocytic bFGF (Pechan et al., 1993), which in turn acts directly on neurons or indirectly through astrocytes (Gómez-Pinilla et al., 1995) to initiate long-lasting changes in sensitivity (Tong et al., 1995; White et al., 1995) and connectivity. The mechanisms whereby bFGF brings about these changes are yet to be explored and may involve the induction of other neurotrophic factors (Horger et al., 1999; Pierce et al., 1999). In addition, the findings presented here lend support to the idea that processes involved in sensitization to stimulant drugs may be similar to those involved in long-term potentiation (LTP) (Wolf, 1998). bFGF promotes the development of LTP (Terlau and Seifert, 1990; Ishiyama et al., 1991), and interestingly, recent results show that LTP can be induced at excitatory synapses on dopaminergic cells in the VTA and SNc (Bonci and Malenka, 1999; Overton et al., 1999).

It should be noted that during the induction phase of the studies reported here, both intra-VTA infusions of bFGF antibody and intraperitoneal injections of CPP reduced the acute locomotor-activating effects of amphetamine (Fig. 1). It is unlikely that this effect was responsible for the lack of sensitization seen on the test days. Considerable evidence shows that increased locomotor activity in response to amphetamine injections during the induction phase is not required for the development of sensitization. Intra-VTA injections of amphetamine do not increase locomotor activity but are sufficient to induce sensitized behavioral or neurochemical responding to subsequent systemic injections; conversely, amphetamine injections into the NAcc that induce locomotor activity do not lead to the development of sensitization (Kalivas and Weber, 1988; Vezina and Stewart, 1990; Vezina, 1993, 1996; Cador et al., 1995). Finally, blockade of the acute effects of amphetamine on locomotor activity is not sufficient to prevent the development of sensitized responding (Stewart et al., 1994; Vezina, 1996). We do not know how blockade of bFGF activity in the VTA alters the acute effect of amphetamine. One possibility is that the antibody interferes with effects of endogenous bFGF on cell firing within this region. bFGF has fast modulatory actions on synaptic transmission in hippocampal neurons through alterations of Ca^{2+} currents (Abe and Saito, 1992; Tanaka et al., 1996).

In summary, we find that the endogenous astrocytic neurotrophic factor bFGF, acting in dopaminergic cell body regions, plays a crucial role in the development of enduring behavioral changes that follow repeated amphetamine treatment. These findings provide new insight into the basis of the long-lasting consequences of repeated exposure to drugs of abuse and point to the similarities between the mechanisms underlying this and other examples of experience-dependent plasticity.

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