Differential Expression of Fos and Zif268 in the Nigrostriatal System After Methamphetamine Administration in a Rat Model of Parkinson's Disease

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KEY WORDS 6-hydroxydopamine; immediate-early gene proteins; basal ganglia; transplantation

ABSTRACT The goal of this study was to examine the topological specificity of methamphetamine-induced activation of the immediate-early gene proteins, Fos and Zif268, in the nigrostriatal system in a unilateral 6-hydroxydopamine (6-OHDA) rat model of Parkinson's disease with or without intrastriatal grafts of fetal ventral mesencephalon. Methamphetamine (3 mg/kg, i.p.) induced Fos-like immunoreactivity (FLI) dominantly in the striatum and the globus pallidus (GP) on the intact side as well as in the substantia nigra pars reticulata (SNr) on the lesioned side in the 6-OHDA rats. Lower levels of methamphetamine-induced FLI in the striatum and GP on the lesioned side were restored by intrastriatal grafts which could completely suppress the methamphetamine-induced rotation. In the striatum, a similar tendency could be observed between Fos and Zif268 immunoreactivity following methamphetamine. However, sparse immunoreactivity of Zif268 could be detected in the GP and SNr on both sides in the 6-OHDA rats. Intrastriatal grafts had little influence on Zif268 expression in these two regions. The differential expression of Fos and Zif268 was observed among the three regions of the nigrostriatal system following methamphetamine in the 6-OHDA rats. This may suggest that Fos and Zif268 therefore possess gene-specific and region-specific functions in the basal ganglia nuclei. **Synapse 62:920–926, 2008.**

INTRODUCTION

Despite intensive study, the character and the function of immediate-early genes (IEGs) in the central nervous system (CNS) have not yet been elucidated. The induction of cellular IEGs may be a critical signal transduction step in neuronal plasticity induced by neurotransmitters and drugs, with the protein products of IEGs functioning to either activate or repress genes that encode the proteins involved in the differentiated functions of target neurons. The induction of the IEG, c-*fos*, in the CNS has thus been proposed to be indicative of synaptic activation, and it may also be involved in converting short-term extracellular signals to long-term intracellular responses (Morgan and Curran, 1991; Sheng and Greenberg, 1990).

Zif268 (also known as NGFI-A, Egr-1, and Krox-24), and also Fos, are transcription factors that may

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regulate neuronal and nonneuronal gene expression in the mammalian brain (Dragunow et al., 1989; Morgan and Curran, 1991). The transcriptional activity of the Fos family of molecules is dependent upon them forming heterodimers, using a leucine-zipper motif, with the Jun family of transcription factors (Kerpolla and Curran, 1991), whereas, members of the Krox family of transcription factors bind to DNA using a zinc-finger motif (Lemaire et al., 1988, 1990). Regional difference among five regions [caudate-putamen (CPu), globus pallidus (GP), entopeduncular nucleus, subthalamic nucleus, substantia nigra pars reticulata (SNr)] of the basal ganglia are observed in the basal expression of Zif268, and constitutive expression of Zif268 occurring mainly in the GABAergic neurons in the CPu may at least in part be maintained by glutamatergic afferents (Ishida et al., 2000).

Various dopaminergic and CNS stimulating drugs such as cocaine, amphetamine, and methamphetamine have been reported to induce (or up-regulate) both the Fos and Zif268 expression in the terminal region of the nigrostriatal dopamine (DA) system, the striatum (Bhat et al., 1992; Hebb and Robertson, 1997; Umino et al., 1995). In rats with a unilateral lesion of the nigrostriatal DA pathway induced by the 6-hydroxydopamine (6-OHDA), systemic administration of an indirect DA agonist such as amphetamine or methamphetamine produces ipsilateral rotational behavior by releasing DA following the stimulation of DA receptors in the intact side of the brain (Ungerstedt, 1971). Methamphetamine-induced rotational behavior is accompanied by the expression of Fos-like immunoreactivity (FLI) in the nigrostriatal components in 6-OHDA rats (Ishida et al., 1998b). This was observed not only in the striatum contralateral to the unilateral 6-OHDA-induced lesion in the nigrostriatal pathway, as reported previously (Abrous et al., 1992; Cenci et al., 1992; Robertson et al., 1989), but also in the SNr ipsilateral to the lesion. The asymmetry in the FLI between the hemispheres following methamphetamine treatment has also been confirmed by other researchers (Hebb and Robertson, 1999; Wirtshafter and Asin, 1999).

The goal of this study was to examine the topological specificity of methamphetamine-induced activation of the IEG proteins, Fos and Zif268 in three regions (medial CPu, GP, SNr) of the nigrostriatal system in a unilateral 6-OHDA rat model of Parkinson's disease with or without intrastriatal grafts of fetal ventral mesencephalon (VM). There have been few reports concerning amphetamine- or methamphetamine-induced Zif268 expression in basal ganglia of an animal model of Parkinson's disease (Hebb and Robertson, 1997). In particular, the effect of intrastriatal dopaminergic transplants on the IEG expression has not yet been elucidated.

MATERIALS AND METHODS

Animals

Male Wistar rats (Japan SLC, Hamamatsu, Japan), weighing 120–130 g at the beginning of the experiment, were used. They were housed in a group of 3–4 rats under a 12 h light/dark cycle with free access to food and water. The experimental protocols used in this study were approved by the ethical committees of animal experimentation at the University of Miyazaki.

6-OHDA lesion and transplantation surgery

The rats were anesthetized with pentobarbital (50 mg/kg, i.p.), and unilateral lesions of the left medial forebrain bundle (MFB) were made by the injection of 8 μg 6-OHDA hydrobromide (Sigma, MA) in 4 μl of sterile saline containing 0.01% ascorbic acid. The stereotaxic coordinates for the lesions were 3.3 mm rostral to the interaural line, 1.3 mm left of the midline, and 6.7 mm ventral to the dural surface. The incisor bar was set 2.4 mm below the level of the ear bars (König and Klippel, 1963). The 6-OHDA solution was delivered by a microinjection pump at 1 μl/min, and the cannula was left in place for 5 min after the end of injection. In addition to the 6-OHDA-treated rats, twelve age-matched rats were used as sham-lesioned controls for the histological experiments. Sham lesions were created by injecting the same amount (4 μl) of saline into the left MFB as described above.

Neural transplantation was performed from fetal VM tissue according to the cell suspension method (Björklund and Dunnett, 1992; Dunnett and Björklund, 1992). Six microliters of the suspension containing 4.8 × 105 cells from 15-day-old rat embryos was injected into two sites of the denervated striatum: (1) AP = 1.0 mm rostral to the bregma, L = 2.5 mm left of midline, V = 5.0 mm ventral to the dural surface, and (2) AP = 0.0 mm caudal to the bregma, L = 3.2 mm left of midline, V = 5.0 mm ventral to the dural surface (König and Klippel, 1963). All graft suspensions were injected at a rate of 1 μl/min, and the syringe was left in place for 5 min after the end of the injection.

Rotational behavior

The motor disturbance was assessed by counting the full-rotations per min in a cylindrical container (30-cm diameter) at 10-min intervals for the first 60 min after methamphetamine (3 mg/kg, i.p.) administration (Nishino et al., 1990; Ungerstedt, 1971). Behavioral screening was carried out after 2 weeks recovery, and the animals that turned no less than 7 turns/min on methamphetamine challenge were included in the study. There is an immediate and almost complete destruction of the DA neurons of the

substantia nigra and of the ventral tegmental area, thus resulting in the near total depletion (2% of normal) of DA in the ipsilateral striatum to the 6-OHDA injections (Ishida et al., 1998a). The rats were tested again for rotational asymmetry at 7 and 15 weeks after the 6-OHDA treatment (at 4 and 12 weeks after transplantation).

Histological procedure

Methamphetamine treatment and subsequent perfusion of the animals was carried out 4–5 months after the induction of the 6-OHDA lesion. Six age-matched control rats were also included in the study in which the rats were treated with an equal volume of saline. Two hours after methamphetamine (3 mg/kg, i.p.) treatment, the rats were deeply anesthetized with an overdose of pentobarbital and were perfused transcardially first with saline followed by 4% paraformaldehyde in 0.1 M phosphate buffer (PB; pH 7.4). The brains were removed immediately and postfixed at 4°C for 1 h in the above fixative. After fixation, the samples were immersed at 4°C for 1 h in 0.1 M PB with 10% sucrose and cryoprotected at 4°C overnight in the same buffer with 30% sucrose. The brains were subsequently cut on a freezing microtome into 50 μm coronal sections for immunohistochemistry. An immunohistochemical examination of Fos or Zif268 expression was performed according to the manufacturer's instructions for use of a streptavidin-biotin system (Histofine SAB-PO(R) kit, Nichirei, Tokyo, Japan). Briefly, biotinylated secondary antibodies were coupled with streptavidin-biotinylated horseradish peroxidase, and the reaction was visualized using diaminobenzidine (DAB) as a chromogen enhanced by cobalt chloride. Between each incubation step, the free-floating sections were thoroughly rinsed with phosphate-buffered saline. The antibodies for c-Fos and Zif268 were rabbit polyclonal antisera (diluted 1:5000 and 1:3000, respectively; Santa Cruz Biotechnology, CA). For each animal and each IEG protein, 3 sections through the CPu approximately 0.7 mm rostral to the bregma, 3 sections through the GP ~1.0 mm caudal to the bregma and 3 sections through the SN ~2.2 mm rostral to the interaural line were selected for quantitative analysis (König and Klippel, 1963). Fos or Zif268 immunoreactivity in the medial CPu, GP, and SNr was quantified by counting the number of cells immunopositive for Fos or Zif268, respectively, in 0.5 mm × 0.5 mm (0.25 mm^2) squares using a 10× microscope objective. Thereafter, the numbers obtained from the 3 sections in each area (medial CPu, GP, or SNr) were averaged to give the results for each animal and each IEG protein. The data are therefore presented as the number of cells immunopositive for Fos or Zif268 per 0.25 mm^2 of striatal, pallidal or nigral tissue (Ishida et al., 1998b).

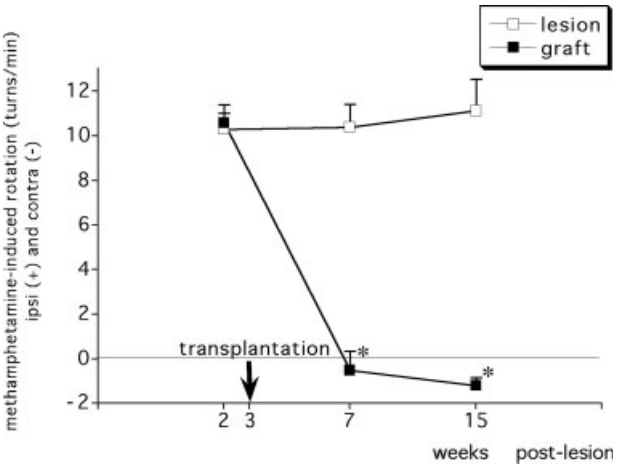

Fig. 1. The mean number of rotations (±SEM) per min over a 60 min test period in response to methamphetamine (3 mg/kg i.p.) are shown for unilaterally 6-OHDA-lesioned (lesion; $n = 12$) and the lesion plus grafted rats (graft; $n = 6$). "ipsi (+)" and "contra (−)" refer to the direction of rotation to side of lesion and transplantation. The decrease in the ipsilateral rotation found in the group receiving fetal VM grafts in comparison to that observed in the lesioned animals was significant at 4 and 12 weeks after transplantation (*$P < 0.01$, two way ANOVA with repeated measures followed by Newman-Keuls test).

Statistical analysis

The data were analyzed by ANOVA followed by post hoc comparisons, when appropriate, using the Newman-Keuls test or the Dunnett's t-test. P values < 0.05 were regarded as being statistically significant.

RESULTS

Rotational behavior

Before transplantation, methamphetamine (3 mg/kg, i.p.) induced strong ipsilateral rotation in 6-OHDA-lesioned rats (mean ± SEM = 10.4 ± 0.5 turns/min). In the lesioned animals ($n = 12$), methamphetamine-induced rotation continued to be observed 15 weeks following induction of the lesion. This behavior was reversed by the intrastriatal graft in the 4th week after transplantation (7 weeks post-lesion), and then continued throughout 12 weeks post-grafting (main effect of groups, $F1,32 = 33.75$, $P < 0.01$; main effect of time, $F2,32 = 21.32$, $P < 0.01$; groups × time interaction, $F2,32 = 25.59$, $P < 0.01$). Some of the grafted animals turned away from the grafted side in a contralateral direction (−0.2 ± 1.2 turns/min at 4 weeks and −1.3 ± 0.9 turns/min at 12 weeks post-grafting; $n = 6$), which was considered to be a functional overcompensation in their rotational behavior (Fig. 1).

Fos and Zif268 immunohistochemistry

In the saline-treated control animals, Fos-positive cells were very sparse in all three regions observed: the medial CPu, GP, and SNr (Fig. 3). In contrast,

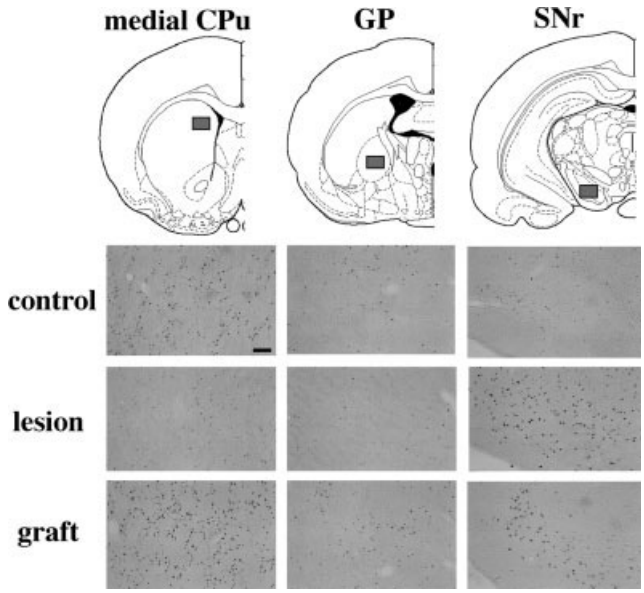

Fig. 2. Fos expression 2 h after methamphetamine (3 mg/kg, i.p.) administration in the basal ganglia nuclei of the control, the lesioned and the grafted rats ipsilateral to the lesion/graft (left side). CPu, caudate putamen; GP, globus pallidus; SNr, substantia nigra pars reticulata. The box in the drawing indicates the location of areas where photomicrographs were taken. Scale bar = 100 μm.

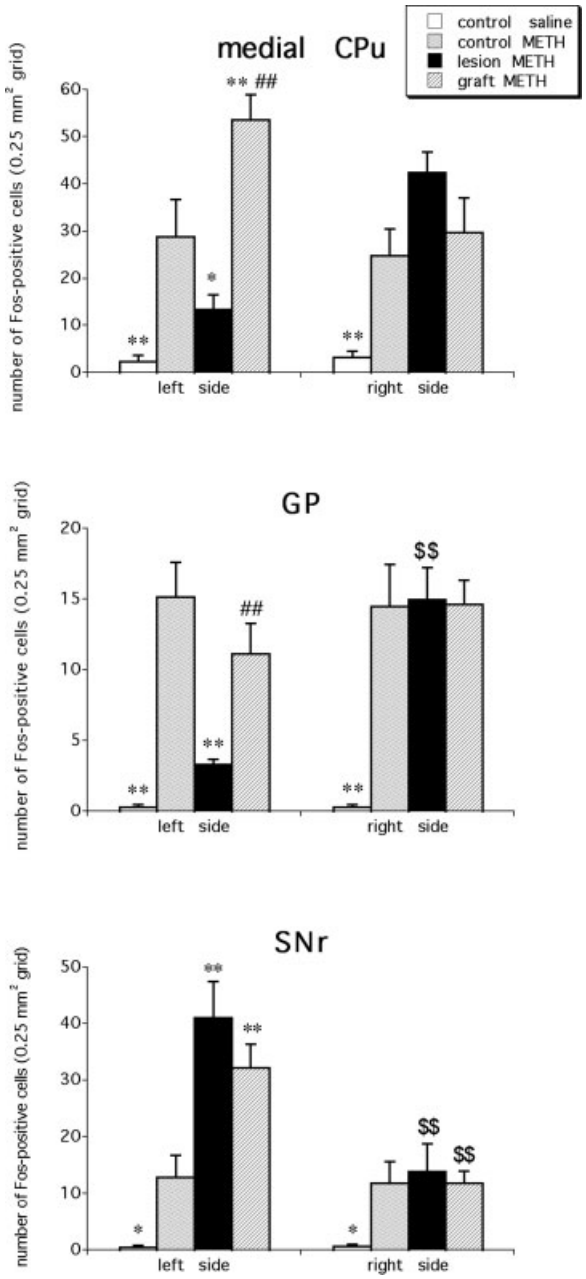

Fig. 3. Density of Fos-positive cells (number/0.25 mm^2) as detected within the medial CPu (top panel), GP (middle panel) and the SNr (bottom panel) in saline-treated controls (n = 6), methamphetamine (3 mg/kg, i.p.)-treated controls (n = 6), methamphetamine-treated lesioned (n = 6) and methamphetamine-treated grafted rats (n = 6). METH, methamphetamine. The results are the means ± SEM. $^{*}P < 0.05$, $^{**}P < 0.01$ in comparison to each corresponding value of the methamphetamine-treated control rats (two-way ANOVA followed by Newman-Keuls test). $^{\#\#}P < 0.01$ for the methamphetamine-treated graft group in comparison to each corresponding value of the methamphetamine-treated lesioned rats (two-way ANOVA followed by Newman-Keuls test). $^{\$\$}P < 0.01$ in comparison to each value in the corresponding ipsilateral (left side) portion of the same group (two-way ANOVA followed by Dunnett's t-test).

Zif268 was expressed in relatively high levels basally in the medial CPu, but sparse in both the GP and the SNr (Fig. 5).

The administration of methamphetamine to the 6-OHDA rats induced Fos expression in the medial CPu and GP on both sides; the number of Fos-positive cells was smaller on the lesioned side than on the intact side especially in the GP (Fig. 3). In contrast, the number of Fos-positive cells in the SNr in the 6-OHDA rats was greater on the lesioned side than on the intact side. In the grafted rats, methamphetamine-induced FLI in the medial CPu on the lesion-grafted side was higher than that in the normal striatum of control animals. The decreased levels of methamphetamine-induced FLI in the GP on the lesioned side were restored by the intrastriatal grafts. However, the hyperexpression of FLI in the SNr on the lesioned side was not altered by the intrastriatal grafts (Figs. 2 and 3).

Methamphetamine induced a similar pattern of Zif268 expression in the medial CPu to that of Fos in the three groups (control, lesion, graft) (Figs. 2 and 4). Regarding the GP and SNr, however, little Zif268 expression was observed on both sides in all three groups even after the methamphetamine administration (Figs. 4 and 5).

DISCUSSION

Constitutive levels of Zif268 were seen in the striatum, where very low levels of Fos were observed, consistent with that seen in previous studies (Ishida et al., 2000; MacGibbon et al., 1995). Constitutively expressed IEGs may perhaps be involved in control-

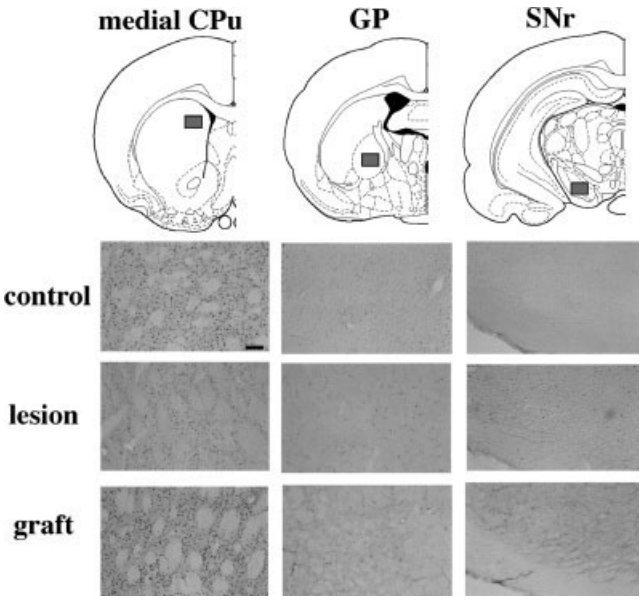

Fig. 4. Zif268 expression 2 h after methamphetamine (3 mg/kg, i.p.) administration in the basal ganglia nuclei of the control, the lesioned and the grafted rats ipsilateral to the lesion/graft (left side). CPu, caudate putamen; GP, globus pallidus; SNr, substantia nigra pars reticulata. The box in the drawing indicates the location of areas where photomicrographs were taken. Scale bar = 100 μm.

ling housekeeping genes stimulated by tonic messengers, such as glutamate through NMDA receptors (Ishida et al., 2000). The genes activated basally may include those genes that sustain neuronal cell function and viability, while the novel messengers arriving at the cell surface, which rapidly and transiently activate IEGs, work to modulate the transcriptional activity of other genes that change the phenotype of the cell depending on the information carried by the messenger. Alternatively, perhaps the IEG proteins present basally are not active, and their activation requires post-translational modifications (phosphorylation, demethylation, etc.) (Seyfert et al., 1990). A previous report suggested that Zif268 may play a role in spontaneously maintaining the inhibitory output of GABAergic neurons in the striatum (Ishida et al., 2000).

Based on the results described previously (Ishida et al., 1996; Schmidt et al., 1983), it appears that an almost complete loss of the DA content is achieved in the denervated striatum in the 6-OHDA-treated rats in the present study. Previous cerebral dialysis and immunohistochemical studies have shown that basal and methamphetamine-induced DA release was recovered and that an abundance of tyrosine hydroxylase-immunopositive cells and fibers could be observed in the lesion-grafted striatum in the grafted rats in which methamphetamine-induced rotation was completely ameliorated similarly in the present study (Ishida et al., 1998a; Nishino et al., 1990).

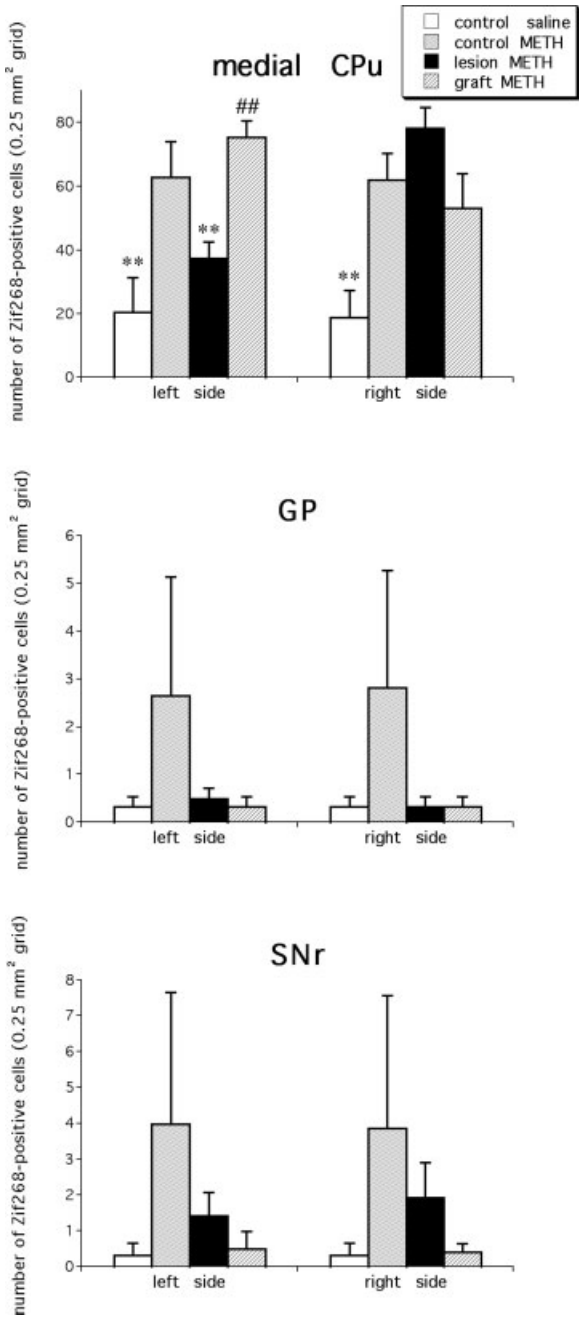

Fig. 5. Density of Zif268-positive cells (number/0.25 mm^2) as detected within the medial CPu (top panel), GP (middle panel) and the SNr (bottom panel) in saline-treated controls (n = 6), methamphetamine (3 mg/kg, i.p.)-treated controls (n = 6), methamphetamine-treated lesioned (n = 6) and methamphetamine-treated grafted rats (n = 6). METH, methamphetamine. The results are the means ± SEM. $^{**}P < 0.01$ in comparison to each corresponding value of the methamphetamine-treated control rats (two-way ANOVA followed by Newman-Keuls test). $^{\#\#}P < 0.01$ for the methamphetamine-treated graft group in comparison to each corresponding value of the methamphetamine-treated lesioned rats (two-way ANOVA followed by Newman-Keuls test).

A large increase in Fos and Zif268 levels were observed in the striatum after methamphetamine administration, as observed in previous studies

(Moratalla et al., 1992; Wang et al., 1994). Similar to the pattern of Fos activation, methamphetamine-induced Zif268 activation was lower in the lesioned striatum and higher (although, not significantly) in the lesion-grafted striatum in comparison to that in the control striatum. However, the drug-regulated expression of these two genes is not identical: the atypical antipsychotic drug clozapine induces *zif268* but not c-*fos* in the caudate-putamen (Nguyen et al., 1992). The differential regulation of c-*fos* and *zif268* has been reported in the dentate gyrus of the hippocampus after the high-frequency stimulation of the perforant path (Cole et al., 1989). The similarity in the distribution of inducible expression suggests that although these two IEGs may differ in their functions in quiescent neurons, they may have analogous or cooperative roles in neuronal responses to methamphetamine in the control, lesioned, or lesion-grafted striatum.

Similar to the results reported previously (Abrous et al., 1992; Cenci et al., 1992), the present study demonstrates that the stimulant effect of methamphetamine on Fos expression can be restored, and furthermore, the density of methamphetamine-induced FLI within the grafted striatum is larger than that observed within the normal striatum. Abrous et al. have suggested (1992) that the exaggerated pharmacological response following intrastriatal grafting of VM might be linked to an abnormal postsynaptic restitution of DA control over the activity of target striatal neurons. Although the lesion-induced motor imbalance was ameliorated completely in the grafted rats, the intrastriatal grafts had little influence on the methamphetamine-induced hyperexpression of FLI in the SNr on the lesioned side. Therefore, the hyperexpression of nigral FLI could be induced independently of the tuning behavior following methamphetamine administration.

The 6-OHDA lesion can lead to the depletion of DA, not only in the striatum but also in the prefrontal cortex, the subthalamic nucleus, and various other limbic targets, which may induce postsynaptic alterations in the DA receptor number and in the sensitivity of various receptor-linked biochemical events in these areas (Campbell et al., 1985; Joyce, 1991; Mishra et al., 1980). The postsynaptic alterations remaining in the denervated areas except for the DA-reinnervated striatum might explain the failure of intrastriatal grafts to exert significant effects on methamphetamine-induced Fos activation in the SNr on the lesioned side. It is suggested that the FLIs in the two discrete sites, medial CPu and SNr, are activated independently by different mechanisms, and furthermore, different neuronal pathways are involved in the methamphetamine-induced rotation and Fos expression in the SNr of 6-OHDA rats.

Although the mechanism by which methamphetamine induces pallidal Fos is unclear, one possibility is that methamphetamine reduces striopallidal transmission through increased DA D_2 receptor activation. This notion is supported in a study by Floran et al. (1997) which showed that methamphetamine or the D_2 agonist, quinpirole, inhibits the release of GABA in the GP of the rat. Also, Black et al. (1997) used positron emission tomography (PET) in the baboon to demonstrate that cerebral blood flow to the GP is reduced significantly after the intravenous administration of a D_2-selective agonist.

In the 6-OHDA rats, a significant difference in the methamphetamine-induced FLI between the lesioned and the intact striata was present also in GP. The side-to-side difference in GP seen in the 6-OHDA rats was no longer present in the grafted animals. As Cenci et al. reported previously (1992); fetal VM transplants normalize DA receptor-mediated function in a primary target of the striatal output neurons, the GP, as well as in the 6-OHDA-lesioned striatum.

In contrast to the striatum, both of the GP and SNr showed little Zif268 activation following methamphetamine challenge in rats of the three groups (control, lesion, graft). It is noteworthy to mention that Zif268 immunoreactivity was not increased in parallel with Fos following methamphetamine administration, indicating that the specific pattern of IEGs activation upon stimulation of dopaminergic neurons seems to be maintained in the basal ganglia.

In conclusion, the differential expression of Fos and Zif268 was observed among three regions (medial CPu, GP, SNr) of the nigrostriatal system following methamphetamine in 6-OHDA-treated hemiparkinsonian rats, thus suggesting the presence of both gene-specific and region-specific functions of Fos and Zif268 in the basal ganglia nuclei. Further studies are necessary to elucidate CNS functions of the IEGs in diverse ways.

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