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D_1 Dopamine Receptor Activation of Multiple Transcription Factor Genes in Rat Striatum

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Abstract: Recent studies have shown that dopamine receptor agonists induce expression of Fos-like immunoreactivity in rat striatal neurons. The protooncogene c-*fos* belongs to a family of immediate early genes that are rapidly induced in fibroblasts by growth factors. In light of previous findings that several immediate early gene mRNAs that encode proven or putative transcription factors are differentially regulated by neuronal stimulation in vivo, we have examined the effect of dopaminergic agents on mRNA levels of several such genes using in situ hybridization and northern blot analysis. *d*-Amphetamine (2.5–10 mg/kg i.p.) causes a rapid but transient dose-dependent increase in *zif268* and *jun*-B mRNA levels in striatum that was abolished by striatal 6-hydroxydopamine lesions or by pretreatment with the specific D_1 receptor antagonist SCH-23390 but not by specific D_2 receptor antagonists. Apomorphine, a dopamine agonist that acts at both D_1 and D_2 receptors, and SKF-38393, a specific D_1 receptor agonist, produce similar mRNA changes in rats pretreated with either 6-hydroxydopamine or reserpine, whereas LY-171,555, a specific D_2 receptor agonist, has no effect. Direct dopamine agonist effects on these immediate early gene mRNA levels are also blocked by D_1 but not by D_2 antagonists. We observed similar, although less robust, changes in c-*fos* and *fos*-B mRNA levels. These results demonstrate that striatal D_1 dopamine receptors are coupled to activation of multiple transcription factor genes, including *zif268* and *jun*-B as well as members of the *fos* family. **Key Words:** *zif268*—*jun*-B—Immediate early gene—In situ hybridization—Dopamine—Amphetamine—SCH-23390. **Cole A. J. et al.** D_1 dopamine receptor activation of multiple transcription factor genes in rat striatum. *J. Neurochem.* **58,** 1420–1426 (1992).

Cell surface receptor stimulation by growth factors or neurotransmitters can elicit the rapid activation of transcription factor genes thought to mediate long-term effects of these signaling agents (Greenberg and Ziff, 1984; Lau and Nathans, 1987; Milbrandt, 1987; Sheng and Greenberg, 1990). In recent studies, we and others have demonstrated that synaptic stimulation of *N*-methyl-D-aspartate receptors elicits activation of the immediate early gene *zif268* (Christy et al., 1988) [also termed *NGF1A* (Milbrandt, 1987), *egr*-1 (Sukhatme et al., 1988), and *Krox-24* (Lemaire et al., 1988)], a transcription factor containing several zinc finger DNA binding motifs, but not c-*fos* or c-*jun*, demonstrating that this group of genes is differentially regulated in vivo (Cole et al., 1989; Wisden et al., 1990). Because several groups have reported that c-Fos-like immunoreactivity in striatum is regulated by D_1 dopamine receptor stimulation (Robertson et al., 1989*a*,*b*; Graybiel et al., 1990; Young et al., 1991), we wondered whether other transcription factor genes are also coupled to this neurotransmitter system.

We have used in situ hybridization and northern blot analysis to examine the responses of mRNAs encoding several immediate early genes, including *zif268*, *jun*-B (Ryder et al., 1988), and *fos*-B (Zerial et al., 1989) as well as c-*fos*, in brain following systemic administration of dopaminergic agents. A preliminary report of these results has been published in abstract form (Cole et al., 1990*b*). Induction of *jun*-B and c-*fos* mRNAs by indirect dopamine agonist treatment has also been reported in abstract form (Iadarola et al., 1990; Moratalla et al., 1990).

MATERIALS AND METHODS

Animal preparation

Male Sprague–Dawley rats (weighing 150–200 g) were used for all experiments. *d*-Amphetamine sulfate, *R*(−)-apomor-

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Abbreviations used: MECS, maximal electroconvulsive seizures; SDS, sodium dodecyl sulfate; SSC, saline–sodium citrate.

phine hydrochloride, *R*(+)-SCH-23390 hydrochloride, *S*(−)-SCH-23388 hydrochloride, *S*(−)-eticlopride hydrochloride, (−)-quinpirole hydrochloride (LY-171,555), cocaine hydrochloride, and mianserin hydrochloride were dissolved in distilled water. Haloperidol, pimozide, *R*(+)-SKF-38393 hydrochloride, and reserpine were dissolved in dimethyl sulfoxide. Drugs were delivered by intraperitoneal injection in volumes of 1 μl/g of body weight. At appropriate intervals, animals were killed by decapitation, and the brains were dissected and rapidly frozen. For blocking experiments, antagonists were given 15 min before agonists. For some experiments animals were pretreated with reserpine (5 mg/kg i.p.) 18 and 3 h before administration of the dopaminergic agonist to be tested.

For 6-hydroxydopamine experiments, animals were pretreated with desipramine (25 mg/kg i.p.) 30 min before intracranial injection (Iversen and Kelly, 1975). Under chloral hydrate anesthesia (400 mg/kg i.p.) animals were placed in a stereotaxic frame. Eight micrograms of 6-hydroxydopamine in 2 μl of 0.9% NaCl with ascorbic acid (1 mg/ml) was injected into the caudate nucleus using a Hamilton syringe positioned at coordinates 0.2 mm anterior and 3.0 mm lateral to bregma and lowered to 4.7 mm below the dura (Javoy et al., 1975; Paxinos and Watson, 1982). Animals were allowed to recover for 7–10 days before experiments.

Maximal electroconvulsive seizures (MECS) were produced in male Sprague–Dawley rats (weighing 175–225 g) by standard techniques (Swinyard, 1972). Following attachment of saline-soaked earclips, electroshock consisting of a 1-s, 100-Hz, 85-mA stimulus of 0.5-ms square-wave pulses was delivered using a UGO Basile ECT unit (model 7801). At these settings, all animals had generalized tonic–clonic convulsions with hindlimb extension.

DNA and RNA probes

Murine *zif268*, rat NGFI-A, human c-*fos*, and mouse *fos*-B cDNA sequences were cloned in Bluescript M13+ (Stratagene, La Jolla, CA, U.S.A.). The murine *jun*-B cDNA sequence was cloned in p-Gem2 (Promega Biotech, Madison, WI, U.S.A.). For RNA probes, plasmids containing full-length or nearly full-length cDNAs for each of the immediate early genes were linearized with appropriate restriction enzymes to produce either antisense or sense transcripts. ^{35}S-Labeled RNA sense or antisense probes were prepared from cDNA sequences using T7, T3, or SP6 RNA polymerase (Promega Biotech) and uridine 5′-[^{35}S](α-thio)triphosphate (New England Nuclear) essentially as described (Melton et al., 1984). For northern blot analysis, inserts were excised from plasmids, gel-purified, and labeled with [α-^{32}P]deoxycytidine 5′-triphosphate using random primer-initiated synthesis with the Klenow fragment of DNA polymerase (Feinberg and Vogelstein, 1983). Mouse *zif268* and rat NGFI-A probes were used interchangeably in these studies and gave similar results.

Northern blots

Total RNA was isolated from rat hippocampus or striatum using the acid guanidinium–phenol extraction procedure of Chomczynski and Sacchi (1987). RNA was separated by electrophoresis through a formaldehyde-containing 1% agarose gel, transferred to nitrocellulose membranes, and probed essentially as described by Linzer and Nathans (1983). In brief, filters were prehybridized in a sealed bag containing 50% (vol/vol) formamide, 4× saline–sodium citrate (SSC) (1× SSC contains 150 m*M* NaCl and 15 m*M* sodium citrate, adjusted to pH 7.0), 4× Denhardt's solution [1× Denhardt's contains Ficoll, polyvinylpyrrolidone, and bovine serum albumin each at 0.02% (wt/vol)], 0.1% (wt/vol) sodium dodecyl sulfate (SDS), 0.1% (wt/vol) sodium pyrophosphate, and 100 μg/ml of sheared salmon sperm DNA. ^{32}P-Labeled probe was added to a final concentration of 2×10^6 cpm/ml, and filters were hybridized overnight at 52°C. Filters were washed in four changes of 2× SSC with 0.1% (wt/vol) SDS at room temperature and then in four changes of 0.1× SSC with 0.1% SDS at 50°C, air-dried, and exposed to x-ray film (Kodak XAR) at −70°C with an intensifying screen for up to 1 week.

In situ hybridization

In situ hybridization was performed as described previously (Cole et al., 1990*a*). Frozen 10-μm-thick sections were mounted on gelatin-coated glass slides and stored desiccated at −20°C. Before hybridization, sections were fixed with depolymerized 4% (wt/vol) paraformaldehyde freshly prepared in phosphate-buffered saline, acetylated with 0.5% (vol/vol) acetic anhydride in 0.1 *M* triethanolamine dissolved in 0.9% (wt/vol) NaCl adjusted to pH 8.0, and delipidated. Hybridization was performed in a moist chamber under unsealed dimethyldichlorosilane (Atomergic Chemetals)-treated coverslips at 56°C using 5×10^5–1×10^6 cpm of probe for each

FIG. 1. Effect of amphetamine on *zif268* mRNA. The left hemisphere is from an animal killed 30 min after amphetamine treatment (5 mg/kg i.p.), whereas the right hemisphere is from a saline-injected control.

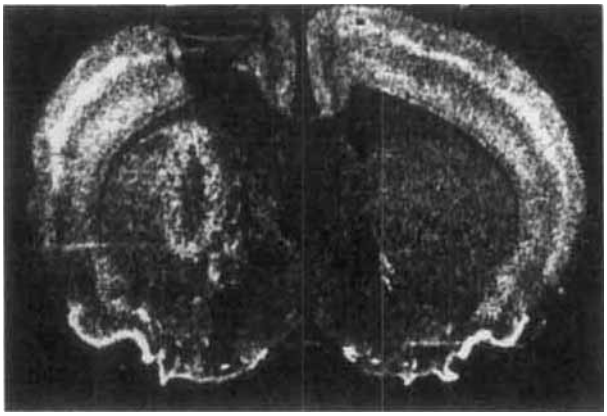

FIG. 2. Effect of apomorphine on *zif268* mRNA levels in 6-hydroxydopamine-lesioned striatum. Ten days after intrastriatal injection of 8 μg of 6-hydroxydopamine into the left caudate nucleus, the animal was treated with apomorphine (2 mg/kg i.p.). Thirty minutes after treatment the animal was killed, and the brain was processed for in situ hybridization with a ^{35}S-labeled *zif268* antisense riboprobe.

slide in 50 μl of hybridization buffer containing 50% (vol/vol) formamide, 10 m*M* dithiothreitol, 600 m*M* NaCl, 1× Denhardt's solution, 1 m*M* EDTA, 0.2 mg/ml of yeast tRNA, and 10% (vol/vol) dextran. After overnight incubation, slides were washed in 2× SSC, treated with 10 μg/ml of RNase A (Worthington) in 2× SSC at 30°C, air-dried, and apposed to autoradiography film (Kodak XAR) at room temperature for 1–5 days.

To ensure specificity of in situ hybridization, studies were done using control and experimental brains comounted in the same tissue block to minimize differences in handling of tissue sections, including freeze–thaw cycles and section thickness. No hybridization of sense strand probes was detected. ^{35}S-Labeled riboprobe complementary to the 3′ noncoding region of *zif268* gave results identical to those obtained using full-length antisense probes. Unless otherwise noted all experiments reported include five or more animals for each condition.

RESULTS

In initial experiments, we used in situ hybridization to examine the effects of amphetamine on levels of *zif268* mRNA in brain. In animals killed 30 min after administration of amphetamine (2.5–10 mg/kg i.p.), we found an increase in *zif268* mRNA levels in the striatum, as well as the overlying cortex (Fig. 1). The rise in *zif268* mRNA level is apparent within 15 min of injection, and levels return to near baseline within 3 h. Amphetamine-induced increases in *zif268* mRNA levels are seen throughout the caudate and putamen but entirely spare the globus pallidus. Similar results were obtained when we examined responses of *jun*-B mRNA, whereas less robust increases in levels of c-*fos* and *fos*-B mRNAs were observed. Increases in *zif268* and *jun*-B mRNA levels were also seen in striatum 30 min after cocaine treatment (10 mg/kg i.p.).

To determine whether the response to amphetamine requires preserved dopaminergic innervation of the striatum, we used intrastriatal 6-hydroxydopamine to lesion dopaminergic afferents selectively. Ten days after intracerebral injections, animals were given amphetamine (10 mg/kg i.p.) or apomorphine (2 mg/kg). Am-

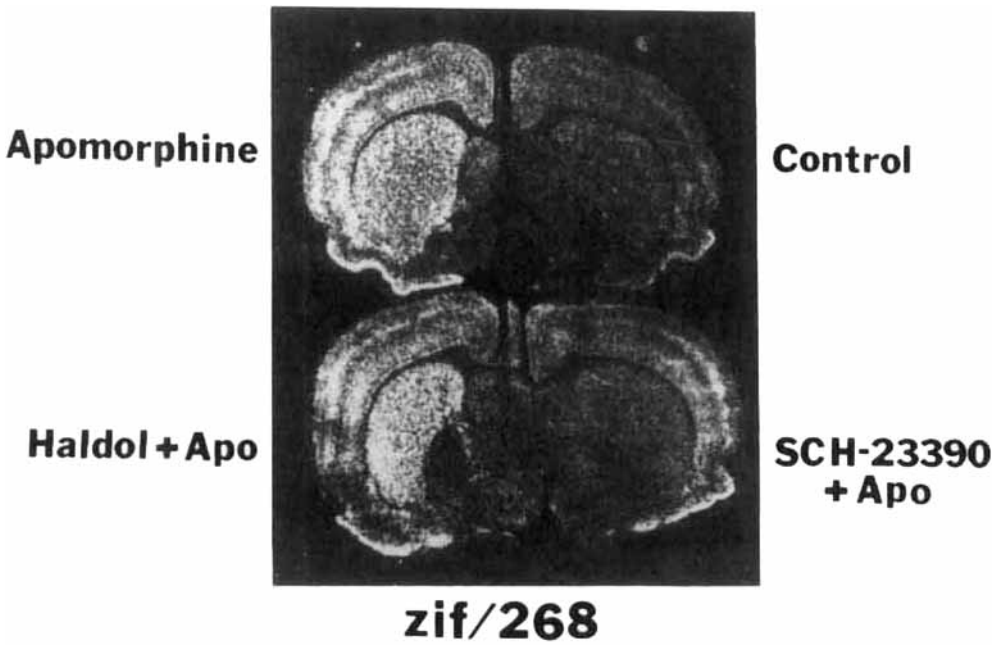

FIG. 3. Effect of dopamine receptor antagonists on apomorphine-induced *zif268* mRNA levels. All animals were pretreated with reserpine (see Materials and Methods). Animals were killed 30 min after saline injection (control), 30 min after apomorphine (2 mg/kg), or 30 min after apomorphine (Apo) following pretreatment with the indicated dopamine antagonist [haldoperidol (Haldol), 1 mg/kg; or SCH-23390, 0.5 mg/kg].

phetamine treatment induced vigorous rotation ipsilateral to the lesion, whereas apomorphine treatment induced rotation contralateral to the lesion, consistent with the establishment of functional receptor supersensitivity. Animals were killed 30 min after agonist treatment. In animals so treated, the *zif268*, c-*fos*, and *jun*-B mRNA response to amphetamine is abolished on the injected side but not on the contralateral side (n = 4). In contrast, treatment with apomorphine causes an increase in each of these mRNA levels in the lesioned striatum but not on the contralateral side (n = 5) (Fig. 2). These results indicate that amphetamine requires preserved presynaptic fibers for its action on this group of immediate early genes and further suggests that the direct dopamine agonist apomorphine can elicit a detectable immediate early gene mRNA response only in denervated striatum. Apomorphine's inability to mimic amphetamine's effect in unlesioned striatum was confirmed in naive animals at doses up to 5 mg/kg and at time points from 15 min to 4 h.

To assess the role of dopamine receptors in mediating amphetamine's effect, we examined whether it was blocked by selective dopamine receptor antagonists. The D_2 dopamine receptor antagonist haloperidol (0.1–3 mg/kg) or the D_1 receptor antagonist SCH-23390 (0.01–1.0 mg/kg) (Hyttel, 1983) was administered 15 min before amphetamine. We found that whereas haloperidol does not block amphetamine's activation of *zif268* or *jun*-B, SCH-23390 completely prevents these responses at 0.1 mg/kg but not at 0.02 mg/kg. SCH-23390's effect was not shared by its enantiomer SCH-23388 (1 mg/kg i.p.; n = 3), which lacks D_1 receptor antagonist properties (Billard et al., 1984), or by mianserin (1 mg/kg i.p.; n = 3), which like SCH-23390 possesses a high affinity for serotonin 5-HT_{1C} and 5-HT_2 receptors (Bischoff et al., 1986; Hess et al., 1986).

Because these results pointed to a role for D_1 dopamine receptors in activation of *zif268* and *jun*-B, we wondered whether these responses could be potentiated by reserpine pretreatment, which has been found to enhance other responses to D_1 receptor stimulation (Vasse et al., 1990). Rats were pretreated with 5 mg/kg i.p. of reserpine 18 and 3 h before administration of dopaminergic agents. Amphetamine (2.5–5 mg/kg) produced a robust activation of *zif268* and *jun*-B, as did the nonselective dopaminergic agonist apomorphine (1–2 mg/kg i.p.) (Figs. 3 and 4). The rise in levels of these mRNAs elicited by both of these agents was blocked by SCH-23390 (0.5 mg/kg i.p.) but not by haloperidol (1 mg/kg i.p.), eticlopride (1 mg/kg i.p.), or pimozide (1 mg/kg i.p.), three chemically distinct D_2 receptor antagonists (Fig. 3). We confirmed the findings of Miller (1990) and Dragunow et al. (1990) that D_2 dopamine antagonists activate immediate early gene mRNA responses in naive animals, making it difficult to interpret the failure of these agents to block dopamine agonist effects. As shown in Fig. 5, after reserpine pretreatment the haloperidol effect on *zif268* mRNA levels is abolished, confirming the notion that this D_2 dopamine antagonist is inactive in blocking apomorphine's effect after reserpine pretreatment.

To examine further the effects of direct dopamine receptor agonists, we used reserpinized animals to check the effect of the selective D_1 agonist SKF-38393 (1–20 mg/kg) (Anderson et al., 1985) and the selective D_2 agonist LY-171,555 (0.5–2 mg/kg) (Nagahama et al., 1986). Whereas SKF-38393 produced an increase in *zif268* and *jun*-B mRNAs in striatum that was blocked by SCH-23390, LY-171,555 had no effect. Similarly, in animals lesioned with unilateral 6-hydroxydopamine injections, LY-171,555 was inactive (n = 5). As reported above for apomorphine, neither of these agents induced a rise in levels of *zif268* or *jun*-B mRNAs in the absence of reserpine pretreatment.

We used northern blot analysis to confirm the results obtained with in situ hybridization. As shown in Fig. 6, mRNA levels of *zif268*, *jun*-B, c-*fos*, and *fos*-B are elevated at 30 min after apomorphine, with lower levels apparent at 90 min. This profile fits well with that observed by in situ hybridization (Fig. 4). Furthermore, as suggested by in situ hybridization, northern blot

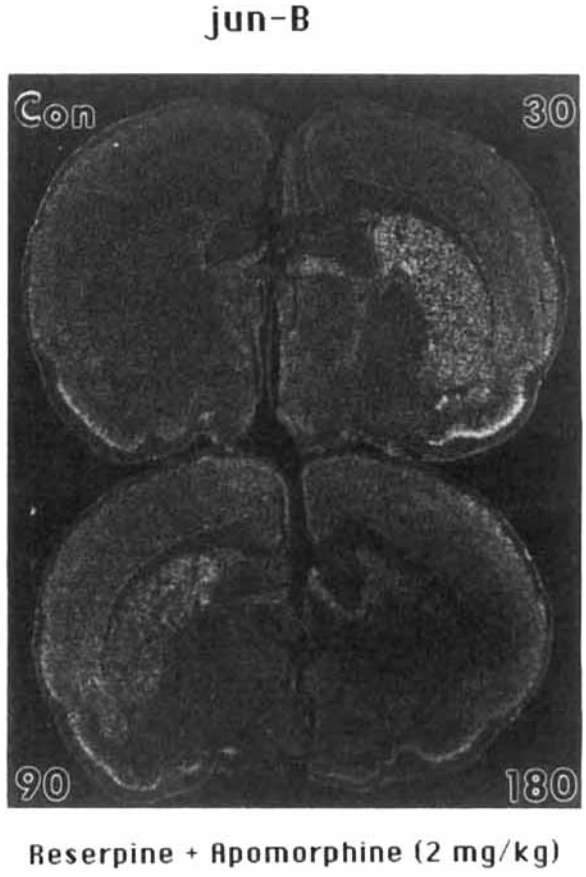

FIG. 4. Time course of *jun*-B mRNA response to apomorphine. Each hemisphere was obtained from a reserpine-treated rat at the indicated time after treatment with apomorphine (2 mg/kg i.p.). The control animal was reserpine-treated and killed 30 min after injection with saline.

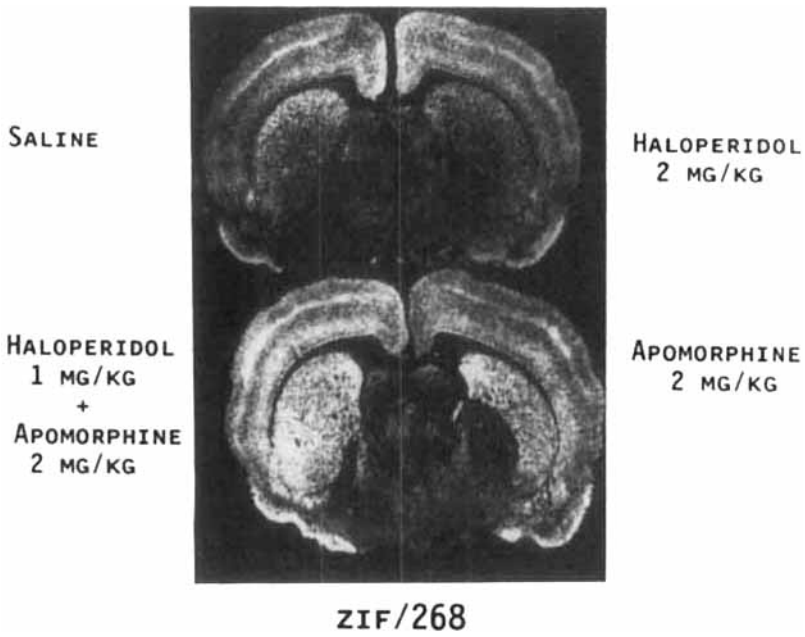

FIG. 5. Effect of reserpine pretreatment on D_2 dopamine antagonist-induced increases in *zif268* mRNA levels. All animals were pretreated with reserpine (see Materials and Methods). Animals were killed 45 min after the indicated antagonist and 30 min after the indicated agonist treatment. Each hemisphere is from a different animal.

analysis shows that whereas *zif268* and *jun*-B levels are increased to values comparable to those observed in hippocampus following MECS, increases in c-*fos* and *fos*-B levels are smaller.

DISCUSSION

Elevation of levels of several transcription factor mRNAs, including *zif268* and *jun*-B, by either amphetamine or direct dopamine agonists is blocked by the selective D_1 receptor antagonist SCH-23390, indicating that dopamine D_1 receptor stimulation is required for the rapid and transient elevation of levels of these mRNAs in striatum. In contrast to the striking rise seen in *zif268* and *jun*-B mRNA levels following activation of D_1 dopamine receptors, we see lesser changes in c-*fos* and *fos*-B mRNA levels. These findings extend several previous reports of increased Fos-like immunoreactivity (Robertson et al., 1989*a,b*; Young et al., 1991) and c-*fos* mRNA levels (Graybiel et al., 1990) to indicate that several transcription factor mRNAs are coupled to D_1 dopamine receptor activation in striatum.

D_1 receptors are coupled to stimulation of adenylate cyclase (Kebabian and Calne, 1979), suggesting that, as demonstrated in cells in vitro, this second-messenger system may mediate the activation of selected immediate early genes (Cho et al., 1989). However, recent studies indicate that D_1 dopamine receptors are also coupled to phosphoinositide turnover via activation of phospholipase C (Felder et al., 1989; Mahan et al., 1990). Accordingly, the intracellular second messenger system mediating the rise in immediate early gene levels mediated by D_1 receptors remains unclear.

Our finding that the indirect dopamine agonists amphetamine and cocaine activate several immediate early gene mRNAs in the naive animal, but the direct agonists appear to increase mRNA levels only in animals pretreated with reserpine or 6-hydroxydopamine, fits well with previous reports (Robertson et al., 1989*a*; Graybiel et al., 1990; Young et al., 1991) regarding c-

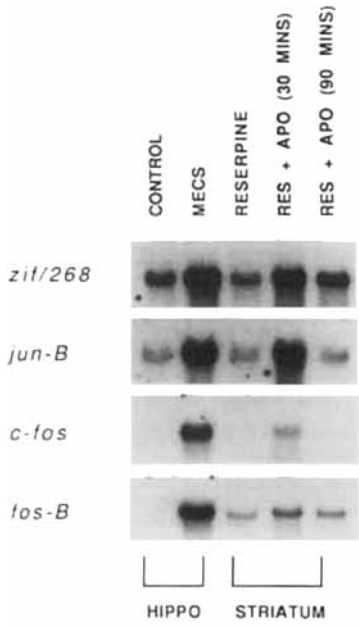

FIG. 6. Comparison of MECS- and apomorphine-induced immediate early gene responses. Total RNA was isolated from hippocampus (HIPPO; lanes 1 and 2) or striatum (lanes 3–5) after the following treatments: lane 1, no treatment (control); lane 2, 30 min after MECS; lane 3, reserpine (5 mg/kg) 18 and 3 h before killing; lane 4, reserpine (RES) pretreatment plus apomorphine (APO; 2 mg/kg) 30 min before killing; and lane 5, reserpine pretreatment plus apomorphine 90 min before killing. Fifteen micrograms of total RNA was loaded in each lane. Replicate filters were prepared and hybridized with the indicated immediate early gene cDNA probes.

Fos-like immunoreactivity following similar treatments. Potential explanations for this apparent disparity include the possibility that direct agonists act as partial agonists that become effective at eliciting this genomic response only after denervation or reserpine treatment, which have been shown previously to potentiate other D_1 receptor-mediated responses. Alternatively, indirect agonists may result in the release of other monoamines that facilitate activation of these genes.

Our observation that *fos*-B mRNA levels are elevated by amphetamine or direct agonist treatment fits nicely with the recent report of Young et al. (1991) that cocaine treatment induces an increase in several Fos-related antigens as assessed by western blot analysis. Recent studies have demonstrated that two forms of Fos-B generated by alternative splicing are induced in brain following seizure activity. These migrate on SDS–polyacrylamide gel electrophoresis with apparent molecular masses of 44 and 35 kDa (Nakabeppu and Nathans, 1991). Accordingly, it appears likely that the 44- and 35-kDa proteins induced by cocaine (Young et al., 1991) represent alternatively spliced forms of Fos-B.

The striking selective involvement of D_1 receptors in activation of these transcription factor genes suggests that this receptor subtype may be particularly important in mediating long-term effects of dopamine on neuronal function. In this context, it is noteworthy that blockade of D_1 receptors prevents sensitization to amphetamine-induced locomotor effects (Vezina and Stewart, 1989). Furthermore, some of these transcription factor genes could be involved in the marked change in neuropeptide mRNA levels observed following treatment with D_1 receptor agonists (Gerfen et al., 1990). Taken together, these studies suggest that identification of the target genes regulated by these transcription factors in striatum will be critical to understanding long-term effects of amphetamine and cocaine, as well as agents used for dopamine replacement in parkinsonism.

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REFERENCES

Anderson P. H., Gronvald F. C., and Jansen J. A. (1985) A comparison between dopamine-stimulated adenylate cyclase and ^{3}H-SCH 23390 binding in rat striatum. *Life Sci.* **37**, 1971–1983.

Billard W., Ruperto V., Crosby G., Iorio L. C., and Barnett A. (1984) Characterization of the binding of ^{3}H-SCH 23390, a selective D-1 receptor antagonist ligand, in rat striatum. *Life Sci.* **35**, 1885–1893.

Bischoff S., Heinrich M., Sonntag J. M., and Krauss J. (1986) The D-1 dopamine receptor antagonist SCH-23390 also interacts potently with brain serotonin (5-HT_2) receptors. *Eur. J. Pharmacol.* **129**, 367–370.

Cho K.-O., Skarnes W. C., Minsk B., Palmieri S., Jackson-Grusby L., and Wagner J. A. (1989) Nerve growth factor regulates gene expression by several distinct mechanisms. *Mol. Cell. Biol.* **9**, 135–143.

Chomczynski P. and Sacchi N. (1987) Single-step method of RNA isolation by acid guanidinium thiocyanate-phenol-chloroform extraction. *Anal. Biochem.* **162**, 156–159.

Christy B. A., Lau L. F., and Nathans D. (1988) A gene activated in mouse 3T3 cells by serum growth factors encodes a protein with "zinc finger" sequences. *Proc. Natl. Acad. Sci. USA* **85**, 7857–7861.

Cole A. J., Saffen D. W., Baraban J. M., and Worley P. F. (1989) Rapid increase of an immediate early gene mRNA in hippocampal neurons by synaptic NMDA receptor activation. *Nature* **340**, 474–476.

Cole A. J., Abu-Shakra S., Saffen D. W., Baraban J. M., and Worley P. F. (1990*a*) Rapid rise in transcription factor mRNAs in rat brain after electroshock-induced seizures. *J. Neurochem.* **55**, 1920–1927.

Cole A. J., Worley P. F., and Baraban J. M. (1990*b*) Dopaminergic regulation of transcription factor mRNAs in striatal neurons *in vivo*. (Abstr) *Soc. Neurosci. Abstr.* **16**, 800.

Dragunow M., Robertson G. S., Faull R. L. M., Robertson H. A., and Jansen K. (1990) D_2 dopamine receptor antagonists induced Fos and related proteins in rat striatal neurons. *Neuroscience* **37**, 287–294.

Feinberg A. P. and Vogelstein B. (1983) A technique for radiolabeling DNA restriction endonuclease fragments to high specific activity. *Anal. Biochem.* **132**, 6–13.

Felder C. C., Jose P. A., and Axelrod J. (1989) The dopamine-1 agonist, SKF 82526, stimulates phospholipase-C activity independent of adenylate cyclase. *J. Pharmacol. Exp. Ther.* **248**, 171–175.

Gerfen C. R., Engber T. M., Mahan L. C., Susel Z., Chase T. N., Monsma F. J. Jr., and Sibley D. R. (1990) D_1 and D_2 dopamine receptor-regulated gene expression of striatonigral and striatopallidal neurons. *Science* **250**, 1429–1432.

Graybiel A. M., Moratalla R., and Robertson H. A. (1990) Amphetamine and cocaine induce drug-specific activation of the c-*fos* gene in striosome-matrix compartments and limbic subdivisions of the striatum. *Proc. Natl. Acad. Sci. USA* **87**, 6912–6916.

Greenberg M. E. and Ziff E. B. (1984) Stimulation of 3T3 cells induces transcription of the c-*fos* proto-oncogene. *Nature* **311**, 433–438.

Hess E. J., Battaglia G., Norman A. B., Iorio L. C., and Creese I. (1986) Guanine nucleotide regulation of agonist interactions at [^{3}H]SCH23390-labeled D_1 dopamine receptors in rat striatum. *Eur. J. Pharmacol.* **121**, 31–38.

Hyttel J. (1983) SCH 23390—the first selective dopamine D-1 antagonist. *Eur. J. Pharmacol.* **91**, 153.

Iadarola M. J., Yeung C. L., Hoo Y., and Quinn J. P. (1990) Elevation of striatal c-*fos* mRNA and AP1 complex formation after treatment with cocaine. (Abstr) *Soc. Neurosci. Abstr.* **16**, 1277.

Iversen S. D. and Kelly P. H. (1975) The use of 6-hydroxydopamine (6OHDA) techniques for studying the pathways involved in drug-induced motor behaviours, in *Chemical Tools in Catecholamine Research, Vol. 1* (Jonsson G., Malmfors T., and Sachs Ch., eds), pp. 327–333. North-Holland, Amsterdam.

Javoy F., Agid Y., and Sotelo C. (1975) Specific and non-specific catecholaminergic neuronal destruction by intracerebral injection of 6-OH-DA in the rat, in *Chemical Tools in Catecholamine Research, Vol. 1* (Jonsson G., Malmfors T., and Sachs Ch., eds), pp. 75–82. North-Holland, Amsterdam.

Kebabian J. W. and Calne D. B. (1979) Multiple receptors for dopamine. *Nature* **277**, 93–96.

Lau L. F. and Nathans D. (1987) Expression of a set of growth-

related immediate early genes in BALB/c 3T3 cells: coordinate regulation with c-*fos* or c-*myc*. *Proc. Natl. Acad. Sci. USA* **84,** 1182–1186.

Lemaire P., Revelant O., Bravo R., and Charnay P. (1988) Two mouse genes encoding potential transcription factors with identical DNA-binding domains are activated by growth factors in cultured cells. *Proc. Natl. Acad. Sci. USA* **85,** 4691–4695.

Linzer D. I. H. and Nathans D. (1983) Growth-related changes in specific mRNAs of cultured mouse cells. *Proc. Natl. Acad. Sci. USA* **80,** 4271–4275.

Mahan L. C., Burch R. M., Monsma F. J. Jr., and Sibley D. R. (1990) Expression of striatal D_1 dopamine receptors coupled to inositol phosphate production and Ca^{2+} mobilization in *Xenopus* oocytes. *Proc. Natl. Acad. Sci. USA* **87,** 2196–2200.

Melton D. A., Krieg P. A., Rebagliati M. R., Maniatis T., Zinn K., and Green M. R. (1984) Efficient *in vitro* synthesis of biologically active RNA and RNA hybridization probes from plasmids containing a bacteriophage SP6 promoter. *Nucleic Acids Res.* **12,** 7035–7056.

Milbrandt J. (1987) A nerve growth factor-induced gene encodes a possible transcriptional regulatory factor. *Science* **238,** 797–799.

Milbrandt J. (1988) Nerve growth factor induces a gene homologous to the glucocorticoid receptor gene. *Neuron* **1,** 183–188.

Miller J. C. (1990) Induction of c-*fos* mRNA expression in rat striatum by neuroleptic drugs. *J. Neurochem.* **54,** 1453–1455.

Moratalla R., Robertson H. A., DiZio P. A., and Graybiel A. M. (1990) Parallel induction of *jun*-B and c-*fos* evoked in the striatum by the psychomotor stimulant drugs cocaine and amphetamine. (Abstr) *Soc. Neurosci. Abstr.* **16,** 953.

Nagahama S., Chen Y. F., Lindheimer M. D., and Oparil S. (1986) Mechanism of the pressor action of LY171555, a specific dopamine D_2 receptor agonist, in the conscious rat. *J. Pharmacol. Exp. Ther.* **236,** 735–742.

Nakabeppu Y. and Nathans D. (1991) A naturally occurring truncated form of FosB that inhibits Fos/Jun transcriptional activity. *Cell* **64,** 751–759.

Paxinos G. and Watson C. (1982) *The Rat Brain in Stereotaxic Coordinates.* Academic Press, New York.

Robertson G. S., Herrera D. G., Dragunow M., and Robertson H. A. (1989*a*) L-DOPA activates c-*fos* in the striatum ipsilateral to a 6-hydroxydopamine lesion of the substantia nigra. *Eur. J. Pharmacol.* **159,** 99–100.

Robertson H. A., Peterson M. R., Murphy K., and Robertson G. S. (1989*b*) D_1-dopamine receptor agonists selectively activate c-*fos* independent of rotational behaviour. *Brain Res.* **503,** 346–349.

Ryder K., Lau L. F., and Nathans D. (1988) A gene activated by growth factors is related to the oncogene v-*jun*. *Proc. Natl. Acad. Sci. USA* **85,** 1487–1491.

Sheng M. and Greenberg M. E. (1990) The regulation and function of c-*fos* and other immediate early genes in the nervous system. *Neuron* **4,** 477–485.

Sukhatme V. P., Cao X., Chang L. C., Tsai-Morris C.-H., Stamenkovich D., Ferreira P. C. P., Cohen D. R., Edwards S. A., Shows T. B., Curran T., Le Beau M. M., and Adamson E. D. (1988) A zinc finger-encoding gene coregulated with c-*fos* during growth and differentiation, and after cellular depolarization. *Cell* **53,** 37–43.

Swinyard E. A. (1972) Electrically induced convulsions, in *Experimental Models of Epilepsy* (Purpura D. P., Penry J. K., Tower D., Woodbury D. M., and Walter R., eds), pp. 433–458. Raven Press, New York.

Vasse M., Chagraoui A., Henry J.-P., and Protais P. (1990) The rise of body temperature induced by the stimulation of dopamine D_1 receptors is increased in acutely reserpinized mice. *Eur. J. Pharmacol.* **181,** 23–33.

Vezina P. and Stewart J. (1989) The effect of dopamine receptor blockade on the development of sensitization to the locomotor activating effects of amphetamine and morphine. *Brain Res.* **499,** 108–120.

Wisden W., Errington M. L., Williams S., Dunnett S. B., Waters C., Hitchcock D., Evan G., Bliss T. V. P., and Hunt S. P. (1990) Differential expression of immediate early genes in the hippocampus and spinal cord. *Neuron* **4,** 603–614.

Young S. T., Porrino L. J., and Iadarola M. J. (1991) Cocaine induces striatal c-Fos-immunoreactive proteins via dopaminergic D_1 receptors. *Proc. Natl. Acad. Sci. USA* **88,** 1291–1295.

Zerial M., Toschi L., Ryseck R.-P., Schuermann M., Muller R., and Bravo R. (1989) The product of a novel growth factor activated gene, *fos*-B, interacts with JUN proteins enhancing their DNA binding activity. *EMBO J.* **8,** 805–813.