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The atypical dopamine D1 receptor agonist SKF 83959 induces striatal Fos expression in rats

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Abstract

The effects of dopamine D1 receptor agonists are often presumed to result from an activation of adenylyl cyclase, but dopamine D1 receptors may also be linked to other signal transduction cascades and the relative importance of these various pathways is currently unclear. SKF 83959 is an agonist at dopamine D1 receptors linked to phospholipase C, but has been reported to be an antagonist at receptors linked to adenylyl cyclase. The current report demonstrates that SKF 83959 induces pronounced, nonpatchy, expression of the immediate-early gene product Fos in the striatum of intact rats which can be converted to a patchy pattern by pretreatment with the dopamine D2-like receptor agonist quinpirole. In rats with unilateral 6-hydroxydopamine lesions SKF 83959 induces strong behavioral rotation and a greatly potentiated Fos response. All of the responses to SKF 83959, in both intact and dopamine-depleted animals, can be blocked by pretreatment with the dopamine D1 receptor antagonist SCH-23390. In intact subjects, SKF 83959 induced Fos expression less potently than the standard dopamine D1 receptor agonist SKF 82958, but the two drugs were approximately equipotent in deinnervated animals. These results demonstrate for the first time that possession of full efficacy at dopamine D1 receptors linked to adenylyl cyclase is not a necessary requirement for the induction of striatal Fos expression in intact animals and suggest that alternative signal transduction pathways may play a role in dopamine agonist induced Fos expression, especially in dopamine-depleted subjects.

Keywords: cAMP; Caudate; Rotation; Dopamine D2 receptor; c-*fos*; Striosome; SKF83959

1. Introduction

The functional distinction between dopamine D1 and D2 receptors was originally drawn based on the observation that stimulation of dopamine D1 receptors activates adenylyl cyclase, whereas stimulation of dopamine D2 receptors does not (Kebabian and Calne, 1979). Substantial evidence suggests, however, that dopamine D1-like receptors may be linked to signal transduction pathways in addition to adenylyl cyclase (Bergson et al., 2005; Friedman et al., 2005; Gautam et al., 1998; Undie et al., 1994; Undie and Friedman, 1990) and it is possible that some of the effects of drugs pharmacologically classified as selective dopamine D1 agonists may be mediated through these alternative pathways. For example, the ability of dopamine D1 receptor agonists to induce a variety of behavioral and electrophysiological effects is not correlated with their ability to stimulate cAMP formation (Arnt et al., 1992; Johansen et al., 1991). These, and other, findings have given rise to the suggestion that there may actually be several subtypes of dopamine D1-like receptors, which may exert their effects through different signal transduction cascades (Arnt et al., 1992; Clifford et al., 1999; Downes and Waddington, 1993; Friedman et al., 2005; Jin et al., 2003; Johansen et al., 1991; Undie et al., 1994). If this notion were correct, it would be of obvious importance to identify the pathways underlying various effects of dopamine D1 receptor agonists. In this regard, there has been substantial recent interest in the phenylbenzazepine derivative SKF 83959 and it has been suggested that this compound may be a useful tool for exploring the functions of dopamine D1 receptors which are not linked to adenylyl cyclase (Zhen et al., 2005).

SKF 83959 binds to dopamine D1 receptors with high affinity (Andringa et al., 1999; Neumeyer et al., 2004) but fails

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to stimulate production of cAMP in a number of experimental models (Andringa et al., 1999; Arnt et al., 1992; Gnanalingham et al., 1995a; Jin et al., 2003). If fact, SKF 83959 is actually able to block the stimulation of adenylyl cyclase produced by conventional D1 agonists (Andringa et al., 1999; Arnt et al., 1992; Jin et al., 2003), indicating that it may be a functional antagonist at adenylyl cyclase linked dopamine D1 receptors. Given its ineffectiveness in stimulating adenylyl cyclase, it is striking that SKF 83959 is able to induce a number of behavioral effects similar to those produced by standard dopamine D1 receptor agonists (Arnt et al., 1992; Downes and Waddington, 1993; Gnanalingham et al., 1995a,b,c; Tomiyama et al., 2001; Zhen et al., 2005), although certain differences are apparent as well (O'Sullivan et al., 2004; Zhang et al., 2005). SKF 83959 has been shown to stimulate phosphoinositide hydrolysis (Jin et al., 2003; Panchalingam and Undie, 2001; Zhen et al., 2005), and it is plausible that the effects of this drug may be mediated through activation of phospholipase C.

Although previous authors have examined the effects of SKF 83959 on behavior in a number of different situations, nothing is yet known about the effects of this drug on the expression of immediate early genes (IEGs), such as c-*fos*. IEGs have been widely examined in recent years as markers of functional neural circuits in the brain (Herdegen and Leah, 1998; Hughes and Dragunow, 1995), and this technique has proven especially useful in studies of the basal ganglia (Robertson et al., 1991). A fundamental result obtained in these studies is that dopamine D1-like agonists are able to induce marked expression of c-*fos* in the striatum. Full agonists at dopamine receptors linked to adenylyl cyclase are able to induce Fos expression in normal animals and an even more vigorous response is produced by these drugs in animals chronically depleted of dopamine (Asin et al., 1995; Asin and Wirtshafter, 1993; Moratalla et al., 1996; Svenningsson et al., 2000; Wirtshafter and Asin, 1994). In contrast, the partial agonist SKF 38393 is unable to induce a pronounced Fos response in the striatum of intact, normosensitive, animals (Robertson et al., 1991), although it is effective in dopamine-depleted subjects (LaHoste et al., 1993). It has been widely assumed that the effects of dopamine D1 agonists on IEG expression are mediated through stimulation of adenylyl cyclase, and some direct evidence is consistent with this view (Konradi et al., 1994; Vincent et al., 1997). In contrast to these findings, however, other studies have suggested that transduction pathways not involving cAMP may also play an important role in the effects of dopamine D1-like agonists (Andersson et al., 2001; Gerfen, 2003; Simpson and Morriis, 1995). In this context, it would seem of substantial interest to determine whether Fos expression can be induced by SKF 83959, given the unique pharmacological properties of this drug. In the current study we therefore investigated the ability of SKF 83959 to promote striatal Fos expression both in normosensitive rats, and in subjects chronically depleted of dopamine. For comparison, we also studied the effects of the structurally related compound SKF 82958, which is a full agonist at adenylyl cyclase linked dopamine D1-like receptors (Gnanalingham et al., 1995a; O'Boyle et al., 1989).

2. Materials and methods

2.1. Subjects

Subjects were 57 adult, male Sprague–Dawley derived rats obtained from a colony maintained by the Psychology Department of the University of Illinois at Chicago. Rats were housed in individual wire mesh cages and handled daily for several days prior to testing.

2.2. Drugs

SKF 82958 ((±)-6-chloro-7,8-dihydroxy-3-allyl-1-phenyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine hydrobromide; molecular weight=410.73) and desmethylimipramine were obtained from the Sigma Chemical Company (St. Louis, MO). SKF 83959 (6-chloro-7,8-dihydroxy-3-methyl-1-(3-methylphenyl)-2,3,4,5-tetrahydro-1*H*-3-benzazepine; molecular weight=398.72) was obtained through the NIMH chemical synthesis program administered by SRI (Menlo Park, CA). SCH-23390 (7-chloro-8-hydroxy-3-methyl-1-phenyl-2,3,4,5-tetrahydro-*H*-3-benzazepine hydrochloride; molecular weight=324.1) and quinpirole (*trans*-(−)-4*aR*-4,4*a*,5,6,7,8,8*a*,9-octahydro-5-propyl-1*H*-pyrazolo(3,4)-quinoline hydrochloride; molecular weight=398.3) were obtained from Research Biochemicals Inc. (Natick, MA).

2.3. Surgery

Operated animals received unilateral injections of 6-hydroxydopamine (6-OHDA, Sigma Chemical Company, St. Louis, MO) into the lateral hypothalamus (8 μg free base in 4 μl of a 0.1% ascorbic acid vehicle) using standard stereotaxic techniques. Surgery was conducted under sodium pentobarbital anesthesia (45 mg/kg) following pretreatment with desmethylimipramine (25 mg/kg) to reduce damage to noradrenergic neurons. Two weeks later, these subjects were injected with apomorphine (0.3 mg/kg, s.c.) and placed in automated rotometers for a period of 120 min. Thirty-one subjects showing at least 200 contralateral rotations were used in further studies which were conducted 3 to 5 months following screening with apomorphine.

2.4. Drug treatments

All treatment groups consisted of between 3 and 5 animals. Intact subjects were injected subcutaneously with either saline or with SKF 82958 at doses of 0.039, 0.156, 0.625 or 2.500 μmol/kg or with SKF 83959 at doses of 0.625, 2.500 or 10.000 μmol/kg. Additional groups of subjects received injections of SCH-23390 (1.0 mg/kg) 30 min prior to injections of SKF 83959 (10 μmol/kg) or of quinpirole (3.0 mg/kg) followed by SKF 83959 2.5 μmol/kg. Animals were then returned to their home cages for a period of 90 min at which time they were anesthetized and perfused as described below. Subjects with 6-OHDA lesions were divided into 7 groups matched as closely as possible on rotation in response to apomorphine and injected

with either saline or with SKF 82958 or SKF 83959 at doses of 0.005, 0.025 or 0.125 μmol/kg at which time they were placed in automated rotometers for a period of 90 min and then sacrificed. Previous pilot studies indicated that the 0.125 μmol/kg dose of SKF 82958 induced a maximal Fos response in the striatum. Rotational scores were not collected for 7 subjects. Rotation and Fos expression were also examined in an additional group of animals who received injections of SCH-23390 (1 mg/kg) 30 min before SKF 83959 (0.125 μmol/kg).

2.5. Perfusion and immunocytochemistry

Animals were deeply anesthetized with sodium pentobarbital (100 mg/kg) and then rapidly perfused at room temperature with saline followed by 10% formalin using a variable pH protocol (Berod et al., 2004). Brains were then removed from the skulls and post fixed in the formalin solution for 1 h at 4 °C. The tissue was then transferred to a solution of phosphate-buffered saline (PBS) containing 20% sucrose where it was stored at 4 °C until the next day. Cryostat sections were then cut through the rostral striatum at a thickness of 35 μm and processed using standard immunocytochemical methods as we have previously described in detail (Wirtshafter and Asin, 2001). The primary antibody was a rabbit anti-c-Fos serum (Oncogene Sciences/Calbiochem, Cambridge, MA, AB5, 25,000×) and antigenic sites were visualized using a Vectastain Elite ABC kit (Vector Laboratories, Burlingame, CA) employing nickel intensified diaminobenzadine as the chromogen. In control sections in which the primary antibody was omitted or replaced by nonimmune rabbit serum, no stained nuclei were seen.

2.6. Quantitative analysis

Fields in the medial striatum measuring 1.08×0.86 mm (width×height) were digitally captured using a Quantimet Q500 image analysis system at a level just caudal to the complete fusion of the longitudinal fissure in the midline of the septum. Fields were edited, when necessary, to remove obvious artifacts and immunoreactive nuclei within these fields were then automatically counted based on their intensity of staining relative to background, size and aspect ratio, as determined in extensive preliminary investigations.

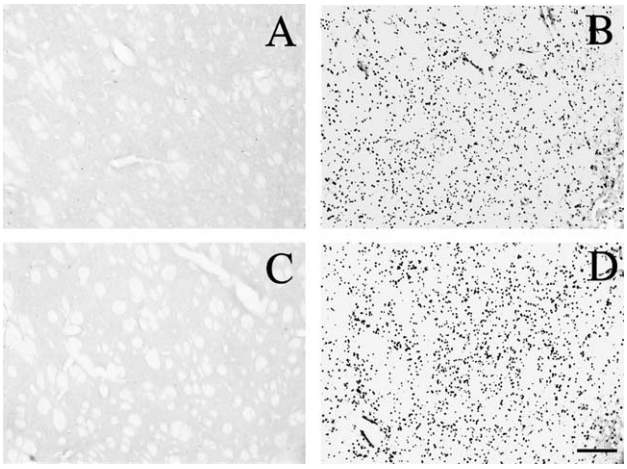

Fig. 1. Photomicrographs displaying Fos-like immunoreactivity in the striatum of intact rats following injections of saline (panel A), SKF 83959 (10 μmol/kg) (panel B), SCH-23390 (1.0 mg/kg) followed by SKF 83959 (10 μmol/kg) (panel C) or SKF 82958 (0.63 μmol/kg) (panel D). Scale bar=100 μm.

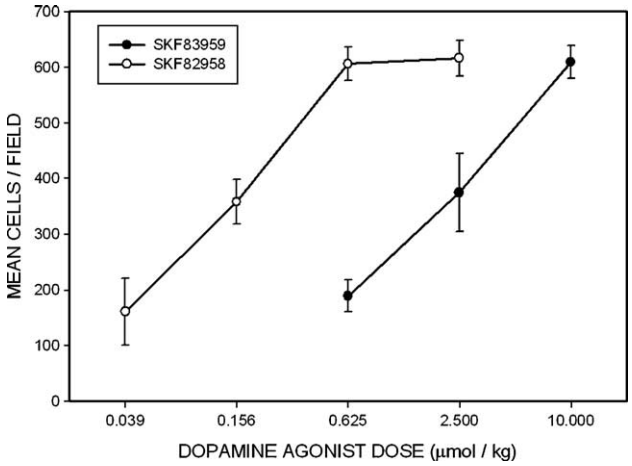

Fig. 2. Mean numbers (±S.E.M.) of cells displaying Fos-like immunoreactivity in 0.93 mm^2 fields in the medial striatum of intact rats injected with various doses of SKF 82958 (open symbols) or SKF 83959 (filled symbols).

3. Results

3.1. Fos expression in intact animals

Animals injected with saline displayed a small number (mean=92.2±29.8 cells/field) of mostly very lightly labeled neurons in the medial striatum. Administration of either SKF 82958 or SKF 83959 led to marked increase in Fos-like immunoreactivity in this region which was distributed in a relatively homogenous fashion (Fig. 1) Quantitative data are shown in Fig. 2 where it can be seen that both drugs increased Fos expression in a dose-dependent fashion. The dose–response curves for the two drugs are almost perfectly parallel, with the curve for SKF 83959 shifted to the right by about 16-fold

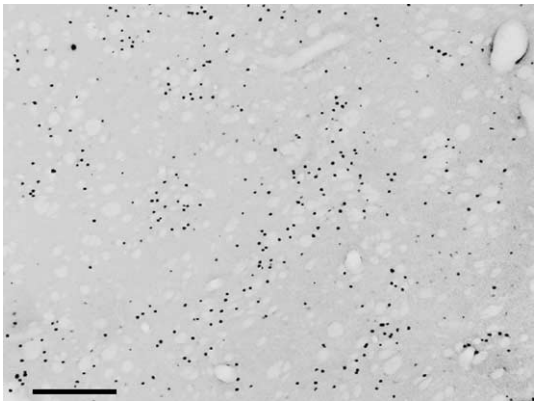

Fig. 3. Photomicrograph of a field in the rostral medial striatum displaying the highly patchy pattern of Fos expression typical of intact rats injected with the dopamine D2-like agonist quinpirole (3 mg/kg) prior to SKF 83959 (2.5 μmol/kg). Scale bar=100 μm.

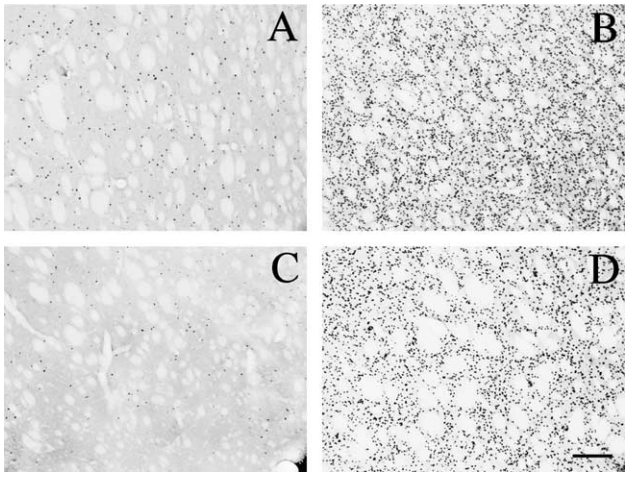

Fig. 4. Photomicrographs displaying Fos-like immunoreactivity in the striatum of 6-OHDA lesioned rats following injections of saline (panel A), SKF 83959 (0.125 μmol/kg) (panel B), SCH-23390 (1.0 mg/kg) followed by SKF 83959 (0.125 μmol/kg) (panel C) or SKF 82958 (0.125 μmol/kg) (panel D). Scale bar = 100 μm.

relative to that for SKF 82958. Analysis of the results for SKF 82958 by means of one-way analysis of variance (ANOVA) indicated a significant effect of drug dose ($F(3,10)=27.64$, $P<0.001$). Fos expression was almost identical after treatment with the two highest doses of SKF 82958, suggesting that the amounts employed were sufficient to induce a maximal response. Analysis of the data from animals treated with SKF 83959 again indicated a significant effect of drug dose ($F(2,10)=4.55$; $P<0.05$). The Fos response produced by the highest dose of SKF 83959 was almost identical to that seen after treatment with either of the two highest doses of SKF 82958, demonstrating that SKF 83959 is at least as efficacious as is SKF 82958. Almost no striatal Fos expression was seen in animals pretreated with SCH-23390 (1.0 mg/kg), suggesting that the response was indeed dependent on stimulation of dopamine D1-like receptors (Fig. 1). In animals injected with quinpirole (3.0 mg/kg) prior to treatment with SKF 83959, intense Fos expression was present in the rostral striatum, but

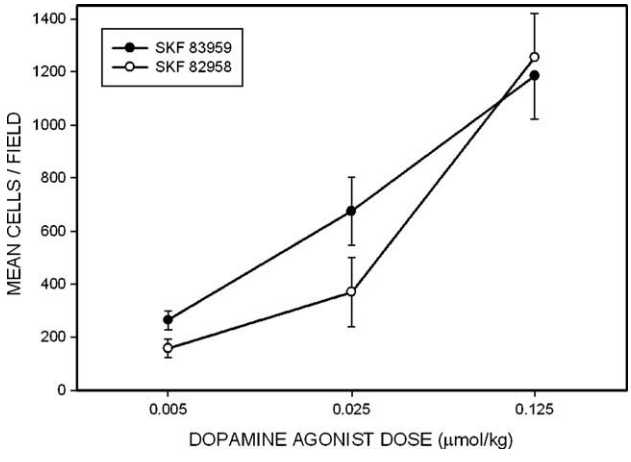

Fig. 5. Mean numbers (±S.E.M.) of Fos-immunoreactive cells in 0.93 mm^2 fields in the medial striatum of 6-OHDA-treated rats injected with SKF 82958 (open symbols) or SKF 83959 (filled symbols).

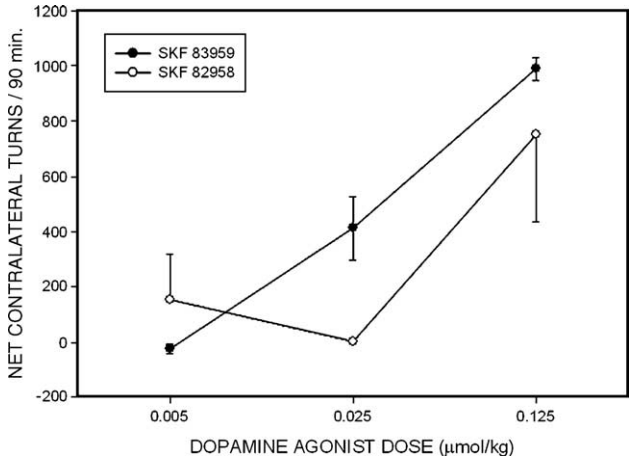

Fig. 6. Mean numbers (±S.E.M.) of net contralateral rotations in the 90-min period following injections of various doses of SKF 83959 (closed symbols) or SKF 82958 (open symbols) in rats with unilateral 6-OHDA lesions.

was distributed in a highly patchy fashion (Fig. 3), in contrast to the homogeneous expression seen after SKF 82958 alone.

3.2. Fos expression in animals with unilateral 6-OHDA lesions.

Saline-treated animals displayed a modest number of lightly immunoreactive cells in the striatum (mean of 204±39 cells/field). Both SKF 82958 and SKF 83959 induced a robust Fos response (Figs. 4 and 5) with individual cells showing much more intense staining than that which was observed in intact subjects. As can be seen from the data presented in Fig. 5, SKF 83959 was at least as effective as SKF 82958 at inducing Fos expression. These data were analyzed by a 2×3 (drug×dose) factorial ANOVA which indicated a significant effect of drug dose ($F(2,19)=20.9$, $P<0.001$), but not of drug identity or of the drug×dose interaction ($P>0.3$), indicating that the effects of equivalent doses of the two drugs did not differ from each other. As was the case in intact animals, the response to SKF 83959 in rats with 6-OHDA lesions could be almost abolished by pretreatment with SCH-23390 (1.0 mg/kg) (Fig. 4C). As reported by previous workers (Arnt et al., 1992; Gnanalingham et al., 1995a), both drugs also induced robust contralateral rotation and analysis of this data by a 2×3 ANOVA again indicated a significant effect of dose ($F(2,12=13.84$; $P<0.001$), but not of drug identity ($P>0.2$) or of the drug×dose interaction ($P>0.1$) (Fig. 6).

4. Discussion

There are two primary results of the current study: First, despite its reported inability to activate adenylyl cyclase, the atypical or "anomalous" (Clifford et al., 1999) D1-like agonist SKF 83959 is able to induce robust Fos expression in the striatum. Second, the relative potencies of SKF 83959 and SKF 82958 for inducing Fos expression appear to be different in intact subjects and in animals chronically depleted of dopamine.

SKF 83959 has been reported to function as an antagonist at dopamine D1 receptors linked to adenylyl cyclase (Andringa et

al., 1999; Arnt et al., 1992; Jin et al., 2003). It has been generally assumed that the induction of Fos expression by D1 agonists in the striatum is mediated primarily through the production of cAMP and the subsequent activation of protein kinase A (Konradi et al., 1994; Robertson et al., 1991; Vincent et al., 1997). Based on these assumptions, one would expect that SKF 83959 would not be able to promote striatal Fos expression. The current results clearly indicate, however, that that SKF 83959 is able to induce pronounced Fos expression in the striatum of both intact and dopamine-depleted animals in a fashion highly similar to that seen after administration of SKF 82958, a full agonist at adenylyl cyclase linked dopamine D1 receptors (Gnanalingham et al., 1995a; O'Boyle et al., 1989). The selective dopamine D1 antagonist SCH-23390 was able to completely antagonize the responses to SKF 83959, showing that the effects of this drug were indeed mediated through a dopamine D1-like receptor. The finding that SKF 83959 is able to induce Fos expression in intact, as well as in deinnervated, animals demonstrates that the occurrence of this response does not require alterations in receptor sensitivity or selectivity such as might occur after chronic depletion of dopamine (Gerber et al., 1988). Pronounced Fos expression in the rostral striatum of intact animals has previously been demonstrated only after administration of dopamine D1 receptor agonists with full efficacy in stimulating adenylyl cyclase (Asin et al., 1995; Asin and Wirtshafter, 1993; Moratalla et al., 1996; Svenningsson et al., 2000; Wirtshafter and Asin, 1994). In contrast, SKF 38393, which is a partial agonist at adenylyl cyclase linked dopamine receptors (Pfeiffer et al., 1982), has been reported to be ineffective in inducing Fos expression in normosensitive animals when administered by itself (LaHoste et al., 1993; Robertson et al., 1991). The current results provide the first demonstration that the possession of full efficacy at adenylyl cyclase linked receptors is not a necessary requirement for the elicitation of Fos synthesis in intact animals, and suggest that the ineffectiveness of SKF 38393 must reflect some other property of this drug.

Although SKF 83959 produced a relatively homogeneous response when given by itself, this drug induced a highly patchy pattern of staining in intact animals pretreated with the dopamine D2-like agonist quinpirole. This pattern of responses is, again, identical to that seen after administration of dopamine D1 receptor agonists possessing full efficacy in stimulating adenylyl cyclase (Capper-Loup et al., 2002; Le Moine et al., 1997; Wirtshafter et al., 1997; Wirtshafter and Asin, 1994) and serves to further emphasize the functional similarity of these drugs with respect to Fos induction. Elicitation of patchy staining patterns by quinpirole in normosensitive rats has previously been reported only when this drug is combined with dopamine D1 agonists; in contrast quinpirole markedly, and uniformly, suppresses the striatal Fos expression induced by a number of other treatments which do not act directly on dopamine D1 receptors (Cook and Wirtshafter, 2000; Schwarting and Hutson, 1996; Struthers and Wirtshafter, 1998).

Analogous to the results on Fos expression obtained here, several previous studies have shown that SKF 83959 is able to reproduce a number of the behavioral effects seen after administration of typical dopamine D1 receptor agonists including induction of intense grooming behavior (Downes and Waddington, 1993), stimulation of orofacial movements (Downes and Waddington, 1993; Tomiyama et al., 2001), and reversal of parkinsonian symptoms in MPTP-treated primates (Gnanalingham et al., 1995c). SKF 83959 has also been reported to induce contralateral rotation in rats with unilateral 6-OHDA lesions (Arnt et al., 1992; Gnanalingham et al., 1995a; Zhen et al., 2005), a result we confirmed in the present study. Given the importance that has been allotted to the linkage between D1 receptors and adenylyl cyclase, the fact that SKF 83959 induces potent effects on behavior and on Fos expression is surprising and several explanations for the effectiveness of this drug have been proposed. It has, for example, been suggested that the antiparkinsonian effects of SKF 83959 may result in part from a blockade of dopamine D1 receptors at extrastriatal sites, which may indirectly produce an alteration in striatal functioning (Cools et al., 2002). The current results do not directly refute this suggestion, but they do demonstrate that SKF 83959 has powerful effects on striatal cells which appear identical to those induced by typical full efficacy agonists and it is difficult to see how this pattern of effects could arise entirely from an action on another brain structure. Another possibility is that the effects seen in intact animals might result from an indirectly mediated potentiation of dopamine release (Andringa et al., 1999). It is unlikely, however, that such a mechanism could account for either the exaggeration of the Fos response we observed in 6-OHDA-treated subjects or for the behavioral effects which have been reported in deinnervated animals (Arnt et al., 1992; Gnanalingham et al., 1995a,b). Another possibility, which has gained few adherents in the behavioral or neurochemical literature, is that certain of the effects of SKF 83959 may indeed be mediated through stimulation of adenylyl cyclase. Even though SKF 83959 is able to antagonize dopamine-induced stimulation of cAMP formation (Andringa et al., 1999; Arnt et al., 1992; Jin et al., 2003), some studies have suggested that this drug may, by itself, have weak intrinsic activity at the adenylyl cyclase linked D1 receptor (Andringa et al., 1999; Gnanalingham et al., 1995a) These reports suggest that caution is necessary in absolutely ruling out a role for adenylyl cyclase in the effects of SKF 83959. Against this possibility, it should be stressed that the reported effects of SKF 83959 on adenylyl cyclase have been marginal in those experiments in which they have been observed, and other experiments have failed to detect any direct effect of SKF 83959 on cAMP formation (Andringa et al., 1999; Arnt et al., 1992; Gnanalingham et al., 1995a; Jin et al., 2003).

The simplest explanation of the current findings is that SKF 83959 induces striatal Fos expression through a mechanism not involving cAMP production. Most workers who have studied the behavioral effects of SKF 83959 have reached an analogous conclusion (Andringa et al., 1999; Arnt et al., 1992; Clifford et al., 1999; Downes and Waddington, 1993; Gnanalingham et al., 1995c; Tomiyama et al., 2001), and, in some cases, independent evidence is available to support such claims (O'Sullivan et al., 2004). Stimulation of dopamine D1 receptors could, in theory, influence IEG expression through a number of mechanisms not

involving adenylyl cyclase (Bergson et al., 2005; Gautam et al., 1998; Undie et al., 1994; Undie and Friedman, 1990). For example, SKF 83959 has been shown to activate phospholipase C through a dopamine D1 receptor linked mechanism (Jin et al., 2003; Panchalingam and Undie, 2001; Zhen et al., 2005). Activation of phospholipase C could stimulate IEG expression through several pathways. One possible mechanism would involve stimulation of the MAPKinase/Erk-1/2 cascade (Sugden and Clerk, 1997) leading to phosphorylation of the small nuclear protein Elk, and the cAMP response element binding protein CREB (Sugden and Clerk, 1997; Sweatt, 2001). Both of these events would be expected to stimulate c-*fos* transcription (Gille et al., 1995; Sheng and Greenberg, 1990). It is possible that the response to standard dopamine D1-like agonists, such as SKF 82958, may involve stimulation of both adenylyl cyclase dependent and independent pathways (Undie and Friedman, 1990), whereas the response to SKF 83959 may be effected principally through adenylyl cyclase independent mechanisms.

Several workers have suggested that chronic depletion of dopamine may alter the transduction mechanisms underlying the immediate-early gene response to dopamine agonists. For example, antisense knockdown of CREB synthesis has been found to attenuate dopamine agonist induced Fos expression in intact animals, but not in animals with 6-OHDA-induced depletions of dopamine (Andersson et al., 2001). Gerfen, on the basis of a number of empirical studies, has proposed the specific hypothesis that dopamine deinnervation results in an irreversible switch from transduction pathways involving the cAMP-dependent protein kinase A to those involving the MAPKinase cascade (Gerfen, 2003). Other evidence, however, suggests that MAPK is involved in the response to cocaine even in intact animals (Valjent et al., 2000). In the current study, we found that SKF 83959 was about 16-fold less potent than SKF 82958 at inducing Fos expression in intact animals but was, if anything, more potent than SKF 82958 at inducing Fos expression in dopamine-depleted subjects. These findings of a shift in the relative effectiveness of the two drugs is consistent with the hypothesis that dopamine depletion may increase the relative importance in striatal neurons of signaling pathways not involving adenylyl cyclase. It is possible that agents which selectively stimulate phospholipase C linked dopamine D1 receptors may prove of especial utility in the treatment of Parkinson's disease.

In summary, the current experiments demonstrate that SKF 83959 is able to potently stimulate striatal Fos expression in both intact and dopamine-depleted animals. These results suggest that transduction pathways not involving adenylyl cyclase may play a more important role in the dopaminergic control of Fos expression than has generally been appreciated.

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