ELSEVIER

European Journal of Pharmacology 349 (1998) 41–47

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Quinpirole attenuates striatal c-*fos* induction by 5-HT, opioid and muscarinic receptor agonists

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Received 20 November 1997; revised 23 February 1998; accepted 27 February 1998

Abstract

Pretreatment with the dopamine D_2 receptor agonist quinpirole (0.025–2.5 mg/kg) produced a marked, dose-dependent, attenuation of the striatal Fos expression induced by the serotonin (5-Hydroxytryptamine, 5-HT) releasing agent fenfluramine (25 mg/kg). Quinpirole (2.5 mg/kg) was also able to drastically attenuate the striatal Fos response produced by injections of the direct 5-$HT_{1/2}$ receptor agonist *N*-(3-trifluoromethylphenyl)piperazine hydrochloride (TFMPP) (5 mg/kg), the selective 5-HT_2 receptor agonist 1-(2,5-dimethoxy-4-iodophenyl)-2-aminopropane hydrochloride (DOI) (6.64 mg/kg), the 5-$HT_{1A/1B}$ receptor agonist RU-24969 (5-methoxy-3-(1,2,3,6-tetrahydropyridin-4-yl)1*H*-indole) (5 mg/kg), the μ-opioid receptor agonist morphine (5 mg/kg) and the muscarinic cholinergic receptor agonist pilocarpine (50 mg/kg). These results are in marked contrast to the previously reported ability of quinpirole to potentiate the response to D_1 dopamine receptor agonists and demonstrate that stimulation of D_2-like receptors can have differential effects on the Fos responses induced by various drugs.

Keywords: Immediate early gene; Dopamine D_2 receptor; Acetylcholine; Fenfluramine; TFMPP (*N*-(3-trifluoromethylphenyl)piperazine hydrochloride); RU-24969; DOI (1-(2,5-dimethoxy-4-iodophenyl)-2-aminopropane hydrochloride); Pilocarpine; Morphine

1. Introduction

Many behavioral and electrophysiological studies have documented the occurrence of synergistic interactions between the effects of dopamine D_1 and D_2-like receptor agonists (Clark and White, 1987) and several recent studies have demonstrated that analogous effects can be demonstrated with respect to the expression of the immediate early gene c-*fos*. For example, in intact animals, a marked striatal Fos response can be induced by combined injections of the partial dopamine D_1 receptor agonist SKF-38393 ((±)-1-phenyl-2,3,4,5-tetrahydro-(1*H*)-3-benzazepine-7,8-diol hydrochloride) and the D_2-like dopamine receptor agonist quinpirole (LaHoste et al., 1993). Injections of the individual compounds in isolation, however, have little effect on striatal Fos expression (LaHoste et al., 1993). Similar synergistic effects have been reported in dopamine depleted animals (Gerfen et al., 1995; Paul et al., 1992) and can also be observed in intact subjects treated with low doses of the full D_1 receptor agonist A-77636 ((1*R*,3*S*) 3-(1′-adamantyl)-1-aminomethyl-3,4-dihydro-5,6-dihydroxy-1*H*-2-benzopyran hydrochloride) (Wirtshafter and Asin, 1994). Synergistic effects of dopamine D_1 and D_2-like receptor agonists have also been observed in several extrastriatal structures (LaHoste et al., 1997; Ruskin and Marshall, 1995; Wirtshafter and Krebs, 1997). It is interesting that combined administration of D_1 and D_2 receptor agonists typically induces a highly patchy pattern of staining in the striatum, whereas more homogenous patterns are observed after dopamine D_1 receptor agonists alone (LaHoste et al., 1993; Paul et al., 1992; Wirtshafter and Asin, 1994). Anatomical studies have shown that the striatum is comprised of neurochemically and connectionally distinct striosomal and matrix compartments (Graybiel, 1990) and the staining seen after combined treatment with dopamine D_1 and D_2 receptor agonists, like that seen after administration of amphetamine (Asin et al., 1996; Graybiel et al., 1990), is concentrated in the striosomal compartment (Paul et al., 1992; Wirtshafter et al., 1997).

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Although it has been the subject of the greatest amount of study, dopamine is by no means the only transmitter known to exert an effect on striatal immediate early gene expression. For example, striatal Fos expression can also be induced by stimulation of serotonin (5-Hydroxytryptamine, 5-HT) (Cook and Wirtshafter, 1995; Leslie et al., 1993; Rouillard et al., 1996; Torres and Rivier, 1994), μ-opioid (Chang et al., 1988; Liu et al., 1994), and muscarinic cholinergic (Bernard et al., 1993; Hughes and Dragunow, 1993) receptors. Since the dopamine D_2-like receptor agonist quinpirole to able to drastically modify the Fos expression induced by selective D_1 receptor agonists, it seemed of considerable interest to determine whether this drug would produce similar modifications in the responses induced by nondopaminergic agents. In the current study, we therefore quantitatively examined the effects of quinpirole pretreatment on the striatal Fos expression induced by injections of the serotonin releasing agent fenfluramine, the direct 5-$HT_{1/2}$ receptor agonist TFMPP (*N*-(3-trifluoromethylphenyl)piperazine hydrochloride), the selective 5-HT_2 receptor agonist DOI (1-(2,5-dimethoxy-4-iodophenyl)-2-aminopropane hydrochloride), the 5-$HT_{1A/1B}$ receptor agonist RU-24969 (5-methoxy-3-(1,2,3,6-tetrahydropyridin-4-yl)1*H*-indole), the μ-opioid receptor agonist morphine and the muscarinic cholinergic receptor agonist pilocarpine. Some of the current results have been presented in abstract form (Cook and Wirtshafter, 1996).

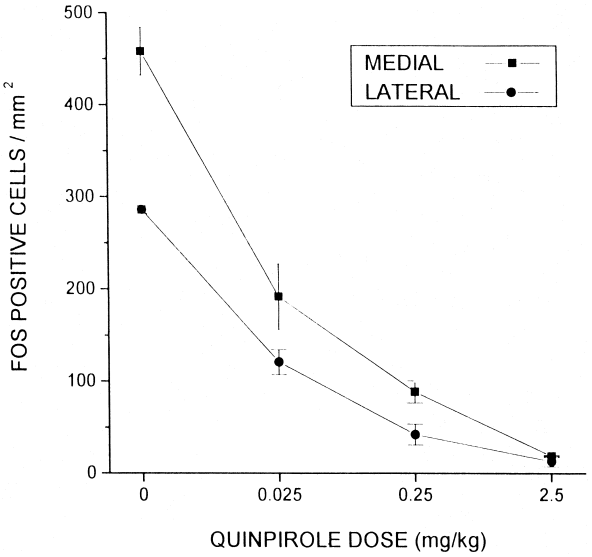


Fig. 1. Effects of quinpirole pretreatment on the Fos responses in the medial and the lateral striatum produced by injections of fenfluramine (25 mg/kg).

2. Materials and methods

2.1. Subjects

The subjects were 70 adult, male Sprague–Dawley derived rats that were obtained from a colony maintained by the Psychology Department of the University of Illinois at Chicago. Animals weighed between 280 and 320 g at the time of injection. Subjects were housed individually in standard, suspended wire mesh cages and were allowed ad libitum access to rat chow and water. A 12:12 h light–dark cycle was maintained throughout the experiment with the temperature regulated between 20–22°C.

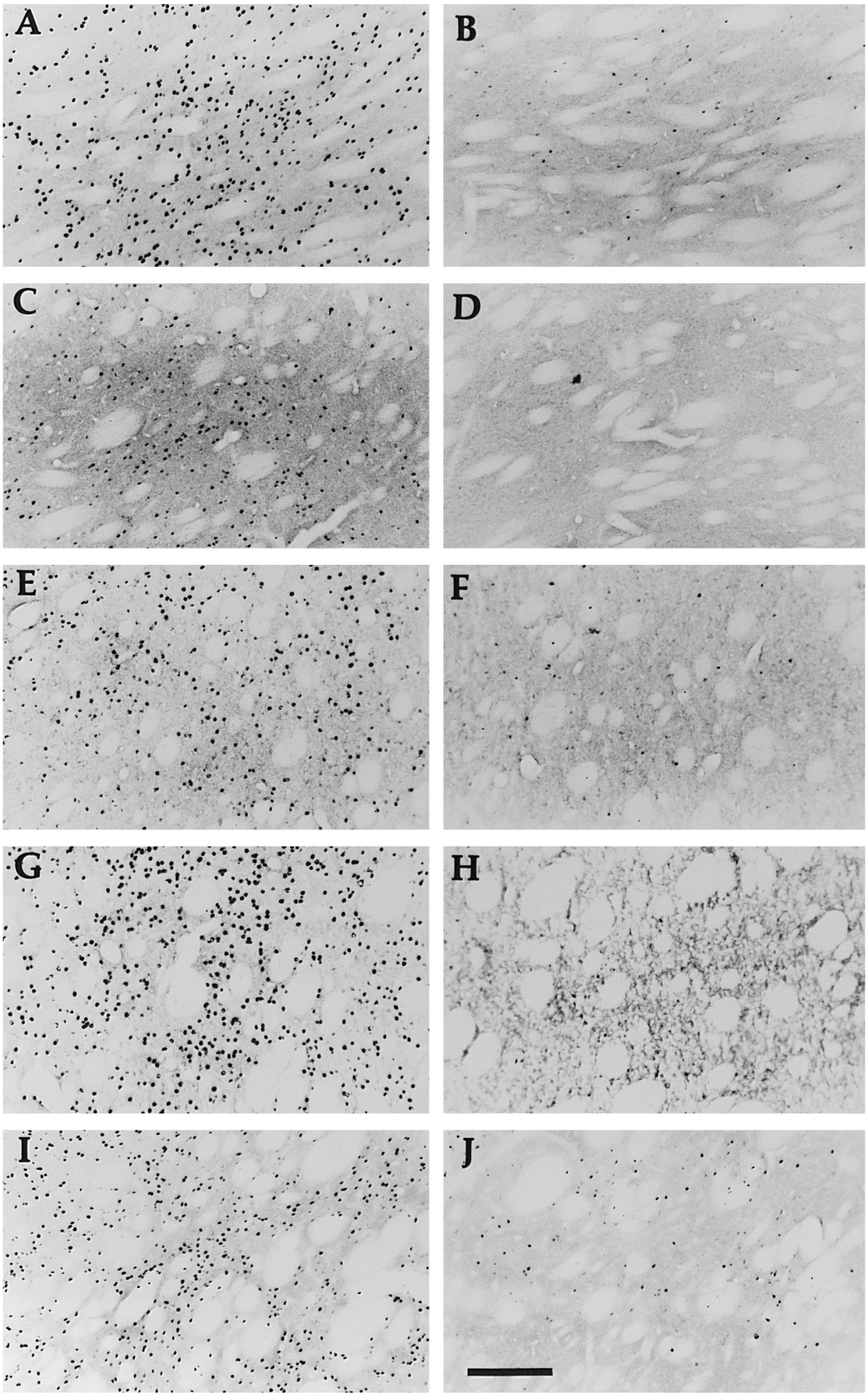
2.2. Drugs

Quinpirole hydrochloride (mol. wt. = 255.8) was obtained from Eli Lilly (Indianapolis, IN). Fenfluramine hydrochloride (mol. wt. = 267.7), pilocarpine hydrochloride (mol. wt. = 244.7) and morphine sulfate (mol. wt. = 668.8) were obtained from Sigma (St. Louis, MO). TFMPP (mol. wt. = 266.7) and DOI (mol. wt. = 357.6) were obtained from Research Biochemicals International (Natick, MA) and RU-24969 (mol. wt. = 276.1) from Roussel UCLAF (Romainville, France). All compounds were dissolved in distilled water and were administered subcutaneously at a constant volume of 1 ml/kg body weight.

2.3. Drug treatments

A dose–response curve was generated for the effects of quinpirole on the striatal Fos response induced by fenfluramine; the effects of quinpirole on the responses to the remaining drugs were evaluated at a single dose chosen on the basis of previous studies of D_1/D_2 interactions in intact animals (LaHoste et al., 1993; Wirtshafter and Asin, 1994; Wirtshafter et al., 1997). In the first experiment, groups of 3–4 animals were injected with either quinpirole (0.025, 0.25 or 2.5 mg/kg) or its vehicle and 15 min later were injected with fenfluramine (25.0 mg/kg). In the remaining studies, rats were injected with either distilled water or with quinpirole at a dose of 2.5 mg/kg and 15 min later were injected with either fenfluramine (25 mg/kg), TFMPP (5.0 mg/kg), RU-24969 (5.0 mg/kg), DOI (6.64 mg/kg), pilocarpine (50.0 mg/kg), morphine (5.0 mg/kg) or vehicle; seven to ten animals were run under each of these conditions. Doses of these compounds were selected based on pilot studies indicating that they

Fig. 2. Photomicrographs of the medial striatum of rats injected with fenfluramine (25.0 mg/kg; A and B), TFMPP (5.0 mg/kg; C and D), DOI (6.64 mg/kg; E and F), RU-24969 (5.0 mg/kg; G and H) or pilocarpine (50.0 mg/kg; I and J). The left hand column (panels A, C, E, G, and I) displays fields from animals pretreated with saline and the right hand column (panels B, D, F, H, and J) fields from animals pretreated with quinpirole (2.5 mg/kg). Scale bar represents 200 μm.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were sufficient to induce clear Fos expression within the striatum.

2.4. Perfusion and immunochemistry

2 h following the second injection, animals were deeply anesthetized with sodium pentobarbital (100 mg/kg) and perfused transcardially at room temperature with 100 ml of normal saline followed by 500 ml of a 10% formalin solution prepared in phosphate buffer (pH 7.2). The brains were then rapidly removed and placed in fresh fixative for 2 h at 4°C after which they were transferred to a solution of 20% sucrose in phosphate buffered saline (PBS) where they were stored overnight at 4°C. The following day, the brains were rapidly frozen and 35-μm cryostat sections were taken through the region of the striatum rostral to the decussation of the anterior commissure. The sections were then rinsed several times in PBS containing 0.2% Triton X-100 and 0.05% sodium azide (PBST) and then placed for 72 h at 4°C in primary sheep anti-Fos serum (Cambridge Research Biochemicals, Wilmington, DE; OA-11-824) prepared at a dilution of 2000:1 in PBST containing 2% normal goat serum. Sections were then rinsed several times in PBST and then placed for 2 h at room temperature in biotinylated secondary rabbit anti-sheep serum (Vector Laboratories, Burlingame, CA) diluted 200:1 in PBST containing 2% blocking serum. After further rinsing, the sections were transferred to the Vectastain Elite ABC reagent (Vector Laboratories) for a period of 90 min. The sections were then rinsed thoroughly in PBS and developed in a solution of 0.05% diaminobenzadine, 0.01% hydrogen peroxide and 0.08% nickel chloride prepared in 0.1 M Tris buffer at a pH of 7.0. The reaction was terminated by transferring the sections to PBS after which the tissue was mounted, dried and coverslipped. In control sections in which the primary antibody was omitted, no nuclear staining was seen within the striatum.

2.5. Quantitative analysis

Data from the quinpirole/fenfluramine dose response study were analyzed using a Leica Quantimet image analysis system. Fields measuring 1.1×1.0 mm located in the medial and in the lateroventral regions of the striatum at a level slightly rostral to the closure of the longitudinal fissure in the septum were digitized. Cells were automatically detected in the captured images based on their staining intensity, size and aspect ratio; detection parameters were kept the same for all of the sections examined and were chosen based on extensive preliminary study. Cells in the remaining studies were counted manually in fields measuring 1.2×1.2 mm with the aid of a camera lucida. The data were analyzed using analyses of variance (ANOVA) followed, where appropriate, by Sheffe's test.

3. Results

Following injections of either vehicle followed by vehicle, or quinpirole (2.5 mg/kg) followed by vehicle, the striatum was virtually devoid of Fos-positive cells (data not shown). Treatment with fenfluramine induced a marked induction of *fos*-like immunoreactivity which appeared relatively homogenous in character. As shown in Figs. 1 and 2A–B, quinpirole produced a marked, dose-dependent suppression of the response to fenfluramine in both the medial ($F(3,10) = 40.0$, $P < 0.00001$). and the lateral ($F(3,10) = 86.2$, $P < 0.000001$) striatum. Post hoc comparisons indicated that, in both striatal regions, all doses of quinpirole significantly suppressed the Fos response rela-

Table 1
Effects of quinpirole pretreatment on drug-induced *fos* expression in the rat striatum

Pretreatment	Treatment (mg/kg)	*n*	Medial (cells/mm^2 ± S.E.M.)	Lateral (cells/mm^2 ± S.E.M.)
Vehicle	Fenfluramine (25.0)	4	441 ± 33	208 ± 14
Quinpirole	Fenfluramine (25.0)	3	13 ± 1[a]	30 ± 10[a]
Vehicle	DOI (6.64)	5	276 ± 39	131 ± 9
Quinpirole	DOI (6.64)	3	63 ± 9[b]	34 ± 6[a]
Vehicle	TFMPP (5.0)	5	474 ± 65	115 ± 12
Quinpirole	TFMPP (5.0)	5	4 ± 1[a]	4 ± 1[a]
Vehicle	RU24969 (5.0)	5	864 ± 89	270 ± 34
Quinpirole	RU24969 (5.0)	5	56 ± 17[a]	14 ± 9[a]
Vehicle	Pilocarpine (50.0)	4	958 ± 119	286 ± 28
Quinpirole	Pilocarpine (50.0)	5	301 ± 55[b]	43 ± 4[a]
Vehicle	Morphine (5.0)	5	105 ± 20	71 ± 18
Quinpirole	Morphine (5.0)	4	10 ± 3[b]	23 ± 11

[a] $P < 0.0001$ vs. vehicle pretreated group.
[b] $P < 0.01$ vs. vehicle pretreated group.

tive to subjects pretreated with saline ($P < 0.001$). The suppressions produced by the highest dose of quinpirole were also significantly larger than those produced by the lowest dose ($P < 0.02$).

Injections of TFMPP, RU-24969, DOI and pilocarpine all induced moderate to robust Fos responses within the striatum and a clear, but somewhat smaller, response was observed after morphine. The striatal response to all of these compounds could, however, be drastically attenuated by pretreatment with 2.5 mg/kg of quinpirole (Fig. 2, Table 1). As shown in Table 1, quinpirole significantly attenuated the responses to all of the drugs studied in both the medial and lateral striatum, with the sole exception of the response to morphine in the lateral striatum, where a substantial trend was none the less observed. The above described ability of quinpirole to suppress fenfluramine induced Fos was also confirmed in this series of experiments using different animals and a different quantification technique than that employed previously (Table 1).

4. Discussion

The present results confirm previous reports that striatal Fos expression can be induced by administration of agonists at 5-HT, μ-opioid and muscarinic cholinergic receptors (Bernard et al., 1993; Cook and Wirtshafter, 1995; Hughes and Dragunow, 1993; Leslie et al., 1993; Liu et al., 1994; Rouillard et al., 1996; Torres and Rivier, 1994). It is likely that at least two different mechanisms are involved in mediating the effects of the 5-HT receptor agonists, since other studies have shown that the 5-HT_2 antagonist ritanserin is able to antagonize the Fos expression induced by DOI, but not that induced by TFMPP or RU-24969 (Cook and Wirtshafter, 1995; Leslie et al., 1993).

Previous studies have demonstrated that quinpirole is able to markedly potentiate the striatal Fos expression induced by SKF-38393 or by low doses of A-77636 (Gerfen et al., 1995; LaHoste et al., 1993; Paul et al., 1992; Wirtshafter and Asin, 1994). In intact animals, combined treatment with quinpirole and dopamine D_1 receptor agonists induces patchy patterns of staining (LaHoste et al., 1993; Wirtshafter and Asin, 1994; Wirtshafter et al., 1997), similar to those observed after treatment with nonselective dopamine receptor agonists (Asin et al., 1996; Graybiel et al., 1990). The major contribution of the current study is the demonstration that, in contrast to these effects, quinpirole pretreatment markedly attenuates the striatal Fos-like immunoreactivity induced by pilocarpine, morphine and several serotonergic compounds. These suppressive effects were apparent in both the medial and the lateroventral striatum and were obtained using quinpirole at a dose similar to those reported to potentiate D_1 receptor agonist induced Fos expression in intact animals (LaHoste et al., 1993; Wirtshafter and Asin, 1994). These findings demonstrate that quinpirole can have different effects on the Fos expression induced by different drugs and strongly support the view that all of the agonists studied here induce striatal Fos expression through mechanisms that are dependent upon dopaminergic function. In other studies (Struthers and Wirtshafter, 1998) we have shown that quinpirole is also able to suppress the striatal Fos expression induced by forced locomotor activity, an effect which may be related to those reported here.

A number of studies have shown that striatal dopamine release or turnover can be increased by injections of all of the 5-HT receptor agonists employed in the current study (Benloucif and Galloway, 1991; Boulenguez et al., 1996; De Deurwaerdere et al., 1995; Gaggi et al., 1997), as well as by injections of opioid (Di Chiara and Imperato, 1988) and muscarinic (Raiteri et al., 1984) receptor agonists. These findings suggest that the ability of these drugs to induce Fos expression might be secondary to their ability to release dopamine. This possibility is supported by findings that the selective dopamine D_1 receptor antagonist SCH-23390 is able to antagonize the Fos expression induced by stimulation of either 5-HT or opioid receptors (Cook and Wirtshafter, 1995; Liu et al., 1994; Rouillard et al., 1996) and we have found that this drug is also able to attenuate pilocarpine induced Fos expression (in preparation). These observations are also consistent with the possibility that some of the drugs examined here may induce Fos expression through a direct action on striatal cell bodies with stimulation of dopamine receptors playing a primarily permissive role in these effects.

If the striatal Fos expression induced by 5-HT, opioid, and muscarinic receptor agonists is indeed dependent upon stimulation of dopamine D_1 receptors, one would expect that any treatment which reduced D_1 receptor stimulation would antagonize these responses. One interpretation of the current results, then, is that quinpirole may have acted as an 'indirect D_1 receptor antagonist' as a result of its ability to stimulate D_2-like autoreceptors thereby attenuating basal or drug stimulated dopamine release. Another possibility is that quinpirole may have suppressed Fos expression through a direct action on postsynaptic dopamine D_2 receptors located on striatal neurons. For example, whereas cAMP mediated protein phosphorylation is believed to play an important role in activation of the c-*fos* gene (Ghosh et al., 1993; Robertson et al., 1995), stimulation of dopamine D_2 receptors is often linked to an inhibition of cAMP formation (Vallar and Meldolesi, 1989). Since D_2 receptors are heterogeneously distributed in different populations of striatal neurons (Hersch et al., 1995; Le Moine and Bloch, 1995), this latter theory would require that the agents studied here induce Fos expression principally in cells containing D_2-like receptors. It should be noted in this context that dopamine agonists appear to induce Fos-like immunoreactivity mainly in striatonigral neurons (Cenci et al., 1992; Robertson et al., 1990), which

have been reported to express primarily D_1 receptors (Gerfen, 1992; Harrison et al., 1990). It is also possible that the effects of quinpirole may have been mediated through a presynaptically mediated suppression of corticostriatal transmission (Maura et al., 1998; Schwarcz et al., 1978; Yamamoto and Davy, 1992).

Although purely excitatory effects on Fos expression are observed when quinpirole is combined with SKF-38393 (Gerfen et al., 1995; LaHoste et al., 1993; Paul et al., 1992) or with a low dose of A-77636 (Wirtshafter and Asin, 1994), a more complex pattern is seen when this drug is coadministered with higher doses of A-77636, which induce substantial Fos-like immunoreactivity by themselves. Under these conditions, quinpirole enhances A-77636 induced staining in the lateral striatum, but actually tends to inhibit it in the medial portion of the rostral striatum (Wirtshafter and Asin, 1994). A more fine grained analysis indicates that quinpirole converts the locally random staining pattern induced by high doses of A-77636 into a markedly 'patchy' pattern (Wirtshafter and Asin, 1994), an effect which, in the rostral-medial striatum, appears to result from a suppression of staining within the matrix compartment, combined with a tendency towards a potentiation in the striosomal compartment (Wirtshafter et al., 1997). Further studies will be needed to determine whether these regionally and compartmentally specific inhibitory effects are related to the global suppressive effects observed in the current study. All of these findings do, however, indicate that stimulation of D_2-like receptors can influence striatal Fos expression in a number of different ways and serve to highlight the complexity of the role played by dopamine D_2 receptors in the functional organization of the striatum.

Acknowledgements

The authors thank Eli Lilly and Roussell UCLAF for their generous gifts of quinpirole and RU-24969, respectively. We also thank Dr. Karen Asin for her many helpful comments on this manuscript. These studies were supported by N.I.H. grant NS-33992.

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