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RAPID COMMUNICATION

Is Stimulation of Both D1 and D2 Receptors Necessary for the Expression of Dopamine-Mediated Behaviors?

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WHITE, F. J., L. M. BEDNARZ, S. R. WACHTEL, S. HJORTH AND R. J. BRODERSON. *Is stimulation of both D1 and D2 dopamine receptors necessary for the expression of dopamine-mediated behaviors?* PHARMACOL BIOCHEM BEHAV **30**(1) 189–193, 1988.—Recent electrophysiological findings have indicated that D1 dopamine (DA) receptor stimulation by SKF 38393 enables the inhibitory effects of the D2 receptor agonist quinpirole on nucleus accumbens neurons. In the present study, a similar interaction was shown for quinpirole-induced stereotyped behaviors. In control rats, SKF 38393 enhanced the stereotyped responses induced by quinpirole, converting lower-level stereotypies (sniffing and rearing) to more intense oral behaviors (licking and gnawing). In rats depleted of DA (79% reduction) by the tyrosine hydroxylase inhibitor α-methyl-p-tyrosine (AMPT), the behavioral effects of quinpirole were abolished. However, quinpirole-induced stereotyped responses were reinstated by SKF 38393 suggesting that D1 receptor stimulation by endogenous DA is necessary for D2 receptor-mediated stereotyped responses (sniffing, rearing). In support of this suggestion, stereotyped behaviors produced by the non-selective D1/D2 agonist apomorphine were not affected by AMPT pretreatment. In contrast to the effects of quinpirole, the ability of SKF 38393 to induce grooming responses was not abolished by AMPT pretreatment or by combined pretreatment with AMPT and reserpine (>99% DA depletion). These results indicate that D1 receptor stimulation enables D2 receptor-mediated stereotyped responses, but that this relationship is not reciprocal since D2 receptor stimulation is not necessary for the grooming response elicited by SKF 38393.

D1 Dopamine receptors D2 Dopamine receptors SKF 38393 Quinpirole

THE existence of two dopamine (DA) receptor subtypes, referred to as D1 and D2, is now well established. The D1 subtype is defined as that receptor at which DA stimulates adenylate cyclase to increase cyclic AMP formation whereas the D2 receptor is either not coupled to adenylate cyclase [10,15] or, in some tissues, may inhibit the enzyme and reduce cyclic AMP formation (see [4] and [14] for reviews).

Recently, several investigators have demonstrated synergistic interactions between D1 and D2 receptors in both electrophysiological and behavioral studies (see [4] for review). Our laboratory has reported electrophysiological evidence suggesting a synergistic interaction between D1 and D2 agonists in the control of neuronal activity within the rat nucleus accumbens (NAc) [18–22]. On a subpopulation of NAc cells which were inhibited by iontophoretic application of both the selective D1 agonist SKF 38393 and the selective D2 agonist LY 141865, simultaneous administration of these two agonists inhibited neuronal activity to a significantly greater extent than either agonist alone [20,22]. More recently, we have reported that SKF 38393 can enhance the inhibitory effects of the D2 agonist quinpirole (LY 171555, the active enantiomer of LY 141865), even on a subset of NAc cells that were not responsive to SKF 38393 administered alone [18,22]. Moreover, following acute depletion of endogenous DA produced by the tyrosine hydroxylase inhibitor α-methyl-p-tyrosine (AMPT), the ability of quinpirole to inhibit NAc neuronal activity was greatly attenuated. However, concurrent iontophoretic administration of the D1 selective agonist SKF 38393, at currents which alone produced little inhibition, "reinstated" the inhibitory effect

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of quinpirole on the same neurons [18,22]. This suggests that endogenous DA may normally act at D1 receptors to provide an enabling action for D2 receptor-mediated inhibition of many NAc neurons.

Behavioral evidence also suggests a synergistic interaction between D1 and D2 receptors. Gershanik *et al.* [6] first reported that reversal of reserpine-induced akinesia required the co-administration of D1 and D2 selective agonists and that inhibition of DA synthesis attenuated the rotational response to D2 agonists, but not to SKF 38393, in rats with unilateral 6-hydroxydopamine lesions of the nigrostriatal DA system. Similar synergistic interactions between D1 and D2 receptors have been demonstrated using standard DA-dependent behaviors such as locomotor activity [3,9] and stereotypy [1, 3, 11, 17] in intact rats as well as rotation in rats with quinolinic acid-induced lesions of the striatum [2]. In the present experiments, such behavioral interactions have been examined further and evidence is presented which suggests that D1 receptor stimulation enables D2 receptor-mediated behavioral responses in a manner similar to the enabling effect observed in our electrophysiological studies of NAc neurons [18,22]. In addition, we report herein that the D1 receptor-mediated grooming response elicited by SKF 38393 [12,13], like the inhibitory effect of this D1 agonist on NAc neurons [22], does not require D2 receptor stimulation, suggesting that D2 receptor stimulation is not necessary for certain functional responses mediated by D1 receptors. Preliminary accounts of these findings have previously been published in abstract form [16, 19, 21].

METHOD

Animals

Male Sprague-Dawley rats weighing between 225–325 g were used in all experiments. The rats were housed in groups of 2–4/cage with food and water available ad lib and were maintained on a 12/12 hr (07:00 on/19:00 off) light/dark cycle.

Behavioral Tests

For the first experiment, rats were injected subcutaneously (SC) with either the selective D1 agonist SKF 38393 HCl (Smith, Kline and French, USA), the selective D2 agonist quinpirole HCl (Eli Lilly and Co., USA), the non-selective D1/D2 agonist apomorphine HCl (Sigma Chemical Co., USA) or a normal saline solution (0.9% NaCl) and were scored with respect to the time spent grooming and the degree of stereotyped behaviors. All observers were trained and blind to the drug treatment. Prior to drug treatment, each animal was habituated to the observation box for 2.0 hr. The observation box was constructed from clear Plexiglas 60 L×60 W×30 H cm with a wire mesh floor resting above standard laboratory bedding.

Each rat was observed individually and continuously for a period of 45 min which began 5 min after the drug injection. The results presented herein are based only on the 15–30 min interval scores (i.e., from 20–35 min post-injection) because most effects were maximal at this time. Each animal was scored every 5 min for the degree of stereotypy, based upon the standard 0–6 rating scale of Creese and Iversen [5], and the amount of time spent grooming (in sec). The grooming scores were based on the total amount of grooming during the 15 min observation period whereas the stereotypy score is based on the mean score from the three 5 min bins within the 15 min observation period. Data from stereotypy measures were analyzed with the Mann-Whitney U-test whereas grooming time data were analyzed with Student's *t*-test.

In the first experiment, an initial phase of testing consisted of control (0.9% NaCl), quinpirole (2 mg/kg), SKF 38393 (16 mg/kg), apomorphine (2 mg/kg), and SKF 38393 (16 mg/kg) plus quinpirole (2 mg/kg) conditions. Each rat was tested only once per week. The various drug treatments were randomly administered for each rat. A second phase of testing involved pretreating each animal with AMPT to obtain an acute depletion of DA (and other catecholamines) and then testing with one of the above drug treatments. The AMPT was administered in two injections: 300 mg/kg (IP) four hours prior to observation and 200 mg/kg (IP) two hours prior to observation, as previously described [3].

In a second experiment, a separate group of rats was pretreated with a combination of reserpine and AMPT. Reserpine (5 mg/kg, IP) was administered 5 hours prior to AMPT (250 mg/kg, IP). One hour following the AMPT injection, one sub-group (n=8) of these pretreated rats was observed for grooming responses to SKF 38393 (16 mg/kg, SC) whereas a second sub-group (n=5) received saline injections. The rats were placed into Plexiglas rectangular boxes (30 L×20 W×25 H cm) and the amount of time spent grooming was determined as described above.

Biochemical Determinations

To determine the degree of DA depletion produced by the two treatment regimens used in the behavioral studies, separate groups of rats received the identical treatment regimens described above. One group received AMPT only whereas the other received the combination of reserpine plus AMPT. The rats which received only AMPT were sacrificed two hours after the last injection whereas those which received reserpine plus AMPT were sacrificed one hour after the AMPT injection. Rats were sacrificed by decapitation, the brains rapidly removed and the striata were dissected on ice-cooled Petri dishes. The levels of DA and the two DA metabolites dihydroxyphenylacetic acid (DOPAC) and homovanillic acid (HVA) were determined by standard HPLC techniques (electrochemical detection). For details, see Hjorth *et al.* [8] and references included therein.

RESULTS

The results of the first experiment are presented in Fig. 1. The relatively large dose of quinpirole was chosen to insure that the lack of a "full-blown" stereotyped response was not due to ineffective doses. Note that, as previously reported [1, 3, 7], the stereotypy scores for quinpirole (approximately 4) were always lower than those for apomorphine because quinpirole never caused the more intense oral forms of stereotypy, i.e., focused licking and gnawing (scores of 5–6), which were always observed with apomorphine (Fig. 1A). In fact, even at higher doses (4 mg/kg), quinpirole still only induced lower level stereotyped responses, primarily focused sniffing and rearing (data not shown).

In contrast to quinpirole, SKF 38393 failed to induce stereotyped behaviors, a finding consistent with many previous reports (see [4] for review). However, when administered together with quinpirole, SKF 38393 enhanced the intensity of the stereotypy induced by quinpirole, changing the characteristic response from sniffing and rearing to a more focused oral stereotypy, typically expressed as licking and, less frequently, gnawing. In fact, co-administration of quinpirole and SKF 38393 significantly increased the stereotypy

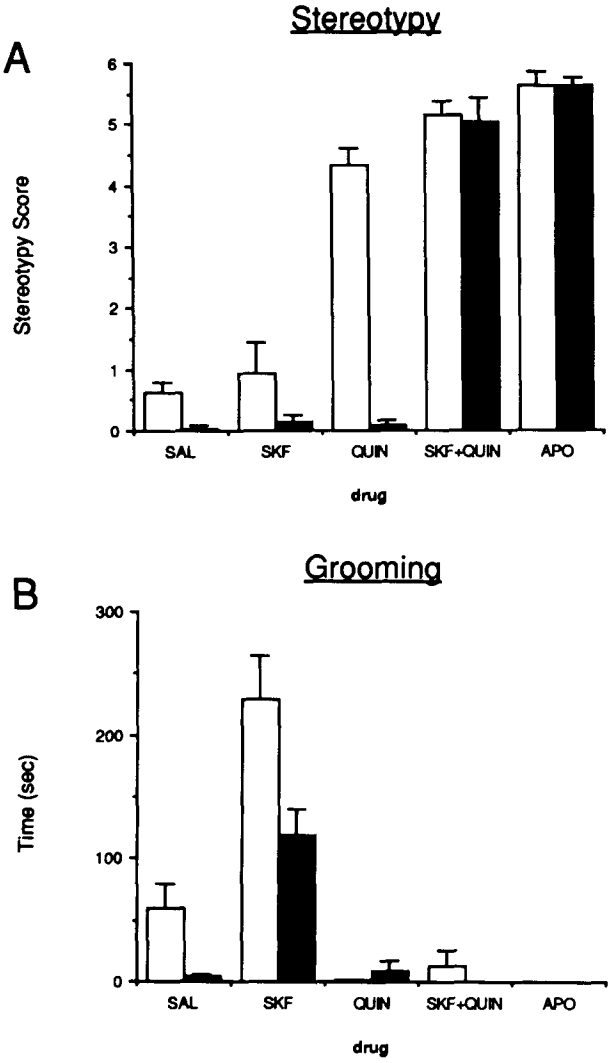

FIG. 1. The ability of various drug treatments to induce stereotyped behaviors (A) and grooming (B) in normal rats and rats depleted of dopamine by α-methyl-para-tyrosine (AMPT). Both quinpirole (QUIN) and apomorphine (APO) were administered at a dose of 2.0 mg/kg whereas SKF 38393 was administered at 16 mg/kg. Each bar represents the mean±the S.E.M. obtained from 8 rats. (A) Stereotypy ratings for QUIN, APO, AMPT+APO, SKF+QUIN and AMPT+SKF+QUIN were all significantly higher than saline (SAL, $p<0.01$). The SKF+QUIN treatment was not significantly different from APO although the APO and QUIN groups were significantly different from one another ($p<0.01$). The effects of QUIN+SKF combination were significantly greater than QUIN alone ($p<0.05$). AMPT pretreatment significantly reduced the effects of QUIN ($p<0.01$); however, the SKF+QUIN combination reinstated the stereotyped behaviors in the AMPT group. (B) SKF 38393 significantly enhanced grooming time and this effect was partially reduced by AMPT pretreatment ($p<0.05$). Open bars: no pretreatment; dark bars: AMPT.

score as compared to quinpirole alone ($p<0.01$) to a level which was also not significantly different from that observed with apomorphine.

Following AMPT pretreatment, the ability of quinpirole to produce stereotyped responses was completely abolished. More importantly, SKF 38393 reinstated the behavioral effects of quinpirole in the AMPT pretreated rats. In contrast

TABLE 1

EFFECTS OF α-METHYL-PARA-TYROSINE, ALONE AND IN COMBINATION WITH RESERPINE, ON STRIATAL LEVELS OF DOPAMINE AND ITS METABOLITES[1]

Treatment	DA	DOPAC	HVA
Control (n=5)	8779 ± 140	861 ± 57	877 ± 43
AMPT (n=4)	1813 ± 156 (21%)*	216 ± 42 (25%)	331 ± 45 (38%)
Reserpine + AMPT (n=4)	45 ± 4.1 (0.5%)	61 ± 5.9 (7%)	177 ± 47 (20%)

[1]All data are presented as ng/g striatal tissue. All treatment values are significantly less than controls ($p<0.01$).

*Numbers in parentheses indicate the percentage of control values.

to the D2 selective agonist quinpirole, AMPT pretreatment failed to reduce the stereotyped behaviors induced by the non-selective D1/D2 DA agonist apomorphine.

As previously reported [13], SKF 38393 caused a significant increase, as compared to saline-treated control rats, $t(14)=31.9$, $p<0.001$, in the amount of time spent grooming. This was a highly robust response in that it was observed in every rat tested (range: 93–376 sec; median=265 sec). This effect was not observed following administration of either quinpirole or apomorphine (Fig. 1B). In rats pretreated with AMPT, all grooming behavior was abolished. However, SKF 38393 restored grooming to a level which was significantly greater than that observed in non-pretreated, saline control rats, $t(14)=15.2$, $p<0.01$, but significantly less than that observed in non-pretreated rats that had received SKF 38393, $t(14)=2.57$, $p<0.05$.

Analysis of striatal catecholamine levels revealed that the AMPT pretreatment regimen employed in the behavioral tests resulted in a 79% depletion of DA (Table 1). To insure that the grooming response elicited by SKF 38393 in these rats was not influenced by the residual (21%) DA, a second experiment was conducted in which a separate group of rats received a combined reserpine/AMPT treatment to deplete DA more completely. This pretreatment resulted in a 99.5% depletion of striatal DA (Table 1). However, as shown in Fig. 2, SKF 38393 still significantly enhanced grooming responses as compared to reserpine/AMPT pretreated rats that received saline injections, $t(11)=17.1$, $p<0.001$. The amount of grooming observed in the reserpine/AMPT pretreated rats which received SKF 38393 was not significantly different from that observed in normal, saline-injected rats, i.e., SKF 38393 reinstated control levels of grooming. Once again, the response to SKF 38393 was robust in that all animals engaged in grooming behavior (range: 35–240 sec; median=54 sec).

DISCUSSION

It has recently been suggested that there exists an obligatory D1/D2 DA receptor interaction in the generation of DA agonist-induced behavioral expression [3]. The present findings support the hypothesis that D1 and D2 receptors function in a synergistic manner to regulate the intensity and form of stereotyped behavior produced by DA agonists in

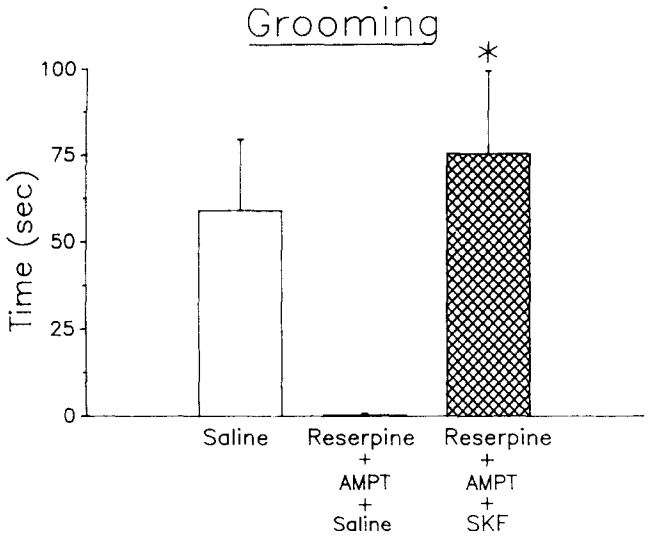

FIG. 2. Grooming behavior induced by a 16 mg/kg dose of SKF 38393 (n=8) as compared to saline (n=5) in rats pretreated with a combination of reserpine (5 mg/kg) and α-methyl-para-tyrosine (AMPT, 250 mg/kg) and in non-treated controls (n=8). In rats that received reserpine/AMPT, SKF 38393 induced a significant increase in grooming as compared to saline ($p<0.001$).

the rat [3], but, more importantly, they also indicate that the interaction takes the form of an absolute requirement of D1 receptor stimulation for postsynaptic D2 receptor-mediated behaviors. Moreover, these findings also indicate that this requirement is not reciprocated since D2 receptor stimulation was not required for at least one form of D1-mediated behavioral expression, i.e., grooming.

It is important to note that the stereotyped behavior produced by the selective D2 agonist quinpirole is less intense than that produced by the non-selective D1/D2 agonist apomorphine. Instead of the stereotyped gnawing behavior observed with apomorphine, quinpirole only induced lower intensity stereotyped responses, primarily focused sniffing and rearing in one location within the observation chamber. This finding differs from that of Braun and Chase [3] who reported that quinpirole produced dose-related increases in locomotor activity with little stereotyped behavior, but are identical to the effects of quinpirole reported by Hess *et al.* [7] and Arnt *et al.* [1]. In addition, the effects observed with quinpirole are similar to those reported with another D2 selective agonist, RU 24213 [12]. The lack of more intense stereotyped responses was not due to the dose chosen since 2 mg/kg is a relatively high dose and since even extremely high doses of quinpirole (48 mg/kg) reportedly fail to induce focused licking and gnawing [17]. However, when SKF 38393 and quinpirole were administered together, the stereotypic behaviors were more similar in quality and intensity to those produced by apomorphine, supporting the suggestion of Braun and Chase [3] that simultaneous stimulation of both D1 and D2 behaviors is required to produce maximal stereotyped behavior.

As several other investigators have recently observed [2, 3, 6, 7], acute depletion of DA produced by the tyrosine hydroxylase inhibitor AMPT significantly attenuated the behavioral effects of a D2 agonist. In the present study, pretreatment with AMPT, at a dose which produced approximately 79% striatal DA depletion, completely abolished the ability of quinpirole to produce stereotypic behaviors. The fact that co-administration of SKF 38393 and quinpirole reinstated the stereotypic response, as previously reported [3], indicates that a certain level of tonic D1 receptor stimulation is provided by endogenous DA under normal conditions and that this D1 receptor "tone" is necessary for D2 receptor agonists to produce the typical D2 receptor-mediated behaviors.

We have recently observed similar relationships between postsynaptic D1 and D2 receptors at the single cell level [18–22]. Originally, we reported that D1 and D2 agonists produced a synergistic inhibition of nucleus accumbens neurons [19,22]. More recently, we have observed that AMPT pretreatment also attenuated the inhibitory effects of iontophoretically administered quinpirole on NAc neurons and that SKF 38393 could "reinstate" the effects of quinpirole [18,22]. Similar findings have been reported for globus pallidus neurons following intravenous administration of D1 and D2 agonists in normal and AMPT pretreated rats [17]. We interpret these electrophysiological and behavioral results as indicating that D1 receptor stimulation enables the functional effects of postsynaptic D2 receptor stimulation.

To determine whether D2 receptor stimulation is also required for D1 receptor-mediated responses, we studied the effects of AMPT pretreatment on SKF 38393-induced grooming behavior. Depletion of DA by AMPT pretreatment completely abolished normal levels of grooming observed in saline control rats. However, in contrast to the stereotyped behaviors induced by quinpirole, SKF 38393 was able to reinstate grooming to a level which was significantly greater than that observed in DA-depleted control rats, but significantly less than that observed in normal rats which received the same dose of SKF 38393. This finding could be interpreted to indicate that grooming behavior does not require D2 receptor stimulation and is, therefore, still present in DA depleted rats. However, it is also possible that D2 receptors in the acutely DA-depleted rat are more sensitive to DA than are D1 receptors, such that the 21% residual DA in the AMPT-treated group was sufficient to provide a necessary, albeit reduced, level of D2 receptor "tone" which therefore caused only a slightly diminished grooming response as compared to normal rats which received SKF 38393. To test this possibility further, additional studies were conducted in which DA levels were decreased by 99.5% with combined acute pretreatment with reserpine plus AMPT. Despite the severe akinesia produced by this treatment, SKF 38393 administration still induced sustained periods of grooming, resulting in mean values which were similar to those observed in normal rats. In fact, grooming was the only behavior in which these animals engaged. Therefore, D1 receptor stimulation resulted in the expression of grooming behavior, even in the near total absence of endogenous DA and, presumably, D2 receptor stimulation. Similarly, Gershanik *et al.* [4] reported that AMPT reduced the rotational effects of the D2 agonist LY 141865, but not those of SKF 38393, in nigral-lesioned rats. Moreover, we have preliminary evidence indicating that AMPT pretreatment failed to diminish significantly the inhibitory effects of SKF 38393 on NAc neurons [21].

In summary, the current findings regarding the DA receptor mechanisms responsible for stereotyped behaviors are similar to those obtained from our electrophysiological studies which indicated that postsynaptic D2 receptor-mediated functional responses are, in some manner, enabled by stimulation of the D1 receptor. Our results indicate that

this relationship is not reciprocal since D1 agonist-induced effects are not abolished, even by near total DA depletion. Taken together, the results of our behavioral and electrophysiological studies indicate that D1 receptor stimulation is necessary for the expression of postsynaptic DA receptor-mediated functional responses. Therefore, alterations of D1 receptor activity may play important roles in the pathophysiology of disorders of DA neurotransmission such as Parkinson's disease and schizophrenia as well as in their pharmacological treatment.

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REFERENCES

1. Arnt, J., J. Hyttel and J. Perregaard. Dopamine D-1 receptor agonists combined with the selective D-2 agonist quinpirole facilitate the expression of oral stereotyped behaviour in rats. *Eur J Pharmacol* **133:** 137–145, 1987.
2. Barone, P., T. A. Davis, A. R. Braun and T. N. Chase. Dopaminergic mechanisms and motor function: Characterization of D1 and D2 dopamine receptor interactions. *Eur J Pharmacol* **123:** 109–114, 1986.
3. Braun, A. and T. N. Chase. Obligatory D1/D2 receptor interaction in the generation of dopamine agonist related behaviors. *Eur J Pharmacol* **131:** 301–306, 1986.
4. Clark, D. and F. J. White. D1 dopamine receptor: The search for a function. *Synapse* **1:** 347–388, 1987.
5. Creese, I. and S. D. Iversen. The role of forebrain systems in amphetamine-induced stereotyped behavior in the rat. *Psychopharmacologia* **39:** 345–357, 1974.
6. Gershanik, O., R. E. Heikkila and R. C. Duvoisin. Behavioral correlates of dopamine receptor activation. *Neurology* **33:** 1489–1492, 1983.
7. Hess, E. J., L. J. Albers, H. Le and I. Creese. Effects of chronic SCH 23390 treatment on the biochemical and behavioral properties of D1 and D2 dopamine receptors: Potentiated behavioral responses to a D2 dopamine agonist after selective D1 dopamine receptor upregulation. *J Pharmacol Exp Ther* **238:** 846–854, 1986.
8. Hjorth, S., K. Svensson, A. Carlsson, H. Wikström and B. Andersson. Central dopaminergic properties of HW-165 and its enantiomers; *Trans*-octahydrobenzo(f)quinoline congeners of 3-PPP. *Naunyn Schmiedebergs Arch Pharmacol* **333:** 205–218, 1986.
9. Jackson, D. M. and M. Hashizume. Bromocriptine induces marked locomotor stimulation in dopamine-depleted mice when D1 dopamine receptors are stimulated with SKF 38393. *Psychopharmacology (Berlin)* **90:** 147–149, 1986.
10. Kelly, E. and S. R. Nahorski. Dopamine D-2 receptors inhibit D-1 stimulated cyclic AMP formation in striatum but not limbic forebrain. *Naunyn Schmiedebergs Arch Pharmacol* **335:** 508–512, 1987.
11. Mashurano, M. and J. L. Waddington. Stereotyped behavior in response to the selective D-2 dopamine receptor agonist RU 24213 is enhanced by pretreatment with the selective D-1 agonist SKF 38393. *Neuropharmacology* **25:** 947–949, 1986.
12. Molloy, A. G. and J. L. Waddington. Dopaminergic behaviour stereospecifically promoted by the D1 agonist R-SKF 38393 and selectively blocked by the D1 antagonist SCH 23390. *Psychopharmacology (Berlin)* **82:** 409–410, 1984.
13. Starr, B. S. and M. S. Starr. Differential effects of dopamine D1 and D2 agonists and antagonists on velocity of movement, rearing and grooming in the mouse: Implications for the roles of D1 and D2 receptors. *Neuropharmacology* **25:** 455–463, 1986.
14. Stoof, J. C. and J. W. Kebabian. Two dopamine receptors: Biochemistry, physiology and pharmacology. *Life Sci* **35:** 2281–2296, 1984.
15. Stoof, J. C. and P. F. H. M. Verheijden. D-2 receptor stimulation inhibits cyclic AMP formation brought about by D-1 receptor stimulation in rat neostriatum but not nucleus accumbens. *Eur J Pharmacol* **129:** 205–206, 1987.
16. Wachtel, S. R., L. M. Bednarz, R. J. Brooderson, S. Hjorth and F. J. White. D-1 dopamine receptor stimulation enables functional responses to D-2 dopamine receptor agonists. *Soc Neurosci Abstr* **13:** 910, 1987.
17. Walters, J. R., D. A. Bergstrom, J. H. Carlson, T. N. Chase and A. R. Braun. D_1 dopamine receptor activation required for postsynaptic expression of D_2 agonist effects. *Science* **236:** 719–722, 1987.
18. White, F. J. D1 dopamine receptor stimulation enables the inhibition of nucleus accumbens neurons by a D2 receptor agonist. *Eur J Pharmacol* **135:** 101–105, 1987.
19. White, F. J. Electrophysiological investigations of the D-1 dopamine receptor. *Clin Neuropharmacol* **9:** 29–31, 1986.
20. White, F. J. and R. Y. Wang. Electrophysiological evidence for the existence of both D1 and D2 dopamine receptors in the rat nucleus accumbens. *J Neurosci* **6:** 274–280, 1986.
21. White, F. J., S. R. Wachtel and L. M. Bednarz. D-1 receptor stimulation enables the electrophysiological and behavioral effects of D-2 dopamine receptor agonists. *Abstr Seventh Eur Winter Conf Brain Res* **7:** 78, 1987.
22. White, F. J., S. R. Wachtel, P. A. Johansen and L. C. Einhorn. Electrophysiological studies in the rat mesoaccumbens dopamine system: Focus on dopamine receptor subtypes, interactions and the effects of cocaine. In: *Neurophysiology of Dopaminergic Systems: Current Status and Future Perspectives*, edited by L. A. Chiodo and A. S. Freeman. Detroit: Lakeshore Press, 1987, in press.