Effects of Full D1 Dopamine Receptor Agonists on Firing Rates in the Globus Pallidus and Substantia Nigra Pars Compacta In Vivo: Tests for D1 Receptor Selectivity and Comparisons to the Partial Agonist SKF 38393

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ABSTRACT
Many studies have used the D1 agonist SKF 38393 to characterize D1 receptor influences on firing rates in basal ganglia nuclei in vivo. However, SKF 38393 is a partial agonist and so may not be ideal for delineating D1 receptor effects. This study characterizes the effects of four full D1 agonists, SKF 82958 (chloro-APB), SKF 81297 (6-chloro-PB), dihydrexidine and A-77636, on the firing rates of midbrain dopamine and globus pallidus neurons. Recordings were done in fully anesthetized or paralyzed, locally anesthetized rats, and drugs were given systemically intravenously. Dihydrexidine, SKF 81297 and A-77636 were free of rate effects on midbrain dopamine neurons (up to 10.2 mg/kg) and also did not antagonize the inhibitory effects of quinpirole. In contrast, SKF 82958 strongly inhibited dopamine cells through activation of D2 autoreceptors (ED50 = 0.70 mg/kg). Of these drugs, SKF 82958 also was the only one to increase pallidal unit firing rates when given alone (at 5.0 but not 1.0 mg/kg); the other compounds appeared to be selective for postsynaptic D1 receptors. The results suggest that SKF 82958 may be more properly classified as a mixed D1/D2 agonist. In addition, all four agonists strongly potentiated the pallidal response to quinpirole, demonstrating a D1 receptor potentiation of D2 receptor effects. The results support the role of D1 receptors in the midbrain and globus pallidus as previously characterized with SKF 38393. The similar actions of partial and full D1 agonists in these systems support evidence for a D1 receptor reserve and possibly an effector system other than adenylate cyclase.

Receptors for the neurotransmitter DA fall into two types, the D1 and D2 receptor subfamilies, distinguished biochemically by their opposing actions on adenylate cyclase (Kebabian and Calne, 1979). These two receptor types are also distinguished by many pharmacological agents. The prototypical selective D1 agonist, the substituted benzazepine SKF 38393 (Setler et al., 1978) and its selective antagonist derivative SCH 23390 (Hyttel, 1983; Iorio et al., 1983) have allowed the specific pharmacological investigation of D1 receptor functions (Clark and White, 1987). SKF 38393 is selective for D1 over D2 receptors in in vitro binding assays (Andersen et al., 1985; Lovenberg et al., 1989; Sibley et al., 1982) and has been widely used in vivo to examine D1 receptor influences on behavior (Braun and Chase, 1986; Gershank et al., 1983; Molloy and Waddington, 1984; Setler et al., 1978), as well as influences on the physiology of the basal ganglia, several nuclei of which express D1 receptors (Boyson et al., 1986; Dearry et al., 1990; Yung et al., 1995). SKF 38393 has been shown to inhibit striatal neurons when applied iontophoretically (Hu and Wang, 1988), and systemic administration excites subthalamic nucleus neurons (Kreiss et al., 1996) and potentiates the excitatory effect of D2 agonists on GP neurons, although alone it is without consistent effect on these latter cells (Carlson et al., 1987a; Walters et al., 1987). Notably, SKF 38393 does not have consistent or robust effects on DAergic neurons of the SNPC in normal animals (Carlson et al., 1987b; Wachtel et al., 1989), in accord with the D2 receptor subfamily classification of the autoreceptors on these cells (Mansour et al., 1990; Sokoloff et al., 1990; Weiner et al., 1991).

Although selective for D1 receptors, SKF 38393 has the disadvantage of being a partial agonist in terms of in vitro adenylate cyclase stimulation, with an intrinsic activity of 45% to 70% of dopamine (Andersen and Jansen, 1990; Arnt et al., 1992; O’Boyle et al., 1989; Setler et al., 1978). Also, it has been suggested that SKF 38393 is poorly absorbed into the brain, based primarily on the greater potency of its more.

ABBREVIATIONS: ANOVA, analysis of variance; DA, dopamine; DHX, dihydrexidine; GP, globus pallidus; SNPC, substantia nigra pars compacta.

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lipophilic 3-N-substituted analogs in causing behavioral activity after peripheral administration (Arnt et al., 1992; Murray and Waddington, 1989). Therefore, the pattern of effects of SKF 38393 on basal ganglia physiology, in particular those cases in which a significant effect is absent, could be due to some extent to the partial agonist nature of this drug or, in situations with systemic treatment, due to poor central absorption.

Since the introduction of SKF 38393, several new compounds have been proposed to be full, selective D₁ agonists. These include the benzazepines SKF 82958 (chloro-APB) and SKF 81297 (6-chloro-APB; Murray and Waddington, 1989; O’Boyle et al., 1989; Pfeiffer et al., 1982), the benz[a]phenanthridine DHX (Lovenberg et al., 1989) and the isochroman A-77636 (Kebabin et al., 1992). These drugs are typically reported as having intrinsic activities for adenylyl cyclase stimulation similar to DA (Andersen and Jansen, 1990; Arnt et al., 1992; Gilmore et al., 1995; Izenwasser and Katz, 1993), although some studies have described SKF 82958, DHX and A-77636 as actually having higher activity than DA (Kebabin et al., 1992; Lovenberg et al., 1989; Mottola et al., 1992; O’Boyle et al., 1989).

Although still D₁ receptor preferring, these latter three compounds have less D₁/D₂ receptor selectivity in vitro than SKF 38393 (Kebabin et al., 1992; Lovenberg et al., 1989; Mottola et al., 1992). Although still D₁ receptor preferring, these latter three compounds have less D₁/D₂ receptor selectivity in vitro than SKF 38393 (Kebabin et al., 1992; Lovenberg et al., 1989; Mottola et al., 1992). However, these compounds have been proposed to be full, selective D₁ agonists.

These full D₁ agonists have been used to further investigate D₁ receptor actions in a variety of experimental preparations. However, few studies have investigated the effects of systemic administration of any of these D₁ compounds on basal ganglia electrophysiology (Heidenreich et al., 1995; Kreiss et al., 1996; Nichols et al., 1992). Hence, the present study has extended the characterization of full D₁ agonist systemic treatment on basal ganglia firing rates, with two major goals. First, the D₁/D₂ receptor selectivity of the full D₁ agonists has been primarily examined in vitro, so it remains unclear whether the systemic doses used for in vivo studies are D₁ receptor selective. Therefore, we have screened these four full D₁ agonists for D₂ activity (in a dose range shown to be maximal for D₁ receptor effects on behavior; Arnt et al., 1992; Darney et al., 1991; Kebabin et al., 1992) by examining effects on GP and SNPC DA neuron firing rates. Drugs with D₂ receptor activity act on postsynaptic D₂ receptors to increase GP firing rates, and they do so in a manner that is dependent on and potentiated by D₁ receptor activity (Carlson et al., 1986; Carlson et al., 1987a). Because presynaptic D₂ autoreceptors are more sensitive to agonists than postsynaptic D₂ receptors (Bergstrom et al., 1986; Carlson et al., 1987a; Skirboll et al., 1979), testing these D₁ agonists for inhibition of SNPC DA neurons offers an even more stringent test for D₂ receptor activity. The second goal was to compare the four full D₁ agonists with the partial agonist SKF 38393 by testing these full agonists in a protocol in which SKF 38393 pretreatment has been demonstrated to potentiate the rate-increasing effects of a subsequently administered D₂ agonist on GP unit activity (Carlson et al., 1987a; Walters et al., 1987).

Methods

Extracellular single-unit recordings were performed in neurologically intact male Sprague-Dawley rats (Tacoma Farms, Germantown, NY), weighing 350 to 450 g, as previously described (Bergstrom and Walters, 1981; Bunney et al., 1973). Dopaminergic cells of the SNPC were recorded in rats anesthetized with chloral hydrate (400 mg/kg i.p.). Supplemental chloral hydrate was given as needed during the experiments. Because general anesthesia has been shown to greatly attenuate the effects of DA agonists on the GP (Bergstrom et al., 1984), GP neurons were recorded in locally anesthetized, paralyzed rats. Under halothane anesthesia, rats were tracheotomized, the trachea was intubated with a cannula and incision sites and pressure points were thoroughly infiltrated with the long-acting local anesthetic mepivacaine HCl. Corneal drying was prevented with the application of Lacri-Lube (Allergan Pharmaceuticals, Irvine, CA). After being placed in a stereotactic instrument, halothane anesthesia was discontinued, and rats were paralyzed with the injection of gallamine triethiodide (16 mg/kg) through a lateral tail vein. Rats then were artificially ventilated on room air at a rate adjusted to maintain expired CO₂ levels between 3.4% and 4.5%. Supplemental of gallamine were given as needed during the experiments. Body temperature of both paralyzed and chloral hydrate-anesthetized rats was maintained at 36º to 38°C with a heating pad. All surgical procedures were in accordance with the National Institutes of Health Guide for Care and Use of Laboratory Animals (Cohen et al., 1985).

Glass microelectrodes were filled with 2 M NaCl containing 1% Pontamine Sky Blue, and microelectrode tips were broken back under microscopic control until in vitro tip impedance measured 2.6 to 6.0 MΩ (at 135 Hz). Microelectrodes were stereotactically guided through drilled skull holes to the following coordinates: for the SNPC, 2.8 to 3.2 mm anterior to lambda, 1.8 to 2.2 mm lateral to the midline and 6.5 to 7.5 mm ventral to dura; for the GP, 0.8 to 1.2 mm posterior to bregma, 2.6 to 3.0 mm lateral to the midline and 5.0–7.0 mm ventral to dura. Electrical signals were passed through an Axoclamp 2A amplifier (Axon Instruments, Burlingame, CA) in bridge mode, and amplified signals were monitored with an oscilloscope and audio monitor. Single-unit activity was isolated with a window discriminator, and firing rate data were collected on a computer with Spike2 software (version 2.18, Cambridge Electronic Design, Cambridge, UK). Dopaminergic neurons in the SNPC were identified on the basis of their characteristic long-duration, biphasic (+/-) or triphasic (+/-/) action potential waveformes. All selected GP units had biphasic type II (+/-) waveforms and had basal firing rates above 10 Hz.

Drugs used include SKF 82958 ([±]-chloro-APB; ([±])-N-allyl-6-chloro-2,3,4,5-tetrahydro-7,8-dihydroxy-1-phenyl-1H-3-benzazepine HBr, SKF 81297 ([±]-6-chloro-APB; ([±]-6-chloro-2,3,4,5-tetrahydro-7,8-dihydroxy-1-phenyl-1H-3-benzazepine HBr, (R)+SCH 23390 ([R]+[S]-7-chloro-8-hydroxy-3-methyl-1-phenyl-2,3,4,5-tetrahydro-1H-3-benzazepine HCl, (S)-(-)-eticlopride HCl and (R)-quinpirole HCl were obtained from Research Biochemicals (Natick, MA). Haloperidol was obtained from McNeil Pharmaceuticals (Spring House, PA). DHX [trans-10,11-dihydroxy-5,6,6a,7,8,12b-hexahydrobenzo[a]phenanthridine] HCl was obtained from Interneuron Pharmaceuticals (Lexington, MA). A-77636 ([1R,3S][1-''adamanthyl]-1-aminomethyl-3,4-dihydro-5,6-dihydroxy-1H-2-benzoypyr] HCl was obtained from Abbott Laboratories (Pomezia, Italy). All drugs were dissolved in distilled water, in 0.001 N HCl before dilution to final volume with distilled water.

Drugs were administered after basal data had been collected for 2 to 5 min for SNPC cells and 5 to 10 min for GP neurons. All drugs (and vehicle) were administered i.v. through a lateral tail vein at 0.5 ml/kg, and doses refer to the weight of the salts.agonist drugs were given at typically given at 1.0 or 5.0 mg/kg, except in dose-response experiments. SCH 23390, eticlopride and haloperidol were given at
0.5, 0.2 and 0.2 mg/kg, respectively. One unit was recorded per rat. At the end of recording, Pontamine Sky Blue was iontophoresed at −15 μA for 20 to 30 min to mark the recording site. Brains were removed and frozen and later sectioned for histological confirmation of the recording site.

Typically, for SNPC cells, the average rate from 10 to 60 sec postdrug was expressed as a percentage of the basal rate within the last minute before drug. For GP neurons, the average rate from 5 to 10 min after drug was expressed as a percentage of the 5 min before drug. Overall effects were analyzed with one- or two-way ANOVA, post hoc comparisons between vehicle and drug treatments were done using Dunnett’s t tests and post hoc examinations of the effect of quinpirole and DA receptor antagonists on GP rates were performed with paired t tests. All post hoc tests were two-sided. Relationships between basal rate and drug effects were studied with Pearson correlations. Dose-response curves were evaluated with Allfit (version 2.7; NICHD, NIH).

**Results**

DAergic neurons of the SNPC. The basal firing rates of the DAergic units studied ranged from 1.0 to 6.3 Hz, with a mean ± SEM of 3.5 ± 0.2 Hz. The effect of 1 mg/kg i.v. bolus D1 agonist administration on firing rate of DAergic neurons is illustrated in figure 1. Basal firing rates of the neurons in these treatment groups were not significantly different (F(4,36) = 0.48, N.S.). ANOVA of drug effects on firing rate 10 to 60 sec after injection revealed a significant effect of treatment group (F(4,36) = 1.42, P < .05). Post hoc comparisons demonstrated that SKF 82958 (1.0 mg/kg) significantly inhibited DAergic units compared with vehicle treatment, whereas the other compounds were not significantly different from vehicle. Of 11 units, 10 were inhibited >30% by SKF 82958; 5 were inhibited by ≥90%. The average inhibition was 69 ± 8%. Although antagonist drugs were typically given 1 to 2 min after SKF 82958, some units were held without antagonist. Two of these units are shown in figure 2, A and B. These cells demonstrated a slow recovery of firing rate after the initial robust inhibition. The units in figure 2, A and B, are also examples of the inverse relationship between the effect of SKF 82958 and basal firing rate (i.e., cells with slower basal firing rates were typically more robustly inhibited by SKF 82958; r = −.74, P < .02, data not shown). Analysis of cumulative dose-response curves to SKF 82958 indicated an ED50 value of 0.70 ± 0.14 mg/kg (fig. 3).

Several methods were used to investigate the DA receptor subfamily involved in the inhibitory SKF 82958 effect. The D1 antagonist SCH 23390 (0.5 mg/kg) failed to reverse the inhibition in three attempts. However, the D2 antagonists haloperidol or eticlopride (each 0.2 mg/kg) were able to completely reverse inhibition due to SKF 82958 in most cases (four of five units; fig. 2C). Also, in four cases, rats were pretreated with SCH 23390 (0.5 mg/kg) 10 min before a bolus of SKF 82958. The D1 antagonist pretreatment did not block the inhibitory effect of 1.0 mg/kg SKF 82958 (fig. 2C), which was 76 ± 16% within the first minute after injection, very similar to the value without pretreatment. These inhibitions were all reversed by haloperidol (0.2 mg/kg). Finally, in four cases, rats were pretreated with this same dose of SCH 23390 10 min before a cumulative dose-response curve to SKF 82958. D1 antagonist pretreatment did not block the inhibitory effect of cumulatively administered SKF 82958, nor did it shift the dose-response curve rightward (fig. 3). The ED50 value for SKF 82958 after the SCH 23390 pretreatment was 0.49 ± 0.07 mg/kg, not significantly different from the ED50 value for SKF 82958 alone (P = .15). However, SCH 23390 pretreatment did increase the slope of the dose-response curve (P < .01). The inhibition due to cumulative SKF 82958, either alone or after SCH 23390 pretreatment, was completely reversed by eticlopride (0.2 mg/kg) in 9 of 9 attempts.

SFK 81297, DHX and A-77636 were tested for possible presynaptic effects at higher doses with cumulative dose-response curves up to 10.2 mg/kg. As shown in figure 3, these drugs had very little rate effect up to 5.1 mg/kg (compared with 82% inhibition by SKF 82958 at this dose). Even after the highest dose, average inhibitions were <25% for all three drugs. Because there is evidence that one of these drugs (DHX) can act as an antagonist at D2 autoreceptors of DAergic neurons (Kilts et al., 1996), rats were injected with cumulative dose-response curves to the D1 agonist quinpirole 10 min after the D1 agonist dose-response curves (fig. 2D). Quinpirole inhibited DAergic cell firing with ED50 values of 7.4 ± 1.3, 5.1 ± 1.0 and 9.6 ± 1.3 μg/kg after DHX, A-77636 and SKF 81297, respectively, and caused complete or near-complete inhibition at higher doses in all cases (n = 4 or 5 for each drug). A similar effect of quinpirole was also found after 1.0 mg/kg bolus DHX (ED50 = 8.1 ± 0.6 μg/kg, n = 4). These ED50 values are similar to published values for quinpirole alone (Carlson et al., 1987a; Kreiss et al., 1995; Wachtel et al., 1989). Eticlopride reversed the effect of cumulatively administered quinpirole in 15 of 15 attempts.

**GP neurons.** GP-type II unit basal firing rates ranged from 12 to 69 Hz, with a mean ± S.E.M. of 32 ± 1.7 Hz. The effects of 1.0 mg/kg D1 agonist injection and subsequent D2 agonist (quinpirole) injection are illustrated in figures 2 and 4. Basal firing rates of the neurons in these treatment groups were not significantly different (F(4,36) = 1.4, N.S.). A two-way ANOVA on firing rates 5 to 10 min postdrug showed no significant effect of D1 agonist treatment (between-subjects factor; F(4,36) = 1.4, N.S.) but did reveal a significant effect of
quinpirole treatment (within-subjects factor; $F_{1,36} = 57.7$, $P < .001$). The interaction of factors ($D_1$ agonist treatment $\times$ quinpirole treatment) did not reach significance ($F_{2,28} = 2.0$, $P = .11$, N.S.). Figure 4 demonstrates that vehicle or the $D_1$ agonists (1.0 mg/kg) alone had minor effects on rate in the large majority of units, although occasional cells had rate increases $>30\%$ (3 of 8 for SKF 81297; 2 of 8 for DHX) or rate decreases $>30\%$ (3 of 8 for SKF 81297). These varied rate responses to $D_1$ agonist alone were not significantly correlated to basal rate ($r = -.29$, N.S.). Although quinpirole (1.0 mg/kg), given 10 min after vehicle, increased GP firing rate 32% on average, this effect was not significant in a post-hoc test. However, post-hoc comparisons indicated that quinpirole significantly increased GP firing rate when given 10 min after any of the $D_1$ agonists at 1.0 mg/kg (figs. 2, E–G, and 4). Furthermore, the mean rate increases in these groups (98–
had rate increases of >25%. This group was somewhat distinguished from other D₁ agonist/quinpirole combinations in that the mean rate increase was only 60%.

Typically, SCH 23390 (0.5 mg/kg) was injected 10 min after quinpirole for GP units. The D₁ antagonist effectively reversed rate increases due to the combination of SKF 81297 and quinpirole, with reversals ranging from 38% to below basal firing rate (not significantly different from basal rates with a paired t test; fig. 2F). The D₁ antagonist also effectively reversed rate increases due to the A-77636/quinpirole combination (reversals ranging from 72% to below basal rate; not significantly different from basal rates; fig. 2G). However, SCH 23390 was poorer in reversing the rate increases after the SKF 82958/quinpirole combination (fig. 2E); reversals ranged from none to 42%. In this group, post-SCH 23390 rates were significantly different from basal rates (P < .02) yet were also significantly different from pre-SCH 23390 rates (P < .02), indicating a significant, albeit partial, reversal. In this group, eticlopride (0.2 mg/kg) was injected 10 min after SCH 23390, and the D₂ antagonist provided 75% to complete reversals in four of five attempts (not significantly different from basal rates; fig. 2E). The one cell that was inhibited by quinpirole after SKF 82958 had a similar response pattern; SCH 23390 was without effect on the inhibition, but subsequent eticlopride gave a 56% reversal. SCH 23390 reversals of DHX/quinpirole effects are described for the 5.0 mg/kg dose of DHX, because of the more consistent rate effects of this higher dose. SCH 23390 (2.5 mg/kg) effectively reversed DHX/quinpirole-induced rate increases, with reversals ranging from 67% to below basal firing rate (not significantly different from basal rates).

**Discussion**

Most previous studies have used the partial D₁ agonist SKF 38393 to characterize D₁ receptor influences on the electrophysiology of GP neurons and the DAergic neurons of the SNPC. The data presented here using full D₁ agonists strongly support this characterization. Systemic SKF 38393 has little effect on the rate of SNPC DAergic units (Carlson et al., 1987b; Wachtel et al., 1989), SKF 81297, DHX and A-77636 are similarly without effect in a dose range that is maximal for D₁ receptor stimulation as measured behaviorally (Arnt et al., 1992; Darney et al., 1991; Kehabian et al., 1992), and although SKF 82958 strongly inhibited these cells, this action is D₂ receptor mediated (see below). D₁ receptor agonists also fail to change SNPC firing rate when applied iontophotically (Carlson et al., 1987b; Wachtel et al., 1989) and do not modulate DA synthesis in vivo (Broederson et al., 1990; Brown et al., 1985; Wachtel et al., 1989) or DA release from mesostriatal terminals in vitro (Lehmann et al., 1983). Modulatory effects of D₁ agonists on SNPC neuron rate have been shown in some preparations (Kelland et al., 1988; Momiyama et al., 1993), but robust D₁ receptor-mediated effects on firing rate occur only after DA depletion in awake, paralyzed rats (Huang and Walters, 1992; Sun et al., 1993), and this action is not mediated by local nigral receptors (Sun et al., 1993). In the GP, SKF 38393 has no consistent influence on type II unit firing rate but will potentiate the excitatory actions of a D₁ agonist (Carlson et al., 1987a; Walters et al., 1987), effects also seen with the full D₁ agonists. This same pattern has been demonstrated for GP im-
mediate-early gene expression (Marshall et al., 1993; Ruskin and Marshall, 1995). The present data indicate that the lack of effect of SKF 38393 (when given alone) on pallidal and SNPC DA neuron firing rate is not simply a consequence of the partial D1 receptor activity of this compound. A similar conclusion applies to the synergism of SKF 38393 with D2 agonists in causing rate increases in the GP. Therefore, the current results show that the electrophysiological influences of D2 receptor activation, as studied with the systemic administration of SKF 38393, are not idiosyncratic to this drug or to substituted benzazepines but are characteristic of the activation of D1 receptors generally.

It should be noted that peripherally administered D1 agonists can have significant effects alone on some basal ganglia nuclei, other than the GP. Specifically, D1 agonists increase firing rate in both the ventral pallidum and subthalamic nucleus (Kreiss et al., 1996; Maslowski and Napier, 1991). Hence, the actions of D1 receptors modulating activity in these nuclei are not dependent on simultaneous agonist-induced activation of D2 receptors, although they clearly can be modulated by D2 receptors (Heidenreich et al., 1995; Kreiss and Walters, 1997). In another basal ganglia nucleus, the substantia nigra pars reticulata, the pattern of D1/D2 receptor influence in neurologically intact rats more resembles the pattern found for GP type II units (i.e., little effect of D1 agonists alone but significant firing rate changes due to concomitant D1/D2 receptor activation), although these latter rate changes include both increases and decreases (Walters et al., 1992; Waszczak et al., 1984).

Although SKF 81297, DHX and A-77636 were apparently free of D2 agonist activity within the tested dose range, peripherally administered SKF 82958 had a novel inhibitory action on the firing rate of SNPC DAergic neurons. Although it is possible that this effect is mediated via the full efficacy activation of D2 receptors by this drug, such an explanation is unlikely because (1) the effect was neither prevented nor reversed by the D1 antagonist drug SCH 23390, (2) it was completely reversed in virtually every tested unit (17 of 18) by either of the D2 antagonists haloperidol or eticlopride and (3) it was not reproduced by the other full D1 agonists examined. These results strongly suggest that the inhibitory effect is due to an agonist action of SKF 82958 on D2 subfamily receptors. In addition, the effect has characteristics typical of autoreceptor activation, with the response being rapid, inhibitory and desensitizing, and the size of the response being...
Because studies have typically reported lower \( K_i \) cell-mediated inhibition of stimulated DA release in cultured cells (Kilts et al., 1996). Yet DHX is free of apparent \( D_2 \) receptor effects in the present study, since it did not inhibit SNPC DAergic units, block quinpirole-induced inhibition of these neurons or excite pallidal units when given alone. Although the effects of combined quinpirole and DHX (at both 1.0 and 5.0 mg/kg) on GP firing rates differed from the effects of other \( D_1/D_2 \) agonist combinations, the differences were subtle. The lack of presynaptic \( D_2 \) agonist and antagonist activity here confirms a preliminary electrophysiological study of intravenous DHX effects on SNPC DAergic units (Nichols et al., 1992). It has been hypothesized that DHX acts as an antagonist at \( D_2 \) receptors linked to \( K^+ \) channels (characterized in pituitary lactotrophs), and as an agonist at those linked to adenylate cyclase (Smith et al., 1996). Increased \( K^+ \) current appears to mediate most electrophysiological effects of autoreceptor activation on midbrain DAergic neurons (Kim et al., 1995; Lacey et al., 1987; Lacey et al., 1988). Therefore, it is surprising that DHX does not antagonize the inhibitory effect of quinpirole on these neurons. It is possible that the specific nature of the interaction among DHX, \( D_2 \) receptors and \( K^+ \) channels depends on the particular \( D_2 \) receptor isoforms or G protein alpha subunit subtypes expressed in the cell type being studied.

A substantial body of work indicates that partial and full \( D_1 \) agonists can have equal efficacies with respect to physiological measures besides adenylate cyclase activation. Iontophoretic application of partial and full \( D_1 \) agonists results in similar inhibitions of nucleus accumbens septi neurons in vivo (Johansen et al., 1991), and systemic administration of partial and full agonists results in comparable rate increases in the ventral pallidum (Heidenreich et al., 1995) and also in the subthalamic nucleus (Kreiss et al., 1996). Similarly, the rank order for potency and/or efficacy of \( D_1 \) agonists for inducing behavioral activation is markedly different from the rank order of efficacy for adenylate cyclase activation (Arnt and Hyttel, 1988; Arnt et al., 1992; Arnt and Perregaard, 1987; Murray and Waddington, 1989). In some of these studies, agonists substantially weaker than SKF 38393 (e.g., SKF 75670 and SKF 83959) are as effective behaviorally as full agonists. The findings presented here support this dissociation, since the full \( D_1 \) agonists (when combined with a \( D_2 \) agonist) had rate-increasing actions on pallidal neurons that were similar in magnitude to that seen with the partial agonist SKF 38393 (Carlson et al., 1987a; Walters et al., 1987). Furthermore, this magnitude of rate increase is also seen after release of the endogenous agonist (DA) by amphetamine (Bergstrom and Walters, 1981; Carlson et al., 1986). Because full and partial agonists can have equivalent maximal effects in systems with spare receptors (for a review, see Ruffolo, 1982), it may be that the \( D_1 \) receptors mediating many of these behavioral and electrophysiological actions include a substantial receptor reserve. Indeed, there is evidence for spare adenylate cyclase-linked \( D_1 \) receptors in the striatum (Battaglia et al., 1986; Hess et al., 1987). There is also electrophysiological evidence for a \( D_1 \) receptor reserve. Selective reduction of \( D_1 \) receptor number by 80% (caused by systemic EEDQ with eticlopride pretreatment) does not affect the ability of the mixed \( D_1/D_2 \) agonist apomorphine to increase GP firing rates, whereas a 60% to 70% reduction in \( D_2 \) receptor number (by EEDQ with SCH 23390 pretreatment) abolished this effect of apomorphine (Walters et al., 1988).

Alternatively, the \( D_1 \) receptors in question may be acting through an effector system other than adenylate cyclase.
The existence of D1 receptors not coupled to adenylate cyclase was proposed soon after the introduction of D1 receptor-specific ligands (Andersen et al., 1985; Mailman et al., 1986), and some electrophysiological effects of D1 agonists are independent of the adenylate cyclase system (Harvey and Lacey, 1996; Johansen et al., 1991; Martin and Waszczak, 1994), although others clearly are not (Cameron and Williams, 1993; Hernandez-Lopez et al., 1997; Schiﬀmann et al., 1995; Surmeier et al., 1995). Recent evidence demonstrates a link between D1 subfamily receptors and phosphatidylinositol hydrolysis (Friedman et al., 1997; Mahan et al., 1990; Pacheco and Jope, 1997; Wang et al., 1995), although studies have not yet investigated the effects of full D1 agonists on this effector system, nor have they investigated the involvement of this system in the electrophysiological effects of D2 subfamily receptors. It will be of particular interest to characterize the properties and efficacies of various D2 agonists for the stimulation of phosphatidylinositol hydrolysis.

The present findings support the role of D2 receptors in basal ganglia electrophysiology as previously characterized with SKF 82958. However, the full D1 receptor agonists tested here are distinguishable pharmacologically. SKF 82958 has D2 agonist activity, most clearly demonstrated at rate-inhibiting autoreceptors. Because of this effect, and because of evidence demonstrating direct interactions of this drug with voltage-activated K+ channels (Nisenbaum et al., in press), SKF 82958 effects should be interpreted as selectively D1 receptor-mediated only with appropriate pharmacological controls. Although apparently free of D2 receptor effects in the present study, DHX has been shown to have a complex interaction with this receptor subfamily in addition to its D2 receptor activity (Mottola et al., 1992; Smith et al., 1996). In contrast, the isochroman A-77636 and the benzazepine SKF 81297 are apparently highly selective D1 receptor ligands in vivo, based on their lack of inhibition of SNPC DAergic cells and (when given alone) lack of excitation of GP neurons. Recently, these four full DAergic agonists have been tested for therapeutic potential in unilateral (Johnson et al., 1995; Vermeulen et al., 1993) and bilateral (Blanchet et al., 1996; Gnanalingham et al., 1995; Keabian et al., 1992; Pearce et al., 1995; Taylor et al., 1991) experimental models of Parkinson's disease in primates, with each drug demonstrating differing antiparkinsonian effects, and well as differing side effects (dyskinesias, tachyphylaxis). It is likely that the particular spectrum of dopamine receptor activity of each of these drugs contributes to these differences and will mark their usefulness as palliative agents in clinical Parkinson's disease.

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