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A comparison of the locomotor stimulant effects of D_1-like receptor agonists in mice

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Abstract

Efficacy in stimulating adenylyl cyclase (AC) has traditionally been used to distinguish dopamine D_1-like receptor agonists from dopamine D_2-like receptor agonists. However, there is a limited association between the effects of D_1-like agonists in behavioral assays and their effectiveness at stimulating AC. Other second messenger actions might contribute to the behavioral effects of D_1-like agonists, as there is evidence for a link to the hydrolysis of phosphoinositide (PI). The present study compared the locomotor stimulant effects of five D_1-like receptor agonists having different efficacies in assays of AC and PI activity. All D_1-like agonists produced long-lasting biphasic effects on locomotor activity. SKF 38393, the prototypical partial agonist (based on AC activity), produced limited changes in locomotor activity, whereas the partial agonists SKF 75670 and SKF 77434 produced locomotor stimulant effects that were similar to or greater than those of the full efficacy agonists SKF 82958 and SKF 81297. However, there did not appear to be a relationship between maximal behavioral effects and AC stimulation or PI hydrolysis. The results suggest a complex relationship between the behavioral effects of D_1-like agonists and their intrinsic efficacies as measured by AC and /or PI stimulation. Although a limited number of compounds were examined, neither second messenger system alone appears to account fully for these behavioral effects. The current classification of D_1-like agonists according to their intrinsic efficacies as defined by AC stimulation needs further scrutiny.
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1. Introduction

Stimulation of adenylyl cyclase (AC) conventionally distinguishes dopamine D_1-like receptor agonists from dopamine D_2-like receptor agonists (e.g. Kebabian and Calne, 1979). However, despite the importance of this intracellular signalling system for the classification of dopaminergic compounds, questions have been raised concerning its significance to the behavioral effects of dopamine D_1-like receptor agonists (Terry and Katz, 1992; Daly and Waddington, 1992; Gnanalingham et al., 1995a,b; Katz et al., 1999; Platt et al., 2001; Sinnott and Nader, 2001; Desai et al., 2003). For example, SKF 83959 is a potent in vitro antagonist of AC-linked dopamine D_1-like receptors (Arnt et al., 1992; Gnanalingham et al., 1995c; Andringa et al., 1999), but its profile of behavioral effects–in particular, the induction of vacuous chewing and enhanced grooming–is similar to that produced by drugs classified as full agonists at D_1-like receptors (Downes and Waddington, 1993). Further, in rats trained to discriminate the partial D_1-like agonist, SKF 38393, from saline, the full agonist, SKF 82958, was less effective in substituting than was the partial agonist SKF 75670 (Desai et al., 2003). Moreover, the behavioral effects of both SKF 83959 and the full agonist A-68930 are retained in D_1-like receptor knockout mice (Clifford et al., 1999), suggesting that at least some of their in vivo effects

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(commonly attributed to actions at D_1-like receptors) may be mediated by other mechanisms. A weak association between the behavioral effects of D_1-like agonists and their effects on AC might imply that current assumptions about their intrinsic efficacies may benefit from a re-evaluation. It would also suggest that other signal transduction mechanisms might be relevant to the behavioral actions of D_1-like receptor agonists. Reports have suggested that D_1-like agonists can stimulate phosphoinositide (PI) hydrolysis, as well as AC (Mahan et al., 1990; Undie and Friedman, 1990; Undie et al., 1994, 2000; Undie, 1999).

The present study assessed the locomotor effects of five dopamine D_1-like receptor agonists which vary in terms of their intrinsic efficacies for stimulating AC and/or PI activity. Although early studies of the prototypical D_1-like receptor agonist SKF 38393 suggested the contrary (e.g. Arnt, 1985; Braun and Chase, 1986; Starr and Starr, 1986), there is now considerable evidence to suggest that SKF 38393 and other D_1-like agonists increase locomotor activity in rats and mice (e.g. Arnt et al., 1992; Tirelli and Terry, 1993; Halberda et al., 1997). In addition, the effects of the indirect dopamine agonist, cocaine, were also examined as a reference compound, given its well-established locomotor stimulant effects.

2. Methods

2.1. Subjects

Subjects were male Swiss–Webster mice (Charles River, Wilmington, MA) weighing 21–30 g at the time of testing. Mice were housed in groups of 5 in a large colony room under a 12-h light/dark cycle with lights on at 07:00, and an ambient temperature of 24±2 °C. Food and water were available at all times, except during testing. Animals were maintained in facilities accredited by AAALAC International, and all experimentation was conducted in accordance with the guidelines of the Institutional Animal Care and Use Committee of the National Institute on Drug Abuse, Intramural Research Program, the National Institutes of Health (NIH Manual 3040-2), and the Guide for Care and Use of Laboratory Animals of the Institute of Laboratory Animal Resources, National Research Council, National Academy Press, 1996.

2.2. Apparatus

Locomotor activity was measured using monitors (Omnitech Electronics Inc., Columbus, OH), each with a horizontal matrix of 16 photobeams, fixed at a height of 2 cm and spaced at 5 cm intervals along the interior perimeter. Eight beams per side crossed the test chamber (transparent acrylic box, $40 \times 40 \times 30$ cm high), which was located within the monitor. One locomotor count was recorded each time the mouse interrupted a single light beam. Locomotor activity counts were collected every 10 min.

2.3. Procedure and drugs

Testing was conducted during the light period of the colony light–dark cycle, between 10:00 and 16:30 h. Each mouse was tested individually and used only once. After injection, the mice were immediately placed in the apparatus for 3 h. The inside surfaces of the chambers were wiped clean with 70% ethanol applied to a paper towel after each session.

Mice received injections of either vehicle or various dopamine D_1-like agonists: (±)-SKF 38393 ((±)-1-phenyl-2,3,4,5-tetrahydro-(1H)-3-benzazepine-7,8-diol HCl), (±)-SKF 77434 ((±)-7,8-dihydroxy-3-allyl-1-phenyl-2,3,4,5-tetrahydro-1H-3-benzazepine-7,8-diol HCl, (±)-SKF 82958 ((±)-6-chloro-7,8-dihydroxy-3-allyl-1-phenyl-2,3,4,5-tetrahydro-1H-3-benzazepine HBr), SKF 81297 (R-[+]-6-chloro-7,8-dihydroxy-1-phenyl-2,3,4,5-tetrahydro-1H-3-benzazepine HBr) (all from Research Biochemicals, Inc.), and SKF 75670 (3-methyl-7,8-dihydroxy-1-phenyl-2,3,4,5-tetrahydro-1H-3-benzazepine HBr; SmithKline Beecham, Philadelphia PA). The effects of the D_1-like agonists were also compared with those of (−)-cocaine HCl (Sigma Chemical Co., St. Louis, MO). All drugs were dissolved in sterile water, except cocaine, which was dissolved in 0.9% saline. Drugs were administered IP at 1 ml/100 g body weight.

Table 1
Stimulation of locomotor activity by D_1-like agonists: comparisons with D_1-like efficacies in stimulating adenylyl cyclase formation and phosphoinositide hydrolysis

Drug	% of maximum stimulation of locomotor activity (drug-vehicle)			Adenylyl cyclase[a] Efficacy (% dopamine)	Adenylyl cyclase[b] Efficacy (% dopamine)	Phosphoinositide hydrolysis[b] Efficacy (% dopamine)
	0–1 h	1–2 h	2–3 h			
SKF 82958	100	100	49	78	[c]	[c]
SKF 81297	53	73	46	[c]	86	68
SKF 77434	55	59	67	[c]	48	54
SKF 75670	72	84	100	21	23	85
SKF 38393	18	17	51	59	63	125

The % of maximum stimulation of locomotor activity was calculated by substracting the peak effect from the vehicle effect.
[a] Data obtained using rats from Izenwasser and Katz (1993).
[b] Data obtained using rats from Undie et al. (1994).
[c] The efficacies for stimulation of AC or PI for these particular drugs were not examined in this study.

2.4. Data analyses

The drugs produced maximal stimulation of locomotor activity at different times post-injection, hence the data were analyzed separately for each of the three one-hour time intervals. These data were evaluated by analysis of variance (ANOVA), followed by Dunnett's *t*-tests to compare individual treatments against vehicle. Values for maximum stimulation of locomotor activity at each time point were determined by subtracting the peak effect from the vehicle effect. In Table 1, for each drug at each time point, data are expressed as a percentage of maximum stimulation of locomotor activity. Percentage maximum stimulation of locomotor activity produced by each of the drugs at any of the three one-hour observation periods was compared with their efficacies in stimulating AC or PI activity. A significance level of $P<0.05$ was assumed throughout.

3. Results

All of the D_1-like receptor agonists stimulated locomotor activity at some dose during at least one of the three time intervals (Fig. 1). During the first hour, SKF 82958 and SKF 75670 both increased locomotor activity significantly at lower doses, but had less effect (or reduced activity in the case of SKF 75670) at the highest doses [$F_{4,25}=10.21$; $P<0.05$ and $F_{4,22}=15.32$; $P<.05$, respectively].

Neither SKF 81297, SKF 77434 [$F_{4,25}$ values ≤ 2.05; P values >0.05] nor SKF 38393 increased locomotion significantly during the first hour, and SKF 38393 [$F_{4,25}=7.10$; $P<0.05$] significantly decreased activity at the highest dose, 343 μmol/kg ($P<0.05$). However, each of these drugs increased activity during later time points. There were significant effects of dose for SKF 82958, SKF 81297, SKF 77434 and SKF 75670 [$F_{4,25}$ values ≥ 8.35; P values <0.05] in the second and third hours after injection, and post-hoc tests indicated significant increases in activity for each drug. For SKF 81297 and SKF 38393 the significant increases in locomotor activity occurred only at the highest doses tested [$F_{4,25}$ values ≥ 6.65; P values <0.05].

Table 1 shows the maximal effects of the D_1-like agonists in stimulating locomotor activity at each of the observation periods, as well as published values for the maximal stimulation of AC and PI activity. The compounds that are most efficacious in terms of stimulating AC (SKF 82958 and SKF 81297), produced different maximum levels of stimulation of locomotor activity, however, as noted above, a

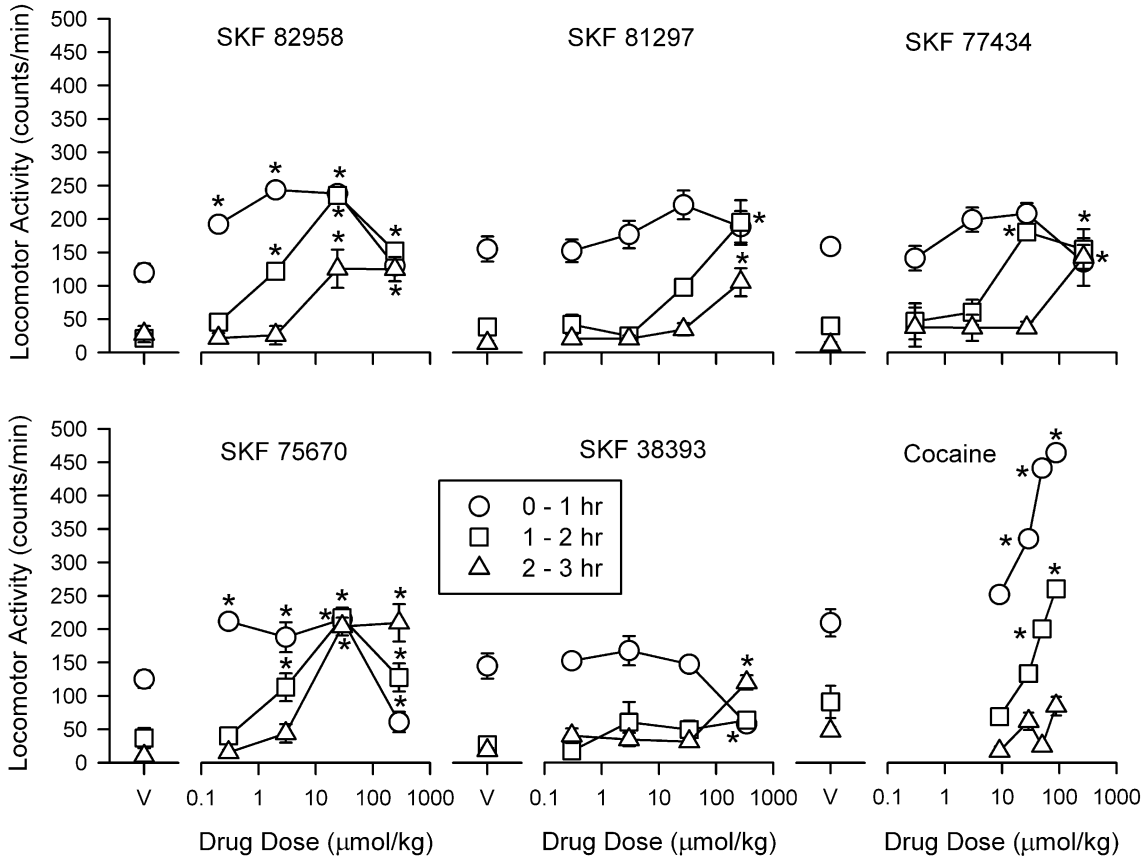

Fig. 1. Effects of dopamine D_1-like agonists SKF 82958, SKF 81297, SKF 77434, SKF 75670, SKF 38393 and the indirect dopamine agonist, cocaine, on locomotor activity over a period of 3 h in Swiss–Webster mice. All drugs were injected immediately before monitoring. Each point shows mean (±SEM) data from a group of 6 subjects ($n=3$ for 0.3 μmol/kg SKF 75670). *indicates significantly different from vehicle group (Dunnetts *t*-test, $P<0.05$, on means derived from main effect of dose).

definitive maximum stimulation of locomotor activity was not determined for the latter drug. Both SKF 77434 and SKF 75670 have less than full efficacy, and they too showed differences in the maximal level of locomotor activity produced. SKF 75670 produced a maximum stimulation of locomotor activity that was comparable to that produced by the full agonist, SKF 82958 during the third hour post-injection. It is notable that although SKF 75670 is the least efficacious drug in terms of stimulating AC, it is as effective at increasing locomotion as the full efficacy agonist SKF 82958 and more effective than the partial agonist SKF 77434 (Table 1).

The prototypical psychostimulant cocaine (9–88 μmol/kg), tested under conditions identical to those of the D_1-like agonists increased locomotor activity dose-dependently during the first two hours after injection; the maximum increase in locomotor activity was obtained between 0–1 h after cocaine injection (Fig. 1). ANOVA revealed significant main effects of dose [$F_{4,25}$ values $\geq$ 15.74; P values $<$ 0.05], and post-hoc comparisons showed that during 0–1 h doses of 29 μmol/kg of cocaine or higher significantly differed from vehicle (Dunnett's t test $\geq$ 3.69; P values $<$ 0.05) and during 1–2 h the highest two doses of cocaine were significantly different from vehicle (Dunnett's t test $\geq$ 4.37; P values $<$ 0.05). Between two and three hours post-injection, no dose of cocaine significantly increased locomotor activity compared to vehicle (Dunnett's t test $\leq$ 2.47; P values $>$ 0.05); although an overall ANOVA revealed a significant effect between various doses of cocaine [$F_{4,25}$ = 6.664; P < 0.05]. It is notable that, for the dose ranges tested, the maximal levels of activity produced by cocaine were more than twice as high as were those produced by any of the D_1-like agonists.

4. Discussion

Consistent with previous reports, the D_1-like agonists stimulated locomotor activity (Arnt, 1985; Meyer and Shults, 1993; Tirelli and Terry, 1993), but less effectively than did cocaine (e.g. Chausmer and Katz, 2002; Schindler and Carmona, 2002). The differences between cocaine and D_1-like agonists may be related to indirect agonist actions mediated by other dopamine receptors, or effects of cocaine at other monoamine transporters (Harris and Baldessarini, 1973; Taylor and Ho, 1978). The stimulation of locomotor activity produced by D_1-like agonists appeared to be different from cocaine, in its duration of action (often $>$ 3 hr), as well as its maximum. Similar long-lasting effects on locomotor activity have been reported in mice given SKF 38393 (Tirelli and Terry, 1993) and in rats given SKF 38393, SKF 77434 and SKF 82958 (Meyer and Shults, 1993).

Interestingly, the maximal stimulation of locomotor activity produced by the partial agonist SKF 75670 was similar to that produced by the full agonist SKF 82958, and greater than that of SKF 77434, a partial agonist with greater efficacy than SKF 75670. Based on other receptor systems, such as the μ-opioid system, a correspondence between the behavioral effectiveness of D_1-like agonists and their intrinsic efficacies could be expected, if the effect observed requires sufficient receptor occupancy (e.g. Walker and Young, 1993; Gerak and France, 1996; Koek et al., 1993; Woods et al., 1988; Zhang et al., 2000). The effectiveness of the partial D_1-like agonists compared to those agonists with greater efficacy provides further evidence for the lack of association between the behavioral effects of dopamine D_1-like agonists and their efficacy in stimulating AC activity. Similar outcomes have been noted before with other behavioral measures: feeding, circling, grooming, locomotor activity and unconditioned motor behaviors, seizures, drug discrimination and self-administration (e.g. Terry and Katz, 1992; Daly and Waddington, 1992; Gnanalingham et al., 1995a,b; Katz et al., 1999; Platt et al., 2001; Sinnott and Nader, 2001; Desai et al., 2003). The present findings along with others, suggest that the stimulation of AC is not a coupling mechanism that is exclusively involved in the expression of the behavioral effects of D_1-like receptor agonists.

The lack of association between behavior and stimulation of AC might suggest the involvement of a second messenger system in addition to, or other than cyclic AMP (e.g. Daly and Waddington, 1992). Indeed, there is literature to support the existence of a non-cyclase coupled dopamine D_1-like receptor that stimulates PI hydrolysis (e.g. Mahan et al., 1990; Undie and Friedman, 1990; Undie et al., 1994, 2000; Clifford et al., 1999; Undie, 1999; Panchalingam and Undie, 2000, 2001; Hasegawa et al., 2001; Tomiyama et al., 2001). A few studies have attempted to assess the relationship between the behavioral effects of D_1-like agonists and their efficacies in stimulating AC activity and/or PI hydrolysis. For example, the D_1-like agonist SKF 83959 which stimulates PI hydrolysis, but lacks AC activity produces grooming behavior (Clifford et al., 1999; McNamara et al., 2002, 2003). On the other hand SKF 83822, a D_1-like agonist that has been reported to stimulate AC but not PI hydrolysis (Undie et al., 1994), fails to induce intense grooming but readily induces other behaviors usually attributed to activity at dopamine D_1-like receptors (O'Sullivan et al., 2004). Thus these authors have suggested that the behavioral effects of D_1-like agonists can be differentiated based on their stimulation of AC or PI activity. Unlike the effects reported for grooming, the present relationships among D_1-like agonists with regard to their stimulation of locomotor activity indicate that stimulation of neither PI hydrolysis nor cyclic AMP is related to this effect. However, this conclusion is cautiously tendered, as it has been reached after examining a limited number of compounds. The possibility also remains that stimulation of locomotor activity produced by D_1-like agonists may be related to both AC and PI stimulation that may occur to varying degrees for different compounds (Undie et al., 1994; Lezcano et al., 2000).

The stimulation of locomotor activity produced by D_1-like agonists, in particular SKF 82958, may be due to

activity at sites other than D_1-like receptors. Makihara et al. (2004) reported that SKF 82958 produced topographies of orofacial movements in the mouse that were different from those produced by SKF 38393 and SKF 83959, suggesting actions of SKF 82958 mediated by other mechanisms. Such an interpretation is supported by the observation that some behavioral effects of D_1-like agonists (A-68930 and SKF 83959) are conserved in D_1 receptor knockout mice (Clifford et al., 1999), indicating a role for mechanisms other than the D_1 receptor for the behavioral effects of at least some D_1-like agonists.

In summary, the present data demonstrate that the relationship between the locomotor stimulant effects of D_1-like receptor agonists and their intrinsic efficacies as measured by stimulation of AC or PI activity is not simple, if it exists at all. Given that differences in efficacy among D_1-like agonists are considered to be important pharmacological characteristics of these compounds (Bergman et al., 2000), the current classification of D_1-like receptor agonists as full or partial agonists based on their intrinsic efficacies may need to be carefully reevaluated.

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