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Differential antagonism of the effects of dopamine D_1-receptor agonists on feeding behavior in the rat

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Abstract. A series of experiments was conducted to examine the effects of dopamine D_1 receptor agonists on food intake in rats. In the first experiment, the D_1 agonist SKF 38393 (3.0–30.0 mg/kg) dose-dependently suppressed feeding during a 40 min food-access period, both in food-deprived rats and in non-deprived rats fed a highly palatable diet. Non-deprived rats were more sensitive to these effects of SKF 38393. Using the limited-access, food-deprivation procedure, a comparison was made between the anorectic effects of three D_1 agonists with differing intrinsic efficacies and receptor selectivities. Rank order of potencies for reducing food intake was SKF 82958 > SKF 77434 > SKF 38393 (ED_{50} values: 0.7, 3.6 and 15.7 mg/kg, respectively). Dose-related, surmountable antagonism by the D_1 antagonist SCH 23390 (0.01 and 0.03 mg/kg) was only obtained with SKF 82958 (0.1–10.0 mg/kg). In contrast to the other compounds, the effects of SKF 38393 were not appreciably altered by the D_1 antagonist. The effects of SKF 82958 were also antagonized by the D_2 receptor antagonist spiperone (0.05 and 0.1 mg/kg), although not in a dose-dependent manner. The present results support a role for D_1 receptors in central feeding mechanisms. They also suggest that the effects of SKF 38393 on feeding may not be mediated exclusively by the D_1 receptor and, further, that SKF 38393 may not serve well in behavioral studies as a prototypical D_1 agonist. The results also demonstrate the need for comparisons among several compounds in studies of D_1 mediated behavioral effects.

Key words: Dopamine – D_1 – D_2 – SKF 38393 – SKF 77434 – SKF 82958 – SCH 23390 – Spiperone – Feeding – Behavior – Rat

The behavioral correlates of dopamine D_1 receptor stimulation have been under scrutiny since the original subdivision of dopamine receptors into two subtypes (Kebabian and Calne 1979; Stoof and Kebabian 1984). The partial agonist SKF 38393 (Setler et al. 1978) has been used as a prototypical reference compound for several years. The behavioral effects of this compound in rodents were originally considered minimal, at least in comparison with the effects of dopamine D_2 receptor agonists, but this view has been changing recently (for reviews, see Clark and White 1987; Waddington and O'Boyle 1989). Perhaps the most prominent behavioral effect observed after administering SKF 38393 is grooming, both in rats (Molloy and Waddington 1984, 1987) and in mice (Starr and Starr 1986a), but not in guinea pigs (Brent 1991). A syndrome of diffuse behavioral activation has also been reported in well-habituated rats (Molloy and Waddington 1985), but this is not reliably observed in all species or test procedures (e.g. Starr and Starr 1986b). The same is true of the induction of perioral behaviors by SKF 38393 (reported by Rosengarten et al. 1983; Johannson et al. 1987; not observed by Murray and Waddington 1989). The D_1 antagonist SCH 23390 (Hyttel 1983; Iorio et al. 1983) is usually reported to be effective at blocking these agonist-induced behaviors, and other D_1 agonists which have become available more recently, such as SKF 75670 and SKF 77434, usually reproduce the effects of SKF 38393 (e.g. Arnt et al. 1988a; Murray and Waddington 1989).

One other behavior which appears sensitive to D_1 receptor agonism is feeding. Long before the advent of receptor subtype-specific compounds it was acknowledged that drugs acting at central dopaminergic sites either as indirect agonists, such as *d*-amphetamine (e.g. Leibowitz 1975), or as direct agonists, such as apomorphine (e.g. Barzaghi et al. 1973), can inhibit food intake across a range of test conditions. Gilbert and Cooper (1985) were first to demonstrate that SKF 38393 can also dose-dependently suppress food intake in rats. This effect seems to be centrally mediated, since the peripheral D_1 agonist fenoldopam was not an anorectic (Rusk and Cooper 1989a). The reduction in food intake is due to the R(+) isomer, can be reproduced by the partial D_1 agonist SKF 75670, and reflects reductions in the frequency of feeding bouts and in the local rate of eating (Rusk and

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Cooper 1989a; Cooper et al. 1990). Treit and Berridge (1990) have shown that the anorectic effect is not due to an enhancement of aversive palatability. Finally, the effect is measurable not only in non-deprived rats given access to a highly palatable diet, or in deprived rats with limited daily food availability, but is also detectable in free-feeding rats (Martin-Iverson and Dourish 1988).

Reductions in feeding behavior are also associated with dopamine D_2 receptor agonists (Rusk and Cooper 1988, 1989b; but see Martin-Iverson and Dourish 1988 for important qualifications), and with antagonists at both the D_1 receptor (e.g. Gilbert and Cooper 1985) and the D_2 receptor (e.g. Schneider et al. 1986), albeit that some D_2 antagonists can cause a short-term increase in food intake in free-feeding rats (Clifton et al. 1991). It would thus seem that any dopaminergic drug can disrupt food intake, as can many other non-dopaminergic agents. However, the fact that D_1 agonists produce these effects in the absence of any stereotypies or competing responses, and do not substantively affect the behavioral sequence associated with feeding, has led to the claim that this class of compounds might act directly on central mechanisms regulating feeding (Gilbert and Cooper 1985; Martin-Iverson and Dourish 1988; Cooper et al. 1990).

The broad aim of the experiments reported here was to examine the anorectic effects of D_1 agonists as a potential model for D_1 receptor agonism. To date, most studies of the behavioral effects of D_1 agonists in intact adult animals have tested single D_1 compounds (most commonly SKF 38393 or its active enantiomer). As regards feeding, the only comparison available is between SKF 38393 and SKF 75670 (Rusk and Cooper 1989a). Furthermore, studies to date have not reliably demonstrated D_1 receptor-specific, dose-related antagonism (Ladurelle et al. 1991; Zarrindast et al. 1991), although D_2 receptor specific antagonism of the anorectic effects of D_2 agonists has been reported (Rusk and Cooper 1988; Ladurelle et al. 1991; Zarrindast et al. 1991).

In the present study we compare three D_1 agonists with differing efficacies (by the adenylate cyclase assay) and binding characteristics. In addition to SKF 38393 we used SKF 77434 and SKF 82958; these are 3-*N*-allyl derivatives of SKF 38393. Intrinsic activities expressed relative to 100 μm dopamine in the adenylate cyclase assay are: SKF 38393, 46.4% ($\pm$ 4.4%); SKF 77434, 47.6% ($\pm$ 8.4%); SKF 82958, 148.8% ($\pm$ 19.5%) (from O'Boyle et al. 1989). Although precise values differ between assays, it appears clear that SKF 77434 has an intrinsic activity comparable with that of SKF 38393, whereas SKF 82958 has an efficacy exceeding that of dopamine (Pfeiffer et al. 1982; Weinstock et al. 1985; Andersen and Jansen 1990). Murray and Waddington (1989) report SKF 38393 to be more D_1 selective in vitro than either SKF 77434 or SKF 82958 (having a 50-fold separation between D_1 and D_2 affinities versus a 10-fold separation for the other two). We examined whether these pharmacological characteristics are related to the anorectic effects of these compounds, and assessed the receptor-specificity of the anorexia by testing each drug in combination with the D_1 antagonist SCH 23390 and by testing the most potent of the agonists after pretreatment with the D_2 antagonist spiperone. In the first experiment we compared two different test procedures to determine which might be most appropriate for repeated testing.

Materials and methods

Subjects. Twenty-one male Sprague-Dawley rats (Charles River, Wilmington MA) were housed individually with free access to water under a 12:12 h light cycle (lights on 07:00 hours). One group of 11 rats (non-deprived) remained on ad lib feeding throughout testing, a second group of 10 rats (deprived) was fed 15 g standard Purina lab chow daily, starting 1 week before testing. Mean weights of the non-deprived rats at the start and finish of experiment 1 were, respectively, 397.8 g (SE = 6.8 g) and 577.5 g (SE = 13.8 g). Mean weights of the eight food-deprived rats which completed all experiments were 374.3 g (SE = 8.3 g) at the start of the study and 372.8 g (SE = 12.4 g) at the end of experiment 3.

Apparatus. All test foods were presented in glass jars 7 cm in diameter, 5 cm high and weighing 238 g. A screw-on aluminium lid with an aperture of 4.5 cm helped to limit spillage. All testing was in the rats' home cages. Non-deprived rats received 40 min daily access to a highly palatable diet (from Gilbert and Cooper 1985) consisting of 50 ml sweetened condensed milk (Eagle brand) mixed with 200 ml tap water and 100 g powdered Purina (#5001) rodent lab chow. Deprived rats received 40 min daily access to the powdered diet only.

Drugs. ($\pm$)SKF 38393 HCl (1-phenyl-2,3,4,5-tetrahydro-(1H)-3-benzazepine-7,8-diol hydrochloride), SKF 77434 (($\pm$)-7,8-dihydroxy-3-allyl-1-phenyl-2,3,4,5-tetrahydro-1H-3-benzazepine hydrochloride), SKF 82958 HBr (($\pm$)-chloro-APB HBr; ($\pm$)6-chloro-7, 8-dihydroxy-3-allyl-1-phenyl-2, 3, 4, 5-tetrahydro-1H-3-benzazepine hydrobromide), R(+)-SCH 23390 HCl (R(+)-CHMB; R(+)-7-chloro-8-hydroxy-3-methyl-1-phenyl-2, 3, 4, 5-tetrahydro-1H-3-benzazepine hydrochloride) and spiperone HCl (R 5147, spiroperidol; 8-[4-(4-fluorophenyl)-4-oxobutyl]-1-phenyl-1, 3, 8-triazaspiro[4, 5] decan-4-one hydrochloride) were obtained from Research Biochemicals Inc. (Natick, MA). All drugs were dissolved in sterile water and injected at 1 ml/kg. The D_1 agonists were all injected IP; SCH 23390 and spiperone were injected SC; physiological saline was injected IP or SC as appropriate.

Data analysis. Data from the linear portions of the dose-response curves were analyzed to calculate ED_{50} values and their 95% confidence limits using standard ANOVA and linear regression techniques (Snedecor and Cochran 1967). When comparisons yielded non-overlapping 95% limits, a significant difference in ED_{50} was assumed. Parallel line bioassay techniques (Finney 1964) were used for relative potency estimates; the values obtained represent the dose (mg/kg) of the standard drug equal to 1 mg/kg of the comparison drug. A significant relative potency difference was assumed when the 95% confidence limits did not include 1.0. Dunnett's tests were used to evaluate differences between pairs of conditions.

Experiment 1

Procedure

Food intake in response to SKF 38393 was compared between non-deprived and deprived rats. Rats were allowed daily access to their given diet for 40 min per day (at approximately the same time of day), 5 days per week. Rats were weighed daily before testing. Drug testing began after 7 days of familiarization to the novel diets. Deprived rats received no other food, except over weekends when they received 15 g per day standard lab pellets (Purina). Drugs were administered to the deprived rats only if their group mean body weight deviated less than 5% from the initial value. At least one

saline injection was interposed between drug injections, with no more than two drug trials conducted each test week; effects of drug doses were determined in mixed order. Injection of saline or SKF 38393 (IP) was 15 min before the feeding jars were placed inside the cages. The jars were removed from the cages 40 min later. The jars and their contents were weighed before and after being presented to the rats, and the subtraction of post- from pre-feeding values provided the measure of food intake.

Results and discussion

SKF 38393 dose-dependently suppressed food intake in both groups (Fig. 1), but was less potent in the food-deprived rats. The ED_{50} values were calculated for each curve, even though regression analysis revealed significant deviation from linearity in both cases. The ED_{50} values (95% confidence limits in parentheses) for the non-deprived and deprived rats were, respectively, 8.2 mg/kg (7.1–9.4 mg/kg) and 15.7 mg/kg (12.8–19.2 mg/kg). These results replicate those of Rusk and Cooper (1989) and Cooper et al. (1990) in demonstrating an anorectic effect of SKF 38393 in both test situations. They also suggest that the palatable-diet procedure is more sensitive than the deprivation procedure to disruption by D_1 agonists.

After testing, daily food intake remained consistent within subjects in the food-deprived group, but declined in the non-deprived group (which showed continuing, large weekly weight gains: for values, see above). Therefore, although the palatable-diet procedure was more sensitive to the effects of the D_1 agonist, it was considered unsuitable for chronic, repeated-measures studies. Therefore all subsequent experiments were with the food-deprived rats.

Experiment 2

Procedure

Using the ten food-deprived rats, a comparison was made of the anorectic effects of three D_1 receptor agonists (SKF 38393, SKF 77434 and SKF 82958) and their antagonism by the D_1 antagonist SCH 23390. First, a dose-response curve was obtained for SCH 23390 (injected SC, 30 min, before food access; saline injected IP, 15 min before access) from which two doses were selected for all subsequent antagonism tests. Agonist-antagonist interactions were then tested using selected doses of SKF 38393 (IP, 15 min before feeding). Second, a dose response curve for the anorectic effects of SKF 77434 was derived in the same way as for SKF 38393; selected doses of SKF 77434 were then used in subsequent antagonism tests, as before. Finally, the same process was repeated using the D_1 agonist SKF 82958. Selected doses of the agonists and antagonist were re-tested during and after experiments 2 and 3 to ensure the reliability of the effects; retest values at the end of the study are given after experiment 3.

Results and discussion

The D_1 antagonist SCH 23390 produced a dose-related reduction in food intake (Fig. 2). The main effect of dose was significant [$F(4,36) = 10.17$, $P < 0.001$], and Dunnett's tests revealed that only at 0.01 mg/kg was the difference between saline and drug not significant (see Fig. 2). Consequently, we chose 0.01 and 0.03 mg/kg (not significantly and just significantly different from control, respectively) as the antagonist doses for subsequent tests.

Dose-response functions for the three D_1 agonists (SKF 38393, SKF 77434 and SKF 82958) and their interactions with SCH 23390, are presented in Fig. 3 (data for SKF 38393 alone are the same as those in experiment 1). The ED_{50} values for SKF 77434 and SKF 82958 were, respectively, 3.6 mg/kg (95% C.L.: 2.8–4.5 mg/kg) and 0.7 mg/kg (95% C.L.: 0.5–0.8 mg/kg); thus both compounds were considerably more potent than SKF 38393, which had an ED_{50} value of 15.7 mg/kg (95% C.L.: 12.8–19.2 mg/kg). None of the compounds were observed to induce obvious perioral movements, although each appeared to elevate levels of grooming, and SKF 82958 at higher doses seemed to increase the incidence of sniffing; however, these behaviors were not quantified.

Antagonism of effects of SKF 38393. There was no dose-dependent antagonism of the anorectic effect of SKF 38393 by SCH 23390 (Fig. 3, left panel). Both antagonist curves deviate from parallelism when compared with the curve of agonist alone, invalidating relative potency estimates. Dunnett's tests revealed no effect of either dose of

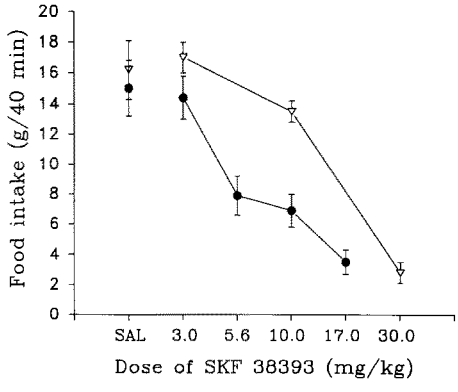

Fig. 1. Effect of different test conditions on the reduction in feeding caused by the D_1 receptor agonist SKF 38393. One group was non-deprived and received 40 min access to a highly palatable diet (●); the other group was 23 h 20 min food-deprived (▽) and given 40 min access to powdered chow. SKF 38393 was injected IP 15 min before food availability

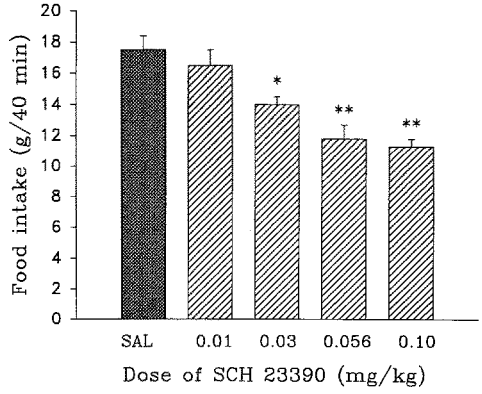

Fig. 2. Effect of the D_1 receptor antagonist SCH 23390 on food intake (measured as g powdered diet consumed during a 40 min access period) in rats deprived for 23 h 20 min. SCH 23390 was injected SC 30 min before and saline IP 15 min before food availability, $*P < 0.05$; $**P < 0.01$ in comparison with saline

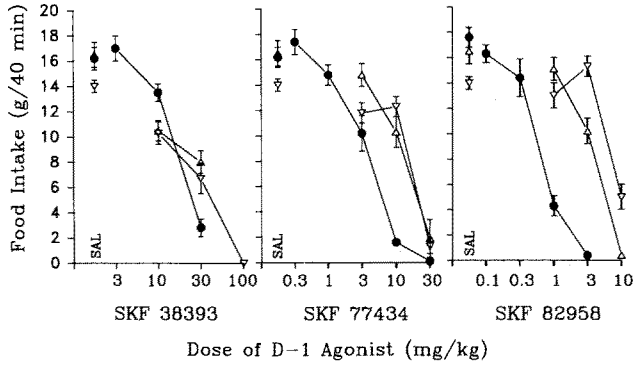

Fig. 3. Comparison of the effects of three different D_1 receptor agonists on feeding, and their interactions with the D_1 receptor antagonist SCH 23390. *Left panel*: SKF 38393; *center panel*: SKF 77434; *right panel*: SKF 82958. SCH 23390 was injected SC 30 min before and the agonist IP 15 min before food availability (●) Saline; (△) SCH 23390 0.01 mg/kg; (▽) SCH 23390 0.03 mg/kg

antagonist at 10 mg/kg of SKF 38393 ($ts < 2.38$, $Ps > 0.05$), but significant antagonism by both doses at 30 mg/kg SKF 38393 (SCH 23390 0.01 and 0.03 mg/kg, respectively: $t = 3.58$, $P < 0.05$; $t = 2.71$, $P < 0.05$).

Antagonism of effects of SKF 77434. In the case of SKF 77434 antagonism by SCH 23390 was indicated by a clear rightward shift in the dose-response function; however, again there was no obvious dependence on antagonist dose (Fig. 3, center panel). This lack of dose-dependence was confirmed by calculating relative potencies of SKF 77434 following pretreatment by 0.01 and 0.03 mg/kg SCH 23390; potencies relative to SKF 77434 alone (95% confidence intervals in parentheses) were, for 0.01 and 0.03 mg/kg SCH 23390 respectively, 3.2 (2.2–4.6) and 2.9 (2.1–3.9).

Antagonism of effects of SKF 82958. The D_1 antagonist SCH 23390 antagonized the effects of SKF 82958. Only with this agonist was dose-related antagonism apparent (Fig. 3, right panel). Relative potencies of SKF 82958 following SCH 23390 at 0.01 and 0.03 mg/kg, respectively, were 4.6 (95% C.L.: 3.5–6.0) and 10.0 (95% C.L.: 7.6–13.6).

Thus, of the three D_1 agonists being compared, only SKF 82958 appeared to interact with the antagonist SCH 23390 in a classical manner. The agonist-antagonist interactions were quantitatively different for each agonist.

Experiment 3

Procedure

Over the course of the final experiment, two rats were eliminated from the sample because of poor health, leaving eight rats. Experiment 3 examined the receptor-specificity of the behavioral effects of the D_1 agonists by testing the D_2 receptor antagonist spiperone (injected SC, 30 min before food access) against selected doses of the D_1 agonist SKF 82958. First, a dose-response function was determined for the anorectic effects of spiperone; then, as with SCH 23390, two doses were selected for tests of antagonism against selected doses of SKF 82958 (in random order).

Results and discussion

Spiperone produced a dose-related decrease in food intake (Fig. 4). The main effect of dose was significant [$F(3,21) = 24.03$, $P < 0.01$], and Dunnett's tests revealed that only the 0.05 mg/kg dose failed to reduce feeding significantly below control levels (see Fig. 4). Thus we selected doses of 0.05 and 0.1 mg/kg (not significantly and just significantly different from saline, respectively) as antagonist doses for combination with SKF 82958.

Figure 5 presents the results of the agonist/antagonist interaction experiment. The 0.05 mg/kg dose failed to produce a parallel shift in the dose-response function, and although there is some indication from the figure that antagonism occurred at 3.0 mg/kg SKF 82958, this was not borne out by ANOVA at this dose [overall at 3.0 mg/kg: $F(2,14) = 3.54$, $P > 0.05$].

The regression of spiperone 0.10 mg/kg in combination with SKF 82958 was not significant [$F(1,19) = 3.90$, $P > 0.05$], making an ED_{50} estimate unreliable; however, the parallel line bioassay demonstrated a relative potency shift of 3.6 (95% C.L.: 1.8–6.9) with respect to SKF 82958 alone. At the 0.1 mg/kg dose, there was clear indication of antagonism by the D_2 antagonist.

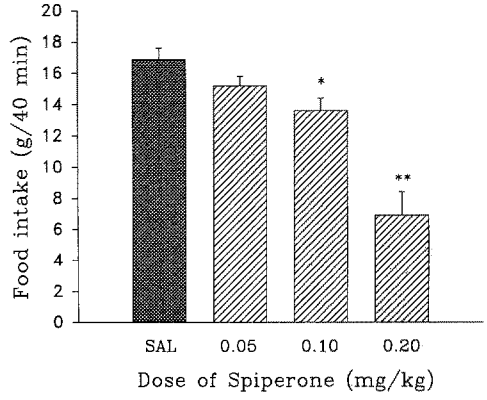

Fig. 4. Effect of D_2 receptor antagonist spiperone on food intake. Details as for Fig. 2

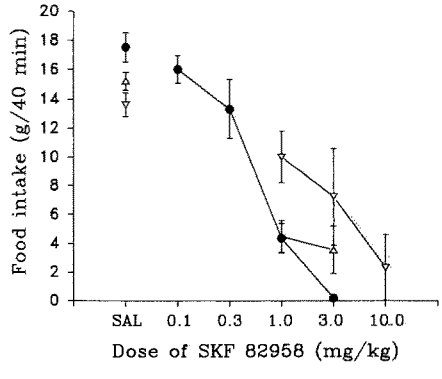

Fig. 5. Effect of pretreatment with D_2 antagonist spiperone on the inhibition of feeding by the D_1 receptor agonist SKF 82958. Details as for Fig. 3 (●) Saline; (△) spiperone 0.05 mg/kg; (▽) spiperone 0.10 mg/kg

Retest of selected doses. Single doses of each D_1 agonist were retested to determine whether sensitivity to the anorectic effects of these compounds changed during the course of the study. Retest values were: SKF 38393 30.0 mg/kg, 1.5 g (SE = 0.6 g); SKF 77434 1.0 mg/kg, 14.3 g (SE = 1.1 g); and SKF 82958 1.0 mg/kg, 3.1 g (SE = 0.7 g). These compare with first-test values of (respectively): 2.8 g (SE = 0.7 g), 14.8 g (SE = 0.8 g), and 4.3 g (SE = 0.8 g). None of these test-retest differences is statistically significant ($Ps > 0.05$).

Discussion

All three dopamine D_1 receptor agonists produced dose-dependent reductions in feeding behavior, with a rank order of potency: SKF 82958 > SKF 77434 > SKF 38393. This equivalence of effect between D_1 agonists confirms and extends the finding that SKF 75670, like SKF 38393, suppresses food intake (Rusk and Cooper 1989). However, the relative potencies differ from those obtained by studying grooming behavior (Murray and Waddington 1989): in this situation the potency ranking is SKF 77434 > SKF 82958 > SKF 38393. Neither test behavior (grooming or feeding) yields results which are in direct accordance with either the in vitro D_1 receptor affinities of these compounds, or their intrinsic activities in stimulating adenylate cyclase (O'Boyle et al. 1989). Although SKF 82958 is the most efficacious by this assay, and the most potent behaviorally, SKF 38393 and SKF 77434 have equivalent cyclase activities but very different behavioral potencies. SKF 38393 has poor brain penetrability, and this may explain its reduced in vivo activity (e.g. Anderson et al. 1987), but caution is required in attributing the limited effects of SKF 38393 to its low lipophilicity, since the drug can produce clear behavioral and physiological effects at low systemic doses (Clark and White 1987). Nevertheless, there is not always a direct correspondence between in vitro and in vivo affinities for D_1 agonists at the D_1 receptor, and indeed the results are not incongruent with the in vivo affinities reported by Andersen and Jansen (1990). Further comparisons between more compounds are necessary before behavioral effects can be meaningfully associated with receptor affinity or effects at the second messenger level. In fact, with regard to the efficacies of D_1 agonists in the adenylate cyclase assay and in behavioral tests, no unequivocal relationship has yet been demonstrated (Arnt et al. 1988a; Arnt and Hyttel 1988; Murray and Waddington 1989). Indeed, drastic reductions in D_1 receptor number and cAMP production using the receptor-inactivating compound EEDQ do not substantively affect behavioral responsiveness even to partial D_1 agonists such as SKF 75670 (Arnt et al. 1988b). Anderson et al. (1990) have taken this apparent absence of a correlation between cyclase activity and behavior as evidence for there being more than one D_1 receptor subtype, perhaps not cyclase-coupled. In fact there have been repeated claims for the existence of multiple D_1 receptor subtypes (e.g. Mailman et al. 1986; see Waddington and O'Boyle 1989), and Sunahara et al. (1991) recently described a receptor (termed D_5) closely homologous to the D_1 receptor but having a higher affinity for dopamine.

The reduction in food intake by SKF 82958 was the most effectively antagonized (and dose-dependently, unlike the other two compounds), whereas the anorectic effect of SKF 38393 was the least clearly antagonized. SKF 38393 was unique in demonstrating no parallel shifts in the dose-response function, although a limited degree of antagonism (but not dose-related) was observed at 30 mg/kg SKF 38393 (see Fig. 3); this is important in that it might suggest a qualitatively different mechanism of action for these behavioral effects of this compound. The profile observed is similar to that reported for the effects of SCH 23390 on reductions of food consumption caused by cocaine (Rapoza and Woolverton 1991). The present result is by no means exceptional. Ladurelle et al. (1991) showed antagonism of SKF 38393-induced anorexia by SCH 23390, but only at a single dose of the agonist. On the other hand, Zarrindast et al. (1991) tested a range of agonist and antagonist doses, and were completely unable to attenuate the anorexia. Instead, the 5-HT antagonist metergoline was effective at blocking the effect. Taken together, these studies imply a qualitatively different mode of action of SKF 38393 in disrupting food intake. In fact, with regard to the behavioral effects of SKF 38393 in general, it may be argued that no unequivocal dose-dependent antagonism by SCH 23390 has yet been reported. Thus although Molloy and Waddington (1985) report blockade by SCH 23390 of grooming induced by R-SKF 38393, the two antagonist doses used both exceed a level which causes profound catalepsy (Meller et al. 1985; Morelli and DiChiara 1985). This problem of excessive dose is common to many studies using this behaviorally-potent D_1 antagonist (e.g. Rosengarten et al. 1983; Molloy and Waddington 1985; Molloy et al. 1986; Murray and Waddington 1990). Other studies indicating no clear dose-dependence in the antagonism of the behavioral effects of SKF 38393 include Kamien et al. (1987), Starr and Starr (1986a) and Witkin et al. (1991). Thus although it is apparent that some behavioral effects of SKF 38393 can be reversed by D_1 antagonists, it appears that at least some of its behavioral actions are not mediated by D_1 receptors (or the same population of D_1 receptors). The lack of dose-dependence in the antagonism of the effects of SKF 77434 is perhaps surprising, given for example that Murray and Waddington (1989) demonstrate dose-dependent antagonism of SKF 77434-induced grooming by R-SKF 83566. Whether the difference is due to the different antagonists or to the different behaviors again must await further study.

The receptor specificity of the effects of SKF 82958 might be questioned due to the antagonism obtained using the D_2 antagonist. Although Clifton et al. (1991) have demonstrated that some D_2 antagonists can increase short-term food intake, this cannot be the case in the present test circumstances (see Fig. 4). Although selectivity of the compound might be important, since the separation between D_1 and D_2 affinities for SKF 82958 is only around 10-fold (O'Boyle et al. 1989), the more selective compound SKF 38393 also produces behavioral effects which are readily antagonized by D_2 receptor ligands, as does SKF 77434 (e.g. Molloy and Waddington 1985;

Molloy et al. 1986; Waddington et al. 1988; Murray and Waddington 1989; Horita and Carino 1991; Zarrindast et al. 1991). The notion that D_1 stimulation can synergistically enhance effects mediated at the D_2 receptor has become widely accepted (e.g. Barone et al. 1986; Braun and Chase 1986; see Clark and White 1987, and Waddington and O'Boyle 1989 for reviews); it is now being suggested that D_2 receptor activation can also facilitate certain effects mediated at D_1 receptors (e.g. Murray and Waddington 1989; Waddington and O'Boyle 1989). This would explain the present result if the anorectic effect of D_1 agonists requires a certain level of D_2 receptor tone. Unlike other instances where D_2 antagonists attenuate the effects of D_1 agonists, the antagonism of food intake reduction cannot be explained according to non-specific motor depression by the antagonist, since in this test situation all agonists and antagonists apparently affect behavior in the same direction. This might make it a particularly interesting model for assessing D_1/D_2 receptor subtype interactions.

Thus the model of feeding-inhibition by D_1 agonists has proven its usefulness in a number of respects. First, it demonstrates a generality of effect across D_1 agonists, and raises the possibility of relating behavior to efficacy and/or selectivity of the compounds; on the other hand, it provides a possible means for differentiating between D_1 agonists on the basis of their interactions with D_1 antagonists. The results indicate that the behavioral effects of SKF 38393 may need to be re-evaluated in the light of its unusual profile of interaction with SCH 23390. Finally, the study suggests that this kind of procedure may be useful for the further examination of interactions between D_1 and D_2 dopamine receptor subtypes.

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