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The Selective Dopamine D_1 Receptor Agonist SK&F 38393: Its Effects on Palatability- and Deprivation-Induced Feeding, and Operant Responding for Food

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RUSK, I N AND S J COOPER *The selective dopamine D_1 receptor agonist SK&F 38393 Its effects on palatability- and deprivation-induced feeding, and operant responding for food* PHARMACOL BIOCHEM BEHAV **34**(1) 17–22, 1989 —A series of experiments investigated the involvement of the dopamine D_1 receptor subtype in relation to feeding responses The selective D_1 agonists, SK&F 38393 (1 0–20 mg/kg) and SK&F 75760 (5 mg/kg), significantly reduced palatable food consumption in nondeprived rats The anorectic effect of SK&F 38393 (10 mg/kg) was additive with that of the selective D_2 receptor agonist, N-0437 (0 3 mg/kg) In nondeprived mice, SK&F 38393 had a stereoselective effect to reduce palatable food intake At a peripherally-selective dose (3 0 mg/kg), the peripheral dopamine D_1 receptor agonist, fenoldopam, had no effect on food intake At 10 mg/kg, however, it exhibited anorectic properties, although this may have been due to some penetration of the blood-brain barrier In rats adapted to a food-deprivation schedule, SK&F 38393 (3 0–30 mg/kg) produced significant dose-dependent reductions in consumption of powdered chow and in lever-pressing for food pellets on a FR8 schedule of reinforcement In rats adapted to a water-deprivation schedule, SK&F 38393 (3 0–30 mg/kg) was substantially less effective in reducing water intake The results are discussed in terms of a possible selective effect of D_1 agonist activity on feeding behaviour

Anorexia Dopamine D_1 receptor Fenoldopam N-0437 SK&F 38393 SK&F 75760 Rats Mice

EVIDENCE indicates that stimulation of centrally-located dopamine receptors can lead to suppression of food. Thus, the dopamine receptor agonists apomorphine (6, 19, 29), 2-di-n-propylamine-4,7-dimethoxyindase, RDS-127 (1), pergolide (15), and the ergot derivatives, bromocriptine, lisuride and lergotrile (9) reduce the consumption of standard laboratory diets during restricted access to food The reductions in food intake are antagonized by a number of dopamine antagonists (18,19), but not by the peripheral dopamine antagonist, domperidone (9,29) Leibowitz and Rossakis have mapped dopamine-sensitive sites in the rat brain, and have shown that the perifornical region of the lateral hypothalamus is most sensitive to the feeding-suppressant effect of dopamine (24) Dopamine antagonists block the dopamine effect (25), while intrahypothalamic injections of sulpiride, a specific D_2 receptor antagonist, elicits feeding and drinking in satiated rats (30)

To a great extent, experimental attention has been largely devoted to drug actions at dopamine D_2 receptors in relation to ingestive behaviour, e g , (4, 11, 30, 32, 34) The relative neglect of drug effects at the D_1 receptor is somewhat surprising, since dopamine release is thought to activate both D_1 and D_2 receptors simultaneously (23,39) Furthermore, dopamine itself has a 15 times greater affinity for the D_1 than for the D_2 receptor (35).

Nevertheless, some evidence for an anorectic effect of the selective D_1 receptor agonist (±)-SK&F 38393 (36) is available We demonstrated a dose-related suppression of palatable food consumption in a 30-min test after SK&F 38393 (3 0–30 mg/kg) (13) Since the reduction in food intake occurred in the absence of gross behavioural stereotypy, we suggested that SK&F 38393 may act directly on feeding mechanisms. More recently, Martin-Iverson and Dourish reported that 5 mg/kg of (±)SK&F 38393 significantly reduced consumption of laboratory chow in a 4-hr test using nondeprived rats (27) They also suggest that stimulation of D_1 receptors may have a direct influence on feeding behaviour It is also noteworthy that, at least in part, *d*-amphetamine's anorectic effect may be mediated through D_1 receptor activation (13)

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In the present series of experiments, we have investigated the effects of (±)-SK&F 38393 more extensively, using a number of feeding response paradigms Its effects were evaluated not only on the consumption of a highly-palatable diet, but also on deprivation-induced feeding, and on operant responding for food under a FR8 schedule of reinforcement The resolved enantiomers of SK&F 38393 were tested separately in mice As a check on the generality of the SK&F 38393 effect, a further centrally-active selective D_1 receptor agonist, SK&F 75760 (35) was also tested in the palatable food paradigm The peripheral dopamine D_1 receptor agonist, fenoldopam (7, 17, 26), was tested to control for possible peripheral changes having an indirect effect on food intake Finally, the effects of (±)-SK&F 38393 on deprivation-induced water consumption in rats were examined, to assess the degree of behavioral specificity of the drug's anorectic effect

METHOD

Animals

The subjects were 105 adult male hooded rats (General strain, 250–400 g) which were bred in the Psychology Department, University of Birmingham, and 28 adult male Swiss CD1 albino mice (27–40 g), purchased from Charles River, U K They were housed singly, and were maintained on a 12-hr light/dark cycle with lights on at 8 a m

Drugs

Racemic SK&F 38393 (1-phenyl-7,8-dihydroxy-2,3,4,5-tetrahydro-1*H*-3-benzazepine) hydrochloride and fenoldopam methane-sulphonate (SK&F 82526, 6-chloro-2,3,4,5-tetrahydro-1-(-4-hydroxyphenyl)-1H-3-benzazepine-7,8-diol, methane-sulphonate) were generously supplied courtesy of Dr Jan Skidmore, Smith Kline & French Research Limited, Welwyn, Herts, U K The resolved enantiomers, R(+)-SK&F 38393 hydrochloride (active) and S(−)-SK&F 38393 hydrochloride (inactive) were purchased from Research Biochemicals Inc A sample of SK&F 75760 hydrobromide was kindly provided by Dr E Nielsen of Novo Industri, Bagsvaerd, Denmark The selective dopamine D_2 agonist, N-0437 (5,6,7,8-tetrahydro-6-propyl[2-(2-thienyl)ethyl]amino]-1-naphthalenol hydrochloride) was supplied by Nelson Research, Irvine, CA The drugs were dissolved in distilled water and administered intraperitoneally Drug doses are expressed in terms of the salts Injection volumes were 1 ml/kg for rats and 5 ml/kg for mice

Procedures

Palatable food consumption Rats were adapted to eating a sweetened mash diet in daily 30-min sessions in their home cages The mash consisted of 50 ml sweetened condensed milk, 150 ml ground rat maintenance diet No 1 (Special Diet Services Ltd, Essex, U K) and 200 ml distilled water The animals were given 40–50 g portions presented in a plastic shallow petri dish, and were considered adapted when baseline levels of intake reached asymptote, after 8–10 days of training By the end of this period, the latency to begin eating the diet was minimal for all animals The food was weighed before and after test sessions to 0 1 g accuracy, and care was taken to collect spillage All tests took place between 12 00 and 16 00 hr during the light period

Twenty naive rats were allocated to two equal groups In one group, each animal was tested on five occasions after 0, 1 0, 3 0, 10 and 20 mg/kg of (±)-SK&F 38393 respectively The order of injections was balanced across subjects, and at least 48 hr intervened between successive injections For the first injection, each dose level (including vehicle) was tested in two animals Thereafter, animals were tested with other injections in order, maintaining two animals per dose level on each day of testing In the second group, each animal was tested on two occasions after 0 or 5 0 mg/kg of SK&F 75760 Half of the animals were injected with vehicle first, and half with SK&F 75760 There was a 48-hr interval between the two injections In a separate drug-combination study, 28 new rats were allocated to four equal treatment conditions vehicle/vehicle, (±)-SK&F 38393 (10 0 mg/kg) + vehicle, vehicle + N-0437 (0 3 mg/kg), (±)-SK&F 38393 (10 0 mg/kg) + N-0437 (0 3 mg/kg) The D_1 agonist was injected 30 min before the feeding test, and the D_2 agonist was injected 15 min later Doses of the two drugs were chosen to give modest reductions in food intake, and were given in combination to determine whether or not their effects are additive To determine whether or not stimulation of peripheral D_1 receptors affects palatable food consumption, 30 new rats were divided into three equal groups They were injected IP with fenoldopam at 3 0 or 10 mg/kg, or with vehicle respectively, 30 min before the feeding test Fenoldopam poorly penetrates the blood-brain barrier, and at 2 0 mg/kg IP is devoid of central D_1 agonist activity in rats (17), at 10 mg/kg, however, there is evidence for slight central activity (17) Hence, if the anorectic effect of SK&F 38393 is centrally-mediated, we expected to find no effect of fenoldopam at 3 0 mg/kg, but possibly some reduction in intake at the higher dose

Because of a limited supply of the compounds, the effects of the R(+)- and S(−)-enantiomers of SK&F 38393 on palatable food consumption were tested in adult mice Individually-housed animals were adapted to eating the sweetened mash in daily 20-min test sessions After 10 days, when levels of intake had reached asymptotic values, animals were injected with vehicle, 3 0, 10 0 or 30 mg/kg of either the R(+)-enantiomer (n = 5 per group) or the S(−)-enantiomer (n = 7 per group) Injections were made 20 min before the feeding test

Deprivation-Induced Feeding

Eight rats were housed individually and were placed on a daily food-restriction schedule to maintain body weight at about 85% of the free-feeding weight The animals were presented with approximately 20 g of powdered laboratory chow in glass jars each day as their sole source of food Water was available ad lib Food intake was measured by weighing before and after the first 30 min of food presentation, spillage being taken into account When stable baseline levels of intake had been achieved (after 10 days), each rat was tested on four occasions, following injection of 3 0, 10 0 or 30 0 mg/kg of (±)-SK&F 38393, or its vehicle, respectively The order of injection was counterbalanced across animals, and there were 48-hr intervals between successive injections

Fixed-Ratio 8 Performance

Nine rats were similarly placed on a daily food-restriction schedule to maintain them at 85% of free-feeding body weight They were trained to lever-press in commercial operant chambers (Campden Instruments) using conventional procedures They were each given several one-hour habituation periods in the chamber, when each lever-press resulted in delivery of a single 45-mg sweetened pellet (Larkhall Laboratories, London) When the lever-pressing response had been shaped by an observer delivering food for successive approximations of the response, each animal was given 10 sessions (20 min duration) in which the reinforcement contingency was changed gradually from a CRF to an FR8 schedule of reinforcement Each rat then had at least one week's training of lever-pressing under the FR8 schedule Each animal

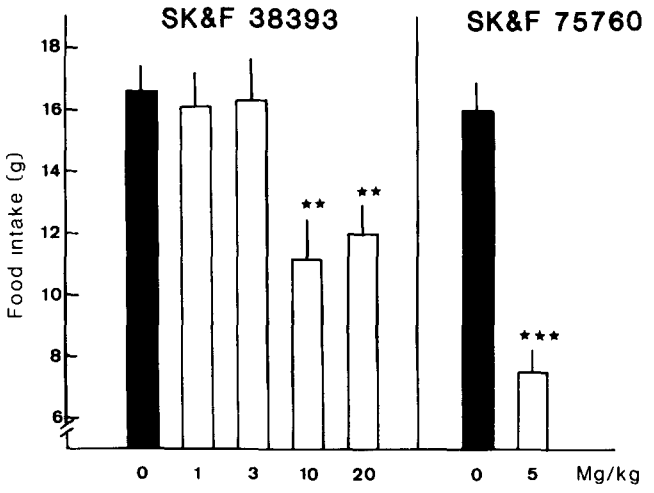

FIG 1 Palatable food consumption in rats was significantly reduced by 10 and 20 mg/kg of SK&F 38393 (left panel), and by 5 mg/kg SK&F 75760 (right panel) 30-min test Results are shown in terms of mean+S E M (N = 10 per condition) Levels of significance in comparison with corresponding vehicle control $*p<0$ 05, $**p<0$ 01, $***p<0$ 005 (Dunnett's t-test)

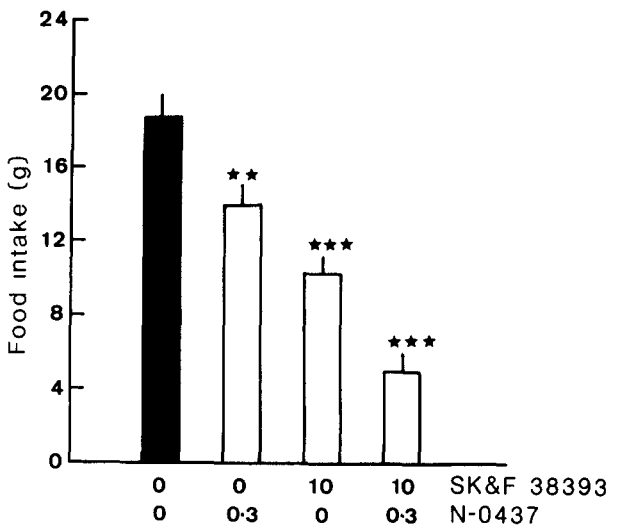

FIG 2 Additive effects of 0 3 mg/kg of N-0437 (a selective D_2 receptor agonist) and 10 mg/kg of SK&F 38393 (a selective D_1 agonist) to reduce palatable food intake in rats Results are shown in terms of mean+S E M (N = 7 per group) Levels of significance see Fig 1 legend

was then tested on four occasions, following injection of vehicle, 3.0, 10 0 or 30 0 mg/kg (±)-SK&F 38393, respectively. The order of injection was counterbalanced across animals, and at least one drug-free day separated successive injections During the 15-min test period, cumulative responses were recorded at 5-min intervals

Deprivation-Induced Drinking

Ten naive rats were housed individually and were placed on a daily 22-hr water-deprivation schedule for 10 days, by which the levels of water consumption in the first 30 min of access to water (in the absence of food) had stabilised. Food was available ad lib in the home cage at all other times. Water intake (ml) in the 30-min period of access immediately following water deprivation was measured by reading levels in graduated cylinders, clipped to the outside of the cages, with the stainless-steel drinking spouts positioned inside Each rat was tested on four occasions, following injection of 3.0, 10 0 or 30 0 mg/kg of (±)-SK&F 38393, or its vehicle, respectively. The order of injection was counterbalanced across animals, and at least 48 hr separated successful injections

Statistical Analyses

The data were analysed using analysis of variance procedures Means for individual drug dose conditions were compared with the corresponding vehicle condition using Dunnett's t-test

RESULTS

Palatable Food Consumption

In rats, (±)-SK&F 38393 significantly reduced palatable food consumption, $F(4,36) = 11\ 63$, $p<0.001$ (Fig. 1) Significant reductions occurred following the administration of 10 mg/kg (33 0% reduction) and 20 mg/kg (27.7%) of SK&F 38393 A greater effect occurred after injection of 5 mg/kg of SK&F 75760 (53%) When (±)-SK&F 38393 (10 mg/kg) was given in conjunction with the selective dopamine D_2 receptor agonist N-0437 (0.3 mg/kg), there was an additive effect to reduce food consumption (Fig 2) In combination, the two compounds reduced intake by 72 6%, separately, SK&F 38393 reduced the level of feeding by 44 8% and N-0437 reduced it by 25 9%

In the fenoldopam experiment, the control level of food intake was 19 9 ± 1.3 g in the 30-min test At 3.0 mg/kg, fenoldopam had no significant effect on intake 17.3 ± 1 1 g However, at 10 mg/kg fenoldopam, the level of food intake was 14.8 ± 1 1 g, which was significantly less ($p<0$ 05, Dunnett's t-test) than the control value

In mice, the active enantiomer R(+)-SK&F 38393 produced significant suppression of food consumption at each dose tested, $F(3,16) = 17\ 5$, $p<0$ 001 At 3.0 mg/kg, intake was reduced by 29.9%; at 30 mg/kg, food intake was potently suppressed by 85 5% (Fig. 3) In contrast, the inactive enantiomer S(−)-SK&F 38393 (3.0–30 mg/kg) had no significant overall effect on food intake, $F(3,24) = 2.55$, N S

Deprivation-Induced Food Intake

In food-deprived rats, (±)-SK&F 38393 (3 0–30 mg/kg) produced a dose-dependent reduction in powdered food intake (Fig 4) At 3 0 mg/kg, food intake was significantly reduced by 18 8%, at 10 mg/kg by 57.2%, while at 30 mg/kg feeding was almost completely suppressed.

Operant Responding for Food

Cumulative levels of lever pressing under a FR8 schedule of food reinforcement following administration of 3 0–30 mg/kg (±)-SK&F 38393 are shown in Fig 5. The results indicate that levels of responding following injection of the vehicle remained relatively constant over the 15-min test SK&F 38393 produced significant dose-related reductions in response rates, which were detectable within the first 5-min period, and in subsequent intervals At 15 min, the reductions in response rates were 7 9% after 3 0 mg/kg (±)-SK&F 38393, 61.7% after 10 mg/kg and 91 7% after 30 mg/kg.

Deprivation-Induced Drinking

The results for the effects of (±)-SK&F 38393 on water

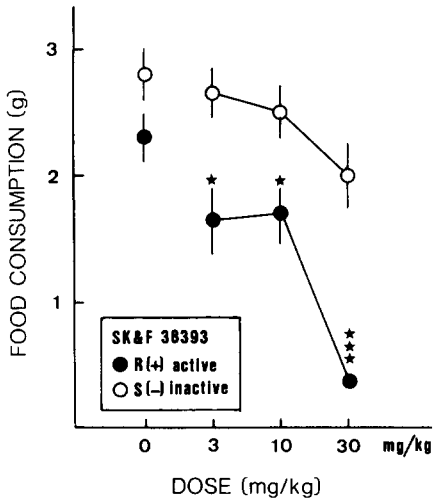

FIG 3 R(+)-SK&F 38393 produced a dose-related reduction in palatable food consumption in mice S(−)-SK&F 38393 had no significant effect on food intake Levels of significance see Fig 1 legend

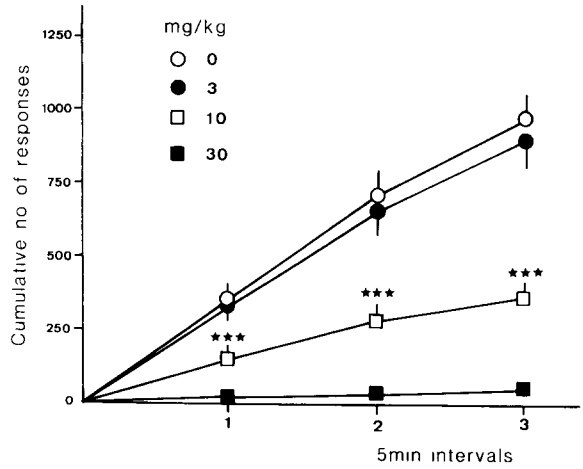

FIG 5 SK&F 38393 dose-dependently reduced operant responding for food on a FR8 schedule of reinforcement in rats The results are shown as mean ± S E M number of cumulative responses over a 15-min session (N = 9 per condition) Responding was significantly attenuated at 10 mg/kg of SK&F 38393, and completely eliminated at 30 mg/kg Level of significance see Fig 1 legend

consumption in water-deprived rats are shown in Table 1 There was a significant, dose-dependent reduction in water intake, $F(3,27) = 10\ 59$, $p<0\ 001$ There was no effect on drinking at 3 0 mg/kg (13 4% reduction), and a significant reduction at 30 0 mg/kg (29 1%) Hence, (±)-SK&F 38393 was considerably less potent in its reduction of deprivation-induced drinking than in its reduction of deprivation-induced feeding

DISCUSSION

The present data confirm earlier findings that the selective dopamine D_1 agonist, SK&F 38393, significantly reduces food intake in the rat (13,27) They also extend previous observations and show that, first, (±)-SK&F 38393 is effective as an anorectic in food-deprived rats, producing a dose-dependent reduction in food intake over the dose range, 3 0–30 mg/kg Second, SK&F 38393, in the form of the R(+)-enantiomer, was very effective in reducing palatable food consumption in mice Third, (±)-SK&F 38393 not only reduces food intake, but also reduces operant responding for food Dopamine D_1 receptor stimulation leads, therefore, to a reduction in appetitive responding in addition to its effects on the consummatory response of food ingestion

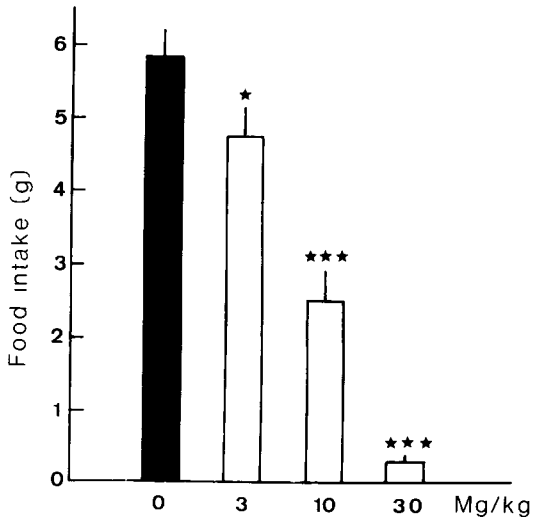

FIG 4 SK&F 38393 produced significant, dose-related reductions in powdered chow consumption in food-deprived rats Results are shown in terms of mean+S E M (N = 8 per group) Levels of significance see Fig 1 legend

Several important pharmacological results emerged from the present series of experiments The stereoselectivity of the SK&F 38393 effect on food intake in mice satisfies a necessary criterion for dopamine D_1 receptor mediation (3,28) However, it must be noted that the comparison between the effects of the enantiomers of SK&F 38393 has yet to be made in rats We report for the first time that SK&F 75760, another selective D_1 agonist, significantly reduced palatable food consumption in rats The relevant D_1 receptors appear to be located centrally, rather than peripherally Fenoldopam (SK&F 82526) is a potent D_1 agonist which only poorly penetrates the blood-brain barrier (17) It is ineffective in small doses in drug discrimination studies in which rats have been trained with a SK&F 38393 cue (3,22) In our experiment, fenoldopam (3 0 mg/kg) had no effect on palatable food consumption, and therefore we conclude that stimulation of peripheral D_1 receptors does not underlie SK&F 38393's anorectic effect At the

TABLE 1

EFFECTS OF SK&F 38393 (3 0–30 mg/kg IP) ON WATER INTAKE IN 22-HR WATER-DEPRIVED RATS

	Dose (mg/kg)			
	0	3 0	10 0	30 0
Intake (ml)	17 9 ±1 1	17 4 ±0 6	15 5* ±0 8	12 7† ±1 0
% Reduction from control	—	2 8%	13 4%	29 1%

Results are shown as mean intake (ml) ± S E M N = 10 per group
Levels of significance in comparison with vehicle control *$p<0$ 05, †$p<0$ 01, (Dunnett's t-test)

larger dose of 10 mg/kg, there may be penetration of fenoldopam into the brain (17), and this would explain the anorectic effect we detected. Lastly, some studies of D_1 and D_2 agonists indicate that they may have opposite effects (5,33) In the present experiments, however, the effects of SK&F 38393 and of the selective D_2 agonist, N-0437, were essentially additive. Thus, there was no evidence of antagonism between the two drugs This is relevant to the anorectic potency of compounds like apomorphine, which stimulate both D_1 and D_2 receptors Effects of mixed D_1/D_2 agonists to reduce food intake may depend on effects mediated by both receptor subtypes

At a biochemical level, it is particularly interesting to note that SK&F 38393 affects neither brain dopamine metabolism (36), nor brain dopamine release (8,21) Its lack of effect stands in striking contrast to the marked changes brought about by selective D_2 agonists Thus, SK&F 38393 furnishes an important example of a drug which acts via dopamine receptors to reduce food intake, in the absence of changes in dopamine metabolism or release This dissociation may have implications for biochemical approaches to the study of brain dopamine and feeding (10, 20, 31, 37).

Reductions in food consumption produced by drug treatments can be problematic and difficult to interpret (12) Nevertheless, there are distinctive features to the pharmacological profile of SK&F 38393 which have a bearing on the question of the behavioural specificity of its anorectic effect. In contrast to D_2 agonists, SK&F 38393 does not induce emesis (36), so that one possible reason for a reduction in feeding is excluded Also, in contrast to D_2 agonists, SK&F 38393 does not induce hyperactivity or behavioural stereotypy in either rats or mice (2, 14, 36, 38, 40) The reduction in food intake cannot readily be ascribed to the interference of competing responses In large doses, SK&F 38393 does induce excessive grooming in rats and mice (28,38). However, we have observed that, at 10 mg/kg, SK&F 38393 produced a reduction in food intake without significantly affecting grooming locomotor activity, or rearing (Cooper, Francis and Rusk, submitted for publication) There is evidence to suggest that the effects of SK&F 38393 on feeding responses are to some degree motivationally specific Thus, deprivation-induced water intake was reduced by only 29%, at the large dose of 30 0 mg/kg of SK&F 38393 In contrast, operant responding for food and deprivation-induced food intake were strongly suppressed at this dose Furthermore, SK&F 38393 has been reported to have no effect on female sexual behaviour in rats, in contrast to D_2 agonists (16) Nevertheless, the specificity of the effects of SK&F 38393 on feeding responses deserve further study, as do the mechanisms by which the drug achieves the suppressant effect on food intake

In summary, the present series of experiments demonstrates that agonist activity at dopamine D_1 receptors leads to reductions in food consumption in both rats and mice. Operant responding for food was also reduced by (±)-SK&F 38393 There are good grounds for the view that SK&F 38393 achieves an anorectic effect which is not secondary to nonspecific motivation or response impairments Finally, it appears possible that more familiar dopaminergic anorectic compounds, like apomorphine and *d*-amphetamine, may owe part of their effect on appetite to stimulation of central dopamine D_1 receptors

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