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Effects of SCH39166 and Domperidone on the Meal Patterning of Male Rats

PETER G. CLIFTON

Laboratory of Experimental Psychology, University of Sussex, Brighton BN1 9QG, UK

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CLIFTON, P. G. *Effects of SCH39166 and domperidone on the meal patterning of male rats.* PHARMACOL BIOCHEM BEHAV **52**(2) 265–270, 1995.—In male rats given free access to food (45 mg pellets) and water, ingestive behavior is structured into meals. The selective dopamine D_1 antagonist SCH39166 had little effect on total food intake, meal size, or feeding rate. However, it did produce a marked, dose-related reduction in drinking that resulted from an increase in intermeal interval with unchanged meal size. Possible peripheral and central explanations of this effect are discussed. In a second experiment, the peripheral dopamine D_2 antagonist, domperidone, was shown to have little effect on either feeding or drinking. A dose of 10 mg/kg did reduce feeding rate, but this probably represents a central effect, because doses that were only slightly higher have previously been shown to reduce stimulant-induced hyperactivity and stereotypy. These experiments confirm the functional distinction between D_1-like and D_2-like dopamine receptors in the control of ingestive behavior, with the D_1 receptor having a greater role in drinking and central D_2 receptors affecting several aspects of feeding behavior.

SCH39166 Domperidone Meal patterning Food intake Water intake

ALTHOUGH the recent description of five families of receptor subtypes for dopamine using molecular biological techniques has been of great importance (27), behavioral studies of dopamine function remain dominated by by the D_1/D_2 distinction suggested by Kebabian and Calne (17). In part, this situation has arisen because selective agonists and antagonists are not yet available for the more recently characterised receptors. In addition, at a behavioral level, it has proved difficult to even provide a clear functional distinction for the roles of D_1 and D_2 receptors. Studies with agonists and antagonists have suggested a variety of possible relationships, depending on the behavioral system under study. For example, both D_1 and D_2 antagonists reduce locomotor activity and may produce catalepsy (14,21). In addition, either D_1 or D_2 antagonists may reduce amphetamine-induced activity or stereotypy (3), although perhaps in rather different ways (24). However, manipulations of D_1 and D_2 receptors do not necessarily produce similar effects. There is evidence of differential effects of D_1 and D_2 manipulations for repetitive jaw movements (26), grooming (28), and sexual behavior (20).

The role of dopamine receptor subtypes also presents a complex picture in the case of ingestive behavior. The D_2 agonists bromocriptine and N-0437 may increase food intake at low doses and suppress intake at higher doses (8,12).There are no data to suggest that D_1 agonists enhance intake at any dose (10). At high doses, both D_1 and D_2 antagonists reduce food intake; this effect is unsurprising, given the reduction of locomotor activity and catalepsy discussed earlier. However, there are also several reports that dopamine antagonists may increase food intake (1,23). Detailed recording of patterns of ingestive behavior, such as meal patterning in freely feeding and drinking subjects, can provide one indication of the behavioral specificity of such effects. Blundell and Latham (4) showed that pimozide, a relatively nonselective dopamine antagonist, could increase meal size and decrease feeding rate; there was little overall effect on food intake. Clifton et al. (9) reported that slowed feeding rate and enhancement of meal size was only characteristic of animals treated with D_2 antagonists. By contrast, D_1 receptor blockade had little effect on feeding rate or meal size, but did greatly reduce water intake over the same period.

This apparent differentiation of the effects of D_1 and D_2 antagonists on meal patterning suffered from several problems of interpretation. First, the functional distinction between D_1 and D_2 antagonists rested on the study of a single example of the former. Here, I report a meal patterning study using a second D_1 antagonist, SCH39166. Although this drug was developed from SCH23390, which was used in the earlier study, it lacks an action at 5-HT receptors (6,15). A second problem arose from the possibility that one or more of the drugs under study might have had peripheral effects that indirectly affected ingestive behavior in addition to any direct effects on CNS mechanisms. Although selective D_1 antagonists that lack central action after systemic administration have not been described, to my knowledge, there are several D_2 antagonists that only poorly penetrate the blood–brain bar-

rier. Here, I show that domperidone, a drug of this type (18), has little effect on intake patterns until given at doses that are likely to have central effects.

METHOD

Subjects and Apparatus

In each experiment, eight male hooded Lister rats from the University of Sussex colony, weighing between 250 and 350 g at the beginning of the experiment, were housed singly in cages (45 × 30 × 30 cm). There was a small (15 × 10 × 8 cm) open-top nest box in one corner of the cage. The cages were held in a single experimental room, maintained at 22–24°C, in visual but not auditory isolation from each other. The room was maintained on a 12L : 12D cycle, with lights off at 1730 h. A single 25 W red bulb provided minimal illumination during the dark phase. Daily handling, weighing, drug administration, and refilling of food and water containers was carried out in the final 30 min ofthe light period.

Drugs

SCH39166 [(−)-*trans*-6,7,7a,8,9,13b-hexahydro-3-chloro-2-hydroxy-*N*-methyl-5H-benzo[d]naptho-[2,1-b]azepine] was kindly provided by Dr. Allen Barnett (Schering-Plough Research Institute, New Jersey), and is a selective dopamine D_1 receptor antagonist (6). It differs from the better known first-generation benzepine SCH23390 in that, in primates but not rats, it has a longer duration of action and a much lower affinity for the 5-HT_2 receptor (6). The drug was dissolved in distilled water and injected IP at doses of 0.3, 1.0, and 3.0 mg/kg. We used the IP route for consistency with our previously published work (9), although it is less effective than the SC route (6).

Domperidone, which was purchased from RBI, St. Albans, UK, is a selective dopamine D_2 receptor antagonist that has a limited capacity to pass the blood–brain barrier [for review, see (5)]. However, high doses (≥20 mg/kg) can reverse apomorphine-induced stereotypy in the rat (11). The drug was dissolved in distilled water and injected IP at doses of 1, 3, and 10 mg/kg.

Procedure

Food (45 mg Camden pellets) and water were freely available throughout the experiment. Intake was recorded using a microprocessor-based system (7). A single pellet was always available in a small hopper attached to one wall of the cage. When this pellet was consumed, it was replaced within a second and the time logged. Only very rarely did the animals drop pellets below the perforated cage floor, and no hoarding was possible in these cages. Therefore, pellet removals were an accurate record of food intake. Water was dispensed from a nozzle situated 15 cm from the food hopper. The change in capacitance produced by licking the nozzle activated a peristaltic pump that provided water, and the times at which the pump was activated were recorded automatically.

The animals were habituated to the room and apparatus for 8 days before the experiment began. Each animal then received, in a counterbalanced order, each of the four possible drug doses (above), with each treatment separated from the next by at least 48 h. Water was delivered at a rate of 1 g every 13 s.

Analysis

Food and water intake patterns were analyzed in two ways. First, the numbers of feeding and drinking responses occurring in 2-h time bins were calculated. Significance was assessed using analysis of variance with repeated measures on time and drug conditions. The second form of analysis examined the patterning of meals into which feeding is structured. This analysis was restricted to the period following drug treatment in which a clear behavioral effect was observed (8 h for SCH39166 and 6 h for domperidone). The first problem in a meal analysis is to define a suitable criterion for meal termination. A criterion of 2 min efficiently separates within and between meal interpellet intervals (7). After this, criterion was applied to the data and meal size was defined as the number of pellets eaten after a first interpellet interval exceeding 2 min and before the next interpellet interval greater than this value. Meal duration was defined as the time between taking the first and last pellets of a meal, and feeding rate was calculated by dividing the number of pellets taken in a meal by its duration. The intermeal interval was defined as the time between taking the last pellet of one meal to taking the first pellet of the next meal. In calculating mean intermeal interval, the latency to the first meal was excluded. In addition, I plotted the distribution of interpellet intervals, as this provides a more sensitive indicator of changes in feeding rate. Drinking was treated in a similar way, except that no measure of drinking rate was obtained.

Very occasional records were lost due to equipment failure; the subsequent statistical analysis used the missing value procedure of the GENSTAT statistical package (13) and resulted, in each case, in the loss of a degree of freedom in the ANOVA.

RESULTS

Experiment 1 — The D_1 Antagonist SCH39166

Daily intake patterns. Food intake was summed into 2-h bins (Fig. 1) and then subjected to ANOVA with drug dose and time bin as the within-subject factors. Food intake varied significantly over the day, $F(11, 77) = 9.09$, $p < 0.001$, in the usual pattern of high intake in the early and late hours of the night and lower intake at other times. There was no main effect of, or interaction with, drug treatment. *F*-Ratios for drug effects remained insignificant when the ANOVA was restricted to the 6-h period following drug treatment, during which time appreciable effects have been seen in other test situations (6). The slight decrease of food intake seen in the

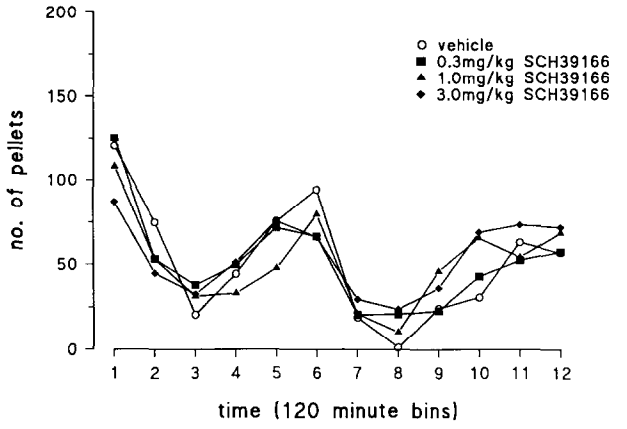

FIG. 1. The number of food pellets eaten in successive 2-h bins after administration of varying dose of SCH 39166, or the vehicle (distilled water), 15 min before the beginning of the dark period. The dark period is bins 1–6 and the light period is bins 7–12.

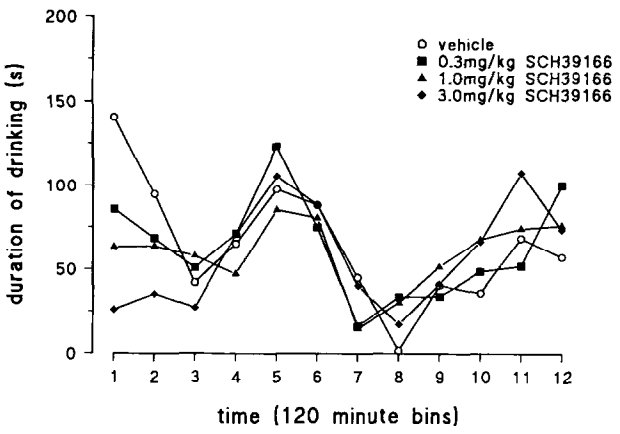

FIG. 2. Water intake, shown as for Fig. 1.

first 2 h after the highest dose of SCH39166 remained well below significance, even when tested with an unprotected *t*-test. By contrast, there were substantial effects on water intake. ANOVA, over 24 h, again summed into 2-h bins, gave a significant effect of time, $F(11, 77) = 4.93$, $p < 0.001$. An analysis restricted to the 8-h period in which drug action was likely, resulted in a main effect of time, drug, and interaction, $F(2, 14) = 8.19$, $p < 0.004$; $F(3, 21) = 5.5$, $p < 0.005$; $F(6, 42) = 2.36$, $p < 0.05$. Examination of Fig. 2 suggests that these statistics can be attributed to the substantial reduction in water intake by either 1.0 or 3.0 mg/kg SCH39166 in the 2-4 h following drug treatment.

Meal patterns and feeding rate. A full analysis of meal parameters was performed for the 8 h following drug treatment (Table 1). ANOVA showed that there was no change in any parameter for feeding after food intake was initiated. However, the latency to feed did increase significantly, $F(3, 21) = 10.49$, $p < 0.001$, although even at the highest dose of SCH39166 the mean latency was only 35 min. After feeding began, feeding rate was unaffected, $F(3, 21) = 1.47$, p approx. 0.25. This conclusion was confirmed by examining the full interpellet interval distribution at each drug dose. There was no hint of a rightward shift at higher doses that would have indicated a slowing of feeding rate during meals (data not shown).

A similar analysis of meal patterning in water intake revealed that the reduction in water consumption shortly after drug treatment arose from a substantial enhancement in latency to drink, $F(3, 21) = 8.31$, $p < 0.001$, and an increase in subsequent intermeal intervals, $F(3, 21) = 3.36$, $p < 0.05$. Meal size during drinking was unaffected by drug treatment, $F(3, 21) = 1.77$, with a slight tendency to increase, rather than to decrease, as drug dose was raised (Table 1).

Experiment 2—The Peripheral Dopamine Antagonist Domperidone

Daily intake patterns. The overall pattern of food and water intake was relatively unaffected by drug treatment. Even when attention was restricted to the first 2-h period following drug treatment, only a slight reduction in food and water intake was apparent at the highest dose (10 mg/kg) of domperidone (Fig. 3). This decline was significant for food intake, $F(3, 20) = 3.92$, $p < 0.05$, but not for drinking, $F(3, 20) = 0.62$, NS.

Meal patterns. Meal patterns for feeding and drinking were analyzed as for Experiment 1 (Table 2). Only rate of feeding was significantly slowed by drug treatment, $F(3, 20) = 12.52$, $p < 0.001$. This change was further examined by plotting the interpellet interval distribution (Fig. 4) for all intervals in the 6 h following drug treatment. There was a clear rightward shift of the distribution at a dose of 10 mg/kg domperidone

TABLE 1

SCH39166 MEAL PARAMETERS

	Drug Dose (mg/kg)					
	0.00	0.3	1.0	3.0	SED	Signif.
Total pellets	212	215	183	189	31	NS
Number of meals	6.00	5.25	4.37	5.12	1.15	NS
Meal size	42.8	55.2	49.1	54.7	11.6	NS
Meal duration	438	550	549	601	107	NS
Feeding rate within meals	0.098	0.097	0.091	0.091	0.0065	NS
Intermeal interval	98	113	87	158	45	NS
Latency	0.6	3.7	6.3	35.9	7.1	†
Total drinks	269	235	176	143	52.1	NS
Number of meals	9.50	10.38	5.87	5.50	1.96	*
Meal size	34.1	24.1	37.6	39.9	7.3	NS
Meal duration	59.6	50.1	80.2	102.6	22.4	NS
Intermeal interval	34.4	43.2	77.0	68.8	15.7	*
Latency	16.0	25.1	44.8	183.7	38.5	†

Each parameter is for the 8 h following drug administration. Meal size is given in pellets (1 pellet = 0.045 g), meal duration in seconds, feeding rate in pellets/s, and intermeal interval/latency in minutes. Feeding rate is shown as the number of pellets eaten per second during the meal. For drinking, duration measures are the number of seconds spent consuming fluid from the water spout (1 g delivered in 13 s). The penultimate column shows the standard error of the difference between means in the analysis of variance for that variable. The final column indicates whether the *F*-ratio from the analysis was significant (* = $p < 0.05$, † = $p < 0.01$).

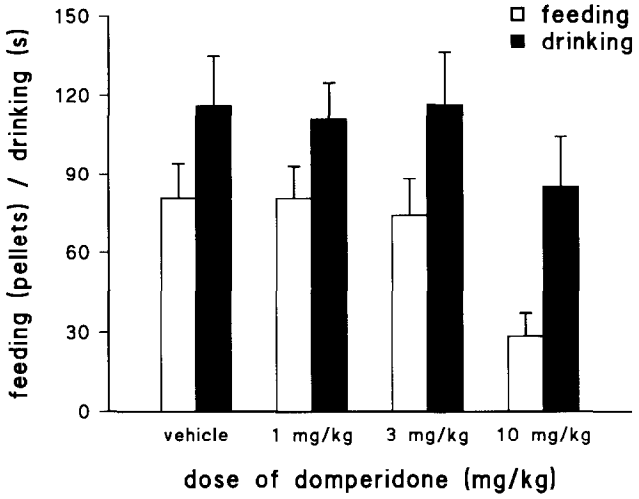

FIG. 3. Food and and water intake for the 2 h following treatment with varying doses of doperidone or vehicle (distilled water). Food intake is shown as the number of 45 mg pellets that were consumed, and water intake as the number of seconds spent drinking; 1 ml of water was delivered every 13 s.

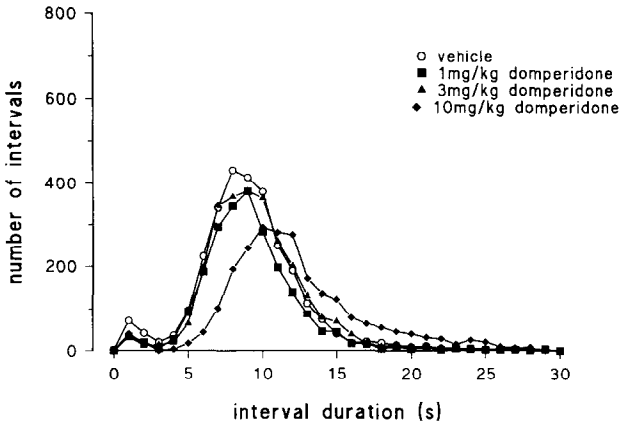

FIG. 4. Distribution of interpellet intervals for the 6 h of food intake following administration of varying doses of domperidone or its vehicle (distilled water). The drug was given 15 min before the beginning of the night period, at which time data collection was also initiated.

that resulted from the modal interpellet interval increasing from 8 to 10 s. A similar analysis of meal organization in drinking produced no significant change in any parameter ($p > 0.1$ in each case).

DISCUSSION

There was a clear contrast between the effects of SCH39166 and domperidone on feeding and drinking patterns. SCH3916 had little effect on feeding patterns but, at the two higher doses tested, produced a considerable suppression of water intake. This reduction in drinking resulted from delays in the initiation of drinking rather than from early termination of drinking bouts. In addition, the highest dose of SCH39166 resulted in a short period after administration in which both food and water intake were reduced. Domperidone, by contrast, had no significant effect on any aspect of water intake, but produced a reduction in food intake and feeding rate at the highest dose tested.

These results provide an interesting contrast with an earlier study using three D_2 antagonists and a single D_1 antagonist (9). In that study, the dopamine D_1 antagonist SCH23390 suppressed the initiation of drinking, but also produced an inconsistent reduction in feeding rate and other small changes in feeding patterns. SCH39166 and SCH23390 differ in that the latter drug, in addition to blocking D_1 receptors, also antagonizes 5-HT_2 receptors, although it has been difficult to obtain functional evidence for this effect (25). It, therefore, seems reasonable to conclude that blockade of D_1 receptors is associated with hypodipsia, but that the slight changes in feeding

TABLE 2

DOMPERIDONE MEAL PARAMETERS

	Drug Dose (mg/kg)					
	0	1	3	10	SED	Signif.
Total pellets	211	169	196	152	35.4	NS
Number of meals	5.37	4.57	5.12	3.50	0.91	NS
Meal size	41.0	44.3	39.4	39.7	6.9	NS
Meal duration	409	413	397	523	81.5	NS
Feeding rate within meals	0.103	0.109	0.099	0.079	0.0051	*
Intermeal interval	69.9	130.8	83	101.9	28.2	NS
Latency	14.8	3.93	8.7	59.8	30.4	NS
Total drinks	240	265	325	254	60.0	NS
Number of meals	9.0	10.2	11.5	6.6	2.63	NS
Meal size	28.8	28.3	30.9	43.0	6.37	NS
Meal duration	67.1	72.8	78.9	91.7	15.5	NS
Intermeal interval	47.1	57.7	44.7	96.6	25.1	NS
Latency	12.8	7.8	5.1	4.5	5.5	NS

Units and definitions are as for Table 1. The analysis was performed for the first 6 h following drug treatment.

patterns observed with SCH23390 may possibly have arisen from an action at 5-HT_2 receptors. It remains unclear as to whether the changes in water intake result from blockade of peripheral or central dopamine D_1 receptors. D_1 receptors are known to mediate certain aspects of renal function. For example, dopamine increases glomerular filtration rate, water loss, and sodium excretion. The latter effects, at least, are mediated by a dopamine D_1 receptor (2,16). Blockade of this receptor might, therefore, reduce water loss and sodium excretion and, hence, reduce drinking. Although the effects of SCH39166 were rapid, with the largest effect on latency to drink, this initial action was probably nonspecific, because feeding was also reduced, and direct observation suggested that the rats were very quiet during this period. The selective action on drinking only became apparent after about 90 min. An indirect effect on drinking as a result of a change in body water balance, would be expected to occur only slowly, as, for example, in the increased drinking seen after diuresis induced by kappa agonists (19). The effect of kappa agonists on water intake was also produced by a change in the frequency with which drinking was initiated, rather than an increase in the amount drunk after initiation of drinking (19).

Alternative explanations of the effect of SCH39166 on drinking might involve a direct central action on neural circuits involved in drinking behavior or might even, given that water is probably not a very rewarding stimulus to a normally hydrated animal, be explained in terms of more effective blockade of behavior motivated by a weak reinforcer (water) than behavior motivated by a strong reinforcer (food). There is evidence that D_1 antagonists may have actions that depend on reinforcement magnitude (22). However, an action of this kind might be expected to reduce the amount of water taken after drinking was initiated, rather than to delay initiation as observed in this study.

The effects of domperidone might be taken as demonstrating that reductions in feeding rate by D_2 antagonists arise through blockade of peripheral D_2 receptors. However, this conclusion seems unwise because, although domperidone is often characterized as a peripheral antagonist, it does have central effects. Costall et al. (11) reported that near-toxic doses of 40–80 mg were required to produce a weak and inconsistent catalepsy in the rat. However, they also reported that doses as low as 20 mg/kg could produce moderate antagonism of amphetamine- or apomorphine-induced stereotypy in the rat, and that doses of as little as 1.25 mg/kg would completely reverse apomorphine-induced climbing in mice. Thus, it seems likely that the slowed feeding rate observed with the four D_2 antagonists studied so far and the enhancement of meal size produced by three of the drugs both reflect action at central, rather than peripheral, dopamine receptors. The failure to see any sign of enhanced meal size with domperidone may indicate that this effect occurs at a different anatomical locus that is less susceptible to limited transfer of domperidone across the blood-brain barrier.

In summary, the first experiment provides additional evidence to support the hypodipsic action of antagonists at dopamine D_1 receptors but does not indicate whether this effect is produced by a peripheral or central mechanism, although the behavioral data would be consistent with an action on water balance via changed kidney function. The second experiment is consistent with the idea that blockade of central dopamine D_2 receptors can reduce feeding rate and enhance meal size and, hence, that central dopamine D_2 receptors are of particular importance in the regulation of feeding behavior.

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