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BRIEF COMMUNICATION

Pharmacological Manipulations of Sucrose Consumption in the Syrian Hamster

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COOPER, S. J. *Pharmacological manipulations of sucrose consumption in the Syrian hamster.* PHARMACOL BIOCHEM BEHAV **33**(3) 721–724, 1989.—Nondeprived, male Syrian hamsters (*Mesocricetus auratus*) were adapted to a daily schedule of 2-hr access to a 10% sucrose solution. Two benzodiazepines, midazolam (1.0–10 mg/kg) and flurazepam (1.0–10 mg/kg), produced dose-dependent increases in sucrose consumption. In contrast, the α_2-adrenergic agonist, clonidine (0.01–0.3 mg/kg), had no effect on sucrose intake. Neither *d*-fenfluramine nor *d*-amphetamine affected sucrose ingestion in the hamsters, except at a large dose (10 mg/kg). Nevertheless, significant, dose-dependent reductions in sucrose consumption were observed after the administration of either opiate antagonists (naltrexone; nalmefene) or selective dopamine D_2 receptor agonists (N-0437; quinpirole). The results are compared and contrasted with previously reported data for rats.

Appetite Benzodiazepines D_2 receptors *d*-Amphetamine *d*-Fenfluramine Clonidine N-0437
Nalmefene Naltrexone Opiates Quinpirole Syrian hamsters Sucrose

ATTENTION has been drawn to the marked differences in ingestional behavior between rats and Syrian hamsters (25). Unlike rats, Syrian hamsters do not increase their food intake in response to food deprivation (33), and do not adapt to schedules of restricted feeding (3). In addition, hamsters fail to show a hyperphagic response to peripherally-administered 2-deoxy-D-glucose (2-DG) (32), although they respond to intracerebroventricular administration of 2-DG (25). The present series of studies was planned to provide more information concerning the pharmacological characteristics of ingestion in the Syrian hamster.

One major proposal about hamsters is that they appear to 'lack an opiate-sensitive feeding system' (17). Thus, the opiate antagonist naltrexone had no effect on food intake in hamsters given access to pellets (16); furthermore, a series of agonists (morphine, keotcyclazocine, meperidine) were also ineffective (17). This lack of response by Syrian hamsters is in marked contrast to the results for rats and many other mammalian species (9). In the same way, it has been reported that hamsters do not respond to the systemic administration of the α_2-adrenergic agonist, clonidine (26), although rats, rabbits and monkeys exhibit a hyperphagic response to clonidine in small doses (12, 22, 30). In addition, the Syrian hamster has been reported to be refractory to the anorectic effect of either dl- or *d*-fenfluramine (27,28). Such failures to identify pharmacological treatments which will affect the ingestional responses of hamsters represent major challenges to our understanding of the possible neurochemical mechanisms of appetite across mammalian species in general. There are some instances of similarity in the responses of hamsters and rats. For example, exogenously-administered gut peptides reduce feeding responses in hamsters (23), as well as rats. The benzodiazepine, diazepam, increased food intake in hamsters (2), as it also does in rats (7,38).

In the present experiments, nondeprived male hamsters were given daily access to a 10% sucrose solution for a 2-hr period in the daytime. Several different kinds of drug treatments were tested to determine if sucrose ingestion in these animals is affected by a number of common pharmacological manipulations: two benzodiazepines, midazolam and flurazepam; clonidine; the opiate antagonists, naltrexone and nalmefene; *d*-fenfluramine; *d*-amphetamine; two selective dopamine D_2 receptor agonists, N-0437 (1, 35, 36) and quinpirole (34,39). Anorectic effects of selective D_2 agonists have recently been reported in rats (6, 10, 21, 29).

METHOD

Animals

Male Syrian hamsters (*Mesocricetus auratus*) were purchased from Wrights of Essex Ltd., Chelmsford, U.K. They were housed individually in stainless steel cages with free access to food (hamster grains) and water. They were maintained on a 12-hr

light:12-hr dark cycle (lights on a 8:00 a.m.) and room temperature was kept constant at 22°C. The animals weighed 75–105 g at the start of testing.

Drugs

Midazolam bimaleate and flurazepam hydrochloride were provided by Roche Products Ltd., Welwyn Garden City, U.K. They were dissolved in isotonic saline, and were injected in doses of 1.0, 3.0 and 10 mg/kg by the intraperitoneal route. Clonidine hydrochloride was dissolved in isotonic saline, and injected IP in doses of 0.01–0.3 mg/kg. Naltrexone hydrochloride was provided by DuPont de Nemours & Co., Glenolden, PA, dissolved in isotonic saline and injected subcutaneously in doses of 0.1–10 mg/kg. Nalmefene HCl was obtained from Key Pharmaceuticals, Harrow, U.K., dissolved in isotonic saline and injected SC in doses of 0.3–10 mg/kg. *d*-Fenfluramine hydrochloride was donated by Servier, Neuilly-sur-Seine, France. It was dissolved in isotonic saline, and injected IP in doses of 0.3–10 mg/kg. *d*-Amphetamine sulphate was a gift of Smith Kline & French Research Ltd., Welwyn, U.K. It was dissolved in isotonic saline, and injected IP in doses of 0.1–10 mg/kg. N-0437 (5,6,7,8-tetrahydro-6-propyl[2-(2-thienyl)ethyl]amino]-1-naphthalenol)hydrochloride was generously supplied by Nelson Research, Irvine, CA. It was dissolved in distilled water to which Tween 80 had been added (2 drops in 10 ml), and injected IP in doses of 0.3–3.0 mg/kg. Quinpirole hydrochloride (LY 171555) was obtained from Lilly Research Laboratories, IN. It was dissolved in distilled water and injected IP in doses of 0.3–3.0 mg/kg. All doses refer to the salts. Injections were carried out 20 min before the sucrose consumption tests. The injection volume was 5 ml/kg.

Procedure

The animals were first familiarized with gentle handling for the first week after arrival in the laboratory. They were then adapted to drinking a 10% sucrose solution from bottles with metal spouts in daily 2-hr periods during the afternoon (2–4 p.m.). The amount of sucrose solution ingested was calculated by successive weighings to the nearest 0.1 g. This adaptation period lasted 2 weeks before drug testing began.

For each drug, each animal was tested under each injection condition, with the order of injection counterbalanced across animals. At least 48 hr separated successive injections. At least 4 days separated successive drug treatments, and baseline measurements of sucrose intake were continued on the intervening noninjection days.

Intake data were first converted to grams of sucrose solution ingested per 100 g of body weight. For each drug, the standardised intake data were analysed by a one-way analysis of variance for repeated measures. Comparisons of individual dose effects against the corresponding vehicle condition were made using Dunnett's *t*-test (37).

RESULTS

Drug-Induced Increases in Sucrose Intake

Table 1 indicates that both midazolam, $F(3,51)=9.02$, $p<0.001$, and flurazepam, $F(3,51)=8.75$, $p<0.001$, produced dose-dependent increases in sucrose consumption over the dose range, 1.0–10 mg/kg. At 10 mg/kg, midazolam produced an 80% increase in intake; flurazepam had less effect (59% increase).

Clonidine (0.01–0.3 mg/kg) failed to have any significant effect on intake.

Drug-Induced Decreases in Sucrose Intake

Both naltrexone, $F(3,51)=3.34$, $p<0.025$, and nalmefene, $F(3,51)=4.97$, $p<0.01$, had significant dose-dependent effects on sucrose intake (Table 2). In each case, significant reductions were detected at 1.0 mg/kg.

However, the animals proved to be refractory not only to the effect of *d*-fenfluramine, but also to that of *d*-amphetamine (Table 3). In both cases, sudden reductions occurred at 10 mg/kg, and there were no effects at smaller doses. In contrast, the hamsters were sensitive to the anorectic effects of selective D_2 receptor agonists (Table 3). Both N-0437, $F(3,51)=7.64$, $p<0.001$, and quinpirole, $F(3,51)=34.01$, $p<0.05$, had dose-dependent effects: in each case, the minimum effective dose was 0.3 mg/kg.

TABLE 1

EFFECTS OF THE BENZODIAZEPINES, MIDAZOLAM AND FLURAZEPAM AND THE α_2-ADRENERGIC AGONIST, CLONIDINE, ON 10% SUCROSE CONSUMPTION IN MALE SYRIAN HAMSTERS

	Dose (mg/kg)			
Drug	0	1	3	10
Midazolam (18)	1.61 ±0.15	2.25* ±0.28	2.52† ±0.17	2.90† ±0.23
Flurazepam (18)	1.52 ±0.11	1.89* ±0.17	2.26† ±0.14	2.42† ±0.21

	Dose (mg/kg)				
	0	0.01	0.03	0.1	0.3
Clonidine (17)	1.59 ±0.15	1.50 ±0.22	1.47 ±0.17	1.15 ±0.14	1.21 ±0.18

Results are shown as mean ± S.E.M. intake (g/100 g body weight). Numbers in parentheses indicate group size. Levels of significance in comparison with the corresponding vehicle control: *$p<0.005$; †$p<0.01$ (Dunnett's *t*-test).

DISCUSSION

The two benzodiazepines, midazolam and flurazepam, both significantly increased sucrose consumption in nondeprived Syrian hamsters. This effect is consistent with recent results obtained in rats (11). Taken together with earlier data (2), these results suggest that benzodiazepine receptors may be involved in the modulation of ingestional responses in hamsters, as they are in rats (8). In contrast, the α_2-adrenergic agonist clonidine did not increase

TABLE 2

EFFECTS OF THE OPIATE ANTAGONISTS, NALTREXONE AND NALMEFENE, ON 10% SUCROSE CONSUMPTION IN MALE SYRIAN HAMSTERS

	Dose (mg/kg)					
Drug	0	0.1	0.3	1.0	3.0	10
Naltrexone (18)	1.54 ±0.16	1.28 ±0.16	—	1.26* ±0.08	—	1.15† ±0.10
Nalmefene (18)	1.66 ±0.13	—	1.49 ±0.14	1.34* ±0.12	1.25† ±0.09	1.21† ±0.09

Results are shown as mean ± S.E.M. intake (g/100 g body weight). Numbers in parentheses indicate group size. Levels of significance: see Table 1 legend.

TABLE 3

EFFECTS OF *d*-FENFLURAMINE, *d*-AMPHETAMINE AND THE DOPAMINE D_2 RECEPTOR AGONISTS, N-0437 AND QUINPIROLE, ON 10% SUCROSE CONSUMPTION IN MALE SYRIAN HAMSTERS

	Dose (mg/kg)					
Drug	0	0.1	0.3	1.0	3.0	10.0
d-Fenfluramine	1.83 ±0.13	—	1.99 ±0.16	1.88 ±0.11	1.81 ±0.12	0.67† ±0.09
d-Amphetamine	1.46 ±0.19	1.50 ±0.16	1.58 ±0.19	1.57 ±0.17	1.51 ±0.21	0.73† ±0.14
N-0437	1.62 ±0.13	1.43 ±0.08	1.32* ±0.10	1.11† ±0.08	—	—
Quinpirole	1.89 ±0.11	1.66 ±0.15	1.61* ±0.13	1.52† ±0.12	—	—

Results are shown as mean ± S.E.M. intake (g/100 g body weight). N = 18 per condition. Levels of significance: see Table 1 legend.

sucrose consumption in hamsters, cf. (26). Clonidine, in small doses, is effective in increasing food consumption in rats, rabbits and monkeys (12, 22, 30, 31), although not in anorectic human patients (5). Since α_2-adrenergic stimulation has been linked with norepinephrine-induced hyperphagia (15,18), it is interesting that hamsters appear to lack a consistent response to intracerebroventricular administration of norepinephrine (25). Unlike rats and other species, therefore, the hamster may not be dependent on noradrenergic mechanisms in the control of its food intake.

The two opiate antagonists, naltrexone and nalmefene, reduce food intake in rats and other mammalian species (9, 19, 20). Opiate antagonists have also been shown to reduce sucrose consumption in rats (14,24). The present data show that both naltrexone and nalmefene produced dose-related reductions in sucrose intake in hamsters. These data therefore refute any general argument that hamsters lack completely opioid mechanisms involved in the control of ingestional responses. Instead they indicate that some, but not all, feeding responses are opioid-dependent in hamsters. Taking into account the earlier observations that pellet-feeding in hamsters is resistant to opioid receptor antagonism (16), the present results suggest that palatability-related factors such as sweet taste may involve the mediation of opioid mechanisms. If this interpretation is correct, then the data for hamsters would be consistent with more extensive evidence obtained in rats that food palatability is opioid-dependent (9).

It may seem surprising that the Syrian hamster is relatively unaffected by either *d*-fenfluramine or *d*-amphetamine. A considerable amount of data attests to their feeding-suppressant effects in rats, and both drugs will reduce sucrose consumption (4). Except at a large dose of 10 mg/kg, however, neither drug affected sucrose ingestion in the hamster. This makes a striking contrast with the data for the opiate antagonists, suggesting that a dissociation may exist between the effects of *d*-fenfluramine and *d*-amphetamine, on the one hand, and those of opiate antagonists on the other, cf. (13).

The relative lack of effect of *d*-amphetamine need not imply, however, that catecholaminergic mechanisms play no part in the control of ingestion in the Syrian hamster. The present results demonstrate, for the first time, that selective dopamine D_2 agonists significantly reduce sucrose consumption in hamsters. These drugs also reduce food intake (6, 21, 29) and sucrose ingestion (10) in rats. Further research should be directed to understanding better the functions of dopamine neurotransmission in relation to the hamster's ingestional responses.

In summary, the present results provide both positive and negative instances of hyperphagic and anorectic responses in Syrian hamsters, in a test of sucrose ingestion. Benzodiazepines, but not the α_2-adrenergic agonist, clonidine, increased sucrose consumption. Opiate antagonists and selective dopamine D_2 receptor agonists reduced sucrose consumption, while *d*-amphetamine and *d*-fenfluramine had no effect on intake, except at a high dose level. Some parallels, at least, exist between the responses of Syrian hamsters and rats to pharmacological treatments which affect ingestion. It will be interesting if such parallels have a bearing upon the behavioral and physiological matches between the ingestional responses of the two species.

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