Pharmacology Biochemistry & Behavior, Vol. 25, pp. 99–106, 1986. © Ankho International Inc. Printed in the U.S.A. 0091-3057/86 $3.00 + .00

Midazolam-Induced Hyperphagia and FG 7142-Induced Anorexia: Behavioural Characteristics in the Rat

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Received 10 February 1986

COOPER, S. J. AND R. E. YERBURY. *Midazolam-induced hyperphagia and FG 7142-induced anorexia: Behavioural characteristics in the rat.* PHARMACOL BIOCHEM BEHAV 25(1) 99–106, 1986.—Non-deprived male rats, familiarized with a highly palatable diet, were treated with 0.3–10.0 mg/kg of the imidazobenzodiazepine midazolam. The increases in consumption of the food observed at larger doses of midazolam were due to increases in the duration of feeding, but not in the rate of eating. These, in turn, were due to increases in the duration of eating bouts, but not in their frequency. The β-carboline FG 7142, a partial benzodiazepine receptor inverse agonist, reduced the consumption of the diet when it was injected at 10.0 and 15.0 mg/kg (IP). The overall duration of feeding was not affected at these doses in the 30 min test, but rate of eating was reduced. However, during the first 5 min interval of the test, when feeding behaviour was most motivated, FG 7142 did significantly reduce the duration of feeding. The effect depended upon a reduction in the duration of eating bouts, but not upon any change in their frequency. Hence, midazolam and FG 7142 had opposite effects on the duration of bouts of feeding. Both midazolam and FG 7142 reduced the frequencies of concurrent grooming, locomotor activity, and rearing in the test of palatable food consumption. Possible explanations for these effects are briefly considered.

FG 7142 Feeding Grooming Locomotion Midazolam Rearing Rat

INCREASES in the level of food consumption can be produced in food-deprived and non-deprived animals by drugs which are agonists at specific benzodiazepine recognition sites [6, 7, 14, 41, 46]. Benzodiazepine-induced hyperphagia shows stereospecificity [18], and can be reversed by the specific benzodiazepine receptor antagonist Ro15-1788 [3,26], in rats [15, 17, 18], rabbits [33], and rhesus monkeys [24]. The increase in food consumption is therefore due to an action at specific benzodiazepine receptors. These receptors are of the 'central-type', since the hyperphagic response is elicited by clonazepam, a ligand which is selective for 'central-type' receptors, but not by Ro5-4864 [15], which is a ligand for 'peripheral-type' sites [21].

An important development in the pharmacology of benzodiazepine receptors has been the introduction of drugs which act as 'inverse agonists' [4,39]. These compounds produce effects which are opposite to those which are associated with 'classical' benzodiazepine agonists [5, 29–31, 34, 36, 37]. They act at benzodiazepine receptors to produce reductions in the consumption of food [13]. The anorectic effect of the β-carboline inverse agonist FG 7142 is reversed by specific benzodiazepine antagonists (Ro15-1788, CGS 8216, ZK 93426), and by benzodiazepine agonists (e.g., midazolam, clonazepam and triazolam) [9, 11, 13]. Combining the two lines of pharmacological evidence for benzodiazepine agonists and inverse agonists, therefore, it appears that bi-directional control of food consumption can be achieved by drug action at central benzodiazepine receptors [10].

The aim of the present study was to supplement these pharmacological studies with detailed behavioural observations of feeding and other activities in the non-deprived rat. Two representative drugs were chosen: midazolam, an imidazobenzodiazepine [38] which increases food intake [13], and FG 7142, a β-carboline inverse agonist which reduces the consumption of food [9,11]. The test of food consumption was one which we have used in previous studies, measuring the intake of a highly palatable diet by non-deprived male rats.

METHOD

Animals

The subjects were 80 adult, naive, male rats (black hooded General strain) which were bred in the animal laboratory of the Psychology department. They were housed in pairs in stainless steel cages with continuous access to standard laboratory food pellets (modified Diet 41B, Heygate and Sons, U.K.). They were maintained under a 12 hr light-12 hr dark cycle (lights on at 7 a.m.) and the room temperature was kept constant at 21–22°C. The animals were accustomed to being handled, and were in the weight range 200–300 g by the start of testing.

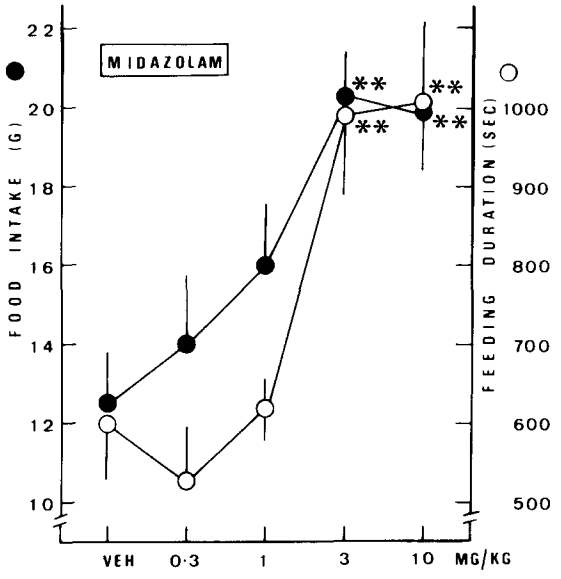

FIG. 1. Hyperphagic effect of midazolam (0.3–10.0 mg/kg) shown in terms of increase in food intake (●), and increase in the duration of feeding (○), in a 30 min test. Results are shown as mean±S.E.M. (N=8 per group). $^{**}p<0.01$, compared with control (VEH) groups (Dunnett's t-test).

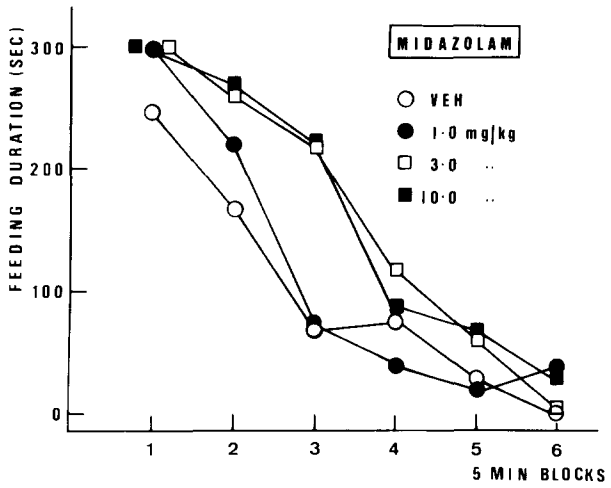

FIG. 2. Time-course of the duration of feeding after midazolam (1.0–10.0 mg/kg), for six five-minute blocks. Results for 0.3 mg/kg were indistinguishable from control values and are therefore omitted. Results shown as mean duration (sec) per 5 min block. N=8 per group.

Procedure

The animals were first familiarized with the highly palatable diet. Each day for 6 consecutive days, animals were transferred to individual test cages, identical to the home cages, for 30 min during the light period. Portions (30–40 g) of freshly prepared diet placed in a clean perspex petri dish was positioned inside each test cage. The diet was made up according to the formula: 50 ml Nestles sweetened condensed milk, 150 ml ground rat maintenance diet No. 1 (Special Diet Services Ltd, Essex, U.K.), and 200 ml distilled water. Within a few minutes of thorough mixing, this food sets to a relatively firm consistency, and tastes very sweet to human tasters. By the end of the adaptation period, the latency to begin eating the diet in the test cage was minimal in all cases. Consumption of the diet was measured by successive weighings to the nearest 0.1 g, and care was taken to collect any food spillage, and to make appropriate corrections to the weighings. The water supply and the rats' standard diet were not available during the palatable food consumption test.

Forty animals were allocated at random to five equal groups, and were injected wtih 0.3, 1.0, 3.0 and 10.0 mg/kg of midazolam bimaleate, or vehicle, respectively. The vehicle was isotonic saline, and solutions were made up immediately before use. Doses are expressed in terms of the salt. Injections were given by intraperitoneal route, in a volume of 1 ml/kg, 20 min prior to the feeding test. On each day of testing, one animal from each group was selected, and was observed individually throughout the 30 min test period. Testing was conducted over 8 consecutive days, and the order of testing was varied across the groups on each day. The remaining 40 animals were also allocated at random to five equal groups, and were injected with 1.0, 3.0, 10.0 and 15.0 mg/kg of FG 7142 (N'-methyl-β-carboline-3-carboxamide), or vehicle, respectively. The vehicle was distilled water to which Tween 80 had been added (2 drops in 10 ml), and the drug was ultrasonically dispersed in the vehicle immediately before use. In a pilot experiment, a dose of 30 mg/kg of FG 7142 produced convulsions in four naive animals, and no further tests were conducted with this dose. Quintero *et al.* [40] also observed convulsions in rats at this dose. Injections were given by intraperitoneal route, 10 min before the feeding test. One animal per group was tested each day over a period of 8 consecutive days.

Each test period was divided into six 5-min blocks, and the following measures were taken within each block: (1) the duration (sec) of each episode of feeding (recorded using a stopwatch to the nearest second); (2) the number of rears (rearing was recorded when the animal stood on its hindlegs and neither forepaw was in contact with the grid floor); (3) frequency of locomotor activity (the number of times the animal crossed with all four paws from one quadrant of the test-cage floor to another); the floor area was 24×27 cm; (4) frequency of episodes of self-grooming. In addition, the total intake of the palatable food was measured for the 30-min test period.

The food-intake data were analysed using a one-way analysis of variance (ANOVA), and other variables were analysed using a two-way ANOVA with a repeated-measures factor for successive time intervals of observation. Comparisons between individual treatment groups and the single control group were carried out using Dunnett's t-test [45].

RESULTS

Midazolam

Food intake. Midazolam (0.3–10.0 mg/kg) had a highly

TABLE 1

MIDAZOLAM-INDUCED HYPERPHAGIA: MICROSTRUCTURE OF FEEDING (30 MIN TEST)

	Midazolam (mg/kg)				
Measure	0	0.3	1.0	3.0	10.0
Bout duration(s)	44.1 ±7.2	43.9 ±5.7	82.5 ±8.6	114.2† ±22.7	110.9† ±15.0
Bout frequency	15.4 ±2.2	11.8 ±0.8	8.1 ±0.9	10.4 ±1.7	9.7 ±1.2
Rate of eating (g/min)	1.28 ±0.08	1.72* ±0.14	1.55 ±0.07	1.30 ±0.10	1.25 ±0.10

Results are shown as mean ± S.E.M. (N=8).
Levels of significance for comparisons with control scores: *$p<0.01$; †$p<0.005$ (Dunnett's t-test).

TABLE 2

EFFECTS OF MIDAZOLAM ON CONCURRENT NON-FEEDING BEHAVIOUR (30 MIN TEST)

	Midazolam (mg/kg)				
Measure	0	0.3	1.0	3.0	10.0
Locomotion (frequency)	67.5 ±14.8	55.0* ±7.0	39.5† ±5.1	19.6† ±7.0	10.1† ±4.6
	—	81.5%	58.5%	29.0%	15.0%
Rears (frequency)	48.1 ±12.2	37.9* ±4.2	19.8† ±1.8	6.3† ±2.5	4.3† ±2.6
	—	78.8%	41.1%	13.1%	8.9%
Grooms (frequency)	31.3 ±3.4	31.5 ±2.0	19.0† ±2.7	9.3† ±4.3	7.6† ±4.0
	—	100.6%	60.7%	29.7%	24.2%

Results are shown as mean ± S.E.M. (N=8). Percent of control scores are shown beneath.
Levels of significance for comparisons with control scores: *$p<0.025$; †$p<0.005$ (Dunnett's t-test).

significant effect on the consumption of food by the non-deprived animals, $F(4,35)=6.07$, $p<0.001$. As Fig. 1 shows, at 3 and 10 mg/kg, midazolam produced significant elevations in the amount of food which was consumed in the 30 min test.

Duration of feeding. Midazolam also significantly affected the total time (sec) which was devoted to feeding in the 30 min test, $F(4,35)=8.08$, $p<0.001$. Figure 1 indicates that highly significant increases in the total duration of feeding occurred at 3 and 10 mg/kg of midazolam. The time-course for the feeding duration measure is shown in Fig. 2. A two-way analysis of variance showed a significant time effect, $F(5,175)=153.2$, $p<0.001$, and a significant drug × time interaction, $F(20,175)=3.26$, $p<0.01$. Control animals ate during much of the first 5 min interval, but the proportion of time devoted to feeding declined rapidly throughout the remainder of the test. By the third 5 min interval the duration of feeding was at a relatively low level. The effect of midazolam was not equal across all time intervals. The predominant change produced by midazolam was to continue the high level of feeding, before the decline in feeding with onset of satiety occurred. For the two highest doses, 3 and 10 mg/kg of midazolam, the duration of feeding remained at a high level throughout the first half of the test.

Microstructure of feeding. The effect of midazolam on the duration of feeding followed from a significant increase in the mean duration of each bout of feeding, $F(4,35)=6.51$, $p<0.001$. Table 1 shows that significant increases in the bout duration occurred at 3 and 10 mg/kg of midazolam. In contrast, the frequency of bouts of feeding did not account for the overall increase in the duration of feeding. There was an effect of midazolam on the rate of eating, $F(4,35)=4.03$, $p<0.01$, and at 0.3 mg/kg produced a significant increase in the rate measure. There was no significant effect on the rate of eating for larger doses of midazolam.

Concurrent non-feeding behaviour. Midazolam (0.3–10.0 mg/kg) produced dose-related reductions in the frequency of locomotion, rears and grooms (Table 2). At 10 mg/kg, these behaviours were virtually absent throughout the entire period of the test. Two-way ANOVAs carried out on the data showed that for the locomotion measure, there was a significant dose effect, $F(4,35)=7.53$, $p<0.001$, time effect, $F(5,175)=3.42$, $p<0.001$, and a dose × time interaction, $F(20,175)=1.90$, $p<0.05$. For the rear measure, there was a

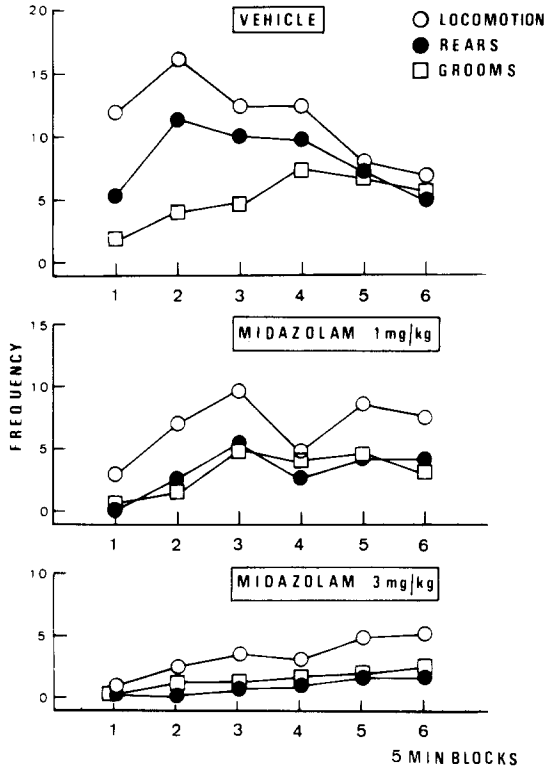

FIG. 3. Time-courses for locomotion, rears and grooms measures, after vehicle and midazolam (1.0 and 3.0 mg/kg) injections. Results are shown as mean frequency of occurrence per 5 min block. N=8 per group.

significant dose effect, $F(4,35)=9.84$, $p<0.001$, a time effect, $F(5,175)=4.94$, $p<0.0001$, but the interaction was not significant, $F(20,175)=1.65$. For the groom measure, there was a significant dose effect, $F(4,35)=11.43$, $p<0.001$, time effect, $F(5,175)=12.2$, $p<0.001$, and a significant interaction, $F(20,175)=1.75$, $p<0.05$. Figure 3 illustrates the time-courses for these behavioural categories following injection of vehicle, and of 1.0 mg/kg and 3.0 mg/kg of midazolam, respectively. In the control group, increases in the frequency of locomotion, rearing and grooming in the second 5 min period coincided with the reduction in the duration of feeding (c.f. Fig. 2). As the test proceeded, the frequency of locomotion and rearing declined again, and by the end of the test period the animals were showing relatively little activity. Following administration of midazolam (3.0 mg/kg), these ancillary activities were largely suppressed and there was no evidence of a compensating rise in the frequency of these behaviours at the time that the duration of feeding had begun to decline sharply by the fourth 5 min interval of the test period. Effects of midazolam were dose-related, with lower doses producing less-marked suppression, as the results for the 1.0 mg/kg dose (Fig. 3) indicate. After 10 mg/kg of midazolam, the non-feeding behaviours were rarely exhibited.

FG 7142

Food intake. The consumption of food was affected by FG 7142 treatments, $F(4,35)=5.33$, $p<0.01$, and intake was significantly reduced at doses of 10.0 and 15.0 mg/kg (Table 3).

Duration of feeding. Unexpectedly, the total duration of feeding was not significantly affected by any dose of FG 7142 (Table 3). There was, however, a significant drug × time interaction, $F(20,175)=3.87$, $p<0.01$, in addition to a significant time effect, $F(5,175)=38.71$, $p<0.001$. The time-course for the feeding duration measure is shown in Fig. 4. Control animals spent much of the first 5 min interval eating, but the proportion of time devoted to feeding subsequently declined (c.f. Fig. 2). Animals treated with 1.0 or 3.0 mg/kg of FG 7142 showed a similar temporal pattern of feeding, but those injected with the larger doses of 10.0 or 15.0 mg/kg of FG 7142 showed a pattern which was distinctly different (Fig. 4). The level of feeding was considerably reduced during the first 5 min interval, but it was then maintained at a relatively constant level throughout the rest of the 30 min test. Consequently, during the latter part of the test, the animals treated with 10.0 or 15.0 mg/kg of FG 7142 were showing higher level of feeding duration than control animals.

Microstructure of feeding. The reduction in the consumption of food could not be linked directly to the overall duration of feeding, as we have indicated. In addition, it could not be attributed to any alteration in the overall frequency of bouts of eating, nor could it be accounted for entirely in terms of a reduction in the overall duration of bouts of feeding (Table 3). Instead, there were highly significant reductions in the average rate of eating, which occurred at 10.0 and 15.0 mg/kg of FG 7142 (Table 3). Animals were markedly less efficient in their consumption of food.

Since there was a considerable reduction in the duration of feeding during the first 5 min interval in animals treated with the larger doses of FG 7142, Table 4 considers this interval in more detail. It is clear that the frequency of feeding bouts was entirely unaffected by FG 7142 at any dose level, and that the reduction in feeding duration was wholly due to significant reductions in bout duration which occurred when the larger doses were administered.

Concurrent non-feeding behaviour. At doses of 1.0–15.0 mg/kg, FG 7142 produced significant reductions in the frequency of locomotion, and rears (Table 5). The frequency of grooming was reduced at 10.0 and 15.0 mg/kg of FG 7142. Two way ANOVAs carried out on the data showed, for the locomotion measure, a significant dose effect, $F(4,35)=4.57$, $p<0.01$, time effect, $F(5,175)=10.99$, $p<0.001$, and a dose × time interaction, $F(20,175)=2.02$, $p<0.05$. For the rear measure, there was a significant dose effect, $F(4,35)=4.37$, $p<0.01$, and a time effect, $F(5,175)=5.02$, $p<0.01$, but no interaction. For the groom measure, there was a dose effect, $F(4,35)=7.49$, $p<0.001$, a time effect, $F(5,175)=4.70$, $p<0.001$, and a significant dose × time interaction, $F(20,175)=1.92$, $p<0.05$. Figure 5 illustrates the time-courses for these behavioural categories following injection of vehicle, and of 10.0 mg/kg and 15.0 mg/kg of FG 7142, respectively. In the control group, increases in the frequency of locomotion, rearing and grooming occurred in the second 5 min period, as was observed in the midazolam experiment (c.f. Fig. 3). At 10.0 mg/kg of FG 7142, the frequencies of these three behaviours were similar to control values, but over succeeding time intervals, the levels of each behaviour were suppressed. At 15.0 mg/kg of FG 7142, the frequencies remained at fairly constant, reduced levels throughout the entire period of the test. Hence, the characteristic time-dependent changes in the frequencies of locomotion, rearing and grooming found in control animals were absent in animals treated with larger doses of FG 7142.

Qualitative description. In addition to the quantitative measures of feeding behaviour, some descriptive comment

TABLE 3

EFFECTS OF FG 7142 ON FOOD INTAKE AND MICROSTRUCTURE OF FEEDING (30 MIN TEST)

Measure	FG 7142 (mg/kg) 0	1.0	3.0	10.0	15.0
Food intake (g)	11.5 ±0.6	13.3 ±1.8	11.7 ±1.7	4.5* ±1.0	6.5* ±1.2
Total feeding duration(s)	404.0 ±20.6	479.8 ±89.0	501.3 ±67.7	398.5 ±38.8	452.8 ±72.6
Bout duration(s)	33.5 ±7.0	30.0 ±3.1	34.1 ±6.8	29.6 ±2.1	22.0 ±0.9
Bout frequency	14.6 ±2.8	16.8 ±2.8	16.5 ±1.9	14.0 ±1.8	20.5 ±3.1
Rate of eating (g/min)	1.75 ±0.15	1.74 ±0.13	1.46 ±0.13	0.66† ±0.09	0.91† ±0.16

Results are shown as mean ± S.E.M. (N=8).
Levels of significance for comparisons with control scores: *$p<0.05$; †$p<0.005$ (Dunnett's t-test).

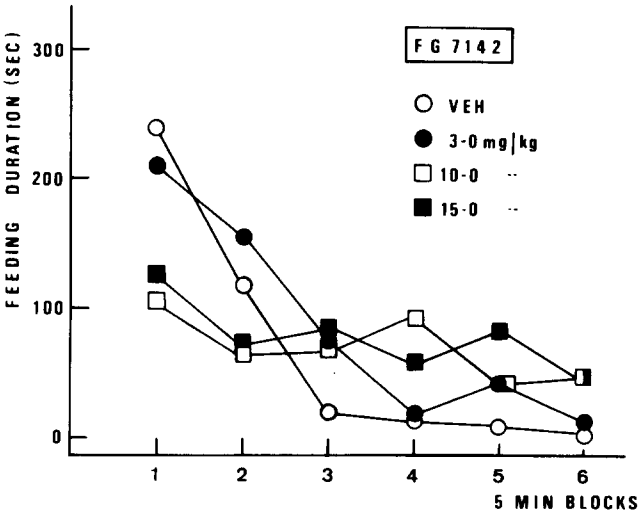

FIG. 4. Time-course of the duration of feeding after FG 7142 (3.0–15.0 mg/kg), for six five-minute blocks. Results for 1.0 mg/kg were indistinguishable from control values and are therefore omitted. Results are shown as mean duration (sec) per 5 min block. N=8 per group.

can be made about animals following the administration of the larger doses of FG 7142. Generally, they appeared more tentative in their eating, and portions of food would be maintained in the mouth, accompanied by chewing, and dropping of food particles, but apparently with less swallowing. The reduction in the rate of eating (Table 3) probably reflects this distinctive appearance of a less avid form of ingestion.

DISCUSSION

The imidazobenzodiazepine, midazolam, produced a dose-related increase in the consumption of a palatable diet by non-deprived male rats, in agreement with earlier findings for benzodiazepines [11, 13, 15, 17, 18]. The hyperphagic effect followed directly from an increase in the duration of feeding, which was expressed as practically continuous eating during the first 5 min, and as eating at well above control levels during the second and third 5-min intervals. During the second half of the 30 min test, the levels of feeding (in terms of duration) were close to the control level. Hence, midazolam prolonged the initial period of avid food consumption, and delayed the course of satiety, but it did not maintain a hyperphagic effect throughout the complete 30-min test period. Rats, which have been partially-satiated before administration of midazolam, also exhibit a hyperphagic response [13], indicating that the benzodiazepine treatment can reverse the progress of satiety. The increase in the duration of feeding observed in the present study was not due to an increase in the frequency of feeding bouts, but to an increase in the mean duration of individual eating bouts. Midazolam did not, therefore, stimulate the initiation of episodes of feeding; instead, the termination of individual bouts of feeding was delayed. Benzodiazepines are not unique in stimulating an increase in the consumption of food by these means. Recently we have shown that the hyperphagic effect of the specific *kappa* opioid receptor agonist U-50,488H [27], was due to an increase in duration of feeding, without change in the rate of eating. Furthermore, the latency to terminate eating was extended [28].

The time-course of feeding which followed treatments with midazolam (Fig. 2) is very similar to that found for drinking water by thirsty rats after administration of midazolam (1.25–5.0 mg/kg) [8]. Water-deprived animals, under control conditions, exhibited continuous drinking for the first 6 min of a drinking test, and then showed rapid satiation, so that after 12 min of the test, drinking had virtually ceased. Animals treated with midazolam maintained a high level of drinking for a longer period during the first half of the test, before showing the onset of satiation. In both cases, therefore, the initial impetus to consume was maintained longer and delayed the rapid decline of the consummatory response as satiety intervenes. The action of midazolam, and of other benzodiazepines, may not, therefore, be specific to feeding responses, although it has not yet been established that a common mechanism underlies their

TABLE 4

EFFECTS OF FG 7142 ON MICROSTRUCTURE OF FEEDING(FIRST 5 MIN BLOCK)

Measure	FG 7142 (mg/kg) 0	1.0	3.0	10.0	15.0
Feeding duration(s)	238.4 ±28.9	217.4 ±16.8	211.8 ±22.0	105.8* ±28.8	126.3* ±29.2
Bout duration(s)	39.1 ±6.9	35.6 ±3.9	36.9 ±7.8	15.7* ±2.9	19.7* ±3.1
Bout frequency	6.5 ±0.9	6.8 ±1.1	6.8 ±0.7	6.4 ±1.3	6.5 ±1.1

Results are shown as mean ± S.E.M. (N=8).
Levels of significance for comparisons with control scores: *$p<0.01$ (Dunnett's t-test).

TABLE 5

EFFECTS OF FG 7142 ON CONCURRENT NON-FEEDING BEHAVIOUR (30 MIN TEST)

Measure	FG 7142 (mg/kg) 0	1.0	3.0	10.0	15.0
Locomotion (frequency)	76.3 ±7.4	61.1† ±8.7	51.3† ±5.9	38.0† ±5.5	42.0† ±6.8
	—	80.1%	67.2%	49.8%	55.0%
Rears (frequency)	54.5 ±6.9	36.0† ±5.8	39.9† ±4.9	23.3† ±4.0	24.4† ±7.1
	—	66.1%	73.2%	40.9%	44.8%
Grooms (frequency)	27.5 ±2.0	31.5* ±2.9	27.6 ±3.2	14.6† ±1.9	17.6† ±3.1
	—	114.5%	100.4%	53.1%	64.0%

Results are shown as mean ± S.E.M. (N=8). Percent of control scores are shown beneath. Levels of significance for comparisons with control scores: *$p<0.01$; †$p<0.005$ (Dunnett's t-test).

hyperphagic and hyperdipsic effects [14]. It is interesting to note that although *kappa* opiate receptor agonists, like benzodiazepines stimulate the consumption of food [16], their action in water-deprived rats is to depress the consumption of water [32,44]. In this respect, therefore, their effect is completely dissociable from that of the benzodiazepines.

Midazolam also produced dose-dependent reductions in the frequency of locomotor activity, rearing, and grooming (Table 2). Vehicle-treated animals displayed a sequence of behavioural change which was indicative of appetite, succeeded by satiety once a meal had been consumed (c.f. [42]). The first 5-min period was devoted principally to feeding; during the second 5-min period there was a transient increase in the frequency of locomotor activity, rearing, and grooming. Later feeding, locomotor activity and rearing continued to decline, while grooming increased slightly in frequency (Figs. 3 and 5). Doses of midazolam which produced a significant hyperphagic effect also produced marked suppression of other behaviours, which was maintained through the 30 min test. This degree of behavioural suppression undoubtedly reflects the sedating effect of midazolam administered to naive animals. The sedation, however, does not account for the hyperphagic effect, since tolerance develops rapidly to the sedative effects but not to the effect on feeding (Cooper and Mistry, unpublished data; [19,46]). Since the suppression of locomotor activity, rearing and grooming remained beyond the time when the hyperphagic effect of midazolam had finished, we suggest that the reduction in non-feeding activity was not simply a result of competition from the increased feeding response. This conclusion is at variance with an earlier analysis of chlordiazepoxide's effects on feeding and concurrent activity [6].

The β-carboline FG 7142, which acts as a benzodiazepine receptor inverse agonist [5, 29, 30, 36], reduced the consumption of food, in agreement with previous reports [9, 11, 13]. Consideration of the microstructural characteristics of feeding, as well as the time-course of feeding, provides some clarification of the nature of the effects of FG 7142 on the consumption of food. It was surprising to us that FG 7142 did not significantly affect the overall duration of feeding in the 30 min test (Table 3). In this respect, therefore, it did not apparently produce an effect which was opposite that of midazolam's. However, an analysis of the first 5-min block, when eating behaviour was at its most motivated in control animals, reveals some interesting further details. During this period, the duration of feeding was reduced, and it was due entirely to a reduction in the mean duration of individual bouts; there was no change in the frequency of bouts (Table

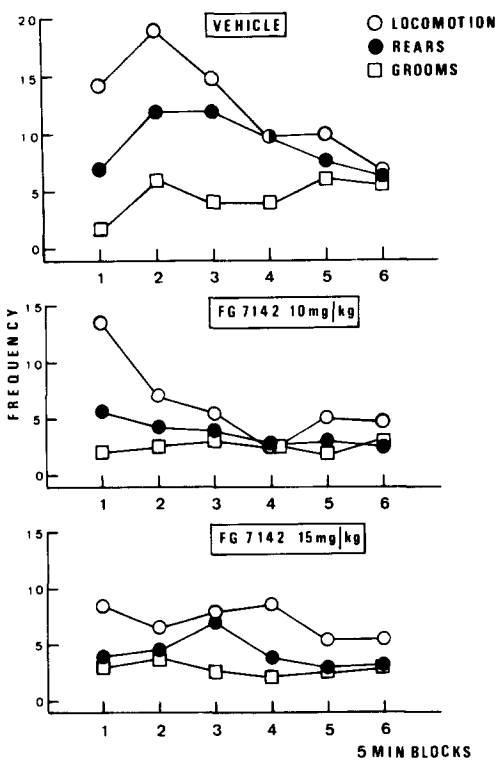

FIG. 5. Time-courses for locomotion, rears and grooms measures, after vehicle and FG 7142 (10.0 and 15.0 mg/kg) injections. Results are shown as mean frequency of occurrence per 5 min block. N=8 per group.

4). Hence, FG 7142 brought about an early finish to eating bouts, but it did not affect the initiation of feeding activity. This is an important result in two respects: first, it suggests that FG 7142 did not interfere indiscriminately with the controls of feeding behaviour; second, its effects do appear to be the opposite of midazolam's. Both drugs affected bout duration, but not bout frequency: midazolam increased the bout duration, while FG 7142 curtailed it. If we subscribe, therefore, to the concept of a 'bi-directional' control of food consumption exerted by agonists acting at benzodiazepine receptors [10], then the focus of the control appears to be on the termination, not the initiation, of bouts of feeding in motivated animals.

In the following intervals of the test, the duration of feeding after treatments with 10.0 or 15.0 mg/kg of FG 7142 remained relatively constant. The tentative nature of the feeding response, which we observed and which was characterized by taking small portions of food, chewing without ingesting, and dropping food particles, was reflected in the low overall rate of eating (Table 3). We have no immediate explanation for this type of behaviour, but it may be relevant that FG 7142 blocked the preference for a saccharin solution in a two-bottle test [12]. Possibly, FG 7142 reduced the palatability of the sweetened diet offered in the present feeding test. We discount the view that FG 7142 enhances aversive responses to all flavours, since it did not increase the rejection of a non-preferred quinine solution [12].

Not only feeding, but also other forms of behaviour were reduced, in terms of frequency, by FG 7142 (Table 5). Self-grooming was reduced, in agreement with an earlier observation in a test of social behaviour in male rats [1]. Significant reductions in the frequency of locomotor activity and rearing also occurred, and these effects occurred at doses of 1.0 mg/kg of FG 7142 and greater. Hence, these responses seemed to be particularly sensitive to the disruptive effect of FG 7142, under the conditions imposed by the test of palatable food consumption.

Other experimenters have reported reductions in behavioural responses following treatments with FG 7142 in doses up to 20.0 mg/kg. Rates of lever-pressing were depressed in a drug discrimination paradigm [43], and in a test of intracranial self-stimulation in the rat [35]. The time spent in active social interaction was reduced after treatments with FG 7142 in male rats [22,23], and aggression was reduced in lactating mother rats [25]. Locomotor activity was reduced in a holeboard test by FG 7142, but not the frequency of head-dipping or time spent in head-dipping [23]. Taken with our present results which show that grooming and rearing activities are also affected by FG 7142, care has to be exercised in trying to account for the effects of the drug. A single, all-encompassing explanation may be insufficient, just as there is unlikely to be a single explanation to cover the multiple behavioural effects of benzodiazepine receptor agonists [20]. The straightforward notion that FG 7142 produces a generalized, non-specific disruption of behavioural responses is not borne out by its lack of effects involving some behavioural measures [23], including the frequency of feeding bouts reported in the present study. Further detailed behavioural analyses of the kind represented by some previously published work [1, 2, 23], and by the present report, should contribute materially to an understanding of those aspects of behaviour which are particularly sensitive to the effects of FG 7142.

ACKNOWLEDGEMENTS

Dr. E. Petersen (Ferrosan, Soeborg, Denmark) generously provided the FG 7142. Midazolam was provided by Roche Products Ltd., U.K. We are grateful to Mr. D. J. Barber for technical assistance.

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