

# Effects of the Dopamine D<sub>2</sub> Agonists Lisuride and CQ 32-084 on Rat Feeding Behaviour

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Received 17 June 1991

FERRARI, F., F. PELLONI AND D. GIULIANI. *Effects of the dopamine D<sub>2</sub> agonists lisuride and CQ 32-084 on rat feeding behaviour.* PHARMACOL BIOCHEM BEHAV 41(4) 683-688, 1992. — The influence on rat-feeding behaviour of lisuride and CQ 32-084, agonists at dopamine D<sub>2</sub> receptors, was examined using two procedures. In a first series of experiments, the apparatus was an X-maze baited with food pellets where individual fasted rats were observed for 5 min. A number of parameters were recorded: latency to tasting and feeding, interval between tasting and feeding, total feeding time, and total grooming time. Lisuride (0.05 and 0.1 mg/kg) and CQ 32-084 (0.05 and 0.5 mg/kg) behaved as stimulants of eating; lisuride (0.4 mg/kg) inhibited the phenomenon. Both drugs always antagonized grooming. Subsequently, when food intake was determined in the home cages of fasted animals lisuride reduced feeding at all doses during the first hour after treatment, while CQ 32-084 had no effect. The data show that the two compounds display different activity on ingestive behaviour according to the dose and experimental model used. Discussion centres on the possible dependence of feeding enhancement in the X-maze on the anxiolytic activity exerted by low D<sub>2</sub> autoreceptorial doses.

Feeding behaviour	Dopamine	D <sub>2</sub> autoreceptors	Lisuride	CQ 32-084	X-maze
Grooming	Anxiety				

THE influence of dopamine (DA) on feeding behaviour is a long-established and well-documented fact (22,26). While it seems certain that stimulation of D<sub>1</sub> receptors inhibits ingestive behaviour (27), the role of D<sub>2</sub> receptors remains a moot point. Some authors have noted an increase in the food intake of rats treated with bromocriptine (31), *d*-amphetamine (27, 41), and N-0437 (8) at doses active on the latter receptors, yet all these drugs, and in particular N-0437, which is a new, highly selective D<sub>2</sub> receptor agonist, have also been reported as causing marked hypophagia (6,32). Moreover, lisuride (7) and apomorphine (40) have been found to reduce food consumption at the same low doses as cause hypomotility, an effect related to D<sub>2</sub> autoreceptor stimulation (11).

All D<sub>2</sub> autoreceptor agonists elicit a typical stretching-and-yawning (SY) syndrome together with sedation (15,28,37,42). This behavioural pattern, which is particularly apparent after the administration of B-HT 920 (12), has also been observed in the case of some ergot derivatives such as lisuride and CQ 32-084 (2,13).

Recent experiments using a new behavioural model, the X-maze feeding test, showed that B-HT 920 not only stimulates rat feeding behaviour but also exerts an anxiolytic effect (17). However, the two effects would appear to be dose dependent, the former occurring at low doses reputed to be selective for D<sub>2</sub> autoreceptors while the latter seems to involve the activation of the  $\alpha_2$  adrenoceptors (20), which occurs at higher

doses (14,18,21,25). The hyperphagia induced by B-HT 920 at low D<sub>2</sub> doses was subsequently reconfirmed during different experiments on food intake using fasted rats (data not yet published).

The purpose of the present study was to investigate the influence in the X-maze feeding test of lisuride and CQ 32-084 at various doses known to stimulate the D<sub>2</sub> receptors and also, probably, the D<sub>2</sub> autoreceptors, given that they typically elicit SY (2,13). Furthermore, to validate the test as a tool for predicting effects on feeding the drugs were administered at the same doses to fasted rats in their home cages and feeding behaviour was monitored over a 6-h period.

## METHOD

### *Animals and Procedure*

Subjects were male Wistar rats (Morini, S. Polo d'Enza, Reggio Emilia, Italy) weighing 200-220 g at the start of the test. They were housed in groups of 10 with food and water ad lib on a 12-h light cycle, from 7 a.m.-7 p.m., for at least 1 wk prior to the start of experiments. Animals were deprived of food for 17 ± 2 h before the tests, which were carried out between 9 a.m. and 1 p.m. by experienced researchers unaware of the drug treatment. Each rat was used only once and there were no fewer than six experimental animals in each treatment group; the exact number of rats used is reported in

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the figures and Table 1. Control animals were handled in the same way.

**Modified X-maze test.** The X-maze apparatus was as previously described (18). In brief, it consisted of a black Plexiglas floor in the shape of a regular cross, each arm of which (two open and two closed by a cover) is flanked with transparent Plexiglas walls that meet at the intersection, giving a square, the "arena." The only modification to it for present purposes was the placing of two food pellets of standard laboratory chow at the far end of each of the four arms (two open and two covered). Twenty-five minutes after IP injection of drugs or saline, animals were placed singly into the central arena of the apparatus, facing an open arm, and their subsequent feeding behaviour observed over a 5-min period by a research assistant using a hand-held stopwatch.

The parameters adopted for the purpose of monitoring feeding behaviour were the following: 1) tasting = first oral contact with one of the pellets, not necessarily followed by feeding; 2) feeding = the first ingestion of food as manifested by mastication—each bout of feeding was deemed complete when the rat stopped chewing and moved away from the pellet; 3) latency to tasting and feeding = the time elapsing between the placing of the rat in the central arena of the X-maze and the first bout of tasting and feeding, respectively; 4) interval between tasting and feeding. We also took into account the overall duration of feeding (total feeding time) and of grooming, as total time spent in scratching, washing, or licking of coat and paws (total grooming).

**Food intake in the home cage.** Rats used for these experiments were housed in individual cages at least 4 days before the tests. On the test day, after fasting, animals were injected IP with the ergot derivatives at different doses or equivolume of saline and immediately afterward returned to their home cages where preweighed food pellets were provided 25 min later. Food intake was measured 0.5, 1, 2, 3, and 6 h after food presentation by collecting and weighing food pellets and spillage.

#### Drugs and Treatments

The following substances were used: lisuride hydrogen maleate (Spofa, Prague, Czechoslovakia) and CQ 32-084

(Sandoz, Basel, Switzerland). The drugs were freshly dissolved in saline at concentrations that allowed the administration of 2 ml/kg IP.

#### Statistical Evaluation

Data relating to latency to tasting and feeding, the interval between tasting and feeding, and total feeding time are expressed in seconds. For those animals that did not taste or feed during the 5-min period of the X-maze feeding test, latencies were arbitrarily taken to be 300 s. Data relating to food intake are expressed in grams of cumulative food ingested at the various times. All values are presented as means  $\pm$  SEM.

Data were analyzed with one-way analysis of variance (ANOVA) followed by Student-Newmann-Keuls (SNK) *t*-test, with the level of significance set at  $p < 0.05$ . "Explained variance" of the behavioral patterns in question are reported in the legends to the figures.

## RESULTS

#### X-Maze Feeding Test

In these experimental conditions, all fasted controls tasted the bait after being placed in the apparatus and subsequently almost all of them actually fed. In previous tests, using older animals of the same strain fasted for a shorter period, we obtained a lower percentage of rats tasting and eating (17). As already reported, controls clearly prefer the covered arms as place of choice for feeding; since this typical pattern was not significantly modified in the various treatment groups, this datum is not graphically represented. As seen in Fig. 1, latency to tasting (a) was reduced by lisuride at 0.05 and 0.1 mg/kg with respect to the controls; at the dose of 0.4 mg/kg, however, lisuride behaved differently, increasing latency to tasting with respect to the other two experimental groups, and this dose also increased the interval between tasting and feeding (c). Latency to feeding (b) was reduced at the dose of 0.1 mg/kg, with respect to the controls and the 0.05 mg/kg-treated group, and enhanced at the dose of 0.4 mg/kg, with respect to the controls and the groups treated at the two lower doses. Total feeding time (d), on the other hand, was

TABLE 1  
EFFECT OF LISURIDE AND CQ 32-084 ON FOOD INTAKE OF FASTED RATS IN THEIR HOME CAGES

Treatment (mg/kg)	Food Intake (g)				
	0.5 h	1 h	2 h	3 h	6 h
Saline a	3.7 $\pm$ 0.1	5.3 $\pm$ 0.5	7.5 $\pm$ 0.7	8.9 $\pm$ 0.7	14.8 $\pm$ 1.1
Lis 0.05	2.4 $\pm$ 0.3*	3.1 $\pm$ 0.4*	5.7 $\pm$ 0.7	7.1 $\pm$ 0.7	12.4 $\pm$ 1.2
Lis 0.1	1.9 $\pm$ 0.4*	3.4 $\pm$ 0.6*	5.2 $\pm$ 1.0	8.1 $\pm$ 1.1	13.3 $\pm$ 2.1
Lis 0.4	2.8 $\pm$ 0.2	3.7 $\pm$ 0.2*	5.4 $\pm$ 0.5	7.3 $\pm$ 0.7	12.7 $\pm$ 0.6
Saline b	2.3 $\pm$ 0.7	3.6 $\pm$ 0.7	4.9 $\pm$ 0.3	5.4 $\pm$ 0.6	8.7 $\pm$ 0.5
CQ 0.05	2.3 $\pm$ 0.5	4.0 $\pm$ 0.5	5.1 $\pm$ 0.8	5.5 $\pm$ 0.8	8.4 $\pm$ 0.9
CQ 0.5	2.1 $\pm$ 0.2	3.1 $\pm$ 0.3	4.7 $\pm$ 0.3	5.4 $\pm$ 0.5	8.9 $\pm$ 0.8
CQ 1	2.1 $\pm$ 0.2	2.9 $\pm$ 0.3	4.4 $\pm$ 0.4	5.9 $\pm$ 0.5	9.6 $\pm$ 0.6

Saline, lisuride (Lis), and CQ 32-084 (CQ) were IP administered 25 min before restoration of food. The experiments with lisuride and CQ 32-084 were carried out on two different days; saline a and b are their respective controls. Values represent the means  $\pm$  SEM of the amount of food cumulatively eaten per rat (six rats were used for each treatment group).

\*Significantly different from controls (ANOVA followed by SNK test).

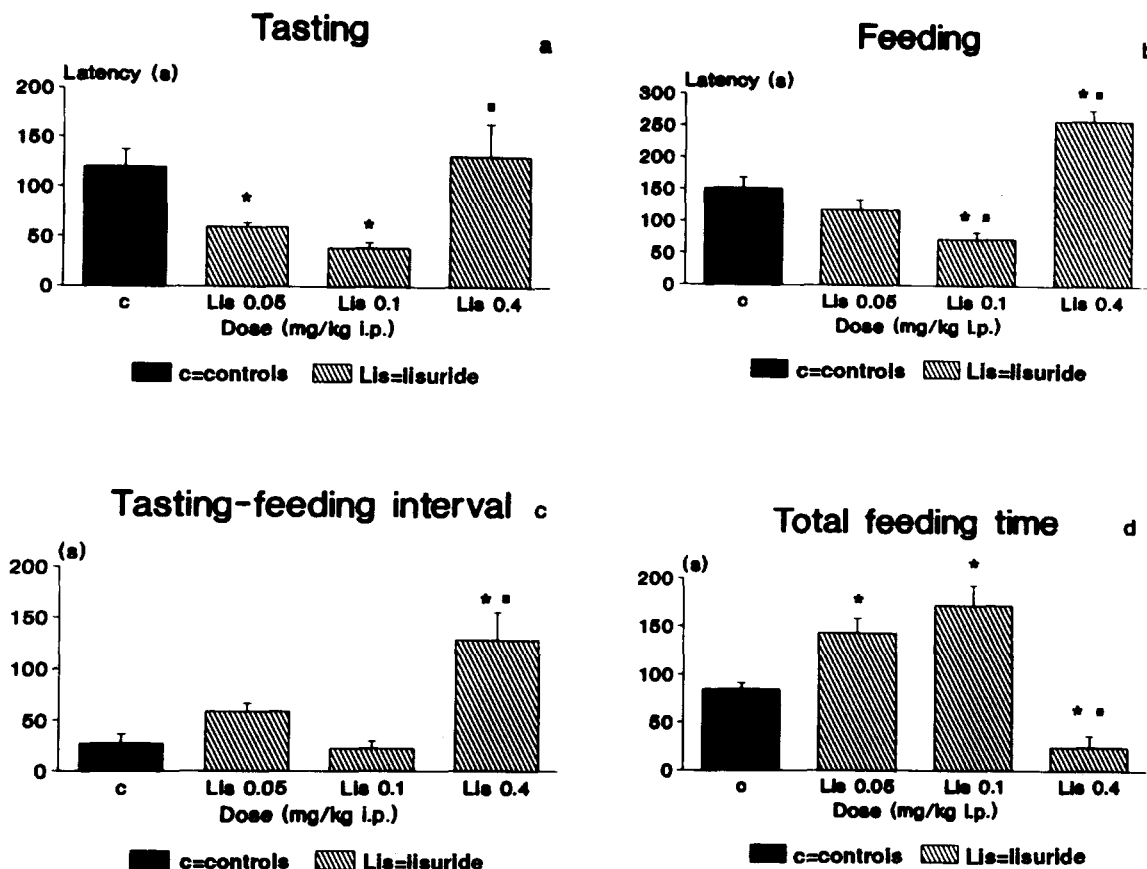


FIG. 1. Effect of lisuride on the X-maze feeding test. Lisuride (Lis) or an equal volume of saline (c) was IP injected into  $17 \pm 2$  h fasted rats 25 min before the test. Histograms represent the mean  $\pm$  SEM of the values per treatment group. *N* of rats for treatment group: c = 12; Lis 0.05 mg/kg = 12; Lis 0.1 mg/kg = 10; Lis 0.4 mg/kg = 6. \*Significantly different from controls (ANOVA followed by SNK test). <sup>#</sup>Significantly different from lower doses (ANOVA followed by SNK test). Explained variance: Fig. 1a, 40.8%; Fig. 1b, 61.4%; Fig. 1c, 52.3%; Fig. 1d, 56.5%.

longer after lisuride at the two lower doses, but much shorter at 0.4 mg/kg with respect not only to controls but also to the other two treatment groups.

Figure 2 shows how feeding behaviour in the X-maze was influenced by CQ 32-084. Latency to (a) tasting and (b) feeding was significantly reduced after 0.05 mg/kg; total feeding time (d) increased at 0.05 and 0.5 mg/kg but was unaffected with respect to controls at 1 mg/kg, which had a significantly different effect from the two lower doses.

#### Total Grooming in the X-Maze

Grooming was always observed in all control rats placed in the new apparatus: Both the ergot derivatives significantly antagonized the phenomenon at all doses (Fig. 3).

#### Food Intake in the Home Cage

As can be seen in Table 1, the cumulative food intake of lisuride-treated rats was significantly lower than that of controls at 30 min for the doses of 0.05 and 0.1 mg/kg and at 60 min for all doses. CQ 32-084 never affected food intake.

The difference in food intake of the two control groups may be ascribed to variable external factors (e.g., body

weight, fasting time, time spent in the home cages prior to the test) and does not invalidate the results, which depend on rigorously controlled intragroup parameters.

#### DISCUSSION

As mentioned above, DA agonists administered at doses selective for D<sub>2</sub> receptors affect feeding behaviour in different ways. Lisuride has been described as a potent, long-lasting anorexigenic in the rat (7) and some of our data partially support this description. Various authors have observed that the D<sub>2</sub> stimulants, including ergot derivatives, administered over a certain dose range induce sedation and elicit a typical SY syndrome (12,28,37,42). Most authors believe that the D<sub>2</sub> receptors involved in this phenomenon are presynaptic (D<sub>2</sub> autoreceptors). Interestingly, a recent report (8) described the biphasic activity on feeding exerted by N-0437, a compound selective for D<sub>2</sub> receptors. The increase in food intake caused by the same low doses that induce SY does in fact suggest involvement of the autoreceptor subtype.

We have repeatedly reported the ability of B-HT 920, an azepine derivative proposed as a selective agonist of D<sub>2</sub> autoreceptors (1), to elicit a marked SY syndrome (12) as well as sedation; and we have speculated, on the basis of deductive

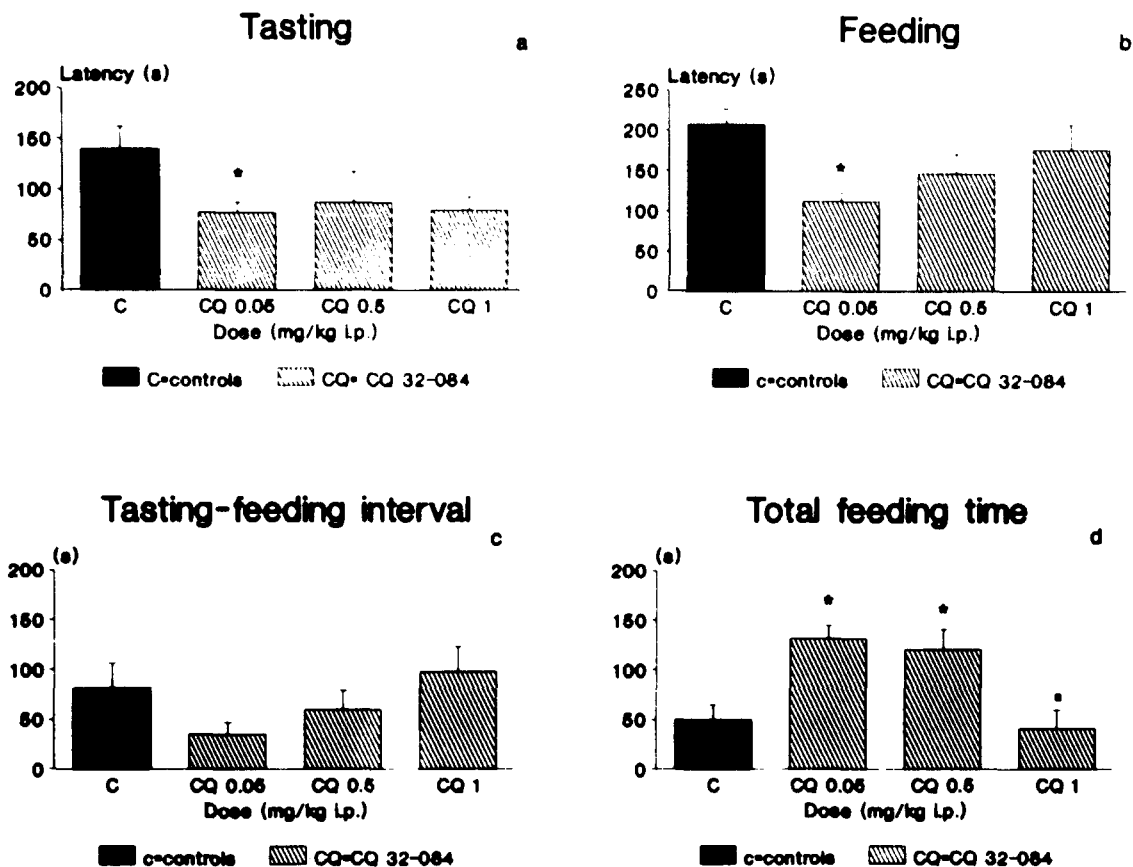


FIG. 2. Effect of CQ 32-084 on the X-maze feeding test. CQ 32-084 (CQ) or an equal volume of saline (c) was IP injected into  $17 \pm 2$  h fasted rats 25 min before the test. Histograms represent the mean  $\pm$  SEM of the values per treatment group. N of rats for treatment group: c = 8; CQ 0.05 mg/kg = 8; CQ 0.5 mg/kg = 6; CQ 1 mg/kg = 6. \*Significantly different from controls (ANOVA followed by SNK test). ■ Significantly different from lower doses (ANOVA followed by SNK test). Explained variance: Fig. 2a, 23.6%; Fig. 2b, 34.5%; Fig. 2c, 17.9%; Fig. 2d, 51.4%.

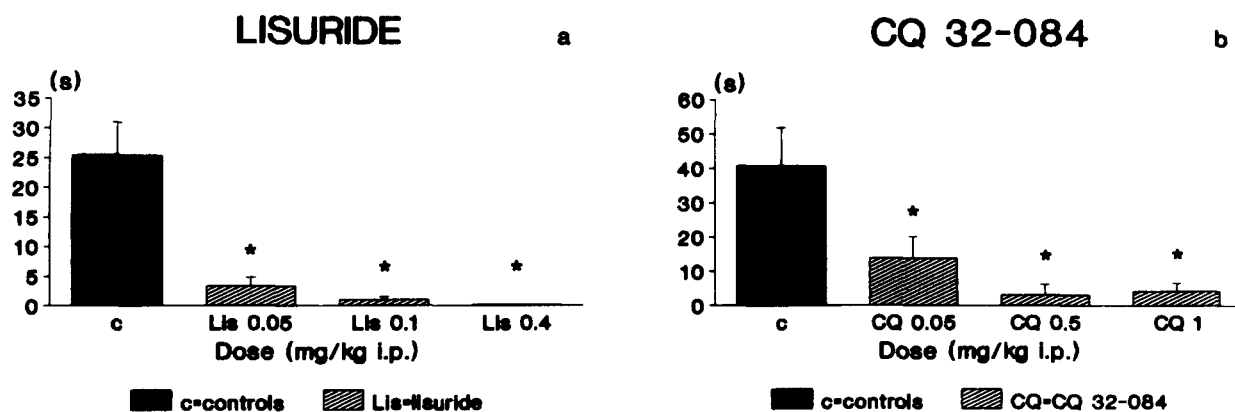


FIG. 3. Effect of lisuride and CQ 32-084 on the total grooming time in the X-maze feeding test. Lisuride (Lis), CQ 32-084 (CQ), or an equal volume of saline (c) were IP injected into  $17 \pm 2$  h fasted rats 25 min before the test. Histograms represent the mean  $\pm$  SEM of the values per treatment group, which are reported in Figs. 1 and 2. \*Significantly different from controls (ANOVA followed by SNK test). Explained variance: Fig. 3a, 51.5%; Fig. 3b, 41.1%.

reasoning, that there may be a correlation between this and the D<sub>2</sub> autoreceptors. Recently, using the X-maze feeding test we demonstrated the hyperphagic activity of B-HT 920 (17), a finding confirmed at the low doses supposed to act on autoreceptors, on a classic test of food intake (data not yet published). Furthermore, the X-maze feeding test confirmed results previously obtained using an unbaited X-maze (18), namely, that B-HT 920 exerts a potent anxiolytic effect; treated animals fed indiscriminately in open and covered arms, whereas controls fed only in the covered arms (17). The behaviour induced in rats treated with B-HT 920 practically mirrored that induced by diazepam (20), which, as is known, exerts both anxiolytic and hyperphagic effects in different experimental models, as well as in man (9,34,35). In our present experiments, lisuride and CQ 32-084 had no significant effect on the choice of environment, and for this reason the finding has not been reported in the figures. However, it is very likely that the stimulation of feeding induced by low doses of both drugs itself reflects their tranquilizing effect in an unfamiliar environment where animals are torn between exploring and eating and are faced with the choice between open and covered arms. This hypothesis is in line with the reported reversal of hyponeophagia by benzodiazepines (10,34).

There is increasing experimental and clinical evidence of the key role of dopamine in the control of anxiety (3,5,24), and in this context the reported anticonflictual effects of low doses of apomorphine in the rat (23) are of particular interest. In our experiments using the X-maze feeding test, we noted that the hyperphagic effect of the two ergot derivatives was accompanied by a marked reduction in grooming. Other authors have also reported that grooming is antagonized by D<sub>2</sub> agonists (32,38) but stimulated by D<sub>1</sub> agonists (29). Furthermore, increased grooming activity associated with anorexia is induced by CRF and ACTH, two putative mediators of several stress-related behavioural responses (16,19,30,39). If grooming in the X-maze is a sign of psychological stress (4,36), as seems likely, the fact that it is antagonized by the two ergot derivatives could be a further indication of their

anxiolytic activity. This would therefore account for the hyperphagic effect of low (autoreceptorial) doses of the drugs in a stressful environment like the X-maze, while higher doses involving other receptors would not necessarily affect feeding behaviour in the same test. In the light of such a hypothesis, the fact that the same doses have different effects on feeding behaviour in rats placed in environments inducing different emotional states (X-maze vs. home cage) is not contradictory. Moreover, it is not improbable that the anorexic effect observed in the home cages only in the first hour after lisuride may be correlated with the extreme drowsiness typically induced by the drug. It is worth remembering that previous studies have shown that lisuride (400 mg/kg) no longer induces SY but other behavioural signs, suggesting a loss of selectivity for the D<sub>2</sub> autoreceptors (2). The same is true of CQ 32-084 (1 mg/kg), which elicits shakes and a certain degree of stereotyped behaviour (13).

In conclusion, since we failed, at least in part, to demonstrate that the results of the X-maze feeding test could be replicated in the test on food intake in the home cage, we now suggest that the hyperphagic effects induced by the low doses of different DA D<sub>2</sub> agonists are dependent on their anxiolytic properties as shown by our experimental model. These properties are particularly pronounced with B-HT 920, which also modifies the typical pattern of preferential eating in the covered arms exhibited by controls (17,20). If it is true that the stimulant effects of D<sub>2</sub> autoreceptors on feeding emerge only, or mainly, in a stress-related situation, the result could be of clinical interest for those human feeding pathologies, for example, anorexia, where stress has been shown to play a fundamental role in precipitating and maintaining the condition and where improvement has been unexpectedly obtained after treatments with DA agonists (33).

#### ACKNOWLEDGEMENTS

This work was supported in part by grants from the Ministero della Pubblica Istruzione (M.P.I.) (60%). CQ 32-084 was a generous gift from Sandoz (Basel, Switzerland).

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