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The Selective Dopamine Uptake Inhibitor GBR 12909: Its Effects on the Microstructure of Feeding in Rats

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VAN DER HOEK, G. A. AND S. J. COOPER. *The selective dopamine uptake inhibitor GBR 12909: Its effects on the microstructure of feeding in rats.* PHARMACOL BIOCHEM BEHAV **48**(1) 135–140, 1994.—Previous experiments have investigated the anorectic effects of mazindol and cocaine, both of which can inhibit dopamine (DA) uptake into presynaptic terminals but do not do so selectively. GBR 12909, however, is an example of a potent and selective inhibitor of DA uptake and, therefore, the present study was concerned with investigating its possible effects on feeding behavior in nondeprived rats given access to a sweetened palatable diet. GBR 12909 (5–20 mg/kg, IP) was injected 2 h before a 60 min observation test. It produced a significant reduction in food intake, as a consequence of a reduction in the duration of feeding, without reducing the rate of eating. This anorectic profile is consistent with earlier findings for mazindol and cocaine. The other main behavioral effect of GBR 12909, observed in the present study, was to induce intense sniffing activity, but, unlike cocaine, it did not suppress grooming or induce hyperlocomotion. This selective behavioral effect of GBR 12909 indicates that sniffing can be isolated as one component of a broader array of components typically associated with DA-related stereotyped behavior.

Dopamine uptake inhibitor GBR 12909 Feeding Sniffing Rats

VAN DER REE and colleagues reported the synthesis of a series of aryl 1,4-dialk(en)ylpiperazines, showing them to be selective dopamine uptake inhibitors (45). The behavioral effects of three of these compounds GBR 12909, GBR 13098, and GBR 13069, were described by Heikkila and Manzino (25). The three compounds increased locomotor activity in mice and induced ipsilateral turning in rats with unilateral lesions of the dopaminergic nigrostriatal pathway. Tritiated members of this series have been used to label the dopamine (DA) uptake site (1,4–5,7,10,26,28,33,34). Andersen confirmed that GBR 12909 is an extremely potent inhibitor of DA uptake using rat striatal membranes (1), while Westerink and colleagues showed that GBR 12909 increased the in vivo release of DA in rat striatum (46). Cocaine is also known to inhibit DA uptake, and it has been proposed that the rewarding effects of cocaine-like drugs are associated with the inhibition of DA uptake (32,38). It follows, therefore, that GBR 12909 may produce cocaine-like behavioral effects, and exhibit reward effects. In support of this hypothesis, GBR 12909 has been found to enhance cocaine-appropriate responding in animals trained to discriminate the stimulus effects of cocaine (19,29,35,47). In addition, stimulant effects of GBR 12909 cross-sensitize with those of cocaine (2). GBR 12909 lowers the threshold for the reward effects of electrical brain stimulation (40), and is self-administered by rats (39) and primates (5,27).

The contributions of central dopamine activity to the control of feeding behavior are still not clearly elucidated, despite two decades of work (3, 8,9,30). Nevertheless, a combination of pharmacological and behavioral analysis provide one source of important evidence with which to assess dopamine's roles. A number of years ago we described the effects of mazindol (21) on feeding in food-deprived rats (17). Mazindol produced a marked reduction in the duration of food ingestion, but had no effect on the rate of eating. Mazindol is an early example of a DA uptake inhibitor (24,26), and was used as an anorectic agent in humans (22). More recently, we have described cocaine's effects in nondeprived rats trained to eat a highly palatable diet (18). Cocaine suppressed feeding in a dose-dependent manner, due to a reduction in the frequency

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of feeding bouts, while the rate of eating remained unaffected (18). However, neither mazindol nor cocaine are selective DA uptake inhibitors and, therefore, it is difficult to assess precisely what contribution DA uptake inhibition makes. Hence, we investigated for the first time the effects of a range of doses of GBR 12909 on feeding behavior in the rat. A microstructural analysis of feeding behavior was undertaken on the basis of observational data, and a range of other behavioral responses in addition to feeding were also recorded.

METHOD

Animals

The subjects were 35 male, hooded rats, bred in our laboratory, weighing 320–450 g. They were housed individually in stainless steel cages with free access to water and food pellets (diet 41B, Heygate and Sons). They were maintained under a 12 L : 12 D cycle (lights on at 0700 h). The room temperature was 22 ± 1°C. Prior to the experiment the animals were handled and weighed daily.

Drug

GBR 12909 (1-[2-[Bis(4-fluorophenyl)methyoxy]ethyl]-4-(3-phenyl-propyl)piperazine dihydrochloride) (mol.wt. 523.5) was dissolved in distilled water, and injected intraperitoneally in a volume of 10 ml/kg. The doses of GBR 12909 (calculated as salt) were 5, 10, 15, and 20 mg/kg, and there was a vehicle control. Injections were given 120 min before the 60 min observation test. The range of doses and injection-test interval were chosen on the advice of Dr. E. B. Nielsen, Novo Industri A/S, Bagsvaerd, Denmark.

Procedure

The animals were first adapted to eating a palatable, sweetened mash. The formula was 50 ml sweetened condensed milk, 150 ml powdered chow (No. 1 ground rat maintenance diet, Special Diet Services Ltd., Essex, UK), and 200 ml tap water, mixed thoroughly and allowed to set. In the first phase (7 days), the rats were given daily access to the sweetened mash in the home cages. They were then adapted to eating the mash served in a small petri dish, which was placed in a clear plastic observation tank (47 × 24 × 19 cm). All observational work was conducted under red light conditions.

The animals were allocated at random to five groups (n = 7 per group), according to the injection dosage (0, 5, 10, 15, or 20 mg/kg GBR 12909). Two hours postinjection, each animal was placed in the observation box for 60 min. Throughout the test period, an observer watched the animal for the first 8 min in each consecutive 10 min interval, and during each 8 min period kept a continuous record of the animal's behavior by entering the start and end of each behavioral episode into a microcomputer (BBC Master). Software (written by Dr. T. C. Kirkham) logged the duration and sequence of each key press. Eight keys were assigned to eight nonoverlapping response categories, and were chosen the basis of pilot work and earlier experiments (8,19). The eight behavioral categories were:

1. feeding—biting, chewing, and ingesting the sweetened mash;
2. locomotor activity—horizontal movement about the test box employing all four limbs;
3. grooming—licking, scratching, or biting at any body surface;
4. rearing to the side—front limbs raised against side of the observation box, with head and upper body raised;
5. rearing in the center—rearing away from the sides of the box;
6. oral acitivity—biting, licking, grawing, vacuous chewing, yawning (but excluding #1 and 3);
7. sniffing—opening/closing of nares, side-to-side, or up-and-down head movements, accompanied by vibrissae movements (but excluding preceding categories);
8. immobility—stationary or resting, not engaged in any of the preceding activities.

The software provided an analysis of the total duration (min) within each response category, the frequency of individual bouts, or episodes for each category, and the mean duration of individual bouts. Food intake was calculated by successive weighings (to the nearest 0.1 g). Any spillage was collected, weighed, and the amount subtracted from the intake measure. The local rate of eating (g/min) was calculated for each test by dividing the amount of food consumed by the total duration of feeding.

Statistical Analysis

The results were analysed using one-way analysis of variance for independent groups, followed by Dunnett's t-test.

RESULTS

Food Intake and Feeding

The nondeprived rats consumed in excess of 15 g of the palatable diet during the 60 min test period. Administration of the selective DA uptake inhibitor GBR 12909 reduced food intake in a dose-related manner, although the effect was significant only at the largest dose tested, 20 mg/kg (Fig. 1). The total time devoted to feeding was significantly reduced at both 15 and 20 mg/kg, but there was no significant effect on the local rate of eating (Figs. 2 and 3). There was a modest effect of GBR 12909 to reduce the frequency of feeding bouts ($p < 0.05$) (Fig. 4), but there was no significant effect on the mean duration of eating bouts.

Locomotion

GBR 12909 reduced the total duration of locomotion significantly, $F(4, 30) = 4.51, p < 0.01$, but this was due in the main to a marked suppression of locomotion occurring at 15 mg/kg (Fig. 5).

Sniffing and Immobility

GBR 12909 had a striking effect to induce excessive sniffing activity, $F(4, 30) = 10.5, p < 0.01$. At the largest dose, 20 mg/kg, the animals spent almost half the 60 min test engaged in this behavior (Fig. 6). Additionally, immobility was markedly suppressed at 20 mg/kg (Fig. 7).

Rearing, Grooming and Oral Activity

GBR 12909 had no significant effects on the total duration for any of these three behavioral categories.

DISCUSSION

This study demonstrated a reduction in the consumption of the palatable diet following administration of GBR 12909, a highly selective dopamine uptake inhibitor. Its suppressant

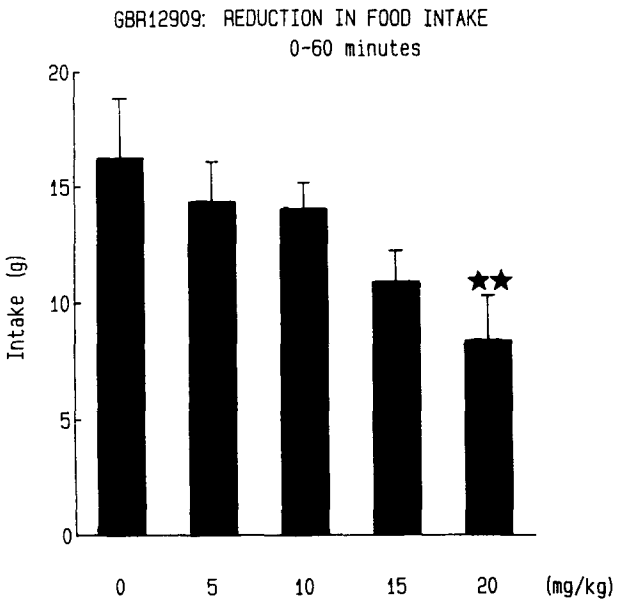

FIG. 1. The anorectic effect of the selective DA uptake inhibitor, GBR 12909, in nondeprived male rats trained to eat a palatable sweetened mash. The results are shown in terms of the total amount of food consumed (g) (mean + SEM) in a 60 min test ($N = 7$ per group). Levels of significance for individual group comparisons against the vehicle control condition: $*p < 0.05$; $**p < 0.01$ (Dunnett's t-test).

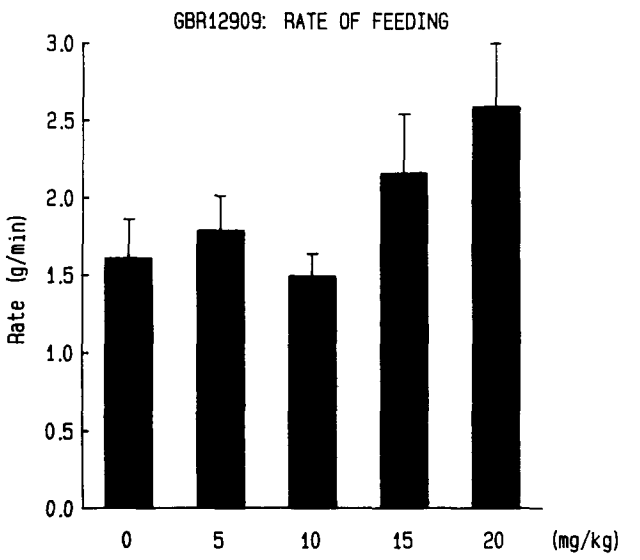

FIG. 3. The DA uptake inhibitor, GBR 12909, had no significant effect on the local rate of eating (g/min). Other details are as described in the legend to Fig. 1.

effect on feeding was due to a reduction in the time devoted to feeding, and not to a reduction in the local rate of eating. These behavioral effects of GBR 12909 are consistent with our earlier work on mazindol (17) and cocaine (18). In the case of cocaine, we noted that the frequency of feeding bouts was reduced, but that the mean duration of individual bouts was largely unaffected (18). GBR 12909 also had no significant effect on the mean duration of feeding bouts. Taken together, therefore, these data indicate that presynaptic inhibition of DA uptake is sufficient to produce some suppression of feeding. Consistent with this, previous evidence indicates that both mazindol- and cocaine-induced anorexia depend on dopaminergic mechanisms (31,37). If, as has been suggested (36), mesolimbic DA neurons are activated during eating, then the additional effects of DA uptake inhibition do not further promote ingestion but appear, instead, to suppress it.

We have also studied the effects of postsynaptic DA recep-

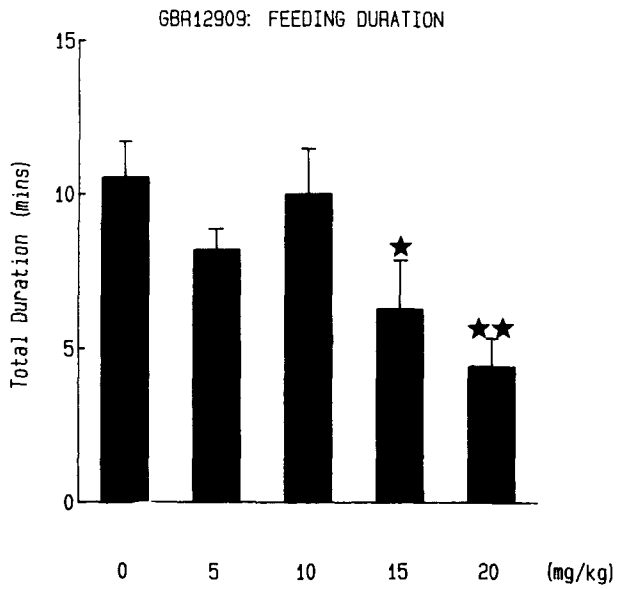

FIG. 2. Effects of GBR 12909 on the total duration of feeding (min) over the 60 min observation period. Other details are as described in the legend to Fig. 1.

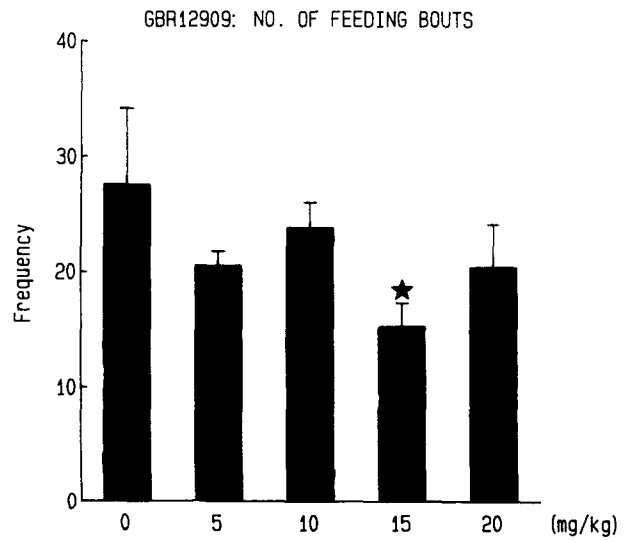

FIG. 4. GBR 12909 tended to reduce the frequency of feeding bouts, but the effect was significant only at 15 mg/kg. Other details are as described in the Fig. 1 legend.

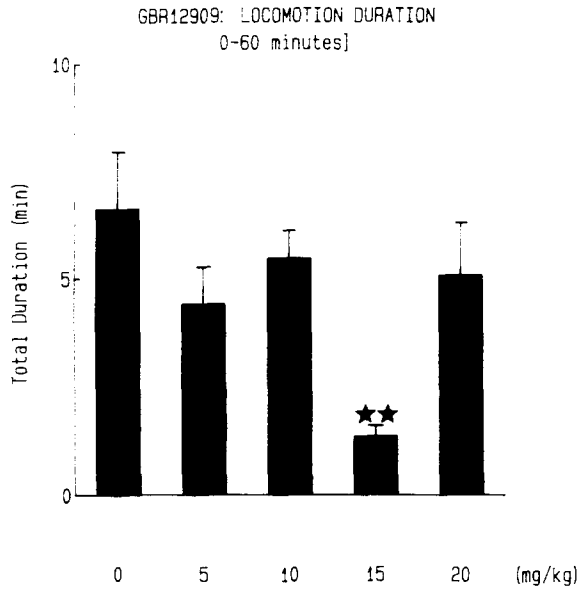

FIG. 5. GBR 12909 had little effect to reduce the total duration of locomotor activity, except for a suppression that occurred at 15 mg/kg. Other details are as described in the Fig. 1 legend.

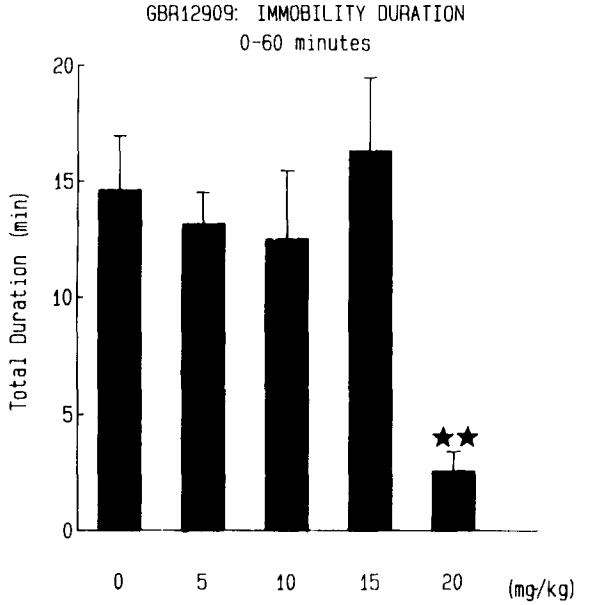

FIG. 7. The duration of immobility (resting) was sharply suppressed at the highest dose of GBR 12909. Other details are as described in the Fig. 1 legend.

tor stimulation using agonists selective for D_1 and D_2 receptor subtypes. Following early work that showed that the prototypical dopamine receptor agonist, apomorphine, has anorectic effects (3,20,23,30), we investigated the effects of the highly selective DA D_2 receptor agonist N-0437 on consumption of a palatable diet in nondeprived rats (41,42,44). Quite unlike the results for the DA uptake inhibitors, N-0437 reduced food intake as a consequence of a decrease in the rate of eating,

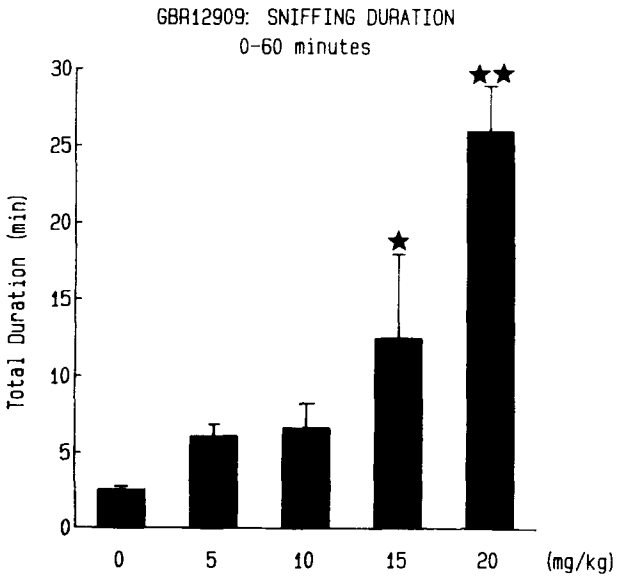

FIG. 6. One of the most striking behavioral effects of GBR 12909 was to produce a dose-related increase in sniffing activity. The figure shows significant increases in sniffing duration at 15 and 20 mg/kg. Other details are as described in the Fig. 1 legend.

without any change in the duration of eating (42). In addition, we have investigated the anorectic effects of selective DA D_1 receptor agonists, such as SK&F 38393, in rats (14,43). One possible explanation for the feeding-suppressant effect of D_1 receptor agonists is that they may induce a state of partial satiety, so mimicking the effects of presatiation (13). This would also explain the recent finding that in sham-feeding rats, which show a satiety deficit (48), SK&F 38393, and CY 208-243 (another example of a D_1 agonist) significantly reduced sucrose consumption (14). In contrast, cocaine had little specific effect on sucrose sham feeding (16). The microstructural analysis of the anorectic effect of SK&F 38393 indicated that it reduced the frequency of feeding bouts, while increasing (at 10 mg/kg) the mean duration of individual feeding bouts. Cocaine suppressed feeding due to a reduction in the frequency of feeding bouts, with little effect on the duration of individual bouts, except for a reduction at a high dose, 30 mg/kg (18). In the present study, GBR 12909 reduced the duration of feeding without affecting the rate of eating. From a behavioral perspective, therefore, while we can exclude D_2 receptor mediation of the anorectic effect of GBR 12909, the data leave open the possibility of some degree of D_1 receptor involvement. However, we cannot extend the idea of the induction of a state of partial satiety to GBR 12909 without more behavioral tests. As we see below, the induction of intense sniffing may account for the suppression of feeding.

Further indications of the relationships between presynaptic DA uptake inhibition and postsynaptic DA receptor stimulation can be derived from comparisons between other behavioral effects of the drug treatments. A pronounced effect of cocaine was to suppress grooming, even at subanorectic doses (18). In contrast, GBR 12909 had no effect on grooming behavior, suggesting that dopamine uptake inhibition may be insufficient to produce this type of suppression. Instead, a striking effect of GBR 12909 was to cause a marked increase in sniffing activity at larger doses. This effect was selective in

that it occurred in the absence of hyperlocomotion, or of overall changes in rearing or grooming. Thus, GBR 12909 selectively elicited just one component of the heterogeneous array of behavioral components normally associated with DA-dependent stereotyped behavior (12). This suggests that factors in addition to the inhibition of DA uptake are required for full expression of DA-related stereotyped behavior in rats. The selective D_2 receptor agonist N-0437 increased the duration of sniffing (at 1.0 mg/kg) and strongly stimulated oral behavior (at 3.0 mg/kg). GBR 12909-induced sniffing may, therefore, have been due, at least in part, to the stimulation of postsynaptic D_2 receptors.

In summary, the selective dopamine uptake inhibitor, GBR 12909, had an anorectic effect due to a reduction in feeding duration without change in the rate of eating, in nondeprived rats eating a highly palatable diet. This anorectic profile is consistent with earlier reports for mazindol and cocaine. However, GBR 12909 also produced intense sniffing, in the absence of either hyperlocomotion or suppression of grooming (both of which are associated with cocaine's effects). Hence, it appears likely that the anorexia and intense sniffing are more closely related to selective dopamine uptake inhibition than are other important elements of the behavioral effects of psychomotor stimulants, like cocaine.

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