Food Intake After Diazepam, Morphine or Muscimol: Microinjections in the Nucleus Accumbens Shell

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SÖDERPALM, A. H. V. AND K. C. BERRIDGE. *Food intake after diazepam, morphine, or muscimol: Microinjections in the nucleus accumbens shell.* PHARMACOL BIOCHEM BEHAV **66**(2) 429–434, 2000.—This study examined the effect on food intake of bilateral microinfusions of the benzodiazepine agents, diazepam and midazolam, the opioid agonist, morphine, and the $GABA_A$ agonist, muscimol into the shell of the nucleus accumbens in rats. Both muscimol (at 0.075 μg, combined bilateral dose) and morphine (1.0 μg) in the nucleus accumbens shell increased feeding as expected. However, it was clear that diazepam (2.5, 5.0, 25, 50 μg) and midazolam (7.5 μg) both failed to enhance feeding even at doses that are effective when microinjected in the brain stem. We conclude that opioid and $GABA_A$ agents promote feeding behavior by acting on receptors in the nucleus accumbens shell, but that benzodiazepines probably act elsewhere in the brain to increase food intake. © 2000 Elsevier Science Inc. All rights reserved.

BENZODIAZEPINES, which facilitate GABAergic neurotransmission, have a number of therapeutic actions, including anxiolytic, sedative-hypnotic, and muscle relaxant effects. Benzodiazepines also have pronounced direct effects on food intake in animals, as originally demonstrated by Wise and Dawson (24), who found that diazepam increased eating of ordinary chow and potentiated lever pressing for food. The facilitation of food intake by benzodiazepines has been shown by a number of studies to be due in part to direct effects on appetite and palatability (2,3,6,7).

The neuroanatomical location of the receptors underlying the hyperphagic effects of benzodiazepines are still unclear, although there is evidence that an important population is contained in the brain stem. For example, the infusion of a small amount of diazepam into the fourth ventricle increases food intake more effectively than microinjections of the same dose into the lateral ventricles (18). Similarly, food intake is enhanced even by microinjections of midazolam delivered directly into the parabrachial nucleus of the pons (9).

Drugs that directly enhance GABA neurotransmitter function, including GABA agonists such as muscimol, also can increase food intake, via receptors in the forebrain nucleus accumbens (10,13,22). The shell region of the nucleus accumbens, in particular, has been implicated in the enhancement of feeding by $GABA_A$ and $GABA_B$ agonists (23), and also in feeding increases produced by drugs that act on other neurotransmitter systems, such as glutamate antagonists (10,22) and opioid agonists (19,22). Most interesting of these drugs, with respect to a comparison to benzodiazepine effects, is the $GABA_A$ agonist muscimol, because both diazepam and muscimol act via different mechanisms to promote the $GABA_A$ receptor at its benzodiazepine site (thus, each potentiates in its own way the opening of chloride ion channels; (5,12,15,21). Because GABA agonists delivered to the nucleus accumbens shell can promote feeding, it raises the possibility that benzodiazepines may also facilitate feeding by acting on receptors in accumbens shell.

The purpose of the present experiments was, therefore, to determine if the shell of the nucleus accumbens plays a similar

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role in mediating increases in food intake caused by benzodiazepines as in mediating increases caused by GABAergic and opioid agonists. To do this, we compared the effect on food intake of microinjections of morphine, muscimol, midazolam, and diazepam delivered directly to the shell of the nucleus accumbens.

GENERAL METHOD

Subjects

Male and female Sprague–Dawley rats (born at the University of Michigan), were housed in pairs in a temperature-controlled colony room. Rats had ad lib access to food and water, and were maintained on a reverse light cycle so that behavioral tests could be administered during their active dark phase (lights off 0700–1900 h). Their weight was 250–350 g in the beginning of each experiment.

Surgical Procedure

Animals were pretreated with atropine methyl nitrate (1 mg/kg IP) and anesthetized with sodium pentobarbital (8 mg/kg IP). They were placed in a stereotaxic apparatus, with bregma and lambda in a horizontal plane, and bilateral intracranial stainless steel guide cannulae (22 gauge, 14 mm long) were surgically placed 1 mm dorsal to the target sites in the shell of accumbens using coordinates from the Paxinos and Watson (16) atlas. The stereotactic coordinates for the shell of accumbens were (relative to bregma): anterior/posterior = +1.5 mm; medial/lateral = 0.9 mm; and dorso/ventral = −6.7 mm, and for the fourth ventricle: anterior/posterior = −11.5; medial/lateral = 0; dorso/ventral = −7. The cannulae were fixed to the skull using dental cement and skull screws. After surgery, dummy cannulae were placed into the guides to prevent occlusion.

Drugs and Doses

Experiment 1 (group A): morphine (sulfate, Sigma, 1 μg), muscimol (5-aminomethyl-3-hydroxysoxazole, Sigma, 0.1 μg), diazepam (7-chloro-1,3-dihydro-1-methyl-5-2H-1,4benzo-diazepin-2one, Steris 25 μg), or vehicle. (group B): morphine (1.0 μg), diazepam (5.0 μg), midazolam (maleate, Roche, 7.5 μg), or vehicle. Experiment 2: muscimol (0.075 μg) or vehicle. Experiment 3: muscimol (0.075 μg), diazepam (25 μg) or vehicle. Experiment 4: muscimol (0.075 μg), diazepam (2.5 μg), or vehicle. Experiment 5: diazepam (50 μg) or vehicle. Experiment 6: diazepam (25 μg) or vehicle. Vehicle was water for all drugs except diazepam, for which vehicle was propylene glycol 40%, alcohol 10%, sodium benzoate 5%, and benzoic acid as buffer. The two types of vehicle were administered alone on separate trials as controls in experiments when corresponding drugs were given. In every case, the stated dose refers to the total dose injected into the brain. Because bilateral microinjections were always given in both the left and right sides of the shell of the nucleus accumbens, each microinjection contained one-half the stated total dose.

EXPERIMENTAL PROCEDURE

Experiment 1: Food Intake After Microinjections of Morphine, Muscimol, Diazepam, Midazolam, or Vehicle Into the Shell of Accumbens

Nondeprived male rats (n = 20) were implanted with bilateral microinjection cannulae in the shell of accumbens. Fourteen rats (group A) were given bilateral microinjections of either morphine (1.0 μg in 0.5 μl), muscimol 0.1 μg), diazepam (25 μg), or vehicle on a given trial. The total testing period was 8 days. Six rats (group B) were given bilateral microinjections of either morphine (1 μg), midazolam (7.5 μg), diazepam (5.0 μg), or vehicle. Each rat received only one agent per day, but received all compounds in counterbalanced order over the course of several days. The total testing period was 10 days (48 h between drug treatments). The morphine, muscimol, and midazolam doses were chosen based on earlier reports of dose ranges that elicited feeding in the literature (9,17,23). The diazepam dose was chosen to be one-half the threshold dose previously found to be effective at increasing food intake when administered into the fourth ventricle (18). Thus, the microinjection into each hemisphere contained 25% of that ventricle threshold dose (18). This total dose is also equivalent to approximately 33% of the threshold dose when diazepam is given into the lateral ventricles, so the microinjection into each hemisphere contained 15% of the dose known to be effective in the lateral ventricle (18).

After the animals had recovered from surgery (5 days) they were habituated to the test procedure over the next 4 days. Each day, rats were transported in their home cages to the test room and placed into the test cages similar to their home cages, in which wood shavings were spread on the bottom. Ordinary fresh rat chow and water were available ad lib. The animals were left in the test cages for 75 min. The amount of food eaten was measured after 15 and 75 min. All the test sessions were conducted between 0900–1300 h.

On the fifth day, each rat received bilateral microinjections into the nucleus accumbens shell immediately before being placed into the test chamber. During the microinjections, the animals were hand held gently in the experimenter's hands while the injection cannulae tip (28 gauge) was lowered through the guide cannulae (the injector tip extended 1 mm below the tip of the guide cannulae). Drug or vehicle was then delivered over a period of 1 min by a microsyringe pump connected by a length of 20 polyethylene (PE) tubing to the injection cannulae. The injectors were left in place for 1 min to allow diffusion. Afterwards, the rats were put in their test cages, where ad lib food and water were again monitored at 15 and 75 min.

Statistical Analysis

Results were analyzed using two-factor ANOVA for repeated measures with drug treatment and time as the independent variables, and food intake as the dependent variable. The post hoc comparisons were made using Newman–Keuls tests.

Histological Verification of Cannulae Placement

After each experiment, rats were anesthetized with sodium pentobarbital (50 mg/kg IP). Each animal was then perfused with saline followed by a 10% formalin solution. The rats were decapitated, and the brains were removed and put in formalin for a period of at least 1 week. The brains were then frozen, sliced in a cryostat, stained and cresyl violet, and the cannulae placements were verified histologically (see Fig. 8). Animals with bad placements were discharged from the experiments.

RESULTS

Figure 1 (group A) shows the effect on drug treatment on food intake. A two-way ANOVA (drug × time) resulted in a significant effect of drug treatment, $F(3, 13) = 5.9$, $p < 0.002$. Post hoc Newman–Keuls comparisons revealed that morphine
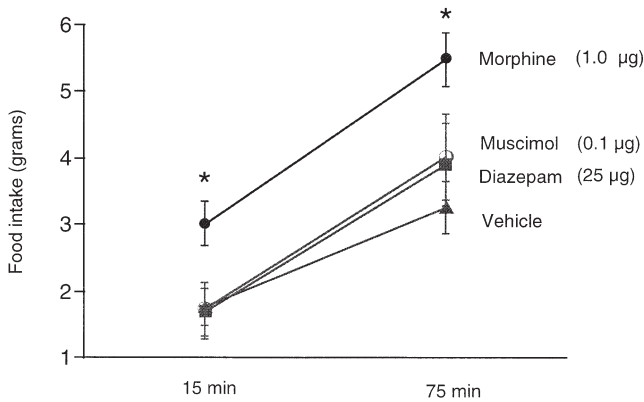
FIG. 1. Feeding stimulated by microinjections into the accumbens shell of morphine (1.0 μg), muscimol (0.1 μg), diazepam (25 μg), or vehicle (group A). Amount of food (chow) eaten after 15 min and 1 h (75 min). Morphine increased food intake over vehicle baseline at both 15 and 75 min ($p < 0.003$). Significant elevations in food intake over vehicle levels are denoted by an asterisk. The results are presented as mean ± SEM.

(1 μg) significantly increased food intake by more than 150% over the vehicle baseline ($p < 0.003$), but diazepam ($p < 0.5$) and muscimol ($p < 0.7$) both failed to alter food intake. After muscimol microinjections, several rats behaved in an agitated fashion, showing unusual exploration and active movement patterns. It remains unclear whether such muscimol-induced behavioral effects were related to the rats' failure to eat.

Figure 2 (group B) shows again, in an independent group of rats, that there was a significant effect of drug treatment on food intake (two-way ANOVA for repeated measures (drug × time) $F(4, 5) = 4.3$, $p < 0.01$; drug interaction $F = 3.8$, $p < 0.02$). Post hoc Newman–Keuls tests indicated there was no significant effect of drug treatment at the 15-min time point, that is, there were no differences in food intake between ani-
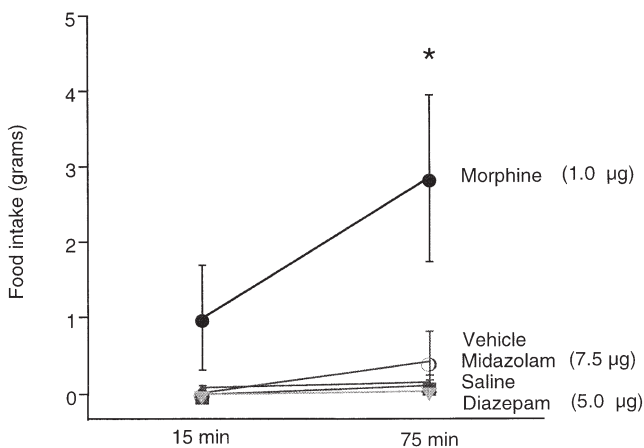
mals given morphine, diazepam, midazolam, water vehicle, or propylene glycol vehicle. However, by 75 min, animals given morphine had ingested significantly more food than all other groups ($p < 0.001$ in each case). At no time did the effect of diazepam differ from that of either propylene glycol vehicle or water vehicle, nor did the effect of midazolam differ from either vehicle.

Experiment 2: Food Intake After Microinjections of Muscimol and Vehicle Into the Shell of Accumbens

In this experiment we aimed to reexamine the capacity of muscimol to elicit feeding when administered to the nucleus accumbens shell. Because increases in food intake after muscimol infusions into this area have been reported by Stratford and Kelley (23), we suspected that our negative results in Experiment 1 might not be conclusive, especially because some rats showed signs of agitation after muscimol that could have inhibited feeding. For these reasons, we decided to repeat the procedures of Experiment 1 with naive rats, but using a slightly lower dose of muscimol, 0.075 μg. This dose has also been reported to stimulate eating (23), but we hoped it might not induce competing behavioral reactions. Twelve naive female rats were implanted with accumbens cannulae and habituated to the behavioral test procedure as in Experiment 1. The rats were then tested as in Experiment 1, receiving microinjections of either muscimol (0.075 μg) or vehicle prior to the feeding test in a randomized within-subjects experimental design. The total testing period was 4 days (2 days microinjection testing, 48 h between drug treatments).

Results. Figure 3 shows that muscimol (0.075 μg) significantly increased food intake over vehicle. A two-way ANOVA (drug × time) resulted in significant effect of drug treatment, $F(1, 11) = 7.0$, $p < 0.02$. Post hoc Newman–Keuls comparisons showed that at both 15 and 75 min rats receiving muscimol into the shell of accumbens ate more than twice as much than they did after receiving vehicle microinjections ($p < 0.02$).

FIG. 2. Feeding stimulated by microinjections into the accumbens shell of morphine (1.0 μg), midazolam (7.5 μg), diazepam (5.0 μg), and vehicles (group B). Amount of food (chow) eaten after 15 min and 1 h (75 min). Morphine increased food intake over vehicle baseline at 75 min ($p < 0.001$). Significant elevations in food intake over vehicle levels are denoted by an asterisk. The results are presented as mean ± SEM.
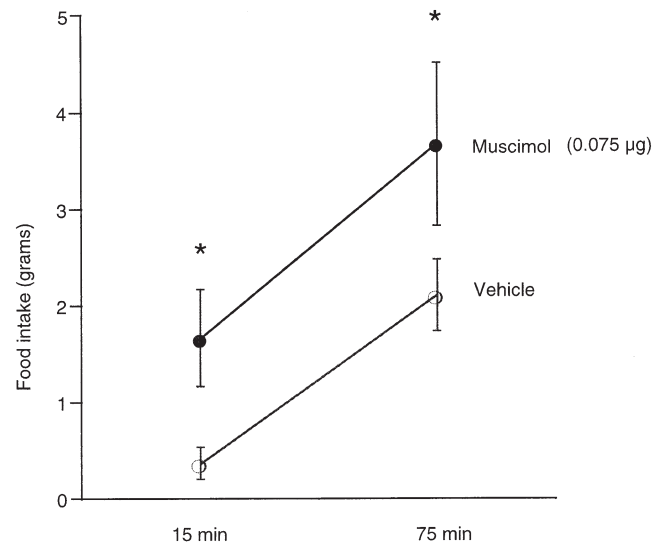

FIG. 3. Feeding stimulated by microinjections into the accumbens shell of muscimol (0.075 μg) and vehicle. Amount of food (chow) eaten after 15 min and 1 h (75 min). Muscimol increased food intake over vehicle baseline at both 15 and 75 min significantly ($p < 0.02$). Significant elevations in food intake over vehicle levels are denoted by an asterisk. The results are presented as mean ± SEM.

Experiment 3: Food Intake After Microinjections of Muscimol, Diazepam, and Vehicle Into the Shell of Accumbens

Once we confirmed in Experiment 2 that muscimol in accumbens shell enhanced food intake, it seemed important to similarly reexamine whether diazepam also could do so in an experiment that compared them both. To answer that question, we used the same procedure as in Experiment 1 and 2. Nondeprived naive rats ($n = 8$) were implanted with accumbens cannulae and received either muscimol (0.075 μg), diazepam (25 μg), or vehicle in an order randomized across subjects. Total testing period was 6 days (48 h between treatments).

Results. Figure 4 shows that there was an effect of drug treatment on food intake. An initial two-way ANOVA (drug × time) was not quite statistically significant, $F(2, 7) = 3.7$, $p = 0.052$. However, a one-way ANOVA testing for differences at the 15-min time point did indicate effect of drug treatment ($F = 4.38$, $p < 0.03$). Post hoc Newman–Keuls tests indicated that at 15 min animals given muscimol ingested significantly more food than animals given diazepam or vehicle ($p < 0.05$ in every case). No other group comparisons were significant. That is, at neither 15 or 75 min did the diazepam group differ from control.

Experiment 4: Food Intake After Microinjections of Muscimol, Diazepam, and Vehicle Into the Shell of Accumbens

In two experiments thus far, diazepam had failed to stimulate feeding when administered at a 25-μg dose into the nucleus accumbens shell. Those results reduced the plausibility of the hypothesis that the nucleus accumbens shell mediates diazepam-induced increases in eating. However, it is conceivable that a 25-μg dose of diazepam is excessively high for direct administration within a brain structure, because it places 15 to 25% of ventricle threshold doses (18) of the drug directly into each half of the accumbens, that is, a higher level than would be present after many behaviorally effective intraventricular microinjections. Therefore, we retested rats from Experiment 2, which had shown significantly increased food intake after muscimol microinjections, with the same muscimol dose again, and with diazepam at one-tenth the dose used in Experiments 1 and 3. Using the same procedure as before,

FIG. 5. Feeding stimulated by microinjections into the accumbens shell of muscimol (0.075 μg), diazepam (2.5 μg), and vehicle (Experiment 3). Amount of food (chow) eaten after 15 min and 1 h (75 min). Muscimol significantly increased food intake over vehicle at both 15 and 75 min ($p < 0.005$). Significant elevations in food intake over vehicle levels are denoted by an asterisk. The results are presented as mean ± SEM.

nondeprived rats ($n = 11$) received either muscimol (0.075 μg), diazepam (2.5 μg), or vehicle. The order of drug administration was randomized across subjects. The total testing period was 6 days (48 h between drug treatments).

Results. Figure 5 shows that there was a significant effect of drug treatment on food intake (overall ANOVA, drug × time), $F(2, 10) = 6.8$, $p < 0.006$. Muscimol (0.075 μg) significantly increased feeding over baseline levels at both 15 and 75 min, (Newman–Keuls test, $p < 0.005$), and again, diazepam (2.5 μg) failed change feeding relative to control. Thus, whereas in Experiments 1 and 3, a 25 μg dose of diazepam failed to induce feeding, in this experiment a smaller dose (2.5 μg) also failed to alter food intake.

Experiment 5: Food Intake After Microinjections of High-Dose Diazepam and Vehicle Into the Nucleus Shell of Accumbens

At three doses (2.5, 5.0, and 25 μg) thus far diazepam failed to alter food intake when given into the nucleus accumbens. As a last test of whether it could be effective at this site, we decided to reverse the logic of Experiment 4, and to test the effect of a much higher diazepam dose (50 μg), which has been shown to be just above threshold for enhancing feeding when given in the fourth ventricle (18). If this dose failed to elicit feeding when given in the nucleus accumbens, it would help rule out the possibility that all our diazepam doses so far were simply below a minimum threshold for a cumbens feeding effects. Animals from Experiment 2 ($n = 11$) received microinjections of either diazepam (50 μg) or vehicle prior to the feeding test. The rats were then tested as in the earlier experiments.

Results. Figure 6 shows that 50 μg diazepam did not alter food intake compared to the vehicle [two-way ANOVA, effect of drug, $F(1, 10) = 0.003$, $p > 0.9$]. Thus, even a dose that was sufficient to enhance feeding when administered into the fourth ventricle, was ineffective when administered into the nucleus accumbens.

Experiment 6: Food Intake After a Microinjection of Diazepam and Vehicle Into the Fourth Ventricle

At all doses tested thus far (2.5, 5.0, 25, and 50 μg) diazepam failed to alter food intake when it was administered into
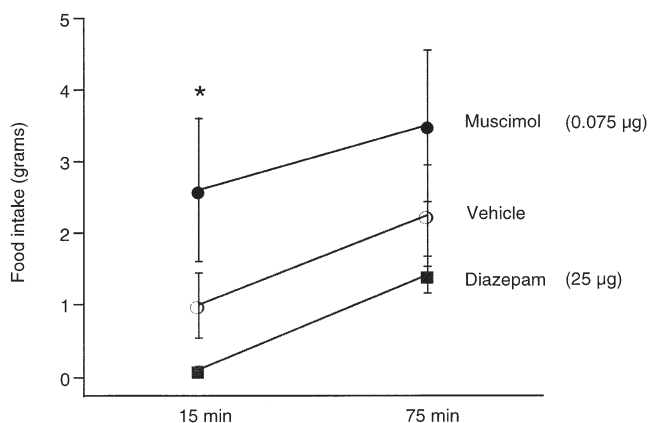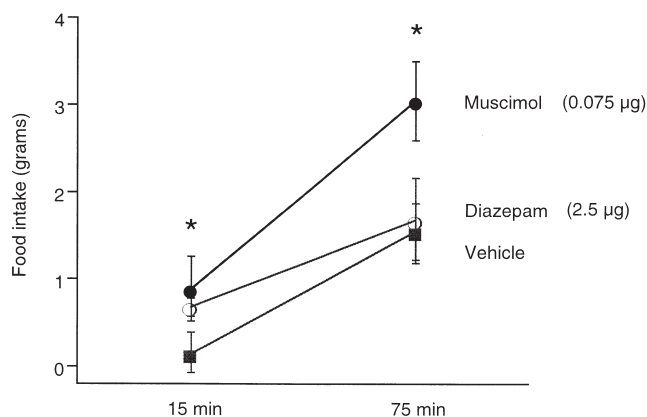

FIG. 4. Feeding stimulated by microinjections into the accumbens shell of muscimol (0.075 μg), diazepam (25 μg), and vehicle. Amount of food (chow) eaten after 15 min and 1 h (75 min). Muscimol significantly stimulated feeding after 15 min compared to diazepam and vehicle ($p < 0.05$ each). Significant elevations in food intake over vehicle levels are denoted by an asterisk. The results are presented as mean ± SEM.
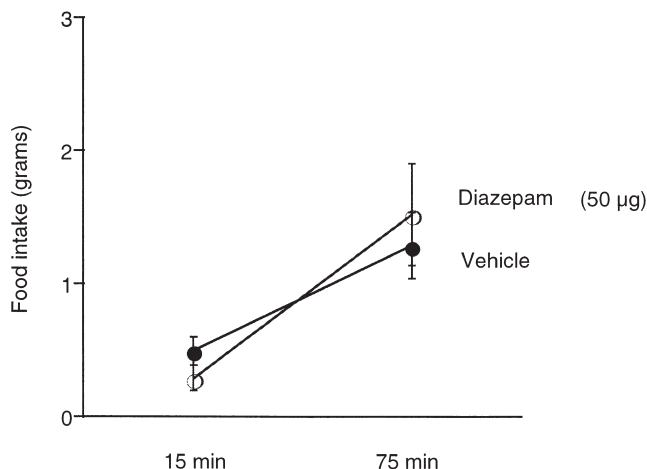
FIG. 6. Microinjections into the shell of accumbens of diazepam (50 μg) and vehicle. Amount of food (chow) eaten after 15 min and 1 h (75 min). The results are presented as mean ± SEM.

FIG. 8. The distribution of injection sites within the shell of accumbens. The different experiments are presented as symbols. Experiment 1, group A = ■, and group B = ■■; Experiment 3 = ▮, and Experiments 2, 4, and 5 = ●. Sections are redrawn from Paxinos and Watson (16). Section numbers refers to placement relative to bregma.

the shell of accumbens. We next sought to replicate the results of an earlier study (18), and reestablish that our most frequently used diazepam dose indeed would increase food intake if it were administered to the brain stem fourth ventricle rather than to the nucleus accumbens shell. Therefore, rats (n = 6) were prepared with a cannula in the fourth ventricle and 25 μg of diazepam or vehicle were administered as in earlier experiments. Cannula placement in the fourth ventricle was later confirmed histologically after ink microinjection.

Results. Figure 7 shows that when diazepam (25 μg) was administered into the fourth ventricle it significantly increased food intake (two-way ANOVA, drug × time) effect on drug, $F(1, 5) = 6.8$, $p < 0.05$. Post hoc Newman–Keuls tests indicated that at 15 min, 1 and 4 h animals given diazepam always ingested more food that when they were given vehicle ($p < 0.05$ in each case).

DISCUSSION

In this study we compared food intake after microinjections into the nucleus accumbens shell of morphine and of three different compounds that promote the function of GABA$_A$ receptors, either directly (muscimol) or indirectly (diazepam and midazolam). Consistent with earlier studies, we found in Experiment 1 that microinjections of morphine into accumbens shell increased the intake of chow pellets (4,8,11,19,22). We also found in Experiments 2 and 3 that food intake was increased after microinjections of 0.075 μg muscimol, which is consistent with the results of Stratford and Kelley (23), although the magnitude of food intake evoked in our study was somewhat less than that found by Stratford and Kelley. The difference in intake may be due to differences in the test procedure, as other observations in our laboratory indicate that intake after accumbens muscimol may be less when wood shavings are present (as in our study) than when nothing but food is in the cage, possibly because wood shavings allow other behaviors to emerge that may compete with eating (treading, head burrowing, etc.; Reynolds and Berridge, personal observations).

By contrast, diazepam and midazolam in the nucleus accumbens shell each failed to induce feeding at any of the doses tested. This is interesting, because diazepam and midazolam facilitates GABA$_A$ neurotransmission, as muscimol does (although through a different mechanism), and therefore, might have been expected to be effective in the same site as muscimol. Yet even the same rats that increased intake in response to muscimol or morphine still failed to increase in response to accumbens microinjections of diazepam or midazolam, even at a dose that would be effective if it were given in the fourth ventricle.

Our results, therefore, confirm that the shell of the nucleus accumbens is important in mediating feeding behavior by both opioid and GABA agonists (19,22). However, they sug-
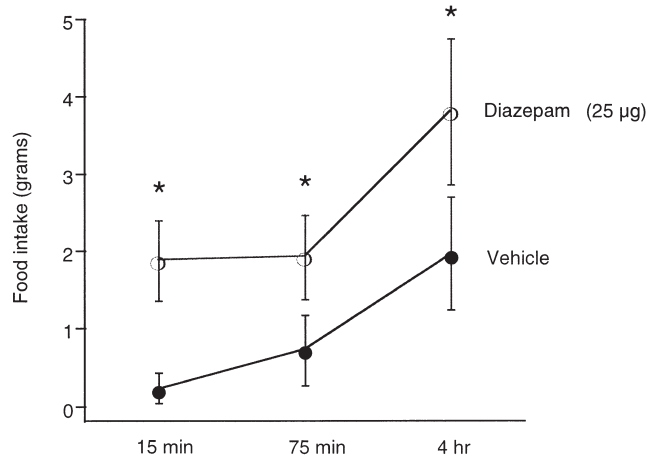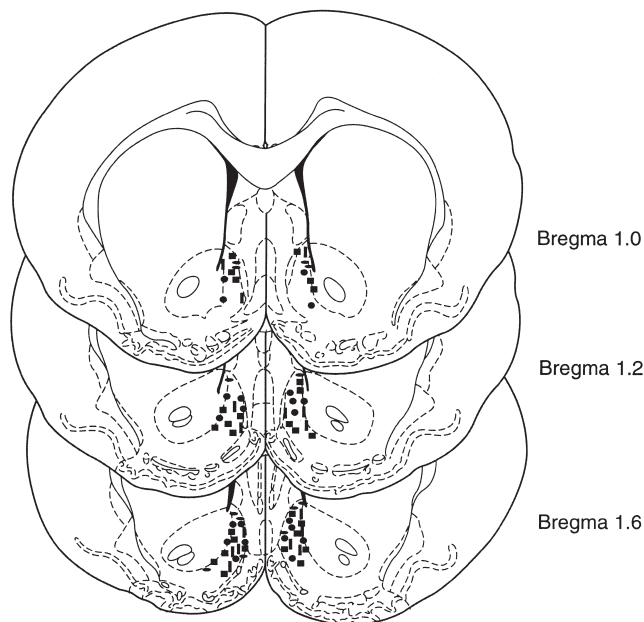

FIG. 7. Microinjections into the fourth ventricle of diazepam and vehicle. Amount of food eaten after 15 min, 75 min, and 4 h. Diazepam (25 μg) increased food intake over vehicle at 15 min, 75 min, and 4 h ($p < 0.05$). The results are presented as mean ± SEM. Significant elevations in food intake over vehicle levels are denoted by an asterisk.

gest that the accumbens may not mediate the increase in feeding stimulated by systemic or intracranial administration of benzodiazepines (3,4,14,20).

Our conclusion about diazepam is preliminary, because it is possible that other doses of diazepam, which were not tested here, might eventually be found to act in the accumbens shell to increase food intake. It would be of interest to confirm our negative results with a larger range of benzodiazepine doses, and to test other benzodiazepine drugs besides diazepam and midazolam. But the benzodiazepine doses tested here could have been expected to increase food intake if injected into other brain sites (9,18). Thus, their failure to elicit feeding in the accumbens shell makes it less plausible to posit that the accumbens mediates benzodiazepine-induced feeding, even though it clearly mediates feeding produced by opioid or direct GABA agonists.

If the nucleus accumbens does not mediate benzodiazepine-stimulated feeding, then what brain structure does? Higgs and Cooper (9) and Pecina and Berridge (18), have suggested that the hyperphagic effects of diazepam may be mediated primarily by the brain stem, and Higgs and Cooper (9) specifically proposed the parabrachial nucleus. Several studies have demonstrated that hyperphagia effects can be triggered by benzodiazepine receptors that lie in the brain stem. Microinjections of diazepam into the fourth ventricle (brain stem) increase the consumption of palatable food, and enhance positive behavioral reaction to sucrose, more effectively than microinjections of the same dose into the lateral ventricles (18). We confirmed the ability of 25 μg diazepam to increase feeding when given in the brain stem fourth ventricle. Similarly, microinjections of midazolam directly into the

parabrachial nucleus within the brain stem pons are able to increase food intake (9). Further, even in a midbrain decerebrate rat, in which a transection has cut off the influence of forebrain receptors and neural circuits on behavior, and left the brain stem to generate taste-elicited behavioral responses on its own, diazepam still enhances the positive behavioral reactions elicited by an oral infusion of sucrose solution (1). Thus, the brain stem is sufficient by itself to mediate at least some forms of ingestive facilitation by benzodiazepines, and even in neurally intact individuals the brain stem contains the primary substrates for mediating benzodiazepine enhancement of food intake. It has remained plausible, however, that the forebrain contained secondary substrates and receptors that also contributed to benzodiazepine-induced feeding. The nucleus accumbens has been among the leading candidates for this role until now, especially because it mediates feeding induced by other agents that promote GABA neurotransmission. Our present results, however, suggest that accumbens receptors do not contribute to benzodiazepine-induced feeding.

In conclusion, the shell of the nucleus accumbens appears to mediate feeding stimulated by opioid or GABA agonists. But if forebrain receptors make any contribution to benzodiazepine-stimulated food intake, the relevant receptors probably are contained by some other forebrain structure than the nucleus accumbens.

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