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Effect of Clonidine on Sucrose Intake and Water Intake Varies as a Function of Dose, Deprivation State, and Duration of Exposure

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FLAHERTY, C. F. AND P. S. GRIGSON. *Effect of clonidine on sucrose intake and water intake varies as a function of dose, deprivation state, and duration of exposure.* PHARMACOL BIOCHEM BEHAV 32(2) 383–389, 1989.—Lick frequency was monitored in five-minute intervals over a one-hour period in rats given access to 8% sucrose (Experiment 1) or water (Experiment 2). Prior to the session, the rats were administered either isotonic saline or clonidine (6.24, 12.5, or 25 μg/kg). In deprived rats (82%) clonidine led to a dose-dependent reduction in licking sucrose early in the test period but, late in the test period, there was a dose-related increase in consummatory behavior. Water intake in deprived rats was depressed by clonidine. In rats maintained on a free-feeding schedule, the higher clonidine doses led to a decrement in sucrose intake over the first 15 minutes of access; whereas the 6.25 μg/kg dose stimulated consummatory behavior, but only during the first five minutes of access. There were no reliable effects of clonidine on sucrose intake late in the access period for the free-feeding rats. Water intake in free-feeding rats tended to be enhanced by the low dose of clonidine, particularly late in the access period. In general, deprivation enhanced sucrose intake and depressed water intake and clonidine exaggerated both of these trends.

Clonidine Sucrose Water intake Deprivation

THE acute administration of clonidine, an alpha-2 agonist, has been reported to increase food intake in monkeys (17,21) and rats (11, 12, 15). However, we previously reported that clonidine (12.5, 25, 50 μg/kg) reduced the consumption of sucrose solution in an incentive contrast experiment (7). Several factors may be relevant for the occurrence of the discrepant results. For example, the animals in our contrast experiment were food-deprived and one previous report found that clonidine increased food intake in satiated rats only (20). However, the interaction of clonidine with deprivation state is not clear since there have been other reports of increased intake in deprived animals as well (18).

Another possible reason for the difference in results obtained in the sucrose intake experiment and other food intake studies relates to duration of exposure to the food substance. In our previous experiment, the rats were given access to the sucrose solutions for only five minutes, whereas in the usual feeding studies, the exposure period is an hour or more.

In Experiment 1 we investigated the effects of clonidine, administered to both free-feeding and deprived rats, on the intake of an 8% sucrose solution over a one-hour period. In Experiment 2 the effects of the same doses of clonidine on water intake were examined.

EXPERIMENT 1

METHOD

Subjects

Twenty-four male Sprague-Dawley derived rats, purchased from Blue Spruce farms, were used as subjects. Twelve of the animals were maintained on ad lib food and water, 12 were deprived to 82% of their free-feeding body weight and maintained at that level by once per day feeding. The food-deprived animals had water continuously available. The mean weight of animals at the start of the experiment was 488 grams and 335 grams for the free-feeding and deprived rats, respectively. All animals were housed singly in standard stainless steel hanging cages and kept on a 14 hour light, 10 hour dark cycle with lights on at 0800 hr. Testing was conducted approximately 3 hours into the light phase of the cycle.

Apparatus

Testing was conducted in six identical metal grid cages (24.5×17.5×18 cm). A centrally located hole (1 cm in diame-

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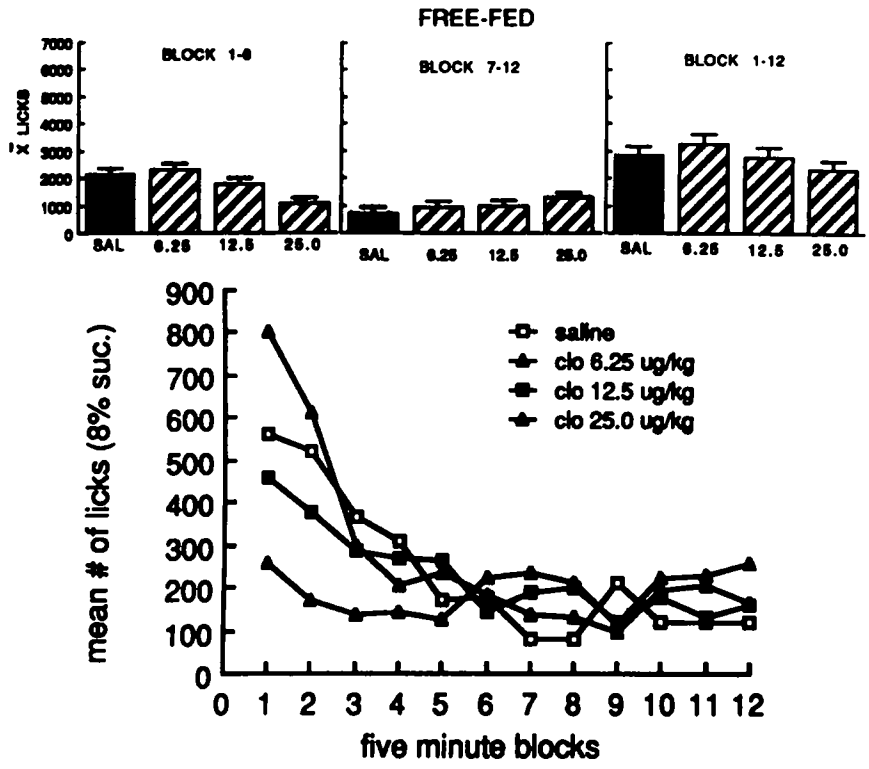

FIG. 1. Top panel: Mean lick frequency for an 8% sucrose solution over the first half, the second half and the total one-hour session as a function of drug condition (saline or clonidine) in free-feeding rats. Bottom panel: Same data examined in five-minute blocks.

ter and 7 cm above the cage floor) was present in one wall of each cage. A graduated cylinder was placed outside of each chamber so that the orifice of the drinking spout was centered in the hole and flush with one wall of the chamber. Licking was recorded through a contact relay circuit by microprocessors.

Procedure

The effect of clonidine on intake was investigated by using a Latin square design selected randomly by the procedures of Fisher and Yates (6). Three animals were assigned to each row of the square. The animals were administered an IP injection of either saline or clonidine (6.25, 12.5, and 25 μg/kg) 30 minutes prior to entry into the testing environment. They were then given access to an 8% sucrose solution for a one-hour period. The animals were run every other day to allow for a "washout" period for the drug, and in addition, to reduce possible temporary effects of the sucrose intake on the animals' ingestion patterns. The entire Latin Square was then replicated starting three days after the completion of the subjects' first run through all conditions of the experiment.

The free-feeding and deprived animals were run at different periods, about one month apart. The same Latin Square design was used for both groups. The sucrose solutions were mixed by weight [sucrose/(sucrose + solvent)] from commercial grade sugar and tap water. The solutions were prepared 24 hours prior to use and were presented at room temperature. Lick frequency was recorded for each five minutes of the one-hour exposure period.

RESULTS

Inspection of the data obtained in the two replications of the Latin Square sequence revealed that the same pattern of results was obtained in each replication—the ordinal relationships of the groups to each other were the same in each case. Thus, the mean score of the two replications was obtained for each subject and used as the unit of analysis.

In general, clonidine, especially at the higher doses and early in the one-hour session, tended to inhibit intake, particularly in the free-fed animals. Enhancing effects of clonidine on sucrose intake were seen primarily in the deprived animals and primarily late in the session. There were occasional exceptions to these general statements in short-term effects of the drug. The data are presented in terms of intake measured in half-hour blocks, in the total one-hour access period, and in terms of five-minute blocks.

Free-Fed Animals

Lick frequency data in terms of half-hour blocks of time and in terms of total licks over the one-hour exposure period are presented in the top panel of Fig. 1. Over the first half-hour (Blocks 1–6) there was a reliable treatment effect, $F(3,30)=12.87$, $p<0.01$, which indicated that the 25 μg/kg dose of clonidine led to a lower lick frequency than all other treatments and that the 12.5 μg/kg dose led to a lower lick frequency than the 6.25 μg/kg dose (lsd tests). Analysis of the second half-hour (Blocks 7–12) indicated no reliable drug effect, $F(3,30)=2.44$, $p>0.05$, nor did analysis of the total one-hour intake period, $F(3,30)=2.88$, $p>0.05$.

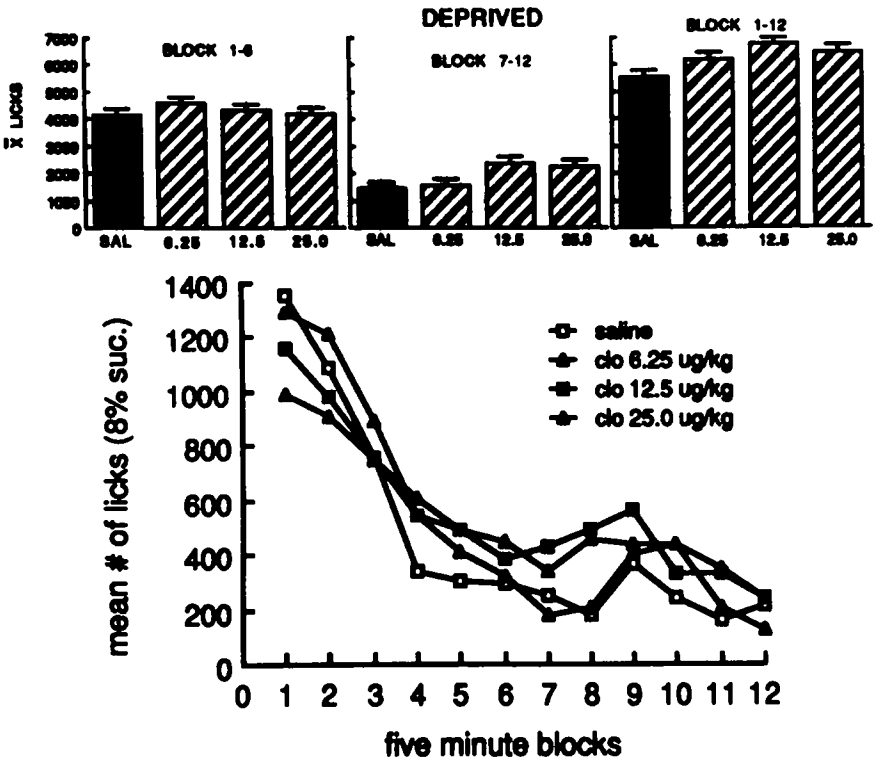

FIG. 2. Top panel: Mean lick frequency for an 8% sucrose solution over the first half, the second half and the total one-hour session as a function of drug condition (saline or clonidine) in rats deprived to 82% of their free-feeding body weight. Bottom panel: Same data examined in five-minute blocks.

Lick frequencies obtained in each five-minute block of sucrose access are presented in the bottom panel of Fig. 1. In the first five-minute block the lowest dose of clonidine produced a reliable elevation in licking (6.25 > saline), whereas the two higher doses of clonidine produced reliable decrements in licking (25 < 12.5 < saline) [Treatment, $F(3,30)=17.60$, $p<0.01$; followed by least significant difference (lsd) tests, $p=0.05$]. In the second five-minute block the 12.5 and 25 μg/kg doses still reliably reduced licking, but the 6.25 μg/kg dose no longer had a reliable effect of enhancing licking [Treatment, $F(3,30)=11.80$, $p<0.01$, followed by lsd tests]. In the third block there was also a reliable treatment effect, $F(3,30)=3.27$, $p<0.05$, indicating that the highest dose of clonidine suppressed licking relative to the saline group. Throughout the remaining nine blocks (forty-five minutes) of exposure to the sucrose solution there were no reliable effects of clonidine on intake when each block was examined individually.

Thus, other than an initial excitatory effect of the 6.25 μg/kg dose, clonidine generally had an inhibitory effect on sucrose intake, particularly at the higher doses and particularly in the earlier minutes of exposure in the free-feeding subjects.

Deprived Animals

The blocked data for the deprived animals are presented in the top panel of Fig. 2, the five-minute data are presented in the bottom panel.

Analysis in terms of half-hour and hour exposure periods yielded the following pattern of results. Over the first half-hour of exposure there was no reliable effect of the drug, $F(3,30)=1.79$, $p>0.10$. However, over the second half-hour there was a reliable drug effect, $F(3,30)=8.50$, $p<0.01$, which indicated that the 12.5 and 25 μg/kg doses led to *more* licking than the saline and 6.25 μg/kg treatments (lsd test). Analysis of the data for the entire one-hour period led to a similar pattern: all drug groups licked more than the saline group. In addition, the 12.50 μg/kg group licked more than the 6.25 μg/kg group, $F(3,30)=8.35$, $p<0.01$, followed by lsd tests.

Examining the data in terms of five-minute blocks showed that clonidine produced a dose-related decrement in licking in the first block, $F(3,30)=8.80$, $p<0.01$. Specific comparisons with the lsd procedure showed the following pattern of significant effects: 25 and 12.5 < saline; and 25 < 6.25. The saline and 6.25 μg/kg group did not differ. There was also a reliable drug effect in the second block, $F(3,30)=5.36$, $p<0.05$. Subsequent lsd tests indicated the following pattern of reliable differences: 25 = 12.5 < saline < 6.25. The only other single Block in the one-hour exposure period in which there was a reliable treatment effect was Block 8, $F(3,30)=5.44$, $p<0.01$. Analysis of these data with the lsd test showed that the two groups that received the higher doses of clonidine (12.5 and 25) licked *more* than the 6.25 clonidine group and the saline group.

Analyses of the nontreatment Latin Square factors [sequence (rows) and ordinal position in the sequence (columns)] indicated no effects of the treatment sequence and a reliable reduction in sucrose intake in the first five-minute block in the first column of the square in both ad lib and

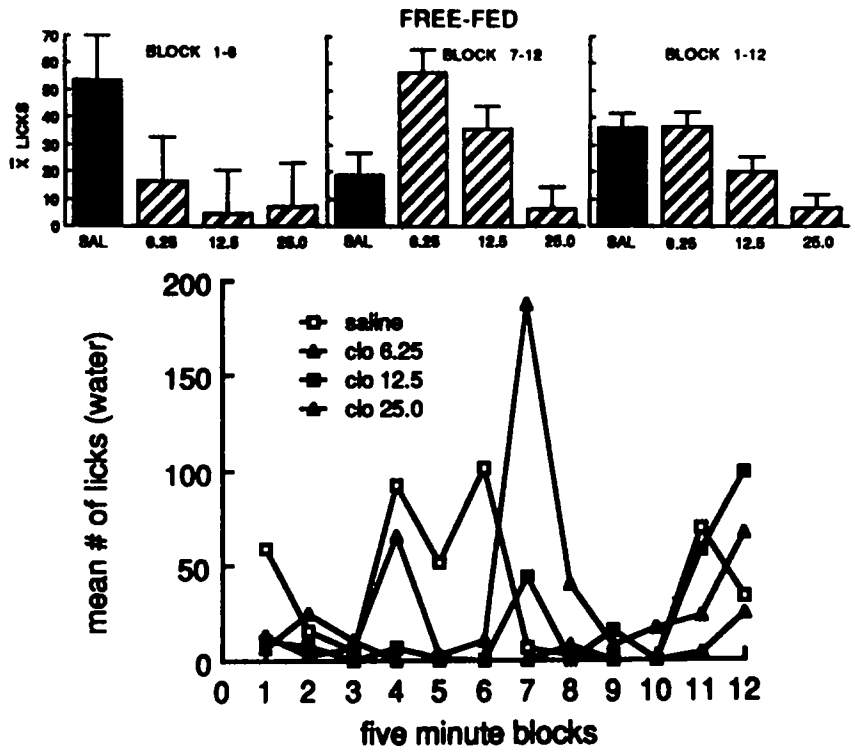

FIG. 3. Top panel: Mean lick frequency for water over the first half, second half and the total one-hour session as a function of drug condition (saline or clonidine) in free-feeding rats. Bottom panel: Same data examined in five-minute blocks.

deprived rats. Since inspection of the data indicated that this column effect did not alter any conclusions reached on the basis of the treatments analysis, the statistics for these non-treatment factors will not be presented in detail.

DISCUSSION

The effect of systemic administration of clonidine on sucrose intake was dependent upon the state of the organism, the dose of the drug and the length of exposure to the tastant. The administration of clonidine to free-feeding animals led to a biphasic result. The lowest dose (6.25 μg/kg) enhanced intake on initial exposure to the sucrose solution, whereas the higher doses of the drug depressed intake. The excitatory effect of the low dose was apparent during only the first five minutes of access; the inhibitory effect of the high doses only during the first 10 minutes of exposure to the sucrose solution. Clonidine did not have a reliable effect on intake over the later part of the exposure period in the free-fed rats.

The results obtained with the deprived animals were somewhat different, but again related to the dose of clonidine and the length of exposure to the sucrose solution. There was no excitatory effect of the lowest clonidine dose on initial exposure—instead there was a dose-dependent decrement in licking. However, in the long term, the higher doses of clonidine led to enhanced intake—an effect that did not occur with the free-feeding animals. Thus, these data suggest that the decrement in intake that occurred in the consummatory negative contrast paradigm (7) was specific to the brief access period to the sucrose solution.

EXPERIMENT 2

Before considering the implications of these results, a second experiment in which the effect of clonidine on water intake was investigated, will be described. A study by Sanger (16) suggested that clonidine, in doses comparable to those used in this experiment, did not influence total water intake over a one-hour period in free-feeding animals. However, we wished to examine water intake in deprived animals as well, and to examine intake in finer detail since Experiment 1 revealed that there may be short-term influences on intake that are not seen when the data are examined in large blocks.

METHOD

Subjects

Forty-eight male Sprague-Dawley derived rats purchased from Blue Spruce were used as subjects. Half of the animals were maintained on a free-feeding schedule and half were food-deprived, as in Experiment 1. Other aspects of the maintenance schedule were the same as those used in Experiment 1.

Apparatus

The apparatus was the same as that used in Experiment 1.

Procedure

This experiment was conducted as a 2×4 factorial design

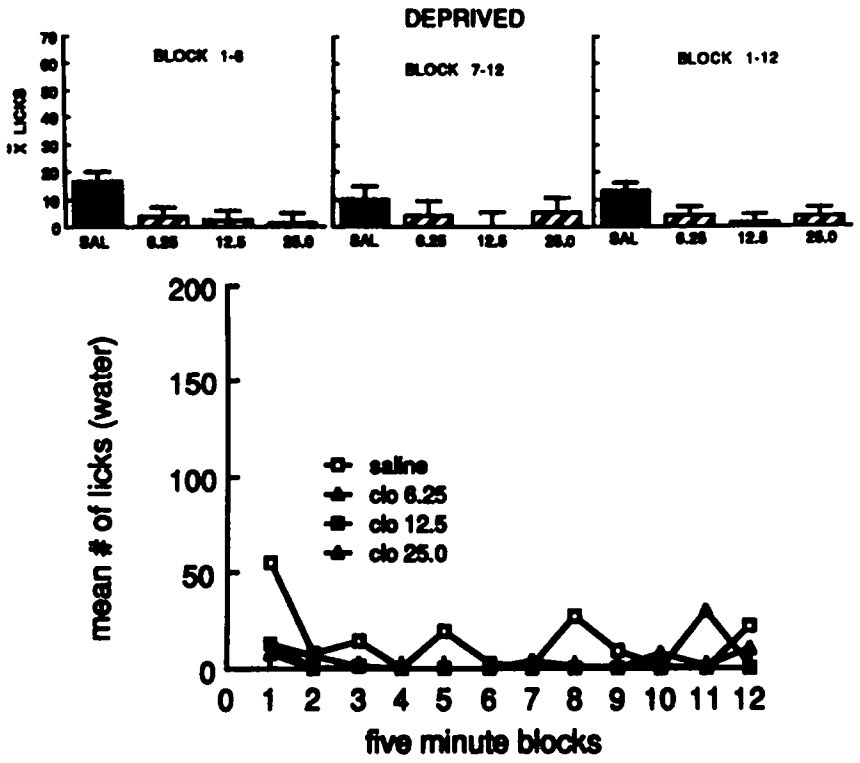

FIG. 4. Top panel: Mean lick frequency for water over the first half, second half and the total one-hour session as a function of drug condition (saline or clonidine) in rats deprived to 82% of their free-feeding body weight. Bottom panel: Same data examined in five-minute blocks.

varying deprivation condition (free-fed versus deprived to 82% of free-feeding weight) and drug condition (saline, or 6.25, or 12.5, or 25 μg/kg of clonidine). The injection was IP 30 minutes prior to the start of the session. Access to the water was given in a room other than the colony room, where the animals were placed in metal cages and given free access to a drinking tube for one hour. Lick frequency was recorded at five-minute intervals through a contact relay circuit and microprocessors.

RESULTS

The free-fed animals consumed more water than the deprived animals, $F(1,31)=13.12$, $p<0.01$, and there was an overall tendency for clonidine to reduce intake in a dose-dependent fashion, $F(3,31)=2.77$, $p=0.058$. However, the effects of the drug on water intake also varied by deprivation condition and by period of exposure [Condition × Drug ×Time block, $F(33,341)=1.71$, $p<0.02$. The data were further analyzed by considering each deprivation condition separately in a fashion parallel to that of Experiment 1.

Free-Fed Animals

The results obtained with the free-feeding animals are presented in Fig. 3—large blocks of time in the top panel, five-minute intervals in the bottom panel. When the data were examined for the first half-hour exposure period only, the tendency for clonidine to suppress intake was not reliable, $F(3,15)=2.14$, $p>0.10$. Over the second half-hour there was a reliable overall effect of the drug, $F(3,15)=3.58$, $p<0.04$. Analysis with the lsd test showed that the lowest dose of clonidine (6.25 μg/kg) reliably enhanced water intake, whereas the 25 μg/kg dose suppressed intake, not reliably below the saline group but reliably below the 6.25 μg/kg clonidine group. Analysis over the entire one-hour period indicated no overall effect of the drug ($p>0.15$).

Inspection of the bottom panel of Fig. 3 suggests a number of differences in block by block intake, but not a clear sign of systematic variation. Analysis of a reliable drug × block interaction, $F(33,165)=1.58$, $p<0.04$, with the lsd test ($p=0.05$) showed several reliable effects. Thus, the saline group licked more than all drug groups in Block 6, more than the two higher clonidine doses in Block 4, and more than the highest clonidine dose in Block 11. The 6.25 μg/kg dose of clonidine led to lick frequencies higher than all other groups in Block 7, and the intermediate clonidine dose (12.5 μg/kg) led to higher lick rates than the saline and 25 μg/kg clonidine group in Block 12. No other differences were reliable.

Deprived Animals

Analysis of the data from the first half-hour of exposure indicated a reliable drug effect, $F(1,16)=18.27$, $p<0.001$. Subsequent analysis with the lsd procedure indicated reliable suppression of water intake by all three drug doses with no dose/response effect (top panel of Fig. 4). Analysis of the data from the second half-hour of exposure showed no reliable effect of the drug ($F<1.00$). Clonidine suppressed intake in the deprived animals over the entire one-hour period,

$F(3,16)=4.31$, $p<0.03$, with all drug doses leading to less intake than the saline condition. There were no reliable differential effects across blocks when intake was examined in terms of five minute periods (bottom panel of Fig. 4).

DISCUSSION

Previous studies have shown that water intake is suppressed in the short-term (1–6 hours) by systemic administration of clonidine, but there is a later enhancement of intake, possibly as a compensatory response (1). A study using low doses of clonidine, doses closely approximating those used in the present experiment, reported no effect on water intake over the first hour of exposure, but there was a later enhancement of water intake (16). Both of these studies used free-fed animals.

In the present study, using a finer-grained temporal analysis, we found complex effects of clonidine on water intake occurring within the first hour of exposure. These effects depended on dose and deprivation condition. The results obtained with the free-fed animals are in agreement with those reported by Sanger (16) in that there was no effect of the drug when the total intake over one hour was examined. But, there was a general pattern of suppression which was reliable, for specific doses, at certain points, such as in blocks representing 15 to 20 minutes, 25 to 30 minutes, and 50 to 55 minutes into the session. Examined in intermediate blocks, in terms of the first versus second half-hour of exposure, it was found that the drug tended to have opposite effects, with a nonreliable tendency for suppression occurring in the first half-hour and an inverse, dose-dependent tendency for enhancement in the second half-hour. In the case of the deprived animals, only suppression occurred and it was most pronounced, and reliable only, in the first half-hour.

The principal purpose of this study was to determine the degree to which the effects of clonidine on sucrose intake reported in Experiment 1 might be related simply to fluid intake and not sugar intake per se. This comparison will be considered below.

GENERAL DISCUSSION

The principal difference between the effects of clonidine on sucrose intake and water intake may be seen by comparing over relatively large blocks of time in the top panels of each of the four figures. In general, deprivation enhanced sucrose intake but reduced water intake and clonidine exaggerated both of these trends. That is, clonidine reliably increased sucrose intake, but reliably decreased water intake, in deprived rats.

The drug had less effect in the free-feeding animals and the effects that were present were more notable in the short-term measures where there was a clear effect of the higher dose of clonidine to suppress intake of both water and sucrose. The 6.25 μg/kg dose had the interesting effect of potentiating sucrose intake in free-fed rats in the first five minutes of exposure and of potentiating water intake in free-fed rats in the last half-hour of exposure.

The substantial differences in the effects of clonidine on sucrose and water intake, particularly in the case of the deprived animals, indicates quite clearly that the effects of clonidine on sucrose intake are not due simply to the effects of the drug on fluid intake per se—the nature of the fluid makes a difference.

The generally reduced intake demonstrated early in the access period in these experiments may be related to the sedative effects associated with clonidine administration. Clonidine (2.5–50 μg/kg) administered IP causes suppressed locomotor activity in an open field in the rat, impaired rotarod performance in the rat, and reduced Y-maze exploration in the mouse (4, 14, 19). The sedative effects of high doses of clonidine (50–200 μg/kg) are reported to peak at 20 minutes postinjection and are sustained for approximately an additional 40 minutes (4). This time span matches the sucrose exposure period in the present study. Thus, it is possible that the generally depressed intake seen in the free-feeding animals was related to this sedative effect and that this sedation was partially offset by the effects of food deprivation, allowing the excitatory effects of clonidine to predominate late in the testing session.

There is another factor that merits consideration regarding the depressive effects of clonidine on intake. We recently reported, as have others, that administration of clonidine results in the elevation of circulating plasma glucose levels (7). Elevated plasma glucose levels may suppress food intake (2, 3, 9). These data may be relevant for the effects of clonidine on food intake for the following reasons. As far as we are able to determine, the reported cases in which clonidine enhanced food intake involved measures determined in the home cage environment. In comparison, our measures were recorded in an environment distinct from the homecage. Since there is substantial evidence indicating that exposure to a novel environment results in subsequent elevation of circulating plasma glucose and corticosteroid levels (8, 10, 13), there is the possibility that the clonidine and novel environment may have had an additive effect on plasma glucose levels raising them to a point sufficient to suppress intake in the nondeprived animals. With respect to the deprived subjects, on the other hand, these additive effects may have been insufficient due to an initial state of deprivation-induced hypoglycemia.

Thus, both sedation and elevated plasma glucose levels could have contributed to the decremental effect of clonidine on sucrose intake in the present experiment, particularly in the free-feeding animals. This experiment was not designed to isolate these factors, but the experiment does show that the short-term decremental effects of clonidine on sucrose intake previously reported are replicable, that the extent of this decremental effect is influenced by clonidine dose, by the duration of exposure, and by the deprivation status of the animals.

Finally, these complex effects of clonidine on sucrose and water intake need to be taken into account when the psychological effects of the drug are investigated in various animal models. For example, it was recently reported by Soderpalm and Engel (18) that a 6.25 μg/kg dose of clonidine has an anxiolytic effect in a modified vogel conflict test, whereas 12.5 and 25 μg/kg have anxiogenic effects. The evidence for this interpretation was that the lowest dose of clonidine enhanced the intake of a glucose solution during shock punishment, but the two higher doses depressed intake. However, this is exactly the pattern obtained in the first five minutes of exposure to sucrose in the free-fed animals in Experiment 1—without the presence of a punishment contingency. It is not possible to say that the results obtained by Solderpalm and Engel were due simply to effects of the drug on intake since there were many differences between their experiment and ours (e.g., their rats had access to glucose, not sucrose, the time between injection and solution access was different, and their animals were water deprived). However, the striking parallel in effects indicates caution when clonidine is used in the context of intake studies.

ACKNOWLEDGEMENTS

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