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BRIEF COMMUNICATION

# Absence of Clonidine-Induced Food Intake in Hamsters

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KATZ, N. L., T. BRNE, J. BOLIN AND R. F. SCHLEMMER, JR. *Absence of clonidine-induced food intake in hamsters.* PHARMACOL BIOCHEM BEHAV **25**(5) 1107–1109, 1986.—Previous studies support an interaction between noradrenergic and opiate systems in the control of food intake. For example, in both rats and rabbits, food intake stimulated by the noradrenergic agent clonidine is reduced by opiate antagonists. The purpose of the present study was to determine whether or not clonidine stimulated the food intake of non-food-deprived hamsters, a species which appears to lack an opiate-sensitive feeding system. Hamsters fed a chow diet did not increase their food intake when injected with clonidine in doses ranging from 0.05 to 0.25 mg/kg. Furthermore, the animals did not increase their intake of sunflower seeds, a preferred diet for hamsters.

Clonidine Feeding Hamsters Preferred diet

SINCE Broekkamp and Van Rossum [4] reported that intrahypothalamic injections of the noradrenoreceptor agonist clonidine stimulated food intake in rats, other investigators have found the same result when the drug was administered peripherally. Intraperitoneal injections of clonidine increased both total food and protein intake in rats allowed to select between diets with high or low protein content [15]. Subcutaneous injections of clonidine increased standard laboratory food and water intake in rats during the 6 hour period following injection [18]. Intraperitoneal clonidine stimulated a short term vigorous food intake in rabbits [23] and profound hyperphagia and subsequent weight gain in Stumptail macaque monkeys [20].

Recently, Sanger [18] reported that the food intake induced by clonidine in rats was reduced by the opiate antagonist naloxone. Naloxone did not produce a competitive antagonism of the effects of clonidine, but the results did suggest an interaction between noradrenergic and opiate systems in the control of food intake. More recently, Katz *et al.* [8] reported that the opiate antagonist, naltrexone, blocked food intake induced by clonidine in rabbits. The study did not resolve the question of whether the ability of opiate antagonists to reverse the effect of clonidine resulted from a dynamic opposition or specific pharmacologic antagonism.

The present study was prompted by the observation of certain investigators that hamsters apparently lack an opiate-sensitive feeding system. Opiate agonists, which stimulated feeding in rats [11,19], failed to do so in hamsters [2,14]. Also, opiate antagonists, which decreased feeding in rats [7], had no effect on the feeding behavior of hamsters [2,13]. Since opiate and noradrenergic mechanisms in the central nervous system may interact to regulate food intake in some species, the present study was undertaken to determine whether clonidine stimulated feeding in a species which appears to lack an opiate-sensitive feeding system.

## METHOD

Food and water intake were measured in adult male Syrian (golden) hamsters (*Mesocricetus auratus*) weighing approximately 100 g. Hamsters were housed individually in plastic cages (45×23×22 cm) in an environmentally controlled room maintained on a 12 hr dark-light cycle (lights on 0600 to 1800) and acclimated to their environment and laboratory diet for seven days before the onset of drug testing. Small plastic cups or clay pots were filled with food, and, to discourage nesting in the cups, each animal was provided with a plastic cup containing yarn.

Experiments were conducted in non-food-deprived animals, since hamsters do not increase food intake following food deprivations [21]. Each experiment began between

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TABLE 1
EFFECT OF CLONIDINE ON HAMSTER FOOD INTAKE

| | 1 Hr | 2 Hr | 24 Hr |
|---|---|---|---|
| Vehicle | 0.37 ± 0.14 | 0.86 ± 0.08 | 8.21 ± 0.80 |
| Clon* (0.05) | 0.57 ± 0.13 | 1.14 ± 0.11 | 8.85 ± 0.43 |
| Vehicle | 0.69 ± 0.13 | 1.14 ± 0.17 | 9.84 ± 0.16 |
| Clon (0.10) | 0.69 ± 0.08 | 1.04 ± 0.05 | 8.93 ± 0.24 |
| Vehicle | 0.49 ± 0.02 | 1.04 ± 0.06 | 10.01 ± 0.43 |
| Clon (0.25) | 0.34 ± 0.02 | 0.72 ± 0.06† | 7.33 ± 1.20 |

Each value is the mean ± the SEM of the total amount of laboratory chow consumed (g) at the end of the stated observation period. N=7 hamsters. Data were evaluated by one-way ANOVA.

*Clonidine. Statistical difference from vehicle control is denoted by: †$p<0.05$. Numbers is parentheses are doses in mg/kg.

1000 and 1200 hr at which time animals and food-filled cups were weighed. After receiving drug or control treatment, hamsters were returned to their home cages where they were observed for designated time periods during different experiments. After each observation period, animals and food cups were reweighed. Food intake during the observation periods was corrected for spillage, spilled food being collected from paper placed beneath a grid floor of each cage just before the experiment began. Food was measured to the nearest mg. Care was taken to check for food hidden in the cheek pouch of the hamsters.

Vehicle and drugs were given intraperitoneally (IP) in a volume of 0.2 ml/100 g. Clonidine HCl was generously supplied by Boehringer Ingelheim Ltd. Dist. Hamsters were selected and dosed at random.

The first study consisted of a series of cross-over experiments. Seven hamsters were given free access to the Purina Rat Chow and water during the acclimation period. On the first day of the test, four animals, randomly assigned to one group, received a dose of clonidine HCl and the remaining group received saline. Total food intake was measured at 1, 2 and 24 hr after injection. On the next test day, the groups were crossed over, so that those animals previously receiving clonidine now received saline and *vice versa*. In this study, doses of clonidine used were 0.050, 0.10, and 0.25 mg(salt)/kg, and drug injections were separated by at least six days.

The second study determined the effect of clonidine on a preferred diet. Ten drug-naive hamsters were given *ad lib* access to hulled sunflower seeds in addition to the standard laboratory chow during the acclimation period. In a Latin square design, animals received saline and each of the following doses of clonidine HCl: 0.025, 0.050, 0.10, 0.25 mg(salt)/kg. Food consumption was measured after two hr. All injections were given at approximately 1000 hr. In order to compare the intake of the two diets, food consumption was expressed in kilocalories based on 3.61 kcal/g for Purina Rat Chow [5] and 6.4 kcal/g for hulled sunflower seeds [9]. Experiments were conducted three times weekly at 48 hr intervals.

Data were evaluated by analysis of variance (ANOVA). The least significance method was used to compare means within the analysis.

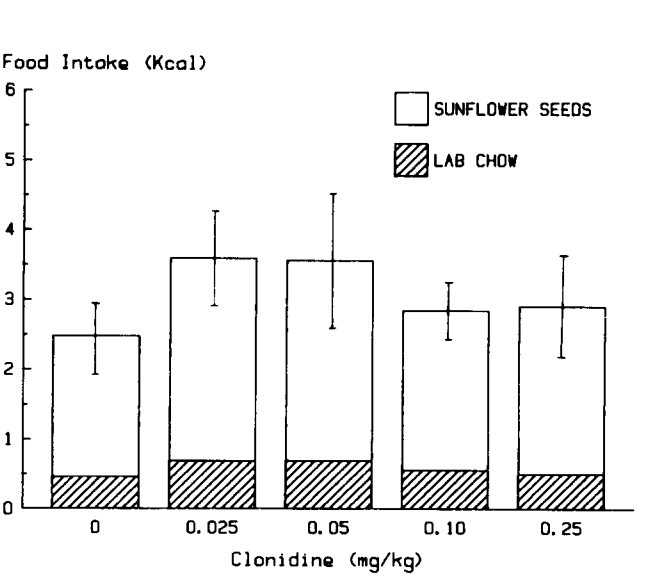


FIG. 1. Mean food intake (±SEM) of hamsters during the 2 hr feeding period following intraperitoneal injections of 0, 0.025, 0.05, 0.10, and 0.25 mg/kg of clonidine. N=8–10 hamsters per dose. The hulled sunflower seed and chow intake of each group are indicated by the open and shaded portions of each bar. Data were evaluated by one-way ANOVA.

## RESULTS

As shown in Table 1, the food intake of hamsters fed a standard laboratory chow diet was not reliably altered over a 24 hr period by doses of clonidine ranging from 0.05 to 0.25 mg/kg. Chow intake at 2 hr only was significantly reduced by the highest dose of clonidine used, 0.25 mg/kg. The 24 hr intake tended to be reduced by the 0.25 mg/kg dose, although the difference from control just failed to reach statistical significance, $0.05<p<0.06$. At this highest dose, the animals appeared neither sedated, ataxic nor incapable of eating.

Hamsters also failed to increase their intake of sunflower seeds following injections of clonidine in doses ranging tenfold from 0.025 to 0.25 mg/kg (Fig. 1). Neither the sunflower seed nor the total caloric intake of hamsters was reliably altered by clonidine. However, a two-way ANOVA (dose × food) of a 2 hr caloric intake indicated that the hamsters ate significantly more kcal of sunflower seeds than of chow diet, $p<0.01$.

## DISCUSSION

The feeding profile of hamsters and rats, recently reviewed by Morley *et al.* [16], displays similarities as well as dissimilarities. Insulin injections caused both hamsters and rats to significantly increase their food intake [3,17]. The opiate narcotic antagonist naltrexone failed to attenuate insulin-induced food intake in both species [12,13]. Dilution of a liquid diet (reduced diet density) produced an increase in the volume of diet ingested in both hamsters and rats [21].

With regard to feeding dissimilarities shown by the two species, hamsters displayed a minimal circadian feeding pattern [25], while rats consumed the majority of their food

during the dark phase of the lighting cycle [24]. Rats, but not hamsters, displayed post-fast hyperphagia [10,21]. Rats, but not hamsters, increased their food intake after 2-deoxy-D-glucose [17,22] and butorphanol [2,11]. Multiple injections of naltrexone decreased rat, but had no effect on hamster, daily food intake and weight gain [13]. Furthermore, rats, but not hamsters, increased food intake after morphine and ketocyclazocine [14].

Sanger [18] demonstrated that clonidine increased food intake during a six hr period following subcutaneous injections in rats. The present study demonstrated that IP injections of clonidine, in doses shown to be effective in rats, rabbits and monkeys, failed to increase total food intake in hamsters, a result indicative of another differential feeding response between the two species.

The present study confirms the work of other investigators who have shown that hulled sunflower seeds are a preferred diet for hamsters. Clonidine failed to alter the food preference as well as total food intake. Mauron *et al.* [15] have shown in rats that IP clonidine increased the intake of a high protein diet, while Fahrbach *et al.* [6] demonstrated that clonidine injected into the paraventricular nucleus increased preference for a carbohydrate diet. Sunflower seeds are high in fat. Hence, the results of either of these investigators suggest that sunflower seeds may not be an appropriate diet to test for clonidine eating in hamsters. This argument is weakened, however, by the finding that peripheral clonidine administration increased the food intake of rats fed a standard laboratory diet [18].

The lack of the clonidine effect in hamsters could have been due to the fact that the latency required to stimulate feeding is much longer than clonidine-induced feeding in other species. In contrast with Sanger [18], Atkinson *et al.* [1] noted an appetite stimulating effect in rats only when daily administration was continued for more than four days. Alternatively, the failure of clonidine to change eating may suggest a lack of importance for monoamines in modifying feeding behavior as has been suggested in hamsters for opiates. Additional studies will need to be done before any definitive conclusion can be drawn.

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