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BRIEF COMMUNICATION

Differential Effects of Clonidine Analogs on Food Intake in Rabbits and Monkeys

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KATZ, N. L., N. SOBASKI, J. SANCHEZ, J. E. YOUNG AND R. F. SCHLEMMER, JR. *Differential effects of clonidine analogs on food intake in rabbits and monkeys.* PHARMACOL BIOCHEM BEHAV **34**(2) 433–437, 1989.—The present study examined the effect of structural analogs of clonidine on feeding in both rabbits and monkeys. In rabbits, lofexidine and tizanidine either did not influence or decreased food intake in contrast to clonidine, which stimulated food intake. Lofexidine elicited easily observed decreases in motor behavior with several of the doses used in the study. Changes in motor behavior induced by tizanidine were more subtle. Conversely, lofexidine and tizanidine significantly increased feeding behavior in Stumptail macaque monkeys, as did clonidine. The results suggest that, in contrast to rabbits, Stumptail monkeys are more useful in searching for an 'orectic' effect of clonidine analogs.

Rabbits Monkeys Clonidine Lofexidine Tizanidine Appetite Feeding

CLONIDINE is an α_2-adrenoreceptor agonist that has been used therapeutically in the management of hypertension in the United States since 1974. Besides its antihypertensive effect, this drug exerts a variety of complicated and incompletely understood peripheral and central pharmacological effects. These include hyperphagia (1), hypomotility (15), hypothermia (19), and sedation (35). In addition, clonidine has been shown to decrease blood vessel responsiveness to both vasoconstrictor and vasodilator drugs (34), block the effects of electrical and pharmacological activation of the locus coeruleus (8), increase serum growth-hormone levels (17), and stimulate adrenoreceptors in the spinal cord (32). Based on the documented pharmacological effects in either animals or humans, the drug has been used to treat anorexia nervosa, diarrhea, menopausal hot flashes, migraine headache, opiate withdrawal syndrome, constitutional growth delay, and spinal spasticity. The varied clinical spectra of clonidine are also shown by treatment with clonidine to control the symptoms of Tourette's syndrome (21), tardive dyskinesia (22), ocular hypertension (11), mania (13), ulcerative colitis (20), smoking cessation (7) and panic anxiety disorder (12). These uses, many of which are based on the ability of clonidine to reduce hyperadrenergic tone, have met with varying degrees of success.

The attempted use of clonidine for various conditions sometimes has been limited by side effects such as sedation, hypotension, and dizziness. As a result, drugs with a chemically similar structure but with less troubling side effects have been sought. For example, tizanidine, which is currently used in clinical trials for the treatment of spasticity associated with various CNS disorders (18,23), does not seem to produce significant reduction of blood pressure (18). Animal experiments on the pharmacology of another clonidine analog, lofexidine, suggest that it is a centrally acting hypotensive agent with less marked sedative effects (10). More recently, the latter drug has been shown to reduce intraocular pressure in animals (5).

We have been particularly interested in the appetite stimulating property of clonidine (14, 27, 28, 33). Drugs which enhance the urge to eat and induce weight gain may be useful for several reasons (2,31). They may be part of an overall treatment plan for patients with anorexia nervosa, bringing patients more quickly to target weight. Also, drugs which reverse weight loss may improve the quality of life of patients with cancer or AIDs.

The purpose of the present study was to examine the effects of the clonidine analogs tizanidine and lofexidine on feeding behavior. Rabbits and Stumptail macaque monkeys were used, since

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previous studies have shown that clonidine reliably increases feeding behavior in these species on systemic administration (14, 27, 28, 33).

METHOD

Rabbits

A series of studies was conducted in male New Zealand rabbits (2–4 kg). Animals were individually housed in metal cages (58 × 61 × 42 cm) in an environmentally controlled room maintained on a 12-hr dark-light cycle and were acclimated to their environment and food for 7 days before the onset of drug testing. Food (Purina Rabbit Chow) and water were provided ad lib. Drugs were dissolved in normal saline in concentrations adjusted so as to be administered as single intramuscular injections of 0.1–0.2 mg/kg of body weight. Experiments were conducted 2 or 3 times weekly at 48–72-hr intervals. Injections were made at approximately 1000 hr. Tizanidine HCl was furnished through the courtesy of the Sandoz Pharmaceuticals Corporation and lofexidine HCl through the Merrell-Dow Pharmaceutical Inc. Clonidine HCl was obtained from the Sigma Chemical Company.

At the beginning of each experiment, both the rabbits and food trays were weighed. After receiving either control or drug treatment, rabbits were returned to their home cages. The amount of food consumed was measured at specified time intervals, spilled food being collected from paper placed beneath the grid floor of each cage just before the experiment began. Food was weighed to the nearest 0.1 g.

Study 1. In a Latin square design, 10 rabbits were to receive a dose of saline and each of the following doses of lofexidine: 0.1, 0.2, 0.4, 0.8 mg(salt)/kg. However, on the third study day, one rabbit died within 24 hr after receiving the 0.8 mg(salt)/kg dose. This dose was then dropped from the regimen. Food intake was measured at 1, 2 and 24 hr after the injections.

Study 2. In a random block design, 10 rabbits received saline and each of the following doses of lofexidine: 0.005, 0.01, 0.02 mg(salt)/kg. Food consumption was measured at 1, 2 and 24 hr after the injections.

Study 3. A series of cross-over experiments was conducted in 10 rabbits. On the first day of the test five animals, randomly assigned to one group, were injected with 0.1 mg(salt)/kg clonidine and the remaining animals were injected with saline. Food intake was measured 1 hr after the injections. On the second day of the test, the animals were crossed over so that those that received the clonidine now received saline and vice versa. The study was replicated using 0.005 mg(salt)/kg lofexidine as the test drug.

Study 4. In a Latin square design, 10 rabbits received a dose of saline and each of the following doses of tizanidine: 0.1, 0.3, 0.5 and 1 mg(salt)/kg. During the study, one of the rabbits developed an infection, and the data obtained from this animal were omitted from the study. Intake measures were determined at 1 and 2 but not 24 hr, since we previously found no significant changes in 24 hr intake after clonidine (33) and lofexidine either did not change or decreased 24-hr intake.

Monkeys

Drug effects were studied in a group of adult Stumptail macaque monkeys (*Macaca arctoides*). One week before the start of the study, the animals were removed from a social colony, weighed, and subsequently each monkey was individually housed in a cage (0.5 × 1 × 1 m) equipped with a standard feeder attached to the outside of the cage. The weights ranged from 8 to 19.5 kg. Monkeys were fed (Agway Monkey Biscuits) at 0800–0815 hr. Food was removed from the cages at 0955–1020 hr after which the animals were injected intramuscularly with saline or test drug. Immediately after injections, preweighed biscuits were placed in the food holders, and the monkeys were allowed to eat for 4.5 hr. This time period comprises the bulk of clonidine-induced eating in monkeys, as we have previously shown that the activity of monkeys centers around eating for about 2 hr after which they continue to eat sporadically for roughly another 2 hr (28). The remaining food was removed from the holders and weighed, along with spillage collected from the trays below the cages. The monkeys were fed again at 1300 hr. Experiments were conducted at 48–72-hr intervals.

Study 1. The study group was composed of 11 females and 1 male. In a random block design, monkeys received saline and each of the following doses of lofexidine: 0.01, 0.05, 0.08 mg(salt)/kg. On the last study day, each animal received 0.08 mg(salt)/kg clonidine.

Study 2. The study group was composed of 10 females and 2 male monkeys which were divided into 6 paired groups and dosed with saline, tizanidine [0.05, 0.1, 0.3, and 0.5 mg(salt)/kg], and clonidine [0.1 mg(salt)/kg] in a Latin square design.

Data were analyzed using a two-way ANOVA. The least significance method was used to compare means within the analysis.

RESULTS

The results of the studies in rabbits are summarized in Table 1. Lofexidine, in doses ranging from 0.005 to 0.4 mg/kg, failed to increase food intake above saline control levels during the first and second hr following intramuscular injections. Rabbits treated with 0.02 mg/kg or more of lofexidine ate less food over a 24-hr time span in comparison with saline-treated controls. When rabbits were given 0.1 mg/kg of clonidine, they exhibited an increase in feeding behavior significantly greater than baseline control levels after 1 hr. Visually, we observed that doses of 0.05 mg/kg lofexidine and greater often affected motor behavior. The animals developed abnormal posturing which was seen as head droop, leaning to one side, and laying on one side unable to lift the head. On occasion, the righting reflex was lost. Also, the eyes frequently exhibited a glazed or 'glassy' appearance. These effects of the drug usually lasted for at least 2 hr.

Rabbits did not increase their food intake above saline control levels during a 1- and 2-hr observation period in response to tizanidine in doses ranging from 0.1 to 1 mg/kg. There was a trend toward an increase above saline control level (6.14 ± 2.40 g) 1 hr after 0.1 mg/kg tizanidine (9.77 ± 0.86 g) which did not reach significance. Food intake decreased below saline control levels 1 and 2 hr after a dose of 1 mg/kg. Motor coordination did not appear to be overtly abnormal with the doses of tizanidine used in the study. However, we did observe that the rabbits did not scamper to the back of their cages when the doors were opened as is often the case. Rabbit muscle tone did not seem taut when the fingers and thumb were placed on either side of the body. However, the animals were not ataxic and could move about their cages normally when pressed.

Figure 1A shows that lofexidine, in doses ranging from 0.01 to 0.08 mg/kg, significantly increased the food intake of monkeys above saline levels during the 4.5-hr observation period. The effect of each dose on food intake was comparable, and no dose differed significantly from any other. No abnormal posturing was observed with the doses used as was seen in the rabbits. A dose of 0.08 mg/kg clonidine increased food intake in the monkeys to the same extent as the lofexidine.

Doses of tizanidine ranging from 0.05 to 0.5 mg/kg signifi-

TABLE 1

EFFECT OF LOFEXIDINE AND TIZANIDINE ON FOOD INTAKE IN RABBITS

	1 Hr	2 Hr	24 Hr
	Lofexidine (LOF) vs. Saline (N = 9)		
Saline	2.74 ± 1.02	8.78 ± 2.00	147.38 ± 13.65
LOF (0.1)	2.48 ± 1.40	3.86 ± 2.28	79.52 ± 14.15*
LOF (0.2)	2.20 ± 1.03	5.11 ± 1.13	87.20 ± 12.34*
LOF (0.4)	0.77 ± 0.18	3.47 ± 1.46	73.80 ± 12.56*
	(N = 10)		
Saline	6.29 ± 1.51	12.47 ± 1.97	144.46 ± 11.98
LOF (0.005)	5.24 ± 1.69	10.61 ± 2.24	129.75 ± 8.49
LOF (0.01)	5.14 ± 1.85	11.05 ± 3.34	122.49 ± 9.02
LOF (0.02)	4.48 ± 1.67	7.68 ± 2.98	94.02 ± 15.68†
	Lofexidine (LOF) and Clonidine (CLON) vs. Saline (N = 10)		
Saline	4.62 ± 0.72	—	—
CLON (0.1)	11.37 ± 2.22*	—	—
Saline	5.46 ± 0.46	—	—
LOF (0.005)	7.64 ± 1.23	—	—
	Tizanidine (TIZ) vs. Saline (N = 9)		
Saline	6.14 ± 2.40	11.70 ± 2.77	—
TIZ (0.1)	9.77 ± 0.86	13.27 ± 1.49	—
TIZ (0.3)	4.62 ± 1.55	9.19 ± 0.97	—
TIZ (0.5)	3.18 ± 1.44	7.76 ± 1.87	—
TIZ (1.0))	1.11 ± 0.66*	4.68 ± 0.93†	—

Each value is the mean ± the SEM of the total amount of laboratory chow consumed (g) at the end of the observation period. Data were evaluated using a two-way ANOVA. Statistical difference from saline control is denoted by: *$p<0.05$ or †$p<0.01$. Numbers in parentheses are doses in mg/kg.

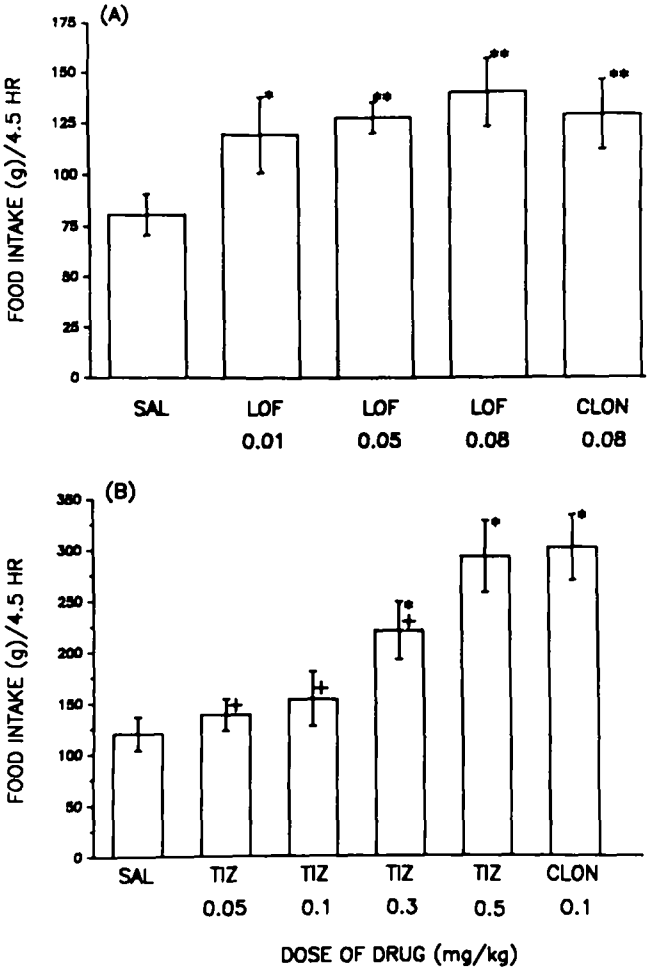

FIG. 1. Mean food intake (± SEM) of monkeys during a 4.5-hr feeding period following intramuscular injections of lofexidine (LOF), tizanidine (TIZ), or clonidine (CLON). N = 11–12 monkeys per dose. Statistical difference from saline control is denoted by *$p<0.05$ or **$p<0.01$. Statistical difference from 0.5 mg/kg TIZ or 0.1 mg/kg CLON is denoted by +$p<0.01$.

cantly increased food intake in an apparent dose-related manner (Fig. 1B). As expected, clonidine, in a dose of 0.1 mg/kg, increased food intake.

DISCUSSION

The central nervous system is implicated in the main actions for which lofexidine, clonidine and tizanidine are chiefly employed. Lofexidine and clonidine are potent hypotensives with a central mode of action. Tizanidine is a centrally acting muscle relaxant. As imidazoline derivatives, lofexidine and tizanidine share structural similarities with clonidine and also share pharmacological properties which are mediated centrally by an interaction with α_2-noradrenoreceptors. For example, in rats, lofexidine and tizanidine shared discriminative stimulus properties of clonidine (16,29), and the selective α_2-noradrenoreceptor antagonist yohimbine was found to antagonize the tizanidine and clonidine discriminative stimulus. Yohimbine was not tested against lofexidine. The mechanism of clonidine-induced feeding has also been attributed to an α_2 agonist effect (9,28), although the location of the receptors (pre- or postsynaptic) has been argued. Hence, it might be expected that lofexidine and tizanidine would stimulate eating unless different affinities, lack of accessibility to critical receptors sites, or intervening side effects precluded the effect.

In this study, the structural analogs of clonidine, lofexidine and tizanidine, exerted a differential effect on food intake in rabbits and monkeys. In rabbits, these drugs either did not influence or decreased food intake. In Stumptail macaque monkeys, they increased food intake over a 4.5-hr period. Clonidine increased food intake in both rabbits and monkeys. The latter result is consistent with our previous findings (14, 27, 28, 33).

An appetite-stimulating effect of the analogs in rabbits may have been obscured by drug-induced sedation suggested by decreased motor behavior. Locomotor activity was drastically affected by doses of lofexidine as low as 0.05 mg/kg. Clonidine has been reported to cause similar deficits in rabbits which were described as being sedated with their heads on the floor, ataxic, and motor incoordinated (6). Clonidine, 0.1 mg/kg, did not produce these effects in the present study, and therefore, lofexidine is the more potent of the two agents in this regard. This finding is opposite the results of Graf *et al.* who reported that lofexidine, in contrast to clonidine, had less marked central sedative effects in mice and rats (10). It should be noted, however, that lofexidine failed to increase food intake in doses below those which caused obvious motor incoordination.

No obvious changes occurred in the motor behavior of rabbits

treated with 0.1 to 1 mg/kg tizanidine. Muscle tone did appear to be decreased in response to touch. In support of this observation, Sayers recorded electromyograms from rabbit gastrocnemius muscles and found that intravenous doses of 0.01–0.037 mg/kg tizanidine inhibited reflex muscle tone (26). These data and observations suggest that the use of rabbits as a model to test the potential 'oretic' effect central noradrenergic agents might be compromised by this species' heightened sensitivity to an initial sedative drug effect. It would be of interest to determine whether or not repeated lofexidine or tizanidine administration results in tolerance to the depressant effects which would allow increases in feeding behavior to be observed. Facilitation of feeding following tolerance to sedation has been reported for opiate agonists (25).

The appetite-stimulating effect of clonidine in monkeys was paralleled by both lofexidine and tizanidine. A better delineated dose-response curve was seen with tizanidine than with lofexidine. Our data suggest that tizanidine was one-half to one-third as potent as clonidine in increasing food intake. Tizanidine is reportedly one-third as potent as clonidine in its α_2-noradrenoreceptor agonist effects on peripheral tissues (30). In contrast to rabbits, the Stumptail monkey model seems to be more useful in searching for clonidine analogs with an 'orectic' effect.

Drug control of weight loss has been attempted with limited success. Megestrol acetate and hydrazine sulfate may cause weight gain and appetite stimulation in patients with cancer (3,31). According to Rockwell *et al.*, cyproheptadine should be the first drug to try in refractory, underweight anorectic patients (24). Clonidine was given to treatment resistent anorexia nervosa patients but was not superior to placebo in increasing the rate of weight gain (2). However, in the latter study, clonidine produced sedation each time it was administered, and this side effect may have limited the potential utility of the drug. There would be an advantage in having a similar drug for which there was a greater separation between the doses producing the appetite-stimulating effect and the doses at which sedation was elicited. This may be difficult to achieve, since both increased feeding behavior and sedation are probably caused by stimulation of central α_2-noradrenoreceptors (4, 9, 28).

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