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Inhibitory Effect of the α_1-Adrenergic Antagonist Prazosin on Food Intake in Pygmy Goats

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ROSSI, R. AND E. SCHARRER. *Inhibitory effect of the α_1-adrenergic antagonist prazosin on food intake in pygmy goats.* PHARMACOL BIOCHEM BEHAV 47(4) 851–856, 1994.—The effect of the intraperitoneally (IP) injected α_1-adrenergic antagonist prazosin (15, 40, 130 and 537 μg/kg b.wt.) on feed intake and plasma free fatty acid (FFA) levels was studied in 12 adult female African pygmy goats. Prazosin produced a dose-dependent long-lasting hypophagia and a dose-dependent increase in plasma FFA levels. The hypophagic effect of prazosin and the elevation in plasma FFA induced by prazosin were abolished by concomitant injection of the β-adrenergic antagonist propranolol (500 μg/kg b.wt.). The hypophagic effect of prazosin (40 μg/kg) was also abolished by concomitant injection of the hypertonic agent angiotensin II (AII: 1 μg/kg). The results suggest that blockade of α_1-adrenergic receptors by prazosin-producing hypotension elicits a counterregulatory sympathetic activation, which reduces voluntary food intake by activation of β-adrenergic receptors. The dose dependence of the inhibition of food intake and of the elevation of plasma FFA after prazosin suggests that the hypophagia due to prazosin may be partly a consequence of elevated plasma FFA.

Prazosin Food intake Pygmy goats FFA

THE α_1-adrenergic antagonist prazosin (400 μg/kg) has been shown to cause a slight reduction in cumulative food intake in sheep in a recent study (8). An explanation was not given for this observation. Since prazosin, commonly used in therapy of hypertonic disorders in man (3), increased plasma FFA levels in pygmy goats (9) and infusion of long chain fatty acids produced an inhibition of feeding in sheep (17), the effect of prazosin on food intake in pygmy goats might be related to increased plasma FFA levels.

We, therefore, tested the effect of various doses of prazosin on feed intake and plasma FFA levels in pygmy goats. Plasma β-hydroxybutyrate (β-HB) concentration was, in addition, determined, because an anorectic effect of β-HB has also been reported (5). Furthermore, we investigated whether activation of β-adrenergic receptors is involved in the action of prazosin on food intake and plasma FFA, because blockade of vascular α_1-adrenergic receptors by prazosin-producing hypotension might activate the sympathetic nervous system via the baroreceptor system (16). In this context the effect of an agent (angiotensin II) antagonizing the hypotonic effect of prazosin on the hypophagic effect of prazosin was also tested.

METHOD

Twelve adult nonlactating female African pygmy goats with a body weight of 26–43 kg (age: 3–7 years) were used for the experiments. The goats were kept in single cages with pelleted food (Hypona Optimal 888, Volg Winterthur, Switzerland) and water ad lib. The floor of the cages was covered with wood shavings and the animal room was kept on a regular dark light : dark cycle of 12 h each (light phase: 0900–2100 h). The substances tested were injected intraperitoneally (IP). The experiments were performed in a crossover design. Each experiment consisted of two trials, which were repeated in counterbalanced order. The data of the two trials were combined.

Recording of Feed Intake

Food was offered in spill-resistant food containers that were fixed on scales (Mettler PM6) (6). The scales were connected to a computer (Hewlett-Packard personal computer, HP85). Scales with food containers were sheltered by wooden boxes. The food containers had a hole on the front side to

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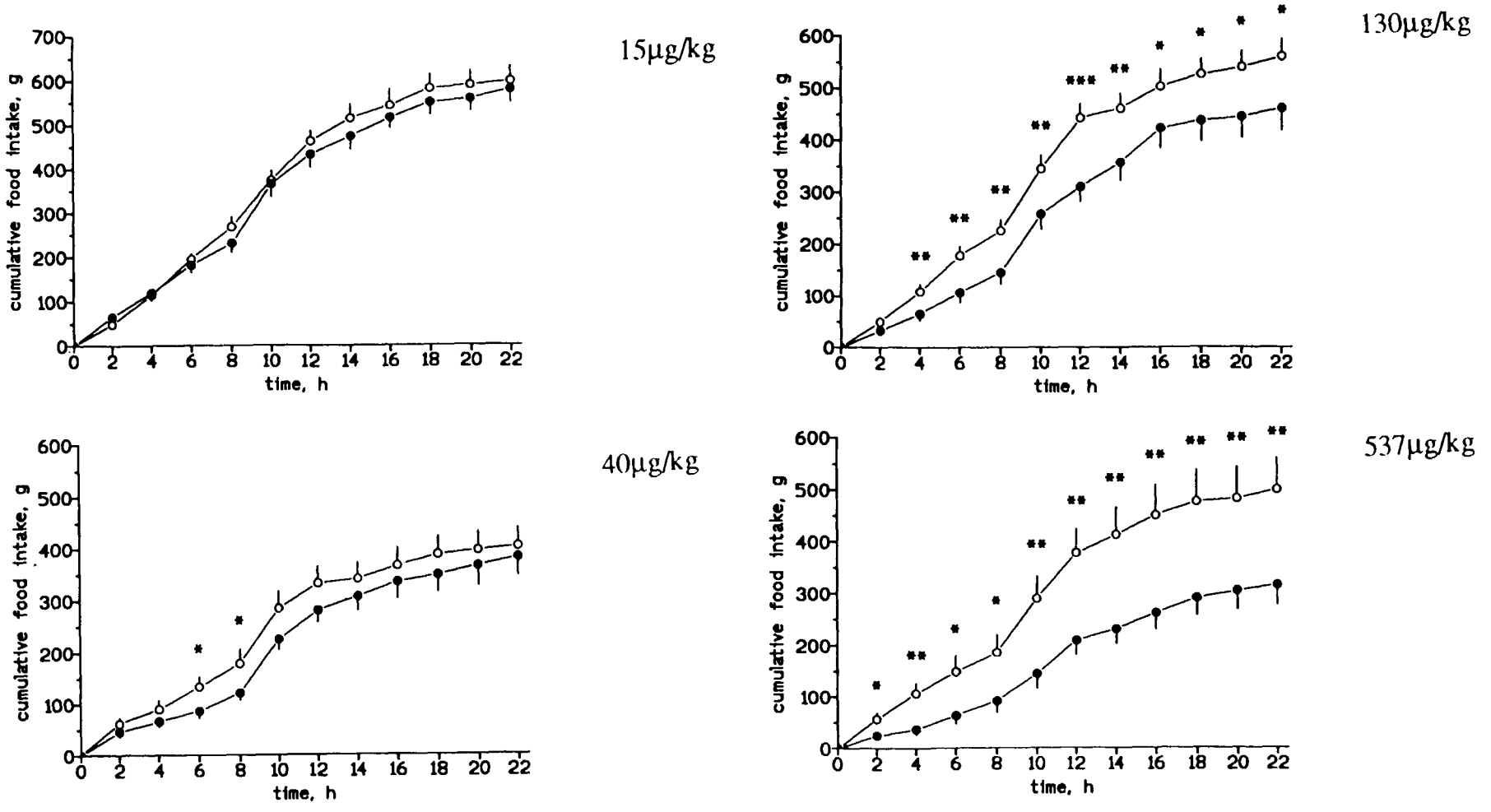


FIG. 1. Dose dependent inhibition of food intake after prazosin (●) compared to controls (○) in pygmy goats. *,**,***Significantly different from control value (*$p < 0.05$; **$p < 0.01$; ***$p < 0.001$).

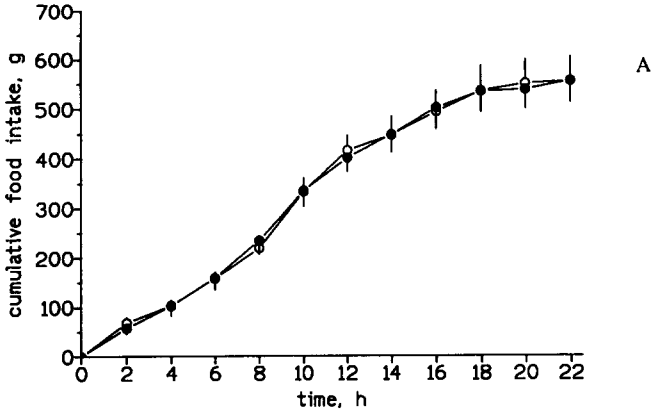
TABLE 1

EATING PARAMETERS IN PYGMY GOATS AFTER PRAZOSIN INJECTION (CONTROL VALUES IN PARENTHESES)

	Prazosin 537 μg/kg		Prazosin 130 μg/kg		Prazosin 40 μg/kg	
Size of first meal (g)	31 ± 5	(60 ± 16)	55 ± 27	(47 ± 10)	36 ± 9	(41 ± 11)
First IMI‡ (min)	181 ± 46*	(64 ± 15)	137 ± 31*	(61 ± 13)	108 ± 43	(63 ± 18)
Meal frequency (22 h)§	10 ± 4	(10 ± 4)	12 ± 1	(12 ± 1)	12 ± 3	(13 ± 2)
Meal size (g) (22 h)§	34 ± 3†	(49 ± 5)	43 ± 4	(51 ± 4)	35 ± 4	(37 ± 3)
Meal duration (min) (22 h)§	28 ± 6	(38 ± 6)	34 ± 5	(35 ± 6)	30 ± 4	(39 ± 15)
IMI‡ (min) (22 h)§	127 ± 20	(93 ± 11)	93 ± 8	(84 ± 9)	99 ± 14	(80 ± 11)

Values are means ± SEM of the individual mean values for the 12 goats.
*Significantly different from control, $p < 0.05$.
†Significantly different from control, $p < 0.001$.
‡IMI = intermeal interval.
§Values calculated over a period of 22 h.

allow unhindered access to food. On test days, food was withdrawn from 0900 to 1100. At 1100 the test substances were injected and the measurement started. Cumulative food intake and meal pattern were recorded during 22 h by the computer. The computer was programmed to recognize when the pattern of food removals fits the preset meal definition and to print out the time of meal taking the size and duration of a meal and the time passed since the end of the preceding meal, i.e., the intermeal interval (IMI). Meals were defined as food removals exceeding 5 g, separated by at least 15 min of nonfeeding (6). Seven experiments were conducted: in Experiments 1, 2, 3, and 4, prazosin (15, 40, 130, 537 μg/kg) or vehicle were injected. In Experiments 5 and 6, prazosin (40 or 537 μg/kg) and propranolol (500 μg/kg) or propranolol alone (500 μg/kg) were injected. In Experiment 7 prazosin (40 μg/kg) and angiotensin II (1 μg/kg) or angiotensin II alone (1 μg/kg) were injected.



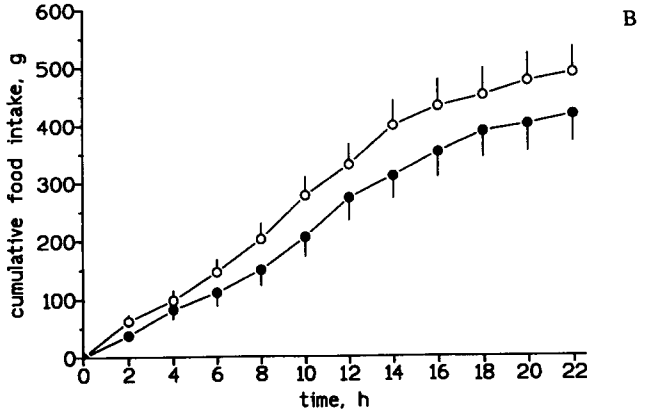


FIG. 2. Blockade of prazosin's (A: 40 μg/kg, B: 537 μg/kg) hypophagic effect by the β-adrenergic antagonist propranolol (500 μg/kg). Propranolol: ○; propranolol + prazosin: ●.

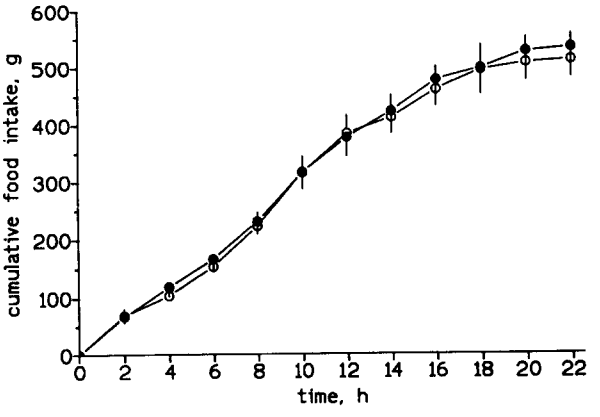


FIG. 3. Blockade of the hypophagic effect of prazosin (40 μg/kg) by angiotensin II (1 μg/kg). Angiotensin II: ○; angiotensin II + prazosin: ●.

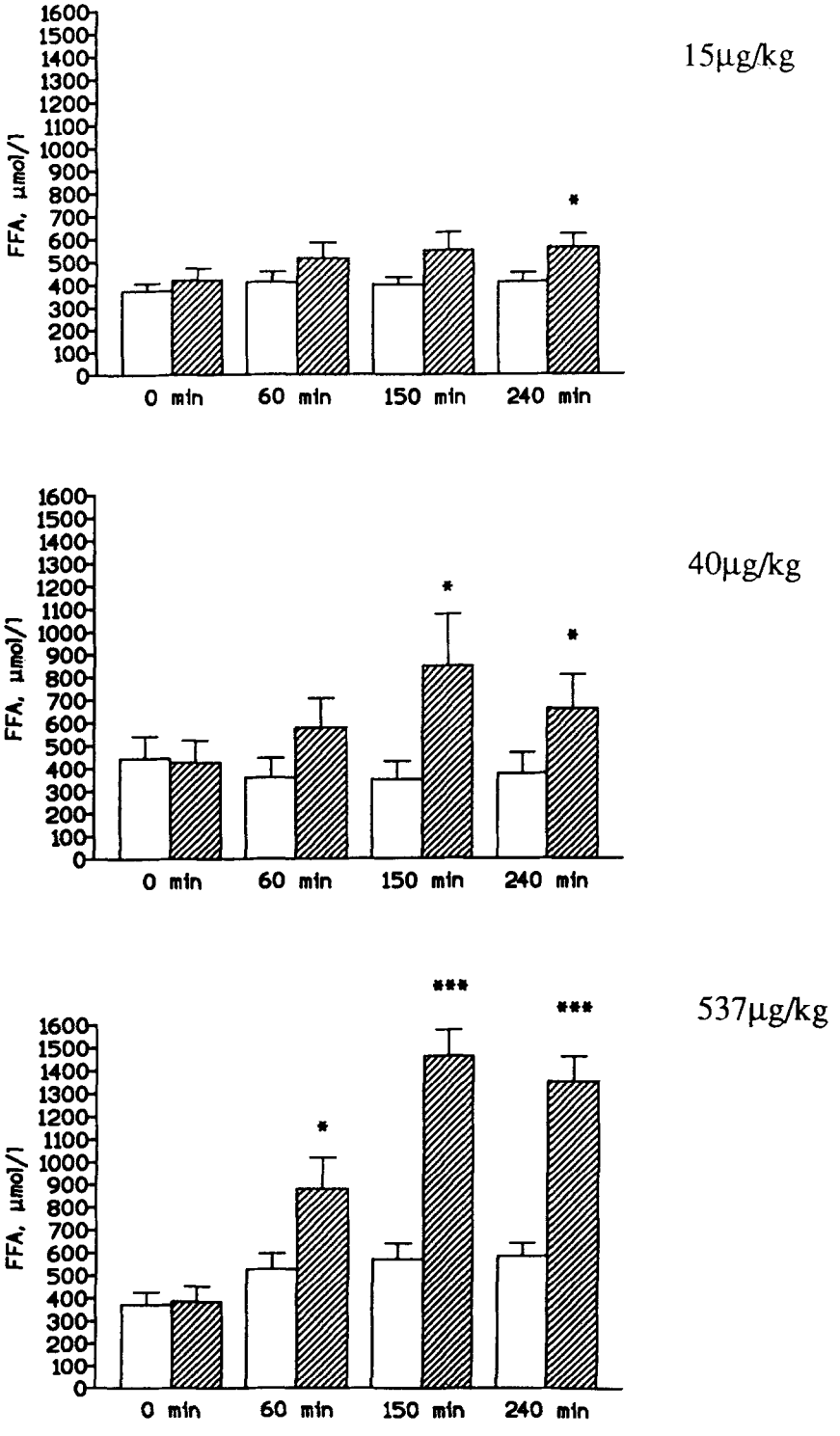


FIG. 4. Dose-dependent elevation of plasma FFA after prazosin injection in pygmy goats. Prazosin: checked bars; control: open bars. *,***Significantly different from control value (*$p < 0.05$; ***$p < 0.001$).

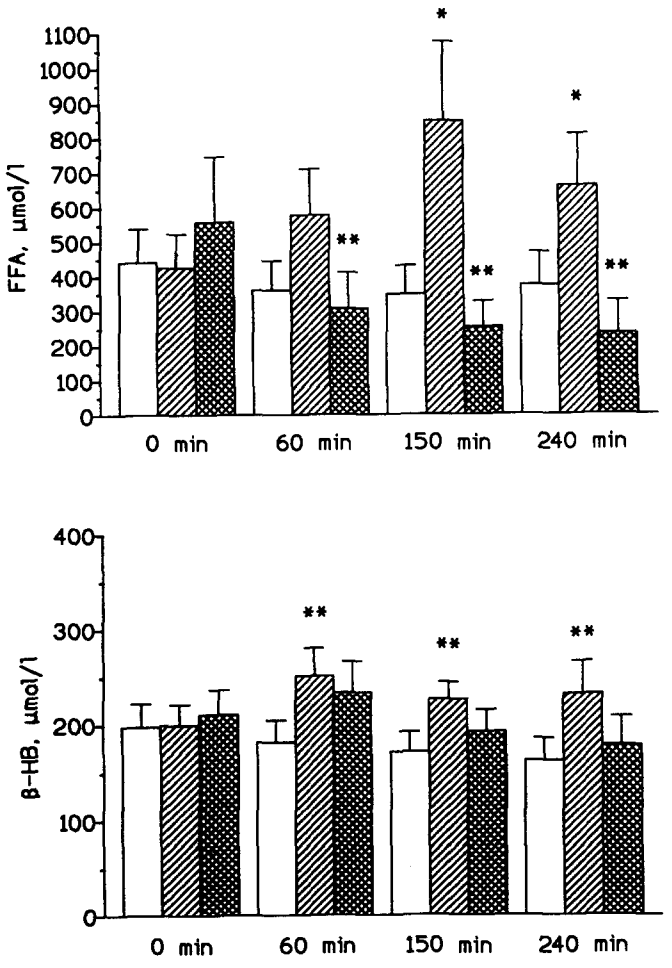


FIG. 5. Blockade of the elevation of plasma FFA and β-HB levels due to prazosin (40 µg/kg) by the β-adrenergic antagonist propranolol (500 µg/kg). Prazosin: checked bars; prazosin + propranolol: crisscross bars; controls: open bars. FFA: *significantly different from control value ($p < 0.05$); **significantly different from prazosin value ($p < 0.01$). β-HB: **significantly different from control value ($p < 0.01$).

Blood Parameters

On test days, feed was withdrawn from 0900 to 1500. At 1100 blood samples were collected by jugular venipuncture from each goat and then the test substances were injected. Further blood samples were collected 60, 150, and 240 min after the injection. Blood samples were collected in EDTA- and Na-fluoride tubes and immediately cooled in ice. Blood plasma was obtained by centrifugation at 4°C and 1086 g. Plasma FFA and β-HB were measured using enzymatic test kits [FFA: NEFA C, Wako Chemicals GmbH, Neuss Germany, β-HB: Sigma Diagnostic Kits 310-A]. Four experiments were conducted: in Experiments 8, 9, and 10, prazosin (14, 40, and 537 µg/kg) or vehicle were injected. In Experiment 11, three groups were formed: prazosin (40 µg/kg) and propranolol (500 µg/kg), prazosin alone (40 µg/kg), or vehicle were injected. Three trials were performed in this case and the data of the three trials were combined. Control injections always consisted of an equivalent volume of a 30% solution of ethanol because prazosin had to be dissolved in 30% ethanol (vol/vol). Injected solutions were freshly prepared on the test day.

The data are presented as means ± SEM. Due to crossover design of the experiments, differences between treatments were statistically evaluated using a two-way analysis of variance (ANOVA) and the Bonferroni post hoc test. p-Values less than 0.05 were considered significant.

Chemicals used

Prazosin HCl, P-7791, Sigma, St. Louis, MO; Propranolol HCl, P-0884, Sigma; Yohimbine HCl, Y-3125, Sigma; Angiotensin II, A-9525, Sigma.

RESULTS

As shown in Fig. 1 the α_1-adrenergic antagonist prazosin produced a significant dose-dependent decrease in food intake in pygmy goats (difference in the anorectic effect of 40 µg and 130 µg/kg prazosin: $p < 0.05$; of 130 µg/kg and 537 µg/kg prazosin: $p < 0.01$. Differences between treatments were evaluated with an ordinary ANOVA and the Bonferroni test). The minimal effective dose was 40 µg/kg. At the highest dose, prazosin (537 µg/kg) caused a nonsignificant decrease of the size of the first meal and a significant prolongation of the first intermeal interval (IMI) (Table 1). At a dose of 130 µg/kg, there was only a prolongation of the first IMI (Table 1). The mean size of meals ingested within 22 h post injection was significantly reduced only at the highest dose, while mean number of meals remained unchanged (Table 1). At the lowest effective dose of prazosin (40 µg/kg) only cumulative food intake was significantly reduced. Propranolol (500 µg/kg) almost completely abolished ($p < 0.01$, compared with Fig. 1) the hypophagic effect of prazosin (Fig. 2). Angiotensin II (1 µg/kg) also abolished ($p < 0.01$, compared with Fig. 1) the hypophagic effect of prazosin (40 µg/kg) (Fig. 3).

Prazosin caused a significant dose-dependent elevation in plasma FFA (Fig. 4). This effect was eliminated by the β-adrenergic antagonist propranolol (500 µg/kg) (Fig. 5). The increase in plasma β-hydroxybutyrate level following prazosin injection (40 µg/kg) seemed to be reduced by propranolol (500 µg/kg) but the effect of propranolol was not significant (Fig. 5).

DISCUSSION

The present results show for the first time a dose-dependent suppressive effect of the α_1-adrenergic antagonist prazosin on cumulative food intake. With regard to feeding pattern, meal size was significantly reduced at the highest dose, whereas intermeal interval was significantly increased at the two highest doses. This reduction in food intake in pygmy goats was accompanied by a dose-dependent elevation of plasma FFA levels. Plasma β-HB reflecting hepatic fatty acid oxidation was also elevated. Because continuous infusion of long chain fatty acids is known to reduce food intake in sheep (17) and an inhibition of fatty acid oxidation produced an increase in food intake in rats (13), the elevation in plasma FFA and β-HB could, in part, be responsible for the reduced food intake after prazosin injection. The concomitant blockade of the elevation of plasma FFA and of the hypophagia induced by prazosin by the β-adrenergic antagonist propranolol is consistent with this hypothesis. The blockade of prazosin's hypophagic effect by propranolol and angiotensin II, in addition, suggests that the hypophagia is related to sympathetic activation induced by hypotension, because both agents produce vasoconstriction (1,7,12).

In the rat, it has been shown that IP injection of catecholamines produce an inhibition of feeding by combined activation of α- and β-adrenergic receptors (4,10,11). Unlike rats, in pygmy goats activation of β-adrenergic receptors alone appears to produce an inhibition of feeding, because the anorexia induced by prazosin was abolished by propranolol.

Because rumen motility and feeding are clearly interdependent (8), it is conceivable that reduced feed intake following prazosin injection is due to reduced rumen motility. However, the minimal dose of prazosin for the inhibition of rumen motility seems to be 200 μg/kg (15), whereas the minimal effective dose for prazosin's anorectic effect was 40 μg/kg (Fig. 1). Moreover, at a dose of 130 μg/kg we did not find a reduction in the frequency of ruminal movements by auscultation.

It is unlikely that prazosin's anorectic effect is due to an effect on the central nervous system because it was demonstrated in various animal species that prazosin does not pass the blood–brain barrier (2,14).

In conclusion, the results obtained suggest that the α_1-adrenergic antagonist prazosin causes reduction of food intake through sympathetic activation. The anorectic effect of prazosin mainly seems to be mediated by activation of β-adrenergic receptors.

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REFERENCES

1. Brezenoff, H. E.; Camilleri, B. The role of angiotensin in the pressor response to propranolol and the hypotensive response to phentolamine. Pharmacol. Res. Commun. 12:539–547; 1980.
2. Dashwood, M. R. Central and peripheral prazosin binding: An in vitro autoradiographic study in the rat. Eur. J. Pharmacol. 86: 51–58; 1982.
3. Forth, W.; Henschler, D.; Rummel, D. Allgemeine und spezielle Pharmakologie und Toxikologie. In: Wissenschaftsverlag, B. I., ed. Zürich. New York: Mannheim; 1983:149.
4. Langhans, W.; Pantel, K.; Scharrer, E. Dissociation of epinephrine's hyperglycemic and anorectic effect. Physiol. Behav. 34: 457–463.
5. Langhans, W.; Pantel, K.; Scharrer, E. Ketone kinetics and D-(−)-3-hydroxybutyrate-induced inhibition of feeding in rats. Physiol. Behav. 34:579–582; 1985.
6. Langhans, W.; Senn, M.; Scharrer, E.; Eggenberger, E. Free-feeding patterns of pygmy goats eating a pelleted diet. J. Anim. Physiol. Anim. Nutr. 59:160–166; 1988.
7. Naden, R. P.; Gant, N. F.; Rosenfeld, C. R. The pressor response to angiotensin II: The roles of peripheral and cardiac responses in pregnant and nonpregnant sheep. Am. J. Obstet. Gynecol. 148:450–457; 1984.
8. Nicholson, T.; Osman, T. E. A. Inhibition of food intake and reticulo-rumen motility of sheep by the alpha-2-adrenoceptor agonist clonidine. J. Vet. Med. A 39:301–312; 1992.
9. Rossi, R.; Scharrer, E. Sympathetic control of plasma levels of free fatty acids and triglycerides in pygmy goats. Small. Rumin. Res. 9:139–147; 1992.
10. Russek, M.; Mogenson, G. J.; Stevenson, J. A. Calorigenic, hyperglycemic and anorexigenic effects of adrenaline and noradrenaline. Physiol. Behav. 2:429–433; 1967.
11. Russek, M.; Vega, C.; Barrera, J.; Soto-Mora, L. M.; Lanzagorta, A.; Racotta, R. Anorexia elicited by different catecholamines in rats. Appetite 9:119–126; 1987.
12. Saeed, M.; Sommer, O.; Holtz, J.; Bassenge, E. α-Adrenoceptor blockade causes β-adrenergic vasodilation by increased catecholamine release due to presynaptic α-blockade. J. Cardiovasc. Pharmacol. 4:44–52; 1982.
13. Scharrer, E.; Langhans, W. Control of food intake by fatty acid oxidation. Am. J. Physiol. 250:R1003–R1006; 1986.
14. Taylor, J. A.; Twomey, T. M.; Schach von Wittenau, M. The metabolic fate of prazosin. Xenobiotica 7:357–364; 1977.
15. Toutain, P. L.; Zingoni, R.; Ruckebusch, Y. Assessment of alpha-2-adrenergic antagonists on the central nervous system using reticular contraction in sheep as a model. J. Pharmacol. Exp. Ther. 223:215–218; 1982.
16. Triedman, J. K.; Cohen, R. J.; Saul, J. P. Mild hypovolemic stress alters autonomic modulation of heart rate. Hypertension 21:236–247; 1993.
17. Vandermeerschen-Doize, F.; Paquay, R. Effects of continuous long-term intravenous infusion of long-chain fatty acids on feeding behaviour and blood components of adult sheep. Appetite 5: 137–146; 1984.