Effects of Histamine H1 Receptors on the Feeding and Drinking Patterns in Pygmy Goats

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ABSTRACT

The goal of these experiments was to determine which histamine receptors are involved in the relationship between drinking and feeding in ruminants. To this end, the effects of the histamine receptor antagonists dexbrompheniramine (H1 receptor antagonist), cimetidine (H2 receptor antagonist), and terfenadine (H1 receptor antagonist) on feeding and drinking patterns of pygmy goats were investigated. Two experiments using dexbrompheniramine [1 and 2 mg/kg of body weight (BW)0.75], two experiments using cimetidine (16 and 32 mg/kg of BW0.75), and two experiments using terfenadine (5 and 11.5 mg/kg of BW0.75) were performed to assess the type and location (periphery or central nervous system) of the histamine receptors involved in the mediation of prandial drinking by pygmy goats. The H1 receptor antagonists dexbrompheniramine (2 mg/kg of BW0.75) and terfenadine (11.5 mg/kg of BW0.75) significantly reduced water intake, but cumulative feed intake did not change. Consequently, the ratio of water intake to feed intake decreased. In contrast, the H2 receptor antagonist did not affect either water or feed intake. Dexbrompheniramine at 2 mg/kg of BW0.75 and terfenadine at 11.5 mg/kg of BW0.75 also decreased draft frequency and decreased the water intake associated with meals. Results showed that blockage of peripheral H1 histamine receptors attenuates the association between water and feed intake in pygmy goats. Therefore, the stimulating effect of feed intake on water intake appears to depend on activation of peripheral H1 histamine receptors.

(Key words: feeding and drinking patterns, drinking, histamine H1 receptor, pygmy goats)

Abbreviation key: CMT = cimetidine, DXB = dexbrompheniramine, TFN = terfenadine.

INTRODUCTION

Water intake associated with feeding dominates the spontaneous drinking behavior of monogastric species (2, 5, 10). Recent studies (6, 16, 19, 20, 21) have shown that this pattern also applies to ruminants. As has been shown in different studies, water intake induced by eating appears to be regulated by various mechanisms including the release of angiotensin (15) and histamine (11, 14). Histamine has been characterized as one of the most important factors in prandial drinking by the rat (11, 14) and the ruminant (19). In the work of Rossi et al. (19), the combined injection of histamine H1 and H2 receptor antagonists decreased prandial drinking by pygmy goats without affecting feed intake.

The goal of the present experiments was to assess the type and location of the histamine receptors involved in the mediation of prandial drinking by pygmy goats. To this end, we injected intraperitoneally the H1 receptor antagonist dexbrompheniramine (DXB) and the H2 receptor antagonist cimetidine (CMT) separately at two different doses and recorded the eating and drinking patterns of the goats. To investigate the role of peripheral histamine receptors in prandial drinking by pygmy goats, we further tested the effect of terfenadine (TFN) on feeding and drinking patterns. Terfenadine is a specific H1 receptor antagonist that has, in contrast to DXB, a limited capacity to penetrate the blood-brain barrier (4, 22).

MATERIALS AND METHODS

Goats and Maintenance

Eight or 12 adult female nonlactating and nonpregnant African pygmy goats (1.5 to 10 yr of age) that weighed 20 to 42 kg were used. The goats were individually housed on wood shavings in pens (1.25 × 1.35 m) located in a room with an artificial cycle of light and darkness. Lights were on from 0900 to 2100 h. The temperature was held constant at 21 ± 2°C. Goats were fed for ad libitum intake a complete

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pelleted diet (86% DM) [Hypona 888; Volg Winterthur, Switzerland; (17)]. Water was always available. Goats were fed from spill-resistant feed containers that were fixed on scales [Mettler PM6; Mettler-Toledo, Greifensee, Switzerland; (17)]. A similar system was used to record water intake (20). Scales with feed or water containers were protected by a wooden box. The feed containers were accessible from the side, and the water containers were accessible from the top. Access areas were big enough to allow unhindered intake of feed and water.

Drugs

The H$_1$ receptor antagonist DXB (1 or 2 mg/kg of BW$^{0.75}$; 0.31 ml/kg) was dissolved in 0.9% saline, and the H$_2$ receptor antagonist CMT (16 or 32 mg/kg of BW$^{0.75}$; 0.31 ml/kg) was first dissolved in acidified (HCl) water and buffered with NaOH to reach physiological pH and osmolality. The H$_1$ receptor antagonist TFN (5 or 11.5 mg/kg of BW$^{0.75}$; 0.15 ml/kg) was dissolved in ethanol. All solutions were freshly prepared on the test day. Control injections consisted of an equivalent volume of the respective vehicle. All compounds were purchased from Sigma Chemical Co. (St. Louis, MO).

The experiments were performed in a crossover design. After 2 h of feed and water deprivation (0900 to 1100 h), the goats were intraperitoneally injected in the paralumbal fossa. Feed and water intakes were recorded for the following 24 h. After 2 d, the experiment was repeated, and the goats were injected in counterbalanced order. In this way, each goat served as its own control. Because of the limited number of goats available (n = 8), the experiments with DXB and CMT were repeated twice, and the data were pooled. All values were computed separately for each goat and for each experiment to provide two treatment values and two control values, which were used to obtain the mean values for each goat. For the two experiments with TFN, 12 goats were included. Therefore, these two experiments were performed in a simple crossover design, and the data were not pooled.

Recording of the Data

The actual weight of the water and feed containers was automatically checked and recorded each minute by a personal computer (AX 386; Epson, Wädenswil, Switzerland). Meals and drafts, respectively, were defined as feed or water removals exceeding 5 g that were separated by at least 15 min of nonfeeding or nondrinking (18, 20). Parameters recorded were cumulative water and feed intakes; meal and draft patterns, including meal and draft size and duration; meal and draft intervals; and meal and draft frequencies. Water intake that occurred 15 min before feeding and 15 min after feeding was considered to be
associated with feeding (19). All parameters were computed separately for each goat. The values are presented as means (±SEM). Differences between treatments were statistically evaluated using the multivariate analysis of variance for repeated measures first and then the paired t test, because each goat served as its own control. Significance was declared at $P < 0.05$.

Figure 2. Effect of the $H_1$ receptor antagonist dexampheniramine at 1 mg/kg of BW$^{0.75}$ (closed symbols) on cumulative water and feed intakes. Open symbols represent controls.

Figure 3. Effect of the $H_2$ receptor antagonist cimetidine at 32 mg/kg of BW$^{0.75}$ (closed symbols) on cumulative water and feed intakes. Open symbols represent controls.
RESULTS

Figure 1 shows that injection of the H1 histamine receptor antagonist DXB at 2 mg/kg of BW\textsuperscript{0.75} decreased water intake for several hours after injection ($P = 0.004$; multivariate repeated measures analysis); however, feed intake did not change (Figure 1). Consequently, the ratio of water intake to feed intake decreased for 6 h after injection [e.g., 3-h value: 1.30 ± 0.34 vs. 0.16 ± 0.05 (control vs. DXB); $P < 0.01$]. A smaller dose of DXB (1 mg/kg of BW\textsuperscript{0.75})
had no significant effect on water intake (Figure 2). The ratio of water intake to feed intake was decreased only at 5 h postinjection [1.30 ± 0.30 vs. 0.60 ± 0.16 (control vs. DXB); \( P < 0.05 \)]. Injection of the H\(_2\) histamine receptor antagonist CMT [16 mg/kg (results not shown) and 32 mg/kg of BW\(^{0.75}\)] affected neither water nor feed intake (Figure 3). At 5 mg/kg of BW\(^{0.75}\), the H\(_1\) histamine receptor antagonist TFN which acts mainly on the periphery (2), tended (\( P = 0.14 \)) to decrease water intake but did not affect feed intake (Figure 4). A smaller dose of TFN (2.2 mg/kg of BW\(^{0.75}\)) did not influence feed and water intake (results not shown). The highest dose of TFN tested (11.5 mg/kg of BW\(^{0.75}\)) reduced water intake (\( P = 0.037 \); multivariate repeated measures analysis), but feed intake did not change (Figure 5). The ratio of water intake to feed intake was decreased after 3 h [1.51 ± 0.43 vs. 0.61 ± 0.27 (control vs. TFN); \( P < 0.05 \)] and 4 h [1.27 ± 0.31 vs. 0.61 ± 0.21 (control vs. TFN); \( P < 0.05 \)].

The eating and drinking patterns in the experiments using DXB at 2 mg/kg of BW\(^{0.75}\) and TFN at 11.5 mg/kg of BW\(^{0.75}\) are shown in Figure 6. Dextromethorphan and TFN significantly decreased draft frequency but not draft size; meal pattern did not change. In addition, DXB and TFN decreased the percentage of drafts associated with meals, but this effect was only significant for goats injected with TFN (Table 1). Cumulative water intake associated with meals was significantly reduced by DXB and TFN (Table 1). Terfenadine also significantly decreased the percentage of meals associated with drafts. For DXB, this effect was not significant (Table 1).

Figure 6. Eating and drinking patterns over a 6-h period after injection of the H\(_1\) receptor antagonists dextromethorphan at 2 mg/kg of BW\(^{0.75}\) (A) or terfenadine at 11.5 mg/kg of BW\(^{0.75}\) (B). Open bars = controls; closed bars = histamine receptor antagonists. Drafts and meals, respectively, were defined as feed and water removals exceeding 5 g that were separated by at least 15 min of nonfeeding or nondrinking. Asterisks represent differences from control values: \(* P < 0.05; \ *** P < 0.001.\)
DISCUSSION

The present experiments attempted to assess the type and location of the histamine receptor responsible for drinking patterns associated with feed intake in pygmy goats. The data presented show, for the first time in a ruminant species, that drinking patterns and the temporal relationship between feed and water intake depend on activation of H1 histamine receptors and that these receptors appear to be located in the periphery.

The blockage of H1 histamine receptors by DXB and TFN caused a partial disruption of the association between feeding and drinking. Indeed, although feed intake was not affected by these compounds, cumulative water intake and the drinking patterns associated with feeding decreased. Therefore, the ratio of water intake to feed intake decreased when H1 receptors were blocked. A decrease in drinking frequency was noted after blockage of H1 histamine receptors by DXB and TFN. Both DXB and TFN also significantly reduced the drinking patterns associated with feeding, but water intake that was not linked to meals was not affected. Therefore, results demonstrate that the H1 histamine receptors are involved in the mechanisms that regulate drinking patterns associated with eating.

The TFN, which acted mainly in the periphery in different animal models (22), disrupted the drinking pattern that is elicited by eating by significantly decreasing the water intake associated with meals and the percentage of meals associated with drafts. This result supports the idea that the drinking patterns associated with eating are mediated by peripheral H1 receptors, which is in agreement with results obtained in rats (14).

The blockage of histamine H2 receptors by CMT had no effect on water or feed intake. Even the highest dose of CMT used, which effectively blocks gastric acid secretion related to feeding in rats (13), had no influence on the water intake of pygmy goats. This observation suggests that the drinking patterns associated with feeding are not mediated by H2 histamine receptors in pygmy goats. This result appears to differ from findings in rats (12, 14) in that the H2 receptor antagonist CMT had some suppressive effect on the drinking pattern elicited by eating in rats that were deprived of food for 24 h (12). Therefore, whether CMT affects the drinking patterns associated with eating under similar conditions in pygmy goats remains to be investigated. Findings for rats have shown that recently discovered H3 histamine receptors appear to be important also in the induction of water intake by eating (12). Therefore, the influence of the H3 receptor on water intake by pygmy goats also remains to be investigated.

The chosen doses of DXB, CMT, and TFN appeared to be of physiological relevance because water intake, but not feed intake, was affected. Larger doses of DXB and CMT have been demonstrated to suppress food and water intake by rats nonspecifically (11). The doses of histamine receptor antagonists were carefully chosen based on behavioral and pharmacological evidence of specificity and effectiveness in animal models and in humans (1, 4, 7, 13, 14). Furthermore, similar doses were also shown to suppress the drinking behavior of rats (12). In in vitro receptor binding studies (22, 23), TFN was shown to possess specific H1 antihistamine activity and to bind preferentially to peripheral rather than to central H1 histamine receptors under in vivo conditions in guinea pigs and

<table>
<thead>
<tr>
<th></th>
<th>DXB Control</th>
<th>2 mg/kg of BW0.75</th>
<th>TFN Control</th>
<th>11.5 mg/kg BW0.75</th>
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<tr>
<td></td>
<td>X SEM</td>
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<tr>
<td>Drafts\a associated with meals, %</td>
<td>73\a 11</td>
<td>33\b 13</td>
<td>58 11</td>
<td>33 12</td>
</tr>
<tr>
<td>Meals associated with drafts, %</td>
<td>27 6</td>
<td>11 5</td>
<td>39\b 9</td>
<td>12\c 5</td>
</tr>
<tr>
<td>Cumulative water intake associated with meals, ml</td>
<td>177\c 41</td>
<td>64\d 32</td>
<td>150\b 48</td>
<td>56\b 39</td>
</tr>
<tr>
<td>Cumulative water intake not associated with meals, ml</td>
<td>26 14</td>
<td>10 9</td>
<td>44 18</td>
<td>49 25</td>
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\a,b\ Means within rows differ (P < 0.01).
\c,d\ Means within rows differ (P < 0.05).
\1\ Data represent mean individual values of feed and water intake for 8 (DXB) or 12 (TFN) goats during 6 h postinjection.
\2\ Meals and drafts, respectively, were defined as feed and water removals exceeding 5 g that were separated by at least 15 min of nonfeeding or nondrinking.
mice because of a lack of significant TFN penetration into the central nervous system (4). Unfortunately, pertinent findings for TFN have not been published for ruminants. The doses of the selective H2 receptor antagonist CMT used in the present study were shown to antagonize gastric acid secretion in monogastric (1) and ruminant species (3, 8) and to suppress, in part, the drinking patterns elicited by eating in the rat (12). Further, in sheep, CMT has been shown to act as a selective H2 receptor antagonist when injected at doses similar to those used here (9).

The present experiments showed, for the first time, that the drinking patterns associated with feeding seem to be controlled by the activation of peripheral H1 histamine receptors in ruminant species. To characterize better the exact location in the periphery and the action of this receptor type in pygmy goats, further studies must be undertaken, and special attention must be paid to mechanisms involved in H1 histamine receptor signal transmission.

**CONCLUSIONS**

The drinking patterns associated with feeding and cumulative water intake by pygmy goats were reduced by antagonism of H1 histamine receptors but not by antagonism of the H2 histamine receptors. Because the H1 receptor antagonist TFN, which mainly acts in the periphery, was able to decrease cumulative water intake and water intake associated with feeding, it was assumed that the drinking patterns elicited by eating were mediated by peripheral H1 receptors of histamine.

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**REFERENCES**


