Suppression of food intake is linked to enteric inflammation in nematode-infected rats

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Faro, Constance J., Roger D. Reidelberger, and Jeffrey M. Palmer. Suppression of food intake is linked to enteric inflammation in nematode-infected rats. Am. J. Physiol. Regulatory Integrative Comp. Physiol. 278: R118–R124, 2000.—Our aim was to investigate the cause-effect relationship between intestinal inflammation induced by infection with enteric stages of Trichinella spiralis and decreased host food intake. A suppression of food intake in T. spiralis-infected rats occurred within the first 24 h postinfection (PI) and was maximized by day 6 PI. Food intake, cumulated over an 8-day PI period, decreased by 59% compared with uninfected animals. The anti-inflammatory glucocorticoid betamethasone 21-phosphate was orally administered to rats in their drinking water to suppress T. spiralis-induced jejunal inflammation. When treated with a low dose of glucocorticoid (5.2 µg/ml), food intake in infected rats was still significantly reduced, but only by 21% compared with glucocorticoid-treated, uninfected rats. At the highest glucocorticoid dose (10.4 µg/ml), food intake was also significantly blunted by oral glucocorticoid treatment. Our results suggest that suppressed host food intake during enteric T. spiralis infection is directly linked to intestinal inflammation.

feeding behavior; Trichinella spiralis; betamethasone 21-phosphate; anti-inflammatory glucocorticoid; mucosal inflammation; small intestine; myeloperoxidase activity

ENTERIC NEMATODE INFECTIONS cause a wide range of gastrointestinal disturbances that can lead to a significant loss in body weight. This loss in body weight has been attributed to nutrient malabsorption, altered metabolism, and decreased food intake (8, 12, 25, 38). Reduced food intake appears to be the primary cause for body weight loss in Trichinella spiralis-infected rats (8). The mechanisms underlying these changes in feeding behavior remain poorly understood.

Several different types of gastrointestinal events are well known to decrease food intake. These include decreased gastric emptying, increased intestinal motility, increased cholecystokinin release, and increased intestinal nutrient absorption (23, 35, 41). Enteric infections with the nematodes Nippostrongylus brasiliensis and T. spiralis produce a range of gastrointestinal disturbances that include increased intestinal motility and propulsive behavior (1, 7, 21, 33), increased mucosal secretion of water and electrolytes (9), decreased activities of enterocyte brush-border enzymes (11, 22), altered responses to brain-gut peptides, including cholecystokinin, a satiety factor (14, 15, 32, 38), and intestinal inflammation (8, 10, 11, 12, 25, 38). Interleukin (IL)-1β and tumor necrosis factor-α (TNF-α) are mediators of nematode-induced intestinal inflammation (26) and are known suppressors of food intake in rats (6, 19, 30, 37, 42). It remains to be determined whether the reduced food intake associated with enteric nematode infection is caused by inflammatory factors or other nematode-induced gastrointestinal events that occur independently of enteric inflammation.

Our aim was to test the hypothesis that reduced food intake during T. spiralis infection in rats is mediated by inflammation-dependent factors. Our approach was to determine whether oral administration of the anti-inflammatory glucocorticoid betamethasone 21-phosphate (i.e., betamethasone) prevents or attenuates the T. spiralis-induced jejunal inflammation and suppression of food intake. Anti-inflammatory actions of glucocorticoids are well known and include suppression of endogenous proinflammatory factors produced by macrophages, monocytes, myeloid granulocytic cells, and lymphocytes (5, 19).

METHODS AND MATERIALS

Animals

Adult male Sprague-Dawley rats (200–225 g; Charles River Laboratories, Madison, WI) were provided care according to guidelines established by the Animal Research Committee of Creighton University. Rats were housed individually in stainless steel, wire mesh-bottomed cages in an isolated room at 24°C with a 12:12-h photoperiod (lights on at 0500). All animals were provided rat chow (Purina no. 5001) and water ad libitum during the initial acclimation period.

Induction of Nematode Infection

 Infective muscle-stage larvae were harvested from the skeletal muscle of T. spiralis-infected CF-1 mice (Charles River Laboratories) as previously described (11, 21). Rats were fasted overnight and anesthetized with ketamine (80 mg/kg body wt im) and xylazine (13 mg/kg body wt im). Each rat received by gavage either an inoculum of 8,000 larvae suspended in 0.2 ml 0.15 M NaCl (saline) or the saline vehicle alone.
Experimental Procedures

Effects of oral betamethasone in uninfected rats. Glucocorticoids are nonspecific anti-inflammatory agents that exert wide-ranging effects on immune system function (5). Unfortunately, glucocorticoids like dexamethasone and its stereoisomer betamethasone, acting primarily through the type II glucocorticoid receptor, possess many undesirable systemic effects that include feeding suppression and weight loss in rodents (17, 18, 36). The use of a nonsteroidal anti-inflammatory drug was not considered because of the well-known toxic effects of this class of compounds directly on the small intestine, especially the epithelium (3, 40). We determined in a pilot study that systemic administration of anti-inflammatory doses of betamethasone by osmotic minipump to rats produced a significant suppression of food intake. We therefore reasoned that oral administration of betamethasone may permit use of smaller doses that provide effective anti-inflammatory therapy to the intestine, yet induce less of a systemic effect on metabolism and feeding after enteric absorption and dilution of the glucocorticoid into the body water volume. Thus the purpose of this experiment was to identify an oral betamethasone dose that would exert efficacious anti-inflammatory activity in the intestine while minimizing systemic effects on food and water intake.

Rats were adapted to a wet mash diet composed of ground rat chow (Purina no. 5001), sucrose, and evaporated milk mixed in a proportion of 500 g, 400 g, and 354 ml, respectively. This diet significantly reduces spillage during feeding. Fresh food was provided each day; daily intake was determined by measuring changes in food container weight to the nearest milligram during the first 3 days of treatment (Fig. 1A). Thus our subsequent experiment examining the effects of oral betamethasone in T. spiralis-infected rats included a 3-day steroid pretreatment period before the inoculation with worms. Figure 1B shows that glucocorticoid treatment had a highly significant dose-dependent effect on cumulative food intake measured over the last 4 days (i.e., days 10–13) of the 8-day betamethasone treatment period [F(4,24) = 6.8, P < 0.001]. Compared with untreated control rats, the minimal effective dose (6.25 µg/ml) decreased cumulative food intake by 35%, whereas higher doses decreased intake by 38% (12.5 µg/ml) and 47% (25.0 µg/ml).

Effects of oral betamethasone in T. spiralis-infected rats. Two doses of betamethasone, 5.2 and 10.4 µg/ml, were used to determine whether oral administration of betamethasone prevents or attenuates T. spiralis-induced jejunal inflammation and suppression of food intake. These doses were chosen because they bracketed the minimum concentration (6.25 µg/ml) of the glucocorticoid that produced a complete block of basal intestinal inflammation in uninfected rats in the preceding experiment. Rats were age- and weight-matched and were randomly divided into the following six groups (n = 8/group): group 1, uninfected; group 2, T. spiralis-infected; group 3, betamethasone-treated (5.2 µg/ml); group 4, betamethasone-treated (10.4 µg/ml); group 5, T. spiralis-infected, treated with betamethasone (5.2 µg/ml); and group 6, T. spiralis-infected, treated with betamethasone (10.4 µg/ml). Betamethasone was added to the drinking water as described above. After 3 days of betamethasone treatment, rats were orally inoculated with either T. spiralis or saline vehicle, and daily food and water intake were measured for an additional 8 days. Body weights were measured at the beginning and end of the experimental period. Segments of jejunum were excised for assay of MPO on the 8th day postinfection (PI).

Statistical Analyses

All data are presented as group means ± SE. The number of animals (n) is indicated for all data. In the first experiment, the effects of the different betamethasone doses on 24-h food and water intake, cumulated food and water intake over 4 days (treatment days 10–13), jejunal MPO, and body weights were evaluated individually using a single-factor repeated-measures ANOVA. In the second experiment, a two-factor repeated-measures ANOVA was used to evaluate the main effects and interaction of betamethasone treatment and T. spiralis infection on 24-h food and water intake, cumulated food intake over the first 8 days after worm inoculation (days 1–8 PI), jejunal MPO, and body weight. Each rat received one of three different betamethasone treatments (0, 5.2, or 10.4 µg/ml) and one of two different T. spiralis doses (0 or 8,000 infective larvae). Planned comparisons of treatment means were evaluated by direct contrasts of means using the software SYSTAT. A probability level of P ≤ 0.05 was considered significant.

RESULTS

Effects of Oral Betamethasone in Uninfected Rats

Food intake. Betamethasone produced a sustained, dose-dependent reduction in food intake that began with a large, transient decrease in intake during the first 3 days of treatment (Fig. 1A). Cumulative food intake measured over the last 4 days (i.e., days 10–13) of the 8-day betamethasone treatment period [F(4,24) = 6.8, P < 0.001]. Compared with untreated control rats, the minimal effective dose (6.25 µg/ml) decreased cumulative food intake by 35%, whereas higher doses decreased intake by 38% (12.5 µg/ml) and 47% (25.0 µg/ml).

Water intake. There was no significant effect of oral betamethasone dose on cumulative water intake over days 7–9 [F(4,22) = 2.0, P > 0.05] or days 10–13 [F(4,20) = 2.5, P > 0.05]. Cumulative water intake measured over the last 4 days (i.e., days 10–13) of the 8-day betamethasone treatment period [F(4,24) = 6.8, P < 0.001]. Compared with untreated control rats, the minimal effective dose (6.25 µg/ml) decreased cumulative food intake by 35%, whereas higher doses decreased intake by 38% (12.5 µg/ml) and 47% (25.0 µg/ml).

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FOOD INTAKE DURING ENTERIC INFLAMMATION IN PARASITISM

Figure 1. Effect of oral betamethasone on daily food intake and cumulative food intake in uninfected rats. A: food intake was measured repeatedly at 24-h intervals; betamethasone treatment was initiated on day 5. B: food intake was cumulated over a 4-day period (days 10–13 in A). Values are means ± SE. Number of animals is indicated in parentheses. Treatment groups compared vs. untreated control (0 µg/ml): *P ≤ 0.05; **P ≤ 0.01; and ***P ≤ 0.001.

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Body weight. Untreated rats gained a significant amount of body weight (~10%) over the 13-day course of the experiment. In contrast, betamethasone decreased body weight gain in a dose-dependent manner [F(4,24) = 18.9, P < 0.001]. Changes in body weight (in g; + indicates gain and − indicates loss) were +31.5 ± 3.5 (n = 6), −0.65 ± 5.4 (n = 6), −65.7 ± 6.0 (n = 6), −85.3 ± 6.6 (n = 6), and −91.2 ± 7.5 (n = 5) for the 0, 0.625, 6.25, 12.5, and 25 µg/ml doses, respectively. Compared with untreated control rats, the minimal effective betamethasone dose (6.25 µg/ml) decreased body weight by 22%, whereas the highest dose administered (25 µg/ml) decreased body weight by 31%.

MPO activity. Betamethasone decreased basal jejunal MPO levels in a dose-dependent manner [F(4,24) = 62.8, P < 0.001 (Fig. 2)]. Compared with untreated control rats, the lowest betamethasone dose (0.625 µg/ml) decreased basal MPO by ~60%, whereas the higher doses decreased basal MPO by >95%.

Effects of Oral Betamethasone on T. spiralis Infection in Rats

Food intake. Figure 3 demonstrates the suppression of food intake in T. spiralis-infected rats that occurred within the first 24 h PI and appeared to be maximal by day 6 PI (day 14 in Fig. 3A). Food intake by nematode-infected rats, cumulated over days 1–8 PI (days 9–16 in Fig. 3A), decreased by 59% compared with uninfected counterparts (Fig. 3B).

Figure 3 also shows the effect of oral treatment with low-dose betamethasone (5.2 µg/ml) on daily food intake (Fig. 3A) and 8-day cumulated food intake (Fig. 3B) in uninfected and T. spiralis-infected rats. Repeated-measures ANOVA demonstrated highly significant main effects of betamethasone treatment [F(1,38) = 18, P < 0.001] and T. spiralis infection [F(1,38) = 112, P < 0.001] on cumulative intake and a significant interaction between betamethasone treatment and T. spiralis infection [F(1,38) = 24, P < 0.01]. The significant interaction indicates that glucocorticoid treatment reversed the nematode-induced suppression of feeding (Fig. 3B). This reversal was not complete because cumulative intake in the infected, betamethasone-treated rats was significantly less than that in the uninfected, betamethasone-treated rats. Thus when treated with low-dose oral betamethasone, food intake in T. spiralis-infected rats was still significantly reduced, but only by 21% compared with uninfected rats also treated with low-dose betamethasone.

Figure 4 shows the effect of oral treatment with high-dose betamethasone (10.4 µg/ml) on daily food intake (Fig. 4A) and 8-day cumulated food intake (Fig. 4B) in uninfected and T. spiralis-infected rats. Repeated-measures ANOVA demonstrated highly significant main effects of betamethasone treatment [F(1,38) = 30.98, P < 0.001] and T. spiralis infection [F(1,38) = 112.25, P < 0.001] on cumulative intake and a significant
interaction between betamethasone treatment and T. spiralis infection \([F(1, 38) = 23.97, P < 0.01]\). The significant interaction indicates that oral glucocorticoid treatment reversed the nematode-induced suppression of feeding (Fig. 4B). This reversal appeared to be complete because cumulative intake in the infected, betamethasone-treated rats was not significantly different from that in the uninfected, betamethasone-treated rats.

**Water intake.** Cumulative water intake measured over the 8-day period postinoculation with worms or vehicle did not differ significantly among treatment groups. Intakes (in ml) were 202.7 ± 32.7 (n = 7), 209.0 ± 14.8 (n = 8), 186.8 ± 18.6 (n = 8), 201.9 ± 21.1 (n = 7), 224.0 ± 27.6 (n = 6), and 231.7 ± 17.2 (n = 8) for uninfected, T. spiralis-infected, low-dose betamethasone-treated (5.2 µg/ml), high-dose betamethasone-treated (10.4 µg/ml), T. spiralis-infected treated with low-dose betamethasone (5.2 µg/ml), and T. spiralis-infected treated with high-dose betamethasone (10.4 µg/ml), respectively. Repeated-measures ANOVA demonstrated no significant main effect of either betamethasone \([F(2, 38) = 0.08, P > 0.05]\) or T. spiralis infection \([F(1, 38) = 0.39, P > 0.05]\) on water intake. There also was no significant interaction between betamethasone dose and T. spiralis infection \([F(2, 38) = 1.11, P > 0.05]\). Thus water intake was relatively constant and equivalent in both uninfected and infected animals regardless of exposure or nonexposure to glucocorticoid in their drinking water.

**Body weight.** Changes in body weight (in g; + indicates gain and − indicates loss) across the experimental period were +47.6 ± 3.4 (n = 7), −41.0 ± 7.9 (n = 8), −34.6 ± 10.2 (n = 8), −50.6 ± 7.3 (n = 7), −64.6 ± 8.4 (n = 6), and −72.3 ± 6.2 (n = 8) for uninfected, T. spiralis-infected, low-dose betamethasone-treated (5.2 µg/ml), high-dose betamethasone-treated (10.4 µg/ml), T. spiralis-infected treated with low-dose betamethasone (5.2 µg/ml), and T. spiralis-infected treated with high-dose betamethasone (10.4 µg/ml), respectively. Repeated-measures ANOVA demonstrated highly significant main effects of steroid treatment \([F(2, 38) = 106.8, P < 0.001]\), T. spiralis infection \([F(1, 38) = 15.9, P < 0.001]\), and time of weight measurement \([P < 0.001]\) and significant interaction between betamethasone treatment, nematode infection, and time of weight measurement \([F(2, 38) = 17.0, P < 0.001]\) on body weight. In contrast to the weight gain observed in the untreated, uninfected rats, rats receiving either low- or high-dose betamethasone showed a significant decrease in body weight compared to the untreated, uninfected rats. This decrease was more pronounced in the high-dose group and persisted throughout the entire experimental period.
betamethasone alone experienced significant loss of body weight. Infection alone also caused a significant weight loss. However, the body weight losses in infected rats treated with oral glucocorticoid were not different from those in rats treated with betamethasone alone [5.2 µg/ml: F(1, 38) = 2.23, P > 0.05; 10.4 µg/ml: F(1, 38) = 0.47, P > 0.05]. Thus the oral betamethasone treatments appeared to completely reverse the nematode-induced loss in body weight.

MPO activity. The effects of oral betamethasone treatment at both doses on MPO in extracts of jejunum obtained on day 8 PI from uninfected and T. spiralis-infected rats are shown in Fig. 5. Repeated-measures ANOVA demonstrated significant main effects of betamethasone [F(2, 38) = 88.38, P < 0.001] and T. spiralis infection [F(1, 38) = 6.27, P < 0.05] but no significant interaction [F(2, 38) = 1.31, P > 0.05]. Nematode infection significantly increased MPO, and both doses of betamethasone significantly decreased MPO in infected and uninfected animals. These findings were corroborated by histological examination of jejunal tissues (data not shown). Oral glucocorticoid treatment at either dose appeared to significantly suppress the appearance and number of infiltrating inflammatory myeloid cells in cross sections of the inflamed jejunum from T. spiralis-infected rats.

**DISCUSSION**

The aim of the present study was to test the hypothesis that reduced food intake during the enteric phase of T. spiralis infection in rats is mediated by inflammation-dependent factors. Our approach was to determine whether oral administration of the anti-inflammatory glucocorticoid betamethasone prevents or attenuates the T. spiralis-induced jejunal inflammation and suppression of food intake. Our results showed that betamethasone significantly reversed nematode-induced inhibition of feeding and weight loss without significantly affecting water intake. Betamethasone also resulted in decreased inflammation-related histopathological changes in jejunal tissues (data not shown) and abolishment of infection-induced increases in jejunal MPO levels. These changes are consistent with the hypothesis that suppressed host food intake during enteric T. spiralis infection is directly linked to the mucosal inflammation evoked during host-parasite interactions in the small intestine.

Reversal of nematode-induced suppression of feeding by oral betamethasone treatment may not necessarily mean that inflammatory factors produced the suppression of feeding. For example, oral glucocorticoid may have killed or impaired the nematodes, thereby significantly preventing or altering their ability to produce humoral factors that affect host feeding independent of inflammation. However, this possibility seems unlikely based upon our observation that food intake by T. spiralis-infected rats still decreased transiently during the first 2–3 days PI despite the presence of betamethasone. Furthermore, evidence obtained in early investigations of intestinal immunity to enteric nematodes in which mucosal inflammation had been suppressed by systemic administration of steroids showed that treatment with these agents resulted in the establishment of chronic infections (28) or prolongation of the intestinal phase of infection with delayed expulsion of worms (24). These findings argue against any direct deleterious effect of glucocorticoids on the worms and support the notion that the action of oral betamethasone during the enteric phase of T. spiralis infection was exclusively immunosuppressive and anti-inflammatory. Our results indicate that the early transient decrease in food intake by T. spiralis-infected rats that was unaffected by steroid could be due to the activation of some other host regulatory factor or mechanism that is not influenced by steroid or dependent on inflammation and/or some early parasite-derived factor that intentionally or unintentionally affects host feeding behavior.

In support of this latter possibility, enteric nematodes including both N. brasiliensis and T. spiralis have been shown to be capable of synthesizing and secreting into host intestinal tissues a variety of substances with putative enzymatic and bioactive properties. These include acetylcholinesterase (16), acetylhydrolase (4), a vasoactive intestinal polypeptide-like molecule (20), biogenic amines, including the neurotransmitter γ-aminobutyric acid (2), a superoxide dismutase-like molecule (27), and a variety of proteinases, including a carboxypeptidase (13, 39). As yet, however, molecules with protease-inhibiting properties like trypsin inhibitor (34), a potent luminal stimulator of secretion of the satiety factor cholecystokinin from the intestinal mucosa (41), have not been identified as secretagogues of enteric nematodes.

Suppression of food intake in T. spiralis-infected rats is a characteristic feature of the integrated host immunophysiologival response to the worms and is associated with histopathological changes in intestinal tissue structure, increased MPO activity, behavioral signs of
gastrointestinal distress, and decreased body weight. The findings of this study support the hypothesis that factors generated during enteric inflammation contribute significantly to the induction of altered feeding behavior in nematode-infected animals.

A reduction of food intake has been associated with other experimental models of gastrointestinal inflammation, including indomethacin-induced ileitis (40), trinitrobenzene sulfonic acid-induced colitis (30, 31), and lippopolysaccharide-induced enteritis (6). Studies using these models have also provided evidence in support of an important role for enteric inflammatory factors in reducing food intake. They have demonstrated the synthesis and release of proinflammatory mediators, including arachidonic acid metabolites, tachykinin-like peptides, and proinflammatory cytokines, including IL-1β and TNF-α, from immune and nonimmune cells in the inflamed gut. Furthermore, IL-1β and TNF-α have been shown to be potent inhibitors of food intake (6, 19, 30, 37, 42). Blockade of IL-1 receptors attenuates the suppression of feeding produced by colonic administration of trinitrobenzene sulfonic acid (30). Enteric nematode infections have much in common with these other intestinal inflammation models in that the production and release of the same general array of inflammatory mediators occurs during mucosal invasion by the worms (21, 26, 29). In light of evidence showing that protein levels and mRNA expression of IL-1β and TNF-α are significantly elevated in the small intestine of spiralis-infected rats (26), it seems reasonable to speculate that these factors might play a pivotal role in mediating the suppression of food intake in the nematode-parasitized host.

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