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Abstract

In rats, the nematode *Nippostrongylus brasiliensis* induces an intestinal inflammation, but after the inflammation had resolved and the worm burden eliminated, morphological alterations of the intestinal wall, mainly consisting of mast cell hyperplasia and enteric nerve remodeling, persist for several weeks. Intestinal signals reaching the brain through the vagus nerve and involving neuropeptides such as CCK, play a role in the control of food intake. Our hypothesis was that neuroimmune alterations of the intestine may alter this control. This work was aimed to evaluate whether post-infection alterations of the intestinal wall may affect the satiety effects of CCK and further, the role of mast cells and their mediators, histamine and serotonin, in post-*N. brasiliensis*-infected rats. In basal conditions, food intake was not different in control and post-infected groups of rats. Post-infected rats were characterized by prolonged satiety effects of both CCK and histamine but not serotonin. The prolonged effect of CCK was reduced when mast cells were previously stabilized by ketotifen, which had no effect per se on food intake. No difference was observed in the increase of food intake induced by CCK-A and CCK-B receptor antagonists in both control and post-infected rats. Mast cell degranulation with compound 48/80 induced severe anorectic effects that lasted for less than 24 h in post-infected rats and as long as 6 days in controls. Thus, in our experimental conditions, i.e., within 30–50 days post-*N. brasiliensis* infection, we observed an enhancement of the anorectic effect of exogenous CCK involving mast cell degranulation and histamine.
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Keywords: Nippostrongylus brasiliensis; CCK; Satiety; Mast cells; Histamine; Serotonin

1. Introduction

Among the numerous factors regulating food intake, intestinal signals are known to play an important role, mainly in meal termination.

Cholecystokinin (CCK) is considered a major mediator involved, through vagal afferents, in the transmission of the gastrointestinal feedback signals that control meal size (Schwartz, 2000). Neuronal signals are conveyed to the central nervous system from nerve endings located at different levels of the digestive wall, from the mucosa to the serosa (Mei, 1994). These anatomical elements lead to suppose that the in-

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tegrity of the intestinal structure is a prerequisite for a normal control of food intake. Aggressions of the intestinal mucosa by chemical compounds, bacteria or parasites occur frequently and often induce functional sequels. For example, development of irritable bowel syndrome commonly occurs after bacterial gastroenteritis in humans (Neal, Hebden, & Spiller, 1997).

Rats infected with the nematode *Nippostrongylus brasiliensis* provide a well-defined model for post-infective neuroimmune alterations of the small intestine. *N. brasiliensis* induces an acute inflammation in the jejunum whose intensity peaks 12–14 days after infection (Castex et al., 1998). This inflammation is characterized by mucosal lesions that consist of villus atrophy and crypt hyperplasia, associated with mast cell activation and leukotriene generation (Arizono & Nakao, 1988; Perdue, Ramage, Burget, Marshall, & Masson, 1989). Thirty days after infection, jejunal inflammation has resolved but mucosal mast cell hyperplasia (Gay, Fioramonti, Garcia-Villar, & Bueno, 2000) and a profound enteric nerve remodeling persist for several weeks (Newlands, Miller, MacKellar, & Galli, 1995; Stead, Kosecka-Janiszewska, Oestreicher, Dixon, & Bienenstock, 1991; Stead, 1992).

Since mast cells produce mediators, such as histamine and serotonin, involved in the control of food intake, disturbances of food intake associated with intestinal mast cell hyperplasia can be supposed. However, the relationships between mast cells and food intake have been poorly investigated. Only one study indicates a swelling of mesentery mast cells during feeding in the rat, an effect mediated through parasympathetic efferent nerves (Rothschild & Gomes, 1988). More interestingly, it has been shown that nutrients which are potent releasers of CCK, such as ovalbumin hydrolyzate, degranulate intestinal mucosal mast cells, an effect mediated through CCK-B receptors (Juanola, Giralt, Jimenez, Mourelle, & Vergara, 1998). Moreover, this CCK-induced mast cell degranulation is involved in the action of CCK to induce a post-prandial pattern of intestinal motility (Juanola et al., 1998).

On the other hand, mast cells are considered key cells in intestinal neuroimmune interactions. There is a close apposition between mast cells and sensory nerve fibers (Stead et al., 1987) and an important number of these fibers are vagal fibers, which provide an anatomical basis for a direct neural communication between intestinal mast cells and the central nervous system (Williams, Berthoud, & Stead, 1997). In addition, the number

of jejunal mast cells in close association with neural processes is increased by 60% after *N. brasiliensis* infection in the rat (Arizono et al., 1990).

Taken together, all these elements lead to suppose that the control of food intake by CCK, which involves a vagal pathway, may be altered after infection by *N. brasiliensis* in rats. Therefore, this work was aimed to evaluate the alterations of the effects of CCK on food intake in post-*N. brasiliensis*-infected rats. We also evaluated the role of mast cells and of two of their mediators, histamine and serotonin (5-HT), in these alterations.

2. Materials and methods

2.1. Animals

Groups of 20 male Wistar rats (10 control groups and 10 post-*N. brasiliensis*-infected groups; Harlan, Ganat, France), initially weighing between 200 and 250 g, were used for these experiments. Rats were housed in individual polypropylene cages under controlled lighting and temperature ($21 \pm 1\,°C$) and accustomed to receive a standard diet (A04, Usine d'Alimentation Rationnelle, Epinay-sur-Orge, France) between 10 a.m. and 2 p.m. for 15 days before experiments. Tap water was provided ad libitum. All animal procedures were approved by the Local Animal Care and Use Committee of the Institut National de la Recherche Agronomique.

2.2. Culture and infection techniques

N. brasiliensis was maintained in continuous culture by harvesting worm eggs from infected rats and growing them to the third larval (L3) stage on vermiculite and filter paper, using a technique described by Jennings, Mulligan, and Urquhart (1963). The appropriate rats were infected by subcutaneous injection of 3000 L3 infective larvae of *N. brasiliensis* in .5 ml sterile saline into the flank. Controls received .5 ml sterile saline.

2.3. Experimental design

For each series of experiments, treatments were applied in parallel to both control and post-infected rats. Rats received food pellets only between 10 a.m. and 2 p.m. Food intake was quantified by weighing food pellets each 30 min for 4 h. Experiments were carried out between 30 and 50 days post-*N. brasiliensis* infection.

CCK (50 µg/kg), serotonin (5-HT; 5 mg/kg), and histamine (2 mg/kg) were injected by intraperitoneal (i.p.) route just before feeding the rats. Devazepide (500 µg/kg, i.p.) and L-365260 (500 µg/kg, i.p.), respectively, CCK-A and CCK-B receptor antagonists, were administered 30 min before feeding. The mast cell degranulator, compound 48/80 (1 mg/kg, i.p.), was injected 1 h before feeding. The mast cell stabilizer, ketotifen, was given for 4 days (1 mg/kg, i.p., b.i.d.), with the last injection being given 30 min before feeding.

2.4. Chemicals

Sulfated CCK-8, ketotifen fumarate, compound 48/80, 5-HT, and histamine were from Sigma (St. Louis, MO, USA) and dissolved in sterile saline. Devazepide and L-365260 were provided by Merck Research Laboratories (Rahway, NJ, USA) and dissolved in dimethyl sulfoxide.

2.5. Data analysis

Food consumption was expressed both in grams of eaten food per 100 g of body weight (Table 1) and normalized to the percentage of food eaten by treated rats compared with that eaten by rats treated with the corresponding vehicle taken as 100% (Figs. 1–6). Results were expressed as means ± SEM for each group. Statistical analyses were performed using analysis of variance (ANOVA), followed by multiple comparison post-test or Student's t test where appropriate. $p < .05$ was considered statistically significant.

3. Results

3.1. Basal conditions

No differences in the amounts of food eaten by rats fed during four hours (thereafter termed

"4 h-food intake") were observed between controls and post-*N. brasiliensis*-infected rats (Table 1).

3.2. Effects of CCK alone

During the first 30 min, CCK (50 µg/kg) reduced food intake in both control and post-infected rats down to 8.7 ± 3.3 and $6.0 \pm 1.3\%$ $p > .05$ of food intake in vehicle-treated rats (thereafter termed "vehicle"), respectively. The anorectic effect of CCK was maintained for the following 30 min in post-infected rats ($32.5 \pm 8.3\%$) but not in controls ($95.1 \pm 23.4\%$; $p < .05$) (Fig. 1).

3.3. Effects of CCK after ketotifen treatment

Ketotifen given alone (1 mg/kg, i.p., b.i.d.) had no effect per se on food intake in both control and post-infected rats during the first hour of feeding (Fig. 2). After ketotifen treatment, the anorectic effect of CCK (50 µg/kg) remained unchanged during the first 30 min in both control and post-infected rats (Fig. 1A) but was reduced for the following 30 min in post-infected rats (69.9 ± 8.5 vs $32.5 \pm 8.3\%$ after CCK alone; $p < .05$) (Fig. 1B).

3.4. Effects of 5-HT

At the dose of 5 mg/kg i.p., 5-HT significantly reduced food intake ($p < .05$) during the first hour of feeding. No significant difference ($p > .05$) was observed between control and post-infected rats (Fig. 2).

3.5. Effects of histamine

Histamine (2 mg/kg) reduced food intake to a similar extent in both control and post-infected rats for the first 30 min of feeding. Reduced food intake, however, persisted for the following 30 min in post-infected but not in control rats (Fig. 3).

Table 1

Average body weight and food intake for 4 h after saline administration in control and post-*N. brasiliensis*-infected rats, 30 and 50 days post-infection

	Controls		Post-infected	
	Weight (g)	Food intake (g/4 h)	Weight (g)	Food intake (g/4 h)
Thirty days post-infection	210.1 ± 3.5	$16.4 \pm .6$	221.9 ± 6.3	$16.0 \pm .5$
Fifty days post-infection	251.0 ± 4.6	$15.2 \pm .6$	252 ± 5.8	$15.3 \pm .7$

(Values represent means ± SEM. No significant difference ($p > .05$) was observed between post-infected and control rats).
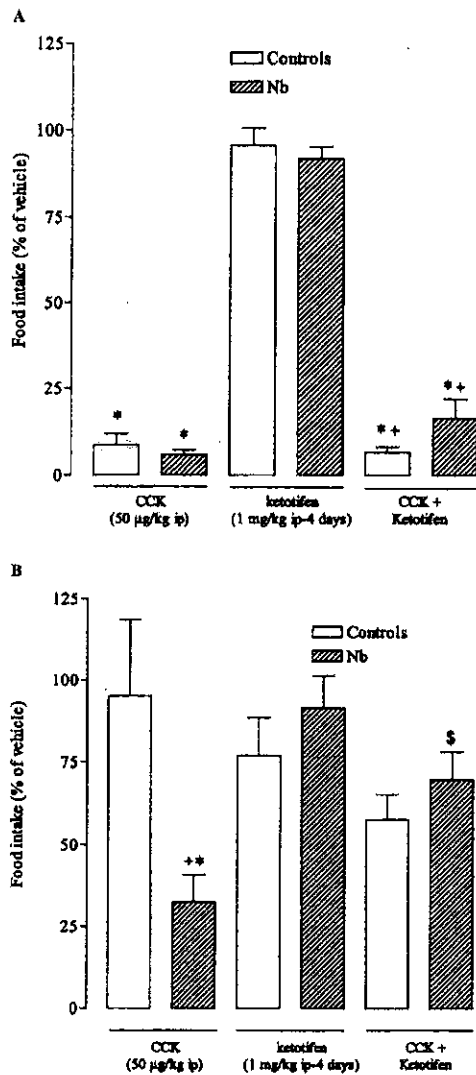
A

B

Fig. 1. Effect of CCK (50 µg/kg, i.p), ketotifen (1 mg/kg i.p., 4 days, b.i.d.), and CCK after ketotifen treatment on food intake in controls and post-*N. brasiliensis*-infected rats during the 0–30 min (A) and 30–60 min (B) periods after CCK administration. Values are expressed in percentage of food intake of vehicle-treated rats (means ± SEM; *n* = 10; *p < .05 compared to vehicle (100%); +p < .05 compared to respective controls; $p < .05 compared to CCK alone).

3.6. Effects of CCK receptor antagonists

Both devazepide and L-365260 (500 µg/kg, i.p.) significantly (p < .05) increased food intake during the first 30 min in control and post-infected rats. This increase remained significant (p < .05)
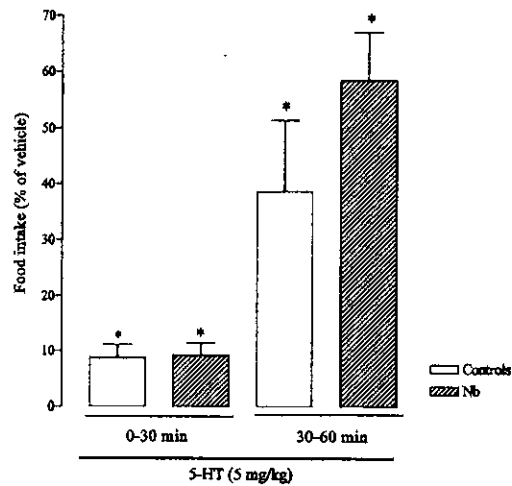

Fig. 2. Effect of 5-HT (5 mg/kg, i.p.) on food intake in control and post-*N. brasiliensis*-infected rats during the 0–30 and 30–60 min periods after 5-HT administration. Values are expressed in percentage of food intake of vehicle-treated rats (means ± SEM; *n* = 10; *p < .05 compared to vehicle, 100%).

within the 4 h of feeding and was similar (p > .05) in both groups (Fig. 4).

3.7. Effect of mast cell degranulation

Compound 48/80 given i.p. 1 h before feeding strongly reduced the 4 h-food intake of both control and post-infected rats. No difference (p > .05) was observed in the responses of both groups. In control rats, however, the effect of 48/80 was longer, with a return to 100% food intake (i.e., that obtained in rats given the vehicle of compound 48/80) only at the seventh day after 48/80 administration. In post-infected rats, 100% food intake was recovered at 24 h after 48/80 (Fig. 5). After ketotifen treatment, the anorectic effect of compound 48/80 was significantly reduced (p < .05) in controls and abolished in post-infected rats (Fig. 6), while 100% food intake was recovered at 24 h after compound 48/80 in both groups (not shown).

4. Discussion

Our results indicate that the reduction of food intake induced by exogenous CCK is prolonged in post-*N. brasiliensis*-infected rats and bring evidence for the involvement of mast cells because this effect was blocked by the mast cell stabilizer, ketotifen. So far, only few studies indicate that
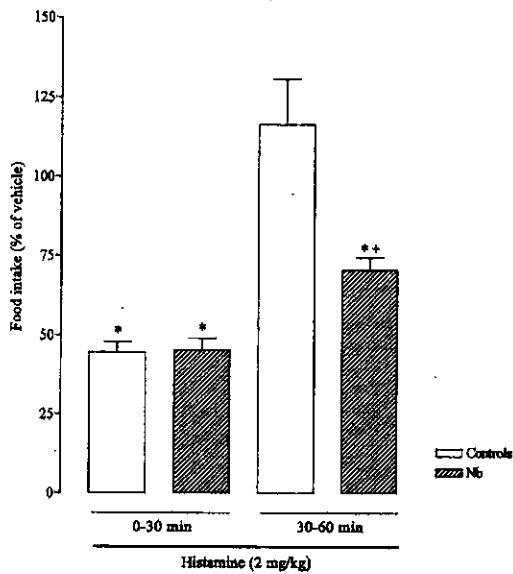
Fig. 3. Effect of histamine (2 mg/kg, i.p.) on food intake in control and post-*N. brasiliensis*-infected rats during the 0–30 and 30–60 min periods after histamine administration. Values are expressed in percentage of food intake of vehicle-treated rats (means ± SEM; $n = 10$; *$p < .05$ compared to vehicle (100%); +$p < .05$ compared to respective controls).
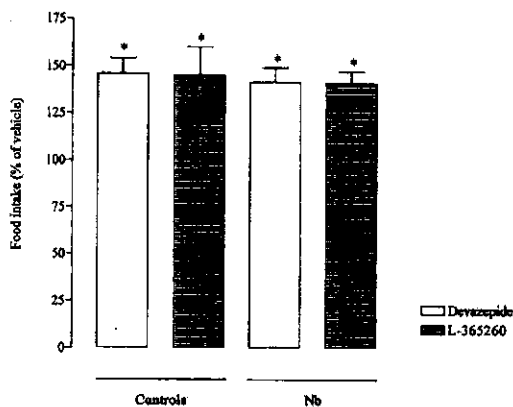

Fig. 4. Effect of CCK-A (devazepide; 500 µg/kg, i.p.) and CCK-B (L-365260; 500 µg/kg, i.p.) receptor antagonists on the 4 h-food intake in controls and post-*N. brasiliensis*-infected rats. Values are expressed in percentage of food intake of vehicle-treated rats (means ± SEM; $n = 10$; *$p < .05$ compared to vehicle, 100%).
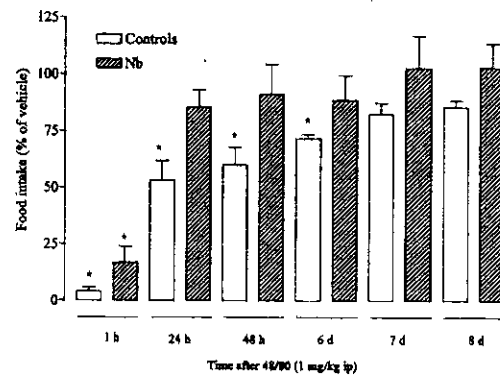

Fig. 5. Effect of the mast cell degranulator, compound 48/80 (1 mg/kg, i.p.), on the 4 h-food intake measured at different times within the 8-day period following its administration in control and post-*N. brasiliensis*-infected rats. Values are expressed in percentage of food intake of vehicle-treated rats (means ± SEM; $n = 10$; *$p < .05$ compared to vehicle, 100%).
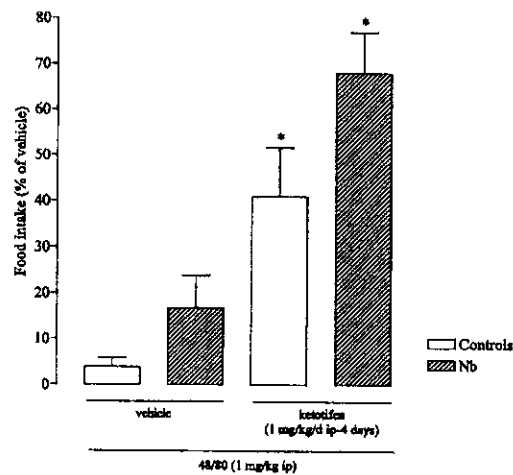
Fig. 6. Effect of compound 48/80 (1 mg/kg, i.p.) on the 4 h-food intake in saline- and ketotifen-treated control and post-*N. brasiliensis*-infected rats. Values are expressed in percentage of food intake of vehicle-treated rats (means ± SEM; $n = 10$; *$p < .05$ compared to vehicle, 100%).

post-prandial gastrointestinal hormones degranulate mast cells. Thus, it has been reported that gastrin stimulates gastric mucosal mast cells (Plebani et al., 1995) and that endogenous CCK, released by an ovalbumin hydrolyzate, degranulates

mucosal mast cells (Juanola et al., 1998). However, CCK receptors have never been identified on intestinal mast cells and an indirect action through a neuronal pathway can be postulated to explain CCK-induced mast cell degranulation. CCK-A and CCK-B receptors have been found localized on vagal afferent neurons (Moriarty, Dimaline, Thompson, & Dockray, 1997), which are known to be in close apposition with mast cells (Williams

et al., 1997). However, we suppose that the satie-togenic effect of CCK depends upon mast cell de-granulation in post-infected rats but not in controls, since the mast cell stabilizer ketotifen was active only in post-infected rats. This can be due to functional differences between intestinal mast cells of naive rats and those resulting from the hyper-plasia induced by nematode infection. For exam-ple, the expression of mouse mast cell protease-1 has been found up-regulated in *N. brasiliensis*-in-fected mice (Scudamore et al., 1997). Similarly, *N. brasiliensis* infection enhances expression of the β-subunit of the mast cell Fc epsilon IgE receptor (Shaikh et al., 1997). Also, CCK-induced mast cell degranulation in post-infected rats can be explained by intrinsic nerve remodeling associated with mast cell hyperplasia, with the proportion of mast cells in close contact with afferent neurons being strongly increased after *N. brasiliensis* infection (Arizono et al., 1990).

We also found that serotonin inhibited food intake in a manner similar to that in control and post-infected rats. The absence of difference was unexpected for several reasons: first, serotonin is produced by rat mast cells; second, several inter-actions between CCK-ergic and serotoninergic control of food intake have been reported (Eberle-Wang, Levitt, & Simansky, 1993; Poeschla, Gibbs, Simansky, Greenberg, & Smith, 1993); and third, serotonin has been found responsible for alterations of digestive functions induced by mast cell degranulation (Bueno, Fargeas, Theodorou, & Fioramonti, 1991; Castex, Fioramonti, Far-geas, More, & Bueno, 1994). On the other hand, histamine reproduced the inhibition of food in-take induced by CCK during the second 30 min period of the 4 h-feeding time. This suggests that histamine may be the mast cell mediator involved in the effects of CCK on food intake in post-in-fected rats. This is in agreement with the in-volvement of H1, H2, and H3 histamine receptors in the CCK inhibition of food intake in rats (At-toub et al., 2001) However, the histaminergic system is known to be implicated in control of food intake at the level of the central nervous system. Consequently, since histamine induced different effects in control and post-infected rats, then alterations of the central histaminergic sys-tem in post-infected rats can be speculated. The histaminergic activity of the central nervous sys-tem has been reported to be involved in the ano-rexia seen in protein malnutrition, which leads to elevated histamine H1 receptors (Mercer, Kelley, Haq, & Humphries, 1996). Interestingly, *N. bra-*

siliensis infection has been found associated with an impairment of protein digestion (Symons & Jones, 1970), which could alter H1 receptors in the central nervous system.

Our data confirm the increase in food intake that was already observed after administration of a CCK-A receptor antagonist (Corwin, Gibbs, & Smith, 1991). Enhanced food intake has also been reported with CCK-B receptor antagonists injected intracerebroventricularly (Dorre & Smith, 1998) whereas L-365260 was administered i.p. in our study. However, both devazepide and L-365260 apparently exhibit good blood–brain barrier pen-etration (Patel, Chapman, Heald, Smith, & Freed-man, 1994; Pullen & Hodgson, 1987) and a central site of action can be postulated for the two com-pounds. The absence of difference in the increase of food intake in control and post-infected rats sug-gests that *N. brasiliensis* infection did not alter the central CCK-ergic control of food intake. In addi-tion, it is well established that the satiety effect of CCK involves the vagus nerve (Lorenz & Goldman, 1982), but the involvement of vagal afferents has been shown to account for the effects of peripher-ally administered exogenous CCK, but not for those of endogenous CCK. The fact that the effect of exogenous but not endogenous CCK differing in control and post-infected rats may be attributed to *N. brasiliensis*-induced intestinal nerve remodeling, which increases the association of mast cells with neural afferent processes (Arizono et al., 1990).

We found that massive degranulation of mast cells by compound 48/80 reduced food intake for one week in control rats. This long-lasting effect is consistent with the decrease in food intake induced by mast cell degranulation in other experimental conditions. For example, in rats sensitized to egg albumin, chronic antigen challenge resulted in the degranulation of mucosal mast cells associated with reduced food intake (Curtis, Patrick, Catto-Smith, & Gall, 1990). In another model, inhibition of food intake by *Escherichia coli* lipopolysaccha-ride was prevented by mast cell stabilization with sodium cromoglycate (Nava & Caputi, 1999). In post-*N. brasiliensis*-infected rats, the effects of 48/80 on food intake were limited to the day of ad-ministration. However, only speculations can be proposed to explain the absence in post-infected rats of the long-lasting effect of compound 48/80 on food intake observed in control rats. Com-pound 48/80 can act directly on mast cells, but also on peripheral endings of capsaicin-sensitive pri-mary afferent neurons to degranulate mast cells, at least in the urinary bladder (Eglezos et al., 1992).

The infection-induced nerve remodeling could explain the reduced duration of 48/80 in post-infected rats, assuming that the neo-innervation would not be able to degranulate mast cells. Another hypothesis could be that mast cells arising from *N. brasiliensis* infection are less sensitive to the action of compound 48/80; these mast cells are mucosal mast cells (Shanahan, Denburg, Fox, Bienenstock, & Befus, 1985), which are known to be relatively insensitive to 48/80 (Metcalfe, Baram, & Mekori, 1997); however, compound 48/80 was administered i.p. in our study and, consequently, did not affect only intestinal mast cells.

In conclusion, our data show that *N. brasiliensis* infection induces long-term changes in the control of food intake in rats during the post-infective stage, i.e., after intestinal inflammation has resolved and the worm burden eliminated. Our results support the participation of intestinal mast cells in the mechanisms of regulation of food ingestion by CCK and suggest histamine as a mediator contributing to the prolonged anorectic action of CCK intestinal infection in rats.

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