Mast Cell Stabilizer Ketotifen [4-(1-Methyl-4-piperidylidene)-4H-benzo[4,5]cyclohepta[1,2-b]thiophen-10(9H)-one Fumarate] Prevents Mucosal Mast Cell Hyperplasia and Intestinal Dysmotility in Experimental Trichinella spiralis Inflammation in the Rat

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ABSTRACT

Trichinella spiralis infection in rats induces hypermotility and an abnormal response to cholecystokinin (CCK) similar to motor disturbances observed in irritable bowel syndrome. Mast cell hyperplasia is also characteristic of this experimental model. The aim of our study was to correlate mast cell activity with the development of dysmotility and to demonstrate whether the mast cell stabilizer ketotifen [4-(1-methyl-4-piperidylidene)-4H-benzo[4,5]cyclohepta[1,2-b]thiophen-10(9H)-one fumarate] could prevent the development of intestine hypermotility. Sprague-Dawley rats were infected with T. spiralis and, 5 days after infection, treated with the mast-cell stabilizer ketotifen (10 mg/kg/day). Twelve days after infection, intestinal spontaneous motor activity and response to CCK were evaluated by means of strain-gauge transducers. Immunohistochemistry for rat mast cell protease II (RMCPII), cyclooxygenase (COX)-2, and inducible nitric-oxide synthase (iNOS) was performed in intestinal specimens. In addition, RMCPII and myeloperoxidase were determined in serum. Infected control rats showed hypermotility, mast cell hyperplasia, increased RMCPII levels, increased myeloperoxidase, and overexpression of COX-2 and iNOS. In contrast, ketotifen-treated rats showed spontaneous intestinal motility and CCK response similar to the noninfected control rats. Mast cell hyperplasia and RMCPII were reduced in ketotifen-treated rats. Inflammatory parameters were less modified by ketotifen, but those animals that received the longest ketotifen treatment showed a slight amelioration in these parameters. These results indicate that mast cells are implicated in the development of hypermotility. The treatment with ketotifen prevented hypermotility and mast cell hyperplasia and diminished mucosal mast cell activity.

Irritable bowel syndrome (IBS) is a functional, multifactorial disease characterized by exacerbated responses to gastrointestinal motor reflexes. Both motor changes and enhanced perception of stimuli arising from the gut are thought to be major contributors for symptom generation (Chey et al., 2001). Causes of IBS are not well defined; however, at least in some cases, it has been associated with a previous mucosal invasive gastrointestinal infection (Parry and Forgacs, 2005). Mast cells are key cells in the response of the intestine to infection and inflammation (He, 2004) as well as in food allergy and other immune responses (Galli et al., 2005). Furthermore, mast cell activation and release of mast cell mediators have been associated with IBS (Barbara et al., 2004).

The experimental Trichinella spiralis infection is a widely used model of experimental intestinal inflammation and postinfectious IBS (Torrents and Vergara, 2000; Bercik et al., 2004; Wheatcroft et al., 2005). Larvae of the parasite invade the duodenum and jejunal mu cosa causing a severe inflammatory reaction that promotes worm expulsion and restoration of health (Palmer et al., 1984; Wang et al., 1991). These changes are concomitant with a severe mast cell hyperplasia that also decreases spontaneously after worm expulsion (Ruitenberg et al., 1979).

ABBREVIATIONS: IBS, irritable bowel syndrome; ketotifen, 4-(1-methyl-4-piperidylidene)-4H-benzo[4,5]cyclohepta[1,2-b]thiophen-10(9H)-one fumarate; CCK, cholecystokinin; MPO, myeloperoxidase; iNOS, inducible nitric-oxide synthase; COX, cyclooxygenase; PI, postinfection; AUC, area under the curve; RMCPII, rat mast cell protease II; VCU, villus-crypt unit(s).
Motor changes due to parasite infection affect all motor patterns from fasting motility to motor response to postprandial hormone CCK (Palmer et al., 1984; Cowles and Sarna, 1991; Torrents and Vergara, 2000; Gay et al., 2001). A close association between mast cells and vagal afferents has been well established (Williams et al., 1997). Furthermore, the exacerbated motor responses during *T. spiralis* infection have been associated with afferent hypersensitivity (Torrents et al., 2002).

Ketotifen is a drug extensively used to prevent mast cell activation (Pothoulakis et al., 1993; Eliakim et al., 1995; Crampton, 2003). We previously demonstrated that ketotifen stabilized intestinal mucosal mast cells in the rat and prevented mucosal mast cell stimulation (Juanola et al., 1998).

The objective of this study was to demonstrate whether the treatment with mast cell stabilizer ketotifen could prevent the development of intestine hypermotility during *T. spiralis* infection. The parameters that have been evaluated in this study are: in vivo motor activity of the intestine by measuring spontaneous activity and the response to CCK, number of mast cells in the intestinal mucosa, activity of mucosal mast cells by monitoring rat mast cell protease II in serum, and evaluation of inflammation by measurement of myeloperoxidase (MPO) in serum and iNOS and COX-2 immunoreactivity in the intestine.

**Materials and Methods**

**Animals.** Male Sprague-Dawley rats (Charles River, Lyon, France), 8 to 10 weeks old and weighing 300 to 350 g, were used in this study. Animals were kept at controlled temperature (20–21°C), humidity (55–60%), and photoperiod (12/12 h) room. Animals were caged in groups of three and had free access to water and a commercial pellet food. At the initiation of ketotifen treatment or after larvae infection, all of the animals were caged individually. All experimental protocols as well as housing and handling of animals were carried out under the supervision and regulations of the ethical committee of the Universitat Autonoma de Barcelona.

**T. spiralis Infection.** Rats were infected by administering 1.0 ml of 0.9% saline solution containing 7500 *T. spiralis* larvae by gavage. The larvae were obtained from female CD1 mice infected 30 to 90 days before as described previously (Castro and Fairbairn, 1969; Torrents and Vergara, 2000).

**Drugs and Substances.** Mast cell membrane stabilizer ketotifen fumarate salt (Sigma Chemicals, St. Louis, MO) was given to each individually caged rat in drinking water as described previously (Juanola et al., 1998). Ketotifen was dissolved in drinking water at a concentration of 0.1 mg/ml, which allowed dosing of ketotifen at 10 mg/kg/day. The amount of water drunk by each rat was controlled daily. If a rat was found to ingest less than the required dose of ketotifen (by drinking less than 30 ml of water), it was rejected for the study. CCK-8, sulfated form (Peptide Institute, Osaka, Japan), was diluted in 1% sodium bicarbonate to 10^-4 M and in buffered saline solution to work concentration.

**Experimental Groups.** For this study, rats were divided into the following groups: noninfected control group, rats that did not receive either parasite larvae or treatment (*n* = 6); ketotifen control group,
noninfected rats treated with ketotifen for 7 days ($n = 4$); infected control group, rats infected with *T. spiralis* ($n = 7$); infected ketotifen 5 group, rats infected with *T. spiralis* and treated from days 5 to 10 postinfection (PI) with ketotifen ($n = 6$); and infected ketotifen 7 group, rats infected with *T. spiralis* and treated with ketotifen from day 5 until the day of the experiment (day 12 PI) ($n = 5$). These two ketotifen groups differ in the time that ketotifen treatment is stopped. In the ketotifen 5 group, the mast cell stabilizer was removed 48 h before conducting the experiment. In contrast, the ketotifen 7 group received ketotifen until the same day of the experiment. In addition, some infected rats were treated with ketotifen for 48 h before the experiment ($n = 3$) or received by gavage the daily dose of ketotifen 1 h before the experiment ($n = 2$). The objective of these last two protocols was to be able to differentiate the long-term effect from possible acute effects of ketotifen. As is shown under Results, results from the ketotifen 5 and 7 groups were practically similar, and the short-time treatment with ketotifen did not modify motor responses in infected rats. These results indicate that the effect observed in the animals treated with ketotifen is due to the treatment and not to the direct effect of ketotifen during the experiment. All motility experiments and the samples were taken on day 12 PI. The reason for choosing this time is that, coinciding with parasite expulsion, there is maximal hypermotility and mastocytosis (Woodbury et al., 1984).

**Animal Preparation for Intestinal Motility Studies.** The night before the experiment, food was restricted to 10 g. We had previously checked that this procedure, which ameliorated stress due to food deprivation, guaranteed a fasting time of at least 6 h, and the complete emptiness of the stomach at the moment experiment was initiated. Anesthesia was induced by inhalation of halothane to allow cannulation with polyethylene tubing of the right jugular vein. Level III of anesthesia was maintained with thiopental sodium bolus infusion in the jugular as required. Body temperature was maintained at 37°C by placing the rat on a heating pad. A tracheotomy was practiced to facilitate spontaneous breathing. The abdomen was opened through a midline incision, and the intestine was exposed. Three strain gauges (3 × 5 mm; Hugo Sachs Elektronik, Hugstetten, Germany) were placed to record circular muscle activity and sutured to the intestinal wall of the duodenum, proximal jejunum, and ileum, respectively. Strain gauges were connected to high-gain amplifiers (MT8P; Lectromed Ltd., Letchworth, Herts, UK), and amplified signals were sent to a recording unit (PowerLab/800; ADInstruments).
Pty Ltd., Castle Hill, Australia) connected to a personal computer running PowerLab software.

**Motor Activity Evaluation.** After an equilibration period of 20 min, spontaneous motor activity for 50 min was recorded, and the number of contractions during the time of recording were counted. Afterward, CCK-8 (3 × 10^{-9} mol/kg/10 min) was i.v. infused in bolus for 10 min, and the area under the curve (AUC) described by the response (phasic and tonic response) was measured.

**Histological Study.** After finishing the experimental protocol, samples of duodenum, jejunum, and ileum were obtained, fixed for 48 h in neutral buffered formalin, embedded in paraffin, cut into 5-μm sections, and stained with hematoxylin-eosin. A scoring based on the inflammatory cell infiltration was used to evaluate the inflammatory process. At the same time, thickness of intestinal muscular layers was measured with a scored microscope. At least four different measures were taken from any sample, and samples from at least four animals of each group were used for the evaluation of the muscle thickness.

**Mucosal Mast Cell Identification.** Immunodetection of RMCPII was carried out on paraformaldehyde-fixed sections using a monoclonal antibody (1:500; Moredun Animal Health, Edinburgh, UK). Detection was performed with avidin/peroxidase (Vectastain ABC kit; Vector Laboratories, Burlingame, CA). Sections were counterstained with hematoxylin and counted at 400× magnification. Positively stained mast cells were counted in three to five sections per animal. Seven to 10 well oriented villus-crypt units (VCU) were examined per section. Analyses of all morphological data were performed blinded to prevent observer bias.

**Immunohistochemistry of iNOS and COX-2.** Immunohistochemistry of iNOS and COX-2 was carried out on paraformaldehyde-fixed sections using either an anti-iNOS antibody (1:100; Neomarkers, Fremont, CA) or anti-COX-2 antibody (1:100; Santa Cruz Biotechnology, Santa Cruz, CA). Detection was performed with avidin/peroxidase (Vectastain ABC kit; Vector Laboratories), and sections were counterstained with hematoxylin.

**Measurement of RMCPII and MPO.** Serum samples were taken in all rats: at time 0, before infection; at 5 days PI, just before the beginning of ketotifen treatment; and at 12 days PI, at the time of motor activity evaluation. RMCPII and MPO concentration in the serum was measured by enzyme-linked immunosorbent assay using commercial kits (RMCPII, Moredun Animal Health; MPO, HyCult Biotechnology, Uden, The Netherlands).

**Data Analysis.** One-way analysis of variance followed by a post hoc Bonferroni test was used to compare motor parameters as well as mast cell number and intestinal wall thickness. RMCPII and MPO concentration results were compared by repeated measures analysis of variance analysis. Differences between groups were considered statistically significant when \( P < 0.05 \). All data are expressed as mean ± S.E.M.

**Results**

**Intestinal Motor Activity**

In the noninfected control group, spontaneous activity of the intestine consisted of single contractions at a variable frequency of one to two contractions every 10 min. In contrast, this pattern of isolated contractions was replaced in infected rats by an irregular pattern with strong groups of contractions (clusters) that alternated with periods of inactivity with a variable frequency of three to four every 10 min or by a continuous irregular activity as shown in Fig. 1B. As a consequence, the total number of contractions in duodenum and jejum was significantly higher in the parasite-infected rats compared with the noninfected control group (Fig. 2).

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Similar changes were observed in the response to CCK-8 infusion (3 × 10^{-9} mol/kg/10 min). CCK induced a contractile response at the duodenum and an inhibitory response in the jejunum of noninfected control rats. In infected control rats, CCK-induced contraction in the duodenum was of a greater magnitude (1368 ± 53.9 AUC compared with 598.4 ± 53.8 AUC in controls), simultaneous with a contractile response of the jejunum that completely overlapped the inhibition observed in noninfected rats. Ketotifen, given either for 5 or 7 days in infected rats, reduced contractile response in the duodenum (777.5 ± 83.4 and 575.5 ± 201.2 in ketotifen 5 and ketotifen 7 groups, respectively). However, the most significant result was that ketotifen in both groups abolished the contractile response in the jejunum and restored the inhibitory response observed in noninfected control rats (Fig. 3). A summary of CCK response in the jejunum in all groups is given in Fig. 4. Ketotifen in noninfected animals did not modify CCK response.

**RMCP II Immunohistochemistry and Mucosal Mast Cell Count**

Mast cells were stained by the RMCP II antibody in the intestinal mucosa. Number of mast cells in noninfected control rats was of five to seven cells per VCU in the duodenum and jejunum. Infection with *T. spiralis* larvae induced a clear mast cell hyperplasia (Fig. 6) (50–60 mast cells per villus-crypt unit in the duodenum and 40–45 cells per VCU in the jejunum). Ketotifen treatment in infected animals significantly reduced the number of mast cells stained by RMCP II compared with the infected control group. These results indicated that ketotifen reduced mast cell hyperplasia. Mast cell number in duodenum and jejunum of each experimental group is shown in Fig. 7. A significant mast cell increase was also observed at the ileum of infected animals (16.20 ± 0.66 per VCU, compared with 3.95 ± 0.25 cells in noninfected rats). Ketotifen treatment also reduced mast cell number in the ileum, although this reduction was more moderate compared to those in serum of noninfected control rats (Fig. 5).

**Evaluation of Inflammation**

**Histological Evaluation.** The infected control group showed signs of inflammation at the mucosa and submucosa of duodenum and jejunum but not in the ileum. A mixed inflammatory infiltrate with neutrophil and eosinophil cells was observed. Ketotifen did not prevent inflammation, but the number of infiltrate cells was smaller (data not shown). Infected rats showed a significant hypertrophy of both muscular layers. This hypertrophy affected all of the areas of the small intestine, including those with no sign of mucosa inflammation as the ileum. Muscular hypertrophy was still observed in ketotifen-treated groups, but muscle layer thickness was of significant less magnitude in the duodenum of infected rats treated with ketotifen (Table 1).

**MPO.** In noninfected control rats, MPO concentration in serum was low at day 0 (517.9 ± 68.62 ng/ml) and remained low during the whole period of study. In contrast, MPO concentration significantly increased in all *T. spiralis*-infected rats. This increase was approximately 6-fold by day 5 PI (814.1 ± 126.3 ng/ml) and reached 7438 ± 2136 ng/ml at day 12 PI. Both ketotifen treatments reduced MPO concentration increase in infected animals, and RMCP II values in ketotifen-treated animals were not significantly different from those in serum of noninfected control rats (Fig. 5).

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**iNOS and COX-2 Immunohistochemistry.** In noninfected control animals, weak iNOS and COX-2 immunoreactivity was only detectable in the cytoplasm of some enterocytes located in the apical side of intestinal villi (Fig. 8A). Infected control animals presented a marked iNOS and COX-2 immunoreactivity throughout the gut wall. This positive immunostaining was particularly noticeable in the epithelial cells, in the cytoplasm of inflammatory cells located in the lamina propria and submucosa, and in both smooth muscle layers (Fig. 8B). No differences were observed in samples from infected animals receiving ketotifen treatment for 5 days (data not shown). In contrast, a general reduction of iNOS and COX-2 immunoreactivity in all intestinal layers was observed in those animals that received the longest ketotifen treatment (Fig. 8C).

**Discussion**

This study demonstrates that mast cell stabilization prevents both mucosal mast cell hyperplasia and exacerbated motor responses in reaction to intestine inflammation. Results show the strong correlation between mast cell activity and the development of intestinal dysmotility, suggesting a potential use of mast cell stabilizers in the treatment of motor disorders observed in postinfectious IBS.

Several studies correlate mast cell activity with the development of functional disorders such as alteration of intestinal permeability (Santos et al., 2001), motor disorders (Gay et al., 2000a), and visceral hypersensitivity (Kreis et al., 1998). We previously demonstrated that activation of mast cells could modify intestinal motility, even in the absence of apparent intestinal inflammation (Saavedra and Vergara, 2005). Moreover, there are also several experimental and clinical studies that report an increase of mast cell activity in both IBS and IBD patients (Raithel et al., 2001; Barbara et al., 2004; He, 2004). Despite this evidence, there are only a few studies that have tested the use of mast cell stabilizers to ameliorate symptoms derived from IBS and IBD (Stefanini et al., 1992, 1995). The use of ketotifen has been reported in a

### Table 1

<table>
<thead>
<tr>
<th>Group</th>
<th>Duodenum</th>
<th>Jejunum</th>
<th>Ileum</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Circular</td>
<td>Longitudinal</td>
<td>Circular</td>
</tr>
<tr>
<td>Noninfected control</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Infected control</td>
<td>43.4 ± 1.43*</td>
<td>32.5 ± 1.31*</td>
<td>45.4 ± 8.16*</td>
</tr>
<tr>
<td>Infected ketotifen 5</td>
<td>104.3 ± 4.26*</td>
<td>45.8 ± 1.59*</td>
<td>94.5 ± 5.07</td>
</tr>
<tr>
<td>Infected ketotifen 7</td>
<td>116.6 ± 4.92*</td>
<td>50.8 ± 2.62*</td>
<td>104.6 ± 4.78</td>
</tr>
</tbody>
</table>

* \( P < 0.001 \) compared with the infected control group.

### Table 2

<table>
<thead>
<tr>
<th>Group</th>
<th>Basal</th>
<th>Day 5</th>
<th>Day 12</th>
</tr>
</thead>
<tbody>
<tr>
<td>Noninfected control</td>
<td>517.9 ± 68.62</td>
<td>502.9 ± 60.02***</td>
<td>572.3 ± 52.98***</td>
</tr>
<tr>
<td>Ketotifen control</td>
<td>475.1 ± 48.49</td>
<td>518.1 ± 51.11***</td>
<td>493.4 ± 44.83***</td>
</tr>
<tr>
<td>Infected control</td>
<td>474.7 ± 61.30</td>
<td>1029.3 ± 97.56</td>
<td>1545.8 ± 157.75</td>
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<tr>
<td>Infected ketotifen 5</td>
<td>514.4 ± 36.56</td>
<td>1018.5 ± 88.24</td>
<td>1260.6 ± 60.88</td>
</tr>
<tr>
<td>Infected ketotifen 7</td>
<td>394.5 ± 47.22</td>
<td>1138.7 ± 85.33</td>
<td>838.4 ± 112.70**</td>
</tr>
</tbody>
</table>

**P** < 0.01 and **P** < 0.001 compared with the infected control group.

### Fig. 8. Immunohistochemical localization of iNOS and COX-2 proteins in duodenum. A, noninfected control rat; B, control infected rat; C, ketotifen 7 rat. Original magnification, 400×.
couple of case reports with one to three patients, but we could only find a pilot study using ketotifen for the treatment of colitis in children (Jones et al., 1998). However, our results demonstrate that ketotifen stabilizes mast cells and prevents all motor alterations induced by inflammation in response to parasite infection.

*T. spiralis* infection is a well accepted model of postinfectious IBS (Bereik et al., 2004; Wheatcroft et al., 2005). It has been widely used to study mechanisms underlying the motor changes induced by inflammation (Vallance et al., 1999; Torrents et al., 2002, 2003; Khan et al., 2005) and constitutes a good model to study the adaptation of the intestine to expel a clear cause of disease. Motor activity of the intestine is due to the activation of stereotyped motor behavior patterns accompanied by secretion and blood flow changes. One of these patterns is the defense program characterized by power propulsive motility (Wood, 2004). However, this motor reaction, if prolonged longer than infection resolution, can be the cause of IBS symptoms (Barbara et al., 2004).

Several studies have demonstrated that power propulsive motility requires remodeling of the enteric nervous system to increase muscle excitation necessary to expel the cause of the disease, the parasite in this case (Palmer et al., 1984; Swain et al., 1992; Torrents and Vergara, 2000; Tanovic et al., 2002). Mast cells are strategically placed to signal the enteric nervous system to program the protective response (Wood, 2004); therefore, our hypothesis was that mast cells were implicated in the development of motor changes. Our results show that the treatment with ketotifen, applied after the full development of inflammation, reverted dysmotility. The ketotifen effect indicates that mast cell activity is determinant for the development of the necessary changes at the enteric nervous system that drive the development of hypermotility.

Two main mechanisms have been suggested for the remodeling of intestinal motor patterns during inflammation: increasing sensitivity of the GI reflexes increasing activity of vagal afferents (Stead, 1992; Gay et al., 2000b; Di Giorgio et al., 2001; Torrents et al., 2002) and modifying sensitivity of the smooth muscle (Tanovic et al., 2002). Mast cells have been located in close connection to vagal afferents. Furthermore, a parallel increase of vagal afferents together with mucosal mast cell hyperplasia and a greater involvement of vagus nerves on CCK response have been reported in another similar model of nematode infection (Stead, 1992; Gay et al., 2001). In our model, the response to CCK is mediated through vagal afferents because it is completely blocked by capsaicin (Torrents et al., 2002). Parasite infection modifies CCK action exaggerating excitatory response through a mechanism that implies nerve growth factor (Torrents et al., 2002). Our present study shows that ketotifen treatment impaired the development of the exacerbation of vagal response to CCK, most probably because of the reduction of mast cell mediator(s) responsible for the development of vagal afferent hypersensitivity. We believe this is the main site of action for the development of hypermotility. However, we cannot rule out the effect of ketotifen reducing muscular thickness as a mechanism of reducing motor response. Our study also shows that mast cell response and muscle hypertrophy occur even at noninflamed areas (ileum) in agreement with other authors’ findings (Tanovic et al., 2002).

Mast cells are bone marrow cells that migrate and differentiate in different tissues in the body. Several factors released locally contribute to both mast cell migration and proliferation including stem cell factor and interleukins (Galli et al., 2005). Our study indicates that mast cell stabilization and, therefore, the decrease of released mediators diminish the “chemotactic call” as demonstrated by the smaller number of mast cells found in the mucosa of treated animals, further contributing to diminish the consequences of parasite infection.

In addition, there are a few studies that indicate that mast cell stabilizers could also ameliorate inflammation (Hogaboam et al., 1993; Pothoulakis et al., 1993), and there is an in vitro study that demonstrated that ketotifen is able to reduce nitric oxide generation in human inflamed intestine specimens (Rachmilewitz et al., 1995). We measured MPO in serum and the expression of iNOS and COX-2 in the intestine. These enzymes have been shown to increase in the *T. spiralis* model (Hogaboam et al., 1996; Torrents et al., 2003; Akiho et al., 2005). COX-2 and iNOS expression was present at all layers of the inflamed intestine. In contrast to hypermotility and mast cell activity, MPO did not vary significantly in ketotifen-treated animals except for those receiving the longest ketotifen treatment. A reduction of both iNOS and COX-2 was also observed in the ketotifen 7 group but not in the ketotifen 5 group. Although ketotifen has a limited effect on inflammation, a more prolonged treatment might induce a more significant reduction of inflammation. In addition, it is necessary to remark that prevention of mast cell hyperplasia and of hypermotility did not result in a worsening of parasite-induced inflammation.

Although the mechanism of action of ketotifen has not yet been well established, and it could be acting in other cell types such as blocking M-currents in neurons (Sato et al., 2005) or inducing necrosis of human eosinophils (Hasala et al., 2005), we think that the main action of ketotifen has been in stabilizing mucosal mast cells. Ketotifen is widely accepted as a mast cell stabilizer (Eliakim et al., 1993; Hogaboam et al., 1993; Abe et al., 2000). A direct effect on mucosal mast cells has been described previously (Abé et al., 2000; Schoch, 2003), and we previously demonstrated, by measuring the RMCPII released in the intestine, that ketotifen stabilizes intestinal mucosal mast cells in the rat (Juanola et al., 1998). In this article, we demonstrate that ketotifen significantly diminishes RMCPII concentration in *T. spiralis*-infected rats, corroborating the effect of ketotifen as an intestinal mucosal mast cell stabilizer. None of the ketotifen effects were reproduced when ketotifen was applied shortly before the experiment was conducted, indicating that our results are not a consequence of the immediate stabilization of mast cells while evaluating motor action but of long-term action on mast cells.

In summary, our study demonstrates that mast cell activity is directly related to the development of motor disorders caused by infection and inflammation. Our results suggest that mast cell stabilizers could be a tool for the treatment of motor disorders in IBD and IBS.

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References


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