Cosensitivity of vagal mucosal afferents to histamine and 5-HT in the rat jejunum

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Received 18 May 2001; accepted in final form 8 May 2002

Kreis, M. E., W. Jiang, A. J. Kirkup, and D. Grundy. Cosensitivity of vagal mucosal afferents to histamine and 5-HT in the rat jejunum. Am J Physiol Gastrointest Liver Physiol 283: G612–G617, 2002. First published May 29, 2002; 10.1152/ajpgi.00206.2001.—A complex sensitivity of afferent nerves in the mesentery of the rat jejunum to systemic administration of histamine has recently been demonstrated. In the present study, we aimed to characterize subpopulations of mesenteric afferents that mediate this afferent nerve response. Multiunit afferent discharge was recorded from mesenteric nerves supplying the proximal jejenum in anesthetized rats. The majority of mesenteric bundles (84%) exhibited biphasic responses to histamine (8 μmol/kg), and these bundles also responded to 2-methyl-5-HT (2m5HT). In contrast, monophasic responses lacked a short-latency component, and these bundles failed to respond to 2m5HT. Single-unit analysis revealed a population of afferents that possessed cosensitivity for 2m5HT and histamine. This population of afferents was absent in chronically vagotomized animals, whereas mucosal anesthesia with luminal lidocaine reversibly converted the biphasic profile to a monophasic one. Ondansetron (500 μg/kg) blocked the response to 2m5HT with no effect on the profile of the histamine response, whereas pyrilamine (5 mg/kg) blocked the histamine response without affecting the response to 2m5HT. We conclude that histamine-sensitive afferents exist in the rat proximal jejunum that also respond to 5-HT via the 5-HT3 receptor. These fibers appear to be vagal afferents originating in the intestinal mucosa and may be involved in the organization of mast cell-mediated responses.

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MUCOSAL MAST CELLS PLAY an important role in the defense against harmful material within the gastrointestinal lumen. During mast cell degranulation, triggered experimentally during intestinal anaphylaxis, mast cell mediators orchestrate motor and secretory responses that serve to dilute and expel antigenic material from the gut (16, 19). Neural mechanisms play an important part in these responses, with both enteric and extrinsic reflexes contributing to the disturbed motor and secretory function. In this respect, it has recently been demonstrated that the terminations of vagal mucosal afferents come into close proximity with mast cells in the lamina propria (21). Such morphological association sets the stage for a functional interaction between afferent neurons and mast cells. A role for both 5-HT and histamine released from activated mast cells is implicated in the mesenteric afferent response to luminal antigen in sensitized animals (11).

It has been reported that activation of second-order neurons in the brain stem, as represented by the expression of Fos in the nucleus of the solitary tract (NTS) during intestinal anaphylaxis, can be attenuated to a similar extent by 5-HT3 and histamine H1 receptor antagonists acting in the periphery, again implying a role for 5-HT and histamine in mast cell to nerve signaling (3, 13). Surprisingly, when treatments with these antagonists are combined, there is no summation of their ability to ameliorate brain stem activation (13). This observation led us to the hypothesis that afferent activity stimulated in the periphery by histamine and 5-HT converges in the brain stem onto a single population of NTS neurons. Selective attenuation of either afferent input following treatment with receptor antagonists may thus be sufficient to reduce activity in these neurons to a level at which c-fos expression no longer occurs, and under these circumstances, the effect of the antagonists would not be additive. However, the level at which convergence of input occurs could be in the brain stem itself and/or in the periphery and, in the case of the latter, could arise in one of at least three different ways.

One possibility is that, during mast cell degranulation, a cascade of events may lead to the sequential release of histamine and 5-HT, with a final common mechanism leading to activation of a single population of vagal afferents. Certainly, 5-HT3 receptors are expressed on the soma of vagal afferents in the nodose ganglia (17), and several studies have demonstrated functional receptors on vagal afferent nerve terminals in the gastrointestinal mucosa (6, 7). However, histamine H1 receptors are also expressed on vagal sensory neurons and are coupled to inhibition of a potassium conductance, leading to increased neuronal firing (10). We have also recently shown (12) that mesenteric afferents (which contain both vagal and spinal afferents)
supplying the small intestine have a complex sensitivity to histamine mediated by H₁ receptors, with a biphasic response profile reflecting both direct and indirect effects on afferent firing. There is, therefore, the potential for both histamine and 5-HT to directly and independently stimulate vagal input to the brain stem. Thus another possibility is that two different subsets of vagal afferents may be activated by either 5-HT or histamine and that the information conveyed by these fibers then converges on the same population of second-order neurons in the NTS. Indeed, there is a wealth of data demonstrating a hugely convergent vagal input to the brain stem (1). However, it is also conceivable that 5-HT and histamine may act through separate receptor mechanisms on the same population of intestinal afferent nerve fibers that convey mast cell-mediated signals to the brain stem. An action at the level of the afferent nerve terminal would explain why both 5-HT₃ and H₁ receptor agonists have an inhibitory effect on mast cell-mediated afferent firing during intestinal anaphylaxis (11).

Thus the aim of this study was to investigate the relationship between histamine- and 5-HT-mediated activation of intestinal afferents in the rat by addressing the following four questions: 1) to what extent do 5-HT and histamine stimulate mesenteric afferent firing? 2) Are the responses to these mediators independent of each other? 3) What population of afferents within the mesenteric afferent bundles respond to these mediators? 4) Is this the same population(s) for both mediators?

METHODS

Afferent recordings from mesenteric nerve bundles. Experiments were performed on Hooded Lister rats (250–350 g body wt), which had been fasted for 12 h with free access to water. The institutional guidelines for the use and care of animals were followed throughout the study. Experiments were performed as previously described (12). In brief, after induction of deep anesthesia (pentobarbital sodium, 60 mg/kg ip), the animals were equipped with a tracheal and a right external and internal jugular vein cannulation. The left carotid artery was cannulated to monitor arterial blood pressure. After laparotomy was performed, a 10-cm loop of jejunum beginning at the ligament of Treitz was cannulated at both ends with two portex tubes to allow intraluminal perfusion with normal saline (1 ml/h) to maintain a luminal pressure at a constant level. A mesenteric nerve was isolated from a single neurovascular bundle that was located ~5 cm distal to the ligament of Treitz. The proximal end of the nerve was cut at a distance of 10–15 mm from the jejunal wall and placed on one arm of a bipolar platinum electrode. A strip of connective tissue was wrapped around the second arm, serving as indifferent electrode. Thus multiunit afferent recordings were obtained from the mesenteric nerve. The electrophysiological signal was amplified (DAM 50; World Precision Instruments, Sarasota, FL) and filtered with a band pass between 100 and 1,000 Hz. Signals were displayed on an oscilloscope (TDS 310; Tektronix, Cologne, Germany) and recorded on a DAT recorder (DTC 60 ES; Sony, Cologne, Germany) for off-line computer analysis (CED1401+ interface board and Spike2 software; Cambridge Electronic Design, Cambridge, UK).

Responses to 2-methyl-5-HT and histamine. A 20-min baseline recording was allowed after the nerve had been prepared for signal stabilization. Thereafter, 2-methyl-5-HT (2m5HT; 160 nmol/kg) and histamine (8 μmol/kg) were administered intravenously, with subsequent administrations following restoration of baseline parameters. As the afferent response to histamine decreased during repeated administration (12), the effect of ondansetron (500 μg/kg) on the responses to 2m5HT and histamine was compared with a group of vehicle-treated animals.

Mucosal anesthesia. Histamine was administered 10 min before, during, and 15 min after jejunal perfusion with 2% lidocaine. Lidocaine was perfused through the cannulated loop of jejunum for 2 min immediately before the administration of histamine. Responses to histamine were compared with those to 2m5HT, and distension was produced by injecting 1 ml of saline into the closed loop to generate a pressure of ~10 mmHg.

Chronic vagotomy. The mesenteric afferent response to histamine (8 μmol/kg) was assessed in five animals following subdiaphragmatic vagotomy performed 2 wk before experimentation to eliminate vagal fibers from within the mesenteric bundles, as described previously (7).

Data analysis. Afferent responses were characterized in terms of discharge frequency (imp/s), response duration (s), and response latency (s). Baseline discharge was determined over a 20-s period immediately before administration of histamine or 2m5HT, whereas the maximum response was quantified as the increase in discharge above baseline during a 1-s period identified as the peak in afferent firing in a sequential rate histogram. In the case of the histamine response, which was often biphasic, the maximum was determined during the first phase, which occurred rapidly (<10 s) following administration, and a second phase, which was more delayed in onset and maintained over a longer time period. During monophasic responses, the first phase was absent. The response profile was analyzed in detail in a total of 18 control experiments, 12 showing a biphasic profile and 6 a monophasic response to histamine. Treatment groups were also subjected to the detailed analysis. In the remaining experiments, the response profile was assessed qualitatively as either biphasic or monophasic for histamine and present or absent for the response to 2m5HT. The latency was a critical factor in this qualitative assessment, because the first phase of the histamine response and the response to 2m5HT occurred after a latency that coincided with the circulation delay following intravenous administration (determined in some experiments by adding dye to injection vehicle and observing its arrival in the intestinal vessels). An increase in afferent firing after a latency >5 s was taken as representing a monophasic response.

In some recordings with exceptional signal-to-noise ratio and a limited number of viable units in the mesenteric nerve bundles, it was possible to perform single-unit analysis by using a process of computerized template matching. Briefly, this procedure relies on the different amplitude and waveform of action potentials within the multiunit recording. Spike2 software automatically sets templates for these action potentials and subsequently extracts the activity of spikes that match these carefully defined templates. These data are used to construct peristimulus histograms of individual units within the whole nerve recording. The parameters used when setting up templates for single action potentials could be varied, but typically we require at least 60% of the data points to match the predefined template with an amplitude error of <2%. The details of this approach have been published previously (8).
Compounds. Histamine was purchased from Sigma (Munich, Germany). Lidocaine (2%) was obtained from Braun Melsungen (Melsungen, Germany), and 2m5HT was from Research Biochemicals International (Natick, MA). Ondansetron was a gift from Glaxo Wellcome (Stevenage, UK). All compounds were dissolved in normal saline.

Statistics. Data are presented as means ± SE. Statistical analysis was performed by using paired or unpaired t-tests as appropriate, with Bonferroni corrections employed for multiple comparisons. Significance was set at $P < 0.05$.

RESULTS

The whole nerve mesenteric afferent response to systemic administration of histamine (8 μmol/kg) was evaluated in 116 nerve bundles during the course of this and a previous study (12). In every case, histamine evoked an increase in afferent discharge, but the response pattern differed according to the bundles’ sensitivity to 2m5HT (160 nmol/kg). In 97 of 116 bundles (84%), 2m5HT evoked a short-latency, powerful but transient burst of afferent firing similar to that described previously (8). In these 2m5HT-sensitive bundles, the response to histamine was biphasic (Fig. 1). In contrast, in the 16% of mesenteric bundles in which this response to 2m5HT was absent, a monophasic rise in afferent discharge was observed following histamine administration.

The biphasic response to histamine consisted of a rapid increase in afferent firing after a latency of $3.3 ± 0.2$ s, reaching an early peak ($30 ± 4$ imp/s above a baseline discharge of $13 ± 2$ imp/s; $n = 12$) within ~1 s of the response onset. This latency is significantly delayed compared with $2.4 ± 0.3$ s following 2m5HT ($P < 0.01$), and the magnitude is significantly reduced compared with $62 ± 13$ imp/s following 2m5HT ($P < 0.05$). The transient response to histamine was followed by a second, larger, and more prolonged increase in afferent firing ($51 ± 6$ imp/s; Table 1). In bundles showing a monophasic response to histamine, the baseline discharge was similar ($16 ± 3$ imp/s; $P > 0.05$) but the early response was absent, as reflected in the significantly longer onset latency ($7.3 ± 0.5$ s), and the remaining response was not statistically different in terms of magnitude or duration from the second component of the biphasic response (Table 1). In all experiments, the afferent response to histamine was accompanied by a decrease in systemic blood pressure and a rise in intestinal pressure. These concomitant effects contribute little to the afferent nerve discharge following histamine, as has been described in detail elsewhere (12).

Histamine responses in 2m5HT-sensitive bundles: single-unit analysis. The absence of an early response to histamine in mesenteric afferent bundles that were devoid of a 2m5HT response raised the possibility that both amines could activate the same population of afferents. This hypothesis was examined using computerized template matching (8) to extract single-unit responses from within the multiunit recordings. A total of 29 histamine-sensitive single units was identified from 10 recordings in which the spike profile could be clearly discriminated. Of these, 10 units responded to 2m5HT and 8 of these showed a prominent first-phase response to histamine (Fig. 2). The remaining 19 units did not respond to 2m5HT and responded to histamine during the second phase of the histamine response.

Some afferents responded to both 2m5HT and histamine, and since the former is known to result from a direct action on a subpopulation of vagal mucosal afferents (7, 8), we hypothesized that this would be true also for the early component of the histamine response, in which case this component would be attenuated by vagotomy and mucosal anesthesia.

Effect of chronic subdiaphragmatic vagotomy. Baseline discharge in vagotomized bundles was not significantly different from control animals ($11 ± 6$ imp/s; $P > 0.05$). However, the response to 2m5HT was absent, and histamine (8 μmol/kg) evoked a monophasic response whose profile was similar to that of the monophasic control animals, although the magnitude was significantly reduced ($P < 0.05$; Table 1).

Effect of mucosal anesthesia. Mucosal anesthesia with luminal lidocaine (2%) converted a biphasic increase in afferent nerve discharge in response to histamine into a monophasic profile in which the early
component was absent (Table 1). An early peak in afferent nerve discharge of \(37 \pm 5\) imp/s above a baseline of \(18 \pm 2\) imp/s occurred \(4.9 \pm 0.9\) s after histamine administration before mucosal anesthesia but was absent during mucosal anesthesia. The early peak returned but was attenuated 15 min after anesthetic washout, reaching \(22 \pm 5\) imp/s after a latency of \(5.9 \pm 1.2\) s (\(P < 0.05\) vs. the control response before mucosal anesthesia). The second component was also significantly attenuated during mucosal anesthesia compared with the response to histamine before luminal lidocaine (\(51 \pm 7\) vs. \(25 \pm 8\) imp/s; \(P < 0.001\); \(n = 6\)). The peak discharge response to 2m5HT was similarly attenuated by mucosal anesthesia (Table 1) and partially recovered on washout.

Afferent sensitivity following histamine or 5-HT receptor antagonists. The observations that sensitivity to 2m5HT and the early histamine response occur in the same population of afferents and are attenuated in parallel by vagotomy and mucosal anesthesia could be explained if the response to histamine was indirect following the release of endogenous 5-HT and subsequent activation of 5-HT3 receptors on the terminals of vagal mucosal afferents. If this were the case, then the response to histamine would be attenuated by treatment with a 5-HT3 receptor antagonist. However, the response to histamine remained biphasic after treatment with ondansetron (500 \(\mu\)g/kg iv; \(n = 4\)). Peak discharge frequency in the first phase of the histamine response was \(33 \pm 7\) imp/s above a baseline discharge rate of \(15 \pm 4\) imp/s after ondansetron compared with a peak of \(27 \pm 5\) imp/s in vehicle-treated animals (\(n = 6\)), and the response latency was \(4.2 \pm 0.5\) and \(3.8 \pm 0.3\) s, respectively. Ondansetron abolished the afferent response to 2m5HT. The histamine H1 receptor antagonist pyrilamine (5 mg/kg) abolished the response to histamine H1 receptor antagonists pyrilamine (5 mg/kg) abolished the response to histamine.

Table 1. Responses to histamine and 2m5HT under the various experimental conditions

<table>
<thead>
<tr>
<th></th>
<th>Control</th>
<th>Ondansetron, 500 (\mu)g/kg</th>
<th>Pyrilamine, 5 mg/kg</th>
<th>Chronic Vagotomy</th>
<th>Mucosal Anesthesia</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Discharge to 2m5HT</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Max (\Delta), imp/s</td>
<td>62 (\pm 13)</td>
<td>61 (\pm 19)</td>
<td>(14.7 \pm 2.7^*)</td>
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<tr>
<td>Latency, s</td>
<td>2.4 (\pm 0.3)</td>
<td>2.6 (\pm 0.7)</td>
<td></td>
<td></td>
<td>(6.3 \pm 2.7^*)</td>
</tr>
<tr>
<td><strong>Characteristics of the histamine response</strong></td>
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<tr>
<td>Profile</td>
<td>biphasic</td>
<td>monophasic</td>
<td>biphasic</td>
<td>monophasic</td>
<td>monophasic</td>
</tr>
<tr>
<td>Latency, s</td>
<td>3.3 (\pm 0.2)</td>
<td>7.3 (\pm 0.5^*)</td>
<td>4.2 (\pm 0.5)</td>
<td>6.8 (\pm 1.1^*)</td>
<td>11.3 (\pm 0.9^*)</td>
</tr>
<tr>
<td>Max (\Delta), imp/s</td>
<td>30 (\pm 4)</td>
<td>absent</td>
<td>33 (\pm 7)</td>
<td>absent</td>
<td></td>
</tr>
<tr>
<td>Second component</td>
<td>51 (\pm 6)</td>
<td>64 (\pm 5)</td>
<td>37 (\pm 12)</td>
<td>30 (\pm 8^*)</td>
<td>25 (\pm 8^*)</td>
</tr>
<tr>
<td>Duration, s</td>
<td>29 (\pm 2)</td>
<td>28 (\pm 4)</td>
<td>30 (\pm 3)</td>
<td>24 (\pm 4)</td>
<td>27 (\pm 3)</td>
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<tr>
<td>(n)</td>
<td>12</td>
<td>6</td>
<td>4</td>
<td>6</td>
<td>6</td>
</tr>
</tbody>
</table>

Values are means \(\pm SE\). 2m5HT, 2-methyl-5-HT; \(\Delta\), change. \(^*P < 0.05\) vs. biphasic control response.
histamine but had no effect on the 2m5HT response (Table 1).

DISCUSSION

Histamine exerts a powerful influence on the firing of mesenteric afferent fibers supplying the rat jejunum. The complexity of the response to histamine reflects the contribution of different fibers supplying different elements within the gut wall. In this respect, there are at least two components to the response profile described previously (12). The first component has a short latency comparable to the circulation time from the jugular vein injection site to the gut wall and a transient period of activation lasting just a few seconds. In contrast, the second component has both a longer latency and a prolonged period of activation. One possible explanation would be that these two components of the response are mediated by different populations of afferents. Analogous to our previous investigations of the mediator 5-HT, the first component potentially arises from a mucosal site of origin (7). This would be in keeping with the potential source of endogenous histamine in the mucosal mast cells that are abundant in the gut wall and closely associated with the terminals of vagal afferent fibers (21). In the rat, mast cells are also a source of 5-HT (4), and this amine also has a powerful influence on mesenteric afferent firing through an action on 5-HT$_3$ receptors on the sensory nerve terminal (8). In the present study, we demonstrate that the majority of mesenteric nerve bundles respond to both histamine and the 5-HT$_3$ receptor agonist 2m5HT. In bundles with this cosensitivity, the histamine response is biphasic with an early component, the profile of which is similar to that to 2m5HT in terms of both latency and duration. In contrast, mesenteric bundles lacking a response to 2m5HT also lacked the early component of the response to histamine. This strong correlation between 2m5HT sensitivity and an early response to histamine suggests that these two amines act on the same population of afferent fibers that is present in most but not all mesenteric nerve bundles. This conclusion is supported by analysis of single-unit activity that indeed identifies some afferents that respond to 2m5HT and histamine with a similar latency and duration. Furthermore, these afferents are distinct from those that show a delayed and prolonged activation. That many of these latter fibers do not respond to distension supports the conclusion of our earlier study (12) that this component of the histamine response is, at least, not completely mediated by mechanosensitive afferents that are activated secondary to a histamine-mediated motor response.

The latency of the response to 2m5HT was shorter than that to histamine, and the magnitude of the response to the former was also greater. This observation may be consistent with the different signal transduction mechanisms for the two amines, with 5-HT$_3$ receptors being ligand-gated ion channels that, on activation, would lead to rapid depolarization and the generation of action potentials (9). The histamine-mediated response, although slower in onset compared with 2m5HT, is still relatively rapid, which is consistent with a direct action of histamine on the G protein-coupled H$_1$ receptor on the sensory nerve terminal. However, the difference in latency to systemic administration of the amines is unlikely to be of functional significance, since these mediators would normally be generated and released from within the gut wall. Indeed, it has been recently demonstrated that vagal afferents respond to 5-HT in the intestinal lumen, which evokes a maintained burst of firing compared with our transient responses to systemic administration (22). Since the terminals lie in the lamina propria, they will be accessible from both the blood and the lumen. The transient nature of the response to 2m5HT and the initial histamine response is likely to arise from the pulse of mediator as it arrives in the gut wall following systemic delivery, whereas the maintained response to luminal exposure may reflect the more prolonged exposure as the mediator diffuses across the epithelial barrier.

One possible explanation for the cosensitivity between 5-HT and histamine could be that one amine causes the release of the other either from mast cells or other sources in the gut wall, especially the enterochromaffin cell. A common mediator may subsequently stimulate the mesenteric afferents. This possibility, however, appears to be ruled out by the observation that the first component of the histamine response is not influenced by 5-HT$_3$ receptor blockade and, vice versa, the 2m5HT response is unaffected by pyrilamine, the H$_1$ receptor antagonist. It would appear therefore that both 2m5HT and histamine exert their action at the level of the afferent nerve terminal. Certainly, 5-HT$_3$ and H$_1$ receptors are expressed on the somata of extrinsic afferents (15, 17), and these are likely to be transported to the periphery with the potential to affect afferent excitability.

2m5HT sensitivity has been shown to rely on the integrity of vagal afferents supplying the intestinal mucosa (7). If this same population mediates the first component of the response to histamine, then one would expect this component to be lost when vagal fibers are eliminated from the bundles after chronic vagotomy or when the terminals of the mucosal afferents are exposed to local anesthetic. From the current data, this indeed appears to be the case. A monophasic response corresponding to the second component of the histamine response in controls was observed in vagotomized animals, indicating that this component of the histamine response is primarily generated by spinal afferents, although the contribution from intestinofugal fibers cannot be discounted at this stage. However, spinal afferents do express H$_1$ receptors, and serosal afferents respond to algesic chemical mediators like bradykinin, a response that can be potentiated by histamine (2). The observation that luminal lidocaine reversibly converted a biphasic response into one in which the first component was absent is indicative of a mucosal population of afferent terminals. In summary, the first component of the afferent nerve response to
histamine appeared to be mediated by 5-HT-sensitive vagal afferents originating in the intestinal mucosa. Classically, the afferent innervation of the gastrointestinal tract can be divided into vagal afferents projecting to the brain stem and spinal afferents projecting to the spinal cord (5). A functional interaction between mucosal mast cells and vagal afferents is suggested under the brain stem activation that follows intestinal anaphylaxis (3, 13), although spinal afferents have also been implicated (20). Previous work from our laboratory has demonstrated a marked mast cell-mediated afferent activation during intestinal anaphylaxis (11). The present observation that cosensitization to 2m5HT and histamine is a property of vagal afferents would enable the central nervous system to spinal cord. Thus afferent sensitivity to mast cell mediators in the bowel wall is suggested to underlie the brain stem activation that follows intestinal anaphylaxis (11). The present observation that cosensitization to 2m5HT and histamine is a property of vagal afferents supports the view that information transfer concerning these events in the bowel wall is transmitted primarily to the brain stem and not the spinal cord. Thus afferent sensitivity to mast cell mediators would enable the central nervous system to perceive mucosal "inflammation" in the upper gastrointestinal tract. Following this central perception, an afferent output from the central nervous system may be conceivable that could serve to organize the peripheral inflammatory response in the gut. Interestingly, there is some data indicating that the central nervous system indeed appears to modulate mast cell function via a vagal afferent pathway (14, 18).

In conclusion, the present experiments consolidate our previous observations, which showed that histamine has the potential to act as a mediator for mast cell signaling to afferent nerve in the intestinal mucosa. We, furthermore, provide evidence that part of the histamine sensitivity of mesenteric afferent nerves is mediated by vagal afferents. These afferents, which appear to be sensitive to both 5-HT and histamine, may act to transmit specific information concerning inflammation in the gut mucosa to the central nervous system.

This study was supported by the Deutsche Forschungsgemeinschaft, Grant no. Kr 1816/3-3.

This study was performed at the University of Tubingen.

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