Involvement of mast cells in basal and neurotensin-induced intestinal absorption of taurocholate in rats

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Gui, Xianyong and Robert E. Carraway. Involvement of mast cells in basal and neurotensin-induced intestinal absorption of taurocholate in rats. Am J Physiol Gastrointest Liver Physiol 287: G408–G416, 2004. First published December 23, 2003; 10.1152/ajpgi.00178.2003.—Neurotensin (NT), a hormone released from intestine by ingested fat, facilitates lipid digestion by stimulating pancreatic secretion and slowing the movement of chyme. In addition, NT can contract the gall bladder and enhance the enterohepatic circulation (EHC) of bile acids to promote micelle formation. Our recent finding that NT enhanced and an NT antagonist inhibited [3H]taurocholate ([3H]TC) absorption from proximal rat small intestine indicated a role for endogenous NT in the regulation of EHC. Here, we postulate the involvement of intestinal mast cells in the TC uptake process and in the stimulatory effect of NT. In anesthetized rats with the bile duct cannulated for bile collection, infusion of NT (10 pmol·kg-1·min-1) enhanced the [3H]TC recovery rate from duodenjejunum by 2.2-fold. This response was abolished by pretreatment with mast cell stabilizers (cromoglycate, doxantrazole) and inhibitors of mast cell mediators (diphenhydramine, metergoline, zileuton). In contrast, mast cell degranulators (compound 48/80, substance P) and mast cell mediators (histamine, leukotriene C4) reproduced the effect of NT. Nω-nitro-l-arginine methyl ester enhanced and l-arginine inhibited basal and NT-induced TC uptake, consistent with the known inhibitory effect of nitric oxide (NO) on mast cell reactivity. These results argue that basal and NT-stimulated TC uptake in rat jejunum are similarly dependent on mast cells, are largely mediated by release of mast cell mediators, and are subject to regulation by NO.

Evidence linking NT with intestinal BA cycling can be summarized as follows. NT secretion and conjugated BA absorption follow a similar pattern, increasing with eating and decreasing with fasting (17). Infusion of NT into fasted rats, at doses giving near physiological blood levels, specifically enhanced intestinal absorption of taurocholate (TC), the primary conjugated BA, without altering that for cholic acid, its unconjugated counterpart (25). More importantly, infusion of NT antagonist SR-48692 inhibited intestinal TC absorption, suggesting a role for endogenous NT in this process (26). The effect of NT was more evident in proximal than in distal intestine, and it appeared to involve carrier-mediated absorption rather than active transport. Although the distal intestine, which is endowed with a specific Na+-BA cotransporter, has been classically regarded as the primary site of BA absorption (31), work indicates that >60% of the TC secreted into rat (41) and pig (33) intestine is absorbed before it reaches the ileum. Thus the work on NT is consistent with this new school of thought that contends that proximal intestine plays a major role in BA cycling and that distal intestine functions mostly to ensure that any remaining BA is not lost into the colon. With this model in mind, NT appears to be a good candidate regulator for BA cycling.

A detailed study regarding the effects of NT on intestinal uptake of model compounds known to permeate the epithelium via specific routes gave results consistent with an effect of NT on paracellular permeability and/or vascular permeability (25). Various physiological and pathological conditions, such as...
food digestion (13), food allergy (52), and inflammation (23), are known to alter epithelial and vascular permeability. Mast cell activation occurs in many of these conditions, and mediators released from mast cells play a prominent role in initiating the permeability change (39). Given that NT is a potent activator of mast cells (8, 55) and that mast cells contribute to its effects on vascular permeability (9) and its involvement in stress-induced reactions (11) and gut inflammation (12), it seems reasonable to propose that the effect of NT on intestinal TC absorption involves mast cells.

The present study aimed to determine whether the enhancing effect of NT on intestinal TC absorption is mast cell dependent and whether it can be reproduced by mast cell mediators. We tested the effects of mast cell stabilizers and stimulants as well as antagonists that specifically block the formation of or actions of histamine, serotonin, leukotriene C₄ (LTC₄), and nitric oxide (NO). Our results implicate mast cells not only in the response to NT, but also in the normal TC uptake process.

MATERIALS AND METHODS

Materials. Sodium chromoglycate, doxantrazole, diphenhydramine, cymetidine, metergoline, indomethacin, NT, TC (sodium salt), PGE₂, substance P, l-arginine, N⁶-nitro-l-arginine methyl ester (L-NAME) hydrochloride, and buffer salts were purchased from Sigma-Aldrich (St Louis, MO). [³H]TC was obtained from New England Nuclear (Boston, MA). LTC₄ was from Cayman Chemical (Ann Arbor, MI). Sano Recherche (Montpellier, France) supplied SR-48692. Stocks of NT (1 mM) and SR-48692 (1 mM; DMSO) were at

Fig 1. Rate of TC uptake from proximal intestine was enhanced by neurotensin (NT) (A), compound 48/80 (B), and substance P (SP; C and D), and these effects were inhibited by mast cell (MC) stabilizers. Infusion of stimuli began at −20 min, [³H]taurocholate ([³H]TC) was injected at 0 min (arrow), and MC stabilizers were given at times shown (arrows). Cumulative recovery (%) of the administered dose of [³H]TC is plotted as a function of time (means ± SE; n = 5). A: enhancing effect of NT (10 pmol·kg⁻¹·min⁻¹) on TC uptake was abolished (P < 0.01) by pretreatment with cromoglycate (1 mg/kg) or doxantrazole (10 mg/kg). B: compound 48/80 (1 μg·kg⁻¹·min⁻¹) enhanced TC uptake (P < 0.01). C: SP (400 pmol·kg⁻¹·min⁻¹) enhanced TC uptake (P < 0.01), but SP (10 pmol·kg⁻¹·min⁻¹) had no effect. D: response to SP (400 pmol·kg⁻¹·min⁻¹) was inhibited by cromoglycate (P < 0.05) and doxantrazole (P < 0.05).
to −0.24%/min (NT). To test the involvement of mast cells in this response, we examined effects of the mast cell stabilizers sodium cromoglycate and doxantrazole on the response to NT. Pretreatment of rats with cromoglycate (1 mg/kg) or with doxantrazole (10 mg/kg) 10 min before testing abolished the effect of NT, giving TC recovery rates similar to that for saline-injected controls (Fig. 1A).

Activators of mast cells mimicked the effect of NT on [3H]TC uptake. Intravenous infusion of the mast cell degranulator compound 48/80 (500 pmol·kg⁻¹·min⁻¹) into biliary fistula rats enhanced the [3H]TC uptake rate by 2.5-fold (Fig. 1B; Table 1). A similar response (Fig. 1C; Table 1) was obtained by infusing substance P (400 pmol·kg⁻¹·min⁻¹), an inflammatory neuropeptide shown to increase mucosal permeability (23). However, substance P was less potent than NT, because it was ineffective at a dose of 10 pmol·kg⁻¹·min⁻¹ (Fig. 1C). Pretreating the rats with mast cell stabilizer cromoglycate or doxantrazole greatly inhibited the response to substance P (Fig. 1D), showing that it was mast cell mediated.

Diphenhydramine blocked the effect of NT on [3H]TC uptake. Because rat mast cells release histamine in response to NT in vitro (8) and in vivo (9), we tested the effects of antihistamines on the [3H]TC response to NT. Pretreatment of rats with H₁-histamine receptor antagonist diphenhydramine (5 mg/kg) given 40 min before testing abolished the TC uptake response to NT (Fig. 2A). In contrast, the H₂-histamine receptor antagonist cimetidine (10 mg/kg) given similarly did not alter the effect of NT (Fig. 2A). These data indicated that histamine, acting via H₁-histamine receptors, was a potential mediator of the response to NT.

Histamine mimicked the effect of NT on [3H]TC uptake. Histamine appears to be rapidly destroyed in the blood circulation of rats, because its half-life is estimated at <1 min (49). When infused into the femoral vein of bile fistula rats, histamine (275 nmol·kg⁻¹·min⁻¹) did not alter [3H]TC uptake (data not shown). However, when given into the mesenteric artery of the intestine, histamine (275 nmol·kg⁻¹·min⁻¹) enhanced the rate of [3H]TC uptake by 2.5-fold (Fig. 2B; Table 1), reproducing the effect of NT. These data indicated that mast cells directed the response to NT.

### Table 1. Effect of mast cell-directed agents on rate of [3H]TC uptake from rat duodenojejunum in vivo

<table>
<thead>
<tr>
<th>Agent</th>
<th>Dose, pmol·kg⁻¹·min⁻¹</th>
<th>[3H]TC Uptake Rate, %/min</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vehicle</td>
<td></td>
<td></td>
</tr>
<tr>
<td>NT</td>
<td>10.0</td>
<td>0.10 ± 0.01</td>
</tr>
<tr>
<td>Compound 48/80</td>
<td>1000.0</td>
<td>0.24 ± 0.04</td>
</tr>
<tr>
<td>Substance P</td>
<td>400.0</td>
<td>0.21 ± 0.04</td>
</tr>
<tr>
<td>Histamine†</td>
<td>2.8 ± 10⁶</td>
<td>0.25 ± 0.02</td>
</tr>
<tr>
<td>LTC₄†</td>
<td>9.6 ± 10⁶</td>
<td>0.31 ± 0.03</td>
</tr>
<tr>
<td>L-NAME</td>
<td>9.3 ± 10⁶</td>
<td>0.30 ± 0.04</td>
</tr>
<tr>
<td>PGE₂</td>
<td>5.7 ± 10⁶</td>
<td>0.10 ± 0.02</td>
</tr>
<tr>
<td>L-Arginine</td>
<td>5.7 ± 10⁶</td>
<td>0.035 ± 0.01</td>
</tr>
<tr>
<td>Cromoglycate†</td>
<td>0.02 ± 0.033</td>
<td></td>
</tr>
<tr>
<td>Doxantrazole‡</td>
<td>0.04 ± 0.008</td>
<td></td>
</tr>
</tbody>
</table>

Values are means ± SE. Agents were infused intravenously with [3H]taurocholate ([3H]TC), which was injected into the duodenojejunum, and the rate of [3H]TC uptake was calculated from the slope of the cumulative uptake profile. NT, neurotensin; L-NAME, N⁶-nitro-L-arginine methyl ester. †Histamine was given intra-arterially and leukotriene C₄ (LTC₄) was given as a bolus. Dosages of cromoglycate and doxantrazole are given in Experimental procedures. ‡Results were significantly different from vehicle control (P < 0.05).
Histamine was a potential mediator of the effect of NT, but only when given locally or released locally (i.e., from mast cells within the intestine, not from distant mast cells). Consistent with this, blood levels of histamine were not elevated during NT infusion into these rats, in that histamine concentration was $\leq 50 \text{ nM}$ before and after 5, 15, and 60 min of 10 pmol $\text{kg}^{-1}\text{min}^{-1}$ NT infusion.

Metergoline reduced the effect of NT on $[^{3}\text{H}]\text{TC}$ uptake. Because NT also stimulates the release of serotonin from rat mast cells, we tested the effect of metergoline, a type 1 serotonin receptor antagonist (9), on the $[^{3}\text{H}]\text{TC}$ uptake response to NT. Pretreatment of rats with metergoline (2 mg/kg) 20 min before testing did not alter basal $[^{3}\text{H}]\text{TC}$ uptake; however, it significantly inhibited (by $\sim 50\%$) the response to NT (Fig. 2C). These data indicated that serotonin participated in the TC uptake response to NT.

Zileuton reduced the effect of NT on $[^{3}\text{H}]\text{TC}$ uptake. When given intravenously to rats, NT stimulates mast cell-dependent leukotriene formation, presumably by enhancing 5-lipoxygenase (5-LOX) activity (9). To investigate the involvement of 5-LOX in the $[^{3}\text{H}]\text{TC}$ uptake response to NT, we tested the effect of zileuton, an orally active 5-LOX inhibitor (10). In rats pretreated with zileuton (100 mg/kg) 60 min before testing, the effect of NT on $[^{3}\text{H}]\text{TC}$ uptake was abolished (Fig. 2D).

LTC$_4$ mimicked the effect of NT on $[^{3}\text{H}]\text{TC}$ uptake. Bolus injection of LTC$_4$ (60 µg/kg) produced an enhancement of $[^{3}\text{H}]\text{TC}$ uptake (Fig. 3A) similar to that produced by NT (Table 1). When infused at a lower dose (10 µg $\text{kg}^{-1}\text{min}^{-1}$), LTC$_4$...
Indomethacin did not alter the effect of NT on $[^3\text{H}]$TC uptake. To investigate involvement of prostaglandins in the $[^3\text{H}]$TC response to NT, we tested the effect of indomethacin, a cyclooxygenase inhibitor (27). NT was as effective in rats pretreated with indomethacin (10 mg/kg) 30 min before testing as it was in control rats (Fig. 3B), indicating that prostaglandins were not essential participants.

PGE$_2$ enhanced the effect of NT on $[^3\text{H}]$TC uptake. By increasing blood flow, vasodilatory prostaglandins such as PGE$_2$ can enhance permeability responses to leukotrienes. Because our results implicated LTC$_4$ in the $[^3\text{H}]$TC uptake response to NT, we tested the effect of PGE$_2$ on the response to NT. Although PGE$_2$ (2 $\mu$g·kg$^{-1}$·min$^{-1}$) by itself had little effect on $[^3\text{H}]$TC uptake (Fig. 3B; Table 1), PGE$_2$ enhanced the response to NT (10 pmol·kg$^{-1}$·min$^{-1}$) approximately twofold throughout the time course (Fig. 3B). These data were consistent with the participation of LTC$_4$ in the TC uptake response to NT and indicated that the response could be potentiated by PGE$_2$.

**1-NAME enhanced $[^3\text{H}]$TC uptake by an effect not involving type 1 NT receptor.** Because NO synthase (NOS) can participate in reactions involving changes in intestinal permeability (38), we tested the effects of agents known to alter its action. We found that the NOS inhibitor 1-NAME (40 mg/kg) given 20 min before testing enhanced $[^3\text{H}]$TC uptake, producing an effect equivalent to that of NT (Fig. 4A; Table 1). NT receptor (NTR1) antagonist SR-48692 (1 mg/kg ip) given 20 min before testing inhibited the response to NT (data not shown) but had little effect on the response to 1-NAME (Fig. 4B), indicating that 1-NAME was not acting via NTR1. These data were consistent with other work showing that 1-NAME can enhance intestinal epithelial permeability by disrupting the stabilizing effects of NO on mast cells (36).

**1-NAME enhanced and l-arginine inhibited the effect of NT on $[^3\text{H}]$TC uptake.** The effect of NT was enhanced by 1-NAME (Fig. 4C; 2-fold increase). In contrast, NOS substrate l-arginine (200 mg/kg), given 20 min before testing, inhibited the effect of NT (Fig. 4D; 90% decrease). These results suggested that NO production acted negatively on the response to NT, which is consistent with prior work showing that NO donors inhibit mast cell reactivity in vivo (53).

Mast cell stabilizers and l-arginine reduced basal $[^3\text{H}]$TC uptake rate. The basal $[^3\text{H}]$TC uptake rate in saline-infused rats was reduced by >50% in animals given cromoglycate, dexamethasone, or l-arginine (Fig. 5; Table 1). Because each of these agents exerted a stabilizing effect on mast cells, these results argue strongly that ≤50% of the basal TC uptake rate was attributable to mast cell-derived activity.

**DISCUSSION**

This paper extends our earlier finding (25, 26) that physiological doses of NT enhance intestinal absorption of TC, the primary conjugated BA in rats, by demonstrating the involvement of mast cells and mast cell mediators in this response. Mast cell stabilizers not only blocked the stimulatory effect of NT but they also diminished the basal rate of TC uptake, implicating mast cells in the physiological process. In addition, the effect of NT was inhibited by preventing mast cell mediators (histamine, serotonin, LTC$_4$) from acting, and it was reproduced by infusion of these mediators. Because intestinal uptake of BA is rate determining for operation of the EHC,
These findings suggest that the NT-mast cell axis could play an important role in regulating the availability of BA to promote lipid digestion and absorption. Although the involvement of mast cells in intestinal inflammation and pathological conditions is well established (27), there is little information on their participation in BA physiology (31). Here, we suggest that intestinal mast cells regulate epithelial and/or vascular permeability to promote the physiological absorption and recycling of BA.

Some NT effects are mediated by mast cells. The idea that mast cells mediate some of the effects of NT has a strong foundation (7). Bolus injection of a large quantity of NT (40 nmol/kg) into rats produces an anaphylactic reaction involving the release of mast cell-derived histamine and leukotrienes (9). The ensuing hypotension, increased vascular permeability, and cyanosis can be prevented by prior treatment with cromoglycate to stabilize mast cells (9) or with compound 48/80 to deplete mast cell mediators (8). Other effects of NT that can be blocked by mast cell stabilizers and antihistaminic agents include vasoconstriction (37), hypothermia (34), and contraction of gastric smooth muscle (43). The ability of NT to bind to and to degranulate isolated mast cells has been demonstrated (8), and the existence of NTR1 on mast cells has been confirmed by mRNA and protein analyses (20, 44). In fact, NT is the only mast cell secretagogue for which a specific G protein-coupled receptor has been identified in mast cells.

**NT and mast cells interact in intestinal mucosa.** In the small intestine, NT is primarily localized to epithelial endocrine

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**Fig. 4.** Nitric oxide synthase (NOS) inhibitor N\(^\circ\)-nitro-L-arginine methyl ester (L-NAME) increased \(^3\)H-TC uptake (A); the effect was independent of NTR1 (B), and it enhanced the response to NT (C); in contrast, NOS substrate (L-arginine) inhibited the effect of NT (D). Stimuli were given at -20 min, and \(^3\)H-TC was given at 0 min (arrow). Cumulative recovery (%) of the administered dose of \(^3\)H-TC is plotted as a function of time (means ± SE; n = 6). A: L-NAME (40 mg/kg bolus, followed by 25 µg·kg\(^{-1}\)·min\(^{-1}\) infusion) enhanced \(^3\)H-TC uptake (P < 0.01). B: pretreatment with SR-48692 (1 mg/kg) did not alter the response to L-NAME, although it blocked the response to NT (data not shown). C: L-NAME enhanced the response to 10 pmol·kg\(^{-1}\)·min\(^{-1}\) NT (P < 0.05). D: L-arginine (200 mg/kg bolus, followed by 1 mg·kg\(^{-1}\)·min\(^{-1}\) infusion) inhibited the response to 10 pmol·kg\(^{-1}\)·min\(^{-1}\) NT (P < 0.05).
cells, although it is also present in neurons of the mucosa, submucosa, and muscular (50). Endocrine and/or paracrine release of NT occurs postprandially (51) and is best stimulated by fatty acids (22), BA (16), and hormones (18). The intestinal mucosa is highly enriched with mast cells, which are often closely opposed to and interacting with enteric neurons (59) and vascular elements (38). As an integral part of the nerve-endocrine-immune network, mast cells participate in aspects of inflammation, and they also contribute to physiological regulation. Examples of the latter include the involvement of mast cells in cholecystokinin-induced disruption of the intestinal migrating motor complex (32) and in distension-induced and substance P-induced intestinal secretion (19). Some evidence attests to the importance of NT-mast cell interactions in inflammation. For example, pretreatment of rats with NTR1 antagonist SR-48692 inhibits stress-induced (11) and toxin A-induced (12) intestinal mast cell activation and the associated changes in intestinal permeability and secretion of PGE2 and mucin. These actions could involve both direct and indirect effects of NT on mast cells, because NT stimulates enteric nerves to secrete acetylcholine and substance P (7), which enhance the release of mast cell mediators (40, 42), and mast cell mediators further stimulate enteric neurons (15, 45). The close relationship between NT and mast cells in pathophysiological situations suggests that their interaction may also be utilized physiologically.

**Mast cell activation is essential for basal and NT-stimulated TC uptake.** Our data show that structurally distinct mast cell degranulators (compound 48/80, substance P, and L-NAME) enhanced the rate of TC absorption, reproducing the effect of NT. In contrast, agents purported to stabilize mast cells (cromoglycate, doxantrasole, L-arginine) reduced basal and NT-stimulated TC uptake. These findings support our contention that mast cells participate in TC uptake and mediate the enhancing effect of NT. Tissue mast cells are heterogeneous, and intestinal mast cells are more sensitive to the inhibitory effects of cromoglycate than are mast cells from other tissues such as lung and skin (46). The fact that cromoglycate totally blocked the effect of NT on TC uptake suggests that this response involves the activation of mast cells within the intestine. There are at least two types of mast cells, mucosal-type mast cells (MMC) and connective tissue-type mast cells (CTMC), in the intestine. Although NT (48) and substance P (56) can stimulate both MMC and CTMC, compound 48/80 is relatively specific for CTMC. Similarly, doxantrasole inhibits the activation of both MMC and CTMC, whereas cromoglycate primarily affects CTMC (47). Our results are most consistent with the involvement of CTMC but do not exclude the participation of MMC in the response to NT. The fact that CTMC are associated with the vasculature suggests that effects on vascular permeability could contribute to NT’s effect on [3H]TC uptake. The localization of MMC just below the epithelial layer suggests that effects on epithelial permeability (36, 54) could also be important.

**Mast cell-derived mediators enhance TC uptake.** The inhibitory effects of pretreating rats with diphenhydramine and zileuton implicate histamine and leukotriene as obligatory participants in the response to NT. The fact that histamine and LTC4 were capable of enhancing TC uptake supports this contention. Metergoline gave partial inhibition of the NT response, suggesting that serotonin could be a minor contributor. In prior work, we showed that in rats NT causes a rapid release of mast cell histamine, followed by leukotriene generation (9). Because histamine stimulates formation of leukotrienes (7), and because LTC4 is a powerful permeability enhancer (27), it seems likely that NT acts by releasing histamine that generates leukotrienes, the final mediators of the response.

Fig. 5. Basal [3H]TC uptake was inhibited by MC stabilizers cromoglycate (A), doxantrazole (A), and L-arginine (B). [3H]TC was injected at 0 min (arrow) and MC stabilizers were given at times shown (arrows). Cumulative recovery (%) of the administered dose of [3H]TC is plotted as a function of time (means ± SE; n = 6). A: basal TC uptake was inhibited 48% by doxantrazole (P < 0.01) and 73% by cromoglycate (P < 0.01). B: basal [3H]TC uptake was inhibited 54% by L-arginine (P < 0.05).
Prostaglandins are known to potentiate the effects of leukotrienes, and here we found that PGE₂, which was ineffective alone, enhanced the response to NT. The fact that systemic blood levels of histamine were not elevated during NT infusion argues that the histamine involved in NT-induced TC uptake was produced locally.

NO and mast cells in intestinal uptake of BA. Whereas excessive NO released by inflammatory cells can damage the intestinal epithelium (24), a low level produced by the intestinal endothelium plays an important role in maintaining the epithelial barrier (1). Thus NO donors decrease epithelial permeability, whereas inhibitors of NOS have the reverse effect (57). These changes have been attributed to the stabilizing effects of NO on intestinal mast cells (35, 53). Here we found that basal and NT-induced TC uptake were inhibited in animals receiving NO donor L-arginine, whereas they were enhanced in animals that received NOS inhibitor L-NAME. These data support our contention that the enhancement of intestinal TC uptake seen in our experiments is caused by mast cell-mediated increases in intestinal permeability, and they also illustrate that this process can be modulated by NO.

Mechanisms involved in regulation of TC uptake. It is possible that NT altered the luminal [³H]TC during our experiments; however, this would not provide an explanation for the observed increase in paracellular permeability observed during development (14) and in pathological conditions involving stress (62), food allergy (39), enteritis (12), and ischemia (61). On the other hand, some findings are at odds with the hypothesis that NT increases TC uptake by increasing intestinal paracellular permeability. In the rat, NT secretion (51) and BA uptake (31) are enhanced in the fed state, yet intestinal paracellular permeability is diminished compared with the fasted condition (63). Although it is possible that NT stimulates TC transport at the level of the epithelium, it seems more likely that its effects on vascular permeability enhance the passage of TC into the circulation. It is commonly thought that passage across the intestinal epithelium is rate determining for absorption of conjugated BA (29); however, the dependence on vascular permeability has not been thoroughly examined (29). Because NT and mast cell mediators alter blood flow and dramatically increase vascular permeability to albumin, it seems likely that these effects contribute to the enhancement of TC uptake in the intestine.

In conclusion, basal and NT-stimulated TC uptake in the rat intestine are similarly dependent on mast cells, are largely mediated by release of mast cell mediators, and are subject to regulation by NO. These findings are consistent with the idea that intestinal NT is an endogenous regulator of EHC whose effects are mediated by the activation of intestinal mast cells. Although the mechanism may involve enhanced transport through the epithelium, our data are most consistent with an effect on vascular permeability and blood flow.

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GRANTS

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