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Involvement of Capsaicin-Sensitive Mechanism(s) in the Antiulcer Defence of Intestinal Mucosa in Rats (42477)

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Abstract. Capsaicin desensitization increases degree and incidence of indomethacin-induced intestinal ulcers in rats, suggesting the existence of a capsaicin-sensitive mechanism(s) in the protection of the intestinal mucosa against indomethacin-induced ulceration. Sensory innervation thus may be involved in the pathogenesis of ulcers of the small bowel, as well as in gastric ulcers. Administration of exogenous CGRP and somatostatin, sensory neuropeptides which are depleted by capsaicin desensitization, does not afford protection toward the capsaicin-induced aggravation of intestinal ulcers. The protective effect of exogenous prostaglandins toward indomethacin-induced intestinal ulceration is not mediated by capsaicin-sensitive nerve fibers.

Capsaicin-sensitive sensory fibers innervate the gastrointestinal tract of various animal species (1–3) and appear to play a relevant role in protecting gastric mucosa toward ulcerogenic agents (4, 5). In fact, systemic capsaicin desensitization increases gastric ulcers induced by pyloric ligation, acid distension (5), indomethacin, ethanol, or cysteamine (4). These studies suggest the existence of a "gastric defense mechanism" sensitive to capsaicin, which may protect the gastric mucosa from ulcerogenic stimuli by releasing neurotransmitters from sensory nerves (4, 5) and/or activating extramural antiulcer mechanisms such as those involving sympathetic reflexes (4) or the adrenal medulla (6). Capsaicin-sensitive nerve fibers have been observed in the rat small intestine (2, 3) and therefore it appeared worthwhile to investigate if an endogenous defense mechanism, similar to that described for the stomach, provides mucosal protection against ulcerogenic factors in the rat small intestine.

Materials and Methods. Male albino rats Sprague–Dawley Morini strain, 200–240 g, were housed 4–5 to a cage, at constant room temperature (21 ± 1°C) and relative humidity (60%), with water and food *ad libitum,* and a 12-hr light–dark cycle (light on 6:00 AM). Each experimental group consisted of 7–10 rats and was chosen by means of a completely randomized schedule (7).

(A) Capsaicin desensitization. Capsaicin (50 mg/kg sc, 4 days before) was administered in a volume of 2 ml/kg dissolved in a vehicle containing 10% Tween 80, 10% ethanol, and 80% saline (8). Controls received the vehicle. When administered in this schedule capsaicin produces a functional impairment of the sensory nerves in the rat small intestine (9).

(B) Indomethacin-induced intestinal ulcers. Indomethacin (Sigma), suspended in an aqueous vehicle containing 0.9% NaCl, 0.5% carboxymethylcellulose, and 0.4% Tween 80 was administered orally at doses of 4, 8, or 12 mg/kg in a volume of 5 ml/kg to select doses inducing a submaximal degree of intestinal ulceration. Animals were killed by CO_2 asphyxiation, 72 hr after indomethacin and the mid small intestine was examined carefully for presence of ulceration by an observer unaware of the treatment. Ulcers extended from the upper jejunum to the terminal ileum and are located first in the mesenteric side of the intestine. The degree of intestinal ulceration was graded according to an arbitrary scale: 0 = normal, 0.5 = lesions not completely distinct, few in number and spaced far apart, 1 = one or two lesions individually distinct and not coalescing to form linear bands with areas of normal tissue between them, 1.5 = distinct lesions between two and six, 2 = numerous lesions coalescing in areas forming linear ulcers, 2.5 = lesions with loops and a little formation of peritoneal exudate, 3 = perforating ulcers and intestinal adhesions with formation of abundant peritoneal exudate.

Oral dmPGE2 (0.01 mg/kg, Upjohn), sub-

0037-9727/87 $1.50

TABLE I. EFFECT OF CAPSAICIN DESENSITIZATION ON INDOMETHACIN-INDUCED INTESTINAL ULCERS

Capsaicin pretreatment	Treatment (mg/kg os)	Intestinal ulcers		
		Animals ulcerated	% Incidence	Degree (mean score)
No	Indomethacin 4	2/9	22	0.11
Yes	Indomethacin 4	7/8	85.7*	0.69**
No	Indomethacin 8	8/8	100	1.38
Yes	Indomethacin 8	8/8	100	2.69*

* $P < 0.05$, ** $P < 0.01$, compared to capsaicin untreated respective group.

cutaneous somatostatin (0.1 mg/kg, Serva), or rat-calcitonin gene-related peptide (0.01 mg/kg, CGRP Peninsula), at doses which have been shown to influence other kinds of gastroduodenal ulceration (10–13), were administered dissolved in saline in a volume of 5 ml/kg, 30 min before indomethacin. Somatostatin and CGRP were tested as they are contained in capsaicin-sensitive fibers (3, 14–16) to assess their potential involvement on the small bowel's mucosal defense mechanism.

(C) Statistical analysis. Percentage incidence of intestinal ulcers was analyzed by means of the χ^2 test. Data relative to degree of intestinal ulcers were analyzed according to the Smirnov test.

Results. Orally administered indomethacin induced small intestinal ulcers in a dose-dependent manner (degree was 0.33 ± 0.14 for the group treated with 4 mg/kg, 1.64 ± 0.32 with 8 mg/kg, 2.9 ± 0.06 with 12 mg/kg; n = 8 or 9 for each group).

As shown in Table I capsaicin desensitization significantly enhanced both incidence and degree of a low dose of indomethacin (4 mg/kg os)-induced intestinal ulcers and the degree of intestinal ulcers induced by a higher dose of indomethacin (8 mg/kg os).

Subcutaneous somatostatin (0.1 mg/kg), CGRP (0.01 mg/kg), or both did not affect degree and incidence of indomethacin (8 mg/kg os)-induced intestinal ulcers either in controls or in capsaicin-desensitized animals (data not shown). On the other hand dmPGE2 (0.01 mg/kg os) reduced the degree of indomethacin (8 mg/kg os)-induced intestinal ulcers both in controls and in capsaicin-desensitized animals (Table II).

Discussion. Indomethacin induces ulcers in the small bowel in a dose-dependent manner by producing a prostaglandin deficiency (12) which reduces the defensive mechanism of the intestinal mucosa and favors the intestinal bacterial overgrowth (17). The latter transforms primary into secondary bile acids (18, 19) and has been held responsible for the mucosal damage. The observation that capsaicin desensitization, which at the dose used in this study produces a functional impairment of sensory neurons in rat small intestine (9), increases the intestinal ulceration induced by indomethacin suggests that (a) capsaicin-sen-

TABLE II. EFFECT OF dmPGE2 ON CAPSAICIN ENHANCEMENT OF INDOMETHACIN (8 mg/kg os)-INDUCED INTESTINAL ULCERS

Capsaicin pretreatment	Treatment (mg/kg os)	Intestinal ulcers		
		Animals ulcerated	% Incidence	Degree (mean score)
No	Vehicle	7/7	100	1.71
No	dmPGE2 0.01	6/7	85.7	0.79*
Yes	Vehicle	7/7	100	3.14**
Yes	dmPGE2 0.01	6/7	85.7	1.57*

* $P < 0.05$ compared to respective vehicle group.
** $P < 0.01$ compared to capsaicin untreated-vehicle group.

sitive sensory fibers play a role in an "intestinal antiulcer defence mechanism(s)" and (b) sensory innervation may be involved in the pathogenesis of indomethacin-induced intestinal ulcers.

Neuropeptides such as CGRP (3, 16), somatostatin (14), and others (20) are depleted by systemic capsaicin desensitization, and local release of neuropeptides has been hypothesized to play a role in the capsaicin-sensitive "gastric defence mechanism" (4, 5). The finding that neither exogenous CGRP nor somatostatin affected the aggravating effect of capsaicin desensitization in indomethacin-induced intestinal ulcers suggests that other neuropeptides and/or other mechanism(s) are involved in this phenomenon.

On the other hand the observation that exogenous dmPGE2 decreased indomethacin-induced intestinal ulcers both in controls and in capsaicin-desensitized animals indicates that, for the indomethacin-induced gastric ulcers (21), the protective effect of exogenous prostaglandins against intestinal ulceration is not mediated through capsaicin-sensitive fibers.

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