analysis of the initial uptake rate of propranolol by rat lung tissue, have confirmed our previous proposal for the saturation process as made from in-vivo and in-vitro investigations that there is a possible contribution from specific, high capacity sites with relatively low affinity, to the extensive pulmonary first-pass removal of the drug from the circulation.

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# Influence of capsaicin-sensitive fibres on experimentally-induced colitis in rats

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**Abstract**—Systemic capsaicin pretreatment worsens trinitrobenzene sulphonic acid-induced colitis but has no effect on colitis induced by ethanol or acetic acid. The influence of capsaicin-sensitive fibres on experimentally-induced colitis seems to depend upon the type of ulcerogenic stimuli in relation to its chronic nature.

Capsaicin, when administered in high doses induces selective degeneration (Jancsò et al 1985) and functional impairment of certain primary sensory neurons (Nagy 1982) innervating various viscera, including the gastrointestinal tract (Sternini et al 1987; Mulderry et al 1988). Subcutaneous capsaicin, at desensitizing doses, increases the degree of gastric ulcers induced by pylorus ligation, acid distension (Szolcsànyi & Barthó 1981), indomethacin, cysteamine or ethanol (Holzer & Sametz 1986), as well as duodenal ulcers induced by dulcerozine or cysteamine (Maggi et al 1987) and small intestinal lesions induced by indomethacin (Evangelista et al 1987).

Since capsaicin-sensitive afferent fibres are present also in the large intestine (Barthó & Szolcsànyi 1981) it appeared worthwhile to determine their potential involvement in the pathogenetic mechanisms of some experimentally-induced colitis in rats.

### Materials and methods

Male albino Sprague-Dawley Nossan strain, 180-210 g, were housed at constant room temperature (21 ± 1°) and relative humidity (60%) and with 12 h light-dark cycle (light on 6.00 am).

*Trinitrobenzene sulphonic acid (TNB)-induced colitis.* The rats were lightly anaesthetized with ether and a rubber cannula (8 cm long) was inserted into the colon via the anus (Wallace 1988). A solution of TNB (120 mg $mL^{-1}$) in 50% ethanol (v/v) was instilled into the lumen of the colon (total volume 0·25 mL). After 24 h or 1 week groups of rats were killed and colonic damage assessed by applying on the distal 8 cm of colon a transparent foil and tracing the borders of the necrotic area. The ulcer areas were weighed to quantitate differences between groups. The excised colonic samples were then blotted, dried overnight at 60°C in an oven and weighed. In control rats, samples of colonic tissue were taken from the same region (their mean ± s.e. weight was 114 ± 8 mg).

*Ethanol-induced colitis.* The rats were fasted overnight and 0·25 mL of 30% ethanol (v/v in distilled water) was administered intrarectally according to the method of Wallace et al (1985). Control rats were given 0·25 mL of saline in place of ethanol. Ten minutes after the ethanol challenge the rats were killed by $CO_2$ asphyxiation.

Ulcers developed in the terminal colon and were scored by an observer unaware of the treatment according to an arbitrary scale was: 0 = no visible damage, 1 = diffuse patches of superficial hyperaemia, 2 = patches of severe hyperaemia, 3 = extensive hyperaemia and haemorrhage (Wallace et al 1985).

*Acetic acid induced colitis.* The rats were fasted overnight and under light ether anaesthesia, the colon was exposed through a midline incision of the abdomen and the colon-cecum junction ligated. Two mL of a 5% acetic acid solution was injected into the lumen of the colon through a 25-gauge needle followed immediately by 3 mL of air which cleared the solution from the colon (Sharon & Stenson 1985). The incision was closed and 24 h later the animals were killed and their colon removed and the ulcers developing in the upper site of the colon scored as described for ethanol ulcers.

*Capsaicin desensitization.* Capsaicin was injected subcutaneously 50 mg $kg^{-1}$ in a volume of 2 mL $kg^{-1}$ two days after birth. Controls received the vehicle constituted by 10% ethanol, 10% Tween 80 in 0·9% NaCl in $H_2O$. The animals were used two months after this treatment.

*Data analysis.* Statistical analysis of the data related to pathologic score was performed by means of Smirnov's test for non-

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Table 1. Effect of capsaicin pretreatment on acetic acid-, ethanol- or trinitrobenzene sulphonic acid (TNB)-induced colitis.

| | | Pretreatments | |
|---|---|---|---|
| Ulcerogen | parameter | Vehicle | Capsaicin |
| Acetic acid | pathologic score | 1·31 ± 0·15 | 0·92 ± 0·23 |
| Ethanol | pathologic score | 1·17 ± 0·21 | 1·58 ± 0·24 |
| TNB (killed at 24 h) | colon dry weight (mg) | 302 ± 18 | 318 ± 35 |
| | ulcer area (% of the excised samples) | 63 ± 5 | 69 ± 7 |
| TNB (killed at 168 h) | mortality (%) | 7 | 31 |
| | colon dry weight (mg) | 349 ± 39 | 567 ± 67** |
| | ulcer area (% of the excised samples) | 40 ± 7 | 63 ± 6* |

n = 8-15 rats for each group.
* $P < 0.05$ and ** $= P < 0.01$ compared with the vehicle group.

parametric data, while all the other data were analysed by means of Student's *t*-test for unpaired samples.

## Results and discussion

Capsaicin-sensitive fibres are involved in the gastroduodenal defence mechanisms (Szolcsànyi & Barthó 1981; Holzer & Sametz 1986; Maggi et al 1987) which seem to act through the release of stored peptides (Maggi et al 1987; Holzer 1988) and/or the participitation of sympathetic reflex arcs (Holzer & Sametz 1986) and adrenal glands (Evangelista et al 1986) activated by different ulcerogenic stimuli.

Our data show that the involvement of the capsaicin-sensitive fibres at colon level depends upon the stimulus given to produce the colitis.

In fact while capsaicin desensitization worsens chronic colitis-induced by TNB, it does not affect TNB, ethanol- or acetic acid-induced acute colitis (Table 1).

When the ulcerogen produces a colitis which develops and resolves rapidly (acetic acid or ethanol, Sharon & Stenson 1985), mechanisms such as those involved in acute inflammation play a major role, while capsaicin sensitive fibres are involved in colitis of chronic nature (TNB-colitis may persist for at least 8 weeks, Wallace 1988).

This paper shows for the first time that the above mentioned fibres exert a defensive factor in the colon against the ulcerogenic stimuli but further studies are needed to clarify their role on the pathogenesis of colitis.

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