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The action of salmon calcitonin on indomethacin-induced gastric ulceration in the rat

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We have recently demonstrated that salmon calcitonin inhibited the development of indomethacin-induced gastric ulceration in the mouse when administered s.c. but not when administered intragastrally (Bates, Buckley & Strettle, 1979). Calcitonin has been shown to inhibit stress-induced gastric ulceration when administered intragastrally in several species (Barlet, 1974; Barlet & Bates, 1974; Hotz, Goebell, Minne & Ziegler, 1974), including the rat (Bates & Barlet, 1974).

We have now investigated the action of salmon calcitonin upon indomethacin-induced gastric ulceration in the rat.

Gastric ulceration was induced over a 5 h period, in starved (24 h) Sprague–Dawley rats, by the administration of indomethacin 40 mg/kg i.p. (Djahanguiri, 1969). The excised stomachs were washed through with 5 ml of distilled water and the pH measured. The ulcers were stained using a modification of the method of Robert & Nezamis (1964). Plasma calcium concentrations were measured using a Corning 940 calcium analyser.

Salmon calcitonin (0.1 MRC u/kg–100 MRC u/kg) caused an inhibition of the development of gastric ulceration when administered either s.c. or intragastrally (Figure 1). Subcutaneously administered calcitonin caused a greater inhibition of ulceration than did intragastral administration (Figure 1). Intragastral administration of 500 MRC u/kg salmon calcitonin failed to give a statistically significant inhibition of gastric ulceration. All s.c. doses of salmon calcitonin (0.1 MRC u/kg–100 MRC u/kg) caused statistically significant decreases in plasma calcium concentrations. This parameter was unaffected after intragastral administration of the hormone. Neither mode of administration caused statistically significant changes in gastric pH.

Thus it is possible to conclude that indomethacin-induced gastric ulceration in the rat, in contrast to the mouse, is sensitive to the antiulcerogenic actions of intragastrally administered calcitonin. In addition,

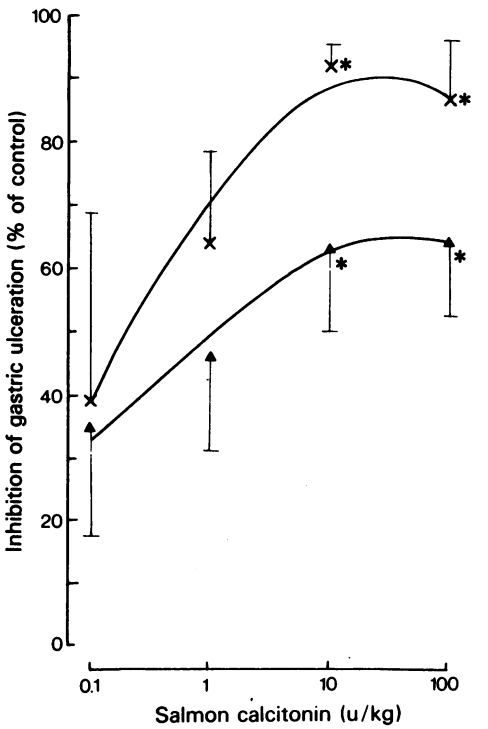

Figure 1. Effect of administration of salmon calcitonin (0.1 MRC u/kg–100 MRC u/kg) by s.c. (×——×) or intragastral (▲——▲) routes on indomethacin-induced gastric ulceration in the rat. Discrete areas larger than 1 mm in any cross-sectional dimension when viewed from the mucosal surface were scored as ulcers and the total number of such areas for each stomach was summed. Salmon calcitonin was administered in a vehicle containing 1 mg/ml bovine serum albumin in either 154 mM saline (s.c.) or distilled water (intragastral). Controls received vehicle only. Results are expressed as mean and s.e. of mean. Each value is the mean of 6 determinations. Statistically significant differences are presented between controls and calcitonin treated animals at the $P < 0.05$ level (*) (Mann-Whitney U test).

it would appear that the differences between the maximum inhibitions observed after these two routes of administration would support the contention that the mechanism(s) of action by these routes may not be identical.

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The effect of combination of aspirin and sodium salicylate on the rat stomach

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The finding that sodium salicylate could inhibit the ulcerogenic action of other non-steroidal anti-inflammatory drugs (NSAIDs) (Ezer, Palosi, Hajos & Szporny, 1976; Hayden, Thomas & West, 1978) is of considerable interest since it raises the possibility that the use of certain combinations of NSAIDs may be better tolerated in man than any of the drugs used alone. It has also been shown, however, that whilst there is a positive correlation between dose and gastrotoxicity for the NSAIDs, there is an optimal lesion-inducing dose above which the number of gastric lesions declines (Hummett, Jennewein & Waldeck, 1976). Thus it is possible that the inhibition of aspirin-induced lesions caused by sodium salicylate may be due, not so much to an antagonism, but rather to a complementary effect, where the combined dose of the two NSAIDs exceeds the optimal lesion-inducing dose.

Table 1 Effect of aspirin and sodium salicylate on the rat gastric mucosa

Dose of drug given (mg/kg)				
Aspirin	*Sodium salicylate*	*Dose expressed as mg salicylate/kg*	*Number of animals*	*Number of lesion mean ± s.e. mean*
		0	10	0.6 ± 0.2
115		87.5	10	25.2 ± 3.2
	102	87.5	10	12.4 ± 2.6
115	102	175	10	35.6 ± 3.6*
230		175	10	37.7 ± 4.1*
	205	175	10	35.0 ± 3.2*
230	205	350	10	7.2 ± 2.4
460		350	10	11.8 ± 3.6
	409	350	10	7.2 ± 2.1

* The number of lesions produced in each group receiving a total of 175 mg salicylate/kg was significantly greater ($P > 0.05$) than in each other treatment group (Student's *t*-test).