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Prevention of experimental gastric ulcer in rats by a substance which increases biosynthesis of acid mucopolysaccharides

Biosynthesis of acid mucopolysaccharides, essential components of the connective tissue, has been much studied. The simplest approach is to investigate the incorporation of $^{35}SO_4$ into cartilage. The uptake of $^{35}SO_4$ is inhibited by steroid and non-steroid anti-inflammatory agents, both *in vitro* and *in vivo* in a dose-response relation (Bollet, 1961; Whitehouse & Boström, 1962; Szigeti, Ezer & others, 1965; Ezer & Boström, 1968).

ϵ-*p*-Chlorocarbobenzoxy-L-lysin-OMe-HCl (KL–11), increased the incorporation of $^{35}SO_4$ into the cartilage of the rat *in vivo* (Szporny, Ezer & others, 1969) and also prevented the inhibition of uptake of ^{35}S caused by prednisolone.

More and more importance is now attached to acid mucopolysaccharides that are present in large amounts in the gastric mucous membrane. Denko (1958) has shown that administration of hydrocortisone to hypophysectomized rats reduced the incorporation of ^{35}S into the tissues of the stomach. Kent & Allen (1966) have found that the $^{35}SO_4$ and glucose-U-^{14}C uptake by the gastric mucosa can be inhibited by sodium salicylate. It now seems equally certain that a significant inhibition of the synthesis of acid mucopolysaccharides can be achieved in the gastric mucous membrane by anti-inflammatory drugs. Perrey (1968) has described a parallel between the erosion of the gastric mucous membrane and the inhibition of glucosamine-6-phosphate synthesis by salicylate treatment. Since great importance is attached to the mucin content of the gastric mucous membrane in protecting the gastric wall against gastric juices, particularly hydrochloric acid, it seems that the damaging effect of anti-inflammatory substances in inhibiting the synthesis of mucopolysaccharides arises in this way.

Table 1. *Incorporation of* $^{35}SO_4$ *in stomach* in vivo *after* KL–11, *sodium salicylate or phenylbutazone*

Treatment Drugs	Doses mg/kg, i.p.	Specific activity of stomach counts/min of each 100 mg of dry tissue Control (no treatment)	Treatment	Change %
KL–11	25	3520 ± 97*	12300 ± 472	+270
KL–11	50	3970 ± 103	18600 ± 1060	+370
Sodium salicylate	500	4530 ± 154	3120 ± 124	− 31
KL–11 + sodium salicylate	50 + 500	4215 ± 137	5700 ± 226	+ 36
Phenylbutazone	150	3870 ± 124	2830 ± 157	+ 27
KL—11 + phenylbutazone	50 + 150	3210 ± 116	10980 ± 484	+340
Fasting for 48 h	—	3725 ± 153	1880 ± 83	− 50

* = s.e. of 10 animals.

Table 2. *The inhibiting effect of KL–11 on the development of Shay ulcers*

Doses mg/kg s.c.	Inhibition of ulcers (%) relative to control value By number	Scoring rate
15	75·3	58·5
25	82·0	69·5
50	94·0	75·0

We have now examined the way in which KL–11 influences the sulphate metabolism of the gastric wall. Male Wistar rats, 100–120 g, were given simultaneously a single dose of KL–11 and $^{35}SO_4$, 50 μCi/100 g, per animal. Radioactivity of the gastric wall was measured 20 h after treatment. It is evident (Table 1) that KL–11 is dose-related in increasing the incorporation of $^{35}SO_4$. Also the incorporation of $^{35}SO_4$ into the gastric mucous can be decreased significantly by sodium salicylate or phenylbutazone. After fasting, $^{35}SO_4$-uptake by the stomach was also diminished. The simultaneous use of KL–11 totally compensated for the effect of the anti-inflammatory drugs and when given simultaneously with phenylbutazone, the two drugs caused a significant increase of sulphate uptake at one control value.

We also investigated the effect of KL–11 on experimental gastric ulcers. Male rats, 100–120 g, were fasted for 64 h and then 6 h after ligating the pylorus, the gastric wall was investigated (Shay, Komarov & others, 1945). The ulcers were evaluated according to Shay & others (1945) and Bonta (1961). KL–11 was administered at the same time that the pylorus was ligated and it was found to inhibit the development of ulcers significantly (Table 2).

According to our hypothesis KL–11 inhibits the onset of experimental gastric ulcer by increasing the synthesis of mucopolysaccharide of the gastric mucous membrane. Thus there seems to be a possibility for developing substances with a new mechanism of action which may play a role in preventing the damaging effect of anti-inflammatory substances exerted on the stomach, and eventually also in the therapy of ulcer.

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Differentiation of β-adrenoreceptors by the use of blocking agents

There is evidence that the β-adrenoreceptor population is comprised of at least two types designated as β-1 and β-2 (Lands, Arnold & others, 1967; Lands, Luduena & Buzzo, 1967). This sub-division was proposed to account for the differing structural requirements of catecholethanolamines for initiating β-sympathomimetic actions in different organs. The sub-division so proposed has been further supported by the recent discovery of β-agonists, such as salbutamol, with selective β-2 actions (Cullum, Farmer & others, 1969).

If β-adrenoreceptors differ significantly in their structural requirements for agonists then it is reasonable to suppose that such receptors could have different structural requirements for antagonists. Thus experiments have been made to measure quantitatively the β-adrenoreceptor blocking action (by use of pA_2 measurements) of two compounds, propranolol and ICI 50 172 (against isoprenaline) at typical β-1 and β-2 type receptors. Previous workers have shown that tissues with similar receptors can be expected to give the same pA_2 with a given antagonist (Arunlakshana & Schild, 1959). ICI 50 172 was chosen in addition to propranolol because some selectivity of blocking action for this compound has been described (Dunlop & Shanks, 1968).

Table 1. pA_2 *values for propranolol and ICI* 50 172 *on isolated tissues of the guinea-pig, rabbit and rat. Isoprenaline was used as an agonist*

Species	Preparation	Receptor type	Propranolol	ICI 50 172
Guinea-pig	Atria-force rate	β-1	8·8	7·3
Rabbit	Ileum	β-1	8·6	7·3
Guinea-pig	Trachea	β-2	8·7	5·4
"	Vas deferens	β-2	8·9*	6·8*
Rat	Uterus	β-2	8·5	5·0

* pA_2 value determined in the presence of 2 μg/ml cocaine.

Table 1 gives pA_2 values for propranolol and ICI 50 172 on isolated tissues of the guinea-pig, rabbit and rat. The pA_2 measurements were made by the method of Arunlakshana & Schild (1959) and each value was the mean of three determinations. The β-adrenoreceptor of the guinea-pig vas deferens although not previously classified, is, on the basis of work done in this laboratory, a β-2 type. Propranolol gave similar pA_2 values at both β-1 and β-2 type receptors and thus showed no selectivity in its blocking action. However, ICI 50 172 had a selective blocking action but did not always differentiate between β-1 and β-2 types since the compound showed highest activity on heart (β-1) and vas deferens (β-2) and much lower activity on ileum (β-1) and trachea (β-2).