However, the levels of PRA in the experimental group rose to 21 ng already in the 1st or 2nd week after the injection.

PATase A in the control animals rose to 40–45 ng immediately after the operation from a preoperative average of 23.4 ng. The high level was maintained for 2 weeks; then it decreased gradually in the 3rd week. In the 5th week, PATase A became lower than the preoperative level. In the experimental group, during the enzyme injection period in combination with suppression on blood pressure elevation, PATase A were usually higher than those in the control group, and became normal 2 weeks after cessation on the injection.

The results suggested that the renin angiotensin system could play an important role in the acute phase of experimental hypertension. The reasons for this conclusion are as follows; 1. the development of hypertension was suppressed by the ATase injection in acute stage, 2. the increase of PRA in the treated group suggested the existence of some feed back mechanism by the treatment with ATase in acute phase.

Zusammenfassung. In der akuten Phase der Goldblatt-Hypertonie der Ratte verhinderte die Injektion von reiner Angiotensinase ein Aussteigen des Blutdruckes. Die Behandlung war unwirksam bei chronischem Hochdruck.

TATSUO KOKUBU[3], SHIRO FUJIMOTO[4], HIROSHI AKUTSU[3], EINOSUKE UEDA[3], KUNIO HIWADA[3] and YUICHI YAMAMURA[3]

The Third Department of Medicine, Osaka University Hospital, Fukushima-ku, Osaka (Japan), and Kinki Central National Hospital for Chest Disease, Sakai (Japan), 19 March 1971

[3] Third Department of Medicine, Osaka University Hospital, Fukushima-ku, Osaka (Japan).
[4] Kinki Central National Hospital for Chest Disease, Sakai (Japan).

Activation of Rat Stomach Histidine Decarboxylase After Inhibition of Acid Secretion with 2-Phenyl-2-(2-Pyridyl)-Thioacetamide (SC-15396)

Gastric histidine decarboxylase in the rat is an adaptive enzyme, its activity being dependent upon the functional state of the stomach[1,2]. Thus, the activity is low after prolongated fasting and is markedly increased after gastrin (pentagastrin) administration, vagal excitation or feeding. The enzyme-activating effect of vagal excitation and feeding – but not that of pentagastrin – is abolished by antrectomy[3–5], indicating that endogenous gastrin is one important factor in the regulation of the enzyme activity. Gastrin release is markedly dependent upon antral pH, a low pH being inhibitory[6]. Recently, vagal denervation and treatment with atropine were found to cause a powerful activation of gastric histidine decarboxylase[5,7]. Since both vagotomy and atropine treatment abolished basal and pentagastrin-stimulated acid secretion[5,7] it was suggested that the resulting high antral pH would stimulate gastrin release, thus activating the histidine decarboxylase. The following concept was advanced[5,7]. All agents (except pentagastrin) and all experimental conditions, which stimulate acid secretion through a direct action on the parietal cell and which do not have a gastrin-releasing effect, will suppress the activity of gastric histidine decarboxylase by lowering the antral pH, thus inhibiting gastrin release. All agents and experimental conditions, which inhibit acid secretion without inhibiting gastrin release, will activate the enzyme by increasing the antral pH, thus stimulating gastrin release.

2-Phenyl-2-(2-pyridyl)-thioacetamide (SC-15396) is an inhibitor of gastric acid secretion. Having no anticholinergic effects, it was introduced as a gastrin antagonist ('anti-gastrin')[8–11]. In the rat and dog, SC-15396 also reduces the secretory response following treatment with histamine, cholinergic drugs and vagal excitation[12–17] and should consequently be regarded as a general inhibitor of gastric acid secretion. From the concept presented above, treatment with SC-15396 should cause activation of gastric histidine decarboxylase as a consequence of the resulting elevation of antral pH. This assumption was tested in the present study.

SC-15396 (Searle, Chicago) was dissolved in dimethylsulfoxide (10 mg/ml) and given s.c. in a dose of 50 mg/kg to rats, fasted for 48 h prior to injection. Control rats (also fasted for 48 h) received DMSO alone (5 ml/kg). All rats were killed 3 or 6 h after the injections. The mucosa of the oxyntic gland area was scraped off the stomach wall and homogenized in 0.1 M phosphate buffer, pH 6.9, to a final concentration of 100 mg (wet weight) per ml. After centrifugation at $10.000 \times g$ for 15 min in a refrigerated centrifuge, aliquots of the supernatant (usually 0.4 ml) were incubated with carboxyl-labelled ^{14}C-L-histidine ($4 \times 10^{-4} M$; 1.3 mC/mmol, New England Nuclear) in the presence of pyridoxal-5-phosphate ($10^{-5} M$) and glutathione ($4 \times 10^{-4} M$) in a total volume of 0.5 ml. The samples were incubated under nitrogen at 37 °C for 1 h under continuous agitation in a metabolic shaker. The histidine

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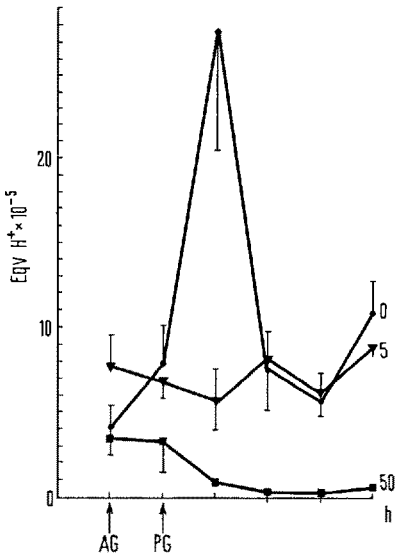
decarboxylase activity was determined by estimating the $^{14}CO_2$ released[18]. All assays were made in duplicate and the enzyme activities were expressed as nanomoles CO_2 formed per mg and hour. The results were corrected for non-enzymatic decarboxylation by incubating identical samples with 1-^{14}C-D-histidine ($4 \times 10^{-4} M$, 1.3 mC/mmol, New England Nuclear) instead of 1-^{14}C-L-histidine, or by using boiled tissue extracts incubated with 1-^{14}C-L-histidine. Usually, both types of blanks were run with each series of determinations. Gastric secretion was studied in Wistar rats, weighing 300–400 g fitted with chronic gastric fistulas[19]. For the collection of gastric juice the fistula rats were restrained in Bollman-type cages. The stomach was rinsed through the fistula with 0.9% warm saline until the return was clear. 10 ml 0.9% saline were given s.c. to replace fluid loss during collection. When the fistula had drained freely for 1 h, 1 h portions of gastric juice were collected. Usually, basal secretion was collected for 2 h, after which the injections were given and the collection continued. The volume of the gastric juice was measured and the acid output determined by titration with 0.02 N sodium hydroxide, using phenolphtalein as indicator. Acid output was expressed as equivalents per hour.



Inhibiton of pentagastrin-induced stimulation of gastric acid secretion by SC-15396 in chronic fistula rats. PG, pentagastrin, 250 µg/kg; AG, SC-15396, 'anti-gastrin', 5 or 50 mg/kg. The same group of rats (6 animals) was used througout. Mean ± S.E.M.

Effect of SC-15396 on gastric histidine decarboxylase activity in normal and antrectomized rats

Treatment	Histidine decarboxylase activity nmoles × 10^{-3}/mg/h, means ± S.E.M. (n) normal	antrectomy
DMSO (5 ml/kg), 3 h	6.9 ± 2.4 (4)	
DMSO (5 ml/kg), 6 h	5.8 ± 1 2 (8)	2.6 ± 1.4 (4)
SC-15396, 3 h	4.4 ± 1.7 (5)	
SC-15396, 6 h	15.4 ± 2.9 (8)	1.9 ± 0.9 (5)

In a dose of 5 mg/kg, SC-15396 prevented the stimulatory effect of a maximal dose of pentagastrin (250 µg/kg); a larger dose of SC-15396 (50 mg/kg) was required to abolish basal acid secretion (Figure 1). 6 h after administration of SC-15396 (50 mg/kg) to normal, fasted, male Wistar rats (150–200 g), the gastric histidine decarboxylase activity was markedly increased as compared with controls (Table). Antrectomy, performed as described in detail elsewhere[5], prevented the enzyme-activating effect of SC-15396 (Table). The results indicate that the enzyme-activating effect of SC-15396 is mediated by some antral agent, possibly gastrin, which is released as a result of the inhibition of acid secretion. This gives further support to the hypothesis that the gastric histidine decarboxylase activity is regulated by endogenous antral gastrin and that a feed-back control exists between gastrin release and acid secretion[5,6]. Not only does a lowered antral pH inhibit gastrin release but elevated antral pH seems to be very effective in stimulating gastrin release[20].

Zusammenfassung. 2-Phenyl-2(2-Pyridyl)-Thioacetamide (SC-15396) ist ein kräftiger Inhibitor von sowohl basaler als auch stimulierter gastrischer Säuresekretion und aktiviert die Histidindecarboxylase in der Magenschleimhaut. Die enzymaktivierende Wirkung von SC-15396 wird durch Resektion des Antrums verhindert. Daraus kann geschlossen werden, dass die durch SC-15396 hervorgerufene Enzymaktivierung eine Folge von erhöhter Freisetzung von antralem Gastrin ist.

R. HÅKANSON and G. LIEDBERG

Departments of Pharmacology and Surgery, University of Lund, S-22362 Lund (Sweden), 25 January 1971.

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Protective Effect of Flavonoids on the Collagen of Lathyritic Rats

The beneficial action of flavonoids in the maintenance or restoration of the normal integrity and permeability of the vessel wall is already known[1]. Various mechanisms have been suggested to explain such an effect, and among these it is possible to consider the action of the flavonoids on collagen.

Since it is possible to modify artificially the normal structure of collagen through the administration of lathyrogenic substances, producing an increase of soluble collagen by a block of the formation of cross-linkages[2], we planned to study the protective effect of flavonoids [*O*-(β-hydroxyethyl)-rutosides (HR) and (+)-catechin ((+)-C)][3] in rats treated by β, β′-iminodipropionitrile (IDPN) and aminoacetonitrile (AAN).

Bearing in mind that the lathyrogens produce some changes in the vascular system[4–7] and that flavonoids