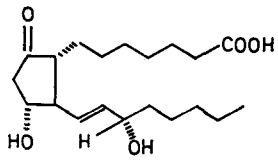
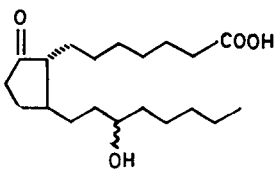
Inhibition of gastric acid secretion by a potent synthetic prostaglandin

The synthetic prostaglandin, 9-oxo-15ξ-hydroxyprostanoic acid (11-deoxy-13,14-dihydroprostaglandin) (AY-22,093), has been examined for its effect on gastric acid secretion in rats using the Shay procedure (Shay, Sun & Gruenstein, 1954) as described by Lippmann (1969) and in rats given repeated small doses of pentagastrin.



PGE$_1$



AY-22,093

AY-22,093 inhibited basal gastric acid secretion and the activity was dose-dependent (Table 1). At 0·8 mg/kg the inhibition was 52%. Similar activity was observed with PGE$_1$ at 0·4 mg/kg. Thus, AY-22,093 was about one-half as active as PGE$_1$.

Pentagastrin, a gastrin-like agent, causes an increase in gastric acid secretion (Barrett, 1966). In a continuous stomach perfusion in anaesthetized rats, subcutaneous injections of pentagastrin made every 20 min gave a steady plateau of gastric acid secretion (Barrett, Raventos & Siddall, 1966). I have examined the effects of repeated injections of a small dose of pentagastrin on gastric acid secretion in rats which were ligated under ether anaesthesia at the pyloric end of the stomach and also at the oesophagus (Levine, 1965). After pyloric ligation the stomachs were washed with 0·9% NaCl until clear. An intraperitoneal injection of 0·5 ml water was given immediately after the oesophageal ligation. Pentagastrin (or vehicle) treatment (1 μg/kg, s.c.) was begun 20 min after the oesophageal ligation and continued at 20 min intervals; the animals were killed by a blow on the head 20 min after the last injection, i.e. 2 h after ligation. The stomachs were removed and the gastric contents emptied into centrifuge tubes. The stomachs were rinsed with twice distilled water to yield a final volume of 5 ml. The samples were centrifuged and titrated (14–17 per group) against 0·01N sodium hydroxide in a direct reading pH meter to pH 7·0 to obtain the total acid. The increase in gastric acid secretion reached a plateau after 4 injections; less variation among the values was observed after 5 injections. The maximum stimulation of gastric acid secretion was about 4 times that of the controls.

The above procedure, employing 5 injections of pentagastrin, was used to determine the effect of AY-22,093 on the induced increase in gastric acid secretion. All animals

Table 1. *Inhibition of basal gastric acid secretion in the rat by AY-22,093*

Compound	Dose mg/kg, s.c.	Gastric acid secretion: m mol acid 4 h ± s.e.	*P*	Gastric acid secretion: % of control
None		0·49 ± 0·04		
AY-22,093	1·6	0·11 ± 0·03	<0·001	23
	0·8	0·24 ± 0·03	<0·001	48
	0·4	0·43 ± 0·06	>0·30	88
PGE$_1$..	0·4	0·22 ± 0·04	<0·001	44
	0·2	0·31 ± 0·04	<0·01	63

Table 2. *Inhibition of pentagastrin-induced gastric acid secretion in the rat by AY-22,093*

Compound	Dose mg/kg	Gastric acid secretion: μ mol acid/2 h ± s.e.	*P*	% of control
None		16 ± 4		
Pentagastrin	0·001 (5x), s.c.	70 ± 16	<0·02	438
AY-22,093	6·4, s.c.	14 ± 1	>0·50	88
+ pentagastrin	0·001 (5x), s.c.		<0·01*	
AY-22,093	3·2, s.c.	38 ± 4	<0·01	238
+ pentagastrin	0·001 (5x), s.c.		>0·10*	
Imipramine	10·0, i.p.	17 ± 3	>0·90	106
+ pentagastrin	0·001 (5x), s.c.		<0·02*	

* Versus pentagastrin.

received an injection of the test compound, or the corresponding vehicle, and the appropriate injection of the other vehicle immediately after oesophageal ligation; there were 7–9 animals in each group. AY-22,093 prevented the increase in gastric acid secretion at 6·4 mg/kg, s.c., but not at 3·2 mg/kg, s.c. (Table 2). Imipramine, in aqueous solution, (10 mg/kg, i.p.) also inhibited the pentagastrin-induced increase.

The synthetic prostaglandin (PGE), AY-22,093, is a potent inhibitor of basal gastric acid secretion. The presence of a saturated bond at C-13,14 in this type of compound is of importance for the high activity since AY-22,093 is 5 times more active than the previously-reported unsaturated derivative (Lippmann, 1969). In contrast to AY-22,093 the naturally-occurring PGE_1 is unsaturated at C-13,14; PGE_1 also contains a hydroxyl group on C-11. The basal gastric acid secretion-inhibitory activity of PGE_1 reported here is similar to that reported previously (Robert, Nezamis & Phillips, 1968; Lippmann, 1969).

The synthetic PGE also inhibits the increase in gastric acid secretion caused by pentagastrin. This type of activity is also exhibited by PGE_1 (Shaw & Ramwell, 1968a,b). Imipramine prevents the pentagastrin-induced increase; imipramine also has been shown to prevent the induced increase caused by reserpine (Lippmann, 1968). I have observed also that imipramine in half the dose used in the present experiments does not prevent the pentagastrin-induced gastric acid secretion. The total dose (5 μg/kg) of pentagastrin used in the present experiments to induce gastric acid secretion is similar to that used (6 μg/kg) in the experiments made in man (Abernethy, Gillespie & others, 1967).

PGE_1 has recently been reported not to inhibit the pentagastrin-induced gastric acid secretion in man (Horton, Main & others, 1968). However, in this respect, human gastric mucosa contains another prostaglandin, PGE_2, (Bennett, Murray & Wylie, 1968). Thus, it is possible that an appropriate synthetic PGE, in contrast to PGE_1, might exhibit an inhibitory activity in man.

Unlike PGE_1, which is optically pure, the synthetic PGE is a racemate with 4 possible isomers and one of these might prove even more active.

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The formation of 5-hydroxytryptophol from exogenous 5-hydroxytryptamine in cat spinal cord *in vivo*

5-Hydroxytryptophol was identified in 1962 as one of the main metabolites of exogenous 5-hydroxytryptamine (5-HT) in rats (Kveder, Iskrić & Keglević, 1962). Its occurrence in human urine (Davis, Cashaw & others, 1966) shows that it is also a metabolite of endogenous 5-HT in man. However, in the central nervous system—where the metabolism of 5-HT is quite vigorous (cf. Bulat & Supek, 1968)—5-hydroxytryptophol has been found, so far, only in the pineal body (McIsaac, Farrell & others, 1965). Several authors (Feldstein & Wong, 1965; Eccleston, Moir & others, 1966) have shown that the rat brain tissue is able to metabolize 5-HT into 5-hydroxytryptophol *in vitro*. The present communication reports the formation of 5-hydroxytryptophol from 5-HT in the spinal cord *in vivo*.

We have chosen the spinal cord for studying the metabolism of 5-HT because lumbar and sacral cord show the highest density of 5-HT nerve terminals in mammalian central nervous system (Fuxe, Hökfelt & Ungerstedt, 1969). The experiments were made with adult cats lightly anaesthetized with thiopentone sodium. The lumbosacral cord was exposed and two fine polyethylene tubes were inserted subarachnoidally, one at L_1 segment (inflow) and the other at S_4 segment (outflow). A closed subarachnoid space was formed by tying the thread around dura at L_1 and S_4 segment. To remove cerebrospinal fluid the subarachnoid space was first washed with 5-HT creatinine sulphate in Krebs-Ringer buffer (1 mg of free base/ml), and then it was filled with the same solution (*ca* 0·5 ml) which was left in contact with the spinal tissue for 90 min. After, the solution was collected and the subarachnoid space washed with 2 ml of Krebs-Ringer buffer. Then, both solutions ("superfusate") were pooled and deproteinized with perchloric acid. The portion of the spinal cord from L_1 to S_4 segment (about 2·27 g) was dissected, dura and arachnoid stripped off, spinal tissue washed with Krebs-Ringer to remove the adsorbed 5-HT and homogenized with 3 volumes of 0·5M perchloric acid.