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The effect of the histidine decarboxylase inhibitor brocresine (NSD-1055) on gastric acid secretion in rats*

M. BECKER AND K.-FR. SEWING

Department of Pharmacology, University of Tübingen, W.-Germany

The effect of the histidine decarboxylase inhibitor brocresine (NSD-1055) given by mouth, intraperitoneally or intravenously on tetragastrin-, histamine- and bethanechol-stimulated gastric acid secretion was examined in rats. Intravenous injection of brocresine slightly reduced the tetragastrin-stimulated secretion. Histamine-stimulated secretion was markedly increased by both intraperitoneal and intravenous injection of brocresine but it had no effect on the bethanechol-stimulated secretion. It was concluded that either histidine decarboxylase is not effectively inhibited by brocresine or any inhibition induced does not affect gastric acid secretion. The enhanced histamine-stimulated secretion points towards an inhibition of diamine oxidase by brocresine.

Histamine has been proposed to be the common final chemostimulator for all physiological (gastrin, vagal stimulation) and pharmacological (i.e. reserpine) gastric acid stimulants (Code, 1965; Levine, 1965; Lorenz & Pfleger, 1968). This assumption is based on the following facts. Large amounts of histamine are present in the gastric mucosa and are stored there in the mast cells and in the so called enterochromaffin-like cells, which are distributed throughout the glandular stomach, the latter histamine stores can be released by cholinergic stimuli and gastrin (Stubrin, Dyce & others, 1965) and have a high rate of turnover. Changes in the histamine metabolism are followed by changes in gastric acid secretion: gastric acid secretion is inhibited by injection of diamine oxidase, the main histamine-metabolizing enzyme (Haverback, Stubrin & Dyce, 1965), whereas the diamine oxidase inhibitor aminoguanidine enhances the secretory response of gastrin and histamine (Amure & Ginsburg, 1964); gastrin is a necessary link for the stimulation of the gastric histidine decarboxylase (Aures, Johnson & Way, 1970).

We describe the effect of the histidine decarboxylase inhibitor brocresine (NSD-1055, 4-bromo-3-hydroxybenzyloxyamine dihydrogenphosphate) on the tetragastrin-, bethanechol- and histamine-stimulated gastric acid secretion in rats.

METHODS

The experiments were made in a randomized order on male rats (FW-49 Biberach, 300–400 g) anaesthetized with urethane (1·25 g/kg, i.p.). Animals were kept in single cages and had free access to drinking water but food was withheld for 24 h. The experiments were divided into three groups: in the first group gastric acid secretion was stimulated by intravenous infusion of tetragastrin (14·4 μg/kg in 15 min), in the

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second with bethanechol (56 μg/kg in 15 min) and in the third with histamine (1280 μg/kg in 15 min). The doses were submaximal and nearly equi-effective. In each group six rats were treated (a) orally, (b) six intraperitoneally and (c) six intravenously with brocresine (100 mg/kg) which was given to sub-groups (a) and (b) 4 h before the experiment was started, and to sub-group (c) between two periods of stimulation (see below). Groups of six animals receiving saline in a corresponding amount and route served as controls. No particular controls were necessary for the (b) sub-group since the effects of the gastric acid stimulants before and after the brocresine were compared.

The effect of an intraperitoneal injection of brocresine (100 mg/kg) given 1 h before the experiments were started on tetragastrin-stimulated acid secretion was compared with a saline-treated group of rats in separate experiments. In addition, brocresine (100 mg/kg, i.v. in 15 min) was infused into three animals to study its effect on basal secretion.

Gastric acid secretion was estimated according to Lai's (1964) method with the modification that bromothymol blue instead of phenolphthalein was used as a titration indicator and that the total acid output less the basal secretion, instead of an average secretion rate per 10 min, was evaluated. For investigating the effects of oral and intraperitoneal administration of brocresine the experiments were performed as follows: After the preparation of the animal, basal secretion was determined for 30 min, then two infusions of the stimulant were given at an interval of 70 min. To study the effect of an intravenous injection of brocresine, 60 min after the second infusion of the stimulant, brocresine (100 mg/kg) in a concentration of 50 mg/ml was slowly injected, 30–40 min later, depending on the time taken to return to base-line secretion, the third infusion was started.

Since the first infusion occasionally gave irregular results in the orally and intraperitoneally pretreated animals, only the effect of the second infusion of the stimulus was compared with the second infusion of the control animals and statistically analysed by the *t*-test for groups. In the intravenous experiments the second infusion of the stimulant was compared with the third and statistically analysed by the *t*-test for pairs.

Compounds. Brocresine (NSD-1055, 4-bromo-3-hydroxybenzyloxyamine dihydrogenphosphate), American Cyanamid Company, Pearl River, N.Y. and Smith & Nephew Research Ltd., Gilston; tetragastrin (Trp.Met.Asp.Phe-NH_2), Dr. Karl Thomae, Biberach; bethanecholcholride, Schuchardt, Munich; histamine dihydrol chloride, La Roche, Grenzach. All weights are given as the base of the compounds. Brocresine was freshly dissolved before each experiment.

RESULTS

The effect of the different routes of administration of brocresine on tetragastrin-, bethanechol- and histamine-stimulated gastric acid secretion and the statistical analyses are summarized in Table 1. The results demonstrate that the tetragastrin-stimulated acid secretion was significantly reduced by 22·4% by an intravenous injection of brocresine. However, the histamine-stimulated secretion was significantly enhanced by intraperitoneal (137·5%) and intravenous (60·3%) injection of brocresine. The stimulating effect of an oral administration of brocresine on tetragastrin- and histamine-stimulated secretion was statistically non-significant. None

Table 1. *The effect of different routes of administration of brocresine* (100 mg/kg) *on tetragastrin-, histamine- and bethanechol-stimulated gastric acid secretion in rats.*

Stimulus	Route for brocresine	Time between pretreatment and experiment	Total acid output (μequiv means ± s.e.) saline	brocresine	change (%)	P
Tetragastrin ..	oral	4 h	14·3 ± 4·1	19·3 ± 3·2	+ 34·9	0·3 < p < 0·4
	i.p.	4 h	16·5 ± 3·0	23·5 ± 5·9	+ 42·4	0·3 < p < 0·4
	i.p.	1 h	12·2 ± 1·7	14·7 ± 2·3	+ 20·5	0·3 < p < 0·4
	i.v.	30–40 min	18·3 ± 2·8	14·2 ± 2·5	− 22·4	< 0·01
Histamine	oral	4 h	41·5 ± 7·7	56·6 ± 4·5	+ 36·4	0·1 < p < 0·2
	i.p.	4 h	25·6 ± 5·3	60·8 ± 9·1	+137·5	< 0·01
	i.v.	30–40 min	21·1 ± 3·0	33·8 ± 5·0	+ 60·3	< 0·025
Bethanechol ..	oral	4 h	21·4 ± 3·1	20·2 ± 3·2	− 5·6	0·7 < p < 0·8
	i.p.	4 h	22·3 ± 4·0	19·6 ± 5·6	− 12·1	0·6 < p < 0·7
	i.v.	30–40 min	32·1 ± 5·0	34·1 ± 4·4	+ 6·2	0·2 < p < 0·3

of the routes had any significant effect on the bethanechol-stimulated gastric acid secretion. The basal secretion was slightly elevated for 20–40 min by a continuous intravenous infusion of brocresine (100 mg/kg) for 15 min.

DISCUSSION

The results demonstrate that brocresine does not effectively inhibit stimulated or unstimulated gastric acid secretion in rats. The tetragastrin-stimulated secretion was slightly depressed by an intravenous injection of brocresine. In contrast the histamine-stimulated secretion was markedly increased by both intraperitoneal and intravenous injection of brocresine.

The results are not in agreement with those of Levine (1965) and of Thayer & Martin (1967) who described a strong inhibitory effect of brocresine (150 mg/kg) on the gastric acid response of the Shay rat to gastrin, pentagastrin, bethanechol, insulin and reserpine. In contrast, Fletcher, Pitts & others (1969) could not detect any inhibition of gastric acid secretion in Pavlov and Heidenhain pouch dogs stimulated with histamine, pentagastrin, gastrin and feeding, after a long term treatment with daily brocresine (75–160 mg/kg) for several weeks. The lack of inhibition in our experiments may be because of the following reasons.

(i) The time elapsed between the pretreatment of the animals and the stimulation of gastric secretion—particularly when brocresine was given intraperitoneally or orally—was too long. However, Levine, Sato & Sjoerdsma (1965) demonstrated a maximal effect 3–6 h after intraperitoneal administration. On the other hand, Wustrack & Levine (1969) found a rapid decline of the histidine decarboxylase-inhibiting activity within 60–90 min after the administration of brocresine. (ii) It is possible that an intact histidine decarboxylase system is not a necessary intermediate step in the stimulating process of gastric acid secretion. Up to now there is no convincing evidence that the decarboxylation of histidine is an essential link in the chemostimulation of gastric acid secretion. In contrast, Johnson & Aures (1970) claimed that histamine is not the mediator for gastric secretion in the rat.

The enhancement of the histamine-stimulated secretion by intraperitoneal and intravenous brocresine suggests an inhibition of the histamine catabolism in the body. Maudsley & Kobayashi (1969) reported a 60% inhibition of the diamine oxidase, the main histamine-metabolizing enzyme, 30 min after the application of brocresine. If such an inhibition is the reason for our findings with histamine, then it is likely that

not brocresine itself but a metabolite is the active principle, since the histidine decarboxylase-inhibiting activity disappears from the plasma at the same time (Wustrack & Levine, 1969) as the optical characteristics of brocresine extracted from rat blood into ethyl ether (Sewing, unpublished). The failure of the orally administered brocresine to provoke the same strong effect on the histamine-stimulated secretion may be the result of metabolism during gastrointestinal absorption. There is no published information on the metabolism of brocresine.

From this study it is concluded that the failure of an inhibition of gastric acid secretion in rats by brocresine leaves doubt about the contribution of the histamine synthesis to the stimulation of gastric acid secretion. Furthermore, the results suggest that the diamine oxidase is inhibited by brocresine.

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