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Inhibition of gastric acid secretion by 4-imidazolyl-3-amino-2-butanone (McN-A-1293), a specific inhibitor of histidine decarboxylase

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Histamine has been proposed for a long time as the final common mediator of gastric acid secretion [1, 2]. It is well documented that stimulation of gastric secretion in the rat by gastrin or vagal excitation is accomplished by increased histidine decarboxylase activity and the release of histamine from mucosal stores [3, 4]. *h*-Hydrazinohistidine (MK-785) and brocresine (NSD-1055), both inhibitors of histidine decarboxylase *in vitro* and *in vivo*, were reported to inhibit basal and stimulated acid secretion in pylorus-ligated rats [5, 6]. These two compounds, however, have been reported to lack specificity for histidine decarboxylase inhibition, and indeed may inhibit a number of decarboxylases by complexing with pyridoxal phosphate [7]. A new inhibitor of histidine decarboxylase, 4-imidazolyl-3-amino-2-butanone (McN-A-1293), has been reported to be a specific inhibitor of fetal rat histidine decarboxylase *in vitro*, to inhibit histidine decarboxylase but not aromatic L-amino acid decarboxylase in rat stomachs, and to be a weak inhibitor of diamine oxidase and imidazole-*N*-methyl transferase [8]. This communication reports the results of an investigation of the effects of McN-A-1293 on gastric secretion in pylorus-ligated rats.

Male Sprague–Dawley rats (180–220 g, Carworth Farms) were allowed only a solution of 8% sucrose and 0.2% sodium chloride *ad lib.* for 48 hr prior to administration of the compounds. The compounds to be tested were dissolved in an aqueous solution and were administered intraperitoneally. One hr later the rats were subjected to ligations of the pylorus [9] while under light (< 20-min duration) ether anesthesia. The rats had no access to the drinking solution during the collection period. Three hours after ligation, the rats were killed by cervical dislocation, and the stomach contents were removed, rinsed with water, and the total contents were centrifuged. The supernatant volumes were measured, and the total acid output was determined by titration to pH 7 using 0.02 N sodium hydroxide. Eight rats were used per group. Levels of significance were determined using Student's *t*-test. 4-(4-Imidazolyl)-3-amino-2-butanone (McN-A-1293) and 4-(4-imidazolyl)-3-acetamido-2-butanone were synthesized by Drs. J. Weis and E. E. Smissman, Department of Medicinal Chemistry, University of Kansas, U.S.A. [10]; 1-imidazolyl-2-amino-3-hexanone and 2,5-di(4-imidazolylmethyl)-3,6-dimethylpyrazine were prepared by Dr. C. R. Rasmussen and B. Twardzik in our laboratories. All but the pyrazine were prepared as their hydrochloride salts. Brocresine (NSD-1055) was generously supplied by Lederle Laboratories, Pearl River, NY.

The administration of McN-A-1293 to pylorus-ligated rats resulted in a dose-dependent inhibition of gastric acid secretion over a range of 25–200 mg/kg, i.p. (Table 1), with an ED_{50} calculated to be 60 mg/kg. The compound was less effective in inhibiting the volume of secretion, with only 39 per cent inhibition being observed at 200 mg/kg.

The effect of structural modification on McN-A-1293 on the potency of inhibition of gastric secretion in rats is also shown in Table 1. 4-Imidazolyl-3-acetamido-2-butanone, the *N*-acetylated derivative of McN-A-1293, produced only a slight (23 per cent) inhibition of acid secretion at 200 mg/kg. At the same dose, 1-imidazolyl-2-amino-3-hexanone, an analogue with a longer alkyl side chain on the ketone moiety, had no significant effect on either volume or acid secretion. These two compounds were also less potent than McN-A-1293 in inhibiting histidine decarboxylase *in vitro* [8].

Table 1. Effects of McN-A-1293 and other compounds on total acid output and secretion volumes in pylorus-ligated rats*

Compound	Dose (mg/kg, i.p.)	Volume (ml ± S.E.)	Inhibition (%)	Total acid output (μ-equiv./3 hr ± S.E.)	Inhibition (%)
4-Imidazolyl-3-amino-2-butanone (McN-A-1293)	200	4.0 ± 0.4	39†	118 ± 27	81†
	100	4.4 ± 0.5	33†	194 ± 67	69†
	50	5.1 ± 0.4	22	385 ± 52	39†
	25	5.7 ± 0.5	13	458 ± 66	27‡
	0	6.6 ± 0·9		630 ± 56	
4-Imidazolyl-3-acetamido-2-butanone	200	5.5 ± 1.7	20	507 ± 95	23
	0	6.9 ± 1.0		655 ± 75	
1-Imidazolyl-2-amino-3-hexanone	200	7.0 ± 0.6	0	625 ± 32	0
	0	6.9 ± 1.0		692 ± 145	
2,5-di(4-imidazolylmethyl)-3,6-dimethylpyrazine	100	5.5 ± 1.7	20	849 ± 115	0
	0	6.9 ± 1.0		655 ± 108	
Brocresine (NSD-1055)	200	3.5 ± 0.5	51†	119 ± 91	83†
	0	7.2 ± 0.5		682 ± 56	

* Total acid output and secretion volumes were measured as described in the text, using six to eight rats per group.
† $P < 0.05$.
‡ $P < 0.10$.

It has been observed [8] that solutions of McN-A-1293 turn dark yellow in neutral or alkaline solutions at room temperature. This phenomenon appears to be due to the formation of a dimer, which is readily oxidized in air and light to 2,5-di(4-imidazolylmethyl)-3,6-dimethylpyrazine. As shown in Table 1, this pyrazine was found to be ineffective as an inhibitor of rat gastric secretion at 100 mg/kg. This compound was also found to be ineffective in inhibiting histidine decarboxylase *in vitro* [8].

Brocresine at 200 mg/kg was found in this study to inhibit markedly both volume and acid secretion in pylorus-ligated rats, confirming earlier observations [6].

Brocresine has been reported to inhibit acid secretion in rats [5, 6, 11]; however, the observation that it also inhibited rat pyloric aromatic L-amino acid decarboxylase [8] and diamine oxidase [12] makes it less desirable as a specific inhibitor. Using the more specific histidine decarboxylase inhibitor, McN-A-1293, a dose-dependent inhibition of acid secretion has now been observed in rats, and this dose-dependent inhibition of acid secretion paralleled the inhibition of pyloric histidine decarboxylase activity previously reported [8]. In addition, analogs of McN-A-1293 which were less effective as histidine decarboxylase inhibitors *in vitro* [8] were found to be poor inhibitors of acid secretion.

These observations with McN-A-1293, a specific histidine decarboxylase inhibitor, provide further support to the hypothesis that endogenously synthesized histamine is involved in gastric acid secretion.

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