*J. Physiol.* (1971), **217**, *pp.* 557–571
*With 6 text-figures*
*Printed in Great Britain*



# METHYL HISTAMINES AND GASTRIC SECRETION

BY C. F. CODE, S. M. MASLINSKI, F. MOSSINI AND H. NAVERT

*From the Mayo Clinic and Mayo Foundation, Rochester, Minnesota, U.S.A. and the Institute of Pharmaceutical Chemistry and Toxicology, University of Parma, Italy*

(*Received 24 March 1971*)

SUMMARY

1. The previous findings that *N*-methylhistamine and *N*-dimethylhistamine are more potent stimulators of gastric secretion than histamine have been confirmed in dogs with Heidenhain pouches or gastric fistulas.

2. In cats with gastric fistulas, doses of *N*-methylhistamine of 0·25 or 0·5 $\mu$mole/hr produced 1·4–1·6 times as much HCl as equimolar doses of histamine.

3. The maximal HCl outputs of dogs with Heidenhain pouches to histamine, *N*-methylhistamine, and *N*-dimethylhistamine were not significantly different, though lesser doses of the *N*-methyl derivatives were required to produce the maxima. At the one-half maximal level, *N*-dimethylhistamine showed a twofold greater potency than histamine.

4. When given slowly or quickly via arteries supplying blood to the stomach of dogs or cats with gastric fistulas or via the artery to a Heidenhain pouch in a dog, 0·1–1·0 $\mu$mole *N*-methylhistamine or *N*-dimethylhistamine produced 4·1–13·9 times as much HCl as equimolar doses of histamine.

5. Injection of histamine or *N*-methylhistamine via the portal vein in two dogs with gastric pouches stimulated less secretion of HCl than injection of the same doses via a systemic vein.

6. The results allow the conclusion that *N*-methylhistamine and *N*-dimethylhistamine are more potent stimulators of acid gastric secretion than histamine in dogs and cats, particularly when delivered directly via the arterial route to the gastric mucosa, and support the prospect that *N*-methylhistamine or *N*-dimethylhistamine or both are natural chemostimulators of the parietal cells.

## INTRODUCTION

Histamine may be methylated at the terminal amino group of its side chain to produce *N*-methylhistamine [4-(2-methylaminoethyl)imidazole] or *N*-dimethylhistamine [4-(2-dimethylaminoethyl)imidazole] or at either of the nitrogen atoms of its imidazole ring to produce 1,4[1-methyl (4-$\beta$-aminoethyl)imidazole] or 1,5-methylhistamine. After *N*-methylhistamine was synthesized by Garforth & Pyman (1935), it was tested by Schnedorf & Ivy (1935) and found to be as potent as histamine in stimulating gastric secretion from Pavlov pouches of dogs. Many years later, Grossman, Robertson & Rosiere (1952) demonstrated that 1,4-methylhistamine does not stimulate the secretion of vagally denervated pouches of the entire stomach of dogs.

When Kapeller-Adler & Iggo (1957) found *N*-methylhistamine and *N*-dimethylhistamine in the urine of humans, the *N*-methyl (side chain) derivatives of histamine ceased being chemical curiosities. Lin, Alphin, Henderson, Benslay & Chen (1962), while studying the physiologic activity of many histamine derivatives, found that *N*-methylhistamine and *N*-dimethylhistamine were more potent than histamine in stimulating gastric secretion. Their observation became more important physiologically when 1,4-methylhistamine was identified in the gastric mucosa during steady-state stimulation of gastric secretion by histamine (Navert, Flock, Tyce & Code, 1967, 1969*a*; Dombro, Huang, Dittbrenner & Ragins, 1969); and particularly later, when with improvement in separation of the methyl derivatives of histamine, Navert, Flock, Tyce & Code (1969*b*) found that *N*-dimethylhistamine was the predominant metabolite of histamine in gastric juice secreted in response to the injection of $^{14}$C-labelled histamine. *N*-methylhistamine and 1,4-methylhistamine were also present in the juice, but in lesser quantities (Navert *et al.* 1969*a*).

These studies raised the question whether methylation of histamine controls the secretagogue action of histamine in gastric mucosa, methylation at one of the nitrogen molecules of the imidazole ring of histamine, producing an inactive compound, or at the terminal amino goup of its side chain, to produce a more potent secretagogue. Intrigued by this possibility, we made a comparative study of the effects of histamine and its methyl derivatives on gastric secretion in cats and dogs.

## METHODS

Twelve conscious, healthy, adult female dogs and four conscious, healthy cats were used. Two dogs and all the cats were provided with gastric fistulas placed close to the antral-corpus junction along the greater curvature and drained with a metal cannula through the mid line. Heidenhain pouches were constructed in eight of the

other dogs, and these pouches were drained by a metal cannula brought to the surface through the mid line or the left mammary line. In each of the remaining two dogs, vagally innervated, mucosal septal pouches (Pavlov type) were constructed and drained through the left mammary line by a metal cannula (Gregory, Hallenbeck & Code, 1942). The fistulas and pouches were made with the dog under sodium thiopentone anaesthesia using the usual surgical asepsis. Between tests, the fistulas were closed with a plug.

All animals maintained their body weight during the period of observation. Secretory tests were not started until at least a week after the gastric fistulas were constructed and at least a month after the pouches were made. The animals were fasted for at least 18 hr before tests were started. The histamine and its derivatives were administered via a catheter placed temporarily in a systemic vein of the foreleg or hind leg or via 'permanent' catheters placed either in a branch of the gastrosplenic artery or in a tributary of the portal vein. The catheters consisted of Silastic tubing. The arterial and portal catheters were placed while the animals were anaesthetized during a separate operation to the construction of the fistula or pouch. The arterial catheters were threaded into a splenic branch of the gastrosplenic artery against the stream of blood. The tip of the catheter was advanced to the junction of the splenic branch and the main artery. Beyond this point the artery continued as a gastric branch and passed directly to the stomach or pouch. Thus, material injected via the catheter was swept by the stream of blood into vessels that supplied blood directly to a pouch or to the greater curvature of the stomach. The venous catheters were placed in a splenic branch of the splenic vein and advanced toward the main trunk of the vein so that injected material was swept directly into the portal system. The catheters were passed through the substance of the spleen and then through the abdominal wall. Between uses, they were kept filled with a solution of heparin. They remained useful from 1 to 3 weeks. Their failure usually resulted from thrombosis of the vessel close to the tip of the catheter.

All doses of histamine and its derivatives were calculated on a molar basis, and in many tests the activity of equimolar doses was compared. The compounds were dissolved in 150 mM-NaCl. Injections were given by constant infusion provided by a pump (5 ml./hr) or by sudden injection from a syringe by hand. Histamine was purchased from Mann Research Laboratories, New York, N.Y. and 1,4-methylhistamine from Calbiochem, Los Angeles, California. Some of the *N*-methylhistamine used in our study was provided by Dr T. M. Lin, Eli Lilly Co., Indianapolis, Indiana. However, most of the *N*-methylhistamine and all of the *N*-dimethylhistamine used in the study was synthesized by one of us (F. Mossini). The purity of the synthesized compounds was confirmed by chemical and light-absorption analysis.

The volume of gastric juice secreted was measured and the concentration of hydrogen ion in it determined by electrometric titration using 0·1 *N* sodium hydroxide and a Radiometer automatic titrator. Acid outputs were calculated from the product of these two determinations. Most perods of collection of juice were 15 min. The animals were trained to stand or rest quietly in a supporting sling during tests. If nausea, as indicated by salivation, retching, or vomiting occurred, the observations were discontinued. The outputs of HCl during the final three to five consecutive 15-min periods of a plateau of secretion, developed by the constant infusion of histamine or its methyl derivatives, were used to calculate the mean 15 min outputs of their steady-state responses. The plateau of secretion was reached in 105–150 min after starting the injections of histamine and in 120–180 min after starting *N*-methylhistamine or *N*-dimethylhistamine. When quick injections (less than 15 sec) were used, the entire output of HCl in response to the injection was determined.

## RESULTS

*Systemic venous injections* (*confirmatory observations*). The observation that *N*-methylhistamine is a more potent stimulant of gastric secretion than histamine was confirmed in three dogs with Heidenhain pouches and in one dog with a gastric fistula. When equimolar quantities of *N*-methylhistamine and histamine were given over the dosage range of 0·5–2·0 μmole/hr by constant, continuous intravenous infusion, the *N*-methyl derivative produced 1·3–1·7 times as much acid as histamine did (Table 1). Because secretory responses of the dogs varied somewhat from day to day, the comparisons between the two substances were made on the same day. Generally, saline solution was given intravenously and continuously throughout the entire period of observation, and *N*-methylhistamine was substituted for histamine after a steady level of secretion had developed and been maintained for 1 hr or more. Histamine was given first in all of the tests because, when its continuous intravenous injection was stopped, secretion ceased within 30 min or very nearly so, while after stopping injection of the *N*-methylhistamines, secretion nearly always continued for longer periods at quite high rates.

These observations in dogs were extended to four cats with gastric fistulas, and the results were similar (Table 1). At dosages of 0·25–0·5 μmole/hr, *N*-methylhistamine produced on the average 1·4–1·6 times as much HCl as histamine did when it was given in equimolar quantities by constant intravenous injection (Fig. 1).

No statistical analysis was made of these results, because in all of the tests in each of the dogs and cats when histamine and *N*-methylhistamine were given consecutively on the same day, *N*-methylhistamine always produced more acid than did histamine.

The maximal secretory outputs of Heidenhain pouches in response to histamine, *N*-methylhistamine, and *N*-dimethylhistamine were determined using constant intravenous infusions and successive doubling of the quantity injected after secretion, at each dosage, had reached a steady state (Code, Blackburn, Livermore & Ratke, 1949). The most detailed studies were done in four dogs of similar body weights, comparing histamine and *N*-dimethylhistamine. The maximal HCl outputs in response to the two substances were not significantly different (Table 2). By expressing the steady-state outputs of each dosage level as a percentage of the maximal output on that particular day, in that dog, the data from the four dogs were normalized and combined to give comparative dose–response curves for histamine and *N*-dimethylhistamine (Fig. 2). The half maximal response was obtained with *N*-dimethylhistamine at a mean dosage of 1·5 μmole/hr and with histamine at 3·0 μmole/hr, indicating

TABLE 1. Gastric acid outputs of dogs and cats in response to equimolar doses of *N*-methylhistamine and histamine given intravenously

| Animals | Preparation | No. of tests | Dose (μmole/hr) | Mean output (m-equiv HCl/15 min) | | Mean output ratio* |
|---|---|---|---|---|---|---|
| | | | | *N*-methyl-histamine | Histamine | |
| 3 dogs (A, B and C) | Heidenhain pouch | 3 | 1·0 | 0·59 | 0·38 | 1·6 |
| | | 3 | 2·0 | 0·96 | 0·73 | 1·3 |
| 1 dog (D) | Gastric fistula | 1 | 0·5 | 3·57 | 2·67 | 1·3 |
| | | 1 | 1·0 | 7·43† | 4·40 | 1·7 |
| 4 cats | Gastric fistula | 3 | 0·25 | 0·60 | 0·38 | 1·6 |
| | | 1 | 0·5 | 0·71 | 0·51 | 1·4 |

* Output ratio of *N*-methylhistamine to histamine.

† In this test, only two 15-min periods of 'plateau' secretion were used because the animal vomited during the third period, and the test was stopped.

at this level of secretion a twofold greater gastric secretagogue action of *N*-dimethylhistamine than histamine when given via a systemic vein. In two tests on two of the dogs using *N*-methylhistamine, the maximal HCl outputs were not significantly different from those of histamine or *N*-dimethylhistamine.

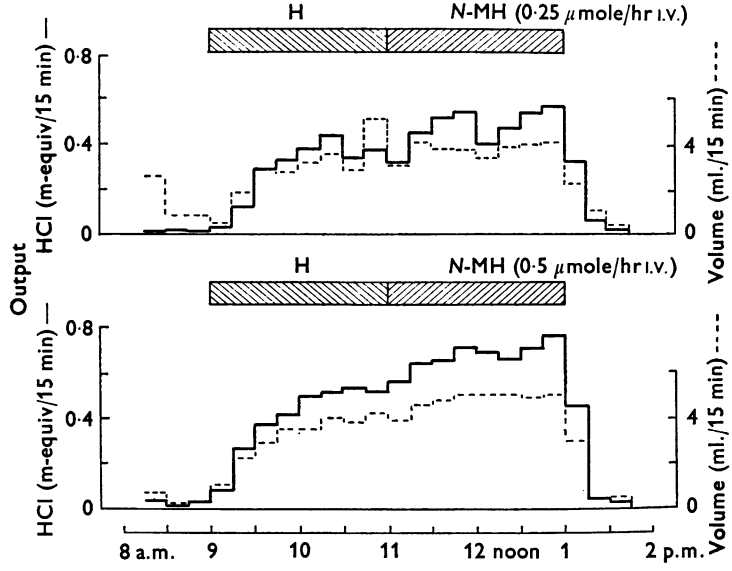


Fig. 1. Comparison of secretory response of two cats with gastric fistulas to equimolar doses of histamine (H) and *N*-methylhistamine (*N*-MH).

TABLE 2. Maximal secretion of hydrochloric acid of four dogs with Heidenhain pouches

| Dog | Body wt. (kg) | Histamine stimulation* No. of tests | Histamine stimulation* m-equiv HCl/hr | *N*-dimethylhistamine stimulation* No. of tests | *N*-dimethylhistamine stimulation* m-equiv HCl/hr |
|---|---|---|---|---|---|
| E | 9·8 | 2 | 3·62 | 2 | 2·99 |
| A | 11·6 | 2 | 4·76 | 1 | 4·58 |
| F | 12·0 | 3 | 4·65 | 2 | 4·07 |
| G | 11·9 | 2 | 2·85 | 2 | 2·69 |

* Differences in secretion not significant, $P = 0{\cdot}09$, paired data.

A similar series of tests were done with 1,4-methylhistamine. It was given by continuous intravenous injection to four fasted dogs, two with Heidenhain pouches and two with Pavlov-type pouches, in doses that started with 2 μmole and were then doubled each hour until 8 μmole/hr

were given. None of these doses stimulated gastric secretion in any of the dogs.

*Intra-arterial injections.* Because *N*-methyltransferase, the enzyme that methylates histamine, is present in the gastric mucosa of various animals, including the dog (Brown, Tomchick & Axelrod, 1959; Dombro *et al.* 1969; Navert *et al.* 1969*a*), *N*-methylhistamine and *N*-dimethylhistamine are likely produced in the mucosa and, if present there as chemical mediators, they should be more effective if delivered directly to the mucosa via its arterial blood supply than when given via a systemic vein. The next experiments were done to test this.

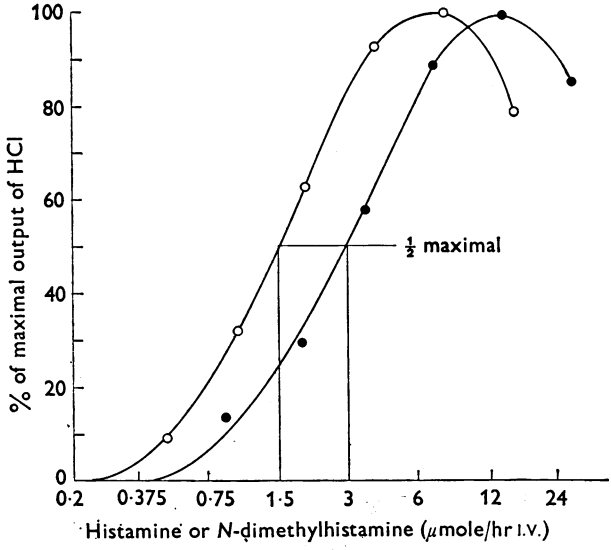


Fig. 2. Mean dose–responses of four canine Heidenhain pouches to histamine and *N*-methylhistamine. Each point is the mean steady-state output of HCl at the indicated dosage level expressed as a percentage of the maximal output. Maximal outputs to histamine and *N*-dimethylhistamine were not different (see Table 2).

When *N*-methylhistamine, *N*-dimethylhistamine, or histamine was given into the artery supplying blood to the greater curvature of the stomach of dogs with gastric fistulas, equimolar quantities of the *N*-methyl derivatives, given slowly over periods of 15 or 30 min or quickly in less than 15 sec, produced 5·8–7·0 times as much acid as histamine (Table 3 and Fig. 3). Almost identical results were obtained in one dog with a Heidenhain pouch (Table 3 and Fig. 4). In one test, with a much larger dose, the differences were not so striking, although *N*-methylhistamine still produced 1·79 times as much HCl as histamine did.

Similar results were obtained when the intra-arterial route was used in

TABLE 3. Output of HCl from gastric fistula or Heidenhain pouch in dogs in response to equimolar doses of *N*-methylhistamine or histamine injected into gastric branch of gastrosplenic artery

| Dog | Preparation | Total dose (intra-arterial) (μmole) | Injection period | Total output (m-equiv HCl) | | Total output ratio* |
|---|---|---|---|---|---|---|
| | | | | *N*-methyl-histamine | Histamine | |
| D | Gastric fistula | 0·5 | 30 min | 7·438 | 1·069 | 7·0 |
| H | Gastric fistula | 0·45 | 15 min | 9·646 | 1·651 | 5·8 |
| | | 0·225 | 15 min | 11·371 | 1·846 | 6·2 |
| E | Heidenhain pouch | 0·5 | < 15 sec | 0·356 | 0·083 | 4·3 |
| | | 0·5 | 30 min | 0·281 | 0·052 | 5·4 |
| | | 1·0 | < 15 sec | 0·725 | 0·145 | 5·0 |
| | | 1·0 | 30 min | 0·555 | 0·135 | 4·1 |
| | | 2·5 | 30 min | 1·127 | 0·629 | 1·8 |

* Output ratio of *N*-methylhistamine to histamine.

two cats with gastric fistulas, *N*-methylhistamine being 5·6–13·9 times as effective as histamine (Table 4 and Fig. 5).

When these experiments had been completed, the arterial cannulas had commenced to occlude in some of the animals, and shortly afterward the

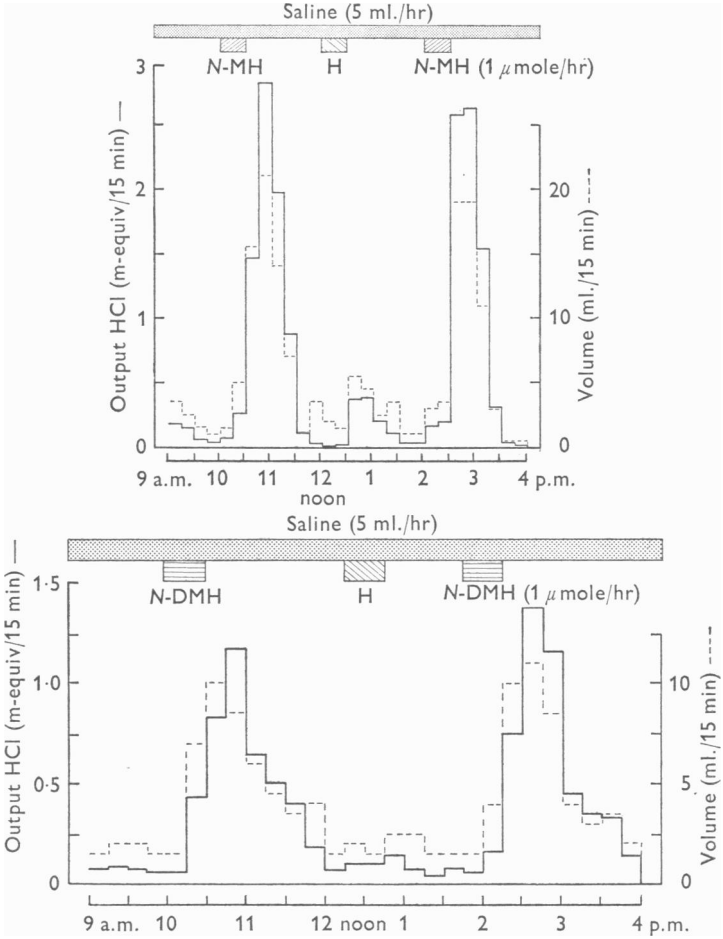


Fig. 3. Comparison between gastric secretory response of *N*-methylhistamine (*N*-MH) (upper chart), *N*-dimethylhistamine (*N*-DMH) (lower chart), and histamine (H), when they were given via a gastric branch of the gastrosplenic artery to a conscious dog with a gastric fistula.

cannulas all closed completely. This prevented us from performing a complete dose–response comparison between histamine and its *N*-methyl derivatives when given via the gastric arterial route. The estimates of their differences in potency, therefore, apply only over the dose ranges used.

*Intraportal injections.* In the search for an explanation of the much

greater effectiveness of *N*-methylhistamine and *N*-dimethylhistamine than histamine, when given via the gastric intra-arterial route, the prospect arose that, although histamine is removed rapidly by the liver (Livingston & Code, 1955; Irvine, Duthie, Ritchie & Waton, 1959; Silen & Eiseman, 1959), possibly *N*-methylhistamine and *N*-dimethylhistamine are not, and

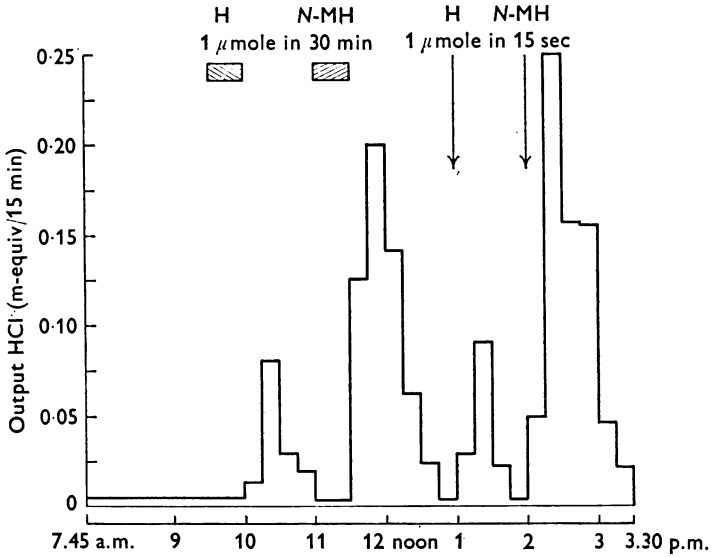


Fig. 4. Comparison of outputs of HCl from Heidenhain pouch in dog in response to slow (30 min) and to rapid (less than 15 sec) intra-arterial injections of equimolar doses of histamine (H) and *N*-methylhistamine (*N*-MH).

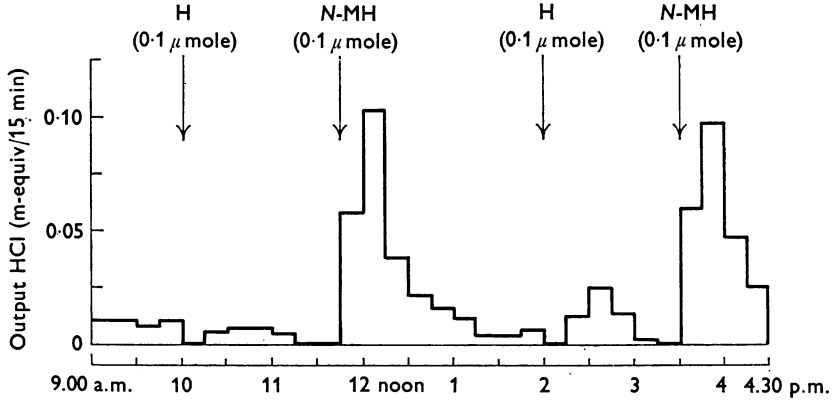


Fig. 5. Comparison of outputs of HCl from gastric fistula in a cat in response to the rapid injection (less than 15 sec) of equimolar doses of histamine (H) and *N*-methylhistamine (*N*-MH) via a gastric branch of the gastrosplenic artery.

their greater effectiveness, particularly via the gastric arterial route, might then be due to their recirculation in greater quantities as compared to histamine. In two dogs, one with a Pavlov-type pouch and the other with a Heidenhain pouch, histamine and *N*-methylhistamine were given via the portal and the systemic venous systems. In two other dogs, with the same types of pouches, *N*-methylhistamine alone was given via both venous systems.

TABLE 4. Output of HCl from gastric fistula in cats in response to equimolar doses of *N*-methylhistamine or histamine injected during a period of less than 15 sec into gastrosplenic artery

| Cat | Dose (intra-arterial), μmole | Total (m-equiv HCl) | | Output ratio* |
|---|---|---|---|---|
| | | *N*-methyl-histamine | Histamine | |
| 1 | 0·1 | 0·245 | 0·036 | 6·8 |
| | 0·5 | 1·071 | 0·191 | 5·6 |
| 2 | 0·1 | 0·194 | 0·0 | — |
| | 0·5 | 0·598 | 0·043 | 13·9 |

* Output ratio of *N*-methylhistamine to histamine.

In every test, both histamine and *N*-methylhistamine were more effective when given via a systemic vein than via the portal vein (Table 5). In the individual animals (Table 5 and Fig. 6), the ratios between the outputs obtained by the two routes revealed that, over the range of doses tested, histamine or *N*-methylhistamine was 1·6–3·6 times more effective when injected into a systemic vein than into the portal vein (Table 5). Because *N*-methylhistamine was much more effective, in all of the tests, when given via the intra-arterial route than via a systemic vein, the greater effectiveness of *N*-methylhistamine than histamine when delivered directly to the gastric mucosa via intra-arterial injection is not due to the greater escape of *N*-methylhistamine from destruction or entrapment by the liver. *N*-methylhistamine appears to be removed as effectively by the liver when given via the portal vein, as is histamine.

## DISCUSSION

The results obtained in this study confirm the finding of Schnedorf & Ivy (1935) that *N*-methylhistamine stimulates gastric secretion and the observation of Lin *et al.* (1962) that *N*-methylhistamine and *N*-dimethylhistamine are more potent gastric secretagogues than histamine. We have also confirmed the observation of Silen & Eiseman (1959) that histamine is more effective in stimulating gastric secretion when given via a systemic

TABLE 5. Comparison of acid outputs of Heidenhain and Pavlov type gastric pouches in response to equimolar doses of histamine and *N*-methylhistamine given for 30 min periods via either a portal or a systemic vein

| Dog | Type of pouch | Compound injected | Dose total (μmole) | Response Total output (m-equiv HCl) Systemic vein injection | Portal vein injection | Output ratio of SV/PV* |
|---|---|---|---|---|---|---|
| I | Pavlov | Histamine | 0·5 | 1·03 | 0·40 | 2·6 |
| | | *N*-methylhistamine | 0·5 | 1·21 | 0·64 | 1·9 |
| | | *N*-methylhistamine | 0·5 | 1·08 | 0·50 | 2·2 |
| K | Heidenhain | Histamine | 2·0 | 0·91 | 0·52 | 1·8 |
| | | *N*-methylhistamine | 0·5 | 1·46 | 0·90 | 1·6 |
| J | Pavlov | *N*-methylhistamine | 0·5 | 1·19 | 0·36 | 3·3 |
| | | *N*-methylhistamine | 0·5 | 2·08 | 1·19 | 1·8 |
| L | Heidenhain | *N*-methylhistamine | 0·5 | 0·79 | 0·22 | 3·6 |

* Systemic vein to portal vein.

vein than via the portal vein. Finally, we have confirmed the observation of Grossman *et al.* (1952) that 1,4-methylhistamine does not stimulate gastric secretion at dosage levels that produce maximal or near maximal secretion when given as histamine or *N*-dimethylhistamine.

Although we did not give histamine via the arterial supply to the gastric mucosa and via a systemic vein on the same day to the same dog, we accumulated many observations on different days, all of which demonstrated in conscious, healthy dogs (in agreement with the findings of

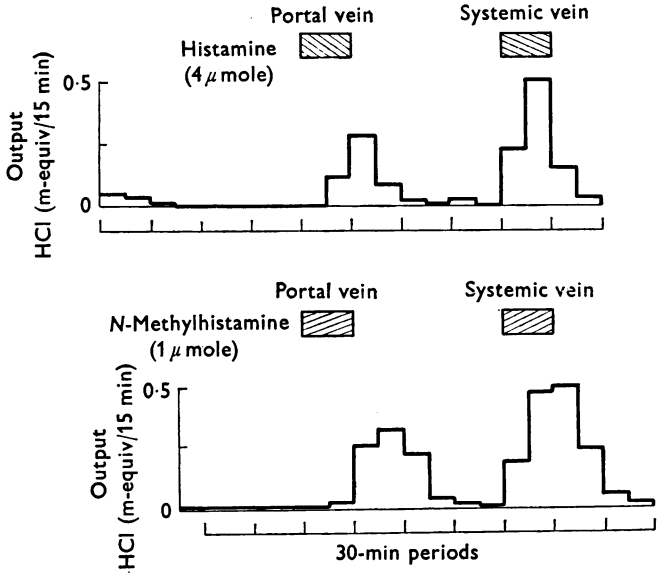


Fig. 6. Comparative effectiveness of histamine and *N*-methylhistamine in stimulating gastric secretion in a dog with a Heidenhain pouch when injection was made into the portal vein or a systemic vein.

Thompson & Vane (1953) in acute canine experiments) that histamine is no more effective when delivered via the arterial supply to gastric mucosa than when given into a systemic vein. The much greater secretory response to *N*-methylhistamine and *N*-dimethylhistamine when they are delivered to the mucosa directly, via the arterial route, indicates that they act more effectively or more directly on the gastric secretory cells than does histamine. The finding raises the question of whether histamine is transformed into one or both of its *N*-methyl derivatives before becoming effective or maximally so.

The results of Born & Vane (1953), obtained with isolated perfused stomachs, suggested the possibility that histamine acts indirectly on the secretory cells of the stomach. They proposed that an interaction between

histamine and blood may be necessary before secretion is stimulated. Our results offer no evidence on this proposal, but do suggest the possibility that part of the delay observed by Born & Vane may be related to the transformation of histamine into *N*-methylhistamine or *N*-dimethylhistamine.

Our observations increase the likelihood that *N*-methylhistamine or *N*-dimethylhistamine or both act as chemical mediators of at least part of the gastric secretagogue action of histamine in those species in which they are produced from histamine, particularly in those species in which they are produced from histamine in the gastric mucosa. Our results leave unanswered the questions of whether histamine itself can stimulate secretion and whether any part of the control of gastric secretion by gastrin, cholecystokinin, or secretin is done by regulation of the methylation of histamine. For secretin, this appears unlikely because, in the dog, secretin has little effect on histamine-induced gastric secretion (Greenlee, Longhi, Guerrero, Nelson, El-Bedri & Dragstedt, 1957; Wormsley & Grossman, 1964).

Bertaccini & Vitali (1964) have compared the effectiveness of *N*-methylhistamine and *N*-dimethylhistamine to that of histamine in producing smooth muscle contraction (guinea-pig ileum and bronchial muscles) and various vascular effects. The *N*-methyl derivative in many of these actions was nearly but not quite as potent as histamine (60–95 % as potent), but *N*-dimethylhistamine was much weaker (5–55 % as potent). The *N*-dimethyl derivative is found in the gastric juice in much greater quantities than the *N*-methyl compound and so may be the preferred product of methylation in the gastric mucosa (Navert *et al.* 1969*a*, *b*). Some of it also appears in the blood, where, at equal concentrations, it would produce fewer side effects than histamine or *N*-methylhistamine, giving a basis for possible preferential production in the mucosa.

## REFERENCES


Bertaccini, G. & Vitali, T. (1964). Pharmacological properties of some imidazole derivatives occurring in nature. *J. Pharm. Pharmac.* **16**, 441–449.

Born, G. V. R. & Vane, J. R. (1953). Gastric secretion induced by histamine. *J. Physiol.* **121**, 445–451.

Brown, D. R., Tomchick, R. & Axelrod, J. (1959). The distribution and properties of a histamine-methylating enzyme. *J. biol. Chem.* **234**, 2948–2950.

Code, C. F., Blackburn, C. M., Livermore, G. R., Jr. & Ratke, H. V. (1949). A method for the quantitative determination of gastric secretory inhibition. *Gastroenterology* **13**, 573–587.

Dombro, R., Huang, M., Dittbrenner, M. & Ragins, H. (1969). Metabolic pathway of histamine in canine gastric mucosa in relation to acid secretion. *Am. J. Physiol.* **216**, 988–994.

GARFORTH, B. & PYMAN, F. L. (1935). 4(5)-$\beta$-Alkylaminoethylglyoxalines. *J. chem. Soc.* **1**, 489–492.

GREENLEE, H. B., LONGHI, E. H., GUERRERO, J. D., NELSON, T. S., EL-BEDRI, A. L. & DRAGSTEDT, L. R. (1957). Inhibitory effect of pancreatic secretin on gastric secretion. *Am. J. Physiol.* **190**, 396–402.

GREGORY, R. A., HALLENBECK, G. A. & CODE, C. F. (1942). A modification of the method of Hollander and Jemerin for making Pavlov pouches. *Proc. Soc. exp. Biol. Med.* **49**, 400–403.

GROSSMAN, M. I., ROBERTSON, C. & ROSIERE, C. E. (1952). The effect of some compounds related to histamine on gastric acid secretion. *J. Pharmac. exp. Ther.* **104**, 277–283.

IRVINE, W. T., DUTHIE, H. L., RITCHIE, H. D. & WATON, N. G. (1959). The liver's role in histamine absorption from the alimentary tract: Its possible importance in cirrhosis. *Lancet* **i**, 1064–1068.

KAPELLER-ADLER, R. & IGGO, B. (1957). Histamine and its derivatives in human urine. *Biochim. biophys. Acta* **25**, 394–402.

LIN, T. M., ALPHIN, R. S., HENDERSON, F. G., BENSLAY, D. N. & CHEN, K. K. (1962). The role of histamine in gastric hydrochloric acid secretion. *Ann. N.Y. Acad. Sci.* **99**, 30–44.

LIVINGSTON, R. H. & CODE, C. F. (1955). Role of the liver in the conjugation of histamine in intact animals. *Am. J. Physiol.* **181**, 428–434.

NAVERT, H., FLOCK, E. V., TYCE, G. M. & CODE, C. F. (1967). The fate of $^{14}$C histamine during gastric secretion. *Physiologist* **10**, 261.

NAVERT, H., FLOCK, E. V., TYCE, G. M. & CODE, C. F. (1969*a*). *N*-methylation of histamine during gastric secretion. *Physiologist* **12**, 313.

NAVERT, H., FLOCK, E. V., TYCE, G. M. & CODE, C. F. (1969*b*). Metabolism of exogenous histamine-$^{14}$C during gastric secretion in dogs. *Am. J. Physiol.* **217**, 1823–1829.

SCHNEDORF, J. G. & IVY, A. C. (1935). Effect of methylhistamine and hydroxyethylglyoxaline on gastric secretion and blood pressure in the dog. *Proc. Soc. exp. Biol. Med.* **32**, 777–778.

SILEN, W. & EISEMAN, B. (1959). The nature and cause of gastric hypersecretion following portacaval shunts. *Surgery, St Louis* **46**, 38–47.

THOMPSON, J. E. & VANE, J. R. (1953). Gastric secretion induced by histamine and its relationship to the rate of blood flow. *J. Physiol.* **121**, 433–444.

WORMSLEY, K. G. & GROSSMAN, M. I. (1964). Inhibition of gastric acid secretion by secretin and by endogenous acid in the duodenum. *Gastroenterology* **47**, 72–81.