EFFECT OF CENTRAL AND PERIPHERAL ACTIONS OF HISTAMINE AND ITS METABOLITE N-ALPHA METHYL HISTAMINE ON GASTRIC SECRETION AND ACUTE GASTRIC LESIONS

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Nα-methylhistamine (Nα-MH) is one of unusual metabolite of histamine that was found in Helicobacter pylori-infected stomach and is believed to interact with specific histamine H₁, H₂ and H₃-receptors to stimulate gastric acid secretion and gastrin release from isolated G-cells but the effects of Nα-MH on gastric mucosal integrity have been little studied. This study was designed; 1) to compare the effect of intraperitoneal (i.p.), intracerebroventricular (i.c.v.) and gastric topical (intragastric i.g.) application of exogenous Nα-MH with that of standard histamine on gastric secretion in rats equipped with gastric fistula (series A) and 2) to compare the effect of i.c.v. administration of histamine and Nα-MH with that of peripheral (i.p. and i.g) application of these amines on gastric lesions induced by 100% ethanol (series B) in rats with or without capsaicin-induced deactivation of sensory nerves. The area of gastric lesions was determined planimetrically, gastric blood flow (GBF) was assessed by H₂-gas clearance method and venous blood was collected for determination of plasma gastrin levels by RIA. Nα-MH and histamine (0.1—10 mg/kg i.p. or i.g.) dose-dependently increased gastric acid output (series A); whereas i.c.v. administration of histamine or Nα-MH inhibited dose-dependently this secretion; the dose attenuating gastric acid output by 50% (ED₅₀) being 4 and 6 µg/kg i.c.v. Both, Nα-MH and histamine (2 mg/kg i.p. and i.g.) attenuated significantly the area of gastric lesions induced by 100% ethanol (series B) while producing significant rise in the GBF and plasma immunoreactive gastrin increments. Central application of Nα-MH and histamine (0.01—5 µg/kg i.c.v.) inhibited ethanol-induced gastric damage whereas higher doses ranging from 10—100 µg/kg of histamine and Nα-MH were significantly less effective. Capsaicin-induced deactivation of sensory nerves by itself augmented significantly ethanol damage and attenuated significantly the protective and hyperemic effects of histamine and its methylated analog applied i.p. but failed to affect significantly those caused by i.c.v. administration of these amines. We concluded that: 1) central histamine and Nα-MH inhibits gastric acid secretion and exhibits gastroprotective activity against ethanol in similar manner to that afforded by parenteral and topical histamine and N-αMH, 2) central N-αMH- and histamine-induced protection involve the enhancement in gastric microcirculation unrelated to neuropeptides released from capsaicin-sensitive afferent nerves, and 3) the major difference between central and peripheral histamine and its methylated analog is the influence on gastric acid secretion which does not appear to play any major role in gastroprotective activity of these agents.
INTRODUCTION

The role of histamine and its metabolites such as Nα-methylhistamine (Nα-MH) in the mechanism of gastric mucosal defense has not been studied. Histamine and agonists of histamine H₁, H₂, and H₃ were shown to afford gastroprotection against ethanol damage, predominantly due to enhancement in the protective mucus secretion (1—3), the decrease in ethanol absorption and the formation of histodilutional barrier (4). Recently, Courillon-Mallet et al. (5) and Beales and Calam (6) reported that *Helicobacter pylori* (Hp) that is considered as major gastric pathogen and first class of carcinogen in the human stomach, produces Nα-MH an unusual metabolite of histamine, that appears to act as a potent stimulant of gastric acid secretion and, therefore, may play an important role in Hp-associated gastric disorders. The possibility that gastrin released by histamine or its metabolite Nα-MH, could contribute to gastroprotection induced by these biologically active amines has not been tested in detail. Furthermore, the effect of histamine and its methylated analogs applied centrally on gastroprotection against the damage induced by corrosive agent such as ethanol remains unknown.

Gastrin plays an important role in gastric secretory functions due to activation of histidine decarboxylase (HDC) in enterochromaffin-like (ECL) cells that can release histamine in the oxyntic mucosa (7, 8). Previous studies demonstrated that hipergastrinemia resulting from inhibition of acid secretion with H₂ antagonists or proton pump inhibitors exerts the trophic effect on the oxyntic mucosa and this was closely correlated with overexpression of HDC mRNA and histamine release (9, 10). Furthermore, gastrin was shown to exhibit gastroprotective action against gastric lesions caused by noxious agents and this effect was attributed to the activation of specific CCK-B receptors by this peptide (11).

This study was designed; 1) to compare the effect of central (intracerebroventricular), topical (intragastric) and parenteral (intraperitoneal) administration of histamine with that of Nα-MH on gastric secretion and gastric lesions induced by 100% ethanol and on accompanying changes in the gastric blood flow (GBF) and 2) to determine the effect of capsaicin-induced deactivation of sensory nerves on histamine- and Nα-MH-induced gastroprotection against ethanol-induced gastric damage and the accompanying changes in the GBF and 3) to evaluate the role of gastrin in the possible gastroprotective effects of histamine and Nα-MH by determination of plasma immunoreactive gastrin levels.
MATERIAL AND METHODS

Male Wistar rats, weighing 180—220 g and fasted for 24 h, were used in gastric secretory tests and in studies on gastroprotection. Studies were approved by the Ethic Committee for Animal Research of Jagiellonian University.

Gastric secretory studies

The effects of Nα-MH and histamine (both purchased from Sigma Co, MO, USA) on gastric acid secretion were examined in 50 conscious rats equipped about 1 month earlier with a gastric fistula (GF) as described previously (12, 14). For the i.c.v. injection of vehicle or both peptides, the GF rats undergone surgery 48 h before the secretory studies according to the method published elsewhere (13). Briefly, under light ether anesthesia, an incision was made along with the mid-line of the skull, the skull bones were cleaned of connective tissue and the point of intersection between the sagittal and coronary sutures was visualized. The point at the distance of approximately 2.5 mm from either sagittal and coronary suture was defined and in this place a small hole in the skull was made, using needle with a sharp end. The hole was made by rotary movement of the needle and the wound of the head was closed by a clip. The GF was opened, the stomach was rinsed gently with about 5 ml of tap water at 37°C. The basal gastric secretion was collected for 60 min and vehicle, histamine and Nα-MH were injected in various doses i.c.v. in a volume of 5 μl using a 10 μl Hamilton microsyringe covered with a plastic tube except for the terminal 4.5 mm of this needle. Vehicle (1 ml of saline), histamine and Nα-MH were injected i.p. or i.c.v. in gradually increasing doses ranging from 0.1—100 μg/kg, each dose being administered on a separate test day. The effectiveness of i.c.v. administration was verified by injecting 10 μl of dye (0.1% toluidine blue). The visualization of dye on the walls of lateral ventricle indicated the exact location of i.c.v. injection. The GF animals were fasted overnight but had free access to water 24 h before the experiment and they were placed in individual Bollman type cages to maintain the minimum restraint necessary. The GF was opened, the stomach was rinsed gently with about 5 ml of tap water at 37°C. The basal gastric secretion was collected for 60 min and NαMH or histamine was administered in gradually increasing doses ranging from 0.1—10 mg/kg i.p. or i.g., each dose being administered on separate test day. In control tests, vehicle (1 ml of saline) was applied i.p. or i.g. and the collection of gastric juice was continued for the final 60 min. The volume and acid concentration of each collected sample of gastric juice were measured and acid outputs (expressed in term of micromoles per 30 min) were determined as described before (12).
Acute gastric lesions were induced by an intragastric (i.g.) application of 100% ethanol similarly to the method described previously by our group using ethanol as a damaging agent (12—14, 18). Briefly, 100% ethanol in a volume of 1.5 ml was administered i.g. to rats by means of a metal orogastric tube. After 60 min, the animals were lightly anesthetized with ether, their abdomen was opened by the midline incision and stomach exposed for the measurement of GBF by means of H-gas clearance technique as described previously (15). For this purpose double electrodes of electrolytic regional blood flowmeter (Biotechnical Science, Model RBF-2, Osaka, Japan) were inserted into the gastric mucosa. One of these electrodes was used for the local generation of gaseous H$_2$ and another for the measurement of tissue H$_2$. With this method, the H$_2$ generated locally was carried out by flow of blood, while the polarographic current detector read out decreasing tissue H$_2$. The tissue H$_2$ clearance curve was used to calculate an absolute flow rate (ml/100g/min) in the oxyntic area as described previously (15). The measurements were made in three areas of the oxyntic mucosa and the mean values of the measurements were calculated and expressed as percent changes of those recorded in the vehicle (saline) treated animals. After the GBF measurement, the stomach was removed, rinsed with water and pinned open for macroscopic examination. The area of necrotic lesions in oxyntic mucosa was determined by computerized planimetry (Morphomat, Carl Zeiss, FRG) (12, 15) by the person who did not know to which experimental group animals belonged.

Determination of plasma gastrin levels

At the termination of some experiments with i.p. or i.g. administration of N$\alpha$-MH or histamine, the animals were anesthetized with ether and the blood samples (about 3 ml) were taken from the vena cava for the radioimmunoassay (RIA) of plasma gastrin levels as described previously (11—13). For comparison, intact rats fasted overnight and given only vehicle saline i.p. were also anaesthetized with ether and the blood samples were collected for the determination of control values of gastrin in plasma. The blood samples collected in heparin coated polypropylene tubes were centrifuged at 3000 rpm for 20 minutes at 4°C, and the supernatant clear plasma was then stored at -80°C until measurement of plasma gastrin levels using RIA. Gastrin antibody No 4562 (final dilution, 1: 100 000) was a gift of Professor J. Rehfeld from Copenhagen, Denmark (11—13). The limit of assay sensitivity was 0.5 mM of sample and the interassay and intra-assay coefficients of variation were 7% and 9%, respectively.
In subsequent studies on gastroprotection induced by histamine and \( \text{N}\alpha\)-MH, two major series (A and B) of experiments were carried out. Series A was used to compare the effects of central (i.c.v.) administration of histamine and \( \text{N}\alpha\)-MH with those obtained with histamine and \( \text{N}\alpha\)-MH given i.p. or i.g. on the gastric mucosal lesions induced by 100% ethanol.

The following groups of rats in series A were used 1) vehicle (1 ml of saline i.p. or i.g.) followed 30 min later by 100% ethanol; 2) \( \text{N}\alpha\)-MH (0.1—2 mg/kg i.p. or i.g.) followed 30 min later by 100% ethanol; and 3) histamine (0.1—2 mg/kg i.p. or i.g.) followed 30 min later by 100% ethanol.

The role of sensory afferent nerves and neuropeptides such as CGRP released from sensitive afferent nerve endings in gastroprotection by histamine was tested in rats with capsaicin-induced deactivation of these nerves (16) (series B). For this purpose the animals were pretreated with capsaicin (Sigma Co., St. Louis, MO) injected s.c. for 3 consecutive days at a respective dose of 25, 50 and 50 mg/kg about 2 weeks before the experiment (16). All injections of capsaicin were performed under ether anesthesia to counteract the respiratory impairment associated with injection of this agent. To check the effectiveness of the capsaicin denervation, a drop of 0.1 mg/ml solution of capsaicin was instilled into the eye of each rat and the protective wiping movements were counted as previously described (16). Control rats received a vehicle injections. All animals pretreated with capsaicin showed negative wiping movement test, confirming functional denervation of the capsaicin sensitive nerves. The experimental protocol included the following study groups, each consisting of 6—8 animals; 1) vehicle (saline 1 ml i.p. or 5 \( \mu l \) i.c.v.) followed 30 min later by 100% ethanol in rats with intact afferent nerves and 2) histamine (standard dose; 5 \( \mu g/kg \) i.p. or i.c.v.) followed 30 min later by 100% ethanol in rats with intact sensory nerves; 3) vehicle (saline 1 ml i.p. or 5 \( \mu l \) i.c.v.) followed 30 min later by 100% ethanol in rats with capsaicin deactivated afferent nerves and 4) histamine (5 \( \mu g/kg \) i.p. or i.c.v.) followed 30 min later by 100% ethanol in rats with capsaicin deactivated afferent nerves.

Statistical analysis

Results are expressed as means ± SEM. Statistical analysis was done using nonparametric Mann-Whitney and Friedman two-way analysis of variance. Differences with \( p < 0.05 \) were considered as significant.
RESULTS

Effects of exogenous Na-MH and histamine on gastric acid secretion

The effects of vehicle, histamine and Na-MH applied i.p. or i.g. in graded concentrations ranging from 0.1 to 10 mg/kg on gastric acid secretion from the gastric fistula in conscious rats are shown in Table 1. In control vehicle-treated rats, basal acid output averaged 109 ± 6 μmol/30 min. Histamine applied i.g. or i.p. at concentration of 0.1 or 1 mg/kg produced a significant increase in gastric

Table 1. Effect of Na-MH and histamine on gastric acid secretion in rats equipped with gastric fistula. Mean ± SEM of 6—8 rats. Asterisk indicates a significant change as compared to basal secretion in rats treated with vehicle (saline). Cross indicates a significant change as compared to the values obtained in rats treated with various doses of Na-MH and histamine applied i.g. or i.p.

<table>
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<th>Type of test</th>
<th>Gastric acid output (μmol/30 min)</th>
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<tr>
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<td>Histamine (mg/kg i.g.)</td>
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acid output (Table 1). Higher doses of histamine (2 mg/kg and 10 mg/kg i.p. or i.g.) also raised dose-dependently the gastric acid output as compared to that observed in vehicle-control animals. In contrast, histamine given i.c.v. in small doses of 0.1 and 1 mg/kg failed to affect acid output but at higher doses resulted in significantly lower output when compared to that attained with histamine applied i.g. or i.p. (Table 1).

When Nα-MH was applied in i.g. or i.p., it resulted in a dose-dependent rise in the gastric acid output that reached significantly higher values as compared to those observed in vehicle-control animals. Nα-MH given i.c.v. reduced dose-dependently the gastric acid output as compared to the value obtained in vehicle-treated animals injected i.c.v. with saline (Table 1).

**Effect of histamine and Nα-MH on the ethanol-induced lesions and accompanying changes in the GBF and plasma gastrin levels**

As shown in Fig. 1, the pretreatment with histamine applied i.c.v. in graded doses ranging from 0.01 μg/kg up to 5 μg/kg reduced dose-dependently the area of gastric lesions caused by 100% ethanol with the threshold reduction

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**Fig. 1.** The area of ethanol-induced gastric lesions and gastric blood flow (GBF) in rats treated intracerebroventricularly (i.c.v.) with vehicle (saline) or with various doses of histamine (0.01–100 μg/kg). Means ± SEM of 6—8 rats. Asterisk indicates a significant change as compared to the vehicle control values. Cross indicates a significant change as compared to the values obtained in rats treated with histamine applied i.c.v. in a doses of 0.1 μg/kg up to 5 μg/kg.
occurring at a dose of 0.1 μg/kg and with the ID$_{50}$ averaging about 1.8 μg/kg of histamine (Fig. 1). Higher doses of histamine (10—100 μg/kg i.c.v.) were less effective in the protection against ethanol-induced gastric damage. The pretreatment with Nα-MH administered i.c.v. in graded doses ranging from 0.01 μg/kg up to 5 μg/kg, attenuated significantly the area of lesions induced by 100% ethanol with the ID$_{50}$ averaging 0.8 μg/kg but when Nα-MH was administered in higher doses (10—100 μg/kg i.c.v.) the gradual disappearance of this protective effect was observed (Fig. 2).

![Fig. 2. The area of ethanol-induced gastric lesions and gastric blood flow (GBF) in rats treated with vehicle (saline) or with various doses of N-alpha-methyl histamine (Nα-MH, 0.01—100 μg/kg i.c.v.). Means ± SEM of 6—8 rats. Asterisk indicates a significant change as compared to the vehicle control values. Cross indicates a significant change as compared to the values obtained in rats treated with histamine applied i.c.v. in a doses of 0.1 μg/kg up to 5 μg/kg.](image)

The GBF in the intact gastric mucosa averaged 48 ± 7 ml/min/100 g (taken as a 100%), and this value was not significantly affected following i.c.v. application of vehicle (saline). The protective effects of Nα-MH and histamine (0.01—5 μg/kg i.c.v.) were accompanied by a significant rise in GBF. When 100% ethanol was applied i.g. to vehicle-pretreated rats, the significant reduction in GBF by about 45% was recorded.

Fig. 3 shows the effect of Nα-MH and histamine applied in a dose of 2 mg/kg i.g. or i.p. on gastric lesions induced by 100% ethanol and the accompanying changes in the GBF and plasma gastrin levels. Both, Nα-MH and histamine
applied i.g. or i.p. attenuated significantly the area of ethanol induced damage but topical Nα-MH was significantly more effective in suppressing these damage than that given parenterally, while histamine was significantly more protective when injected parenterally than topically. The protective effect of Nα-MH and histamine applied i.g. and i.p. was accompanied by a significant rise in GBF and plasma gastrin levels but no significant difference between these parameters was observed following their topical and parenteral administration.

**Effect of deactivation of sensory nerves with capsaicin on histamine and Nα-MH-induced gastroprotection and GBF**

Fig. 4 shows the effect of histamine and Nα-MH applied either i.c.v. or i.p. on gastric lesions induced by ethanol in capsaicin-deactivated rats as compared to those with intact sensory nerves. Deactivation of primary afferent nerves with parenteral pretreatment with neurotoxic dose of capsaicin (about 2 weeks before the experiment) augmented significantly the area of ethanol-induced...
gastric lesions while attenuating significantly the GBF as compared to vehicle-treated rats with intact sensory nerves (Fig. 4). In rats with capsaicin-induced deactivation of afferent nerves, the protective activity of histamine and Nα-MH applied i.p. or i.c.v. in a dose of 5 μg/kg, respectively. Mean ± SEM of 6—8 rats. Asterisk indicates a significant change as compared to the value obtained in vehicle-treated gastric mucosa. Cross indicates a significant change as compared to the value obtained in histamine- and Nα-MH-treated animals without capsaicin-denervation.

**DISCUSSION**

This study shows that Nα-MH, a methylated analog of histamine, stimulates gastric acid secretion and exhibits gastroprotective activity against...
acid-independent mucosal damage induced by 100% ethanol in similar manner to that afforded by native histamine. This gastric acid stimulatory and protective activity were observed after intragastric and parenteral application of both Nα-MH and histamine. In contrast, central administration of histamine and N-αMH resulted in a significant inhibition of gastric acid secretion and when applied in smaller doses ranging from 0.01—5 μg/kg, both amines reduced dose-dependently the lesions induced by ethanol and enhanced significantly the GBF. Interestingly, with higher doses of histamine and N-αMH (10—100 μg/kg i.c.v.), a progressive increase in the area of these lesions followed by the fall in the GBF were observed. Our study demonstrated that the protective and hyperemic effects afforded by central N-αMH and histamine were unaffected by capsaicin-induced deactivation of sensory afferents while beneficial effects of topical and parenteral application of these amines on ethanol damage were partly attenuated by capsaicin denervation suggesting involvement of sensory neuropeptides in the protective and hyperemic effects of these amines. This indicates that peripheral N-αMH- and histamine-induced protection involve the enhancement in gastric microcirculation that could be unrelated to neuropeptides released from capsaicin-sensitive afferent nerves but could be mediated by the release of gastrin from antral mucosa. This notion is supported by our finding that plasma gastrin levels was significantly elevated in rats treated with histamine and its methylated analog along with the protection against ethanol injury and hyperemia observed in animals pretreated with these amines.

It is well known that ECL-containing and releasing histamine and gastrin G cells and the interaction of their products such as histamine and gastrin plays an important role in the gastric secretory stimulation (17—19) but the role of these ECL- and G products in the mechanism of gastric integrity has been little studied. The ECL cells produce and secrete histamine in response to gastrin but the possibility that histamine influences the G-cells to release of gastrin and results in hypergastrinemia and subsequent gastroprotection has been little tested. In particular, there is no information available whether Nα-MH, which is unusual metabolite of histamine that was originally proposed to exhibit ulcerogenic activity in the stomach (20) and was detected recently in the human stomach infected with Hp (5, 6, 21, 22), can influence the acute gastric lesions induced by strong irritant such as ethanol and accompanying alterations in plasma levels of gastrin. Our previous study revealed that both exogenous gastrin-17 and endogenous gastrin released by feeding exhibit gastroprotective activity against lesions induced by corrosive agents such as ethanol and this effect is mediated by specific CCK-B receptors and may involve the release of a potent vasoactive mediator such as nitric oxide (NO) (11). Exogenous gastrin and hypergastrinemia of endogenous origin are known to exert trophic effect in the oxyntic mucosa of the rat stomach including the growth of ECL-cells,
which are the predominant endocrine cell type in this part of the stomach (17—19, 23).

Histamine and agonists of H₁, H₂ and H₃ receptors were reported to stimulate gastric acid secretion and to afford gastroprotection in various models of gastric mucosal damage (1—3, 24, 25) but the hypothesis that gastrin is involved in these protective effects of histamine and its side-chain methylated metabolite such as Nα-MH, has not been explored. Histamine and histidine decarboxylase (HDC), a key enzyme in histamine biosynthesis were recently implicated in the mechanism of gastric integrity by the observation that healing of chronic ulcers is accompanied by downregulation of HDC mRNA and reduction in histamine release from the ECL cells at the ulcer margin suggesting that this mechanism may contribute to the prolongation of ulcer healing (26). The metabolism of histamine in the gastric mucosa includes the ring methylation via histamine methyltransferase (HMT) and then degradation by monoamine oxidase (MAO) or diamino oxidase (DAO). Recently, the gastric mucosa infected with Hp was shown to induce the side-chain methylation of histamine and production of Nα-MH, that was found to be a potent releaser of gastrin from rabbit isolated G-cells in vitro (5, 6), suggesting that the stimulation of gastrin release by Nα-MH could be responsible for the hypergastrinemia accompanying Hp infection.

It is established that administration of histamine H₂ receptor antagonists such as ranitidine and cimetidine promote gastrin release through the elevation of an intragastric pH due to their antisecretory action (12, 26). We have recently demonstrated that histamine attenuated stress-induced gastric lesions and enhanced the protective effect of ranitidine and omeprazole due to increase in the gastric microcirculation and inhibition of the cytokine cascade (27). In the present report, we found that gastric stimulatory action of Nα-MH on gastric acid secretion can be demonstrated by either intragastric and systemic application of gradually increasing doses of this histamine metabolite. Moreover, Nα-MH was significantly more potent in stimulation of gastric secretion after topical than parenteral application suggesting the importance of paracrine stimulation of gastrin release from antral G-cells by this metabolite of histamine. Similarly, Nα-MH applied i.g. exhibited greater degree of attenuation of ethanol induced gastric lesions than after systemic administration of this amine. Both increase in gastric secretion and protection induced by Nα-MH and histamine applied topically against ethanol damage were paralleled by the marked increment in plasma gastrin and gastric blood flow suggesting that the protective and hyperemic action of Nα-MH and histamine in the rat stomach could be mediated by the enhanced gastrin release (28—30).
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