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Metabolism and Function of Gastric Histamine in Health and Disease

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ABSTRACT

Histamine is not uniformly distributed in the human and animal organisms, but occurs in high concentrations in the gastric mucosa. The enzymes responsible for its metabolism—histidine decarboxylase, histamine N-methyltransferase and diamine oxidase—seem to be less predominantly localized in the stomach. Considerable effort was necessary to detect and measure histamine formation in the gastric mucosa. This was a controversial subject that only was solved recently. Histamine inactivation by histamine methyltransferase occurs in man in the fundic gastric mucosa that has reasonable enzymic activity. However, liver, spleen and intestine show much higher activities indicating less specificity of histamine catabolism in the gastric mucosa. Finally, diamine oxidase activity was once thought to be absent in the corpus mucosa, but more recently, moderate activities of this enzyme were found in several species, including man. Thus, histamine metabolism in the gastric mucosa is by no means unique in mammalian tissues, but the presence of these enzymes may be regarded as an indicator of its physiological function.

To some extent enzymic activities involved in histamine formation and inactivation are regulated in the process of acid secretion. Histidine decarboxylase and histamine N-methyltransferase activities are enhanced by gastrin, but are not influenced by vagal stimulation. Hitherto, only histamine methylation was found to be diminished in duodenal ulcer disease.

Vagotomy and histamine H_2-receptor antagonists modulate histamine catabolism by histamine methyltransferase. The implication of these findings for treatment of duodenal ulcer are discussed.

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Distribution of Histamine in the Gastric Mucosa

Histamine occurs in the gastric mucosa in high concentrations (Table 1). In several mammalian species, the intestinal mucosa and the lungs are also rich in histamine. In birds, reptiles, amphibia and fishes, histamine content of the acid-producing area of the stomach far exceeds other tissues.[1]

Within the stomach, histamine is chiefly located in the mucosa (Fig. 1); the histamine content ratio (gastric mucosa:muscle) is about 4:1 in man, 2:1 in monkeys, 3:1 in pigs and 2:1 in cows. Within the gastric mucosa of all mammalian species investigated (except the rat) histamine is chiefly located in "typical" and "atypical" mast cells.[2–7] In whole tissue preparations of human corpus mucosa, quantitative studies using histamine assays in combination with morphometric methods indicate that more than 95% of stored histamine is located in these mast cells (Fig. 2).[8,9] The average histamine content of an individual mast cell in the human corpus mucosa is 2.7–3.2 pg histamine dihydrochloride/cell. This is in excellent agreement with quantities found in dogs (4 pg/cell).[3,10]

Mast cells in the corpus mucosa are situated both in the vicinity of small blood vessels (arterioles, capillaries) (Fig. 3a), and in the middle of a mass of parietal cells (Fig. 3a–d). Histamine secreted from these cells can reach the parietal cells, the target cells in this paracrine system. The 4 histological pictures from pig corpus mucosa demonstrated:

(1) the paracrine relationship of histamine in the acid-producing gastric mucosa;

(2) findings contrary to the observation of Riley and West,[11] inventors of the histamine-mast cell story.[12]

These authors described non-mast cell histamine stores in pig gastric mucosa. We confirmed their findings in pig corpus and antrum mucosa if the tissue was fixed with lead acetate in the usual way.

TABLE 1.

Histamine Content in Tissues of Various Species—a Phylogenetic Study (after Lorenz et al.[1], Triodl et al.[71], Lorenz et al.[49])

	Histamine content [μg/g]				
Species	*Corpus Mucosa*	*Liver*	*Ileum Mucosa*	*Lungs*	*Kidney*
Man	43	4	17	23	2
Monkey	97	3	71	263	10
Pig	100	21	198	222	2
Dog	117	38	83	64	1
Cow	44	34	82	—	—
Rabbit	13	2	4	17	2
Rat	36	3	8	8	1
Pigeon	14	2	2	3	2
Turtle	10	1	1	2	5
Frog	3	1	1	1	1
Trout	6	1	2	1	1

Histamine estimation by a fluorometric assay which was tested for its specificity. Histamine expressed as histamine dihydrochloride/g fresh weight. (—) not determined.

However, using Carnoy and sublimate-salicylate solutions[13] as fixatives, we preserved the cells that stained with toluidine blue at pH 4.0.[3]

One of the great benefits of development of histamine H_2-receptor antagonists has been the renewed interest in the unsettled problems of histamine location, metabolism and function in gastric mucosa.[14]

Basic Aspects of Histamine Metabolism

Most textbooks of biochemistry mention histamine metabolism by histidine decarboxylases (HDC), histamine methyltransferase (HMT) and diamine oxidase (DAO; Fig. 4), but fail to mention the transamination, nucleotide formation and acetylation/deacetylation. Formation of side-chain methylated histamine in gastric mucosa is doubt-

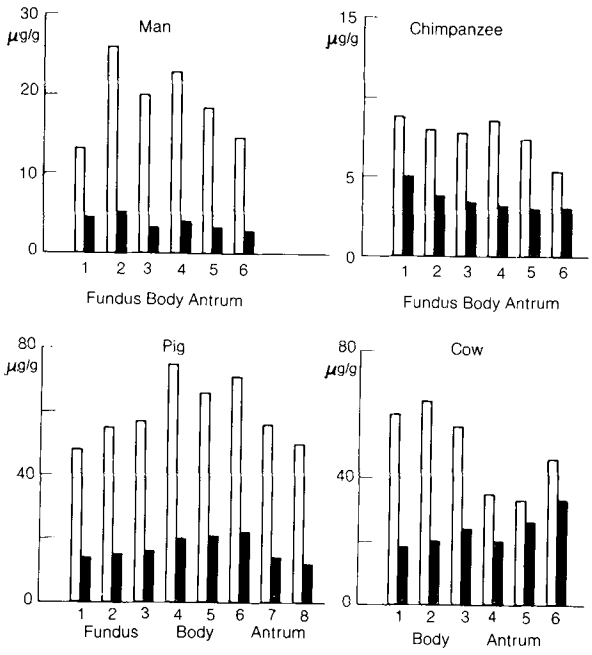

Figure 1. Distribution of histamine in the stomach of man, chimpanzee, pig and cow (after Lorenz et al.,[3] with permission). Mean values from 3 human subjects and 2 animals tested from each species. Preparation of the mucosa (□) and musculature (■).

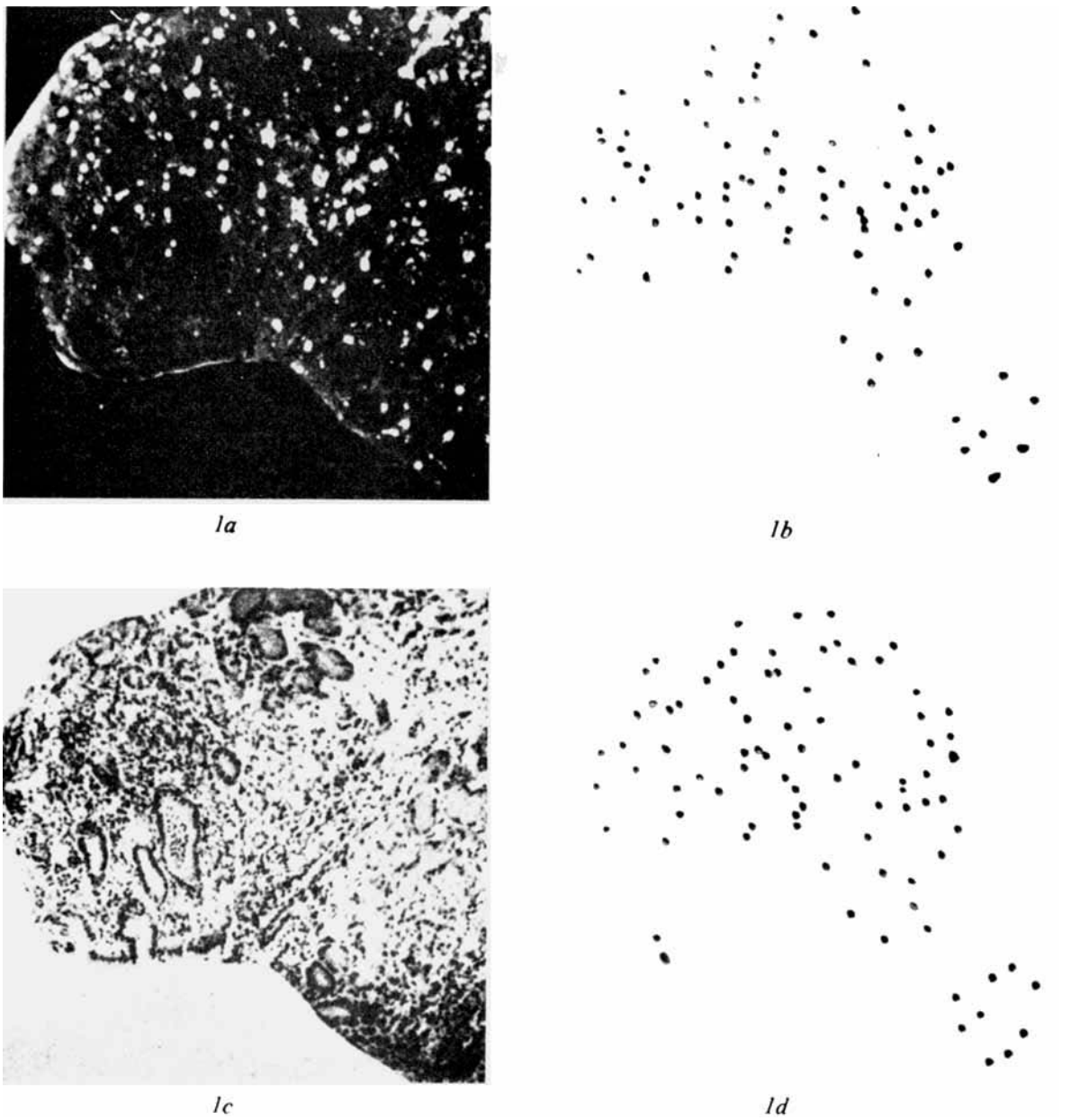

Figure 2. o-Phthaldialdehyde staining cells (histamine-containing cells) and toluidine blue staining cells (mast cells) in a biopsy specimen of human corpus mucosa (transcription technique) (after Neugebauer and Lorenz,[29] with permission). Histamine shown by o-PD vapor was identified by microspectrofluorometry (1a). Mast cells were stained by toluidine blue in the same section (1c). The result of transcription for o-PD cells is demonstrated in (1b), that for mast cells in (1d). The cells were counted with the aid of a screen. Magnification 120-fold. For further conditions, see Mohri et al.[8]

ful;[15] the presence or absence of N^{τ}, N^{α}, N^{α}-trimethylhistamine and N^{τ}, N^{α}-dimethylhistamine,[16] in gastric mucosa has not been studied. Histamine formation by HDC has been a subject of debate during the last 20 years. Waton[17,18] suggested that histamine could be absorbed from the intestinal chyme like a vitamin and transported to various tissues.

Werle[19] and Werle and Zeisberger[20] demonstrated histamine formation *in vitro* in the gastric mucosa of various mammals including man by an

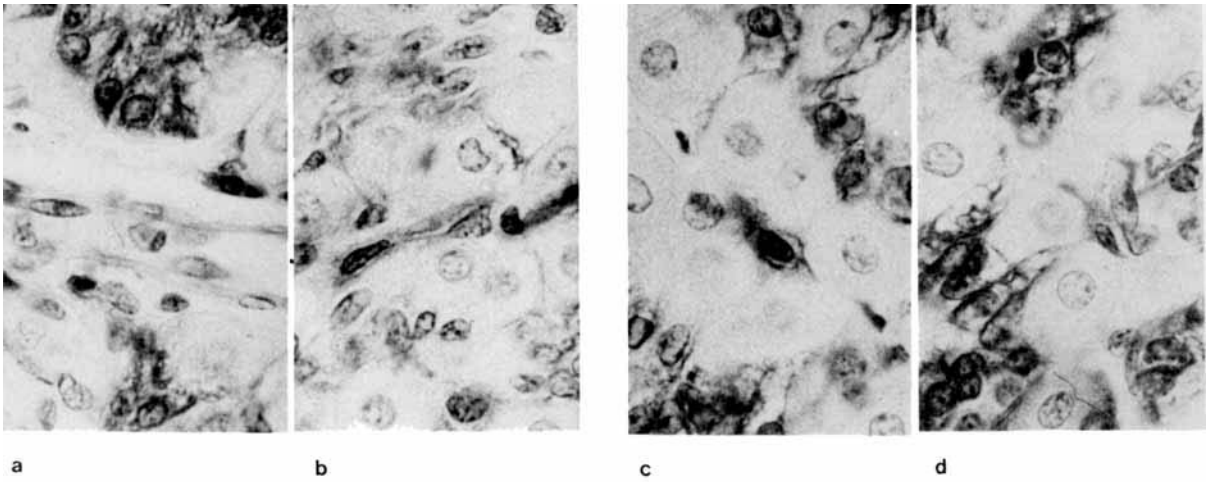

Figure 3. Mast cells in pig corpus mucosa in the immediate vicinity of parietal cells ("rosette phenomenon"). The tissue was fixed by Carnoy solution, embedded in paraffin, cut in 3μ sections and stained with 0.2% toluidine blue at pH 4.0 according to Lorenz et al.[4] Magnification 1200 fold. Parietal cells are the light pellucid cells, chief cells are mainly dark, blue cells, while mast cells take a red-violet stain. Note the "rosette phenomenon," especially in 3c.

alkaline (unspecific) histidine decarboxylase, but the physiological significance of this enzyme was questioned.[21] Acid (specific) HDC was first demonstrated in the oxyntic gland area of the rat stomach by Schayer;[22] later this enzyme was claimed to be only located in enterochromaffine-like cells[23] that do not store or form histamine in most other species.[2] Now acid (specific) histidine decarboxylases have been demonstrated in the gastric mucosa of all mammals investigated[24–26] but these findings were questioned on the basis of methodological errors.[27] This controversial issue is compiled in Table 2. A number of workers in the field found histamine formation in all species studied, whereas others could

TABLE 2.

Controversial Findings and Hypotheses on the Occurrence of an Acid (Specfic) Histidine Decarboxylase in the Gastric Mucosa of Various Mammals (after Neugebauer and Lorenz[29], with permission).

Species	*Yes!*	*No!*
Human subject	Kahlson, 1964 Lindell, Westling, 1966 Lorenz, 1969 Noll, Levine, 1970 Dencker, 1973	Håkanson, 1969
Dog	Kahlson, 1964 Lorenze, 1969	Aures, 1968 Kim, Glick, 1968 Aures, 1969
Rabbit	Werle, Lorenz, 1964 Lorenz, 1969	Adalanson, Owman, 1966 Aures, 1969 Lorenz, 1977
Guinea-pig	Kahlson, 1964 Lorenz, 1967 Lorenz, 1969 Bergmark, 1976	Aures, 1969

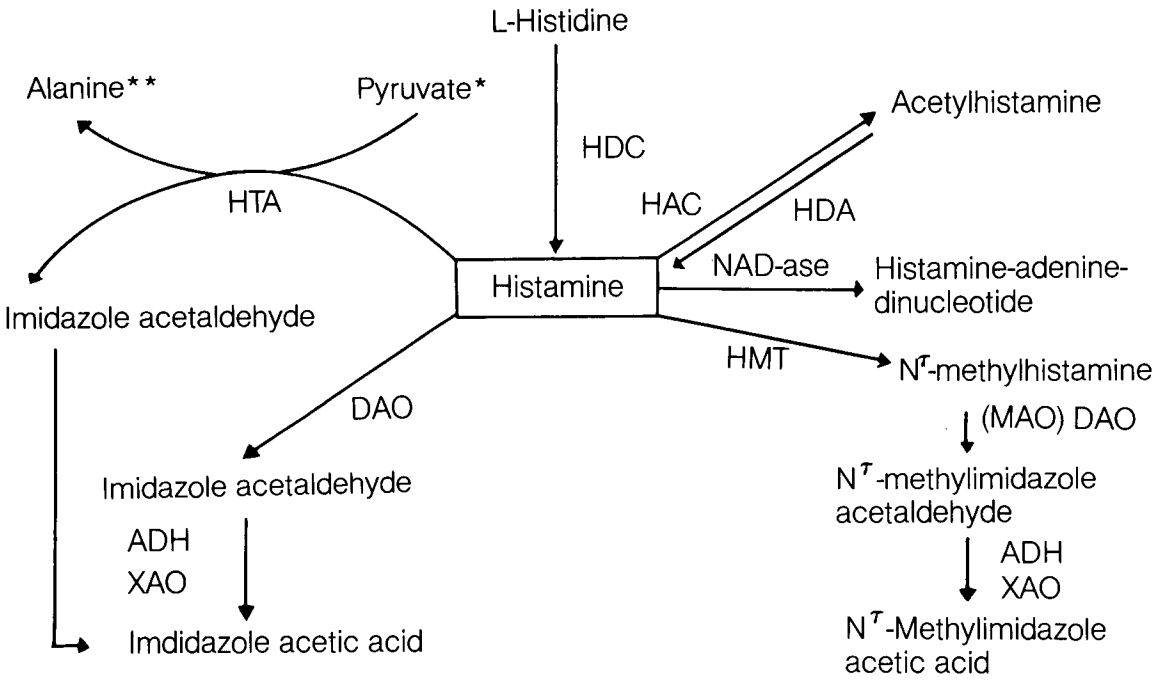

Figure 4. Pathways of histamine synthesis and catabolism in mammals (after Neugebauer and Lorenz[89], with permission).
HDC = Histidine decarboxylase (E.C. 4.1.1.22),
HAC = Histamine transacetylase,
NAD-ase = Diphosphopyridine nucleotidase (E.C. 3.2.2.6),
HMT = Histamine methyltransferase (E.C. 2.1.1.8),
MAO = Monoamine oxidase (E.C. 1.4.3.4),
DAO = Diamine oxidase (E.C. 1.4.3.6),
ADH = Alcohol dehydrogenase (E.C. 1.2.1.3),
XAO = Xanthinoxidase (E.C. 1.2.3.2),
HTA = Histamine transaminase,
HDA = N-acetyl histamine deacetylase.
*Pyruvate = Pyruvate, Phenylpyruvate, p-Hydroxyphenylpyruvate,
**Alanine = Alanine, Phenylalanine, Tyrosine.

TABLE 3.

Reliability and Practicability of the Modified Schayer Method for Measuring Acid Histidine Decarboxylase Activity in Gastric Mucosa (after Neugebauer and Lorenz,[29] with permission).

Criterion	*Evaluation*
Sensitivity	0.2 pmol histamine formed
Specificity	Unchanged
Precision	cv% = 9.0 (n = 10)
Accuracy	Recovery 45.6 (41.5–56.2) (mean and range, n = 10)
Convenience and time spent	1 run/week 60 samples/run and person
Suitable for routine assay	1500 samples were tested in one year

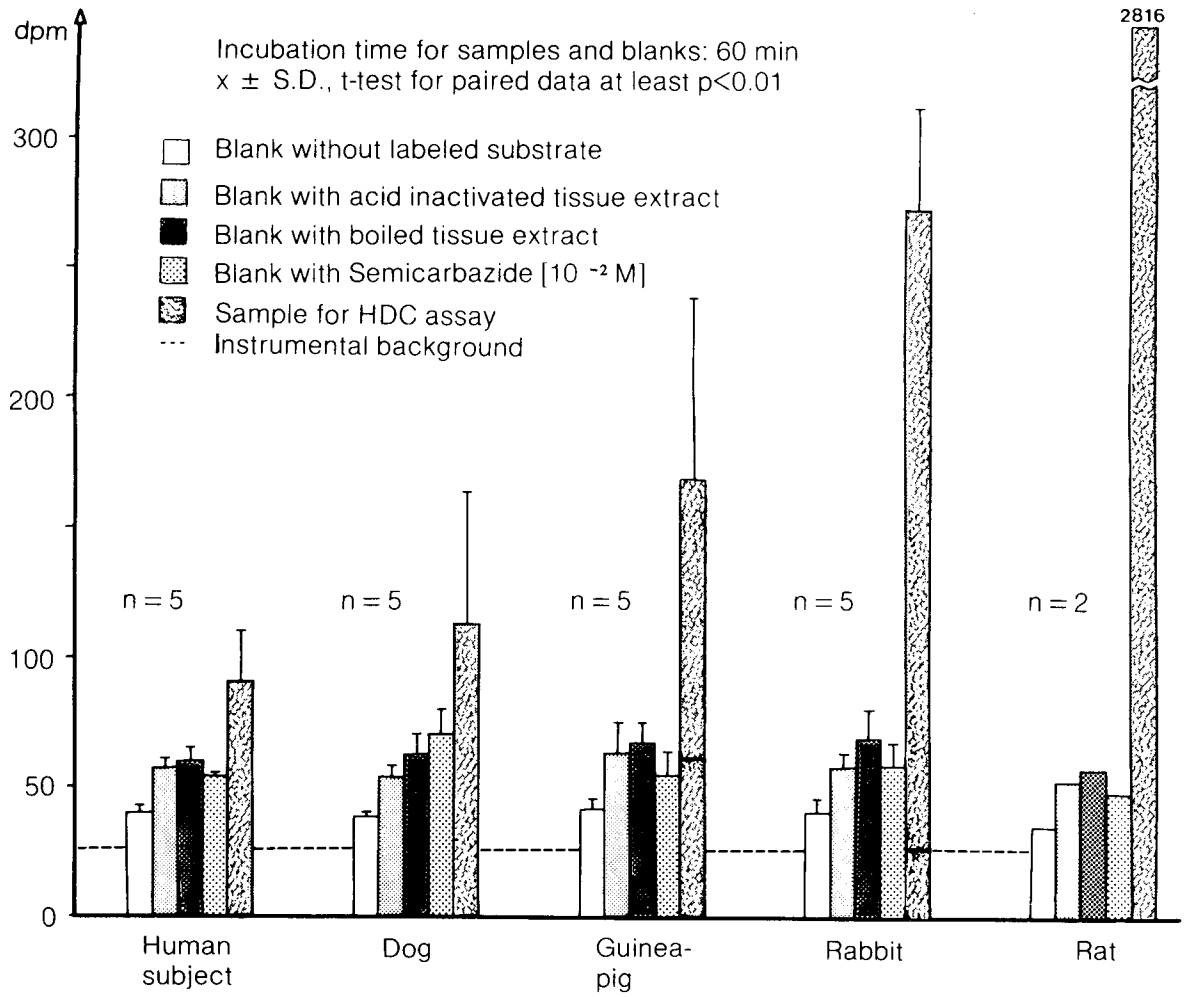

Figure 5. Radioactivity formed by corpus mucosa extracts of 5 mammalian species compared with that of several blanks (after Neugebauer and Lorenz,[29] with permission).
n = number of experiments. For further details, see Neugebauer and Lorenz.[29]

not detect any HDC activity. Lorenz et al.[28] confirmed the results of Aures et al.[27] but also showed that their $^{14}CO_2$ assay was unreliable for measuring HDC activity in species other than the rat. Neugebauer and Lorenz[29] developed a new assay for the acid HDC that simplified Schayer's tedious and time-consuming procedure while retaining the high specificity of the original assay[30] (Table 3). Using this assay, acid HDC activity was demonstrated in all species investigated independent of the blank used, including one with the decarboxylase inhibitor semicarbazide (Fig. 5). The latter substance was claimed by Aures et al.[27] to inhibit non-enzymatic decarboxylation thus simulating enzymatic histamine formation in Kahlson's experiments. This was shown not to be true (Fig. 5) since the work of Neugebauer and Lorenz[29] and Beaven et al.[7,31] (confirmed the previous findings of Lorenz et al.[26] The data in this latter article are summarized in Table 4. Lorenz et al.[26] emphasized the importance of tissue preparation and measurement of initial velocity of histamine formation especially in tissues like the stomach that have high activities of acid HDC. The critical dependence on tissue preparation was substantiated by Beaven et al.[7,31] who demonstrated 90% loss of the enzymic activity after disrupting mast cells by sonication.

Compared to other enzymes in amine metabolism, the activity of acid HDC in gastric mucosa cannot be regarded as high, an important consideration in human pathological states.

TABLE 4.

Activity of the Acid (Specific) Histidne Decarboxylases in Crude Extracts of the Gastric Mucosa (after Neugebauer and Lorenz[89], with permission).

	Histidine decarboxylation in pmoles histamine formation/min and mg protein					
Species	*n*	*Fundus*	*n*	*Corpus*	*n*	*Antrum*
Man	7	10.6 ± 2.6	12	7.1 ± 1.4	3	4.0 ± 1.2
Monkey	3	18.7 ± 7.7	5	4.6 ± 1.8	3	7.2 ± 1.7
Dog	3	38.4	2	46.5	2	26
Cat	1	7.4	—	—	—	—
Pig	4	202 ± 105	4	60 ± 14	4	77 ± 18
Cow	—	—	2	44.7	2	24.0
Rabbit	2	15.2	2	5.1	2	2.9
Guinea-pig	3	16.4 ± 9.1	3	13.8 ± 1.5	3	13.1 ± 0.8
Rat	—	—	10	29.3 ± 6.8	—	—

Mean values ± standard deviation. In cows, the rennet bag has been used. In rats, the glandular portion of the stomach after removing the rumen has been used. n = number of animals tested, but in cats, rats and guinea pigs the organs of 10 animals have been pooled. For further conditions, see Lorenz et al.[26]

Occurrence and Properties of Histamine Methyltransferase (HMT) and Diamine Oxidase (DAO) in Gastric Mucosa

In contrast to HDC, the activity of HMT in the human and mammalian[32,33] gastric mucosa is more easily detected, but there are few studies of its physiological or pathological significance. The distribution of HMT in human tissues has not been studied in detail, and little comparative data are available[29,34] (Table 5).

Enzymic activity is relatively high in corpus mucosa compared to brain in guinea pig;[31,32] the HMT activity in the antrum mucosa, liver and kidney frequently exceeds that of the corpus mucosa.[34] Thus, the enzymic activity is in accord with a physiological function of histamine in the gastric mucosa, and its localization to parietal cells is significant. Porcine gastric mucosa[31] has the highest activities of HMT and is used for purification and characterization of the enzyme (Table 6).

Donor and acceptor substrate pH-optimum and Km values are in accordance with a physiological function of the enzyme. Low concentrations of histamine (10^{-10}M) are quickly inactivated by gastric HMT.[35] Histamine H_1- and H_2-receptor antagonists generally have a biphasic effect on HMT with activation at low concentrations and inhibition at high concentrations and inhibition at high concentrations.[5,16,36] This is discussed in a later section.

The histamine-degrading enzyme, DAO, has a role in the gastric mucosa similar to that of HDC. Code felt that absence of DAO from gastric mucosa would favor a physiological role for histamine in gastric secretion,[37] but in all systems there are high activities of degrading enzymes for physiological mediators. Thus, we re-examined DAO activity in gastric mucosa (Fig. 6).[28,38,39]

TABLE 5.

Distribution of Histamine Methyltransferase in Human Tissues (after Neugebauer and Lorenz[89], with permission).

		Activity of the enzyme [pmol/(min × mg protein)]	
Tissue	*n*	*x ± S.D.*	*Range*
Gastric mucosa			
Corpus	7	70 ± 31	24–100
Antrum	6	94 ± 15	75–117
Ileum	3	79 ± 30	60–113
Colon	5	53 ± 27	37– 98
Liver	5	425 ± 147	238–648
Lungs	2	88	—
Kidney	4	226 ± 99	84–288

The tissues were obtained during surgery in a study on the distribution of histamine in human subjects (see Table 1). Incubation of the crude extracts and the isotope assay were carried out, according to Barth et al.[36]

TABLE 6.

Enzymatic Properties of Gastric Histamine Methyltransferase (after Neugebauer and Lorenz[89], with permission).

Attribute	*Specification*
pH-optimum	7.4
Donor substrate (D)	S-Adenosyl-L-methionine
K_m-values for D	$0.87 \pm 0.24 \times 10^{-5}$[M] (n = 8)
Acceptor substrate (A)	Histamine
K_m-values for A	$1.71 \pm 0.27 \times 10^{-5}$[M] (n = 22)
SH-group reagents (p-CMB etc.)	Strong inhibitors
Activators	Some methylated histamines, H_1-and H_2-receptor antagonists
Inhibitors	Methylated histamines, H_1- and H_2-receptor antagonists antimalarial drugs

Data were obtained chiefly from pig antrum and fundus mucosa.

TABLE 7.

Diamine Oxidase Activity in the Gastric Mucosa of Patients Suffering from Gastric Adenocarcinoma (after Kusche et al.[38])

Localization of Tissue Sample	*Diamine Oxidase Activity [nmol/min × g tissue]*
Oral from carcinoma:	
10 cm	4.8 (3.7–12.5)
5 cm	4.6 (2.8–30.0)
Carcinoma	8.0 (0.1–35.0)
Adjacent to carcinoma	28.0 (10.0–51.0)
Aboral from carcinoma	21.4 (18.8–53.6)

Median (range), n = 6.

Enzymic activity is found in all areas of the human gastric mucosa except the cardia. Activity is very low in the fundus, moderate in the corpus mucosa and somewhat higher in the antrum especially near the pylorus. DAO activity, however, is very high in the vicinity of a gastric carcinoma (Table 7) and in regions of intestinal metaplasia. Biochemical changes precede the pathohistological alterations of the gastric mucosa.[39] Since DAO activity is found in leukocytes in acute and chronic inflammation,[40,44] the role of local inflammatory cells in "physiological" histamine degradation is unknown. In addition, increased intestinal metaplasia in gastric ulcer and in gastric carcinoma is often associated with moderate to high DAO activity in the non-involved portions of corpus mucosa. Thus, a new hypothesis can be forwarded to explain the extremely low gastric acid secretion in patients with gastric carcinoma and a fairly "normal" gastric mucosa in the non-infiltrated parts of the stomach.

The enzymic properties of DAO are compiled in Table 8 for human and pig intestinal DAO. Histamine pH-optimum and histamine K_m-values are in accordance with a physiological function of the enzyme. The substrate specificity and product effects are summarized in Table 9. The product of histamine methylation, N^τ-methylhistamine, which is a strong inhibitor of HMT,[42] was found to be a better substrate of intestinal DAO than histamine itself, a finding that is at variance with the accepted role of monoamine oxidase B in degradation of N^τ-methylhistamine.[48] We found that intestinal monoamine

TABLE 8.

Enzymatic Properties of Human and Pig Intestinal Diamine Oxidase (after Neugebauer and Lorenze[89], with permission).

Attribute	*Specification*	
	Man	*Pig*
pH-optimum	7.0 (P)	7.6–7.8 (P)
	6.7 (H)	7.5–8.0 (H)
Substrates	Putrescine, Histamine etc.	Putrescine, Histamine etc.
K_m-values [M]	—	1.2×10^{-4} (P)
	—	5×10^{-5} (H)
50% inhibition by aminoguanidine [M]	1.1×10^{-8} (P)	3×10^{-7} (P)
		8×10^{-7} (H)
50% inibition by pargyline [M]	no inhibition	no inhibition

(P) = putrescine, (H) = histamine

oxidase was unable to catabolize N^{τ}-methylhistamine,[44] in contrast to the enzyme in brain.[43] Burimamide, metiamide and cimetidine all inhibit human intestinal DAO,[45] but the strongest inhibitor *in vitro* is impromidine, a histamine H_2-receptor agonist.[46] In gastric secretion DAO not only catabolizes histamine but also facilitates histamine inactivation by HMT by removing the product of histamine methylation. Augmentation of gastric secretion by the DAO blocker aminoguanidine is direct evidence for the physiological significance of this enzyme system.[47]

Histamine Release and Uptake

Histamine release can be considered as a special mechanism of "forming" free, biologically active histamine, whereas uptake or re-uptake into the mast cell stores is "inactivation." Similar models are common for other neurotransmitters, but for histamine this mechanism has not been elucidated.

Unlike gastrin, a gastric hormone, histamine is not secreted into the gastric venous blood in measurable quantities[48] (Table 10). Neither aminoguanidine, a very potent inhibitor of DAO, nor the histamine H_2-receptor antagonist burimamide, which is a very strong inhibitor of gastric HMT, have a significant effect on gastric venous histamine in dogs. In contrast, both aminoguanidine and burimamide elevate plasma histamine concentrations in dogs given exogenous histamine intravenously[49] or subjected to intestinal ischemia to release endogenous histamine.[50] Gastric arteriovenous histamine ratios sig-

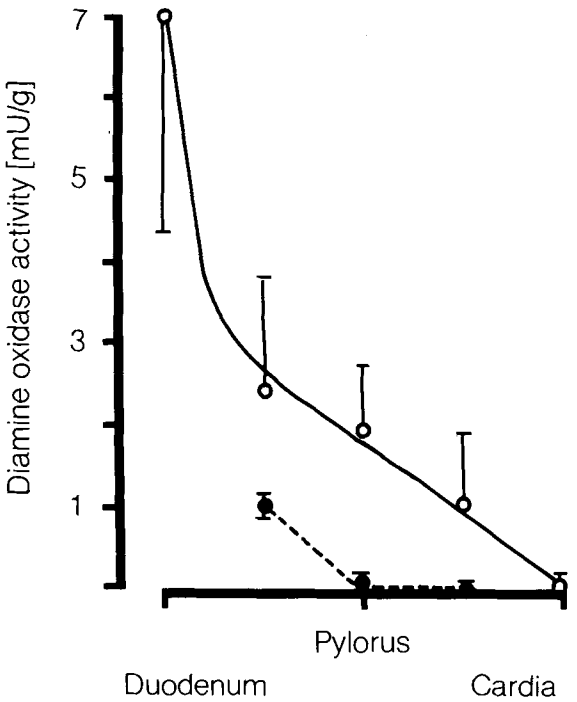

Figure 6. Diamine oxidase activity in duodenal and gastric mucosa of human subjects and rabbits (after Neugebauer and Lorenz,[29] with permission).
$\bar{x} \pm$ S.D. O——O men (n = 3–10); ●---● rabbits (n = 5).

TABLE 9.

Deamination of Histamine and its Derivatives by Human Intestinal Diamine Oxidase

Amine	*Final concentration* 5 *mmol*	1 *mmol*	0.1 *mmol*
Histamine	57	71	100
N^{τ}-Methyhistamine	160	191	175
2-Methylhistamine	108	140	203
N^{π}-Methyhistamine	31	34	38
5-Methylhistamine	24	37	52
5-Ethylhistamine	0	79	56
N^{α}-Methylhistamine	0	0	0
N^{α}, 5-Dimethylhistamine	0	0	0
N^{α}, N^{α}-Dimethylhistamine	0	0	0

100 = 1.2 nmol/min at 0.1 mmol histamine concentration. For further conditions, see Bieganski et al.[86]

nificantly less than unity indicate histamine uptake.[48] In addition, radiolabeled histamine is taken up by the gastric mucosa of several mammals.[17,51] For this reason, histamine uptake and reuptake after its release have to be seriously considered as a physiological mechanism to control the local concentration.[48]

In human subjects, slightly elevated venous plasma histamine levels are observed for a very short time during pentagastrin infusion,[52] but not following insulin injection (0.2 U/kg i.v.).[9] Peripheral venous plasma levels are markedly elevated by histamine infusion. (Fig. 7). However, the same amounts of histamine appear in the gastric aspirate after both insulin and intravenous histamine infusion. It is thus reasonable to conclude that histamine in gastric juice does not originate from blood, but from the gastric mucosa. Indeed, the gastric aspirate and the saliva elicited by cholinergic stimuli[53,54] are the only body fluids that contained free histamine in concentration of about 10 ng/ml (Fig. 8). These high concentrations of histamine need more explanation than just simple filtration, transudation or transport from plasma into the gastric juice.[55]

TABLE 10.

Plasma Histamine Concentrations in the Aorta and Gastric Veins of Dogs Following the Injection of Pentagastrin (after Lorenz et al.[48], with permission).

	Plasma histamine concentrations [ng/ml] following pentagastrin injection [6 μg/kg i.m.]													
	Aorta							*Gastric veins*						
Exp. No.	*0*	*5*	*15*	*30*	*45*	*60*	*90 [min]*	*0*	*5*	*15*	*30*	*45*	*60*	*90 [min.]*
No inhibitors of histamine catabolism														
1	0	0	0.1	0	0	0.3	0	0	0.1	0	0	0	0	0
2	0	0	0	0	0	0	0.3	0	0.3	0	0	0.1	0	0.1
3	0	0	0	0	0	0	0	0.1	0.1	0	0.1	0	0	0
Aminoguanidine (100 mg/kg i.v. 15 mins. before pentagastrin)														
4	0.7	0.7	0.6	0.5	0.5	0.6	0.7	0.5	1.1	0.8	0.9	0.7	1.1	1.1
5	0	0	0	0	0.1	0	0	0.4	0.5	0.8	—	0.3	0.5	0.4
6	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Aminoguanidine (10 mg/kg) and burimamide (10 mg/kg) i.v. 15 mins. before pentagastrin														
7	0.2	0	0.6	0.6	0.4	—	—	0.6	0.6	0.5	1.1	—	—	—
8	0.8	0.6	0.5	0.5	1.0	0	—	0.6	0.6	0.9	0	0.6	0	—
9	1.1	0.6	0.8	1.0	0.5	0	—	0.2	1.6	1.1	0.5	0.2	0.2	—

Single values in 9 anesthetized dogs.

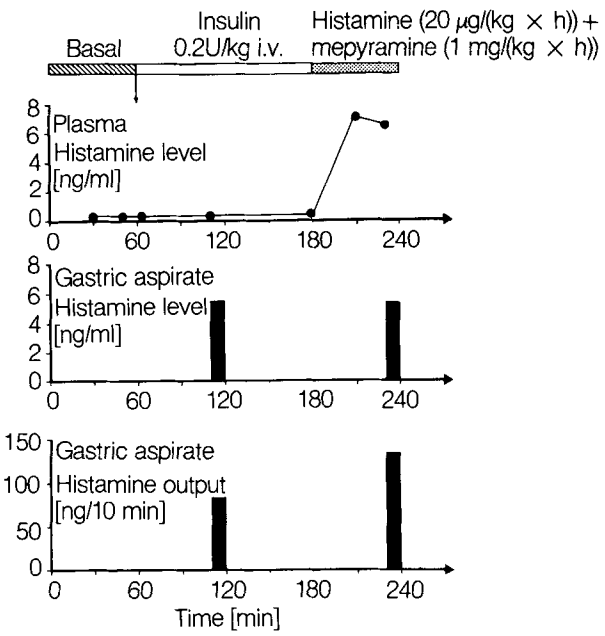

Figure 7. Histamine in human plasma and gastric aspirate following insulin injection and histamine infusion. (after Lorenz et al.,[9] with permission).

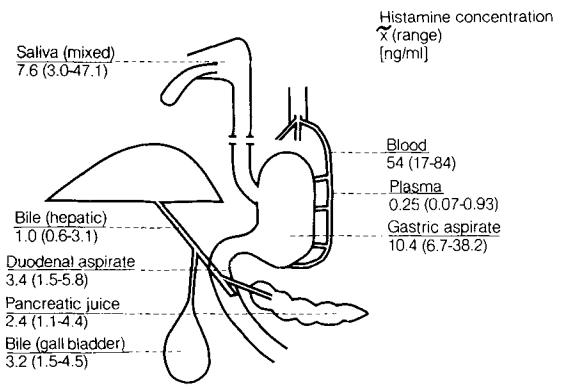

Figure 8. Possible sources of histamine in gastric aspirate in man (after Lorenz et al.,[9] with permission). Medians and ranges of histamine levels in several body fluids.

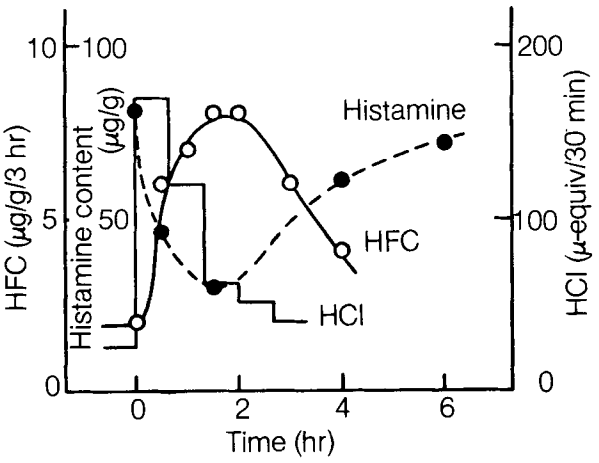

Figure 9. Changes in histamine contents and histidine content decarboxylase activity of rat gastric mucosa following stimulation of acid secretion by gastrin) (after Kahlson et al.,[25] with permission). Injection given at zero time. The curve of HCl secretion represents the mean of 16 experiments in 8 rats provided with a whole stomach fistula.

Influence of Stimulators of Gastric Acid Secretion on Histamine Release and Metabolism

Histamine storage and metabolism are influenced by stimulators of gastric acid secretion. In rats, mobilization of histamine by gastrin and insulin is accompanied by an increase in histamine formation (Fig. 9).[25,56] In the rat histamine formation and storage involve special mucosal cells (APUD cells) while human,[52] canine[57] and feline[58] mucosal mast cells are the storage sites for histamine.[2,3,8,59]

Not only HDC but also HMT activities are altered by feeding or administration of various gastric stimulants. Increases in guinea pigs after feeding are restricted to the acid-producing area of the stomach (Table 11). The HDC and HMT response to pentagastrin injection is dose- and time-dependent and specific for gastrin and gastrin-like peptides (Table 12). Vagal excitation by insulin hypoglycemia and parasympathomimetic agents, however, do not increase enzymic activity (Table 13).

Results completely in agreement with those obtained in guinea pigs have recently been obtained in dogs with gastric fistula[57] (Fig. 10). Mucosal HMT activities were inversely proportional to tissue histamine contents in both basal and stimulated states. Pentagastrin decreased the mucosal histamine stores and increased HMT activity. 2-Deoxy-D-glucose and insulin-induced vagal excitation had no effect on mucosal histamine and HMT activity. These findings may be helpful in interpreting data on mucosal histamine contents in normal human subjects and in duodenal ulcer patients and in patients treated by drugs and surgical procedures. At present there are no data on modulation of gastric DAO activity by stimulants of gastric secretion.

TABLE 11.

Increase of Histamine Methyltransferase Activity in the Guinea Pig Stomach after Feeding (after Barth et al.[88], with permission)

Gastric Region	*Enzymic activity (pmol/ [minutes × mg protein])*		*Change (± %)*	*Significance*
	Fasted	*Fed*		*Fasted vs. Fed*
fundus	297.6 ± 62.5	375.8 ± 63.8	+26	$P < 0.020$
corpus	317.8 ± 35.3	373.0 ± 56.8	+17	$P < 0.020$
antrum	278.7 ± 55.1	275.6 ± 31.0	−1	ns

Mean values ± SD; 11 animals in both groups. All had fasted for 24 hours. Then the fed group had access to food for 2 hours. Statistical evaluation by Student's *t*-test.

TABLE 12.

Increase of Histamine Methyltransferase Activity in the Guinea Pig Stomach after Feeding (after Barth et al.[88], with permission)

Dose (μg/kg)	*Time after stimulation (Minutes)*	*Enzymic activity (pmol/ [minutes × mg protein])*		*Increase (%)*	*Significance*
		0.9% NaCl	*Pentagastrin*		*Pentagastrin vs. 0.9% NaCl*
10	60		319.5 ± 29.4	+2	ns
50	60	313.4 ± 25.8	354.2 ± 47.6	+13	$P < 0.050$
100	60		370.8 ± 38.8	+18	$P < 0.005$
100	15		348.8 ± 53.1	+25	$P < 0.005$
100	30	279.1 ± 36.4	363.8 ± 62.3	+30	$P < 0.005$
100	60		316.4 ± 60.5	+13	$P < 0.15$; ns

Mean values ± SD; the 11 animals in each group were killed at the indicated time intervals after intramuscular administration of pentagastrin or 0.9% NaCl (1–2 ml/kg); statistical evaluation by Student's *t*-test. ns = not significant.

Alterations in Histamine Storage and Metabolism in Duodenal Ulcer Patients: Effect of Vagotomy

Histamine storage and metabolism, especially that in the gastric mucosa, is influenced by numerous genetic, hormonal and environmental factors.[60,67] Thus, defining the role of histamine in peptic ulcer pathogenesis will involve all these factors as prognostic factors,[68–70] 2 prospective controlled clinical trials were designed to answer 2 questions:

(1) Is histamine storage or release altered in human peptic ulcer?

(2) Is histamine catabolism by HMT altered in human peptic ulcer?

Designs, methods and most of the results of these clinical trials have been reported in detail.[5,71–74] In summary, the histamine content in the corpus mucosa of "normal" (control) subjects was 42.6 μg histamine dihydrochloride/g tissue (Fig. 11). It was significantly lower in duodenal ulcer patients, a difference that was independent of sex and age. This finding was specific for duodenal ulcer patients (Table 14). One case with Zollinger-Ellison syndrome showed extremely low histamine levels; one case with atrophic gastritis showed extremely high histamine content.

TABLE 13.

Influence of Parasympathomimetic Drugs on Histamine Methyltransferase Activity in the Guinea Pig Stomach (Corpus) (after Barth et al.[88], with permission)

Gastric Secretagogue	*Dose*	*Enzymic activity (pmol/[minutes × mg protein])*		*Change (± %)*
		0.9% NaCl	*Drug*	
carbachol	5μg/kg		186.0 ± 26.2	+7
	10 μg/kg	173.9 ± 17.3	189.2 ± 30.7	+8
	50 μg/kg		190.7 ± 32.8	+8
insulin	0.5 IU/kg		228.9 ± 27.8	+6
	1.0 IU/kg	215.2 ± 29.6	231.2 ± 35.4	+7
	5.0 IU/kg		221.7 ± 22.3	+3
2-deoxy-D-glucose	50 mg/kg		193.4 ± 11.2	−1
	200 mg/kg	194.8 ± 32.5	215.6 ± 25.9	+11
	500 mg/kg		203.1 ± 36.5	+4

Mean values ± SD; the 11 animals in each group were killed 30 min after intramuscular administration of the secretagogues or 0.9% NaCl (1–2 ml/kg). Statistical evaluation by Student's *t*-test revealed no significant differences on a 5% level between drug- and NaCl-treated groups.

TABLE 14.

Histamine Contents in Human Corpus Mucosa of Patients Suffering from Various Diseases (after Troidl et al.[71], with permission).

Diagnoses	*n*	*Histamine content (μg/g)*	
		Median or single values	*Range*
Gastric ulcer	10	37.2	15.5–98.8
Hiatal hernia	6	37.2	13.4–66.8
Cholecystitis	4	48.0	31.7–71.0
Gastric erosions	3	43.0	28.7–61.7
Z. E. syndrome	1	13.3	—
Atrophic gastritis	1	95.8	—
Pancreatitis	1	40.3	—
Oesophageal varices	1	63.0	—
Obesity	2	40.9, 45.7	—

n = number of patients

Troidl et al.[71] and Man et al.[52] explained these differences on the basis of histamine release, but Peden et al.[75] attributed them to differences in smoking habits between the control and the duodenal ulcer group. Vagotomy reversed the findings in duodenal ulcer disease; postvagotomy values were higher than control[72] (Fig. 12).

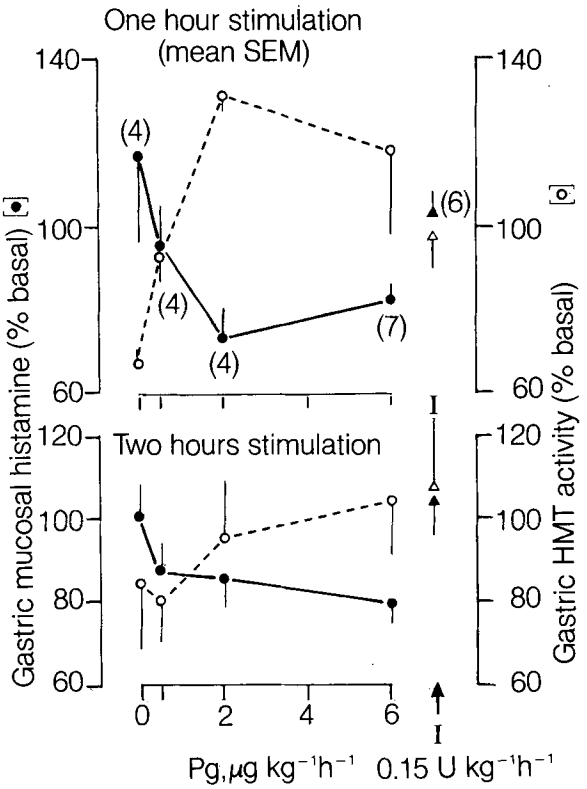

Figure 10. Influence of pentagastrin and insulin infusion on gastric mucosal histamine contents and gastric mucosal histamine methyltransferase (HMT) activities in dogs with gastric fistula.[57]

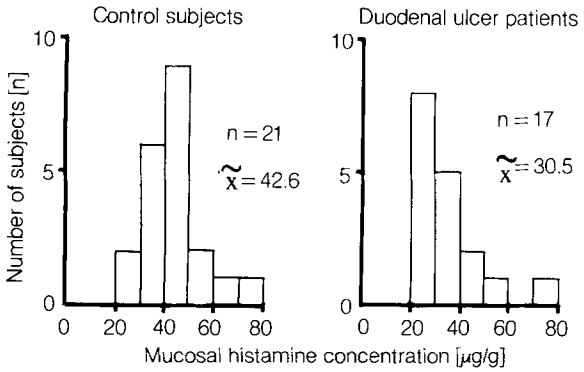

Figure 11. Histograms of histamine concentrations in human corpus mucosa of control subjects and duodenal ulcer patients (after Troidl et al.,[71] with permission). Only male subjects are included. $\tilde{x}$ = median. Statistical significance (Mann-Whitney test) between the 2 groups of individuals $p < 0.025$.

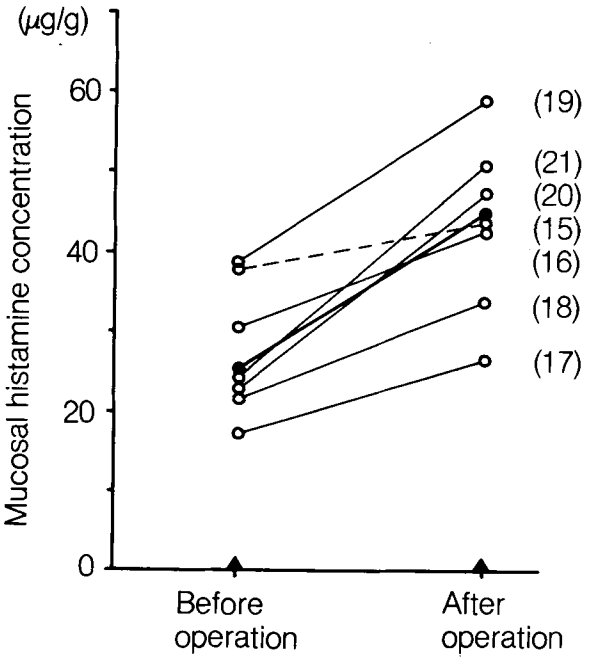

Figure 12. Histamine content in the corpus mucosa of duodenal ulcer patients before and after selective gastric vagotomy with drainage (after Troidl et al.,[72] with permission).

Acid secretion (basal and peak acid output)[76] in control subjects and duodenal ulcer patients before or after operation showed no relation to mucosal histamine levels.[48] If, however, a pentagastrin dose response was performed in each subject to define peak acid output, a highly significant negative correlation was found between the secretory response and the mucosal histamine level.[5] Furthermore, there was a direct relationship between the reduction in acid output after vagotomy and the increase in mucosal histamine concentration (Fig. 13). These findings suggest a relationship between mucosal histamine content (histamine storage) and the secretory capacity in man.

The interpretation that the increased mucosal storage of histamine after vagotomy is coupled with reduced histamine release is supported by measurement of histamine outputs in the basal secretion of duodenal ulcer patients before and after vagotomy (Table 15). After vagotomy, basal histamine concentration in the gastric aspirate increased but, due to a decreased volume of the secretion, the histamine output fell by about 30% corresponding to the increase in mucosal histamine content. However, in one of the patients an incredible increase of histamine output was observed. The histamine values

TABLE 15.

Basal Histamine Content and Output in Gastric Aspirate of Duodenal Ulcer Patients Before and After Selective Proximal Vagotomy (SPV).

	Histamine content (ng/ml)				
Patient No.	*before SPV*		*after SPV*		
	Test 1	*Test 2*	*Test 1*	±	*% change*
1	16.8	15.7	41.5	+	150
2	9.4	5.0	50.1	+	435
3	17.6	10.7	1450	+	8100
4	3.7	6.1	70.3	+	1900
5	4.4	10.3	18.9	+	330
$\bar{x}$	10.4	9.6	45.2*	+	704
	Histamine output (µg/h)				
1	2.15	3.13	1.31	−	39
2	1.81	1.54	1.40	−	23
3	2.84	2.10	65.25	+	2200
4	4.64	2.82	2.13	−	54
5	1.60	1.76	1.42	−	11
$\bar{x}$	2.61	2.72	1.57*	−	31.8*

The 1 hour basal secretion was measured when the insulin test was performed 7 days after operation. *$\bar{x}$ calculated without including the data of patient No. 3. Histamine assay, according to Parkin et al.[82]

TABLE 16.

Inhibition of Acid (specific) Histidine Decarboxylase (HDC) of Rabbit Gastric Mucosa (fundus-corpus) by Histamine H_2-Receptor Antagonists.

Histamine H_2-Receptor Antagonist	*Final Concentration [M]*	*HDC activity [f mol × min^{-1} and mg protein^{-1}]*	*%*
No inhibitor	—	5.34 ± 0.54	100
Cimetidine	5×10^{-3}	4.65 ± 0.91	87
	5×10^{-4}	4.06 ± 0.53	76
	5×10^{-5}	5.08 ± 0.60	95
Ranitidine	5×10^{-3}	5.28 ± 0.92	99
	5×10^{-4}	5.07 ± 1.14	95
	5×10^{-5}	4.51 ± 0.67	84

Incubation conditions and ^{14}C-histamine assay by a modiied Schayer procedure according to Neugebauer and Lorenz.[29] $\bar{x}$ ± S.D. from 4 experiments per concentration of the inhibitor.

were reproducible, and quality control of the assay permitted the conclusion that methodological errors could be excluded when explaining these data. Since we have postoperative data from 3 other patients that are similarly high, it may be asked whether we are dealing with a subclass of peptic ulcer patients? It seems absolutely impossible that such high amounts of histamine can be delivered from any other compartment than the gastric mucosa.

The second controlled clinical trial was conducted in 53 male patients. HMT activity was determined by a modified isotope assay in biopsy specimens from the gastric corpus mucosa of control subjects, duodenal ulcer patients and after various operations for duodenal ulcer, including 12 subjects with selective gastric vagotomy + Heinecke-Miculicz pyloroplasty[73] (Fig. 14).

Duodenal ulcer patients had significantly lower HMT activities than healthy control subjects. The findings of Barth et al.[73] were confirmed recently by Peden et al.[75] This was in contrast to the findings of Mendez-Diaz et al.[57] in healthy dogs where a decreased mucosal histamine content was inversely correlated to an increased HMT activity. Perhaps in duodenal ulcer patients the regulatory function of HMT in histamine inactivation is impaired. After vagotomy with drainage or selective proximal vagotomy, HMT activity is increased (Fig. 14c). No change was found after gastric resection with Billroth I and II anastomosis.[73] Both histamine storage[72] and HMT activity[73] is lowered in patients with recurrent ulcer after vagotomy. All these findings emphasize a disturbance of histamine storage and metabolism in association with peptic ulcer and an influence of therapeutic regimens on this regulatory impairment. The role of histamine H_2-receptor antagonists on histamine storage and metabolism *in vitro* and *in vivo* remain to be defined.

Effects on Histamine H_2-receptor Antagonists on Enzymes of Histamine Metabolism and on Mucosal Histamine Levels

The histamine H_2-receptor antagonists, cimetidine and ranitidine, did not exert significant effects on rabbit gastric histidine decarboxylase (Table 16). The small inhibition observed with rather high doses of the antagonists was not clearly dose dependent and can therefore be ignored.

In contrast to their minor effect on HDC activity, histamine H_2-receptor antagonists had a marked effect on HMT activity of pig fundus mucosa (Fig. 15). Burimamide showed only a strong inhibition of the enzyme, while metiamide, cimetidine and ranitidine exerted a dual action on HMT. At low concentrations an activation of the enzyme occurred while at high concentrations a more or less pronounced inhibition was seen. There were prominent

differences among the latter three H_2 antagonists. Metiamide was a strong activator and in rather high doses also a strong inhibitor of HMT. Cimetidine was similarly effective in activation but was a much less potent inhibitor, whereas ranitidine was only a weak activator but a potent inhibitor of the enzyme.

The *in vitro* effects of histamine H_2-receptor antagonists on gastric HMT[16,36,77] also seem to have clinical relevance. Biologically active plasma histamine concentrations are slightly increased in human volunteers after injection of H_1- + H_2-receptor antagonists[78] and considerably elevated after burimamide in dogs.[49] Shepherd et al.[79] observed an increased excretion of N^t-methylhistamine in duodenal ulcer patients during treatment with metiamide; therefore, the strong activating effect of the drug on HMT *in vitro* was also demonstrated in human patients. If the stimulation of HMT activity by metiamide and cimetidine does contribute to the inhibition of gastric secretion by these two drugs, ranitidine must act almost solely at the histamine H_2-receptors. Thus, the mode of action of cimetidine and ranitidine on gastric secretion may, in part, be different.

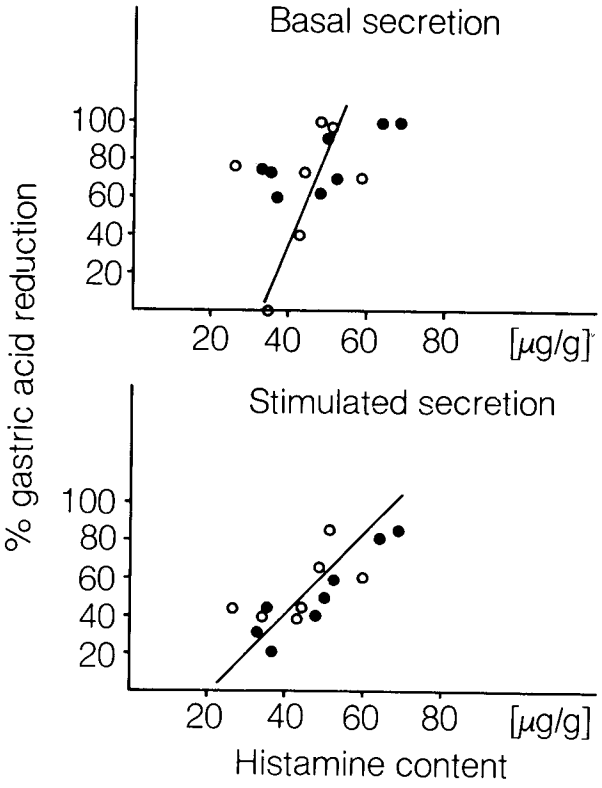

Figure 13. Correlation between acid reduction and mucosal histamine content in patients after vagotomy (after Lorenz et al.,[5] with permission).
Open and closed circles refer to two different trials in the same study. Data analysis performed using least squares linear regression.

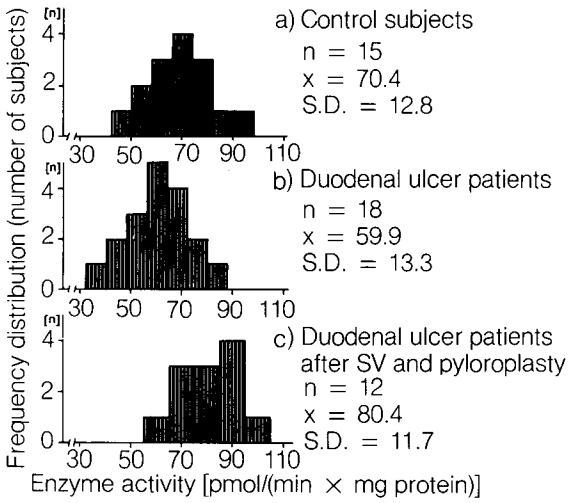

Figure 14. Histograms of histamine methyltransferase activity in corpus mucosa of male control subjects and duodenal ulcer patients before and after vagotomy (after Neugebauer and Lorenz,[29] with permission).
SV = selective proximal vagotomy.

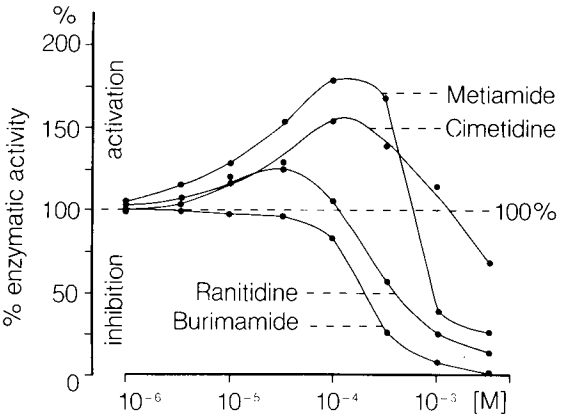

Figure 15. Inhibition and activation of purified histamine methyltransferase from pig fundus by histamine H_2-receptor antagonists.
Enzymic activity without addition of the drugs equalled 100%. It corresponded to 3.3 nmol/(min x mg protein) (n=4). For incubation conditions and the isotope assay with S-adenosyl-L- [^{14}C-methyl]-methionine. See Barth et al.[10]

Histamine H_2-receptor antagonists not only influence gastric HMT activity but also effect histamine storage and release. Man et al.[80] showed that cimetidine increased gastric mucosal histamine levels in duodenal ulcer patients to the same extent as vagotomy (Fig. 16). Perhaps cimetidine inhibits histamine

release from mucosal mast cells. Indeed, such a mechanism is suggested for both gastric secretin and for immunological reactions including histamine release from human basophils.[81] Histamine H_2-receptor antagonists do not only prevent histamine release but also induce histamine release *in vivo*.[78,82] This effect may be pronounced in certain human individuals and may cause serious side effects of the drugs such as cardiac arrhythmias and hypotension.[82]

Hypothesis Relating Gastric Mucosal Histamine, the Vagus Nerve and Duodenal Ulcer Disease

If we accept the model of gastric acid stimulation by acetylcholine, histamine and gastrins[48] as a very tenable hypothesis, the following mechanisms for the development of gastric hyperchlorhydria in duodenal ulcer disease can be considered (Fig. 17):

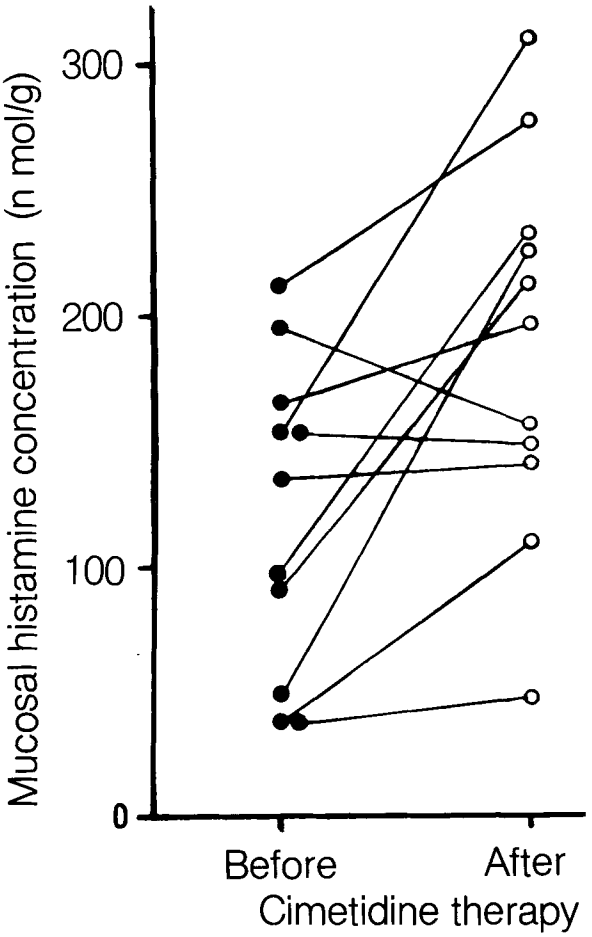

Figure 16. Gastric mucosal histamine contents in patients before and after receiving cimetidine (after Man et al.,[80] with permission). n = 11. ● before treatment, ○ after treatment.

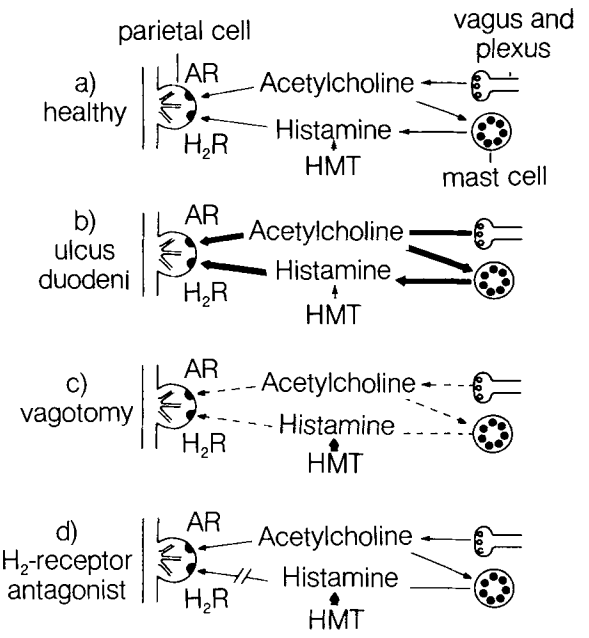

Figure 17. Mechanisms for stimulation of gastric acid secretion in normal subjects, duodenal ulcer patients, after vagotomy and during histamine H_2-receptor antagonist treatment (after Lorenz et al.,[5] with permission).
→ enhanced effect, → normal effect, —> diminished effect.
AR = acetylcholine receptor, H_2R = histamine H_2-receptor.

1. An increase vagal drive, augmented histamine release, and diminished histamine inactivation cause gastric hypersecretion and hyperchlorhydria (Fig. 17b).
2. Vagotomy abolishes the vagal drive, decreases histamine release and enhances histamine inactivation and causes a reduction in basal and pentagastrin stimulated acid secretion (Fig. 17c).
3. Histamine H_2-receptor antagonists such as cimetidine and ranitidine block the effects of the released histamine at the H_2-receptors of the parietal cells and increase histamine inactivation (i.e. stimulation of HMT) to effect a reduction of acid secretion (Fig. 17d).

The role of gastrin in this concept can be either through histamine release or by a direct effect on parietal cells. There is, however, little evidence that the latter are changed by peptic ulcer, vagotomy or administration of histamine H_2-receptor antagonists.

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