HISTAMINE, HISTAMINE H_2-RECEPTOR ANTAGONISTS, GASTRIC ACID SECRETION AND ULCERS: AN OVERVIEW

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ABSTRACT

Histamine, a biogenic amine, is involved in allergic reactions and asthma. The involvement of histamine in peptide ulcers is reviewed here. The discovery, distribution, synthesis, catabolism, and pharmacological effects of histamine are briefly described. Histamine actions are mediated by more than one type of receptor. The discovery, development and mode of action of H_2-antagonists is discussed. A brief comparison of the clinical profiles (dosage regimen, metabolism and drug interactions) of the four currently used H_2-antagonists (cimetidine, ranitidine, nizatidine and famotidine) is given. Furthermore, due to their ability to bind to cytochrome P-450, these compounds have the potential to interfere with the hepatic clearance of other drugs which are also metabolised by the mixed-function oxidase system in man. Therefore, a brief discussion of their adverse effects and drug interactions is included. Modulation of gastric acid secretion, in particular the role of cAMP and the proton pump, is described. Peptic ulcer is a major disease in the Western world and the aetiology and treatment of peptic ulcer are summarised.

KEY WORDS

histamine, histamine H_2-receptors, histamine H_2-receptor antagonists, peptic ulcers, gastric acid secretion

1. INTRODUCTION

Histamine has long been known to be involved in allergic reactions and asthma. This review aims to collate the literature on histamine involvement in peptic ulcers. Some historical background, essential in the appreciation of the physiological importance of histamine, is included. The discovery of histamine H_2-receptors and the understanding of their role in peptic ulcers have paved the way to the development of effective anti-ulcer drugs.

2. HISTAMINE

2.1 Discovery of histamine

Windhaus & Vogt /1/ in 1907 were the first to report the synthesis of histamine (4(5)-imidazolylethylamine) (Fig. 1). In 1910, Ackerman /2/ showed that histamine was produced from histidine by bacterial decarboxylation.

Histamine is a biogenic amine belonging to the group of substances known as *autacoids*. The term autacoids (Greek, self healing substances) encompasses the following groups: (a) biogenic amines [histamine and serotonin (5-hydroxytryptamine, 5-HT)]; (b) peptides and purines, and (c) lipid derivatives. Biogenic amines are organic

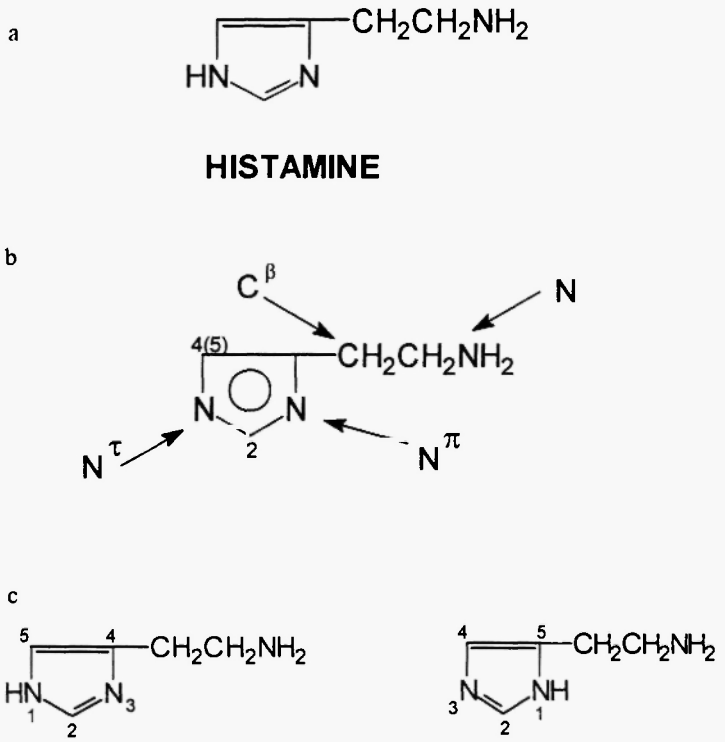


Fig. 1: (a) The structure of histamine; (b) Histamine numbering /5/; (c) Tautomers of histamine.

bases of low molecular weight, arising as products of metabolic processes in animals, plants and microorganisms. They comprise aliphatic, alicyclic and simple heterocyclic compounds.

2.2 Occurrence and distribution of histamine

Histamine is a ubiquitous substance, occurring widely in both the animal and vegetable kingdoms. Its main mammalian sites are mast cells, gastric mucosa (particularly in the acid-secreting parietal cells), basophylic leucocytes, central nervous system (CNS), and in humans also the bone marrow. The tissue stores of histamine in the liver, lung, skin and many other tissues are in the mast cells.

2.3. Synthesis of histamine

Histamine is synthesised from the amino acid histidine via a decarboxylation reaction (Fig. 2), mediated by two enzymes requiring pyridoxal-5-phosphate (the coenzyme form of vitamin B_6) as a cofactor. The enzymes catalysing the formation of histamine from histidine are the highly specific L-histidine decarboxylase and the less specific and less active aromatic amino acid decarboxylase (dopa decarboxylase). Using ^{14}C-L-histidine, it was found that in humans about 5 mg of histamine is formed daily /3/.

2.4 Catabolism of histamine

The main pathways of catabolism of histamine are shown in Fig. 2. Studies carried out using ^{14}C-histamine showed that catabolism exhibits marked quantitative inter-species variation: in man the major metabolite is 1-methylimidazole-4-acetic acid (N^{τ}-methylimidazolyl-acetic acid) (60% of administered label), followed by imidazole-4-acetic acid (25%) and N-methylhistamine (8%), with histamine being only 1% of the administered dose. In the rat, on the other hand, the major metabolite is imidazole-4-acetic acid (51%) followed by histamine (12%), 1,methylimidazole-4-acetic acid (6%), N-methylhistamine (4%) and N-acetylhistamine (3%).

2.5 Tautomerism of histamine

Histamine exists in two tautomeric forms as shown in Figure 3. At the physiological pH of plasma (pH 7.4), the amino group of the ethyl-

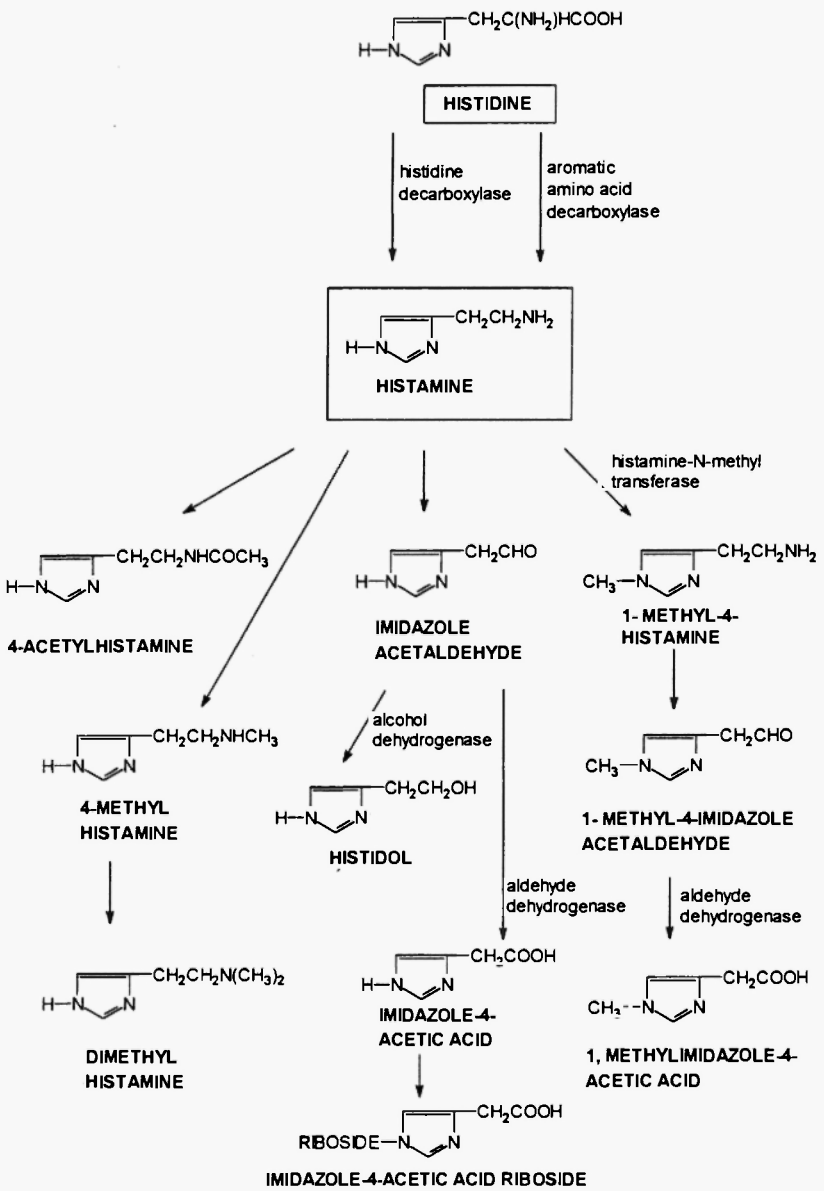
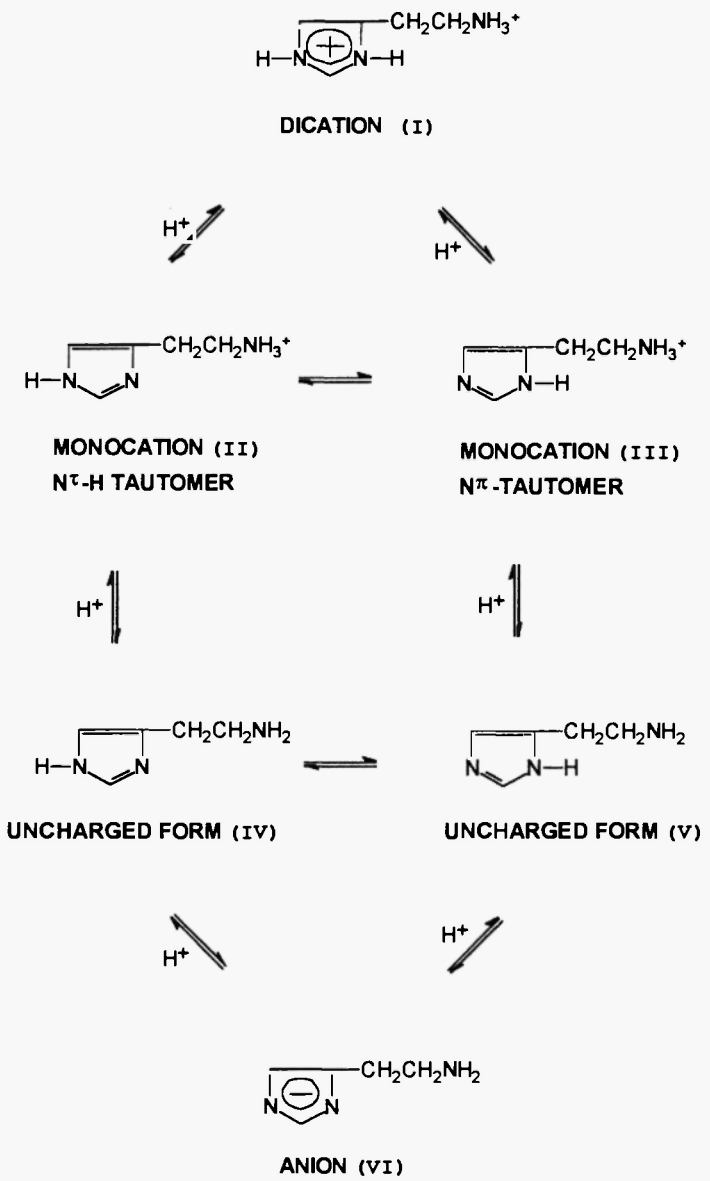


Fig. 2: Major routes of synthesis and metabolic disposition of histamine.



From Burger's Medicinal Chemistry [5]

Fig. 3: Histamine ionisation and tautomerisation.

amine side chain of histamine (pKa 9.8) is protonated, and hence in the body histamine exists as the ionised species.

2.6 Release of histamine

Histamine is released from mast cells and basophils by two general processes of degranulation: non-cytolytic and cytolytic (for review, see /26/). Cytolytic release is an energy-independent, Ca^{2+}-independent process, which occurs when the plasma membrane is damaged, involving leakage of cytoplasmic contents.

Cytolytic release can be induced by phenothiazines, H_1-receptor antagonists, and some of the narcotic analgesics. Non-cytolytic release is thought to involve specific binding of a ligand to a receptor in the plasma membrane of the mast cell or basophil.

Non-cytolytic release is an ATP- and Ca^{2+}-dependent process, characterised by exocytosis of the secretory granules, eventually culminating in cell degranulation. In addition to histamine release, this causes the release of chemotactic factors, neutral protease, prostaglandin D_2, leukotriene C_4 and D_4 (SRS-A, slow-reacting substance of anaphylaxis), leukotriene B_4, platelet activating factor, and other enzymes. Non-cytolytic release can be caused by several drugs, including heroin, morphine, codeine, d-tubocurarine, doxorubicin, and guanethidine.

2.7 Pharmacological effects of histamine

The response to injected histamine exhibits marked species differences; for example, whereas man and guinea-pig are very sensitive to injected histamine, the rat is relatively resistant /4/. The major actions of histamine in man are summarised in Table 1. The effects of histamine are mediated by histamine receptors (Section 3).

3. THE DISCOVERY OF HISTAMINE H_2-RECEPTORS

3.1 Introduction

There are three types of histamine receptors found so far, designated H_1-, H_2- and H_3-receptors. This classification is based on the actions of selective agonists of histamine on tissues known to contain these receptors.

TABLE 1

Major actions of histamine in humans

ORGAN / SYSTEM	ACTION	EFFECT	RECEPTOR
CARDIOVASCULAR SYSTEM	• *Dilation of arterioles, capillaries, and small veins*	Hypotension, flushing, tissue oedema, and tachycardia	H_1 H_2
	• *Triple response of Sir Thomas Lewis*	Erythema, flare and wheal	H_1 H_2
	• *Heart: direct*	Increased rate, force of contraction, cardiac output	H_2
	• *Histamine "shock"*	Loss of blood volume, fall in venous return and cardiac output	H_1 H_2
		Decreased A-V conduction	H_2
	• *Heart: indirect*	Tachycardia	-
SMOOTH MUSCLE	• *Contraction of smooth muscle in gut and bronchi*	Cramps, diarrhoea, bronchospasm	H_1
EXOCRINE GLANDS	• *Stomach*	Secretion of acid, pepsin, intrinsic factor	H_2
PERIPHERAL NERVOUS SYSTEM	• *Direct stimulation of nerve endings*	Itch and pain	H_1
	• *Axon reflex*	Flare of triple response	H_1 H_2
	• *Adrenal medulla*	Adrenaline/noradrenaline release	H_1
HAEMATOPOETIC SYSTEM	• *Neutrophils*	Reduced release of lysosomes on phagocytosis	H_2
	• *T-lymphocytes*	Reduced release of lymphokines	H_2
	• *B-lymphocytes*	Reduced release of antibody	H_2
	• *Mast cells*	Increase in cAMP and histamine concentrations	H_2

From /43/

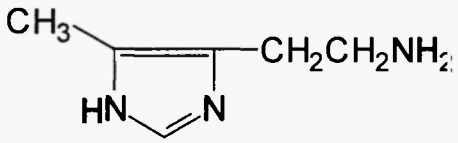
Even though most of the actions of histamine had been identified since the early part of this century and drugs to counteract some of these effects had been developed, it was not until 1966 that the possibility of there being more than one type of histamine receptor was

realised /6/. The first type of histamine receptor was called H_1. The second type of histamine receptor (designated H_2-receptor) was described in 1972 by Black and coworkers /7/. H_3-Receptors were first reported in 1983 by Arrang and associates /8/ who suggested their presence in the brain. Subsequently, in 1987, Ishikawa and Sperelakis /9/ provided evidence for their existence in the autonomic nervous system of the guinea-pig.

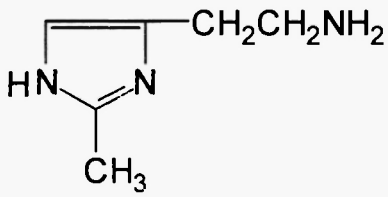
3.2 Identification of the H_2-receptors

Typical antihistaminics, such as mepyramine and related drugs, were found to inhibit some of the actions of histamine (such as the contraction of smooth muscle from various organs, e.g. gut and bronchi, /6/) but not others (such as (a) the secretion of acid by the stomach, (b) the increase in heart rate /10/, and (c) the inhibition of contractions in the rat uterus /11/). Black *et al.* in 1972 /7/, at the laboratories of Smith, Kline and French Ltd. in Hertfordshire, therefore set out find a histamine antagonist to inhibit histamine-induced gastric acid secretion.

Black *et al.* /7/, using histamine as the chemical starting point, attempted, by modifying its structure, to design and synthesise an antagonist. In order to assay agonist and antagonist activities of these new compounds, they used the quantitative histamine responses in five tissue systems. Two H_1-receptor systems were used: (1) the contractions of an isolated piece of guinea-pig terminal ileum, and (2) the contractions of the body of the stomach of an anaesthetised rat. Three non-H_1-receptor systems were also employed: (1) gastric acid secretion measured by the pH of the lumen-perfusate of an anaesthetised rat; (2) the contraction frequency of an isolated piece of guinea-pig right atrium, and (3) the contractions (electrically evoked at one minute intervals) of an isolated piece of rat uterine horn. It was found that 4(5)-methylhistamine (Fig. 4), like histamine, increased the contraction frequency of the guinea-pig right atrium (a non-H_1-receptor system) but had only 0.2% of the histamine activity on the guinea-pig ileum (an H_1-receptor system). 2-Methylhistamine (Fig. 4), on the other hand, had a significantly greater effect on the ileum than on the atium /7/. This finding indicated the existence of two distinct types of histamine receptor.



4(5)-METHYLHISTAMINE



2-METHYLHISTAMINE

Fig. 4: The structure of 4(5)-methylhistamine and 2-methylhistamine.

4. THE DEVELOPMENT OF H_2-RECEPTOR ANTAGONISTS

4.1 Introduction

There are several reviews on the development of H_2-antagonists (e.g. /5,12,13/). Therefore, the subject is described here only very briefly.

The compounds synthesised by Black *et al.* /7/ were also tested for their ability to inhibit histamine-stimulated gastric acid secretion in anaesthetised rats (a non-H_1-receptor system). Their assumption was that if H_2-receptors were present, it would be reasonable to expect inhibition. This work was based on the hypothesis that if a compound was to act as a histamine antagonist, it would have to be recognised by the receptor, then bind more strongly than histamine, but not trigger off the usual response.

Compounds found to be active were also tested on isolated tissue systems in order to ensure that it was the H_2-antagonistic activity of these compounds that reduced gastric secretion rather than the activity of other types of inhibitors of gastric secretion.

4.2 The search for an antagonist: the first steps

Histamine was used as the chemical starting point and structural modifications were carried out in order to alter its chemical properties. N^{α}-Guanylhistamine (Fig. 5a), one of the first compounds developed showing weak H_2-antagonist activity, is still a partial agonist /14/. Despite its weak H_2-antagonist activity, this compound provided the stepping stone to the development of H_2-antagonists.

Lengthening the side chain by one carbon resulted in SKF 91486 [3-(imidazol-4-yl)propylguanidine] (Fig. 5b). This compound was found to have increased H_2-antagonist activity but still retained some agonist activity.

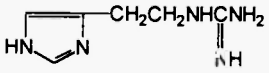
Replacing the guanidinium group of SKF 91486 with a thioureido moiety gave SKF 91581 (Fig. 5c), a thiourea analogue of SKF 91486, with decreased antagonist activity but which was not an agonist.

4.3 The development of burimamide

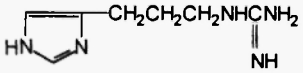
Lengthening the side chain of SKF 91581 by one carbon resulted in burimamide (Fig. 5d), a compound 100 times more potent as a histamine antagonist than N^{α}-guanylhistamine and with no agonist activity. Burimamide was shown to be a highly specific competitive antagonist on non-H_1 tissue systems, thereby defining histamine H_2-receptors and allowing burimamide to be defined as an H_2-receptor antagonist. Burimamide, however, lacked sufficient activity after oral administration and the search continued for a more active antagonist.

4.4 The development of metiamide

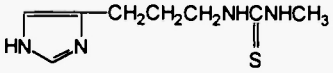
The introduction of a sulphur linkage in the side chain of burimamide and of a methyl group on the imidazole ring resulted in altered imidazole tautomerism and furnished metiamide (Fig. 5e), a compound with increased antagonist activity. Metiamide was the first H_2-antagonist to progress as far as the clinical trials stage. In a small



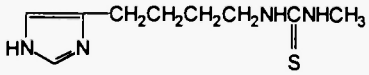
(a) N^{α}-GUANYLHISTAMINE



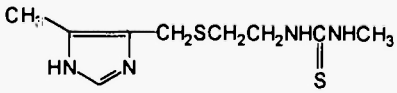
(b) SKF 91486



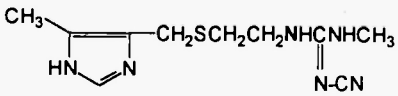
(c) SKF 91581



(d) BURIMAMIDE



METIAMIDE



CIMETIDINE

Fig. 5: (a) N^{α}-Guanylhistamine; (b) 3-(imidazol-4-yl)-propylguanidine (SKF 91486); (c) SKF 91581; (d) burimamide; (e) metiamide; (f) cimetidine.

number of duodenal ulcer patients, however, this compound caused agranulocytopoenia and kidney damage (believed to be linked to the presence of the thioureido moiety) and it was therefore withdrawn.

The guanidine derivative of metiamide, obtained by replacement of the C=S by C=NH giving a basic side chain, had reduced antagonist activity, making it unsuitable for further development.

4.5 The development of cimetidine

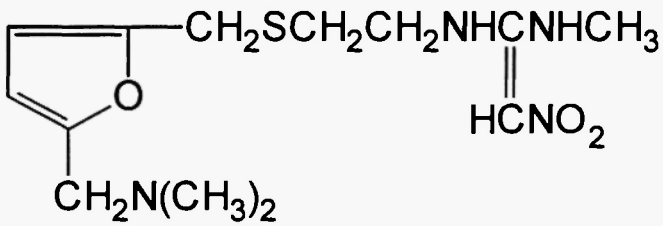
Introducing a cyano substituent on metiamide decreased basicity and increased activity as a competitive inhibitor of gastric acid secretion. The resulting compound, cimetidine (Fig. 5f), represented 10 years of chemical research into the field of H_2-antagonists. The introduction of cimetidine into medicine in 1976, under the trade name Tagamet®, as the first H_2-antagonist for clinical use, revolutionised the treatment of peptic ulcers.

4.6 The development of ranitidine

It later became apparent that the imidazole ring was not an absolute necessity for H_2-antagonist activity as was first thought. In ranitidine (Fig. 6), developed by Glaxo, the cyano group on the side chain of cimetidine was replaced by a nitro group and the imidazole ring by a furan ring. Ranitidine proved to be an even more potent H_2-receptor antagonist than cimetidine and with fewer side effects. It was the second H_2-antagonist to be introduced into the market. It was marketed in 1981 as Zantac® and is currently the best-selling drug world-wide.

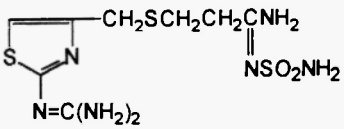
4.7 The development of other H_2-antagonists

Subsequent research has culminated in the evolution of several more, potentially useful, H_2-antagonists. Some of these, such as famotidine (YM 11170, Pepcid®) (Fig. 7a) and nizatidine (Eli Lilly,

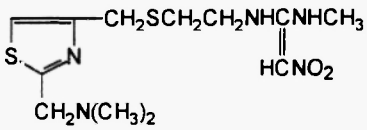


RANITIDINE

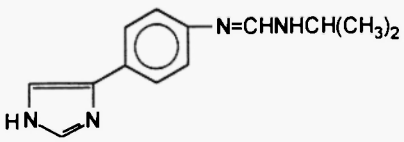
Fig. 6: The structure of ranitidine.



(a) FAMOTIDINE



(b) NIZATIDINE



(c) MIFENTIDINE

Fig. 7: (a) Famotidine; (b) mizatidine; (c) mifentidine.

Axid®) (Fig. 7b) have been introduced for clinical use, while the development of others has been abandoned either due to their unacceptably high level of toxicity [such as tiotidine (ICI 125211), loxtidine (AH 23844), lamtidine (AH 22216), lupitidine (SKF 93479)], or due to their low degree of oral absorption [e.g. oxmetidine (SKF 92994)] /12/.

Several more potentially useful H_2-antagonists are being developed and are currently at various stages of clinical trials. Some of these include mifentidine (DA 4577) (Fig. 7c), IT-066, etindidine (BL 5641), sufotidine, icotidine, zaltidine (CP57,361-1).

Cimetidine, ranitidine and tiotidine are prototype first generation H_2-antagonists, while mifentidine and zaltidine are considered prototypes of second generation H_2-antagonists.

4.8 Properties of H_2-antagonists

H_2-Antagonists are a structurally diverse group of weak bases with varying lipophilicity, but generally good aqueous solubility; they are stable in solution at slightly acid pH; they have a very bitter taste in solution /12/.

H_2-Antagonists must fulfill the following structural requirements: they must have an ionic group attached to a heterocyclic or aromatic ring structure, which is attached via a four or five atom chain, to

groups capable of hydrogen-bonding. All H_2-antagonists in clinical use (Fig. 5f, 6, 7a, 7b) consist of molecules in which a heterocycle is linked via a thioether chain to a non-basic nitrogen which carries substituents that delocalise the nitrogen lone pair of electrons /27/.

5. MODE OF ACTION OF H_2-ANTAGONISTS

5.1 H_2-Antagonists act as competitive antagonists

Pharmacologically, these compounds act as competitive antagonists with reversible effects, the compounds being readily displaced from the receptors. It is thought that the H_2-antagonists form some sort of reversible association complex with the H_2 receptors: the H_2-antagonist ring (e.g. imidazole, furan, etc.) engages the receptor at the site that would otherwise bind the imidazole ring of histamine and the rest of the H_2-antagonist molecule contributes additional binding by interacting with some accessory region. The length of the H_2-antagonist side chain affects the degree of binding to the receptor /5/. Once an agonist (e.g. histamine, pentagastrin) with the required affinity has occupied the receptor, it elicits a response. This is in contrast to an antagonist, such as the H_2-antagonists described, which merely occupy the receptor without eliciting a response. For a more detailed discussion on the mode of action of H_2-antagonists, the reader is referred to /5/.

6. THE CLINICAL PROFILES OF H_2-ANTAGONISTS

6.1 Introduction

Currently there are four clinically useful H_2-receptor antagonists; these are cimetidine (first marketed in 1976), ranitidine (1980), nizatidine (1987) and famotidine (1989).

6.2 Preparations, routes of administration and dosage regimen

All four clinically used H_2-antagonists (cimetidine, ranitidine, nizatidine and famotidine) can be given orally or by injection. The preparations available, routes of administration and dosage are described below. The dose regimens described refer only to treatment of peptic ulcers and not to other associated diseases (such as Zollinger-Ellison

syndrome, oesophagitis, gastritis, duodenitis or Mendelson's syndrome, which are also successfully treated with this class of compounds).

(a) Cimetidine

Cimetidine is available for oral use as tablets containing 200, 300, 400, or 800 mg, as a syrup containing 200 mg/5 ml, and as a suspension containing 100 or 200 mg/5 ml. In addition, cimetidine is also available as intravenous injection (100 mg/ml), and as intravenous infusion (4 mg/ml). Active duodenal or benign gastric ulcers are usually treated with 800 mg cimetidine at bedtime. Other recommended doses are 300 mg four times a day or 400 mg twice daily. Treatment is usually continued for 4 to 8 weeks. A maintenance dose of 400 mg at night, or 400 mg morning and night is also administered for the prevention of recurrence of duodenal ulcers.

(b) Ranitidine

Ranitidine is available as tablets (150 or 300 mg), as a syrup (75 mg/5 ml), and as intravenous or intramuscular infusions (25 mg/ml). The recommended dosage for ranitidine is 150 mg twice a day or 300 mg at bedtime. Intramuscular or intravenous infusions (50 mg every 6 to 8 hours) are also sometimes given. Treatment usually lasts between 4 and 8 weeks. Ranitidine can also be administered prophylactically (150 mg daily). A maintenance dose of 150 mg at night is recommended.

(c) Famotidine

Famotidine is available as tablets containing 20 or 40 mg. For treatment of benign gastric ulceration, famotidine is administered at a dose of 40 mg at night for 4 to 8 weeks, while for maintenance, 20 mg are administered at night.

(d) Nizatidine

Nizatidine is available in capsules (150 or 300 mg). For treatment of benign gastric and duodenal ulceration, it is recommended that 300 mg be taken at night or 150 mg twice daily for 4 to 8 weeks. For maintenance, 150 mg at night for up to a year is the usual recommended dose.

6.3 Absorption and pharmacokinetics

The pK_a values of the clinically used H_2-antagonists are: cimetidine 6.7, ranitidine 8.2, famotidine 7.1 and nizatidine 8.2 /27/. In the stomach, these compounds are ionised (protonated), hence they are effectively not absorbed from this site.

Following oral administration, H_2-antagonists are, on the whole, absorbed well and rapidly (mostly from the intestinal tract). Plasma peak concentrations are achieved within 1 to 4 hours, with peak levels and areas under the curve (AUC) being dose dependent. Nizatidine has an oral bioavailability of about 90%, cimetidine 70%, while the bioavailability of the other compounds is limited to 50-65% for ranitidine, and 40% for famotidine. The half-life of elimination of cimetidine, rantidine and famotidine is 2-3 hours; nizatidine has the shortest half-life (about 1.3 hours) /27,33/.

6.4 Metabolism and excretion

Most of the reports on the metabolism of H_2-antagonists refer to their *in vivo* metabolism, with the information being obtained by analysis of products excreted from the body.

Metabolic biotransformation is not always a prerequisite in the elimination of a drug from the body. For example, due to their hydrophilic nature, metabolic biotransformation of cimetidine, rantidine, famotidine and nizatidine is of minor importance; these compounds are cleared largely by renal excretion. A brief discussion of the metabolic fate of the four clinically relevant H_2-antagonists is presented here. For more detailed discussion, the reader is referred to references /27-32/.

(a) Cimetidine

Metabolism of cimetidine in man occurs via oxidation, hydrolysis and conjugate formation. Cimetidine is excreted mainly in the urine, with over 70% being recovered 24 hours after administration, while 5% is excreted in the faeces. Unchanged cimetidine is the largest urinary component (63%), followed by the polar N'-glucuronide metabolite (24%) /30/. Smaller amounts of cimetidine sulphoxide, 5-hydroxymethylcimetidine, cimetidine guanylurea and cimetidine guanidine are also detected. In faecal samples, both unchanged cimetidine and its sulphoxide are detected.

(b) Ranitidine

After oral administration, there is significant "first-pass" hepatic metabolism of ranitidine /29/. Unchanged ranitidine accounts for 27% of the administered dose, while ranitidine-N-oxide accounts for 3.5%. Desmethylranitidine (1.7%) and ranitidine-S-oxide (1.1%) are also detected /29/. After an intravenous dose, the majority (68%) is excreted unchanged in the urine; metabolites are also mainly excreted in the urine, with about 2% in the bile. The N-oxide accounts for 5-7% of the dose, desmethylranitidine for 2.4% and the S-oxide 1.7%. The furoic acid analogue is also detected /27,29,32/.

(c) Nizatidine

After a single oral dose of ^{14}C-nizatidine, unchanged drug accounted for about 65% of the urinary radioactivity. The main metabolite was the N-oxide, and accounted for about 5% of the dose. The sulphoxide is also a minor metabolite.

(d) Famotidine

Renal excretion of famotidine ranges from 17-30% of the administered dose, with 82-89% of the drug being unchanged. Sulphoxidation plays a minor part in the metabolic elimination of famotidine. Famotidine does not undergo biotransformation of its sulphonamide or thiazole groups.

6.5 Adverse effects

The large number of patients treated with cimetidine and ranitidine is largely reflected by the variety of adverse effects which have been reported. The incidence of reactions, however, is low, and they are mostly minor. The limited function of H_2-receptors in organs other than the stomach, together with the poor penetration of these drugs across the blood-brain barrier, probably explain the low incidence of adverse reactions.

Cimetidine has a 5% incidence of adverse effects. The most common ones are altered laxation, headache, dizziness and nausea, myalgia, skin rashes and itching. Central nervous system-related symptoms appear to be more common in the elderly and in patients with

impaired renal function. Adverse effects reported following long-term therapy in male patients with high doses of cimetidine include loss of libido, impotence and gynaecomastia. These are attributed to the ability of cimetidine to bind to testosterone receptors and thus exert anti-androgenic effects, and to the ability of the drug to enhance secretion of prolactin. The other H_2-antagonists do not bind significantly to testosterone receptors and have not been found to induce gynaecomastia. Reversible bone marrow depression, hepatitis, or anaphylaxis have also been reported following treatment with cimetidine, albeit very rarely. In addition, cimetidine causes a slight increase in creatinine plasma concentration by competitively inhibiting its renal tubular secretion (see /33/ and references therein).

6.6 Drug interactions

H_2-Antagonists drug interactions have been extensively reviewed elsewhere (e.g. /27,28,32,35-36/), hence only a brief discussion is presented here.

Cimetidine binds to cytochrome P-450 (P450) and therefore slows the metabolism of other drugs that are metabolised by this enzyme. Such drugs include warfarin, phenytoin, theophylline, phenobarbital, many benzodiazepines, propranolol, nefedipine, digitoxin, quinidine, mexiletine, and tricyclic anti-depressants such as imipramine /27,33/.

Other H_2-antagonists have also been shown to interact weakly with P450 /27/. Ranitidine at therapeutic doses has not been unequivocally proven to affect hepatic clearance of other drugs. What has been clearly demonstrated, however, is that ranitidine does not produce any clinically relevant drug interactions mediated by inhibition of hepatic metabolism. In addition, ranitidine has no effect on the pharmacokinetics of warfarin and diazepam or on prothrombin time.

Famotidine does not affect the metabolism of antipyrine, aminopyrine, theophylline, diazepam or phenytoin and has no effect on warfarin pharmacokinetics or prothrombin times /27/.

Nizatidine does not bind readily to P450, therefore it does not show any clinically relevant effect on the clearance of drugs metabolised by the mixed-function oxidase system in man /27/.

7. MODULATION OF GASTRIC ACID SECRETION

7.1 Introduction

This section deals with the modulation of gastric acid secretion, while Section 8 describes the role of gastric acid in the initiation, maintenance and relapse of peptic ulcers.

The parietal cells (oxyntic cells) of the stomach secrete isotonic hydrochloric acid (which contains 150 mEq of chloride ions and 150 mEq of hydrogen ions per litre), and intrinsic factor. The formation of this highly acidic secretion requires a lot of energy, and parietal cells have high oxidative metabolic capacity to meet the demand. The gastric mucosa is protected from the irritative and digestive properties of gastric acid by a layer of mucus secreted by the mucous-secreting (goblet) cells. The zymogenic (chief) cells secrete pepsinogen (the enzyme pepsin precursor), and gastric lipase, while the enderoendocrine cells secrete the hormone gastrin.

Gastric secretion is regulated by both nervous and hormonal mechanisms. Nervous mechanisms involve local autonomic reflexes (which involve both muscarinic and nicotinic neurons), and the parasympathetic fibres of the vagus nerves. Hormonal regulation takes place by means of the hormone gastrin. These two mechanisms working together produce a synergistic effect.

Some authors believe that acid secretion is mediated by three separate receptors (acetylcholine, histamine and gastrin receptors) on the parietal cell /15/, while others, especially with the advent of H_2-antagonists, believe that histamine is the final common mediator /16/. A summary of the regulatory mechanisms of gastric acid secretion is depicted in Fig. 8.

7.2 The role of G proteins, adenylate cyclase and cyclic AMP

Histamine is thought to elicit its response by stimulating adenylate cyclase (AC), which catalyses the intracellular conversion of ATP to cyclic AMP (cAMP), hence causing an increase in intracellular cAMP concentration in the gastric mucosa. The hormone- or histamine-receptor complex (H-R-C) has a high affinity for adenylate cyclase, so that a hormone-receptor-adenylate cyclase complex (H-R-AC-C) is formed, which increases the enzyme activity and leads to a rise in the intracellular concentration of cAMP.

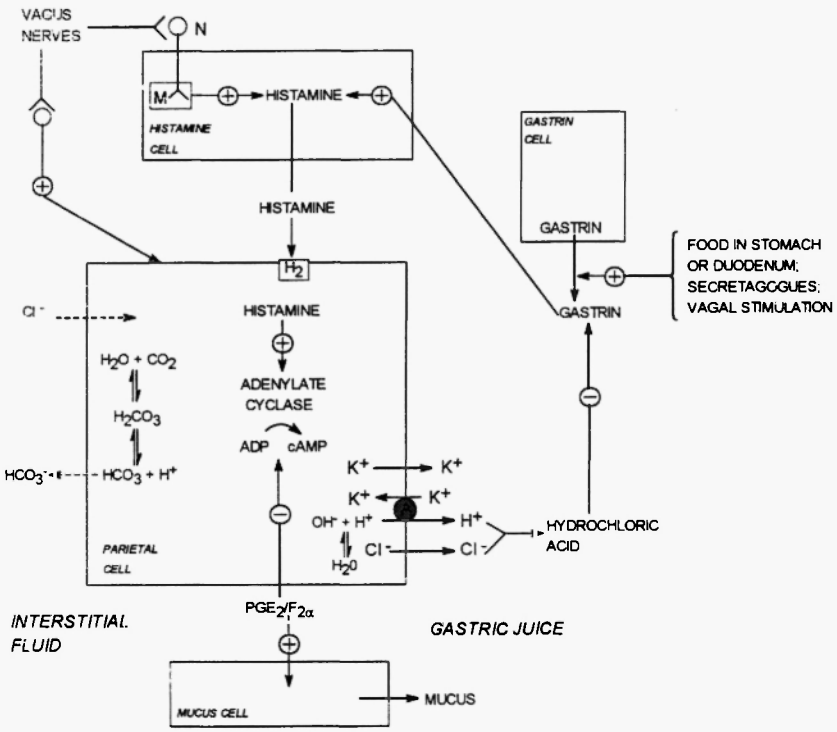


Fig. 8: Mechanism and physiological control of gastric acid secretion. **A** represents the parietal cell H^+,K^+-ATPase.

Adenylate cyclase is a large (185 kDa) integral membrane protein. In order to be activated, this enzyme requires the presence of G protein (or nucleotide-binding component), a 42 kDa peripheral membrane protein. This protein derives its name from its ability to bind guanyl nucleotides (GDP and GTP). G Protein consists of three polypeptide chains (α, β and γ) linked to the cytoplasmic surface of the plasma membrane (hence the name peripheral membrane protein). The GDP or GTP binding site is found on the α chain. When GDP is bound, the α chain binds strongly to the β and γ chains, and is therefore inactive. The G protein is converted from the inactive GDP form into the active GTP form by the exchange of GTP for bound GDP, a process catalysed by the H-R-C but not by the unoccupied receptor, i.e., the activated α chain releases from the β and γ subunits and in turn activates the adenylate cyclase. In other words, the H-R-C activates adenylate

cyclase by facilitating the regeneration of the GDP to the GTP complex. The G protein is a GTPase so that the GTP bound to the G protein is slowly hydrolysed to GDP and the protein is inactivated. Therefore, the flow of information is from receptor to G protein and then to adenylate cyclase, as shown in Figure 9 /34-37/. An "empty" or transient intermediate is formed during the replacement of GDP by GTP in the guanine nucleotide binding site of the GTPase /37/ (not shown in Fig. 9).

Cyclic AMP transmits the histamine (or hormone) signal by activating cAMP-dependent protein kinase. The resulting increase in

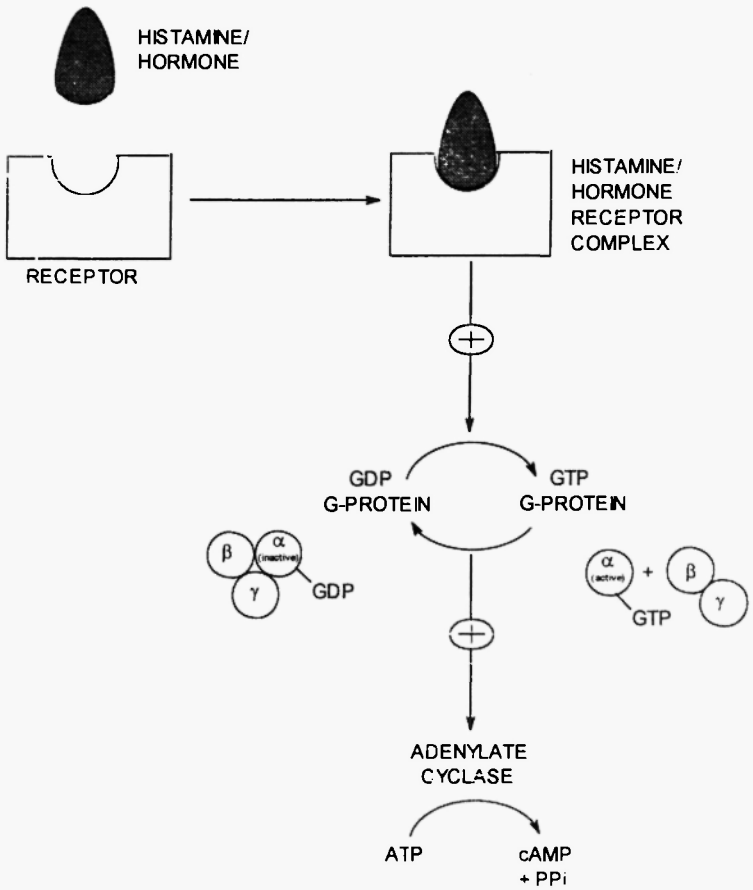


Fig. 9: Flow of information in the activation of adenylate cyclase.

intracellular cAMP increases the extent of binding to the cAMP-dependent protein kinase, which increases the activity of this enzyme. This enzyme consists of two catalytic (C) (38 kDa) and two regulatory (R) (49 kDa) subunits. When the regulatory and catalytic subunits are associated, the enzyme is inactive, whereas when the catalytic subunits are dissociated from the regulatory subunits, the enzyme is active. Binding of cAMP to the regulatory subunits causes dissociation and therefore increases the activity of the enzyme:

$$\underset{\text{inactive enzyme}}{C_2R_2} + 2\ cAMP \Leftrightarrow \underset{\text{active enzyme}}{2R\text{-}cAMP} + 2C$$

C is the active form of the kinase catalysing the phophorylation of a number of intracellular proteins (Fig. 10), such as glycogen kinase, triacylglycerol lipase, pyruvate kinase, glycogen synthase, acetyl CoA carboxylase, initiation factor, and cholesterol esterase. Phosphorylation of membrane proteins plays an important role in the control of transport of both metabolites and ions /17, 38-42/.

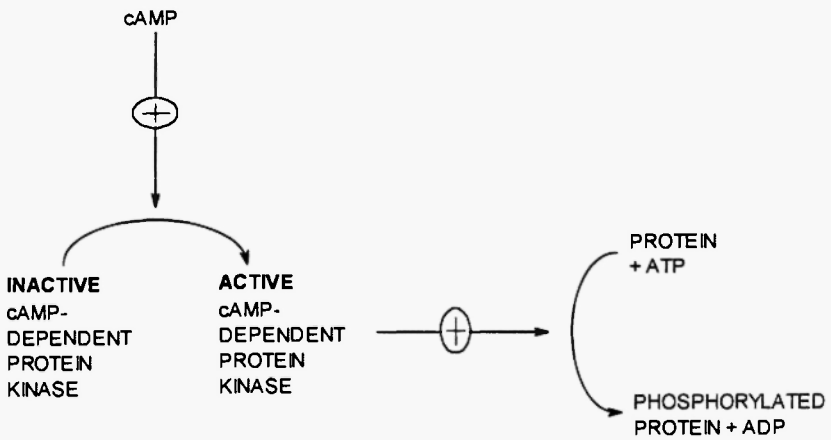


Fig. 10: cAMP-mediated phosphorylation of proteins.

7.3 The role of H^+,K^+-ATPase

(a) Introduction

The H^+,K^+-ATPase is a membrane-bound enzyme found primarily in the parietal cells of the stomach. It is an ionic pump whose function is to maintain the H^+ gradient between the parietal cells and the gastric lumen. The H^+,K^+-ATPase utilises ATP to catalyse the transmembrane exchange of H^+ from cell to lumen and K^+ from lumen to cell (Fig. 11).

The catalytic cycle of the H^+,K^+-ATPase is similar to that of the Na^+,K^+-ATPase and Ca^{2+}-ATPase. These enzymes are known as E_1E_2 ATPases; their molecular weights are about 100 kDa; they have two distinct sequential forms of phosphorylated intermediate. The catalytic cycle of the H^+,K^+-ATPase is thought to proceed as follows:

$$H^+_C + ATP + E_1 \Leftrightarrow H.E_1.ATP \Leftrightarrow H.E_1\text{-}P + ADP \quad [1]$$

$$H.E_1\text{-}P + K^+_L \Leftrightarrow H^+_L + K.E_2\text{-}P \quad [2]$$

$$K.E_2\text{-}P \Leftrightarrow K.E_2.P \Leftrightarrow E_1 + Pi + K^+_C \quad [3]$$

$$\mathbf{H^+_c + ATP + K^+_L \Leftrightarrow H^+_L + ADP + Pi + K^+_c} \quad [4]$$

where E_1 and E_2 represent two different conformational forms of the enzyme; the "dash" forms (e.g. E_1-P) represent covalent association as a phosphoenzyme; the "dot" forms (e.g. $K.E_2.P$) represent ionic associations; the subscripts C and L represent cytoplasmic and luminal locations, respectively, for the transported ions /17,42/.

(b) Morphological changes in the parietal cell associated with secretion

Electron microscope studies have shown that ultrastructural changes take place in gastric mucosal cells when a stimulus is applied. These changes are summarised in Fig. 12.

Briefly, in resting or non-secreting cells, the apical membrane bordering the secretory canaliculi has short, stubby microvilli, and the cytoplasmic space adjacent to the canaliculi is packed with tubulovesicles. When the cells are stimulated, the tubulovesicles almost disappear and the apical microvilli become greatly elongated; thus the surface area of the apical membrane increases up to 10-fold. On withdrawal of the stimulus (or by addition of appropriate inhibitors), the cell reverts to its resting form. These ultrastructural changes form the

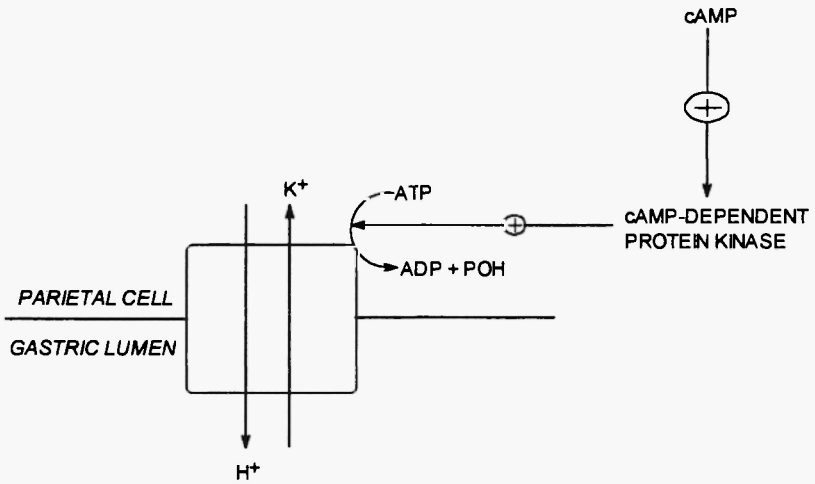


Fig. 11: Highly diagrammatic representation of the transmembrane exchange of H^+ and K^+ the parietal cell H^+,K^+-ATPase.

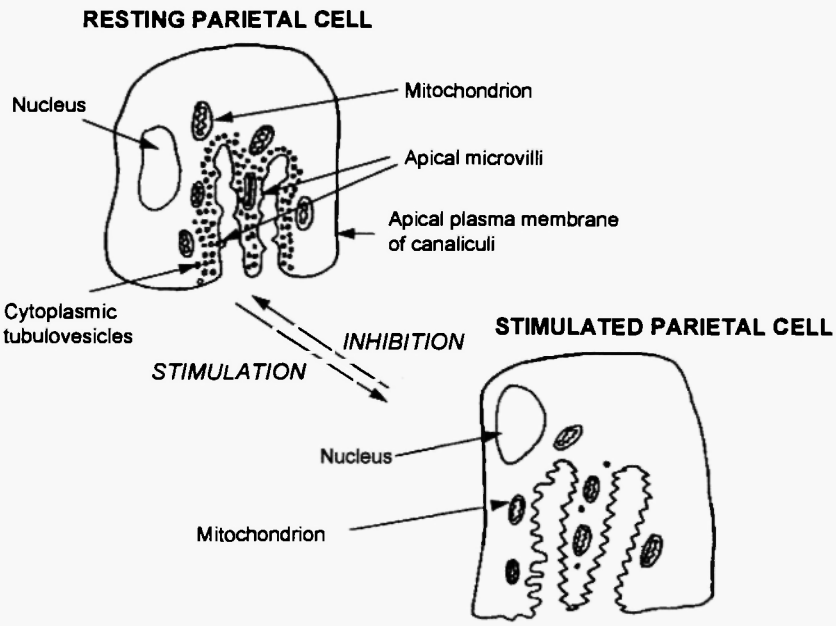


Fig. 12: Schematic representation of parietal cells at rest and after stimulation, as viewed under the electron microscope. The membrane transformations between cytoplasmic tubulovesicles and apical plasma membrane bordering the secretory canaliculi form the basis of the membrane recycling hypothesis of hydrochloric acid secretion.

basis for the membrane recycling hypothesis of hydrochloric acid secretion /17/.

(c) Localisation of the H^+,K^+-ATPase

Differential centrifugation of gastric mucosa has revealed differences in the subcellular distribution of the H^+,K^+-ATPase. In resting gastric mucosa, approximately 80% of the H^+,K^+-ATPase is found in the microsomal fraction derived from the tubulovesicles of the parietal cell. In maximally stimulated stomach, however, the enzyme was found predominantly in larger membrane vesicles derived from the apical canalicular membrane of the stimulated parietal cell, and which are called stimulation-associated (s.a.) vesicles /18/. These vesicles are more permeable to KCl than the microsomes derived from the tubulovesicles /19/. The results of these authors show that in changing from rest to maximally histamine-stimulated hydrochloric acid secretion and reverting to conditions of nil secretion, there is an apparently cyclic distribution of H^+,K^+-ATPase activity.

In purified microsomes from resting cells, the ATP-hydrolysing sites (i.e. the cytoplasmic surface) face outside and the H^+,K^+-ATPase is the dominant protein; a 60-80 kDa glycoprotein is also present.

In H^+,K^+-ATPase-rich membrane vesicles from stimulated cells only about 25-40% of the ATP-hydrolysing sites are exposed to the outside, with the rest of the enzyme being "cryptic" (contained as vesicles within vesicles and/or in vesicles with their cytoplasmic surface facing inside) /20/. As well as H^+,K^+-ATPase, these vesicles contain two other important proteins: actin (40 kDa) and an 80 kDa protein. The significance of these proteins is discussed below.

Proton transport in gastric microsomes from resting cells is considerably slower than in stimulation-associated vesicles. This is due to their different permeabilities to KCl. Whereas microsomes are relatively impermeable to K^+ and Cl^-, stimulation-associated vesicles are readily permeable to these ions, considerably more so than they are to H^+.

(d) Regulation of gastric hydrochloric acid secretion

On the basis of the above observations, Forte and his co-workers have proposed a mechanism by which gastric hydrochloric acid secretion is regulated /17/. In resting cells, the H^+,K^+-ATPase is contained in tubulovesicles. Since the permeability of these vesicles to K^+

and Cl^- is very low, the H^+,K^+-ATPase activity is limited and there is very little accumulation of H^+ in the lumen. When the parietal cell is activated, the tubulovesicles fuse with the apical canalicular membrane thereby transferring the H^+,K^+-ATPase to that surface. The high permeability of the luminal membrane to K^+ and Cl^- causes the flow of KCl from the cell to the lumen. This process provides K^+ for the pump which in turn exchanges H^+ and Cl^- for K^+, thereby resulting in HCl secretion into the lumen and K^+ re-entry into the cell. The catalytic cycle of the H^+,K^+-ATPase was discussed above in Section 5.1. Fig. 13 depicts diagrammatically the parietal cell activation.

7.4 The role of phosphorylation in parietal cell stimulation

As mentioned earlier, phosphorylation of proteins and enzymes plays a major role in their regulation, by either activating or deactivating them. In order to investigate the effect of phosphorylation on parietal cell stimulation, rabbit gastric glands were incubated in the presence of ^{32}P, and protein phosphorylation and ^{32}P turnover were assessed /21/. In stimulated cells, an increase in the incorporation of ^{32}P into the 80 kDa and 120 kDa proteins of the stimulation-associated vesicles, coupled by an increase in H^+,K^+-ATPase, was observed. The 120 kDa protein is thought to migrate from the cytosol to the apical plasma membrane at the time of stimulation which correlates with the increased ^{32}P activity in the s.a. vesicle /22/. The function of the 120 kDa protein, however, is still unknown. On the other hand, the 80 kDa protein appears to be part of the apical plasma membrane and does not recycle into the tubulovesicles when the stimulated cells resume their resting states. The amount of phosphorylation of this 80 kDa protein is, however, dependent on the stimulation.

7.5 The role of actin and the 80 kDa protein

Actin microfilaments support the apical microvilli. They are anchored at the microvillar tip and extend down the length of the microvilli, often up to 1 mm into the cytoplasm. Antibodies against F-actin were used in order to visualise the actin microfilaments. It was found that the staining of F-actin in the form of a fibrillar network similar to that of the 80 kDa protein was consistent with the known distribution of the microfilaments which support the microvilli.

The fact that actin and the 80 kDa protein are major components of the parietal cell apical membrane suggests some interaction between

them. In fact it was recently demonstrated that the protein retains its co-localisation with the actin networks in detergent-resistant cyto-skeletons. It has been suggested that this protein may function to facilitate the incorporation of H^+,K^+-ATPase into the membrane and that this process may be regulated by phosphorylation /17/.

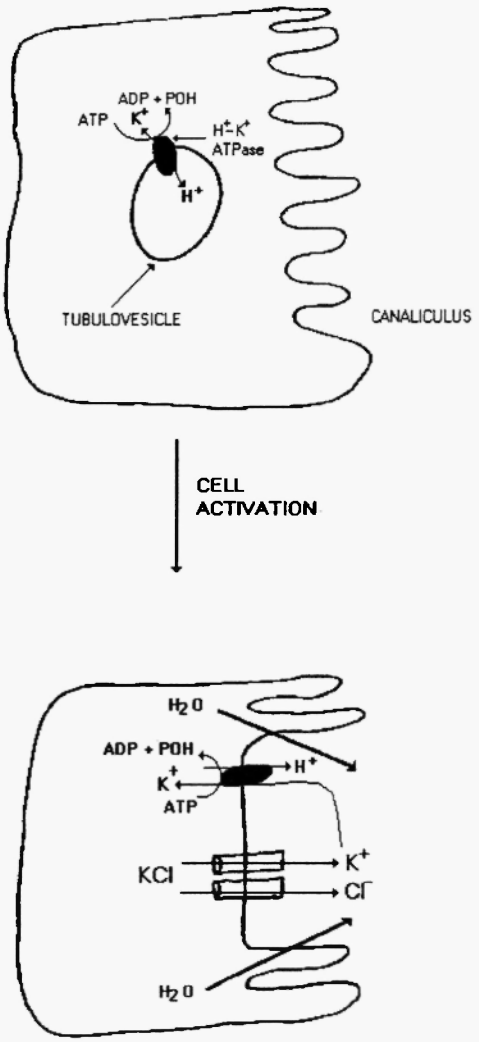


Fig. 13: Schematic representation of parietal cell activation. H_2O flux into the canaliculus is osmotically driven by net solute flux.

8. PEPTIC ULCER

8.1 Introduction

Peptic ulcer is a major disease in many areas of the world. Contrary to previous belief, peptic ulcer is now recognised as two separate diseases with different attributes, prognosis and risks. A peptic ulcer is an acute or chronic ulceration of the digestive tract, occurring in an area accessible to gastric secretion.

It has been postulated that ulcers result from an imbalance between attack factors (which damage the integrity of duodenal or gastric mucous membranes) and defence factors (which preserve the mucosal surface intact). Attack factors, or offensive agents, may include gastric acid, pepsin, bile and other constituents of duodenal contents, drugs (such as aspirin and other non-steroidal anti-inflammatory drugs), alcohol, smoking and microorganisms (such as *Campylobacter pylori*). Defence mechanisms include mucosal blood supply, mucus, bicarbonate, prostanoids, and cellular regeneration and restitution processes. It is not yet clear whether diet plays a role in the pathogenesis of peptic ulcer disease.

Duodenal ulcers are the more common form of the disease and comprise about 80% of all ulcers. They are more common in men than in women, whereas *gastric ulcers* occur to a similar extent in both men and women. Duodenal ulcers are more prevalent in the professional and executive groups (white-collar workers) as opposed to gastric ulcers which occur to a similar extent in all socio-economic groups. Age and genetic factors are also important in ulcer development.

Duodenal ulcers can be treated very successfully with H_2-antagonists, with symptom alleviation usually with 24-48 hours and ulcer healing within 4-6 weeks /27/. Healing rates for gastric ulcer are comparable. Ulcer is a chronic condition, requiring long-term treatment, as many patients relapse even after apparently effective therapy /27/.

8.2 Aetiology of peptic ulcer

(a) Pepsin

Although it has been shown that pepsin may also be important in the pathogenesis of peptic ulcer, it has not been studied in as much detail as gastric acid. Pepsin is thought to bring about its effect by

disrupting the mucus-bicarbonate barrier which normally protects the epithelial surface of the gastrointestinal tract.

(b) Campylobacter pylori

C. pylori is a spiral, flagellated microorganism which is found in the narrow band between the antral epithelial cells and the surface of the mucus layer. Misiewicz /23/ has reviewed the possible role of *C. pylori* in the pathogenesis of duodenal ulcer. Briefly, this micro-organism produces urease and consequently ammonia, raising the pH of its environment, hence enabling the organism to survive. In addition, ammonia is cytotoxic to gastric epithelial cells. The high acid output may give rise to gastric metaplasia to the duodenum, which may become inhabited by *C. pylori*, leading to mucosal injury and sub-sequent ulceration. If the peptic ulcer is solely due to the presence of this microorganism, treatment with H_2-antagonists allows ulcers to heal but does not prevent relapse. Therefore another approach to the treatment of peptic ulcer is to interfere with the microorganism. For example, bismuth compounds cause detachment of *C. pylori* from the gastric epithelium with subsequent lysis of the bacteria.

(c) Prostaglandins

Prostaglandins (PG) are synthesised in response to tissue injury and some (e.g. PGE_2) can readily inhibit gastric acid secretion. It has been proposed that a deficiency of PG may have an aetiological role in peptic ulcer, but it is not yet clear whether exogenous PGs may be useful in the treatment of gastric ulcers or duodenal ulcers.

(d) Environmental factors

It has been shown that smoking increases relapse of ulcers and that NSAIDs are associated with perforation and haemorrhage of ulcers. The role of ethanol, however, is still doubtful. Stress may also play a role in the development or recurrence of peptic ulcers.

(e) Secretion of acid

Although many patients with duodenal ulcers are hypersecretors of gastric acid, many are not, while gastric ulcer patients tend to have normal or even low acid outputs. Gastric acid seems to play a key role

in the initiation and maintenance of chronicity and relapse of peptic ulcer. Circumstantial evidence for this is provided by the success of H_2-antagonists in accelerating the healing of peptic ulcers and the significantly lower relapse rate during maintenance therapy /23-25/.

8.3 Treatment of peptic ulcers

General measures for the treatment of peptic ulcers include stopping smoking, and taking antacids. Other measures include:

(a) H_2-Antagonists, such as cimetidine and ranitidine, which bind to the H_2-receptor and block gastric acid secretion;
(b) Antacids, such as calcium carbonate, magnesium hydroxide, aluminium hydroxide, which are weak bases and neutralise the acid in the gastric lumen;
(c) Selective antimuscarinics, such as pirenzepine, which specifically inhibits gastric acid and pepsin secretion;
(d) Prostaglandin analogues, such as misoprostol, which are also used clinically to inhibit gastric acid secretion;
(e) Chelates, such as tripotassium dicitratobismuthate, a bismuth chelate, which eradicate *C. pylori*, thereby promoting healing of gastric and duodenal ulcers;
(f) Complexes such as sucralfate, which act by protecting the mucosa from acid-pepsin attack;
(g) Proton pump inhibitors, such as omeprazole, which are thought to inhibit gastric acid secretion by blocking the H^+,K^+-ATPase (proton pump) in the gastric parietal cell;
(h) Other ulcer healing drugs, such as carbenoxolone, which act by protecting the mucosal barrier from acid-pepsin attack, and increasing mucosal mucin production.

Antacids are the most commonly used self-medication taken by peptic ulcer patients. Often, however, the doses taken are too low to produce an optimal effect. A further disadvantage associated with the use of antacids is the frequent dosing required and the side effects they produce.

H_2-Receptor antagonists provide a very specific therapy for peptic ulcers, as the only peripheral role of H_2-receptors in humans appears to be the regulation of gastric acid secretion. H_2-Receptor antagonists are used in the Zollinger-Ellison syndrome, reflux oesophagitis, stress ulcers, short bowel syndrome and some hypersecretory states /33/.

They are also used in the routine prophylaxis during and after major operations. Although H_2-receptor antagonists do not block cholinergic receptors or gastrin receptors, they also inhibit gastric acid secretion brought about by gastrin, cholinergic agents, food, and reflux vagal stimulation /33/. In fact, it has been shown that H_2-receptor antagonists are a safer form of peptic ulcer treatment than antacids /26/.

Even though sucralfate promotes peptic ulcer healing with a minimum of side effects, its efficacy is lower than that of H_2-receptor antagonists.

Prostaglandin analogues, such as misoprostol, although used clinically, are not as effective as H_2-receptor antagonists /26,33/.

Antimuscarinics decrease basal gastric acid secretion by 40 to 50%. M_1-Receptor antagonists, such as pirenzepine and telenzepine, inhibit the secretion of gastrin, mucus and HCO_3^-, and are as effective as H_2-receptor antagonists in healing gastric and duodenal ulcers.

Bismuth compounds have been a well known self-medication for gastrointestinal upsets for many years. Their action is thought to be brought about via their inhibition of pepsin activity, induction of mucus and secretion, interaction with proteins in the ulcer crater, and by causing detachment and lysis of *C. pylori* from gastric epithelium.

In patients with hypergastrinaemia (as in the Zollinger-Ellisson syndrome) or in those whose peptic ulcer cannot be controlled by H_2-receptor antagonists or other forms of treatment, proton pump inhibitors, such as omeprazole, are especially useful. However, concerns over their safety exist, as they have been shown on some occasions to induce gastric carcinomas, due to the complete inhibition of gastric acid production.

9. CONCLUSIONS

The discovery, distribution, synthesis, catabolism, conformations and pharmacological effects of histamine were briefly described. The discovery, development, and mode of action of H_2-antagonists were discussed. A brief discussion of their clinical profiles, including adverse effects and their interactions with other drugs in the body, was given. Modulation of gastric acid secretion, and in particular, the role of cAMP and the proton pump were described. Finally, the aetiology and treatment of peptic ulcer were discussed.

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