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The Fate of Released Histamine: Reception, Response and Termination

P.K. Rangachari

Department of Medicine, McMaster University, Hamilton, Ontario, Canada

Histamine released from ECL cells elicits responses from a variety of cellular targets in the vicinity. Three sets of receptors are involved (H_1, H_2 and H_3). Receptor occupation is promptly transduced into cellular responses. The responses, in turn, are terminated by diverse mechanisms: enzymatic inactivation, cellular uptake and desensitization at the receptor level. Under specific pathological conditions, histamine effects could be exaggerated by the presence of derivatives that may be of marginal relevance under physiological conditions.

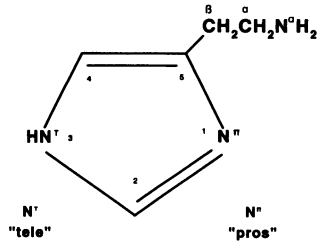
INTRODUCTION

The enterochromaffin-like cell (ECL cell) plays a crucial role in the regulation of gastric acid secretion [1], using as its preferred messenger, histamine. Molecules that function as messengers in a biological system must be produced and received by target cells that respond in specific ways to their presence. The actions of the messenger must be terminated to permit the target cell to respond to the next message [2]. Histamine is no exception. This presentation will highlight some of the above elements. Since other presentations in this session deal with the production of histamine, I will focus largely on the consequences of histamine release. Thus, I will discuss the reception and responses of target cells in the stomach and the mechanisms by which the message is terminated. In the interests of space, I have chosen to cite recent reviews more often than the original articles.

In the ECL cell, histamine ([2-(4-imidazolyl)ethylamine]) is produced by the decarboxylation of histidine by histidine decarboxylase (see Figure 1). The regulation of the enzyme in the ECL cell has been a subject of much study [1, 3] and will be the subject of other presentations in this symposium. The histamine that is synthesized is packaged into granules and released in response to diverse stimuli. Of these, gastrin acting on a gastrin/CCK-B receptor plays the major role. Other agonists that increase histamine secretion include acetylcholine, prostaglandins, isoproterenol and VIP, and the inflammatory cytokine, interleukin 1. Inhibition of secretion involves somatostatin, CGRP and histamine itself [1].

Once released, histamine functions as a messenger eliciting responses from a variety of target cells in the neighborhood of the ECL cell (see Figure 2). These cells are abundant in the basal third of the mucosa which is rich in chief cells rather than parietal cells. The histamine released must reach the major target cell, the parietal cell, by diffusion or capillary transport [4]. Other targets include surface epithelial cells, chief cells, smooth muscle cells, immunocompetent cells, vascular and neural elements and the ECL cell itself which also responds to the released histamine.

[a]*To whom all correspondence should be addressed:* Dr. P.K. Rangachari, McMaster University, HSC-3N5C, 1200 Main St. West, Hamilton, ON, L8N 3Z5 Canada. Tel.: (905) 525-9140, Ext., 22589; Fax: (905) 522-3454; E-mail: chari@mcmaster.ca.



Histamine

Figure 1. Shows the structure of Histamine and the nomenclature suggested by Black and Ganellin [39]. There are three nitrogens. Of these, the side-chain N is termed alpha to distinguish it from the two ring N which are termed pros (π) for the one closer to and tele (τ) for the one further from the side-chain.

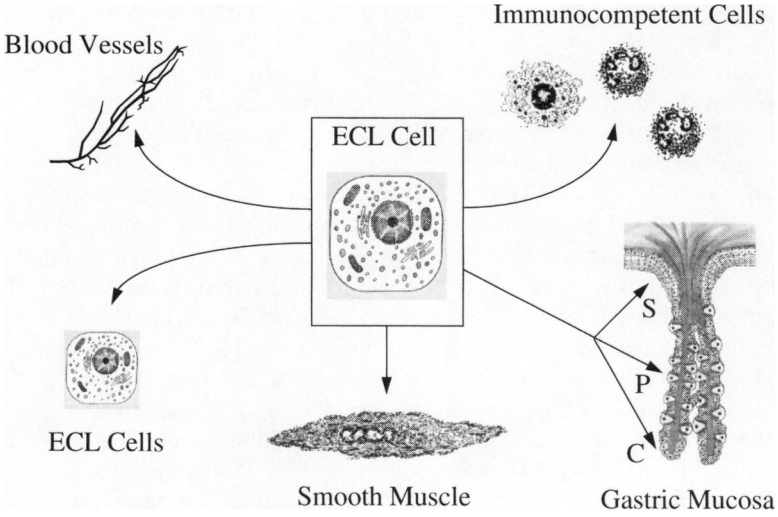


Figure 2. Shows the potential targets for histamine released from the ECL cell. On the gastric mucosa, potential cells include surface epithelial (S), parietal (P) and chief (C) cells.

RECEPTION

In any communication system, it is essential to have a system that receives and responds to the message. In biological systems, the receiving elements are broadly categorized as extracellular or intracellular receptors. With respect to histamine, the extracellular receptors have been well studied. Although reports exist for the existence of intracellular receptors, these must be viewed with some skepticism at the current moment. The receptors for histamine are expressed on a variety of target cells in proximity to the ECL cell.

Table 1. Histamine receptor sub-types.

Features	H_1	H_2	H_3
Selective agonists:	• 2-pyridylethylamine • 2-thiazolylethylamine • 2-(3-trifluoromethyl) phenyl histamine	• Dimaprit • Impromidine • Amthamine	• R(-)αmethyl-histamine • Imetit • Immepip
Selective antagonists:	• Mepyramine • Chlorpheniramine • Triprolidine	• Ranitidine • Tiotidine	• Thioperamide • Clobenpropit • Iodophenpropit
Coupled to:	• Coupled to phosphoinositol metabolism	• Adenylate cyclase activation	• Negative coupling phospholipase activation
Cell types:	• Smooth muscle cells (muscularis mucosae) arterioles • Surface cells • ECL cells	• Parietal cells • Smooth muscle cells (muscularis mucosae) arterioles • Surface cells	• ECL cells

The standard pharmacological approach to the classification of receptors involving the careful use of selective agonists and antagonists [5] has led to the current classification of histamine receptors into three general categories: H_1, H_2 and H_3 [6] . The salient characteristics of each of the three receptor subtypes are summarized in Table 1.

The H_1 receptor responds not only to histamine, its natural agonist but also preferentially to several synthetic analogues (2 pyridylethylamine, 2 thiazolyl ethylamine). The responses to stimulation are markedly inhibited by a large number of synthetic compounds of varying selectivity. The reference compounds in general use are mepyramine (pyrilamine) and chlorpheniramine. The latter compound is particularly useful for experimental purposes as the d(+) form is approximately two orders of magnitude more potent than the l(-) form in some systems. The original H_1 antagonists readily penetrated the blood-brain barrier and produced sedation. In an attempt to mitigate against these, a new series of compounds have been produced that are potent and effective H_1 antagonists [6].

The H_2 receptor responds not only to histamine but to selective agonists, such as dimaprit and impromidine. Dimaprit is a highly selective H_2 agonist that has virtually no agonist effects on H_1 receptors but is a moderately active H_3 antagonist. Impromidine is more potent than histamine as an H_2 agonist and is an antagonist at H_3 and H_1 receptors. For experimental studies the preferred H_2 antagonists are cimetidine, ranitidine and tiotidine. The agonists that act preferentially on the H_3 receptors include R(–)-α-methylhistamine and a more recently described compound, imetit [6, 7]. The antagonists for this receptor include the H_2 agonist, impromidine, as well as thioperamide and more recently clobenpropit derived from the highly active agonist imetit [6]. The possibility that subtypes of the H_3 receptor (labeled H_{3A} and H_{3B}) may be present needs exploration and confirmation [7].

The availability of these pharmacological tools permits exploration of the effects of histamine on a variety of cellular systems. The classical pharmacological approaches have been immensely strengthened by molecular biological approaches which have led to the cloning of the genes for the H_1 and H_2 receptors and the deduction of the amino acid sequences of the receptor proteins.

The genes for the H_1 receptor have been cloned from several species (bovine, rat, guinea-pig, and human). The genes code for proteins that are between 486 to 491 amino acids and show considerable homology. The proteins bear the hall mark of the classical G-protein coupled receptors (7 transmembrane domains, with phosphorylation sites for protein kinase A and protein kinase C as well as N-terminal glycosylation sites). The deduced structures show a very large intracellular loop and a very short C-terminal tail. Although the different receptors show over 90 percent homology in the intracellular domains, there is greater variability in the long intracellular loop or in the N-terminal tails.

The genes that encode for the H_2 receptors have been cloned from several species (dog, human, rat). They too encode for proteins that exhibit the structural features of G-protein coupled receptors. In contrast to the H_1 receptor protein, the H_2 receptor proteins have short third intracellular loops and relatively long C-terminal tails. It is believed that these features are associated with positive coupling to the adenylyl cyclase system.

In contrast to the H_1 and H_2 receptors, the low abundance of H_3 receptors has made characterization difficult. Nevertheless, it has been recently reported that a protein has been purified from the human gastric tumoral cell line HGT-1 that bound labeled N-methylhistamine which was inhibited by thioperamide and (R)-α-methylhistamine, suggesting that this could be linked to H_3 receptors [8]. Molecular biological approaches may ultimately lead to the cloning of the gene for the third histamine receptor as well.

As mentioned above, there are many cellular targets for the histamine that is released from the ECL cell. The expression of specific receptors on these target cells vary. The classic example of an H_2 receptor is that observed on the parietal cell in a variety of species (4). The muscularis mucosal smooth muscle at least in dogs expresses both H_1 and H_2 receptors [9, 10]. Non-parietal cells from the stomach of diverse species appear to have either H_2 receptors alone or both H_1 and H_2 receptors The former situation is seen in rats [11] and guinea-pigs [12] and the latter in rabbits [13]. On the arterioles in the gastric vasculature both H_1 and H_2 receptors have been described [14]. The responses of the chief cell are species dependent and highly variable, at least *in vitro*. The effects are antagonized by cimetidine, suggesting an H_2 receptor [15].

RESPONSE

Reception of a message must be followed by appropriate action otherwise the message is wasted. Cells have evolved exquisite mechanisms to translate information received into meaningful action. A limited repertoire of intracellular signals is used in various combinations to link occupation of external receptors to physiological responses. In the case of G-protein coupled receptors, a class to which both H_1 and H_2 receptors belong, the occupation of the receptors is linked to the activation of a G-protein which in turn leads to the activation of various effectors. Transduction mechanisms involving histamine involve changes in either cyclic nucleotides, principally cAMP or intracellular Ca. cAMP is generated from ATP by the activation of adenylyl cyclase, which is controlled by two GTP-binding proteins, that either stimulate or inhibit the enzyme. Alterations in intracellular calcium could stem from either release of intracellular Ca from internal stores or by an increase in the influx of extracellular Ca. In the former case, a key role is played by inositol phosphates that are mobilized from membrane phospholipids by the activation of phospholipase C.

Current opinion links H_1 receptors to the phospholipase-C dependent hydrolysis of phosphoinositides with consequent changes in intracellular Ca and H_2 receptors predominantly with the activation of adenylyl cyclase and the generation of intracellular cAMP [6]. But as with all generalisations exceptions exist. Alterations in Ca, produced as a result of

an H_1 response could in turn activate a number of other second messengers principally cAMP, cGMP, nitric oxide or arachidonic acid metabolites [6]. Conversely, H_2 effects that are not related to activation of adenylyl cyclase have been described in several systems including the parietal cell, transformed hepatoma-derived HEPA cells and HL-60 promyelocytic leukaemic cells. Recent studies with transfected HEPA cells and CHO cells are particularly interesting as they demonstrate the promises and pitfalls of molecular biological approaches to these problems. It had been shown that the transfection of mouse L cells with a plasmid containing an insert of the coding region of the H_2 receptor from canine parietal cells led to a histamine-stimulated increase in cAMP that was inhibited by cimetidine. This was an elegant demonstration of the linkage between H_2 receptor activation and adenylyl cyclase stimulation [16]. Later studies by the same group complicated the picture. They showed that in HEPA cells transfected with the canine H_2 receptor gene, histamine increased not only cAMP levels but also inositol triphosphates and intracellular Ca. These effects were inhibited by cimetidine but not by diphenhydramine or thioperamide testifying to the selectivity of the effects seen. That forskolin was unable to alter intracellular Ca suggested that it was the histamine response that was coupled to the two separate pathways [17]. On the contrary, in another cell system, CHO cells, expression of human H_2 receptors, did not lead to any alterations in intracellular Ca or inositol phosphates [6]. Expression of cloned rat H_2 receptors in the same cell system led to the demonstration of another cAMP-independent effect of histamine stimulation – the marked inhibition of arachidonic acid release induced by other stimulants [18]. The demonstration of these novel effects may be related to the level of expression of the specific receptors which may alter the balance between receptive and transducing elements. It is thus imperative that the data obtained from such studies be placed in context of what is known from physiological experiments.

The transduction mechanism linking occupation of H_3 receptors to the observed physiological responses have not been clearly defined. Given that the effects are predominantly inhibitory, several possibilities exist ranging from inhibition of adenylyl cyclase activity to inhibition of phopholipase C activation or Ca release. A recent report suggests that in the HGT-1 gastric tumor cell line, a negative coupling exists between the occupation of H_3 receptors and phospholipase C activation [8]. Other reports link the receptor to a reduction in entry of extracellular Ca. If the studies on the other two receptors are any indication, it is likely that H_3 receptors would be linked to one predominant mode of operation with exceptions being noted under particular set of circumstances.

The transduction of the message received is not an end itself. It must be followed by appropriate action. The consequences of the transduction are obviously related to the functional capacity of the target cell. Thus in response to the same agonist, smooth muscle cells either contract or relax whereas the parietal cell produces HCl. The sequence of events linking occupation of H_2 receptors on the parietal cell to the secretion of acid are complex. A current paradigm links alterations in levels of cAMP to the activation of protein kinases which in turn phosphorylate a variety of intracellular proteins. Since the process of acid secretion by the parietal cell is a complex one [19] involving concerted morphological and biochemical transformations, the number of candidate proteins is large ranging in location from cytosolic, microsomal and membrane proteins. More recent studies suggest that H_2 receptor activation led to an increased expression of mRNA for the α subunit of the gastric H/K-ATPase itself [20, 21].

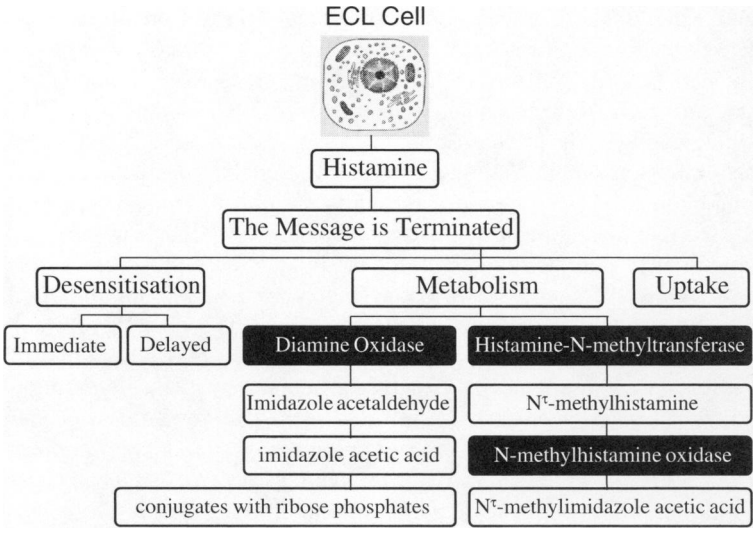


Figure 3. Shows schematically the mechanisms responsible for the inactivation of histamine. Of the two metabolic pathways, methylation is predominant in the stomach.

TERMINATION

The efficient operation of any information system demands the presence of mechanisms that terminate responses to a particular message to ensure that the system is ready to respond to the subsequent one. To forget is as important as it is to remember. It is no surprise that biological systems have evolved interesting mechanisms for that purpose. The messenger molecule may be inactivated enzymatically or be internalized. Alternatively the responding system may get desensitized. These possibilities have been documented for histamine (Figure 3).

Two major enzymatic systems exist to inactivate histamine [22]. Diamine oxidase was the earliest system to be described. It converts histamine initially to imidazole acetaldehyde and subsequently to the corresponding acid which is then conjugated with ribose-phosphate. The second system involves methylation of the imidazole nitrogen and is carried out by histamine methyltransferase. The enzyme is widely distributed and is of particular relevance in the stomach where it is the major inactivating mechanism [23, 24]. It catalyses the transfer of a methyl group from S-adenosyl-L-methionine to histamine producing N-tele-methylhistamine which can be subsequently oxidized to the corresponding acetic acid derivative. In the canine fundic mucosa, the enzyme was primarily associated with parietal cells [25]. Inhibition of the enzyme leads to an enhanced response to both histamine and pentagastrin [22] . In rabbit gastric glands, methylation occurs intracellularly and a histamine uptake process that is dependent on external sodium. In the rabbit gastric mucosa, the methylated histamine is released preferentially into the serosal solution [26]. A more complex process has been demonstrated in fibroblasts and pulmonary endothelial cells where histamine is methylated by transferases and the methylated product converted by exogenous diamine oxidase from diverse sources such as activated neutrophils to N-tele-methylimidazole acetic acid which is transported into the cell by a process that appears to be dependent on external Na and Cl [27]. The characteristics of this process are at variance with the more conventional Na-dependent uptake processes

that have been described, and the relevance to the case of histamine inactivation in the stomach is unclear at present. However in the case of inflammatory states, the presence of neutrophils could provide an impetus for such a mechanism in the metabolic disposition of histamine.

Inactivation of the messenger molecule is not the only means by which biological messages are terminated. A more powerful control can be exercised at the level of the receptive element itself. Such processes can be distinguished on the basis of the time frame in which the events occur (rapid/slow), the generality of the process (receptor-specific or homologous)/general (heterologous) or on the basis of the particular mechanism involved (loss of function/loss of receptors). The term desensitisation should be used to define loss of receptor function by any mechanism and the much-abused term "down-regulation" should be confined to instances where there is a clear demonstration of a reduced number of receptors either due to reduced synthesis and/or enhanced degradation [28, 29].

As mentioned earlier, the histamine receptors belong to the generic class of G-protein coupled receptors. The attenuation of the responses noted in members of that family involve three major mechanisms. Initially the receptors are uncoupled from their respective G-proteins due to phosphorylation by serine/threonine kinases leading to a reduction in responsiveness.The receptors are then internalized and finally degraded to lead to a reduction in receptor numbers. These processes that have been analyzed in great detail with the prototypical β-adrenergic receptor have also been demonstrated with histamine receptors.

Short term desensitisation has been demonstrated with both H_1 and H_2 receptors in several different cells [30-33]. Homologous H_1 receptor desensitisation has been demonstrated in intestinal smooth muscles from different regions [34]. In those preparations, the desensitisation appeared to involve a modification of the H1 receptor. In HeLa cells histamine acting on H_1 receptors produced a biphasic response [30], an initial rapid increase in intracellular Ca due to release from intracellular stores and a later sustained increase due to influx of extracellular Ca. Desensitisation seen with the first phase was independent of the protein kinase C pathway whereas that observed with the second phase was dependent on the activation of the protein kinase C pathway. Rapid desensitisation has also been shown with H_2 receptor stimulation in several cell types including HGT-1 tumor cells and U937 monocytic cells [32, 33]. These effects were accompanied by an attenuation in the production of cAMP. In HEK 293 cells, Smit et al. [35] noted a rapid internalization of the histamine receptor which was blocked by an endocytosis inhibitor phenylarsine. Since forskolin did not induce internalization, the process occurred by a cAMP-independent pathway. More prolonged exposures to histamine lead to a "down-regulation" of histamine receptors in CHO cells as demonstrated with binding of labeled iodoaminoptentidine [36]. There appeared to be two distinct pathways that were either dependent or independent of cAMP.

VARIATIONS UNDER PATHOLOGICAL CONDITIONS

Much of the information discussed above has been obtained from experimental animals or from normal human tissues. It is possible that the disposition of histamine under pathological conditions could be significantly different. Two such conditions would be discussed below. It has been noted above that the primary inactivating system in the stomach is histamine methyl transferase that produces N-tele-methyl histamine by methylation of the ring nitrogen. The product is essentially inactive. Although the presence of side-chain methylated compounds in human urine had been documented as early as 1957, and Code et al. [37] had shown that these N-methyl derivatives were potent secretagogues, their relevance to human physiology has remained obscure. A more recent report [38] suggests that in the antral region of stomachs of patients infected with *Helicobacter pylori*, there was an enhanced activity of N-histamine methyltransferase and the presence of N-methylhista-

mine which is now known to be an potent agonist of H_3 receptors. Significant amounts of the side-chain methylated compound and a high level of N-histamine methyltransferase activity was seen in three cultured strains of the organism. This raises the possibility that the metabolism of histamine could be altered in infected patients and the activity of the secretagogue may be altered. The authors suggest that infection could alter the regulation of acid secretion in opposite directions. Autoinhibition by stimulation of H_3 receptors could reduce histamine formation, but the inhibitory effect on antral somatostatin could lead to hypergastrinemia which may enhance acid secretion. These arguments are however speculative at present. Another situation in which altered histamines could become important is in inflammatory states where neutrophils abound. Hypochlorous acid generated by the activity of myeloperoxidase present in neutrophils could lead to the formation of chloramine derivatives that could contribute to the pathophysiological effects observed [39, 40]. Thus these altered products can maintain and exaggerate the effects of the native molecule.

SUMMARY

Histamine released from enterochromaffin-like cells can affect diverse cellular targets in the vicinity of that cell by occupying different sets of receptors. The responses elicited can be terminated by diverse mechanisms. Under specific pathological states, the effects of histamine can be exaggerated by the production of novel derivatives which may not be significant under normal conditions.

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