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Macrocyclic Polyamines as a Possible Chemical Model for Histamine H_2-Receptors

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An 18-membered macrocyclic hexaamine, [18]aneN$_6$, interacts with histamine and its H_2-agonist dimaprit at physiological pH to yield stable 1 : 1 complexes with simultaneous liberation of H^+, which mimics the histamine H_2-receptor–agonist interaction and the resulting gastric acid secretion. The polyamine H_2-receptor model does not interact with the histamine H_1-agonist 2-pyridylethylamine. Our model does interact with the H_2-antagonists cimetidine, metiamide, famotidine and ranitidine to form more stable 1 : 1 complexes than with the H_2-agonists, which offers a possible chemical model for the pharmacological ability of the H_2-antagonists to competitively block H_2-receptors and inhibit the gastric acid secretion induced by histamine. The known structural features distinguishing between histamine H_1- and H_2-agonist, and between histamine H_2-agonist and -antagonist are reevaluated in terms of our model.

Keywords——macrocyclic polyamine; histamine H_2-receptor; cimetidine; gastric acid secretion; receptor model

The physiologic actions of histamine are mediated by at least two distinct receptor types.[1,2] The ability to contract guinea-pig ileum and gallbladder is mediated by histamine's actions at H_1-receptors.[3] These actions are selectively induced by H_1-agonists,[1] and are competitively inhibited by the classical antihistamines such as mephyramine and diphenhydramine (H_1-antagonists).[3] On the other hand, other histamine responses such as increased gastric acid secretion and relaxation of guinea-pig gallbladder are selectively stimulated by H_2-agonists and are competitively antagonized by H_2-antagonists.[4-6] Recently the H_2-antagonists were shown to be highly effective clinically in reducing hypersecretion of gastric acid and proved to be of therapeutic value in duodenal ulcer disease.[7]

The pharmacological evidence suggests that H_2-antagonists inhibit gastric acid secretion through blockage of histamine H_2-receptors in the gastric mucosa.[7] Structurally, H_2-antagonists are closely related with histamine, as typically illustrated by cimetidine[8] (for structures and H_1, H_2 classification of the compounds mentioned in the text, see Chart 1). The H_2-receptors, like the H_1- and all other drug receptors, are defined operationally, and have not been characterized by physico-chemical methods; the entities corresponding to these receptors remain totally unknown. Thus, it is not surprising that intrinsic problems of H_2-receptors binding with H_2-agonists and -antagonists have never been seriously considered chemically, although studies from the standpoint of structure–activity relationship have been carried out from a practical viewpoint, *i.e.*, the development of new, more efficient H_2-antagonist drugs. The basic (molecular) understanding of receptor recognition is no closer, however, since the increasing diversity in chemical structure of recently available H_2-antagonists or their lessening structural resemblance to the original histamine is creating confusion as to the structural requirements for the antagonists.

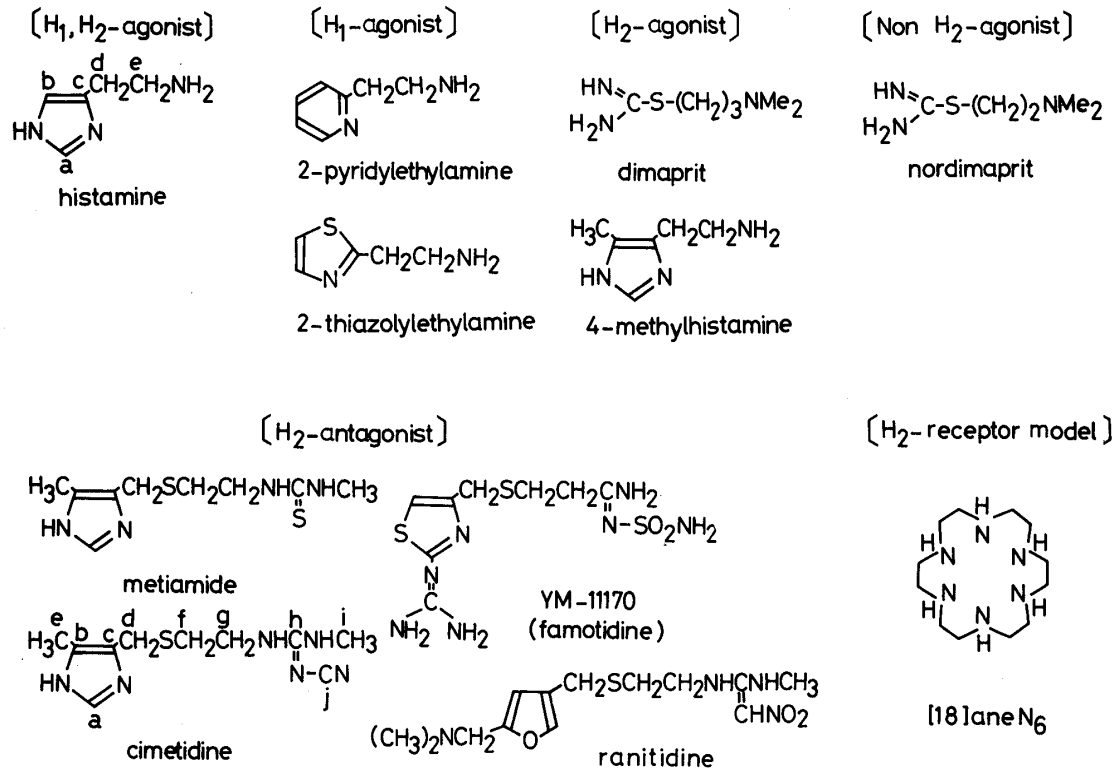


Chart 1

Herein we present a simple chemical model of the H_2-receptors that form reversible association complexes with H_2-agonists and H_2-antagonists. Our receptor model, moreover, can distinguish H_2-agonists from H_2-antagonists in the same manner as biological H_2-receptors: the interaction with the former causes an acid-releasing response, while the interaction with the latter triggers no response. Thus, our chemical model can offer a new interpretation of the known structural features distinguishing histamine H_2-agonists from H_2-antagonists.

In seeking a suitable receptor model for the actions of histamine, we have looked for organic compounds that can interact with histamine. Earlier, we found that certain macrocyclic polyamines such as [18]aneN$_6$ or [16]aneN$_5$ incorporate three protons into their macrocyclic cavities at neutral pH and the resulting triprotonated species H_3L^{3+} form stable ion-pair complexes with bidentate polyoxyanions such as polycarboxylate,[9] phosphates,[10] or carbonate anions.[11] An interesting consequence of the complexation of highly protonated amines with bicarbonate anion HCO_3^- at pH 7 was the concomitant release of H^+, wherein the driving force for the liberation of H^+ from the weak acid HCO_3^- is provided by the bidentate CO_3^{2-} complexation, which might chemically mimic the gastric acid (HCl) secretion from the weak carbonic acid.[11] These facts, combined with a recent finding that the protonated polyamines can bind with neutral bidentate ligands such as catechol,[12] first led us to choose macrocyclic polyamines for the recognition of the possible bidentate histamine ligand. We then studied the relevant drugs listed in Chart 1.

Experimental

Materials——Histamine, urea, thiourea, nitroguanidine, and cyanoguanidine were purchased from Nakarai, 2-Pyridylethylamine, dimaprit, and famotidine are gifts from Yamanouchi Pharmaceutical Co. Cimetidine and metiamide were donated by Fujisawa-Smith Kline and French Co. Nordimaprit[8] was synthesized by refluxing 1-(*N*,*N*-dimethyl)-amino-2-bromoethane HBr with thiourea in dry dimethylformamide (DMF), and was then purified by recrystallization from EtOH: mp 178—180 °C, ^{1}H-NMR (CD_3OD): δ 3.12 (s, 6H, $N(CH_3)_2$), 3.32 (m, S–CH_2–),

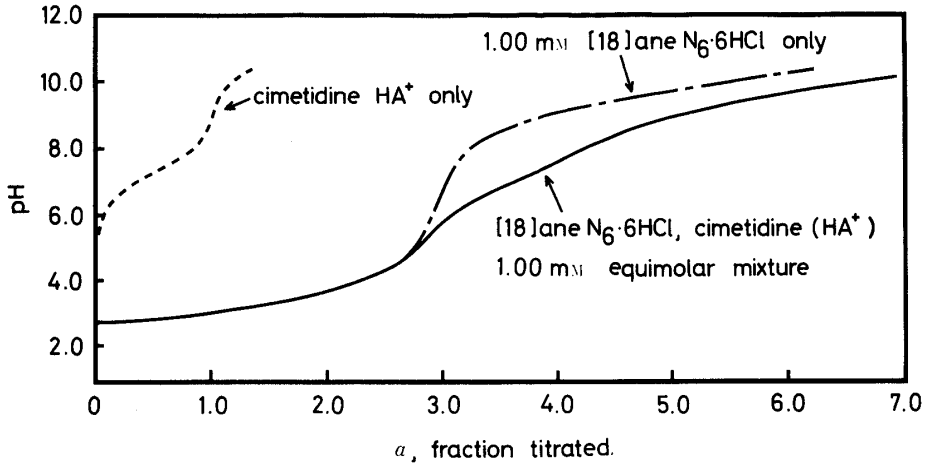


Fig. 1. pH-Titration Curve of Monoprotonated Cimetidine (HA^+) with NaOH in the Absence and Presence of [18]ane$N_6 \cdot 6HCl$

3.63 (m, 2H, N–CH_2–). Macrocyclic polyamines [18]aneN_6[13] and [16]aneN_5[14] were synthesized according to the reported methods.

Polarographic Method——The polarographic procedures were the same as those applied to the previous macrocyclic polyamine-polycarboxylate,[9]-phosphate,[10] and -catechol systems.[12] The special features of the dropping mercury electrode and of all the other apparatus were described elsewhere.[15] The half-wave potentials $E_{1/2}$ of the reversible polarograms of macrocyclic polyamines (L) in the presence of histamine (A), *etc.*, shifted in the same manner as in the presence of polycarboxylates,[9] phosphates,[10] and catechols.[12] Hence, an identical treatment of the data has been applicable.

Potentiometric Method——Potentiometric titrations were performed with a Mettler automatic pH titrator at 25.0 ± 0.1 °C under a nitrogen atmosphere. The mixed protonation constant pK_a's of histamine homologues were determined by titrations with 0.2 N NaOH of a solution typically containing 10^{-3} M with the ionic strength (I) made up to 0.2 M with $NaClO_4$. Complexation constants for L-A were determined by titrations with 0.2 N NaOH of solution containing 10^{-3} M L and 10^{-3} M A (both in fully protonated forms) at I 0.2 M. A typical titration curve is shown in Figure 1 for the case of [18]aneN_6 with cimetidine. The values of $-\log[H^+]$ were estimated from pH reading at $I=$ 0.2 M: $-\log[H^+]=\text{pH}-0.13$.

^{13}C-NMR Measurements——The ^{13}C-NMR spectra were recorded on a Hitachi FT-NMR spectrometer (22.6 MHz) at 35 °C. 1,4-Dioxane was used as the internal reference. To prepare a histamine (or imidazole) sample for ^{13}C-NMR, a weighed amount of the solute was dissolved in 98.8% D_2O to make a 0.25 M (0.5 M) solution with or without equivalent [18]aneN_6 and then the internal reference was added. The pD was then adjusted to 7.8 by addition of DCl. For the cimetidine sample, 0.1 M cimetidine in CD_3OD was first prepared, then a half-equivalent each of [18]aneN_6 (unprotonated) and [18]ane$N_6 \cdot 6HCl$, was added.

Results

The complexation has been examined quantitatively by the anodic polarographic technique which we had previously used to study the polyoxyanion[9-11] and catechol complexes,[12] and by pH-metric titration. Qualitative evidence for the chelation and the chelation sites was provided by the ^{13}C-NMR spectra.

Polarographic Measurements

Similar, well-defined waves for macrocyclic [18]aneN_6 (representing $Hg^0 + L \rightleftarrows HgL^{2+}$) in the absence and in the presence of histamine or its agonist, or antagonist (H_mA^{m+}, where A denotes a neutral form) in borate buffers permitted determination of the complex stoichiometries, the number $(n+m)$ of protons involved in the complexation, and the complex formation constants K.[12] The effects of histamine concentration (at a given pH) and of pH (at a given histamine concentration) on the anodic half-wave potential $E_{1/2}$ for L were all found to fit a theoretical eq. (1) for 1 : 1 complex formation (for derivation of eq. (1), see refs 10—13); see Table I and Fig. 2.

TABLE I. Representative Data on the Effects of [Histamine (or Relevant Compounds)] and pH Anodic Wave Potentials $E_{1/2}$ of [18]aneN$_6$ (0.3 mM) in Borate (0.03 M) Buffer (I=0.2 M and 25 °C)

$10^3 \times$ [histamine], M	pH	$\Delta E_{1/2}$, mV	Left-hand side of eq. 1
Histamine			
10.0	9.00	4.8	1.57×10^2
20.0	9.00	8.3	3.14×10^2
40.0	9.00	13.4	6.27×10^2
20.0	8.51	9.4	1.75×10^4
20.0	8.02	7.6	5.89×10^5
Cimetidine			
5.0	9.34	3.7	5.02
5.0	9.01	7.9	4.73×10
5.0	8.50	12.0	1.23×10^3
10.0	8.50	18:1	2.48×10^3

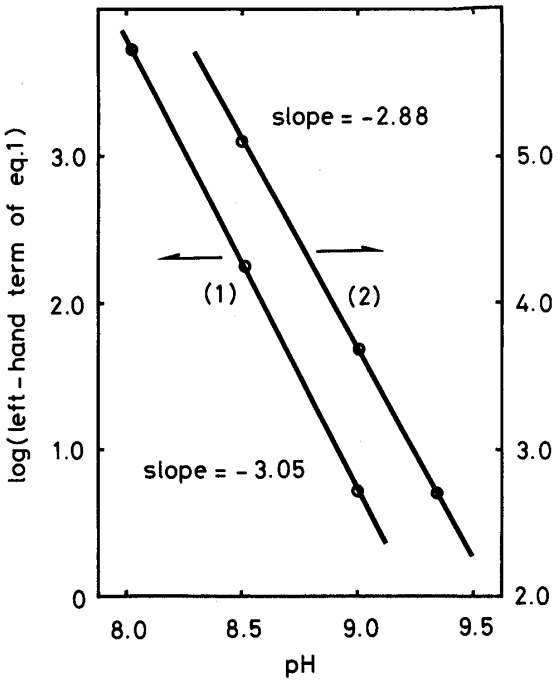


Fig. 2. Plots of Logarithmic (Left-Hand Side of Eq. 1) against pH for [18]aneN$_6$ (0.3 mM) – Histamine (20.0 mM) (1) and [18]aneN$_6$ (0.3 mM) – Cimetidine (5.0 mM) (2) in Borate Buffer (0.03 M) at I=0.2 M and 25 °C

$$\left[\text{antilog}\left(\frac{\Delta E_{1/2}}{0.0296}\right)-1\right](\alpha_H)_L\cdot(\alpha_H)_A = K\cdot[A][H^+]^{(n+m)}K_1K_2\cdots K_6\cdot K'_1K'_2 \quad (1)$$

The symbols are defined by (2)—(5).

$$K_i=\frac{[H_iL^{i+}]}{[H_{i-1}L^{(i-1)+}][H^+]} \quad (2)$$

$$K'_j=\frac{[H_iA^{j+}]}{[H_{i-1}A^{(j-1)+}][H^+]} \quad (3)$$

$$K=\frac{[H_nK^{n+}-H_mA^{m+}]}{[H_nL^{n+}][H_mA^{m+}]} \quad (4)$$

$$(\alpha_H)_L = [L]_{uncomplexed}/[L^0]$$
$$= 1 + [H^+]K_1 + [H^+]K_1K_2 + \cdots [H^+]^6 K_1K_2 \cdots K_6 \quad (5)$$
$$(\alpha_H)_A = [A]_{uncomplexed}/[A^0]$$
$$= 1 + [H^+]K_1' + [H^+]K_1'K_2' \quad \text{(for histamine)} \quad (6)$$

The K and $(n+m)$ values were determined graphically (see Fig. 2) as before,[9-12] and are summarized in Table II. The anodic waves in the presence of famotidine showed fairly poor reversibility. However, from the pH dependence and the concentration dependence, one can safely estimated K as 1×10^4. Complexation has not been detected between lower polyamine macrocycles (such as [16]aneN$_5$ or [14]aneN$_4$) and histamine.

TABLE II. 1:1 Association Constants K and K_{App} for [18]aneN$_6$ with Histamine-like Compounds at 25 °C and $I = 0.2$ M[a]

Histamine-like compound	Mixed protonation constant ($\log K_j$)	$(n+m)$ value	Assigned complex formula	K,[b] M^{-1}	K_{App},[c] M^{-1} (pH = 7.4)
Histamine	9.70, 6.02	3.0_5[d]	$H_3L^{3+} - A^0$	$1.1_1 \times 10^3$[d]	$5.1_0 \times 10^0$[d]
2-Pyridyl -ethylamine	8.95, 4.00			No interaction	
Dimaprit	9.66, 8.25	3	$H_3L^{3+} - A^0$	$1.3_2 \times 10^4$[e]	$8.5_7 \times 10^0$[e]
Nordimaprit	9.32, 7.29	3	$H_3L^{3+} - A^0$	$5.9_8 \times 10^3$[e]	$3.8_6 \times 10^1$[e]
Metiamide	7.14	3	$H_3L^{3+} - A^0$	$4.2_5 \times 10^1$[e]	$2.6_2 \times 10^1$[e]
Cimetidine	7.20	2.8_8[d]	$H_3L^{3+} - A^0$	$5.5_5 \times 10^2$[d]	$3.2_5 \times 10^2$[d]
				$7.7_2 \times 10^2$[e]	$4.7_4 \times 10^2$[e]
Famotidine	6.70	3	$H_3L^{3+} - A^0$	$1.0_0 \times 10^4$[d]	$7.9_6 \times 10^3$[d]
Ranitidine	8.71	3	$H_3L^{3+} - A^0$	$6.1_0 \times 10^3$[e]	$2.7_2 \times 10^2$[e]
Urea		3	$H_3L^{3+} - A^0$	$4.5_5 \times 10^1$[d]	$4.3_5 \times 10^1$[d]
Thiourea		3	$H_3L^{3+} - A^0$	$2.1_8 \times 10^2$[e]	$2.0_8 \times 10^2$[e]

a) Confidence limits (each for 3—5 experimental runs) are within $\pm 10\%$.
b) $K = [H_nL^{n+} - H_mA^{m+}]/[H_nL^{n+}][H_mA^{m+}]$, where A denotes a completely proton dissociated form of histamine-like compounds and L the unprotonated form of [18]aneN$_6$.
c) $K_{App} = [H_nL^{n+} - H_mA^{m+}]/[L]_{uncomp}[A]_{uncomp}$ $(= K \times K_1K_2K_3[H^+]^3/(\alpha_H)_L(\alpha_H)_A)$, where $[L]_{uncomp}$ = total concentration of uncomplexed [18]aneN$_6$, $[A]_{uncomp}$ = total concentration of uncomplexed histamine-like compounds.
d) Determined by the polarographic method using eq. (1).
e) Determined by the pH-metric titration method using eq. (8).

Potentiometric Measurements

The titration curves of a mixture of [18]aneN$_6$ (L) and a histamine-like compound (A) both in fully protonated forms (see Fig. 1) are assumed to represent overlapping equilibria (2), (3) and (4). The sum of $[H^+]$ $(= \alpha_{H^+})$ and $[Na^+]$ (from NaOH titrant), α, at titration point a with A = cimetidine (monoacidic base) is expressed by eq. (7), which can be rewritten as eq. (8) by appropriate substitution of eqs. (5) and (6)′ and rearrangement, provided $C_L = C_A$.

$$(\alpha_H)_A = [A]_{uncomplexed}/[A^0]$$
$$= 1 + [H^+]K_1' \quad \text{(for cimetidine)} \quad (6)'$$
$$\alpha = aC_L + [H^+]$$
$$= 6[L] + 5[HL^+] + 4[H_2L^{2+}] + \cdots + [H_5L^{5+}]$$
$$+ [7-(m+n)][H_nL^{n+} - H_mA^{m+}] + [A] \quad (7)$$

$$K[H^+]^{m+n}K_1K_2\cdots K_6\{[7-(m+n)]C_L-\alpha\}^2(\alpha_H)_L(\alpha_H)_A$$
$$=\{\alpha(\alpha_H)_L(\alpha_H)_A-C_L[\beta_L(\alpha_H)_A+(\alpha_H)_L]$$
$$\times\{[7-(m+n)](\alpha_H)_L(\alpha_H)_A-\beta_L(\alpha_H)_A-(\alpha_H)_L\} \quad (8)$$

Where

$$C_L=[L]_{\text{uncomplexed}}+[H_nL^{n+}-H_mA^{m+}] \quad (9)$$

$$\beta_L=6+5[H^+]K_1+\cdots+[H^+]K_1K_2\cdots K_5 \quad (10)$$

For A=cimetidine, K was calculated by assuming $n=3$ and $m=0$, as determined by the polarographic method. Plots of eq. (8) were linear and passed through the origin. The slope gives a K value of $7.7_2\times10^2$ (see Table II), which is in good agreement with the polarographic value of $5.5_5\times10^2$.

TABLE III. Chemical Shift Changes (in Hz) of ^{13}C-NMR Resonances of Histamine, Cimetidine, and Imidazole[a] in the Presence of [18]aneN$_6$

	a	b	c	d	e	f	g	h	i	j
Histamine[b]	−0.68	+1.36	−0.68	0	0					
Cimetidine[c]	+0.68	0	−1.39	0	+1.39	0	0	−0.71	+2.07	+1.39
Imidazole[d]	−2.04	−0.68								

a) For positioning of carbon atoms (a, b, c ···), see Chart 1.
b) 0.25 M solution in D_2O. Equivalent amount of [18]aneN$_6$ was added and the pH was adjusted to 7.8.
c) 0.10 M solution in MeOH. Half-equivalent each of [18]aneN$_6$ and [18]aneN$_6\cdot$6HCl was added.
d) 0.5 M solution in D_2O. Equivalent amount of [18]aneN$_6$ was added and the pH was adjusted to 7.8.

^{13}C-NMR Measurements

Since the polarographic and pH-metric methods indicated 1:1 interactions between macrocyclic polyamines and histamine congeners, we were interested in confirming this result using natural abundance ^{13}C-NMR spectroscopy. Chemical shifts were measured relative to dioxane, 67.4 ppm. Chemical shifts assignments of cimetidine were made with reference to the work of Dabrowiak *et al.*[16] The spectrum of the mixture appeared to be well separated into two discrete regions, thus allowing unambiguous spectral interpretation (Table III). We found that in the system of interacting molecules (histamine and cimetidine), there were significant upfield or downfield shifts for carbons a, b, and c on the imidazole (see Chart I), and these differ from the shifts of imidazole molecule having negligible interaction (assessed from the polarographic data). We also found other significant shifts for carbons at the cyanoguanidine moiety in the case of cimetidine. We thus conclude that the interacting sites of cimetidine are imidazole N (1-position) and cyanoguanidine N's, as concluded for Cu(II) chelation.[16]

Discussion

Chemistry of Complexation

We have now firmly established that the triprotonated macrocyclic hexaamine [18]aneN$_6$ captures neutral species of histamine and histamine-related compounds in 1:1 complexes H_3L^{3+}-A^0 in aqueous solutions of physiological pH. Just like polyanion[9-11] and neutral donor chelates[12] the histamine and its various homologues could serve as multidentate donor ligands to the 18-membered hexaamine +3 cation, which has a suitable ring size and conformation for ionic hydrogen bonding interaction. The fact that smaller-sized macrocyclic pentaamines possessing +3 charge (*e.g.* [16]aneN$_5$) show little interaction with

histamine indicates that certain geometrical requirements are imposed on the macrocyclic cations. The chelating structure is essential for the histamine congeners to bind with H_3L^{3+}. Thus, histamine can offer two donor sites, the imidazole N and the side chain N. The coordination is most likely at the N adjacent (N^{π})[8] to the side chain as deduced from the ^{13}C-NMR spectral shifts for the imidazole ring carbons, which significantly differ from the spectral changes for a mixture of imidazole and [18]aneN_6 under identical conditions; see Table III. A separate polarographic experiment showed no coordinating ability with imidazole alone.

The ^{13}C-NMR studies of [18]aneN_6 (at the $3H^+$ salt, prepared from a mixture of half-equivalents of H_6L^{6+} and L^0) and cimetidine in CD_3OD revealed the occurrence of a similar association at imidazole N^{π} and somewhere around the cyanoguanidine N's. Earlier, cimetidine was shown by ^{13}C-NMR spectroscopy to bind to Cu^{2+} through these two N groups.[16] Since the cyanoguanidine alone cannot bind to H_3L^{3+} (from the polarographic result), the chelation is essential for cimetidine binding with H_3L^{3+}. Similarly, the multidentate ligand natures of dimaprit, nordimaprit, metiamide, and famotidine would permit their association with the macrocyclic cations.

Thiourea is a more efficient ligand than urea, a fact suggesting a better N donor ability for the former bidentate due to the lesser electronegativity of the S (*vs.* O) atom.

Biological Relevance. Interaction of [18]aneN_6 with Histamine H_2-Agonists

Physiologically the most intriguing consequence from the 1 : 1 interaction of the macrocyclic polyamine (the major species is H_3L^{3+}) with H_2-agonist histamine and dimaprit (which exist mostly in protonated forms, see log K_i values in Table II) at physiological pH is the concomitant liberation of protons from the protonated amino groups of the H_2-agonists (see Fig. 3). In accordance with expectation, mixing an equal volume of an [18]aneN_6 solution and a dimaprit solution (both at 2.50 mM and pH 7.15) immediately lowered the solution pH to 6.95, which lends support to the occurrence of complexation with simultaneous release of H^+.

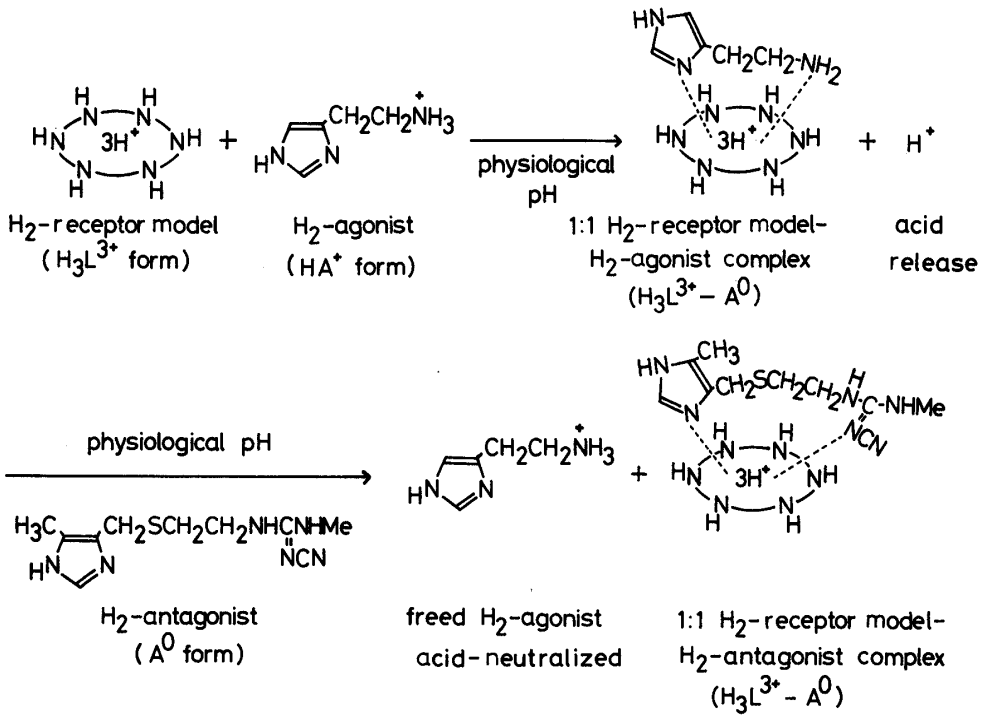
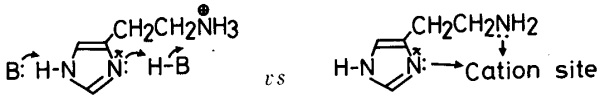


Fig. 3. A Schematic Representation of the Interaction of Histamine with [18]ane$N_6 \cdot 3H^+$ with Concomitant H^+-Release and Its Competitive Blockage by Cimetidine to Inhibit the Acid Secretion

Regarding highly concentrated amino (or basic) groups as the possible primary active site of histamine H_2-receptors in parietal cells, one might be tempted to compare the biological reaction of gastric acid secretion to a direct chemical response to the agonist-receptor interaction. While the present simple chemical fact may be irrelevant to the complex pharmacological phenomenon, our chemical model at least can give an explanation as to why dimaprit recognizes the histamine binding site of H_2-receptors and works as a strong H_2-agonist despite its structural dissimilarity to histamine. The common bidentate ligand properties with similar molecular size may allow dimaprit to adapt to the molecular locus for histamine in H_2-receptors.

Our H_2-receptor model, moreover, showed no affinity toward the H_1-agonist 2-pyridylethylamine that is structurally similar to histamine. The poorer basicity of pyridyl nitrogen may not fulfill the bidentate requirements for effective binding with the H_2-receptor model. These chemical arguments may well be relevant to the pharmacological fact that 2-thiazolylethylamine ($pK_a \sim 1.5$)[8] is not an H_2-agonist but rather an H_1-agonist, and also to the reduced H_2-activities of histamine derivatives with an electron-withdrawing group attached to the imidazole.[1,8] Steric factors diminishing the chemical bidentate efficiency of histamine also seem to reduce the pharmacological H_2-agonist activities. Thus, while 4-methylhistamine retains appreciable H_2-activities, 2-methylhistamine is a very weak H_2-agonist.

In earlier discussions[1,8] of functional chemical requirements for H_2-agonists, it was noted that I is a physiologically important form of histamine, so that histamine might be involved as a proton-transfer agent. Our discussion of chelation to H_2-receptors is not incompatible with the previous structural identification of H_2-agonists,[8] and may rather be complementary. However, our model (II) may add the concept that the basic (free) form of the side-chain amine group could be more important for recognition of H_2-receptor sites. This argument is linked with the following argument for H_2-antagonists.



I II

The pharmacological H_2-agonist activity of nordimaprit is drastically reduced despite the minor chemical alteration (a CH_2 less) leading to dimaprit. Our H_2-receptor model may not be refined enough to distinguish these two kinds of compounds (see affinity constants in Table II), or it may be argued that the evaluation of biological actions is complex and that lower pharmacological activity may not wholly result from weaker affinity but may rather result from inferior efficacy.

Histamine H_2-Antagonists

The macrocyclic hexaamine further recognizes the histamine H_2-antagonist cimetidine to yield a stable 1 : 1 complex, wherein the H_2-antagonist would bind to H_3L^{3+} as a bidentate donor ligand in a similar fashion to H_2-agonists. However, unlike the side-chain of H_2-agonists, which are protonated at neutral pH, the side-chain amine donor of cimetidine[17] is unprotonated and hence no acid liberation occurs upon complexation with the macrocyclic cation. This contrast in chemical responses is analgous with the pharmacological H_2-receptor response of gastric acid secretion to H_2-agonists and antagonists.

The survey of other H_2-antagonist structures leads to a uniform assessment of the most critical molecular requirement[18] for H_2-antagonists in terms of the N function of the side chain; without exception the compounds are unprotonated at physiological pH, due to the

reduced basicities resulting from attachment of an electron-withdrawing group, *i.e.*, thiourea (for metiamide),[19,20] cyanoguanidine (cimetidine, tiotidine),[21] nitroguanidine (ranitidine),[20] sulfonamide amidine (famotidine),[21] or isocytocine (oxametidine).[22] As required in the chelation of H_2-agonists, the other donors of H_2-antagonists are imidazole, dimethylamine on furan (ranitidine) or guanidine attached to thiazole (famotidine). We have tested the interaction of other available H_2-antagonists, metiamide, famotidine, and ranitidine, with our H_2-receptor model and found that they indeed form 1 : 1 complexes.[24]

Furthermore, the competitive affinity of histamine and H_2-antagonists for H_2-receptors is chemically mimicked by our model. Using the 1 : 1 complexation constants K and protonation constants, one can derive apparent complexation constants K_{app} at physiological pH 7.4 (see Table II) which permit estimation of the equilibrium shift for H_3L^{3+} – histamine + cimetidine $\rightleftarrows$ H_3L^{3+} – cimetidine + histamine greatly to the right. All of these and the preceding results are schematically summarized in Figure 3, which gives a chemical visualization of the competitive blockage of the histamine-induced acid secretion by H_2-antagonists. Another chemical fact, *i.e.*, that famotidine has a higher affinity than cimetidine for [18]aneN_6, parallels the pharmacological fact that the former is some 160 times more potent than the latter in inhibiting the dimaprit-induced acid secretion.[22] The relative complexation constants K_{app} for metiamide and cimetidine are also compatible with the relative H_2-antagonist activities against gastric acid secretion.[8]

Certainly, the pharmacological action of histamine leading to gastric secretion is complex and may involve, after the initial interaction with receptor sites, numerous and successive biochemical events such as initial activation of adenyl cyclase and final H^+/K^+ exchange at adenosine triphosphatase in parietal cells.[24] Hence the present chemical observation of H^+ release by H_2-agonists and its competitive blocking by H_2-antagonists on a macrocyclic hexaamine may be only phenomenal and may not serve to rationalize the true pharmacological mechanism. Neither can the present result be interpreted as indicating that the H_2-receptor sites are densely populated with amine functions. Naturally, care must be taken when assuming that agonists and antagonists compete for an identical site of receptors or that pharmacological activity of agonists is the direct consequence of the chemical interaction with receptors. By the same token, lack of activity may be due to other factors rather than failure to activate the same receptors. Nevertheless, the translation of the biological definition of drug receptors into chemical terms seems to offer a new means of differentiation or systematization of the diverse range of H_2-agonists and antagonists, as well as providing a new basis for structure–activity considerations in gastric acid secretion. We believe that a more refined chemical model would not only assist the designing of new H_2-antagonists but might also serve as a "receptor antagonist" that would specifically intercept histamine before its access to H_2-receptors.

References and Notes

1) G. J. Durant, C. R. Genellin, and M. E. Parsons, *J. Med. Chem.*, **18**, 905 (1975).
2) J. W. Black, V. P. Gerskowitch, and P. Leff, in "Pharmacology of Histamine Receptors," ed. by C. R. Ganellin and M. E. Parsons, Wright. PSG, Bristol, 1982, p. 1.
3) A. S. F. Ash and H. O. Shild, *Brit. J. Pharmacol.*, **27**, 427 (1966).
4) J. W. Black, W. A. M. Duncan, C. J. Durant, C. R. Ganellin, and E. M. Rarsonn, *Nature* (London), **236**, 385 (1972).
5) C. R. Ganellin, *J. Med. Chem.*, **24**, 913 (1981).
6) G. J. Durant, T. H. Brown, J. C. Emmett, C. R. Ganellin, H. D. Prain, and R. C. Young, in "The Chemical Regulation of Biological Mechanisms," ed. by A. M. Creigton and S. Turner, Special Publication No. 42, The Royal Society of Chemistry, London, 1982, p. 27.
7) R. W. Brimblecombe, W. A. M. Duncan, G. J. Durant, J. C. Emmett, C. R. Ganellin, G. B. Leslie, and M. E. Parsons, *Gastroenterology*, **74**, 339 (1978).

8) C. R. Ganellin, in the book cited in ref. 2, pp. 10—102, and references therein.
9) E. Kimura, A. Sakonaka, T. Yatsunami, and M. Kodama, *J. Am. Chem. Soc.*, **103**, 3041 (1981).
10) E. Kimura, M. Kodama, and T. Yatsunami, *J. Am. Chem. Soc.*, **104**, 3182 (1982).
11) E. Kimura, A. Sakonaka, and M. Kodama, *J. Am. Chem. Soc.*, **104**, 4984 (1982).
12) E. Kimura, A. Watanabe, and M. Kodama, *J. Am. Chem. Soc.*, **105**, 2063 (1983).
13) J. E. Richman and T. J. Atkins, *J. Am. Chem. Soc.*, **96**, 2268 (1974).
14) M. Kodama and E. Kimura, *J. Chem. Soc., Dalton Trans.*, **1975**, 104.
15) M. Kodama and E. Kimura, *J. Chem. Soc., Dalton Trans.*, **1976**, 2335.
16) F. T. Greenaway, L. M. Brown, J. C. Dabrowiak, M. R. Thompson, and V. M. Day, *J. Am. Chem. Soc.*, **102**, 7782 (1980).
17) E. Hädicke, F. Frickel, and A. Frank, *Chem. Ber.*, **111**, 3222 (1978).
18) G. J. Durant, J. C. Emmett, C. R. Ganellin, P. D. Miles, H. D. Prain, M. E. Parsons, and G. R. White, *J. Med. Chem.*, **20**, 901 (1977).
19) D. J. Gilman, D. F. Jones, K. Oldham, J. M. Wardleworth, and T. O. Yellin, in the same book of ref. 6, pp. 58—75.
20) J. Bradshaw, M. E. Butcher, J. W. Clitherow, M. D. Dowle, R. Hayes, D. B. Judd, J. M. McKinnon, and B. J. Price, in the book cited in ref. 6, pp. 45—57.
21) *a*) M. Takeda, P. Takagi, and H. Maeno, *Japan J. Pharmacol.*, **31** (Suppl.), 222 (1981); *b*) M. Takeda, Abstracts of Papers, 4th Symposium on Medicinal Chemistry, Tokyo, 1982, p. 66.
22) R. C. Blakemore, T. H. Brown, G. J. Durant, J. C. Emmitt, C. R. Genellin, M. E. Parsons, and A. C. Rasmussen, *Brit, J. Pharmacol.*, **70**, 105 (1980).
23) We also confirmed that another structural form of H_2-antagonist (containing a benzene ring instead of imidazole) TZU-0460 (*N*-{3-[3-piperidinylmethylphenoxy]propyl}acetoxyacetamido) (Japanese Patent No. 55-7760) similarly forms a 1 : 1 HA^+–H_3L^{3+} complex with [18]aneN_6: $K \approx 1 \times 10^4\ M^{-1}$.
24) C. F. Code, in the book cited in ref. 2, pp. 217—235.