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PERSPECTIVE

Genomics Meets Histamine Receptors: New Subtypes, New Receptors

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Whether the job is waking the brain after a peaceful sleep, initiating gastric secretion when dinner is served or orchestrating the elements of inflammation after a mosquito bite, histamine has been a known biological messenger for decades (Green, 1964; Eichler and Farah, 1966). At the end of the twentieth century, in the midst of the genomics and bioinformatics revolution, researchers in this field knew of the existence of only three histamine receptors (H_1, H_2, and H_3). But histamine receptors are catching up! Not only have multiple forms of the H_3 receptor recently been described but also a new histamine receptor, H_4, has now been identified.

The presently-known histamine receptors (H_1, H_2, and H_3) are all G protein-coupled molecules and they transduce extracellular signals via Gq, Gs, and Gi/o, respectively (Hill et al., 1997; Lovenberg et al., 1999). Not surprisingly, classic pharmacology studies (Ash and Schild, 1966; Black et al., 1972; Arrang et al., 1983) argued for their existence decades before they were cloned (Gantz et al., 1991; Yamashita et al., 1991; Lovenberg et al., 1999). Likewise, heterogeneity among H_3 receptors had long been suspected based on agonist kinetics (West et al., 1990), radioligand binding characteristics (Cumming et al., 1991; Alves-Rodrigues et al., 1996), peripheral versus central nervous system pharmacology (Leurs et al., 1996; Harper et al., 1999), and other functional studies (Schlicker et al., 1992; Schworer et al., 1994), but the absence of subtype-selective compounds prevented firm classification.

Although the H_1 and H_2 receptors were cloned nearly a decade ago (Gantz et al., 1991; Yamashita et al., 1991), the H_3 receptor was not cloned until 1999 (Lovenberg et al., 1999). However, this elucidation of the H_3 receptor structure in man and other species (Lovenberg et al., 1999, 2000; Tardivel-Lacombe et al., 2000; Drutel et al., 2001) quickly led to discoveries of the H_3 receptor subtypes and the closely related H_4 receptor, which are discussed presently. Recent molecular studies have shown that a single form of the H_3 gene can give rise to multiple mRNA isoforms, named H_{3A}, H_{3B}, and H_{3C} in the rat (Drutel et al., 2001), and H_{3L} and H_{3S} in the guinea pig (Tardivel-Lacombe et al., 2000). The variants all are known to differ in the structure of their third cytoplasmic loops, although the relevant splicing mechanisms remain uncertain (Tardivel-Lacombe et al., 2000; Drutel et al., 2001). Thus far, similar variants in human samples have not been identified (Liu et al., 2000), although the existence of multiple, somewhat different H_3 isoforms in humans was reported recently (Wellendorf et al., 2000). The H_3 receptor isoform that seems to be most predominant in human brain corresponds to the rat H_{3A} and the guinea pig H_{3L}. In the January 2001 issue of this journal, pharmacological differences in the H_3 receptor subtypes, as well as evidence for a differential distribution of the subtypes in rat brain, were presented (Drutel et al., 2001). Considering the current interest in the H_3 autoreceptor (Morisset et al., 2000), the ability of the H_3 heteroreceptor to regulate the activity of many brain transmitters (Hill et al., 1997; Hough, 1999) and the potential for developing new H_3 pharmacotherapies [e.g., in attention deficit/hyperactivity disorder, Alzheimer's disease, obesity, and others (Leurs et al., 1998; Tedford, 1998)], the characterization of the H_3 receptor subtypes is of considerable significance.

Phylogenetic (Leurs et al., 2000) and homology analysis (Lovenberg et al., 1999) of the H_3 receptor showed it to be surprisingly different from the previously cloned H_1 and H_2 receptors, a likely explanation for the delay in its discovery. Indeed, at the time of the H_3 receptor cloning, its homology to *any other known* G protein-coupled receptor was only 31% (Leurs et al., 2000). Because of this, the search for new receptors in a family more closely related to the H_3 receptor seemed promising. As described in the accompanying articles (Liu et al., 2001; Nguyen et al., 2001; Zhu et al., 2001) and in other recent (Oda et al., 2000) and concurrent (Morse et al., 2001) articles, screening of libraries and public databases for H_3-like fragments succeeded and led to the cloning and preliminary characterization of what is now referred to as the H_4 receptor. This receptor is a 390-amino-acid, 7-transmembrane G protein-coupled receptor, with a 37 to 43% homology to the H_3 (58% in transmembrane regions). All of the current

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studies report identical amino acid sequences for the receptor (Liu et al., 2001; Morse et al., 2001; Nguyen et al., 2001; Zhu et al., 2001); this sequence varies slightly from that of the original H_4 report (Oda et al., 2000). The human H_3 and H_4 receptors possess very similar genomic structures; both have two introns and three exons (Liu et al., 2001; Zhu et al., 2001), although the receptors are localized on different chromosomes (20 and 18, respectively). In addition, like the H_3 receptor, the H_4 receptor seems to couple to Gi/o [and possibly to other pathways (Oda et al., 2000)], thereby inhibiting forskolin-activated cAMP formation (Zhu et al., 2001). Evidence for a plasma membrane localization and agonist-stimulated internalization of H_4 has also been presented (Nguyen et al., 2001). Notably, the distribution of the H_4 receptor is quite different from that of the H_3 receptor. In contrast to a nearly exclusive brain localization for the H_3 receptor, the H_4 receptor shows highest levels in bone marrow and leukocytes (particularly eosinophils and neutrophils), with moderate levels in spleen and small intestine. Mast cells may also contain the H_4 receptor (Zhu et al., 2001). Northern analyses and other preliminary expression studies reported the absence of the H_4 receptor in the central nervous system (Oda et al., 2000; Morse et al., 2001; Nguyen et al., 2001). However, in situ hybridization studies in mouse (Zhu et al., 2001) and RNase protection assays in human samples (Liu et al., 2001) yielded evidence for a brain localization.

In general, the H_4 studies show excellent agreement on the preliminary pharmacology of the new receptor. Reported potencies of histaminergic compounds in competing against [^{3}H]histamine binding to the various H_4 clones are highly correlated across four laboratories (Fig. 1). However, results with [^{3}H]pyrilamine binding on another H_4 clone are discrepant (Fig. 1). These results, along with the lack of activity of pyrilamine on the H_4 receptor reported by other labs (Table 1), raise a question regarding the suitability of pyrilamine as radioligand for studying the H_4 receptor. Although the reasons for this discrepancy are not clear, it should be noted that [^{3}H]pyrilamine (also known as mepyramine) has been used as a radioligand for the H_1 receptor, but was later shown to also bind specifically to certain cytochrome isozymes, thus yielding false positives for the H_1 assay (Leurs et al., 1989; Liu et al., 1994).

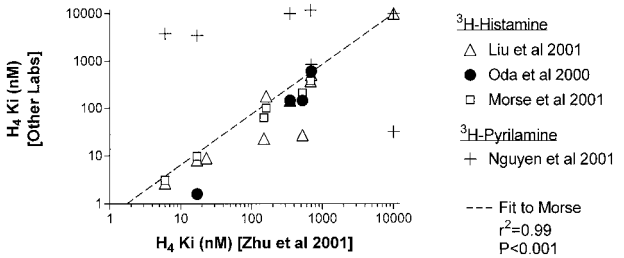

Fig. 1. Correlations of K_i values for the H_4 receptor across laboratories. Values for the human recombinant H_4 receptor are shown for some of the compounds in Table 1 as reported from five laboratories. K_i values are from competition experiments with [^{3}H]histamine (abscissa, Zhu et al., 2001) plotted against K_i values from other studies using either [^{3}H]histamine or [^{3}H]pyrilamine. The dashed line shows the linear regression of values from Zhu et al. (2001) plotted against those from Morse et al. (2001). Potency values agreed well across the H_4 clones when labeled histamine was used ($P < 0.01$), but not when labeled pyrilamine was used. The clones had identical H_4 sequences except for one (Oda et al., 2000), which differed by three amino acids. Values plotted as 10,000 nM were reported to be inactive at that concentration.

Given the structural similarities of the receptor, it is not surprising that the pharmacologies of the H_3 and H_4 receptors overlap (Table 1; Fig. 2). The high-affinity H_3 agonists also have H_4 agonist activity, but with a reduced potency. Most notable is (*R*)-α-methylhistamine, which shows several hundred-fold weaker activity at H_4 versus H_3 receptors. Thioperamide, the prototypical H_3 antagonist, also has appreciable H_4 antagonist activity (Table 1; Fig. 2). Some data (Liu et al., 2001) even suggest that this drug may be an inverse agonist at H_4 receptors, similar to recent results showing this effect on H_3 receptors (Morisset et al., 2000). Most of the results suggest that thioperamide has a 5- to 10-fold lower potency at the H_4 receptor than at the H_3 receptor (Table 1; Fig. 2). The H_3 antagonists clobenpropit and burimamide also have a lower affinity for the H_4 receptor, but these compounds show partial agonist activity at the new receptor. Most promising for pharmaceutical development are data showing the existence of potent, non-imidazole H_3 antagonists (e.g., compound 17 in Table 1 and Fig. 2) that *lack* activity at the H_4 receptor (Table 1). Taken together, these results suggest that H_4 responses are activated by low doses of histamine, but not by (*R*)-α-methylhistamine, and are blocked by large doses of thioperamide (an imidazole) but not by non–imidazole-containing H_3 antagonists. Although compounds capable of selectively acting at the new receptor have not yet been described, the atypical antipsychotic drug clozapine (discussed further below) shows moderate H_4 and no H_3 activity (Fig. 2), and thus may be a lead in this direction.

The above characteristics suggest that the H_4 receptor has been with us longer than we realized. Raible et al. (1994) reported a histamine-activated increase in cytosolic calcium in human eosinophils; the effect was sensitive to thioperamide and partially mimicked by burimamide but not by low concentrations of (*R*)-α-methylhistamine. Similarly, the histamine-induced inhibition of serotonin release in intestinal enterochromaffin cells resembles an H_4 response with respect to pharmacology and tissue expression (Schworer et al., 1994). It is also likely that the "histamine uptake" discovered in bone marrow hematopoietic cells (Corbel et al., 1997) represents in-fact binding of [^{3}H]histamine and other ligands to the H_4 receptor, based on the pharmacology. In some of these studies, the potency of thioperamide can be difficult to interpret because of a large species difference (up to 10-fold) in the affinity of thioperamide for the human versus the rat H_3 receptor (Lovenberg et al., 2000); the difference is controlled by only two amino acid substitutions (Ligneau et al., 2000). There are other reported effects of thioperamide that are not reversed by H_3 agonists, and the H_4 receptor must now be considered in these cases. For example, thioperamide increases extracellular levels of both histamine and γ-aminobutyric acid in brain, but only the former effect is reversed by H_3 agonists (Yamamoto et al., 1997). Of course, thioperamide actions are not restricted to the H_3 and H_4 receptors; it has some affinity at other sites as well [e.g., 5-HT_3 (Leurs et al., 1995)] and may even be found to have activity at additional, unknown histamine receptors. Although the new H_4 work accounts for the existence of some novel histamine receptors previously suggested to exist, it cannot account for others. For example, HTMT [6-[2-(4-imidazolyl)ethylamino]-*N*-(4-trifluoromethylphenyl)heptanecarboxamide], the histamine

derivative that suppresses lymphocyte function by a novel receptor (Khan et al., 1986), is not active at the H_4 (Table 1). Similarly, improgan, a cimetidine congener that induces analgesia by a mechanism distinct from known histamine receptors (Hough et al., 2000), also had low affinity for the H_4 site (Table 1).

The newly discovered effects of clozapine on the H_4 receptor (Table 1, Fig. 2) add a new chapter to the longstanding relationship between psychosis, antipsychotic drugs, and brain histamine (Green et al., 1977; Raucher et al., 1977). Chlorpromazine, the first neuroleptic, was developed from the early H_1 antagonists, and many neuroleptics have activity at both H_1 and H_2 receptors (Hough and Green, 1984). Activity at the former is thought to contribute to the sedative profile of these drugs, and H_2 antagonists may be beneficial in treating psychosis (Rosse et al., 1996). The atypical neuroleptic clozapine was reported to have moderate activity on the rat brain H_3 receptor (Rodrigues et al., 1995), an effect confirmed on the rat (Kathmann et al., 1994) but not on the human receptor (Table 1). Although the K_i value for clozapine on the H_4 receptor is relatively high (500–700 nM, Table 1), plasma and brain concentrations associated with clinical responses meet or exceed these values (Baldessarini and Frankenburg, 1991) Even more interesting is that clozapine seems to be an *agonist* at H_4 receptors (Oda et al., 2000; Liu et al., 2001). Although we do not yet know the consequences of H_4 receptor stimulation in the hippocampus (Zhu et al., 2001) or in eosinophils, it seems quite possible that patients taking clozapine are recipients of both actions. Whether this receptor participates in either the therapeutic or toxic effects of this drug is an intriguing question which remains to be answered; it is tempting to speculate that the eosinophilic

TABLE 1

Potencies of histaminergic drugs on four histamine receptors.

K_d or K_i values are given for the compounds shown. Compound numbers are referenced in Fig. 2. Except where noted otherwise, bioassay K_d values are from guinea pig ileum[a] and atrium[b] (Hill et al., 1997).

#	Drug	H_1[a]	H_2[b]	H_3[c]	H_4[d]	H_4[e]	H_4[f]
1	Histamine			5.4	8.1	17	9.7
2	Pyrilamine	0.4	5,200	>10,000	>10,000[g]	>10,000	
3	Diphenhydramine	1.0	>10,000	>10,000	>10,000		
4	Cyproheptadine	3.1[h]	37[i]	>10,000	>10,000		
5	Cimetidine	>10,000	800	>10,000	>10,000	>10,000	
6	Ranitidine	>10,000	200	>10,000	>10,000		
7	Dimaprit	>10,000[j]	1,100[k]	825	377	677	380
8	Impromidine	3,400	63[k]	67	12.3		
9	Burimamide	>10,000	7,800	84	180	160	100
10	Imetit[l]			0.3	2.7	6	3.1
11	Immepip[l]			0.4	9	23	
12	(R)-α-Methylhistamine[l]			0.7	146	348	140
13	N-methyl-histamine[l]			0.5	23	149	63
14	Thioperamide	>10,000	>10,000	25[m]	27	519	210
15	Clobenpropit	>10,000	>10,000	0.6	12.8		7.2
16	Clozapine	2.8[n]	100[o]	>10,000[p]	510	693	
17	4-(3-Piperidin-1-yl-propoxy)-benzonitrile			25	>10,000		
18	HTMT					1229	
19	Improgan[q]	>10,000	>10,000	33,000		6,000	

[a] Guinea pig ileum (Hill et al., 1997).
[b] Guinea pig atrium (Hill et al., 1997).
[c] K_i values for competition against [^{3}H]N-methylhistamine binding on the human recombinant H_3 receptor (Liu et al., 2001).
[d] K_i values for competition against [^{3}H]histamine binding on the human recombinant H_4 receptor (Liu et al., 2001).
[e] K_i values for competition against [^{3}H]histamine binding on the human recombinant H_4 receptor (Zhu et al., 2001).
[f] K_i values for competition against [^{3}H]histamine binding on the human recombinant H_4 receptor (Morse et al., 2001).
[g] T. Lovenberg, unpublished observations.
[h] Radioligand binding (Tran et al., 1978).
[i] Adenylate cyclase (Green et al., 1977).
[j] Bioassay (Ganellin, 1982).
[k] Bioassay EC_{50} values (Hill et al., 1997).
[l] Highly selective H_3 agonists (Hill et al., 1997).
[m] Thioperamide has up to a 10-fold higher potency on the rat H_3 receptor (Lovenberg et al., 2000).
[n] Radioligand binding (Baldessarini and Frankenburg, 1991).
[o] L. Hough and J. P. Green, unpublished observations.
[p] Clozapine has activity on the rat (Kathmann et al., 1994; Rodrigues et al., 1995), but not the human H_3 receptor (Lovenberg et al., 1999).
[q] See Li et al. (1996) for improgan K_d values.

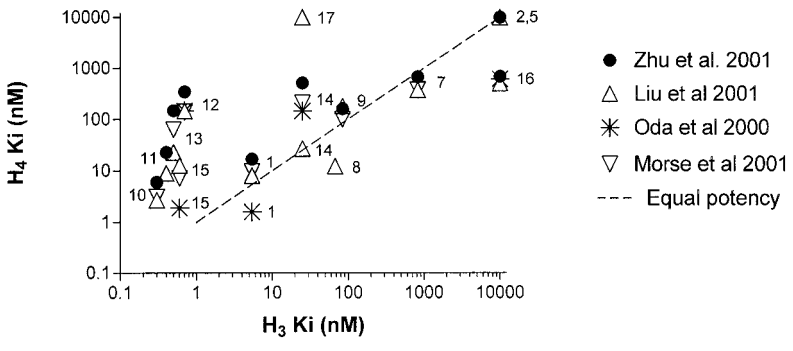

Fig. 2. Relationship between H_3 and H_4 receptor potency. Data for some compounds in Table 1 are plotted as H_3 K_i value (abcissa, Table 1) versus H_4 K_i value (ordinate). H_4 values are derived from competition experiments with [^{3}H]histamine from the studies identified. When more than one laboratory studied the same compound, a single H_3 K_i value is plotted against more than one H_4 K_i value. Compound numbers correspond with those in Table 1. Values plotted as 10,000 nM were reported to be inactive at that concentration.

agranulocytosis, which often limits clozapine effectiveness, might be related to the H_4 receptor (Oda et al., 2000).

Much additional work on the H_4 system is needed. H_4 receptor subtypes may be found based on similarities to H_3. The activities of the histamine metabolites need to be assessed on this receptor, because several of these metabolites have biological activity (Phillis et al., 1968; Thomas and Prell, 1995), and histamine metabolism is highly regulated in some cases (Haddock et al., 1990). Finally, H_4-selective drugs will need to be developed that can further define the biological roles for this receptor and lead to unique pharmacotherapies. All indications suggest that many more receptors for histamine remain to be discovered.

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