Journal of Cellular Biochemistry 40:183–192 (1989)
Molecular and Cellular Mechanisms of Human
Hypersensitivity and Autoimmunity 83–92

Molecular and Cellular Analysis of Histamine H1 Receptors on Cultured Smooth Muscle Cells

Masato Mitsuhashi and Donald G. Payan

Howard Hughes Medical Institute Laboratories and the Department of Medicine, University of California, Medical Center, San Francisco, California 94143

Histamine is an important mediator of immediate hypersensitivity for both animals and humans. The action of histamine on target tissues is believed to be mediated by specific cell surface receptors, especially H1 and H2 receptors for hypersensitivity and inflammatory reactions, which involve stimulation of smooth muscle contractility, alterations in vascular permeability, and modifications in the activities of macrophages and lymphocytes. Although the nature of histamine receptors in the brain and peripheral tissues has been studied extensively by many laboratories, the molecular mechanism of histamine receptor-mediated reactions is not fully understood, mainly because histamine receptors are incompletely characterized from the biochemical point of view. In previous studies, we have found that the cultured smooth muscle cell line DDT_1MF-2, derived from hamster vas deferens, expresses low-affinity histamine H1 receptors and responds biochemically and functionally to H1-specific stimulation (Mitsuhashi and Payan, J Cell Physiol 134:367, 1988). This cell line provides a model for analyzing the biochemical responses of H1 receptor-mediated reactions in peripheral tissues. In this review, we summarized our recent progress in the study of low-affinity H1 receptors on DDT_1MF-2 cells.

Key words: histamine H1 receptor, calcium, protein kinase C

Histamine is an important mediator of immediate hypersensitivity for both animals and humans [1–3]. For example, in healthy human subjects, an intradermal injection of histamine induces a wheal and flare response similar to that seen in urticaria [4]. Inhalation of histamine provokes bronchoconstriction [5], and intravenous injection of histamine results in a rapid decrease in blood pressure similar to that seen in anaphylactic shock [6]. Serum levels of histamine are also increased in patients with hymenoptera-sting hypersensitivity during the acute phase of anaphylactic shock [7]. Moreover, human blood basophilic leukocytes in patients with allergic disorders release histamine in vitro in response to specific and nonspecific stimuli [8].

In mammalian species, histamine is synthesized by histidine decarboxylase [9] and stored in all tissues in amounts ranging from less than 1 $\mu g/g$ to over 100 $\mu g/g$ [10]. Histamine is then released in conjunction with other potent chemical mediators in

Received July 6, 1988; accepted January 3, 1989.

response to specific IgE-mediated [11] or nonspecific mechanisms [12] from the tissue mast cells [13] or blood basophilic leukocytes [14]. The action of histamine on target tissues is believed to be mediated by specific cell surface receptors, especially H1 and H2 receptors for hypersensitivity and inflammatory reactions, which involve stimulation of smooth muscle contractility, alterations in vascular permeability, and modifications in the activities of macrophages and lymphocytes [1,15].

In the central nervous system, histamine is synthesized by a different histidine decarboxylase from that of mast cells [16] and is known to be a neurotransmitter via H1 and H2 receptors [17] and the newly identified H3 receptors [18]. H3 receptors are present in presynaptic locations in rat brains and inhibit the release of histamine. The precise mechanisms for the actions and interactions among these three types of histamine receptors are still unknown. Although the nature of H1 and H2 receptors has been extensively studied by many laboratories [19], the molecular mechanism of histamine receptor-mediated reactions is not fully understood, mainly because the three classes of histamine receptors are incompletely characterized from the biochemical point of view. Furthermore, recent studies indicate that H1 receptors do not comprise a homogenous population and that brain H1 receptors might be different from H1 receptors in peripheral tissues [20].

In previous studies, we have found that the cultured smooth muscle cell line, DDT_1MF-2, derived from hamster vas deferens [21], expresses low-affinity histamine H1 receptors and responds biochemically and functionally to the H1-specific stimulation [22]. This cell line provides a model for analyzing the biochemical responses of H1 receptor-mediated reactions in peripheral tissues [22,23]. Recently, H1 receptors on DDT_1MF-2 cells have been solubilized and purified to homogeneity and exhibit similar binding characteristics to those of intact cells [24]. In this review, we summarize our recent progress in the study of low-affinity H1 receptors on DDT_1MF-2 cells, and contrast them to high-affinity H1 receptors in the brain.

HETEROGENEITY OF H1 RECEPTORS

The contractile response of guinea pig ileum smooth muscle to histamine has led to detailed functional and structural studies of H1 receptors [25]. Moreover, the lack of H2 receptors on guinea pig ileum [26] also accelerated the development and analysis of newly synthesized H1 agonists and antagonists. An early demonstration of the presence of H1 receptors on membrane fractions of guinea pig ileum smooth muscle was carried out by Hill et al. [27] using the radiolabeled H1-specific antagonist, [^{3}H]-pyrilamine. Furthermore, the K_d from [^{3}H]-pyrilamine binding studies correlated with the EC_{50} of the contractile response of guinea pig ileum to histamine, suggesting that [^{3}H]-pyrilamine binding sites were specific H1 receptors. However, a similar number of [^{3}H]-pyrilamine binding sites were demonstrated on rat, guinea pig, and rabbit ileal membranes, although the contractile effects of histamine varied widely in these species [28]. The dissociation constant (K_d) of [^{3}H]-pyrilamine also varied widely from 0.7 nM to 219 nM in various tissues (Table I) [29–34]. The difference of activity of H1 antagonists was also demonstrated in the functional assays with an IC_{50} ranging from 30 pM to 10 μM (Table I) [35–42]. Moreover, the subclasses of H1 receptors were detected in various tissues using different radiolabeled ligands (Table II) [43–47].

TABLE I. Summary of Activities of the H1-Specific Antagonist Pyrilamine

Assay	Species	Tissue	K_d/IC_{50} of pyrilamine	Reference no.
[^{3}H]-pyrilamine binding	Guinea pig	Ileum	1.3 (K_d, nM)	27
	Guinea pig	Brain	0.7	29
	Guinea pig	Bladder	0.7	30
	Mouse	Brain	6.0	31
	Human	Astrocytoma	3.3	32
	Human	Neutrophils	52.0	33
	Human	Monocytes	3.8	34
	Human	T-helper cells	5.0	34
	Human	T-suppressor	44.6	34
	Human	B-cells	14.2	34
	Hamster	SMC[a]	219.0	26
Contraction response	Guinea pig	Ileum	0.8 (IC_{50}, nM)	27
	Guinea pig	Bladder	1.2	30
	Porcine	Trachea	21.2	35
	Guinea pig	Vas deferens	250–5,000	36
Cytosolic Ca^{2+} release	Rat	SMC	0.03	37
Glycogen hydrolysis	Mouse	Brain	11.0	38
Prostaglandin E synthesis	Human	Synovial cell	0.3 μM	39
Ion transport	Rabbit	Colon	0.3 μM	40
^{45}Ca efflux	Mouse	SMC	1 μM[b]	41
cGMP formation	Human	Lung	10 μM	42

[a]Cultured smooth muscle cells.
[b]Chlorpheniramine.

[^{3}H]-pyrilamine binding studies indicate that extracellular sodium, manganese, magnesium, and guanine nucleotides selectively alter the agonist affinity in guinea pig brain membranes [22], and dithiothreitol also increased agonist affinity in guinea pig ileum [48]. This might suggest that the heterogeneity of H1 receptors is due to the microenvironments in which H1 receptors are present or influenced by additional interaction with G-proteins, as demonstrated with other G-protein-coupled membrane receptors [49]. Because recent gene cloning techniques have identified different isoforms of receptor genes than would have been expected from the known receptor pharmacology, as in the case of muscarinic acetylcholine receptors [50], GABA receptors [51], and glycine receptors [52], H1 receptor heterogeneity might also be explained on this basis.

TABLE II. Subclasses of H1 Receptors

Radiolabeled ligands	Species	Tissues/cells	K_d of each subclass	Reference no.
[^{3}H]-histamine	Cat	Intestine	5.0 μM, 77 μM	43
[^{3}H]-pyrilamine	Rat	Liver	4.2 nM, 21 nM	44
	Human	Lung	81.0 pM, 7 μM, 320 μM	42
	Human	Lymphocytes	4.0 nM, 55 μM	45
[^{3}H]-doxepine	Guinea pig	Brain	0.3 nM, 25 nM	46
[^{125}I]-iodobolpyramine	Guinea pig	Brain	50.0 pM, 150 pM	47

FUNCTIONAL H1 RECEPTORS ON THE CULTURED SMOOTH MUSCLE CELLS

The analysis of H1 receptors in whole tissue is difficult to interpret because of the heterologous population of cell types and the heterogeneity of H1 receptors. The advantage of established cell lines is that a homogeneous cell population can be studied directly. In a previous study using a cloned cell line, DDT_1MF-2, [^{3}H]-pyrilamine binding indicated a single class of binding sites by three separate methods of determination, such as kinetic data (rate of association/dissociation), saturation (binding of labeled ligand), and competition experiments (displacement of labeled ligand by unlabeled ligand) with resulting similar K_d values ranging from 102–953 nM [22]. These K_d values are 100–1,000-fold higher than those of guinea pig ileum and mammalian brains. However, the H2-specific antagonist (cimetidine) and the H3-specific antagonist (thioperamide, data not shown) are less potent than the H1-specific antagonist (pyrilamine, diphenhydramine, and chlorpheniramine) [22]. These data suggest the presence of low-affinity H1 receptors on DDT_1MF-2 cells.

Results from a number of laboratories has demonstrated that histamine increases $[Ca^{2+}]_i$ by H1-specific mechanisms and that the elevation of $[Ca^{2+}]_i$ may be an early event in the metabolic events resulting in smooth muscle contraction. Recently, using the intracellularly trapped dye quin-2, Matsumoto et al. [37] have reported that histamine activated cell surface H1 receptors on rat aortic smooth muscle cells to increase their $[Ca^{2+}]_i$. In our previous study [22], changes in $[Ca^{2+}]_i$ on DDT_1MF-2 cells were evaluated with the sensitive fluorescent indicator fura-2 rather than quin-2. Our results confirm that histamine increased $[Ca^{2+}]_i$ in a dose-dependent manner with an EC_{50} of 3×10^{-5} M and that the effect of histamine was inhibited by H1 receptor antagonist, but not by H2 receptor antagonist [22]. The dose of chlorpheniramine that inhibited histamine-induced increases of $[Ca^{2+}]_i$ was 100 nM, which is a concentration of the same order of magnitude as the K_d values of pyrilamine derived from equilibrium binding. In Figure 1, histamine increases $[Ca^{2+}]_i$ in a dose-dependent manner. These changes are significant despite the high basal level of $[Ca^{2+}]_i$ on DDT_1MF-2 cells (200–500 nM) and the rapid efflux of $[Ca^{2+}]$ into the extracellular space [41].

Since histamine increased $[Ca^{2+}]_i$ even in calcium-free solutions (Fig. 1), the increases in $[Ca^{2+}]_i$ are most likely due to the release of Ca^{2+} from intracellular stores. This might indicate that H1 receptors on DDT_1MF-2 cells are coupled to the phosphatidylinositol pathway and induce hydrolysis of phosphatidylinositol with formation of inositol-1,4,5-trisphosphate and diacylglycerol, leading to Ca^{2+} release and probable activation of protein kinase C (PKC), as shown in smooth muscle of guinea pig ileum [53], rabbit aorta [54], and guinea pig brain slices [55].

Numerous studies have demonstrated that the elevation of $[Ca^{2+}]_i$ activates the calcium-calmodulin-dependent myosin light-chain kinase which results in myosin phosphorylation and the subsequent polymerization of actin, which is an essential step for smooth muscle contraction [56]. In order to assess the relationship between the elevation of $[Ca^{2+}]_i$ and the contractile response of DDT_1MF-2 cells to histamine, we have previously examined the change of cell shape by phase contrast light microscopy [57]. Although histamine-induced contraction of cultured smooth muscle cells [58] and cultured mesangial cells [59] were observed microscopically, the quantification of the contractile response of individual DDT_1MF-2 cells could not be accomplished in detail by light microscopy alone because DDT_1MF-2 cells did not spread uniformly on tissue

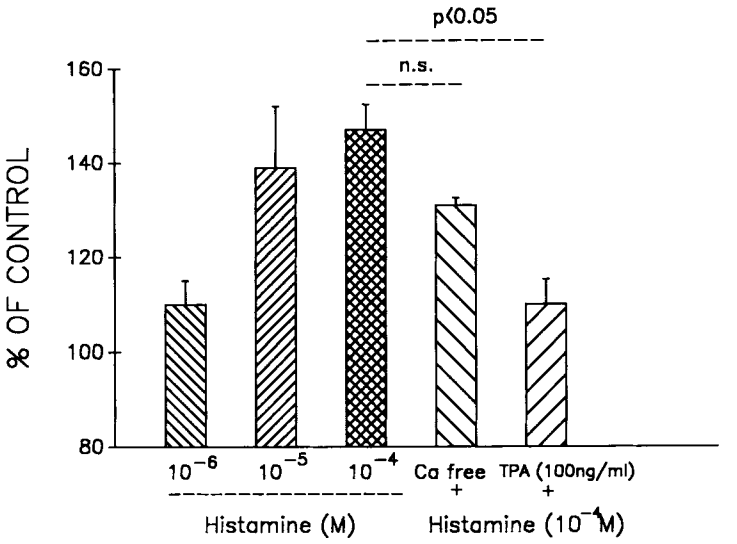

Fig. 1. Histamine-induced stimulation of changes in cytosolic calcium in DDT_1MF-2 cells. DDT_1MF-2 cells at a density of 1×10^7 in 1 ml Hanks' Balanced Salt Solution (HBSS) containing 0.1% Bovine Serum Albumin (BSA) were incubated with 2.5 μM fura-2 for 60 min at 37°C and the intracellular fura-2 signals were measured at 340 nm or 380 nm exitation and 510 nm emission in a fluorescence spectrophotometer as described previously [22]. For the TPA-induced down-regulation of H1 receptors, 5×10^6 DDT_1MF-2 cells were suspended in 15 ml Dulbecco's modified Eagle's medium (DME) containing 5% fetal calf serum (FCS) and seeded into 25 cm^2 tissue culture flasks. After 2 days, medium was replaced with 0.1% BSA-DME and the cultures were continued for another 24 h for cell quiescence. Cells were then incubated with 100 ng/ml of TPA at 37°C for 2 h. Cells were then resuspended in fresh HBSS containing 0.1% BSA at a density of 1×10^7 cells/ml, and incubated with 2.5 μM fura-2 as described above. The increase of $[Ca^{2+}]_i$ is expressed as the percentage of basal level of $[Ca^{2+}]_i$. Each data point represents the mean ± SEM of 3–17 determinations.

culture plates. Therefore, the degree of intracellular actin polymerization was assessed by a DNase inhibition assay, based on the inhibition of DNase-I by nonpolymerized actin, but not polymerized actin [60]. As a result, histamine induced the polymerization of intracellular actin in DDT_1MF-2 cells in a dose-dependent manner with an EC_{50} of approximately 1×10^{-5} M, which is comparable to that of $[Ca^{2+}]_i$ (3×10^{-5} M), but lower than the IC_{50} of histamine derived from pyrilamine binding (3×10^{-4} M) [22]. These data suggest that occupancy of a fraction of cell surface binding sites may be sufficient to trigger a maximal functional response as previously described in mouse brain slices [38]. The inhibitory effect on actin polymerization of 10^{-6} to 10^{-7} M chlorpheniramine was also similar to the concentrations which inhibit rises in $[Ca^{2+}]_i$, which is of the same order of magnitude as the K_d values of pyrilamine derived from equilibrium binding (2.19×10^{-7} M).

Flow cytometric evaluation has been used to further quantify histamine-induced changes in cell shape by the combination of forward light scatter and 90° light scatter as previously described for human leukocytes [61]. Our experiments demonstrate that the cell shape of DDT_1MF-2 cells was significantly changed by the addition of 3×10^{-4} M histamine. These data suggest that [^{3}H]-pyrilamine binding sites on the surface of DDT_1MF-2 cells are functionally active and are capable of inducing contraction of individual cells.

REGULATION OF CELL SURFACE H1 RECEPTORS

The biochemical mechanisms of desensitization or down-regulation of cell surface receptors for mediators are important in the modulation of hypersensitivity phenomena. Experimental evidence indicates the presence of different biochemical pathways for receptor regulation depending on the type of ligand and target cell [62]. For instance, incubation of clonal astrocytoma cells with dibutyryl adenosine cyclic monophosphate (cAMP) produced a refractory state to both catecholamines and prostaglandins, suggesting that cAMP can mediate heterologous desensitization [63]. The prostaglandin E-mediated heterologous desensitization observed in fibroblasts appears to involve uncoupling of the guanine nucleotide binding protein from the catalytic unit of adenylate cyclase [64]. Moreover, recent evidence suggests that protein kinase C (PKC) exerts down-regulation of inositol coupled receptors in various cell types [65].

Desensitization of histamine H1 receptors has been reported with respect to the histamine-elicited contraction of smooth muscle [66], histamine-induced stimulation of guanosine cyclic monophosphate (cGMP) accumulation in clonal neuroblastoma cells [67], and histamine-mediated glycogen hydrolysis in mouse brain slices [31]. However, the mechanism by which H1 receptor-mediated desensitization occurs is not entirely understood. H1 receptor stimulation has been shown to induce the breakdown of inositol phospholipids [53–55] and increase $[Ca^{2+}]_i$ [22,37]. These data suggested that desensitization of H1 receptors may be mediated via the activation of PKC.

12-O-tetradecanoylphorbol-13-acetate (TPA) has been shown to directly activate PKC by substituting for diacylglycerol with resultant alteration in the density on cell surface receptors for molecules known to modulate cell growth [68]. Furthermore, TPA activation of PKC in DDT_1MF-2 cells has been extensively studied by Leeb-Lundberg et al. [69,70] and Cowlen et al. [71]. Therefore, we examined the effect of TPA on specific [^{3}H]-pyrilamine binding of DDT_1MF-2 cells. As expected, specific [^{3}H]-pyrilamine binding sites were reduced by pretreatment with TPA, but not the Kd [23]. The TPA analogue, 4α phorbol 12,13-didecanoate, which does not activate PKC, failed to induce down-regulation of H1 receptors. TPA-induced down-regulation of H1 receptors was inhibited by pretreatment with 1-(5-isoquinilinesulfonyl)-2-methylpiperazine dihydrochloride (H-7) [72], a PKC inhibitor, in a dose-dependent manner [23]. The H-7 analogue, H-8, which is a less potent inhibitor of PKC [72], but a potent inhibitor of cyclic nucleotide dependent protein kinase, had no effect on H1 receptors. Moreover, as shown in Figure 1, TPA inhibited histamine-induced increases in $[Ca^{2+}]_i$. These data suggest that H1 receptors on DDT_1MF-2 cells are functionally regulated by PKC.

Recent work demonstrates that PKC phosphorylates epidermal growth factor (EGF) receptors [73], insulin receptors [74], transferrin receptors [75], and α_1-adrenergic receptors [69]. However, the determination of whether PKC directly phosphorylates H1 receptors will require further knowledge of the protein constituents of H1 receptors than is currently available.

BIOCHEMICAL CHARACTERISTICS OF H1 RECEPTORS

H1 receptors solubilized from various tissues have demonstrated similar binding characteristics to those of the original intact tissues. For example, [^{3}H]-doxepine binding activity was solubilized by 1% digitonin from rat and guinea pig brain membranes [76], [^{3}H]-pyrilamine binding activity was solubilized by digitonin from guinea pig brain

membranes [77,78], [^{3}H]-histamine binding activity was solubilized by 1% Triton X-100 from cat small intestine [43], and [^{3}H]-histamine binding activity was solubilized by 1% Nonidet 40 from calf thymocyte membranes [79]. Recently, [^{3}H]-pyrilamine binding activity was also solubilized by 1% digitonin from DDT_1MF-2 cells [24]. The K_d of [^{3}H]-pyrilamine on solubilized DDT_1MF-2 cells was 172 ± 81 nM, which is equivalent to that on the intact cells.

The reported molecular size of membrane-bound H1 receptors in both bovine and human cerebral cortex by target size analysis has demonstrated an approximate size of 160,000 daltons [80]. However, the molecular weight of soluble H1 receptors from guinea pig brain was shown to be approximately 430,000 by gel filtration [76]. The difference of molecular weight is most likely due to the presence of digitonin-H1 receptor complexes. Recently, Ruat et al. [81] have used irreversible photoaffinity labeling to specifically label H1-binding proteins in cell membranes. They synthesized [^{125}I]-iodoazidophenpyramine, a highly potent H1 receptor antagonist derived from pyrilamine. Upon irradiation, 5% of the bound radioactivity was covalently incorporated into H1 receptors of guinea pig brain membranes. SDS-gel electrophoresis analysis indicated that the molecular weight of H1 receptors was 350,000–400,000 daltons in the absence of 2-mercaptoethanol, and the molecular weight decreased to 47,000–56,000 daltons in the presence of 2-mercaptoethanol, which is similar to the molecular weight of the receptor on calf thymocyte membranes [79]. This suggests that H1 receptors may have one or more disulfide bridges resulting in a higher molecular weight complex. Furthermore, in the presence of protease inhibitors, labeling of the 56,000 dalton peptide increased at the expense of the 47,000 dalton peptide. This also suggests that the 47,000 dalton peptide was a proteolytic product of the 56,000 dalton peptide.

In our recent studies [24], the protein with [^{3}H]-pyrilamine binding activity was also purified with gel filtration, chromatofocusing followed by reverse phase HPLC. The final material was a single peak on reverse-phase HPLC and a single band of apparent molecular weight 39,000 daltons on SDS-PAGE, which exhibited specific [^{3}H]-pyrilamine binding activity. This molecular weight of H1 receptors on DDT_1MF-2 is smaller than that reported by Ruat et al. [81], and might also be due to proteolytic degradation. Since Garbarg et al. [78] also reported that H1 receptors were glycoproteins using lectin affinity chromatography, part of the difference in molecular weight might also be due to receptor glycosylation. More recently, we have raised a rabbit polyclonal antibody against the 39 kD protein by subcutaneous implantation of dried SDS-gels containing the band of interest. Preliminary results demonstrate that antiserum inhibits [^{3}H]-pyrilamine binding to DDT_1MF-2 cells in a dose-dependent manner (Fig. 2). These data strongly suggest that the 39,000 protein purified from DDT_1MF-2 cells is the low-affinity histamine H1 receptor, and should result in the identification of an H1 receptor gene and further elucidate the molecular mechanism of histamine responses.

ACKNOWLEDGMENTS

The authors would like to thank Dr. E.J. Goetzl, C. Koo, and J. Sherman for their helpful comments and suggestions, and P.F. Dazin for his technical assistance in the FACS analysis. This work was supported by Grants AI19784 and NS21710 from the National Institutes of Health.

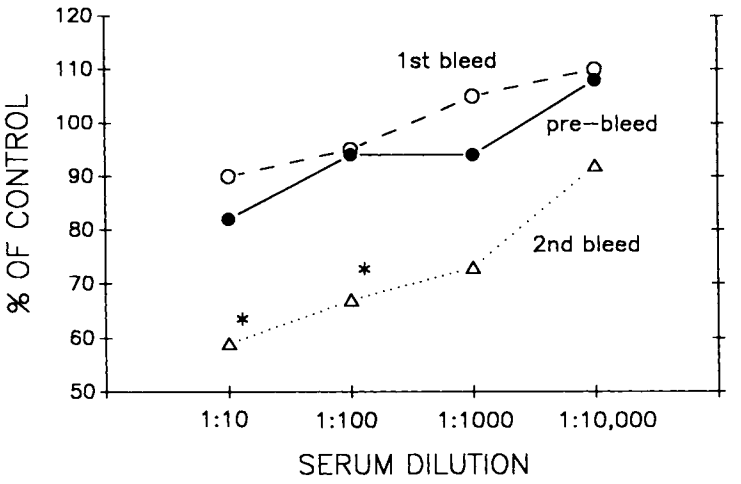

Fig. 2. Inhibition of [^{3}H]-pyrilamine binding. DDT$_1$MF-2 cells were removed from flasks and resuspended in HBSS containing 5 mM histidine at a density of 1×10^6/ml and [^{3}H]-pyrilamine binding was performed with 100 nM [^{3}H]-pyrilamine as described previously [22,23] in the presence of various concentration of polyclonal antibodies against 39,000 dalton H1 receptor protein. Each data point is expressed by the mean of the percentage of control [^{3}H]-pyrilamine binding from two to three separate experiments performed in duplicate. $*P < 0.05$.

REFERENCES

1. Beer DJ, Matloff SM, Rocklin RE: Adv Immunol 35:209, 1984.
2. Beaven MA: N Engl J Med 294:30, 1976.
3. Beaven MA: N Engl J Med 294:320, 1976.
4. Lewis T, Harmer IM: Heart 14:19, 1927.
5. Curry JJ: J Clin Invest 25:785, 1946.
6. Dale HH, Laidlaw PP: J Physiol (Lond) 52:355, 1919.
7. Mitsuhashi M, Natsukawa S, Obara T, Ezoe H: Jpn J Allergol 31:1122, 1982.
8. Sobotka AK, Valentine MD, Benton AW, Lichenstein LM: J Allergy Clin Immunol 53:170, 1974.
9. Schayer RW: In Rocha e Silva M (ed): "Handbook of Experimental Pharmacology." New York: Springer-Verlag, 1966, pp 688–725.
10. Beaven MA: In Ganellin CR and Parsons ME (eds): "Pharmacology of Histamine Receptors." Bristol, London, Boston: Wright PSG, 1982, pp 103–145.
11. Ishizaka K, Ishizaka T: J Immunol 99:1187, 1967.
12. Morrison DC, Roser JF, Cochranw CG, Hensen PM: Int Arch Allergy Appl Immunol 49:172, 1975.
13. Riley JF, West GB: In Rocha e Silva M (ed): "Handbook of Experimental Pharmacology." New York: Springer-Verlag, 1966, pp 116–135.
14. Geaham HT, Lowry OH, Wheelwright F, Lenz MA, Parish HH: Blood 10:467, 1955.
15. Black J, Gerskowitch VP, Leff P: In Ganellin CR and Parsons ME (eds): "Pharmacology of Histamine Receptors." Bristol, London, Boston: Wright PSG, 1982, pp 1–9.
16. Riley JR: "The Mast Cells." Edinburgh: Livingstone, 1959.
17. Schwartz JC: In Rocha e Silva M (ed): "Handbook of Experimental Pharmacology." New York: Springer-Verlag, 1966, pp 351–391.
18. Arrang JM, Garbarg M, Lancelot LC, Lecomte JM, Pollard H, Robba M, Schunack W, Schwartz JC: Nature 327:117, 1987.
19. Ganellin CR: In Rocha e Silva M (ed): "Handbook of Experimental Pharmacology." New York: Springer-Verlag, 1966, pp 10–102.
20. Le Fur G, Malgouris C, Uzan A: Life Sci 29:547, 1981.
21. Norris JS, Gorski J, Kohler PO: Nature 248:422, 1974.

22. Mitsuhashi M, Payan DG: J Cell Physiol 134:367, 1988.
23. Mitsuhashi M, Payan DG: Life Sci 43:1433, 1988.
24. Mitsuhashi M, Payan DG: Mol Pharmacol: 1989, in press.
25. Dale HH, Laidlaw PP: J Physiol (Lond) 41:318, 1910.
26. Black JW, Duncan WAM, Durant CJ, Ganellin CR, Parsons EM: Nature 236:385, 1972.
27. Hill SJ, Young JM, Marrian DH: Nature 270:361, 1977.
28. Chang RSL, Tran VT, Snyder SH: J Pharmacol Exp Ther 209:437, 1979.
29. Chang RSL, Snyder SH: J Neurochem 34:916, 1980.
30. Kondo M, Taniyama K, Tanaka C: Eur J Pharmacol 114:89, 1985.
31. Quach TT, Duchemin AM, Rose C, Schwartz JC: Mol Pharmacol 20:331, 1981.
32. Nakahata N, Martin MW, Hughes AR, Hepler JR, Harden TK: Mol Pharmacol 29:188, 1986.
33. Wescott S, Kaliner M: Inflammation 7:291, 1983.
34. Cameron W, Doyle K, Rocklin RE: J Immunol 136:2116, 1986.
35. Driver A, Mustafa SJ: Eur J Pharmacol 139:287, 1987.
36. Vohra MM: Agents Actions 11:208, 1981.
37. Matsumoto T, Kanaide H, Nishimura J, Shogakiuchi Y, Kobayashi S, Nakamura M: Biochem Biophys Res Commun 135:172, 1986.
38. Quach TT, Duchemin AM, Rose C, Schwartz JC: Mol Pharmacol 17:301, 1980.
39. Taylor DJ, Woolley DE: Ann Rheum Dis 46:425, 1987.
40. McCabe RD, Smith PL: Am J Physiol 247:G411, 1984.
41. Brown RD, Prendiville P, Cain C: Mol Pharmacol 29:531, 1986.
42. Casale TB, Rodbard D, Kaliner M: Biochem Pharmacol 34:3285, 1985.
43. Uchida M, Takagi K: Jpn J Pharmacol 27:9, 1977.
44. Imoto M, Tsuchie K, Tanaka M, Sugiyama S, Ozawa T: Biochem Biophys Res Commun 127:885, 1985.
45. Casale TB, Wescott S, Rodbard D, Kaliner M: Int J Immunopharmacol 7:639, 1985.
46. Tran VT, Lebovitz R, Toll L, Snyder SH: Eur J Pharmacol 70:501, 1981.
47. Korner M, Bouthenet M-L, Ganellin CR, Garbarg M, Gros C, Ife RJ, Sales N, Schwartz J-C: Eur J Pharmacol 120:151, 1986.
48. Donaldson J, Hill SJ: Br J Pharmacol 90:263, 1987.
49. Koo C, Lefkowitz RJ, Snyderman R: J Clin Invest 72:748, 1983.
50. Barnard EA: Nature 335:301, 1988.
51. Levitan ES, Schofield PR, Burt DR, Rhee LM, Wisden W, Koehler M, Fujita N, Rodrigues HF, Stephenson A, Darlison MG, Barnard EA, Seeburg PH: Nature 335:76, 1988.
52. Akagi H, Miledi R: Science 242:270, 1988.
53. Donaldson J, Hill SJ: Br J Pharmacol 85:499, 1985.
54. Villalobos-Molina R, Garcia-Sainz JA: Eur J Pharmacol 90:457, 1983.
55. Daum PR, Downes CP, Young JM: Eur J Pharmacol 87:497, 1983.
56. Kamm KE, Stull JT: Annu Rev Pharmacol Toxicol 25:593, 1985.
57. Mitsuhashi M, Payan DG: Life Sci 40:853, 1987.
58. Gunther S, Alexander RW, Atkinson WJ, Gimbrone MA: J Cell Biol 92:289, 1982.
59. Sedor J, Abbound HE: J Clin Invest 75:1679, 1985.
60. Blikstad I, Markey F, Carlsson L, Persson T, Lindberg U: Cell 15:935, 1978.
61. Salzman GC, Crowell JM, Martin JC, Trujillo TT, Romero A, Mullaney PF, LaBauve PM: Acta Cytol 19:374, 1975.
62. Sibley DR, Lefkowitz RJ: Nature 317:124, 1985.
63. Su YF, Cubeddu LX, Perkin JP: J Cyclic Nucleotide Res 2:257, 1976.
64. Kassis S, Fishman PH: J Biol Chem 257:5312, 1982.
65. Nishizuka Y: Science 233:305, 1986.
66. Gosselin RE, Gosselin RS: J Pharmacol Exp Ther 184:494, 1973.
67. Taylor JE, Richelson E: Mol Pharmacol 15:462, 1978.
68. Castagna M, Takai Y, Kaibuchi K, Sano K, Kikkawa U, Nishizuka Y: J Biol Chem 257:7847, 1982.
69. Leeb-Lundberg LMF, Cotecchia S, Lomasney JW, DeBernardis JF: Proc Natl Acad Sci USA 82:5651, 1985.
70. Leeb-Lundberg LMF, Cotecchia S, DeBlasi A, Caron MG, Lefkowitz RJ: J Biol Chem 262:3098, 1987.
71. Cowlen MS, Toews ML: J Pharmacol Exp Ther 243:527, 1987.
72. Hidaka H, Inagaki M, Kawamoto S, Sasaki Y: Biochemistry 23:5036, 1984.
73. Cochet C, Gill GN, Meisenhelder J, Cooper JA, Hunter T: J Biol Chem 259:2553, 1984.

74. Bollag GE, Roth RA, Beudoin J, Mochly-Rosen D, Koshland DE Jr: Proc Natl Acad Sci USA 83:5822, 1986.
75. Davis RJ, Johnson GL, Kelleher DJ, Anderson JK, Mole JE, Czech MP: J Biol Chem 261:9034, 1986.
76. Toll L, Snyder SH: J Biol Chem 257:13593, 1982.
77. Gavish M, Chang RSL, Snyder SH: Life Sci 25:783, 1979.
78. Garbarg M, Yeramian E, Korner M, Schwartz J-C: In Ganellin CR, Schwartz JC (eds): "Frontiers in Histamine Research." New York: Pergamon Press, 1985, pp 19–25.
79. Osband M, McCaffrey R: J Biol Chem 254:9970, 1979.
80. Kuno T, Kubo N, Tanaka C: Biochem Biophys Res Commun 129:639, 1985.
81. Ruat M, Korner M, Garbarg M, Gros C, Schwartz JC, Tertiuk W, Ganellin CR: Proc Natl Acad Sci USA 85:2743, 1988.