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Distribution, Properties, and Functional Characteristics of Three Classes of Histamine Receptor

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I. Introduction

HISTAMINE was first isolated in pharmacologically active amounts from biological tissues approximately 60 years ago (Beavan, 1982). Since that time, research interest in the receptors that mediate the pharmacological actions of this biogenic amine has waxed and waned over the decades, reaching a peak each time a new histamine receptor is announced and then returning to a much lower plateau level of activity. This general low level of interest belies the fact that histamine receptors are probably better served with receptor-selective ligands than many of their more popular small molecule and peptide counterparts.

Three classes of histamine receptor have now been identified, the latest of which (H_3-receptor) was confirmed recently with the aid of highly H_3-selective ligands (Arrang et al., 1987a; Hill, 1987a; Schwartz et al., 1986a). Recent advances in histamine receptor research have included studies with radioactive probes for the individual receptor recognition sites and the elucidation of the effect of histamine receptor stimulation on intracellular signaling processes. The purpose of this article is to review the distribution, properties, and functional characterisitics of the three classes of histamine receptor and to explore our current understanding of the receptor-effector mechanisms underlying the principal pharmacological actions of this important, yet often underrated, biogenic amine.

II. Physiological Role: From Autacoid to Neurotransmitter

Histamine is closely associated with mast cells in almost all tissues (Riley and West, 1966; Beavan, 1982) and its long established role as a mediator of inflammation led to its general description as an autacoid or local hormone. Much interest has concentrated on the large list of pharmacological agents, in addition to immunoglobulins, that can produce mast cell degranulation and the biochemical events associated with histamine release (Goth and Johnson, 1975; Beavan, 1981; Kaliner, 1979; Beavan et al., 1984a,b; Maeyama et al., 1986). However, not all tissue histamine is associated with mast cells, and, depending upon species, histamine has been detected in basophils (Graham et al., 1955), platelets (Goth, 1978; Saxena et al., 1989), enterochromaffin-like cells (Hakanson et al., 1974; Soll et al., 1981), endothelial cells (Karnushina et al., 1980), and neurones (Schwartz et al., 1980a, 1986a). In addition, there is some evidence that histamine synthesis can be induced, and histamine made available in an unstored diffusable form, in tissues undergoing rapid tissue growth or repair (Kahlson and Rosengren, 1968, 1971; Lewis and Mangham, 1979; Bartholeyns and Fozard, 1985). These additional sites of histamine synthesis and storage suggest that there are alternative physiological roles for histamine.

In the gastric mucosa, the advent, in 1972, of selective antagonists of the H_2-receptors responsible for the acid secretory properties of histamine confirmed a physiological role for this amine in the control of parietal cell function (Black et al., 1972; Code, 1982). It is still puzzling, however, that in some species histamine is present in enterochromaffin-like cells (Hakanson et al., 1974; Soll et al., 1981), whereas in others gastric histamine appears to be stored exclusively in gastric mucosal mast cells (sometimes known as histamocytes) (Code, 1982; Soll et al., 1979). Furthermore, the exact role that histamine plays in the control of gastric acid secretion is still open to question, and it remains to be established whether histamine is the final common mediator of acid secretion or whether H_2-receptor stimulation amplifies the direct effect of acetylcholine or gastrin on the parietal cell (Black and Shankley, 1987).

Histamine is widely distributed within the mammalian central nervous system (CNS)† (Adam and Hye, 1966; Taylor and Snyder, 1971; Taylor et al., 1972; Lipinski et al., 1973), and there is strong evidence that this amine may additionally have a role as a neurotransmitter or neuromodulator (Prell and Green, 1986; Schwartz et al., 1986b). Histamine is present in both neuronal (Schwartz, 1977; Schwartz et al., 1980a, 1986a) and nonneuronal compartments (Edvinsson et al., 1977; Grzanna and Shultz, 1982; Hough et al., 1985) in mammalian brain, and recent immunohistological studies have succeeded in mapping the histaminergic pathways in rat (Watenabe

† Abbreviations: CNS, central nervous system; 5-HT, 5-hydroxytryptamine; DTT, 1,4-dithiothreitol; GTP, guanosine 5′-triphosphate; GMP, guanosine 5′-monophosphate; AMP, adenosine 5′-monophosphate; mRNA, messenger ribonucleic acid; IP_3, inositol-1,4,5-trisphosphate; DG, diacylglycerol.

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et al., 1983; Watenabe et al., 1984; Panula et al., 1984; Takeda et al., 1984; Pollard et al., 1985; Steinbush et al., 1986; Pollard and Schwartz, 1987; Inagaki et al., 1988) and guinea pig (Airaksinen and Panula, 1988) brain. The arrangement of the histaminergic fibres resembles in many ways that of the other two biogenic amines, noradrenaline and 5-hydroxytryptamine (5-HT), in that the histamine cells bodies are restricted to a discrete brain region (i.e., the magnocellular nuclei in the posterior hypothalamus) but send ascending projections to most areas of the forebrain. In addition, there is evidence for a descending histaminergic pathway to the spinal cord (Inagaki et al., 1988; Wahlestedt, et al., 1985).

Preliminary reports have also indicated the presence of histaminergic fibres in rabbit retina (Ando-Yamamoto et al., 1987), rat vas deferens (Campos, 1988), and guinea pig stomach and colon (Hakanson et al., 1983). The exact role that histamine plays within the CNS is largely subject to speculation, but it has been implicated in the control of arousal (Kalivas, 1982; Bristow and Bennett, 1988; Kiyono et al., 1985), cardiovascular homeostasis (White, 1965; Brezenoff and Jenden, 1969; Sinha et al., 1969; Finch and Hicks, 1976; Klein and Gertner, 1981), temperature regulation (Shaw, 1971; Brezenoff and Lomax, 1970; Sweatman and Jell, 1977; Cox et al., 1976; Nowak et al., 1979; Pilc and Nowak, 1980), and neuroendocrine mechanisms (Weiner and Ganong, 1978; Prell and Green, 1986; Donoso and Alvarez, 1984; Roberts and Calcutt, 1983).

III. Histamine Receptor Classification and Chemical Probes

Histamine receptors have been divided into three major subtypes, H_1, H_2, and H_3 on the basis of quantitative in vitro studies in isolated peripheral tissues and brain slice preparations. Histamine receptors were initially subdivided by Ash and Schild in 1966 when they introduced the term H_1 receptor to describe the class of histamine receptors that was sensitive to inhibition by low concentrations of classical antihistamines (now synonymous with H_1-receptor antagonists) such as promethazine and mepyramine. Prior to this, it was well established that only certain of the responses to histamine were sensitive to these agents.

Classic H_1-receptor-mediated responses include contraction of many visceral smooth muscles including guinea pig trachea, uterus, and the longitudinal smooth muscle of the ileum (Dews and Graham, 1946; Arunlakshana and Schild, 1959; Ash and Schild, 1966; Chand and Eyre, 1975). However, a number of responses to histamine, most notably stimulation of acid secretion from the gastric mucosa, the chronotropic response of guinea pig right atrium, and the inhibition of electrically evoked contractions of rat uterine horn, were resistant to antagonists such as mepyramine (Ash and Schild, 1966; Black et al., 1972). The receptor responsible for these latter responses was eventually defined as the H_2-receptor by Sir James Black and his colleagues at Smith Kline and French in 1972 when they succeeded in developing a selective antagonist of this response, namely, burimamide (Black et al., 1972; Brimblecombe et al., 1975). The third histamine receptor (H_3) was originally postulated in 1983 to explain the atypical pharmacological properties of the histamine autoreceptor responsible for controlling the release of histamine from rat cerebral cortical slices (Arrang et al., 1983). The existence of this new histamine receptor subtype, however, was not confirmed until these same authors reported the pharmacological properties of two potent and selective H_3-ligands in 1987 (Arrang et al., 1987a).

A. Chemical Probes

1. H_1-receptor. A large number of compounds, with very different structures, have been developed as competitive antagonists of the histamine H_1-receptor (Casy, 1977; Ganellin, 1982), although as pointed out by Black et al. (1982) the competitive nature of many of these compounds has been assumed rather than tested. The principal selective antagonist for the H_1-receptor is mepyramine because of its high affinity (K_D = 0.8 nM) and good receptor selectivity (Hill, 1987b). Schild analysis of the nature of the antagonism of H_1-receptors produced by this H_1-antagonist has confirmed its competitive nature (Schild slope = 1.0) in both guinea pig ileum and cerebellar brain slices (Donaldson and Hill, 1985; 1986c). Many H_1-antagonists, particularly promethazine and diphenhydramine, have marked muscarinic receptor antagonist (Burgen and Harbird, 1983) and membrane-stabilising properties (Seeman and Weinstein, 1966). However, fortunately, mepyramine is very selective if used at concentrations below 100 nM. Above this level, mepyramine will nevertheless antagonise other responses, e.g., muscarinic receptors (>10 μM) (Reuse, 1948; Burgen and Harbird, 1983), H_2-receptors (>5 μM) (Trendelenburg, 1960), monoamine reuptake (1 μM) (Young et al., 1988a), and histamine-N-methyltransferase activity (>10 μM) (Taylor, 1973). Triprolidine and chlorpheniramine are particularly useful chemical tools for the classification of H_1-receptors because they exist as geometric and optical isomers, respectively. D(+)-Chlorpheniramine (*S* configuration) is approximately two orders of magnitude more potent than L(−)-chlorpheniramine as an H_1-antagonist in both guinea pig ileum and guinea pig cerebral cortical slices (Hill and Young, 1981; Roth and Govier, 1958; Hill et al., 1981), thus confirming the stereoselective requirements for antagonist binding to the H_1-receptor recognition site. (+)- and (−)-4-methyldiphenhydramine also differ by two orders of magnitude in their affinity for the H_1-receptor (Treherne and Young, 1988c). The geometric isomer *trans*-triprolidine is three orders of magnitude more potent than its *cis*-counterpart as an antagonist of H_1-receptor-mediated responses in guinea pig ileum and is one of the most potent compounds available (K_D = 0.1 nM) (Ison et al., 1973). The tricyclic antidepressant

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doxepin has a similar high affinity for the H_1-receptor (K_D = 0.06 nM) (Figge et al., 1979; Aceves et al., 1985) and has similarly proved to be a valuable chemical probe.

A common side effect of H_1-antagonist administration in vivo is sedation (Faingold, 1966) which appears to be related to occupancy of cerebral H_1-receptors (Quach et al., 1979; 1980a). Most H_1-receptor antagonists readily cross the blood-brain barrier, but a number have been developed recently that penetrate poorly into the CNS and appear devoid of central depressant effects. These include terfenadine (Wiech and Martin, 1982; Rose et al., 1982), mequitazine (Quach et al., 1979; Uzan and Le Fur, 1979; Le Fur et al., 1981), astemizole (Van Wauwe et al., 1981; Laduron et al., 1982; Niemegeers et al., 1982), and temelastine (Brown et al., 1986a). Temelastine is one of the most potent (K_D = 0.3 nM) and competitive of the non-brain-pentrating compounds, but the determination of the affinity of both astemizole (Laduron et al., 1982) and terfenadine (Cheng and Woodward, 1982) for the histamine H_1-receptor is complicated by their very slow dissociation from the H_1-receptor in vitro. Indeed, in vivo studies with astemizole have revealed that H_1-receptor occupancy is maintained for up to 6 days in guinea pig lung following oral administration of astemizole (Laduron et al., 1982). The nature of the antagonism produced by astemizole and terfenadine is unclear, but a covalent interaction with the H_1-receptor seems unlikely from a consideration of the chemical structures of these two drugs (Laduron et al., 1982; Carr and Meyer, 1982).

A number of agents are available that bind covalently to the H_1-receptor. Phenoxybenzamine (Kenakin and Cook, 1976, 1980b) and benzilylcholine mustard (Reasbeck and Young, 1973) both cyclise and form aziridinium ions in aqueous solutions at neutral pH and subsequently bind irreversibly to the H_1-receptor. Neither of these compounds binds specifically to the H_1-receptor (El-Fakahany and Richelson, 1981; Reasbeck and Young, 1973), but they can provide important information concerning agonist affinity and efficacy in well-characterised H_1-receptor systems (Donaldson and Hill, 1987). Several photoaffinity probes have been developed that bind irreversibly, following photolysis, to the histamine H_1-receptor. These include azide derivatives of both histamine (O'Donnell et al., 1981, Horstemeyer et al., 1986) and the 5-HT_2-receptor antagonist, ketanserin (Wouters et al., 1985a,b; Schotte and Leysen, 1988). One of the most potent and specific photoaffinity ligands, iodoazidophenpyamine, is a derivative of mepyramine and has a K_D of 0.01 nM under equilibrium conditions (i.e., before ultraviolet irradiation) (Ruat et al., 1988).

Unlike the situation with antagonists, the H_1-receptor is poorly served by agonists that demonstrate selectivity for this histamine receptor subtype. Both 2-methylhistamine and 2-thiazolylethylamine show some, but not marked, selectivity for the H_1-receptor (table 2). 2-Pyridylethylamine and betahistine are the other two agents most commonly used as H_1-agonists, but their relative potencies for the H_1- and H_2-receptors differ by only a factor of 3 or 4 (Hill, 1987b). A number of compounds act as partial agonists on the H_1-receptor, but this property is strongly dependent upon the transducing efficiency of the H_1-receptor-mediated response under study, e.g., low efficacy agonists such as 2-methylhistamine and 2-pyridylethylamine act as partial agonists on the histamine-induced inositol phosphate response in guinea pig cerebral cortex (Donaldson and Hill, 1986b) but as full agonists in guinea pig ileum (Ganellin, 1982) where the spare receptor reserve is relatively large (Reasbeck and Young, 1973; Nickerson, 1956). SKF 71473 and N,N,-diethyl-2-pyridylethylamine, however, do act as partial agonists in this latter tissue producing maximal responses of 58 and 23%, respectively, of that produced by histamine (Donaldson and Hill, 1987; Durant et al., 1973; Kenakin and Cook, 1980a).

2. H_2-receptor. The development of antagonists of the histamine H_2-receptor ranks as one of the classic examples of rational drug design and development. Burimamide was the first compound to be described that had a higher affinity for the histamine H_2-receptor than the H_1-receptor (Black et al., 1972; Ganellin, 1978). However, it has recently been shown to be two orders of magnitude more potent as an antagonist of histamine H_3-receptors (Arrang et al., 1983) than of H_2-receptors and should, perhaps, now be considered as a selective H_3-receptor antagonist. Other H_2-receptor antagonists have, however, been developed from burimamide, including metiamide (Ganellin, 1978) and cimetidine (Brimblecombe et al., 1975), and these do not possess marked H_3-receptor affinity (table 1). Following the successful application of cimetidine as a treatment of conditions involving excessive secretion of gastric acid in man, a large number of compounds have been developed as H_2-receptor antagonists (Ganellin, 1985). Ranitidine (Bradshaw et al., 1979;

TABLE 1
*Antagonist potencies of histamine receptor antagonists**

Antagonist	K_D (nM)		
	H_1	H_2	H_3
Mepyramine	0.8[a]	5,200[b]	>3,000[c]
Cyclizine	5.0[d]	1,600[e]	>580[f]
(+)-Chlorpheniramine	0.4[g]	1,200†	>58[f]
(−)-Chlorpheniramine	204[g]		>58[f]
Cimetidine	450,000[h]	800[h]	33,000[c]
Ranitidine	>100,000[i]	200[i]	>1,200[f]
Tiotidine	>30,000[j]	15[k]	17,000[c]
Burimamide	290,000[l]	7,800[l]	70[f]
Impromidine	Agonist[f]	Agonist[f]	65[f]
Thioperamide	>100,000[m]	>10,000[m]	4.3[m]

* Source of data: [a] Hill and Young (1981), [b] Trendelenburg (1960), [c] Arrang et al. (1985c), [d] Ganellin (1982), [e] Johnson et al. (1979b), [f] Arrang et al. (1983), [g] Hill et al. (1981), [h] Brimblecombe et al (1975), [i] Cavannagh et al. (1983), [j] Donaldson et al. (1988b), [k] Yellin et al. (1979), [l] Black et al. (1972), [m] Arrang et al. (1987a).

† Data from racemic mixture.

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Daly and Price, 1983), famotidine (Takeda et al., 1982; Ganellin, 1985), nizatidine (Lin et al., 1983), and roxatidine (Sewing et al., 1988; Dammann et al., 1988) have followed cimetidine into clinical practice, but the list of compounds available as research tools is very much longer (Ganellin, 1985). Tiotidine is one of the most potent H_2-receptor antagonists available with a K_D value of 15 nM (Yellin et al., 1979; Cavanagh et al., 1983; Trzeciakowski and Levi, 1980) and negligible activity against H_1- and H_3-receptors (table 1). Other H_2-antagonists with K_D values of approximately 10 nM include famotidine (17 nM) (Ganellin, 1985; Takeda et al., 1982), lupitidine (16 nM) (Blakemore et al., 1981), and mifentidine (24 nM) (Donetti et al., 1984), however, the usefulness of these agents as research tools is limited at present because none of them have been evaluated against the H_3-receptor. Similarly, SKF 93319 may prove to be a particularly useful compound, if it is shown to have low potency against the H_3-receptor, because it has similar yet high affinity for both the H_1- (K_D = 21 nM) and H_2- (K_D = 32 nM) receptors (Blakemore et al., 1983; Harvey and Owen, 1984). A number of compounds have been described, notably L-643,441 (Torchiana et al., 1983) and E1309 (Bottomley et al., 1985), that appear to bind irreversibly to the H_2-receptor, and the latter compound has been used successfully to determine H_2-agonist affinities and efficacies in guinea pig right atrium (Bottomley et al., 1985).

The established potent H_2-receptor antagonists generally have a poor ability to cross the blood-brain barrier, and although this property is advantageous for selective actions on peripheral tissues, such as the gastric mucosa, it has limited their utility in the study of the functions of histamine in the CNS. Recently, zolantidine has been reported to be a potent selective brain- penetrating histamine H_2-receptor antagonist (K_D = 25 nM) (Calcutt et al., 1988). However, of all the receptor systems it has been tested against the one notable, and perhaps most important, exception is the H_3-receptor. Further studies are therefore needed before zolantidine can be effectively used to investigate CNS behavioural effects of H_2-receptor stimulation.

4-Methylhistamine was the first agonist described that discriminated between the H_2- and H_1-receptors (Ganellin, 1982). 4-Methylhistamine shows selectivity for the H_2-receptor, having approximately 41% of the potency of histamine as an H_2-agonist in guinea pig right atrium but only a relative potency (histamine = 100) of 0.2 on the H_1-receptor in guinea pig ileum (Ganellin, 1982). However, the discriminative properties of 4-methylhistamine depend very much on the relative concentrations and transducing efficiencies of the different histamine receptors in a given tissue. For example, in guinea pig ileum, where both H_1- and H_2-receptor stimulation can produce contractile activity, the actual concentrations of 4-methylhistamine required for activation of H_2- and H_1-receptors differ by only a factor of 5 (Barker and Hough, 1983).

Both dimaprit (Parsons et al., 1977) and impromidine (Durant et al., 1978) discriminate exceedingly well between H_2- and H_1-receptors. Impromidine is the only analogue with a relative potency greater than histamine itself (table 2), but in addition it possesses marked antagonist potency at histamine H_3-receptors (Arrang et al., 1983). In contrast, dimaprit is devoid of activity at H_3-receptors and is therefore the only compound available for selective stimulation of H_2-receptors.

3. H_3-receptors. As mentioned above the term H_3-receptor was originally coined to explain the atypical pharmacological properties of the autoreceptor controlling histamine release in the CNS. Several existing H_1- and H_2-agonists and antagonists were particularly potent as inhibitors of this H_3-receptor response including impromidine (K_D = 65 nM; H_2-agonist), burimamide (K_D = 70 nM; H_2-antagonist), betahistine (K_D = 6.9 μM; H_1-antagonist), and SKF 91486 (K_D = 88 nM; H_2-antagonist). In the case of the two H_2-receptor antagonists, burimamide and SKF 91486, their affinities for the H_3-receptor were approximately two orders of magnitude higher than their affinities for the H_2-receptor (Arrang et al., 1983; Arrang et al., 1985a). The identity of this novel H_3-receptor has now been confirmed with the development of a selective and competitive H_3-antagonist, thioperamide, which is active in the nanomolar range and which, unlike the above mentioned compounds, can also cross the blood-brain barrier (Arrang et al., 1987a).

Nα-Methylhistamine and Nα-,Nα-dimethylhistamine are both potent H_3-receptor agonists but show little selectivity between the three classes of histamine receptor (Arrang et al., 1983; table 2). A notable feature of the H_3-receptor, however, is that it has stereochemical requirements for agonist binding which are different from those of the other two histamine receptors. This was first observed with the stereoisomers of Nα-methyl-α-chloromethylhistamine and α-Nα-dimethylhistamine which showed a high degree of stereoselectivity for the H_3-receptor (but low agonist activity), whereas the com-

TABLE 2
*Relative potencies of histamine receptor agonists**

Agonist	H_1	H_2	H_3
Histamine	100	100	100
Nα-Methylhistamine	72	74	270
Nα-,Nα-Dimethylhistamine	44	51	170
2-Methylhistamine	16.5	4.4	<0.08
2-Thiazolylethylamine	26	2.2	<0.01
4-Methylhistamine	0.23	43	<0.008
Dimaprit	<0.0001	71	<0.008
Impromidine	<0.001	4810	Antagonist
R-(α)-Methylhistamine	0.5	1.0	1550
S-(α)-Methylhistamine	0.5	1.7	13

* H_1 and H_2 data from Ganellin (1982); H_3 data from Arrang et al. (1983, 1987a, 1985c).

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pounds showed no stereoselectivity for the H_1-receptor and the reverse stereoselectivity on the H_2-receptor (Arrang et al., 1985c). *R*-(α)-methylhistamine is the most potent H_3-agonist available, being at least one order of magnitude more potent than histamine itself (table 2). The *S* isomer, on the other hand, is two orders of magnitude less potent than *R*-(α)-methylhistamine as an H_3-agonist, but the two isomers show no stereoselectivity and very low potency on the other two classes of histamine receptor.

IV. Distribution, Properties, and Functional Characteristics of Three Histamine Receptors

A. Histamine H_1-Receptor

1. *Receptor properties, distribution, and purification.* a. ANTAGONIST RADIOLIGANDS AND DISTRIBUTION OF H_1-RECEPTORS. The study of the distribution and biochemical properties of the histamine H_1-receptor have been greatly aided by the development of radioactive probes for the receptor recognition site. The first H_1-selective radioligand for the H_1-receptor, [^{3}H]mepyramine, was introduced in 1977 (Hill et al., 1977) and used to label H_1-receptors in the longitudinal smooth muscle of guinea pig ileum. This tissue was selected for these preliminary studies because it represented the tissue on which most quantitative pharmacological studies of H_1-receptor antagonism had been performed. [^{3}H]Mepyramine binding in homogenates of the longitudinal smooth muscle-myenteric plexus preparation was characterised by a saturability of specific binding and the dissociation constants determined for a wide range of H_1-receptor antagonists, including the stereoisomers of chlorpheniramine, agreed closely with those determined from studies of contractile activity (Hill and Young, 1981; Hill et al., 1977). Following these initial reports, H_1-receptor binding sites have now been demonstrated using [^{3}H] mepyramine in a wide range of tissues including: mammalian brain (Hill et al., 1978; Hill and Young, 1980; Chang et al., 1979b; Tran et al., 1978; Kanba and Richelson, 1984); retina (Arbones et al., 1986; Sawai et al., 1988); airway (Carswell and Nahorski, 1982; Casale et al., 1985a; Driver and Mustafe, 1987), intestinal (Hill et al., 1977; Hill and Young, 1981), genitourinary (Kondo et al., 1985; Mitsuhashi and Payan, 1988), and vascular (Hide et al., 1988; Chang et al., 1979a) smooth muscle; adrenal medulla (Chang et al., 1979a), liver (Imoto et al., 1985); endothelial cells (Hide et al., 1988); astrocytoma cells (Nakahata et al., 1986); cerebral microvessels (Peroutka et al., 1980); and lymphocytes (Casale et al., 1985b; Cameron et al., 1986). It should be noted, however, that in some tissues [^{3}H]mepyramine additionally binds to secondary non-H_1-receptor sites (Hill and Young, 1980; Hadfield et al., 1983; Chang et al., 1979b).

A number of chemically different antagonist radioligands have been used as probes of the H_1-receptor, although many of them are limited in their utility to particular tissues or species because of significant binding to secondary receptor sites, high nonspecific binding, or species difference in antagonist potencies (see below). [^{3}H]Mianserin (Peroutka and Snyder, 1981) and [^{125}I]7-amino-8-iodoketanserin both have high affinity for 5-HT_2 receptors in addition to histamine H_1-receptors; consequently, their use as H_1-ligands is effectively limited to those tissues (e.g., guinea pig cerebellum) that have low levels of the non-H_1-receptor site. [^{3}H]Doxepin has been used successfully in guinea pig, rat, and human brain (Tran et al., 1981; Kanba and Richelson, 1984; Taylor and Richelson, 1982), but in most cases the binding to brain membranes is complicated by the presence of a substantial amount of a secondary binding component. In addition, the high affinity of doxepin (K_D = 0.1 nM) can lead to problems of interpretation because of a substantial depletion of the free concentration of this antagonist under normal assay conditions (Taylor and Richelson, 1980; Hill, 1987b).

[^{125}I]Iodobolpyramine is a high-affinity (K_D = 0.15 nM) and high-specific activity (2000 Ci/mmol) radioligand which has been developed from mepyramine and which has particular utility as a probe for H_1-receptors in guinea pig brain (Korner et al., 1986). Its slow dissociation rate at 25°C has enabled [^{125}I]iodobolpyramine to be used for detailed autoradiographic mapping of histamine H_1-receptors in the guinea pig CNS (Bouthenet et al., 1988). Unfortunately, it has not been possible to demonstrate H_1-receptor-specific binding of [^{125}I]iodobolpyramine in rat brain membranes or tissue sections (Korner et al., 1986). The reason for this is unclear, but it may be a consequence of high nonspecific binding and the lower affinity of the ligand in rat brain (Korner et al., 1986). Autoradiographic analysis of H_1-receptors in rat brain has been possible, however, with [^{3}H]mepyramine (Palacios et al., 1981a,b) which has a very slow dissociation rate from the H_1-receptor when cooled to 4°C (Wallace and Young, 1983). [^{3}H]Mepyramine has also been used in autoradiographic studies of primate spinal cord (Ninkovic et al., 1982), guinea pig cerebellum (Palacios et al., 1981a; Palacios et al., 1979), and the cerebellum of various mutant mouse strains (Rotter and Frostholm, 1986).

Two other H_1-receptor ligands have been developed recently which may prove very useful research tools. [^{125}I] Iodoazidophenpyramine is a potent H_1-antagonist derived from mepyramine which upon ultraviolet irradiation covalently binds to H_1-receptor proteins (Ruat et al., 1988). At 25°C and in the dark [^{125}I]iodoazidophenpyramine binds selectively and competitively to the H_1-receptor in guinea pig cerebellar membranes with a K_D value of 0.01 nM, which makes it one of the most potent H_1-receptor antagonists available. [^{3}H](+)-N-Methyl-4-methyldiphenhydramine is a quarternary radioligand that has potential for use in labeling H_1-receptors in intact cells (Treherne and Young, 1988c). It has a high

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affinity for the H_1-receptor in guinea pig brain (K_D = 0.88 nM) and a lower affinity for muscarinic receptors (K_D = 90 nM), although in those tissues with a large concentration of muscarinic receptors a selective muscarinic antagonist may have to be included in the incubation medium (Treherne an Young, 1988c).

b. RECOGNITION SITE PROPERTIES AND PURIFICATION. A notable feature of binding studies with radioactive H_1-receptor antagonists in mammalian brain membranes is that there are striking species differences in the antagonist potencies and the regional distribution of H_1-receptor-binding sites (Hill, 1987b). For example, in guinea pig brain the highest density of H_1-receptors is found in cerebellum (Hill et al., 1978; Chang et al., 1979b), whereas in many other species, including man, this region is characterised by a relatively low H_1-receptor density (Chang et al., 1979b; Hill and Young, 1980; Taylor et al., 1982; Bielkiewicz and Cook, 1985; Kanba and Richelson, 1984).

The difference in binding potencies of a range of H_1-receptor antagonists for the H_1-receptor in guinea pig and rat brain is illustrated in table 3. The K_D values obtained in rat brain for some, but not all, antagonists are quite different from those obtained in the guinea pig from binding studies in brain homogenates (table 3), functional studies in guinea pig brain slices (Hill et al., 1981; Daum et al., 1984; Donaldson and Hill, 1985; Hill, 1987b), or both binding and contractile studies in guinea pig ileum (Hill and Young, 1981). In most respects, however, the characterisitics of [^{3}H]mepyramine binding in rat brain are those expected of an H_1-receptor, and where they have been determined, the K_D values for H_1-receptor antagonists determined from functional responses to H_1-receptor stimulation in this tissue agree reasonably well with the binding values (Brown et al., 1984; Claro et al., 1986, 1987). Similar differences (compared with guinea pig tissues) in H_1-receptor antagonist properties have been reported in other species including man (Chang et al., 1979b; Kanba and Richelson, 1984), rabbit (Chang et al., l979b, Al-Gadi and Hill, 1985), and monkey brain (Bielkowicz and Cook, 1985). These species differences are not restricted to central tissues and low-affinity binding constants for H_1-receptor antagonists have been reported in rat liver (Imoto et al., 1985), porcine trachea (Driver and Mustafe, 1987), and rabbit aorta (O'Neill and Patil, 1975; Fleisch et al., 1974). In the case of two smooth muscle cell lines (DDT_1MF-2 and BC3H1) the K_D values for mepyramine are nearly two orders of magnitude greater than those obtained in guinea pig tissues (i.e., 276 and 219 nM) (table 3) (Mitsuhashi and Payan, 1988a, 1989a), and yet functional H_1-receptor responses, sensitive to inhibition by H_1-antagonists of approximately 100 nM, can be clearly demonstrated in these cell lines (Mitsuhashi and Payan, 1988a,b; Brown et al., 1986b). The above observations, taken together, suggest that there are differences in the structural identity or membrane environment of H_1-receptors in different tissues and species (Hill, 1987b).

TABLE 3
*Heterogeneity of antagonist binding to histamine H_1-receptors**

Antagonist	K_D(nM)		
	Guinea pig brain	Rat brain	DDT_1-MF-2 and BC3H1 cells
Mepyramine	0.8	9.1	276
Triprolidine	0.2	5.6	3800
(+)-Chlorpheniramine	0.8	9.1	1000; 100†
(−)-Chlorpheniramine	200	500	10,000
Doxepin	0.1	0.1	900
Promethazine	1.4	1.8	
Temelastine	0.9	32.5	
(+)-N-Methyl-4-methyldiphenhydramine	0.9	7.0	
Bolpyramine	1.2	5.4	
Diphenhydramine	13	17	1000†

* Data from Hill and Young (1980), Aceves et al. (1985), Brown et al. (1986a, b), Korner et al. (1986), Treherne and Young (1988c), Toll and Snyder (1982), Chang et al. (1979), Mitsuhashi and Payan (1988a, 1989a).
† Data from inhibition of functional responses.

Solubilisation of the H_1-receptor protein from both guinea pig and rat brain membranes has been achieved with digitonin (Gavish et al., 1979; Toll and Snyder, 1982; Garbarg et al., 1985; Treherne and Young, 1988a). In these studies the species difference in H_1-antagonist properties between rat and guinea pig is retained in the solubilised preparation, suggesting that there are real differences in the receptor proteins rather than the membrane environment of the receptors (Toll and Snyder, 1982). The molecular mass of the digitonin-solubilised H_1-receptor protein in guinea pig brain, determined from sucrose-gradient centrifugation and gel filtration, was 430 kDa, but it is quite likely that digitonin molecules in the complex represented about 240 kDa of this molecular mass (Toll and Snyder, 1982). Radiation inactivation target size analysis of the H_1-receptor in bovine and human cerebral cortex agrees with this estimate and puts the molecular size of the H_1-receptor protein at 160 kDa (Kuno et al., 1985). A similar estimate has been made by target size analysis in rat liver (160 kDa), although in guinea pig liver the value is notably lower (107 kDa) (Wang et al., 1986).

Studies with the irreversible photoaffinity label [^{125}I] idoazidophenpyramine using sodium dodecyl sulphate/polyacrylamide gel electrophoresis analysis have provided the most convincing data concerning the molecular size of the H_1-receptor in guinea pig cerebral cortex (Ruat et al., 1988). Under reducing conditions, this ligand specifically labels two peptides with molecular masses of 47 to 49 and 55 to 59 kDa, the latter being generated by hydrolysis of the former (Ruat et al., 1988). However, under nonreducing conditions (i.e., in the absence of 2-mercaptoethanol), a higher molecular weight protein is labeled with an apparent molecular mass of 350 to 400 kDa (Ruat et al., 1988). It is, therefore, tempting to

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speculate that H_1-receptor-binding site may be linked to other protein subunits by one or more disulphide bonds (see below). A comparison of the electrophoretic mobilities of photoaffinity-labeled H_1-receptors from several guinea pig brain regions and rat, mouse, and pig brain revealed only two specifically labeled bands with molecular masses of 41 to 47 and 56 kDa, respectively (Ruat and Schwartz, 1989). Thus, there is no obvious physicochemical difference in the H_1-receptors to explain the species-dependent heterogeneity of antagonist-binding properties referred to above.

In BC3H1 cells, where the binding affinity of H_1-receptor antagonists varies with their morphological state, [^{3}H]mepyramine binding to H_1-receptor-binding proteins has been measured following their elution from sodium dodecyl sulphate/polyacrylamide gels (Mitsuhashi and Payan, 1989a). Differentiated cells (which show high-affinity H_1-antagonist binding) exhibit a single N-glycosylated H_1-binding protein with a molecular mass of 68 kDa. In contrast, in undifferentiated cells, where the binding of antagonists has much lower affinity, an additional binding protein which is not glycosylated can be deduced with a molecular mass of 40 kDa (Mitsuhashi and Payan, 1989a). These data suggest that different states of receptor glycosylation may contribute to the heterogeneity of H_1-receptor-binding properties. Interestingly, Garbarg et al. (1985) have shown that the H_1-receptor in guinea pig cerebellum is N-glycosylated.

The low-affinity H_1-receptor in DDT_1MF-2 cells, which express a large number of H_1-receptors (approximately 10^7 receptors/cell), has been solubilised and purified to homogeneity by sequential gel filtration, chromatofocusing, and reversed phase high-pressure liquid chromatography (Mitsuhashi and Payan, 1989b). The calculated molecular weight of the purified protein is 38 to 40 kDa on sodium dodecyl sulphate polyacrylamide gel electrophoresis. This is smaller than the H_1-receptor protein detected in brain (Ruat et al., 1988) but similar to the nonglycosylated H_1-receptor in BC3H1 cells (Mitsuhashi and Payan, 1989a) which has a similar low affinity (K_D approximately 280 nM) for mepyramine to that observed in DDT_1MF-2 cells (Mitsuhashi and Payan, 1988a, 1989b). The purified protein retains the same H_1-receptor profile as the intact cells and has a calculated number of [^{3}H]mepyramine-binding sites of 31 pmol/μg protein, which suggests that one molecule of mepyramine binds to one molecule of the purified 38 to 40 kDa protein (Mitsuhashi and Payan, 1989b).

The exact structure of the H_1-receptor awaits the the determination of the amino acid sequence of this purified protein and the application of molecular biological techniques, but one can predict that it will most likely resemble that of other receptors coupled to intracellular messenger production (e.g., the β-adrenoceptors and muscarinic receptors) and comprise seven transmembrane loops (Dohlman et al., 1987; Bonner et al., 1987; Frielle et al., 1988). In the case of the β_2-receptor, the ligand-binding site appears to be located within one of the hydrophobic domains of the receptor protein (Strader et al., 1987; Dixon et al., 1987). This raises the possibility that the H_1-antagonist-binding site is also within some hydrophobic portion of the receptor. In this respect, it is interesting that hydrophobic interactions may play a significant role in the kinetics of binding of [^{3}H]mepyramine to the H_1-receptor in guinea pig brain (Treherne et al., 1988b). The rate constants for receptor association and dissociation of [^{3}H]mepyramine are notably temperature dependent (Wallace and Young, 1983; Treherne and Young, 1988b). For example, at 4°C the dissociation of [^{3}H]mepyramine from H_1-receptors is negligible during a 120-min period (Wallace and Young, 1983), whereas at 37°C it is very fast (Treherne and Young, 1988b). A similar apparent change in H_1-antagonist kinetic properties has been observed in contractile studies in guinea pig ileum (Cook et al., 1985).

C. CHARACTERISTICS OF H_1-AGONIST BINDING. A range of H_1-agonists has been shown to inhibit [^{3}H]mepyramine binding in membranes prepared from guinea pig cerebral cortex (Daum et al., 1982), guinea pig intestinal smooth muscle (Hill and Young, 1981), and porcine tracheal smooth muscle (Driver et al., 1987). In general, agonist binding is characterised by a relatively low affinity. For example the binding affinity of histamine for the H_1-receptor in the longitudinal smooth muscle of guinea pig ileum is 5.7×10^4 M^{-1} (Donaldson and Hill, 1987), which agrees well with the value of 1.8×10^5 M^{-1} determined indirectly from contractile studies using an irreversible antagonist (Donaldson and Hill, 1987). The composition of the incubation medium can have a marked effect on the binding properties of H_1-agonists while producing negligible effect on H_1-antagonist binding (Chang and Snyder, 1980). Sodium ions (100 mM) decrease the binding affinity of H_1-agonists by one order of magnitude, whereas the divalent cations, magnesium and manganese (both at 1 mM), increase agonist affinity (Chang and Snyder, 1980). An involvement of a guanine nucleotide regulatory G protein in H_1-receptor transduction processes is suggested by the ability of guanine nucleotides to decrease the binding affinity of histamine in guinea pig brain membranes, histiocytic lymphoma cells and human astrocytoma cells (Chang and Snyder, 1980, Nakahata et al., 1986; Driver et al., 1989). In the human astrocytoma cell line 1321N1, this effect of guanine nucleotides was accompanied by an increase in the slope parameter (Hill slope), from a value less than unity (indicative of a heterogeneity of binding) to a value not significantly different from unity (i.e., indicative of simple mass action kinetics) (Nakahata et al., 1986). This was not prevented by pertussis toxin treatment, which suggests that the G protein involved is not related to G_1 (Nakahata et al., 1986).

An involvement of disulphide bonds in H_1-receptor

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structure and function has been alluded to earlier (see above). The possibility that the H_1-receptor-binding subunit might be coupled to other protein components in guinea pig brain (Ruat et al., 1988) is supported by the fact that the disulphide bond-reducing agent, 1,4-dithiothreitol (DTT), can modify agonist (but not antagonist) binding and histamine-induced second-messenger formation in both guinea pig cerebral cortex and cerebellum (Donaldson and Hill, 1986a,b). In addition, DTT has been shown to potentiate H_1-receptor-mediated contractile activity in both visceral (Donaldson and Hill, 1986d) and vascular smooth muscle (Fleisch et al., 1973, 1974; Carroll and Glover, 1977). These effects of DTT on H_1-agonist action are specific to the H_1-receptor because a similar potentiation of agonist activity is not observed with other smooth muscle spasmogens or agents that increase second-messenger formation in guinea pig brain (Fleisch et al., 1973; Donaldson and Hill, 1986b; Donaldson and Hill 1986d).

A detailed analysis of the effect of DTT on functional responses in both smooth muscle and guinea pig brain slices indicates that the potentiation is due to an increase in both agonist affinity and agonist efficacy (Donaldson and Hill, 1986b; Donaldson and Hill, 1987). The change in H_1-agonist affinity induced by DTT is also observed in binding studies with [^{3}H]mepyramine in both of these tissues (Donaldson and Hill, 1986a; 1987; Carmen-Krzan, 1984). It remains to be established, however, whether the effects of DTT on agonist efficacy and affinity are a consequence of common or different mechanisms. For example, one possibility is that DTT may increase the coupling between the receptor and a G protein, leading to an increase in both agonist affinity and efficacy (Donaldson and Hill, 1986b). The binding data obtained in brain membranes would be consistent with this hypothesis because the effect of DTT was accompanied by a reduction in the Hill coefficient (Donaldson and Hill 1986a). Alternatively, the increase in efficacy may be unrelated to the change in agonist affinity and arise from an effect of DTT on a more distal, yet still early (given the selectivity of action on H_1-responses), stage of the stimulus-response process.

The thiol-alkylating agent, N-ethylmaleimide, has a similar effect to DTT on [^{3}H]mepyramine binding in guinea pig brain membranes in that it reduces the IC_{50} values obtained for H_1-agonists without altering the specific binding site capacity or equilibrium dissociation constant of mepyramine (Yeramian et al., 1985). This effect is accompanied by a decrease in the Hill coefficient, indicating a heterogeneity of agonist binding. Two-site analysis of H_1-agonist binding in brain membranes suggests that both N-ethylmaleimide and DTT stabilise a proportion of the H_1-binding sites in a high-affinity state (Yeramian et al., 1985; Donaldson and Hill, 1986a). These data suggest that disulphide-sulphydryl exchange may be involved in the conformational changes induced by H_1-agonists such that either alkylation of sulphyryl groups or reduction of disulphide bonds can stabilise these sites in a reduced (high-affinity) state.

2. Interactions with membrane transduction processes. a. INOSITOL PHOSPHOLIPID HYDROLYSIS. Stimulation of a wide range of cell surface receptors leads to an increase in the intracellular level of calcium ions. An early event that has been reported to be associated with the activation of all calcium-mobilising receptors is the hydrolysis of membrane inositol phospholipids (Michell, 1977; Berridge, 1984; Berridge and Irvine, 1984; Berridge, 1987; Downes, 1986; Abdel-Latif, 1986). In most tissues, receptor stimulation leads to the hydrolysis of phosphatidylinositol-4–5-bisphophate leading to the formation of inositol-1,4,5-trisphosphate (IP_3) and 1,2-diacylglycerol (DG) (Berridge, 1984; Berridge and Irvine, 1984; Berridge, 1987; Abdel-Latif, 1986). Inositol-1,4,5-trisphophate, which is released into the cytosol, has been shown to mobilise calcium from intracellular stores (Berridge, 1987), whereas 1,2-diacyglycerol, which is retained within the membrane environment, activates protein kinase C (Nishizuka, 1984, 1986; Berridge, 1987). In many tissues, formation of inositol-1,3,4,5-tetrakisphosphate from inositol-1,4,5-trisphosphate occurs (Batty et al., 1985; Tennes et al., 1987), and this molecule may have a role in controlling calcium influx and refilling of the intracellular stores (Irvine and Moore, 1986; Morris et al., 1987; Berridge, 1987; Berridge and Irvine, 1989).

i. Histamine-stimulated inositol phospholipid hydrolysis. Initial indirect studies of histamine-stimulated incorporation of [^{32}P]P_i into membrane inositol phospholipids in rat brain (Friedel and Schanberg, 1975; Subramanian et al., 1980, 1981) and guinea pig ileum (Jafferji and Michell, 1976a,b) indicated that histamine could stimulate the breakdown of membrane inositol phospholipids. This was later confirmed using the more direct measure of [^{3}H]inositol phosphate accumulation in the presence of lithium ions, which inhibits inositol monophosphatase, following prelabeling of tissues with [^{3}H]myoinositol (Berridge et al., 1982; Brown et al., 1984; Daum et al., 1983, 1984).

In guinea pig brain slices, the regional distribution and pharmacological characteristics of the inositol phosphate response to histamine closely parallels that of the histamine H_1-receptor (Daum et al., 1983, 1984; Donaldson and Hill 1985, 1986b). Thus, guinea pig cerebellum contains the largest inositol phospholipid response to histamine, and this is selectively inhibited by H_1-receptor antagonists with K_D values similar to those determined on other H_1-receptor-mediated responses (Daum et al., 1984; Donaldson and Hill, 1985). Similar H_1-receptor-mediated responses have also been detected in rat cerebral cortex (Brown et al., 1984; Claro et al., 1986, 1987) and mouse cerebral cortex (Kendall and Hill, 1988).

Studies in both guinea pig and mouse brain slices have shown that histamine can stimulate the formation of

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inositol mono-, bis-, tris-, and tetrakisphosphates in lithium-containing media (Donaldson and Hill, 1986c; Carswell et al., 1985; Whitworth and Kendall, 1988). Under these conditions, after 10-min incubation most of the inositol trisphosphate fraction contains inositol-1,3,4-trisphosphate which results from metabolism of the tetrakisphosphate (Whitworth and Kendall, 1988). In the absence of lithium, however, the increase in all four inositol phosphates is reduced (Whitworth and Kendall, 1988). This contrasts with the data obtained following muscarinic receptor stimulation in the same tissue where the accumulation of inositol-1,3,4,5-tetrakisphosphate is markedly larger in the absence of lithium (Whitworth and Kendall, 1988). The simplest explanation of this is that histamine H_1- and muscarinic receptors may stimulate different pathways of inositol phospholipid metabolism. This contention is supported indirectly by the observed differences between the inositol phospholipid responses to these two receptor systems in their sensitivity to temperature (Carswell et al., 1987), extracellular calcium (Kendall and Nahorski, 1984; Carswell et al., 1985), and modulation by other receptor systems or potassium depolarisation (Hollingsworth et al., 1986; Hill and Kendall, 1987; Kendall and Hill, 1988; Eva and Costa, 1986).

Analysis of the concentration-response relations for H_1-receptor agonists in different regions of guinea pig brain suggests that there may be a spare receptor reserve in guinea pig cerebellum but not in cerebral cortex (Carswell and Young, 1986). Thus, although the EC_{50} value for histamine-induced inositol phospholipid hydrolysis in guinea pig cerebellum is lower than the K_D value obtained from binding studies, the values in guinea pig cerebral cortex are similar (Carswell and Young, 1986). A similar conclusion can be drawn from data obtained with 2-methylhistamine, $N\alpha$-$N\alpha$-dimethylhistamine, and 2-pyridylethylamine. In both brain regions these compounds act as partial H_1-agonists on inositol phospholipid hydrolysis; however, in cerebellum the maximum response they elicit (with respect to histamine) is very much larger (Carswell and Young, 1986; Donaldson and Hill, 1986b). Evidence for a lack of a spare receptor reserve in the H_1-receptor-mediated inositol phospholipid response to histamine has also been obtained in rat cerebral cortex (Claro et al., 1986) and human astrocytoma cells (Nakahata et al., 1986).

The interaction between histamine H_1-receptor stimulation and phospholipase C has been proposed to involve a guanine nucleotide-binding protein (Donaldson and Hill, 1986b; Taylor and Merritt, 1986; Litosch, 1989; Berrie et al., 1989). Direct evidence for this has been recently provided by Claro et al. (1989) who demonstrated an H_1-stimulation of inositol phospholipid hydrolysis in rat cerebral cortical membranes. In this study, histamine potentiated the response to guanosine 5′-triphosphate (GTP)-(γ)-S in the presence of magnesium adenosine 5′-triphosphate and low Ca^{2+}, but the effect was only observed when 1 mM deoxycholate was included in the incubation medium. A similar, but much smaller, histamine response has also been observed in membranes from 1321N1 cells in the absence of deoxycholate (Orellana et al., 1987).

Histamine-stimulated inositol phospholipid hydrolysis has been demonstrated in a number of peripheral tissues, including canine and bovine trachea (Grandory et al., 1987; Hall and Hill, 1988; Hall et al., 1989; Madison and Brown, 1988), bovine adrenal chromaffin cells (Plevin and Boarder, 1988; Noble et al., 1986), human umbilical endothelial cells (Lo and Fan, 1987; Resink et al., 1987; Pollock et al., 1988), guinea pig ileum (Donaldson and Hill, 1985; Best et al., 1985; Mallows and Bolton, 1987; Bielkiewicz-Vollrath et al., 1987), guinea pig bladder (Iacavou et al., 1988), and guinea pig aorta (Lonchampt et al., 1988). In most of these tissues, pharmacological characterisations of the inositol phospholipid response to histamine is consistent with an H_1-receptor-mediated response. However, in the longitudinal smooth muscle-myenteric plexus preparation of guinea pig ileum, the situation is more complex (Donaldson and Hill, 1985, 1986c). Although data obtained with 2-pyridylethylamine in this tissue suggest that there is an H_1-receptor-mediated inositol phosphate response, the H_1-response to histamine itself appears to be masked by a larger mepyramine-insensitive component (Donaldson and Hill, 1985, 1986c).

A similar observation has been made in neonatal rat brain (Claro et al., 1987). The exact mechanism underlying this non-H_1-receptor effect is unclear, but it may be secondary to neurotransmitter release (e.g., from the myenteric plexus) produced by the indirect tyramine-like action of histamine which has been observed at high concentrations of agonist (Young et al., 1988b). Consistent with this hypothesis is the fact that the histamine-induced inositol phosphate response in guinea pig ileum is sensitive to inhibition by the tachykinin antagonist, [D-Pro^4,D-Trp^{7,9,10}] substance P-(4–11) (Baily et al., 1987).

An increasing number of studies have also been performed in cultured cells, and histamine-H_1-receptor-stimulated inositol phospholipid hydrolysis has now been demonstrated in human astrocytoma cells (Nakahata et al., 1986; Nakahata and Harden, 1987), rat brain primary astrocytes (Pearce and Murphy, 1988; Arbones et al., 1988), rat cerebellar granule cells (Xu and Chuang, 1987; Dillon-Carter and Chuang, 1989), NG108–15 cells (Tohda and Namura, 1989), and N1E-115 cells (Oakes et al., 1988). In both NG108–15 and 1321N1 cells, the H_1-receptor-stimulated inositol phospholipid hydrolysis has been shown to be insensitive to pertussis toxin pretreatment (Tohda and Nomura, 1989; Nakahata et al., 1986).

ii. Histamine-induced calcium mobilisation. One

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of the physiological consequences of producing a raised intracellular level of inositol-1,4,5-trisphosphate is mobilisation of intracellular calcium. Although only small rises in the actual level of inositol-1,4,5-trisphosphate following H_1-receptor stimulation have been demonstrated in a number of tissues (Pollock et al., 1988; Whitworth and Kendall, 1988; Bielkiewicz-Vollrath et al., 1987), the larger accumulations of the metabolites inositol-1,3,4-trisphosphate and inositol-1,4-bisphosphate suggest that the flux through inositol-1,4,5-trisphosphate may be quite large. A release of calcium from intracellular stores by histamine H_1-receptor stimulation has been demonstrated in endothelial cells (Pollock et al., 1988; Jacob et al., 1988), airway smooth muscle (Kotlikoff et al., 1987; Takuwa et al., 1987), rat aorta (Matsumoto et al., 1986), BC3H1 cells (Brown et al., 1986b), and 1321N1 astrocytoma cells (McDonough et al., 1988), although in most cases there is also an appreciable stimulation of transmembrane calcium influx. In differentiated N1E-115 neuroblastoma cells, most of the calcium signal appears to be secondary to an influx of extracellular calcium (Oakes et al., 1988).

Measurement of the effects of H_1-receptor stimulation on intracellular calcium in single endothelial cells has revealed repetitive spiking calcium transients whose frequency is dependent upon the concentration of histamine (Jacob et al., 1988). Oscillatory activation of calcium-dependent potassium channels by H_1-receptor stimulation has also been noted in HeLa cells (Sauve et al., 1987). These studies have shown that this phenomenon is due to release of intracellular calcium because single-channel recordings were made in a patch electrode that contained no histamine (ruling out a direct interaction with the potassium channel) and could be initiated in calcium-free media (Suave et al., 1987). The mechanism underlying these oscillations in intracellular calcium concentration remains to be established, but several possibilities have been put forward (Jacob et al., 1988; Berridge and Irvine, 1989).

The mobilisation of intracellular calcium by histamine can be desensitised in homologous fashion (at the level of the receptor) by prior H_1-agonist exposure (Brown et al., 1986b; Hishinuma and Uchida, 1988; Dillon-Carter and Chuang, 1989; Mitsuhashi and Payan, 1988a) or by prior exposure with an agonist of a receptor that mobilises calcium from the same intracellular pool (heterologous desensitisation) (Hishinuma and Uchida, 1988; McDonough et al., 1988; Brown et al., 1986b). The mobilisation of intracellular calcium by histamine in airway smooth muscle can be prevented by phorbol esters which activate protein kinase C (Kotlikoff et al., 1987; Murray et al., 1989), and it has been suggested that protein kinase C may produce desensitisation at the level of the histamine H_1-receptor (Mitsuhashi and Payan, 1988b).

iii. Modulation by other receptor systems. A notable feature of the inositol phosphate response to histamine in brain slices is that it is very sensitive to modulation by activation of receptors, which themselves do not stimulate phosphoinositide hydrolysis (Hill and Kendall, 1989; Linden and Delahunty, 1989). This was first observed in guinea pig cerebral cortex where adenosine receptor stimulation selectively augments the inositol phosphate response to histamine (Hollingsworth et al., 1986; Hill and Kendall, 1987). The pharmacological classification of the adenosine receptor involved is unclear, but recent data suggest that it is not the A_2-receptor responsible for stimulating cyclic adenosine 5′-monophosphate (AMP) accumulation in this tissue (Hill and Kendall, 1987; Alexander et al., 1989).

In mouse cerebral cortex, human cerebral cortex, and rat striatum, adenosine receptor agonists *inhibit* rather than augment the inositol phospholipid hydrolysis elicited by histamine (Kendall and Hill, 1988; Kendall and Firth, 1989; Petcoff and Cooper, 1987). The inhibitory response to adenosine in mouse cerebral cortex, where the only detailed pharmacological analysis has been performed, has a similar specificity for H_1-induced inositol phospholipid hydrolysis and is pharmacologically indistinguishable from the response in guinea pig cerebral cortex (Hill and Kendall, 1987; Kendall and Hill, 1988; Alexander et al., 1989). Inhibition of histamine-induced inositol phospholipid hydrolysis has also been demonstrated in rat cerebral cortex following stimulation of γ-aminobutyric acid receptors (Crawford and Young, 1988) and in rat hippocampus by excitatory amino acids (Baudry et al., 1986). The excitatory amino acid N-methylaspartic acid was able to additionally inhibit the inositol phosphate responses to carbachol and potassium depolarisation (Baudry et al., 1986), whereas γ-aminobutyric acid produced no effect on muscarinic receptor-mediated responses (Crawford and Young, 1988). The mechanism underlying these augmentation and inhibitory effects remains to be established, but the possibilities include (*a*) the presence of an inhibitory G protein (Linden and Delahunty, 1989; Hill and Kendall, 1989) coupled to phospholipase C, (*b*) a receptor-receptor interaction analogous to the γ-aminobutyric acid-benzodiazepine relationship (Costa and Guidotti, 1979), and (*c*) the intermediacy of another second messenger such as cyclic AMP (Hill and Kendall, 1989) (fig. 1).

Cyclic AMP does not appear to be involved in the modulatory effects of adenosine in the CNS (Alexander et al., 1989) but almost certainly accounts for the inhibition of the H_1-inositol phosphate response by β_2-adrenoceptor stimulation in bovine and canine tracheal smooth muscle (Hall and Hill, 1988, Hall et al., 1989; Madison and Brown, 1988) (fig. 2). Thus, the histamine-stimulated accumulation of inositol phosphates can be inhibited by a range of agents that increase cyclic AMP levels in these tissues, including forskolin, vasoactive intestinal polypeptide, and cyclic AMP phosphodiesterase inhibitors or mimic the action of cyclic AMP, e.g.,

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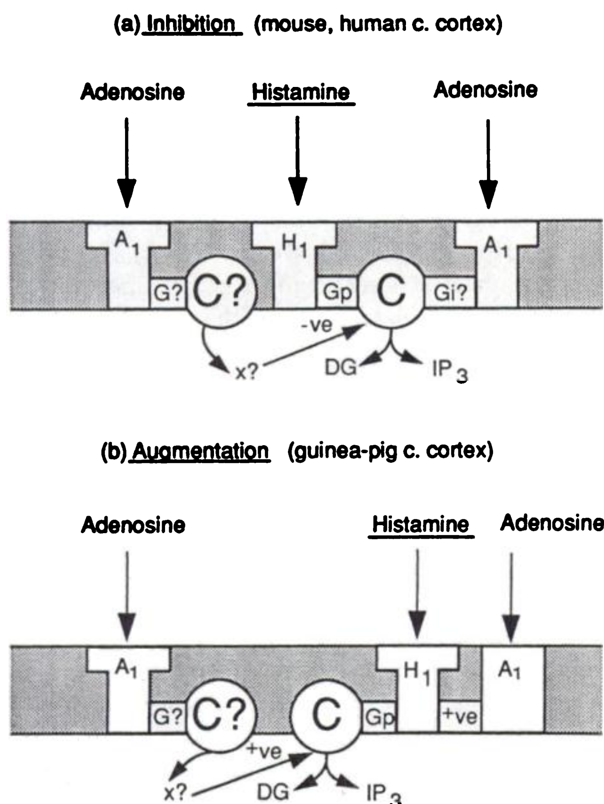

FIG. 1. Potential mechanisms contributing to (a) the inhibition or (b) the augmentation of histamine-stimulated inositol phospholipid hydrolysis in mouse, guinea pig, or human cerebral cortical slices. a, Inhibition may be mediated via the generation of an inhibitory second messenger (x) or by the action of an inhibitory adenosine receptor-coupled G_i protein acting directly on phospholipase C. b, Augmentation may be mediated via the generation of an intracellular second messenger (x) or by a positive interaction between the two receptors concerned. −ve, negative interaction site; +ve, positive interaction site.

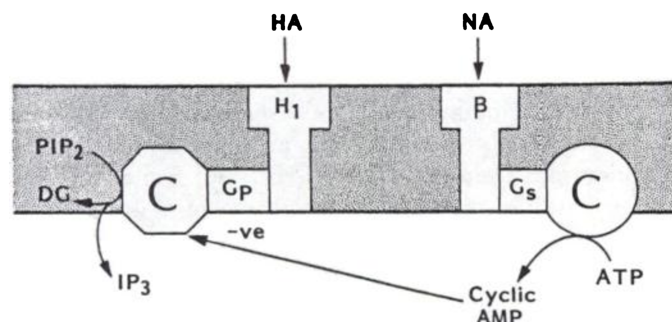

FIG. 2. Inhibition of histamine-stimulated inositol phospholipid hydrolysis by β-adrenoceptor stimulation in bovine tracheal smooth muscle. Abbreviations: PIP_2, phosphatidylinositol-4,5-bisphosphate; Gp, G protein coupled to phospholipase C; HA, histamine; NA, noradrenaline; Gs, stimulatory G protein coupled to adenylate cyclase; C, enzyme catalytic unit.

membrane-permeant analogues of cyclic AMP (Hall et al., 1989; Madison and Brown, 1988). However, in keeping with the suggestion raised above that muscarinic receptors may stimulate different pathways of inositol phospholipid metabolism, the inositol phosphate response to carbachol was relatively resistant to the effects of raised cyclic AMP levels in both bovine and canine tracheal smooth muscle (Hall and Hill, 1989a; Madison and Brown, 1988).

b. CONTROL OF ION CHANNELS. The effect of histamine H_1-receptor stimulation on the opening of plasma membrane ion channels is an area in which little, and often indirect, evidence is available. Most information has come from studies of the calcium dependence of histamine-induced contractile activity in various smooth muscle preparations, particularly guinea pig intestinal smooth muscle. Histamine can initiate smooth muscle contraction by releasing calcium from intracellular stores (see above) or by opening either receptor-operated or voltage-operated calcium channels (Bolton, 1979).

In intestinal smooth muscle, histamine can activate ion channels permeable to Na^+, K^+, and probably Ca^{2+} leading to depolarisation, an increase in action potential discharge, and smooth muscle contraction (Bolton et al., 1981; Bolton and Clark, 1981). It seems likely that the depolarisation produced (approximately 35 mV; Bolton et al., 1981) is sufficient to open voltage-operated calcium channels which are at least partly responsible for smooth muscle contraction, because histamine-induced contractions can be inhibited by dihydropyridine antagonists such as nifedipine and potentiated by Bay K 8644 (Morel et al., 1987). Dihydropyridine-sensitive calcium channels also appear to contribute to the histamine H_1-receptor-mediated contractile response of human airway smooth muscle (Drazen et al., 1983; Horio et al., 1984; Raeburn et al., 1986; Black et al., 1986; Marthan et al., 1987). The exact nature and mechanism underlying the histamine H_1-receptor-stimulated inward current remains to be elucidated by patch-clamp analysis. However, studies of the muscarinic receptor-stimulated inward current in intestinal smooth muscle, which is very similar to the H_1-induced current (Bolton et al., 1981), suggests that it may be regulated by a calcium-dependent rather than G protein-mediated mechanism (Lim and Bolton, 1988). The raised intracellular calcium concentration in these cells is accompanied by discharge of spontaneous outward currents due to stimulation of calcium-activated potassium channels (Bolton and Lim, 1989; Komori and Bolton, 1989). An activation of calcium-dependent potassium channels following H_1-receptor stimulation has recently been demonstrated in single-cell measurements of differentiated N1E-115 neuroblastoma cells, where raised intracellular calcium appears to arise predominantly from calcium influx via receptor-operated channels (Oakes et al., 1988), and HeLa cells, where calcium is released predominantly from intracellular stores (Sauve et al., 1987).

A study of histamine-induced inward currents using patch-clamp has been described in human endothelial cells (Bregestovski et al., 1988). In these cells the inward current appears to involve activation of cationic channels that require extracellular calcium and are activated by raised intracellular levels of calcium. At the present time

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it seems likely that histamine may activate these channels by inducing a release of intracellular calcium subsequent to a rise in inositol trisphosphate levels (Resink et al., 1987: Pollock et al., 1988), because bath-applied histamine was able to evoke channel activity in cell-attached patches without histamine in the pipette (Bregestovski et al., 1988).

In guinea pig left atria, histamine H_1-receptor stimulation causes a prolongation of action potential duration and an increase in the force of contraction which is composed of initial and late-developing components (Amerinin et al., 1982; Borchard and Hafner, 1986; Hattorri et al., 1988a). The prolongation of action potential duration appears to be produced by an H_1-receptor-mediated decrease in outward potassium currents (Hattorri et al., 1988a). The second component of the positive inotropic effect of H_1-receptor stimulation is sensitive to inhibition by dihydropyridine calcium channel antagonists and nickel, but Hattorri et al. (1988a) proposed that this may be secondary the inhibition of outward potassium currents and prolongation of the action potential by H_1-receptor stimulation. The initial component of the positive inotropic response was insensitive to calcium channel blockade and is almost certainly a consequence of increased inositol phospholipid hydrolysis in guinea pig left atria (Sakuma et al., 1987, 1988) and inositol-1,4,5-trisphosphate-induced release of Ca^{2+} from cardiac sarcoplasmic reticulum (Nosek et al., 1986).

C. MODULATION OF CYCLIC AMP ACCUMULATION. **i. Augmentation.** Histamine is one of the most potent stimulants of cyclic AMP accumulation in guinea pig and rabbit brain slices (Daly, 1977; Hill et al., 1981; Daum et al., 1982; Kakiuchi and Rall, 1968; Al-Gadi and Hill, 1985, 1987). This elevation of cyclic AMP levels produced by histamine appears to involve two separate mechanisms. Histamine can stimulate adenylate cyclase directly via H_2-receptors (see below) or it can augment the cyclic AMP responses to histamine H_2-, vasoactive intestinal polypeptide-, or adenosine A_2-receptor stimulation via an activation of histamine H_1-receptors (Al-Gadi and Hill, 1985, 1987; Palacios et al., 1978a; Hill et al., 1981; Magistretti and Schorderet, 1985; Hollingsworth and Daly, 1985; Gannon and Hough, 1988; Gannon et al., 1989; Garbarg and Schwartz, 1988; Hill and Kendall, 1989; Hill, 1987b) (fig. 3).

The first evidence for an involvement of both H_1- and H_2-receptors in the cyclic AMP response to histamine was obtained in guinea pig hippocampal slices (Palacios et al., 1978a). Data obtained with selective H_2-receptor antagonists were consistent with competitive antagonism of a single homogenous class of H_2-receptors. Thus, all H_2-antagonists tested produced parallel displacements of histamine dose-response curves (Palacios et al., 1978a). However, when selective H_1-receptor antagonists were used a more complex picture emerged. In hippocampal slices, the concentration-response curve for histamine

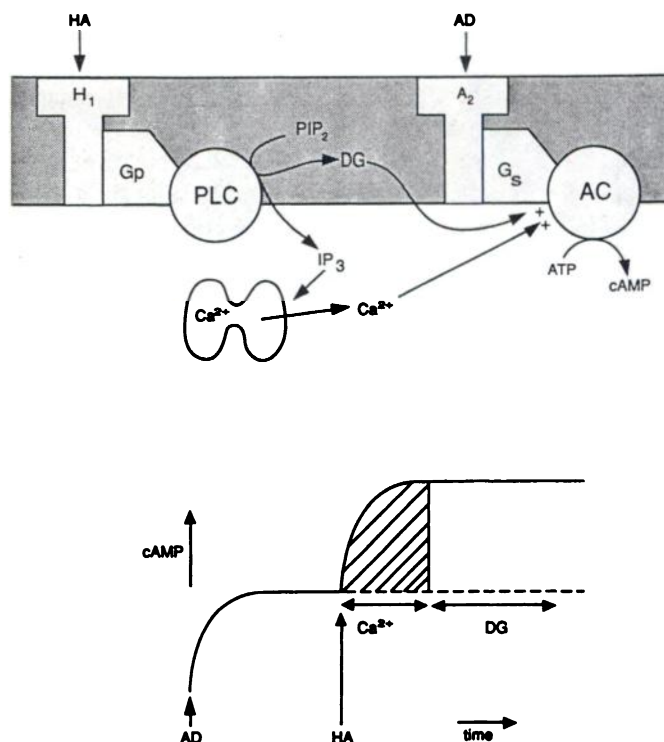

FIG. 3. Mechanisms of augmentation of adenosine stimulated cyclic AMP accumulation by histamine in guinea pig cerebral cortex. Activation of H_1-receptors leads to the formation of IP_3 and DG from phosphatidylinositol-4,5-bisphosphate (PIP_2). IP_3 releases Ca^{2+} from intracellular stores which initiates the augmentation of cyclic AMP synthesis, and DG appears to be responsible for the maintenance of the augmentation response. The lower trace shows the calcium and DG-dependent phases of the augmentation of cyclic AMP accumulation produced by histamine. Abbreviations: HA, histamine; AD, adenosine; Gp, stimulatory G protein linked to PLC; PLC, phospholipase C; AC, adenylate cyclase; Gs, stimulatory G protein linked to AC.

was modified in a complex manner such that responses to high concentrations of histamine appeared to be inhibited in a competitive manner, whereas the response to low concentrations of histamine were unaffected (Palacios et al., 1978a). Similar data have also been obtained in rabbit cerebral cortical slices (Al-Gadi and Hill, 1985).

The complex effect of H_1-antagonists in these preparations, coupled with the apparent competitive nature of the antagonism produced by H_2-antagonists (Palacios et al., 1978a; Al-Gadi and Hill, 1985), indicates that the H_1-receptor-mediated response depends on the prior stimulation of H_2-receptors. Thus, H_1-receptor stimulation is not having a direct effect on adenylate cyclase activity but is enhancing the effect of the H_2-receptor stimulus. Support for this hypothesis has been provided by the use of H_1- and H_2-selective agonists (Palacios et al., 1978a; Al-Gadi and Hill, 1985; Hill, 1987b), and a mathematical model describing this type of interaction has recently been described (Gannon et al., 1989).

A clearer picture of the augmentation of cyclic AMP accumulation produced by H_1-receptor stimulation has emerged from studies using adenosine A_2-receptor stimulation as the direct stimulus of adenylate cyclase activ-

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ity in cerebral cortical slices (Hill et al., 1981; Daum et al., 1982; Donaldson et al., 1988b; Shonk and Rall, 1987; Hill and Kendall, 1989). In the presence of H_2-receptor antagonists (to remove any effect of histamine on H_2-receptors), it can be demonstrated that histamine H_1-receptor stimulation does not alter basal cyclic AMP levels in the absence of exogenous and endogenous adenosine (Donaldson et al., 1988b). However, in the presence of adenosine, histamine produces a large augmentation of cyclic AMP accumulation which can be mimicked by a range of H_1-agonists and competitively antagonised by selective H_1-antagonists (Daum et al., 1982; Hill et al., 1981).

It appears that this response to H_1-receptor stimulation is associated with a rather small spare receptor reserve because a number of H_1-agonists (e.g., 2-methylhistamine, $N\alpha$,$N\alpha$-dimethyhistamine, and 2-pyridylethylamine), which are full agonists in peripheral tissues, appear to act as partial agonists in this system (Daum et al., 1982). This postulate is supported by studies with DTT which increases the maximal cyclic AMP response to these agonists in guinea pig cerebral cortex (Donaldson and Hill, 1986b) and has been shown to increase H_1-agonist efficacy in both central and peripheral tissues (Donaldson and Hill, 1986b, 1987).

Similar, but smaller, indirect effects of H_1-agonists on cyclic AMP accumulation have been reported in dissociated brain cells from adult guinea pigs (Kanba and Richelson, 1983) and synaptoneurosomes isolated from guinea pig cerebral cortex (Chasin et al., 1974; Daly et al., 1980; McNeil et al., 1980; Creveling et al., 1980; Gannon et al., 1988, 1989).

Little is yet known of the intracellular mechanisms by which H_1-receptor stimulation can produce an augmentation of cyclic AMP accumulation. It seems most likely that another second messenger is involved because the effect is lost in broken cell preparations (Hegstrand et al., 1976; Green et al., 1977; Coupet and Szuchs-Meyers, 1981; Hough et al., 1980; Gannon et al., 1989). The products of inositol phospholipid hydrolysis, DG and inositol phosphates, have been implicated in this response via their actions on calcium mobilisation and protein kinase C, respectively (Hollingsworth et al., 1985; Danoff and Young, 1987; Schwabe et al., 1978; Garbarg and Schwartz, 1988; Donaldson et al., 1989).

Phorbol esters, which stimulate protein kinase C, have been shown to augment the cyclic AMP response to 2-chloroadenosine and H_2-receptor stimulation in guinea pig cerebral cortical synaptoneurosomes (Hollingsworth et al., 1985) and slices of guinea pig cerebral cortex (Donaldson et al., 1989) and hippocampus (Garbarg and Schwartz, 1988). A role for calcium in the augmentation response has been proposed on the basis of experiments in which extracellular calcium has been removed or chelated with [ethylenebis(oxyethylenenitrilo)]tetraacetic acid prior to agonist administration (Schwabe et al., 1978; Al-Gadi and Hill, 1987; Garbarg and Schwartz, 1988). Removal of extracellular calcium 2 min prior to histamine addition markedly reduces (by approximately 70%) the augmentation response (Schwabe et al., 1978; Donaldson et al., 1989), whereas chelation of extracellular calcium 20 min prior to H_1-agonist administration abolishes the response in guinea pig cerebral cortical slices (Donaldson et al., 1989). However, because intracellular calcium levels are also depleted by these interventions (Donaldson et al., 1989; Al-Gadi and Hill, 1987), these experiments provide no information concerning the source (extracellular versus intracellular) of calcium ultilised during H_1-receptor stimulation.

Studies with a variety of antagonists of both voltage-dependent and voltage-independent calcium channels indicate that only Ni^{2+} (1 mM) can produce a significant and selective attenuation of the H_1-receptor-mediated augmentation of cyclic AMP accumulation, although 60% of the H_1-response remained in the presence of this calcium channel antagonist (Donaldson et al., 1989). These data suggest that the major portion of the response to H_1-receptor stimulation is mediated via a mobilisation of intracellular calcium, presumably as a consequence of inositol phospholipid hydrolysis (Daum et al., 1984; Donaldson and Hill, 1985, 1986c) but also depends on influx of extracellular calcium. This may be via voltage-independent channels responsible for refilling intracellular stores of calcium (cf. Hallam et al., 1988a,b) or via voltage-dependent T channels which are also inhibited by Ni^{2+} (Hofmann et al., 1987).

When extracellular calcium is chelated with [ethylenebis(oxyethylenenitrilo)]tetraacetic acid once a steady level of cyclic AMP has been achieved within cells after histamine addition, a temporal difference in the calcium sensitivity of the response to H_1-receptor stimulation is revealed. In marked contrast to the data obtained when calcium is removed prior to histamine addition, the maintenance of the H_1-induced augmentation of cyclic AMP accumulation is unaffected by extracellular calcium removal (Donaldson et al., 1989). This does not appear to be due to a change at the level of the H_1-receptor and suggests that calcium is important for the initiation and early stages of the augmentation response but is less important for the maintenance of the response (Donaldson et al., 1989). The maintence of the response could, therefore, be achieved by the activation of protein kinase C via the production of DG (fig. 3). In this respect, it is interesting that the response to phorbol esters is insensitive to removal of extracellular calcium prior to phorbol administration (Donaldson et al., 1989) and that phorbol esters can phosphorylate the catalytic unit of adenylate cyclase purified from bovine brain (Yoshimasa et al., 1987).

The indirect effect of histamine H_1-receptor stimulation on cyclic AMP accumulation could be mediated either at the level of cyclic AMP synthesis or by inhibi-

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tion of phosphodiesterase activity. However, kinetic analysis of the interaction between H_1-receptors and adenosine A_2-receptors in slices of guinea pig cerebral cortex indicate that the activity of the phosphodiesterase isoenzymes involved in metabolising the cyclic AMP produced in response to histamine and adenosine agonists (Donaldson et al., 1988a; Stanley et al., 1989) is not inhibited by H_1-receptor activation (Donaldson et al., 1988b). These data, therefore, suggest that histamine H_1-receptor stimulation is augmenting the synthesis rather than inhibiting the metabolism of cyclic AMP. An augmentation of cyclic AMP accumulation by H_1-receptor stimulation has also been noted in cultured cells from bovine adrenal medulla (Boarder et al., 1988).

ii. Inhibition. In the human astrocytoma cell line 1321N1 activation of H_1-receptors produces an inhibition rather than an augmentation of isoprenaline-induced cyclic AMP accumulation (Nakahata et al., 1986). A similar effect is seen in these cells following muscarinic receptor stimulation (Evans et al., 1984; Hughes and Harden, 1986). Measurement of the rate of fall of cyclic AMP levels after removal of the β-adrenoceptor stimulus with propranolol indicates that both histamine H_1- and muscarinic receptor agonists enhance phosphodiesterase activity in these cells (Nakahata et al., 1986; Masters et al., 1985). Neither receptor system appears to negatively couple to adenylate cyclase and the decrease in cyclic AMP accumulation is insensitive to pertussis toxin but can be inhibited by the phosphodiesterase inhibitor 3-isobutyl-1-methylxanthine (Nakahata et al., 1986; Masters et al., 1985; Evans et al., 1984; Hughs and Harden, 1986). Both receptor systems, however, markedly increase phosphoinositide hydrolysis and mobilisation of intracellular calcium in 1321N1 cells (Nakahata et al., 1986; Nakahata and Harden, 1987; McDonough et al., 1988; Hepler et al., 1987). The presently available data are consistent with the hypothesis that muscarinic and histamine H_1-receptors mobilise intracellular calcium in these cells, leading to increased activity of the calcium-calmodulin-activated isoform of phosphodiesterase (Tanner et al., 1986).

d. CYCLIC GUANOSINE 5′-MONOPHOSPHATE (GMP) ACCUMULATION. H_1-receptor stimulation is associated with a rapid and marked increase in cyclic GMP accumulation in the murine neuroblastoma clone N1E-115 which peaks approximately 30 s after application of histamine and then rapidly returns to basal levels (Richelson, 1978; Taylor and Richelson, 1979; Fredrickson and Richelson, 1979). This response has an absolute dependence on extracellular calcium (Richelson, 1985), but no changes in intracellular calcium levels could be detected in populations of N1E-115 cells loaded with the bioluminescent protein aequorin using the hyperpermeabilisation technique (Snider et al., 1984). More recently, however, this research group has been able to observe transient increases in intracellular levels of calcium in response to histamine (due to influx of calcium) in single cells microinjected with aequorin (Oakes et al., 1988). A similar finding has also been reported by Ohsako and Deguchi (1984) using quin-2. H_1-receptor stimulation is also followed by a release of arachidonic acid in these cells, which following metabolism via the lipoxygenase pathway to a lipoxygenase product may also contribute to the stimulation of cyclic GMP formation (Snider et al., 1984). Interestingly, lipoxygenase products have been proposed to have a second-messenger function in *Aplysia* sensory cells (Piomelli et al., 1987).

Only limited information is available concerning the effect of histamine on cyclic GMP accumulation in the mammalian tissues. Histamine has been reported to raise cyclic GMP levels in rabbit cerebral cortical slices (Lee et al., 1972), guinea pig brain slices (Daly, 1977), guinea pig bronchial and tracheal smooth muscle (Duncan et al., 1980), and bovine trachealis (Katsuki and Murad, 1977), but full receptor characterisations of these responses have not been performed. An H_1-receptor-mediated increase in cyclic GMP accumulation has, however, been demonstrated in blocks of bovine superior cervical ganglion (Study and Greengard, 1978) and human umbilical artery (Clyman et al., 1975, 1976). In both cases, the H_1-receptor-mediated increase in cyclic GMP appeared to involve influx of extracellular calcium because it was mimicked by the calcium ionophore A23187 and abolished by removal of extracellular calcium (Study and Greengard, 1978; Clyman et al., 1976).

3. Overview of major functional H_1-receptor responses. a. SMOOTH MUSCLE CONTRACTION. Contraction of intestinal smooth muscle is one of the best characterised H_1-receptor responses (Arunlakshana and Schild, 1959; Ash and Schild, 1966; Donaldson and Hill, 1986d, 1987; Glover, 1979). In smooth muscle cells that freely generate action potentials, e.g., intestinal smooth muscle, modulation of action potential discharge is one of the most important mechanisms of varying tension, because action potentials are propagated in these cells and can generate tension in cells remote from those in which they originated (Bolton, 1979; Bolton et al., 1981). Thus, at low concentrations of histamine, H_1-receptor stimulation leads to an increase in the frequency of action potential discharge in longitudinal smooth muscle of guinea pig ileum (Bolton et al., 1981) and taenia coli (Bulbring and Burnstock, 1960). At higher concentrations an appreciable depolarisation occurs and action potential discharge ceases (Bolton et al., 1981). It seems likely that histamine produces these effects by opening receptor-operated ion channels, permeable to Na^+, K^+, and Ca^{2+} ions, leading to depolarisation and activation of voltage-dependent Ca^{2+} channels (Bolton et al., 1981). Consistent with these findings is the fact that the contractile response to H_1-receptor stimulation in intestinal smooth muscle is largely sensitive to inhibition by dihydropyridine-based

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antagonists of voltage-dependent calcium channels (Morel et al., 1987).

However, the tension developed by high concentrations of histamine in intestinal smooth muscle is partly resistant to nifedipine, indicating that a component of the contractile response may be mediated by inositol-1,4,5-trisphosphate-induced release of calcium from intracellular stores (Morel et al., 1987; Bolton and Lim, 1989). There is evidence that histamine can induce inositol phospholipid hydrolysis in this tissue (Donaldson and Hill, 1985; Best et al., 1985), but the situation is complicated by the presence of an appreciable non-H_1-receptor component in the response to this agonist (Donaldson and Hill, 1985, 1986c). Nevertheless, an H_1-receptor-mediated production of inositol-1,4,5-trisphosphate has been demonstrated in guinea pig ileal smooth muscle at very early times after agonist administration, which could produce mobilisation of intracellular calcium stores (Bielkiewicz-Vollrath et al., 1987).

A clearer picture regarding the involvement of the inositol phospholipid second-messenger system has evolved in nonexcitable smooth muscles such as bovine and canine tracheal smooth muscle and vascular smooth muscle, where the contractile responses to spasmogens are less sensitive to removal of extracellular calcium (Bruschi et al., 1988; Black et al., 1986; Takuwa et al., 1987). In these tissues, H_1-receptor-stimulation elicits a marked transient increase in intracellular free Ca^{2+} followed by a very much lower, yet still raised, plateau level over the next few minutes (Takuwa et al., 1987; Kotlikoff et al., 1987; Matsumoto et al., 1986; Panettieri et al., 1989). The secondary sustained phase of contraction involves calcium influx through channels that are not inhibited by dihydropyridine calcium antagonists (Takuwa et al., 1987), whereas the initial calcium transient is due to release of calcium from intracellular stores (Takuwa et al., 1987; Kotlikoff et al., 1987; Matsumoto et al., 1986).

As discussed above, histamine can elicit inositol phospholipid hydrolysis in these tissues (Hall and Hill, 1988; Madison and Brown, 1988; Lonchampt et al., 1988; Van Amsterdam et al., 1989; Hall and Chilvers, 1989) and a recent report has demonstrated that histamine produces a transient increase in the mass of inositol-1,4,5-trisphosphate in bovine tracheal smooth muscle (Chilvers et al., 1989) which precedes the transient calcium signal (Takuwa et al., 1987; Kotlikoff et al., 1987). The discrepancy between the short lifetime of the intracellular calcium signal (in calcium-free media) and the sustained contractile response to smooth muscle spasmogens indicates that other mechanisms are operating during the maintenance of contraction. The most likely mediator of this effect is the other product of inositol phospholipid hydrolysis DG. Thus, it has been proposed that, by activating protein kinase C, diacylglycerol is able to contribute to the maintenance of tone by increasing the sensitivity of the contractile proteins to calcium (Dale and Obianime, 1985; Park and Rasmussen, 1985; Karaki, 1989).

Studies in cultured canine airway smooth muscle cells have indicated that activation of protein kinase C by diacylglycerol can attenuate the histamine-induced increase in intracellular free Ca^{2+} (Kotlikoff et al., 1987). This suggests that activation of protein kinase C not only contributes to the maintenance of contraction but also limits the duration of the calcium-dependent component. Studies in membranes prepared from airway smooth muscle cells indicate that protein kinase C activation inhibits the calcium response to histamine by inhibiting the formation of inositol-1,4,5-trisphosphate (Murray et al., 1989).

The inositol phosphate response to histamine is also inhibited by smooth muscle relaxants which raise intracellular levels of cyclic AMP (Hall and Hill, 1988; Hall et al., 1989; Madison and Brown, 1988). Preliminary studies with fluoroaluminates indicate that this effect is mediated at the post-receptor level (Hall and Hill, 1989c). However, it is notable that the inositol phosphate response to muscarinic receptor stimulation in both canine and bovine tracheal smooth muscle cells appears insensitive to cyclic AMP-elevating agents or membrane-permeant analogues of cyclic AMP (Madison and Brown, 1988; Hall and Hill, 1989a). Elevation of tissue cyclic AMP content probably leads to tissue relaxation through a range of different mechanisms including phosphorylation of myosin light-chain kinase (Silver and Stull, 1982), membrane hyperpolarisation (Fujiwara et al., 1988), effects upon Ca^{2+}-gated K^+ channels (Kume et al., 1989), and sequestration of intracellular calcium (Mueller and Van Breeman, 1979). However, the fact that smooth muscle relaxants inhibit the initial stimulus for smooth muscle contraction elicited by both histamine and 5-HT (Hall and Hill, 1989b) may explain why the contractile responses to these spasmogens is more sensitive to inhibition by cyclic AMP-elevating agents than the response to carbachol (Torphy et al., 1987).

In segments of guinea pig whole trachea, the cyclic GMP phosphodiesterase inhibitor, MandB 22948, has been shown to abolish the inositol-1,4,5-trisphosphate response to histamine and carbachol but not the contractile responses to these two agents (Langlands et al., 1989). No such inhibition of inositol phospholipid hydrolysis by MandB 22948 has, however, been observed in smooth muscle cells from bovine tracheal smooth muscle (Hall et al., 1989). The reason for the discrepancy between contraction and inositol phospholipid hydrolysis in guinea pig trachea remains to be established, but it is possibly a consequence of the heterogeneity of the tissue preparation and different cellular location of the two responses.

b. ENDOTHELIAL CELL FUNCTION. A striking feature of the action of histamine H_1-receptor stimulation on the

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cardiovascular system is its effect on the leakage of plasma proteins from various vascular beds (Majno and Palade, 1961; Majno et al., 1969; Grega, 1986; Svensjo and Grega, 1986; Meyrick and Brigham, 1983; Killackey et al., 1986). This change in vascular permeability is particularly striking in postcapillary venules and has been attributed to endothelial cell contraction and the formation of junctional gaps of up to 1 μm diameter between adjacent endothelial cells (Grega, 1986; Meyrick and Brigham, 1983; Heltianu et al., 1982). Endothelial cells possess the necessary contractile proteins, actin and myosin, for such a mechanism (Becker and Nachman, 1973), and histamine H_1-receptors have recently been detected in endothelial cells using [^{3}H]mepyramine (Hide et al., 1988).

The effect of histamine on endothelial cell contraction has been elegantly demonstrated in confluent monolayers of microcarrier cultured human umbilical vein endothelial cells in which histamine (EC_{50} = 30 μM) induces cell retraction and small openings between adjacent cell junctions leading to staining of the underlying microcarrier beads with Evans blue dye (Killackey et al., 1986). Consistent with a role of excitation-contraction coupling in these effects, complete reversal of the effect of histamine (0.1 mM) on endothelial cell permeability can be demonstrated within 0.5 h of removal of the histamine H_1-receptor stimulus (Killackey et al., 1986). A similar observation has been made in vivo, where the vascular leakage of fluorescein-labeled dextran from postcapillary venules in the hamster cheek pouch induced by locally applied histamine (10 μM) returns to basal levels after 25 min and can be demonstrated repeatedly at 30-min intervals (Svensjo and Grega, 1986).

This dynamic profile is consistent with a pharmacological effect of histamine on the contractile state of the endothelium, rather than pathological damage, and raises the possibility of utilising drugs that produce relaxation of the endothelial contractile apparatus as antipermeability drugs. There are several reports of drugs reversing the extravasation of macromolecules in various organs, and in endothelial cell monolayers in culture, induced by histamine (Svensjo and Grega, 1986). β_2-adrenoceptor agonists (e.g., isoprenaline and terbutaline), prostaglandin E_1, and the phosphodiesterase inhibitors 3-isobutyl-1-methylxanthine and theophylline are all effective antipermeability drugs (Killackey et al., 1986; Svensjo and Roemphe, 1985, Grega, 1986). These agents are effective stimulants of cyclic AMP accumulation in endothelial cells from various vascular beds (Hopkins and Gorman, 1981; Karnushina et al., 1983; Leitman et al., 1986) and this second mesenger may mediate relaxation of endothelial cells by interfering with the phosphorylation of myosin light-chain kinase. The one exception may be 3-isobutyl-1-methylxanthine which appears to have effects on phospholipase C and phospholipase that are independent of raised cyclic AMP levels (Hong, 1983; Whorton et al., 1985; Brotherton et al., 1982). Several glucocorticoids, including dexamethasone and methylprednisolone, and arginine vasopressin have also been tested in vivo and shown to prevent histamine-induced increases in vascular permeability (Svensjo and Grega, 1986). In the latter case, the use of vasopressin analogues that produce little vasoconstriction has suggested that the effect of these agents on endothelial cell permeability may be independent of changes in vessel diameter (Adamski et al., 1985).

The role of the endothelial cell contractile machinery and the cytoskeletal microfilament system in junction gap formation is supported by indirect evidence that demonstrates that endothelial cells undergo shape changes and increased plasma protein leakage following stimulation with the calcium ionophore A23187 (Thomas, 1985). Furthermore, the effect of histamine on vascular permeability can be prevented in calcium-free medium and by cytochalasin B which interferes with actin polymerisation (Northover, 1985; Liddell et al., 1981). More direct evidence for a role of intracellular calcium has come from studies using fluorescent calcium-sensitive dyes. Histamine has been shown to produce a significant rise, via H_1-receptor stimulation, in the intracellular concentration of free Ca^{2+} in cultured human umbilical vein endothelial cells from a resting level of 0.1 μM to micromolar levels (Carter et al., 1988; Rotrosen and Gallin, 1986; Pollock et al., 1988; Hamilton and Sims, 1987). The response to histamine is characterised by a transient peak due to the release of intracellular calcium followed by a lower, but still elevated, steady level of intracellular Ca^{2+} which appears to be due to calcium influx (Rotrosen and Gallin, 1986; Carter et al., 1988). The role of intracellular calcium in the initial response was confirmed with the use of calcium-free media and the calcium entry inhibitors, Ca^{2+} and Mn^{2+} (Rotrosen and Gallin, 1986; Carter et al., 1988). It was notable, however, that an influx of extracellular calcium and continued H_1-receptor stimulation was required for a sustained elevation of $[Ca^{2+}]_i$ (Rotrosen and Gallin, 1986; Carter et al., 1988; Hallam et al., 1988a; 1989).

The best evidence for a role of extracellular calcium has been provided by the studies of Hallam et al. (1988a, 1989) who investigated bivalent-cation influx into human enothelial cells by following the ability of Mn^{2+} to enter cells and quench the fluorescence of the intracellular dye Fura-2. These authors and others have shown that histamine stimulates an influx of divalent cations which is sensitive to inhibition by Ni^{2+} but which is not modified by organic Ca^{2+} channel blockers, such as D600 and verapamil, the calcium activator Bay K 8644, or depolarisation with high potassium concentrations (Rotrosen and Gallin, 1986; Hallam et al., 1988a; Hallam and Pearson, 1986). Interestingly, however, Hallam et al. (1989) showed that calcium influx and refilling of the intracellular cacilum stores can occur in the absence of

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H_1-receptor stimulation, i.e., following addition of the H_1-receptor antagonist mepyramine after prior discharge of the intracellular calcium pool with histamine. This suggests that there is a mechanism operating in these cells that is sensitive to the state of the intracellular store. This mechanism does not, however, appear to rely on the intracellular calcium concentration because bivalent cation influx can take place after $[Ca^{2+}]_i$ has returned to basal levels (Hallam et al., 1988a). Patch-clamp studies in human endothelial cells have confirmed that there are no voltage-activated ionic currents in these cells but have revealed a calcium-dependent cationic channel that is activated by histamine (Bregestovski et al., 1988). These inward currents require the presence of external calcium and are activated by raised cytoplasmic calcium concentrations; however, the ionic selectivity of these channels has not been investigated, and it remains to be established whether calcium can permeate these channels (Bregestovski et al., 1988).

Uncoupling of endothelial cells and the formation of gap junctions between endothelial cells is not the only possible response to the raised levels of intracellular calcium in endothelial cells. Histamine H_1-receptor stimulation in these cells is also accompanied by synthesis of prostacyclin (Brotherton, 1986; McIntyre et al., 1985; Carter et al., 1988; Resink et al., 1987; Jaffe, 1987) and platelet-activating factor (McIntye et al., 1985), release of Von Willebrand factor (Hamilton and Sim, 1987), and the secretion of endothelium-derived relaxant factor (van De Voorde and Leusen, 1983; Toda, 1984; Satoh and Inui, 1984). This factor, which has recently been identified as nitric oxide (Palmer et al., 1987; Vanhoutte, 1987), is responsible for the relaxant effect of H_1-receptor agonists on precontracted arterial vessels (Van De Voorde and Leusen, 1983; Furchgott et al., 1984). In the case of prostacyclin release, a clear relationship has been established between mobilisation of intracellular calcium induced by thrombin, adenosine 5′-triphosphate, and histamine and the synthesis and release of this arachidonic acid metabolite (Carter et al., 1988; Hallam et al., 1988c). In general, the prostacyclin response is rather transient in nature but can be prolonged to some extent by the presence of extracellular calcium (Hallam et al., 1988c). In the case of the other endothelial cell responses to histamine that are much longer lasting, e.g., platelet-activating factor, endothelium-derived relaxant factor, uncoupling of endothelial cell junctions, and Von Willebrand factor production, they almost certainly rely on calcium influx to maintain a raised $[Ca^{2+}]_i$ for a sufficient period (Hamilton and Sims, 1987; McIntye et al., 1985; Singer and Peach, 1984; Northover, 1985; Liddell et al., 1981).

Rapid advances in technology have enabled the measurement of calcium responses to histamine H_1-receptor stimulation in single fura-2-loaded endothelial cells (Jacob et al., 1988). These studies provided rather unexpected results in that they revealed a characteristic pattern of repetitive spiking calcium transients at low concentrations of histamine (0.1 to 3 μM) whose frequency increased with raised levels of histamine (Jacob et al., 1988). At higher concentrations of histamine (10 to 100 μM), an initial $[Ca^{2+}]_i$ spike was followed by a lower plateau phase similar to that observed in populations of endothelial cells. In the absence of extracellular calcium, the spiking activity at low histamine concentrations progressively decayed (Jacob et al., 1988). These data suggest that the responses to low concentrations of histamine in the concentration range 0.1 to 10 μM, at which significant effects on prostacyclin, platelet-activating factor, and Von Willebrand factor release can be demonstrated (Jacob et al., 1988; Hamilton and Sim, 1987; McIntyre et al., 1985; Resink et al., 1987), may be regulated by the frequency of the oscillations in $[Ca^{2+}]_i$ rather than the amplitude of the calcium transients. In contrast, responses that require higher concentrations of histamine and the concerted action of more than one endothelial cell (e.g., effects on permeability) may require sustained elevation of $[Ca^{2+}]_i$ in neighbouring cells.

Histamine-stimulated hydrolysis of inositol phospholipids, which provides the second messenger (IP_3) responsible for mobilisation of intracellular calcium, has been demonstrated in human umbilical vein endothelial cells and shown to be mediated via H_1-receptors (Lo and Fan, 1987; Resink et al., 1987; Pollock et al., 1988). High-pressure liquid chromatography analysis of the inositol phosphate isomers produced confirmed that the calcium-mobilising inositol trisphosphate isomer (IP_3) is produced in these cells following short stimulations of histamine H_1-receptors (Pollock et al., 1988). However, it remains to be established whether IP_3 levels oscillate in these cells or whether other explanations are required to explain the oscillations in $[Ca^{2+}]_i$ (Jacob et al., 1988; Berridge and Irvine, 1989).

c. STIMULATION OF HORMONE RELEASE. Histamine has been shown to affect the secretion of a number of hormones from the posterior and anterior pituitory (see Donoso and Alvarez, 1984; Roberts and Calcutt, 1983 for reviews). However, only limited information is available concerning the involvement of H_1-receptors in these responses, and this seems to be confined to a positive influence of H_1-receptor stimulation on the secretion of vasopressin and corticotropin (Donoso and Alvarez, 1984; Roberts and Calcutt, 1983). The best evidence for a role of histamine H_1-receptors in hormone release has come from studies of catecholamine release from the adrenal medulla.

It has long been established that histamine H_1-receptors can elicit the release of catecholamines from adrenal glands (Emmelin and Muren, 1949; Trendelenburg, 1954; Staszewska-Barczak and Vane, 1965; Yoshizaki, 1973; Robinson, 1982), and this has been recently confirmed in primary cultures of adrenal chromaffin cells (Livett

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and Marley, 1986; Noble et al., 1988). Histamine can induce the release of both adrenaline and noradrenaline from cultured bovine adrenal chromaffin cells in a concentration- and calcium-dependent manner via an action on H_1-receptors (Livett and Marley, 1986). Calcium channel antagonists markedly reduced this response to histamine, but it was notable that a small residual catecholamine release could still be demonstrated under these conditions (Noble et al., 1988). This suggests that release of intracellular calcium may also have a role in this response, and the reports that H_1-receptor stimulation is associated with inositol phospholipid hydrolysis in these cells (Noble et al., 1986; Plevin and Border, 1988; Kley, 1988) is consistent with this hypothesis.

In addition to its effect on catecholamine secretion, histamine is also a potent secretogogue for the opioid peptides Leu- and Met-enkephalin in adrenal chromaffin cells (Bommer et al., 1987). This response is mediated by histamine H_1-receptors, is markedly reduced by inhibitors of voltage-dependent calcium channels, and is completely attenuated by the nonspecific calcium channel blocker Co^{2+} (Bommer et al., 1987). These data suggest that the release of opiate pentapeptides is primarily dependent upon the activation of calcium channels, although a minor role of IP_3-induced release of intracellular calcium cannot be excluded. After prolonged exposure (approximately 48 h) to histamine, there is a profound compensatory increase in cellular peptide content which appears to be secondary to a four- to fivefold increase in the messenger ribonucleic acid (mRNA) levels coding for the proenkephalin A precursor (Bommer et al., 1987; Wan et al., 1989; Kley et al., 1987). Interestingly, expression of phenylethanolamine-N-methyltransferase mRNA, which is colocalised with proenkephalin A mRNA in adrenal chromaffin cells is not activated by histamine (Wan et al., 1989).

A feature of the effect of histamine on inositol phospholipid hydrolysis in bovine adrenal chromaffin cells, when compared to the action of other secretogogues, is that it produces a different profile of inositol phosphate formation (Plevin and Border, 1988). Thus, although histamine gives one of the largest overall accumulations of total inositol phosphates in these cells, it gives a relatively small accumulation of the calcium-mobilising inositol trisphosphate (Plevin and Border, 1988). This may lead to a greater relative production of DG and activation of protein kinase C by stimulating hydrolysis of phosphatidylinositol or phosphatidylinositol monophosphate than many of the other agents. A role for protein kinase C in the regulation of proenkephalin A mRNA expression has recently been suggested (Kley, 1988). Protein kinase C activation may also have an important role in the feedback control of histamine-stimulated proenkephalin A mRNA expression because its activation by phorbol esters can inhibit histamine-induced inositol phospholipid hydrolysis (Kley, 1988).

d. EFFECT ON CARDIAC MUSCLE. It is well known that histamine, which is a normal constituent of the mammalian heart, can produce an increase in the force of cardiac contraction (Levi et al., 1982; Wolff and Levi, 1986). In most species the positive inotropic effect of histamine is mediated by H_2-receptors and associated with a stimulation of adenylate cyclase acitivity (Levi et al., 1975; Reinhardt et al., 1976; Hattori et al., 1983; McNeill and Verma, 1974; Johnson, 1982). However, in guinea pig left atria (Reinhardt et al., 1974; Steinberg and Holland, 1975; Hattori et al., 1983; Hattori et al., 1988a) and rabbit papillary muscle (Hattori et al., 1988b), histamine H_1-receptor stimulation produces a positive inotropic effect that is not associated with an increase in cyclic AMP levels (Reinhardt et al., 1977; Verma and McNeill, 1977).

The inotropic action of histamine in guinea pig left atria is composed of two components and accompanied by a prolongation of action potential duration (Amerinin et al., 1982; Borchard and Hafner, 1986; Hattorri et al., 1988a). The prolongation of action potential duration has been ascribed to an inhibition of outward potassium currents (Hattori et al., 1988a). The second phase of the inotropic response is inhibited by dihydropyridine calcium channels and nickel (Hattori et al., 1988a) but may be a consequence of the extended duration of the action potential rather than a direct enhancement of a slow inward calcium current because histamine is unable to restore contractile and electrophysiological responses in guinea pig left atrium depolarised by high K^+ solutions (Mantelli et al., 1982; Hattorri and Kanno, 1985).

The initial phase of the inotropic response appears to be due to release of intracellular calcium because it is insensitive to calcium channel antagonists but can be inhibited by ryanodine (Hattori et al., 1988a). Histamine H_1-receptor stimulation has been shown to stimulate inositol phospholipid hydrolysis in this tissue, and this could provide the initial stimulus for calcium release (Sakuma et al., 1988; Hattori et al., 1989). A rapid production of inositol-1,4,5-trisphosphate occurs with 15 s in this tissue and then progressively increases during the next 20 min (Sakuma et al., 1988). This is fast enough to account for the initial phase of the inotropic response to histamine, but evidence obtained with phorbol esters and nonspecific inhibitors of phospholipase C suggests that other mechanisms may be operating (Hattori et al., 1989).

e. CEREBRAL GLYCOGENOLYSIS. Histamine exerts a powerful stimulant effect on the breakdown of glycogen in mammalian brain slices, suggesting that it may have an important role in modulating carbohydrate metabolism in cerebral tissues (Quach et al., 1978, 1980b, 1981). Noradrenaline, which also stimulates glycogenolysis in mouse and chick cerebral cortex, stimulates cyclic AMP formation via an action on β-adrenoceptors, which, in turn, leads to the conversion of phosphorylase b to phos-

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phorylase a and a breakdown of cerebral glycogen (Quach et al., 1978; Nahorski et al., 1975). However, in the case of histamine the glycogenolytic response is mediated entirely by calcium-mobilising H_1-receptors (Quach et al., 1980) Thus, the maximum glycogenolytic response to histamine in mouse cerebral cortex can be markedly reduced by lowering the calcium content of the media (Quach et al., 1980). This suggests that phosphorylase b kinase may be activated in this tissue by calcium as well as by cyclic AMP-protein kinase A activation. For example, there is some evidence that phosphorylase b kinase can be activated by calcium ions in both brain and liver (Assimocopoulos-Jeannet et al., 1977; Ozawa, 1973).

Studies with the phosphodiesterase inhibitor 3-isobutyl-1-methylxanthine indicate that the glycogenolytic response to histamine can be significantly potentiated by phosphodiesterase inhibition (Quach et al., 1980). Furthermore, dibutyryl cyclic AMP, but not dibutyryl cyclic GMP, can promote glycogen hydrolysis in slices of mouse cerebral cortex (Quach et al., 1978). These studies raise the possibility that cyclic AMP may play a role in the H_1-receptor-mediated glycogenolytic response in mouse cerebral cortex. It is known that H_1-receptor stimulation can augment the cyclic AMP responses to vasoactive intestinal polypeptide and adenosine (Magistretti and Schorderet, 1985; Alexander et al., 1989), thus a synergistic interaction between histamine and an endogenous activator of adenylate cyclase (e.g., vasoactive intestinal polypeptide) may contribute to a cyclic AMP-dependent component of the glycogenolytic response to histamine.

B. Histamine H_2-Receptor

1. Ligand-binding studies. The first radioligand developed as a probe for the H_2-receptor was [^{3}H]cimetidine in 1978 (Burkard, 1978). Early studies in both guinea pig cerebral cortical membranes (Burkard, 1978; Rising et al., 1980; Warrender et al., 1983) and membranes from various rat brain areas (Kandel et al., 1980; Kendall et al., 1980; Subramanian and Slotkin, 1981; Devoto et al., 1980; Smith et al., 1980) demonstrated a high-affinity saturable component of binding that could be displaced by burimamide, metiamide, or cimetidine with dissociation constants that correlated well with those determined from inhibition of a classic H_2-receptor response such as the chronotropic response of isolated guinea pig atria. However, it is now clear that the binding site labeled by [^{3}H]cimetidine represents some imidazole recognition site other than the H_2-receptor. Evidence against a selective labeling of H_2-receptors with this radioligand has principally come from the negligable displacement of [^{3}H]cimetidine binding (IC_{50} values > 1 mM) produced by the potent non-imidazole H_2-antagonists, tiotidine and ranitidine (Smith et al., 1980; Warrender et al., 1983). Furthermore, a number of imidazoles that do not possess H_2-receptor-binding activity produce a marked and potent displacement of [^{3}H]cimetidine binding from guinea pig cerebral cortex and gastric mucosa membranes (Warrender et al., 1983).

In rat and guinea pig brain membranes, Cu^{2+}, Pd^{2+}, and Ag^{2+} ions can markedly increase the specific binding site capacity of [^{3}H]cimetidine and alter the inhibitor potencies of various H_2-receptor agonists and antagonists (Kendall et al., 1980; Warrender et al., 1983; Ozawa et al., 1985). It has been suggested that under these experimental conditions, [^{3}H]cimetidine may label a biologically relevant H_2-receptor recognition site (Kendall et al., 1980). However, this site still remains insensitive to non-imidazole compounds such as ranitidine and tiotidine in the presence of Cu^{2+} ions (Warrender et al., 1983). [^{3}H]Ranitidine (Bristow et al., 1981) and [^{3}H] metiamide (Rosenfeld et al., 1976) have similarly proved unsuitable as H_2-selective radioligands. Almost certainly, all of these compounds suffer from their rather low absolute binding affinities for the H_2-receptor which are in the 0.1 to 1.0 μM range.

[^{3}H]Tiotidine, which has a higher affinity than both cimetidine and ranitidine for the H_2-receptor, has successfully labeled H_2-receptors in a number of guinea pig brain regions (Gajtkowski et al., 1983; Norris et al., 1984; Smith et al., 1986), although earlier studies in rat and guinea pig hippocampus were not successful (Maayani et al., 1982). In guinea pig cerebral cortical membranes, the saturable binding of [^{3}H]tiotidine can be displaced by a wide range of H_2-receptor antagonists of diverse chemical structure with potencies that correlate well with their ability to inhibit H_2-receptor responses in guinea pig atrium and gastric mucosa (Gajkowski et al., 1983; Rising and Norris, 1985).

Labeling of peripheral tissues, which are known to possess functional histamine H_2-receptors, has proved difficult with [^{3}H]tiotidine (Rising and Norris, 1985). For example, little success in specifically labeling the H_2-receptor recognition site has been achieved in guinea pig atria and gastric mucosa (Rising and Norris, 1985). The only real success has been achieved in homogenates of guinea pig lung parechymal tissue where H_2-receptors produce relaxation of parenchymal smooth muscle (Foreman et al., 1985a,b). It was notable in this study that high concentrations of H_2-ligands displaced [^{3}H]tiotidine from nonspecific sites that comprise a high proportion of the total binding of this radioligand (Foreman et al., 1985a). In kidney membranes, however, the displaceable binding of [^{3}H]tiotidine appears to be exclusively to such non-H_2 sites (Rising and Norris, 1985).

The problem of high nonspecific binding and difficulties in confidently defining the extent of nonspecific binding in peripheral tissues is also shared by a derivative of tiotidine, [^{3}H]ICIA 5165 (Nielsen, 1986). However, unlike the situation with [^{3}H]tiotidine, labeling of H_2-receptors with this ligand has been achieved in homogenates of guinea pig gastric mucosa (K_D = 10 nM, B_{MAX} = 15 fmol/mg protein; Nielsen, 1986).

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Some studies have utilised [^{3}H]histamine as a potential probe for the H_2-receptor (Kandel et al., 1980; Palacios et al., 1978b; Barbin et al., 1980; Cybulsky et al., 1981; Wells et al., 1985; Steinberg et al., 1985a,b,c; Batzri et al., 1982a,b; Osband and McCaffrey, 1979). Early work in homogenates of rat brain concluded that the high-affinity binding of [^{3}H]histamine (K_D = 7 nM) was to neither H_1- or H_2-recognition sites (Kandel et al., 1980; Barbin et al., 1980). However, later, one of these groups proposed that [^{3}H]histamine may label a high-affinity agonist state of the H_2-receptor (Wells et al., 1985; Steinberg et al., 1985a,b,c). Thus, there is an excellent correlation between the ability of a wide range of H_2-antagonists to inhibit the specific binding of very low concentrations (nM) of [^{3}H]histamine in rat brain homogenates and their ability to inhibit the H_2-mediated chronotropic response of guinea pig right atria (Wells et al., 1985; Steinberg et al., 1985b). Agonists also inhibit [^{3}H]histamine binding in this tissue but do so in a characteristic biphasic manner (Wells et al., 1985; Steinberg et al., 1985c).

Solubilization of [^{3}H]histamine-binding sites in rat cerebral cortex (Cybulsky et al., 1981) markedly changes the binding characteristics of these sites (Wells et al., 1985). The correlation between H_2-antagonist potency and displacement of [^{3}H]histamine is lost, whereas the binding properties of H_2-agonists revert to a simpler situation, consistent with an interaction with a single class of recognition sites (Wells et al., 1985). The authors propose that H_2-agonists and antagonists may bind at different sites within the membrane, or more likely within the transmembrane loops of the receptor protein, such that the inhibition of [^{3}H]histamine binding by H_2-antagonists represents an allosteric effect which is uncoupled following solubilisation with digitonin (Wells et al., 1985, Steinberg et al., 1985b,c). At present, however, this hypothesis is at variance with the reported competitive nature of the inhibition of H_2-receptor-stimulated adenylate cyclase activity by H_2-receptor antagonists in mammalian brain membranes (Green et al., 1977; Kanof and Greengard, 1979a).

In guinea pig gastric mucosal cells [^{3}H]histamine binds with much lower affinity (approximately 10 μM) than in rat brain membranes (Batzri et al., 1982a,b). The rank order of potency of H_2-agonists as displacers of [^{3}H] histamine is identical with that obtained for stimulation of cyclic AMP accumulation (Batzri et al., 1982a). However, although cimetidine, metiamide, ranitidine, and tiotidine all displace [^{3}H]histamine from gastric mucosal cells, there were marked discrepancies in their K_D values obtained from inhibition of [^{3}H]histamine binding and H_2-stimulated cyclic AMP formation (Batzri et al., 1982b). For example the K_D for tiotidine for the cyclic AMP response was 0.04 μM, but the K_D for the [^{3}H] histamine recognition site was only 5 μM. Given that these measurements were made in intact cells where any allosteric interaction between antagonist- and agonist-binding sites should still be functional, these data suggest that [^{3}H]histamine is not labeling the pharmacologically relevant H_2-recognition site.

It is clear from the above discussion that [^{3}H]tiotidine and [^{3}H]ICIA 5165 are the only H_2-radioligands available that can be used with confidence in certain, but by no means all, tissues. It therefore seems that an alternative radioligand is still required to explore the distribution and molecular characterisitics of the histamine H_2-receptor.

2. Interaction with effector systems. a. ADENYLATE CYCLASE. Histamine is a potent stimulant of cyclic AMP in many cells (Johnson, 1982) and particularly those of CNS origin (Daly, 1977). Pharmacological studies in brain slices (Al-Gadi and Hill, 1985; Palacios et al., 1978a), gastric mucosal cells and glands (Batzri et al., 1982a,b; Chew et al., 1980; Gespach et al., 1982; Soll and Wollin, 1979), dog fat cells (Grund et al., 1975; Keller et al., 1981), cardiac myocytes (Warbanow and Wollenberger, 1979), vascular smooth muscle (Reinhardt and Ritter, 1979), basophils (Lichtenstein and Gillespie, 1975), and neutrophils (Busse and Sosman, 1977) indicate that H_2-receptor stimulation is intimately involved in these responses.

A direct stimulation of membrane adenylate cyclase by H_2-receptor activation was first demonstrated in broken cell preparations of guinea pig cardiac muscle (Klein and Levey, 1971; Verma and McNeill, 1974; Johnson and Mizoguchi, 1977; Johnson et al., 1979a,b; Kanof and Greengard, 1979b; Johnson, 1982) and brain (Hegstrand et al., 1976; Kanof et al., 1977; Kanof and Greengard, 1979a; Green and Maayani, 1977; Green et al., 1977; Olianas et al., 1984). Guanine nucleotides are necessary for histamine-induced activation of adenylate cyclase activity in both of these tissues (Johnson et al., 1979a; Kanof et al., 1977), consistent with the role of the GTP-binding G_s subunit in the receptor transduction process (Gilman, 1987). Interestingly, if the stable analogue guanosine-5′-(β,γ-imino)-triphosphate (GppNHp) is used in place of GTP the EC_{50} values determined for H_2-agonists are decreased relative to those obtained in the presence of GTP in guinea pig and human myocardium (Johnson et al., 1979a; Bristow et al., 1982a). Furthermore, the agonist efficacy of many agonists that behave as partial agonists in the presence of GTP, e.g., dimaprit and impromidine, increases in the presence of GppNHp (Johnson et al., 1979a, Bristow et al., 1982a). However, the mechanism underlying these differences remains to be established.

Histamine H_2-receptor-stimulated adenylate cyclase has also been demonstrated in homogenates from guinea pig (Gajtkowski et al., 1983; Tsai and Yellin, 1983), rabbit (Sung et al., 1973; Katsumata and Yagi, 1976), and human (Simon and Kather, 1977) gastric mucosa, cerebral microvessels (Karnushina et al., 1980), and brain

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regions of a number of other species including the rat (Hegstrand et al., 1976; Green et al., 1977; Ozawa and Segawa, 1988), rabbit (Hough and Green, 1981), and monkey (Newton et al., 1982). In view of the current problems with radioactive probes for this receptor, the demonstration of an H_2-receptor-mediated adenylate cyclase or cyclic AMP response is probably the best marker available for mapping the distribution of H_2-receptors in different tissues.

A feature of the H_2-receptor-stimulated adenylate cyclase activity in mammalian brain is its sensitivity to inhibition by a range of psychotropic drugs (Hill, 1987b). Thus a number of neuroleptics (Spiker et al., 1976; Kanof and Greengard, 1978), antidepressants (Green, 1983; Kanof and Greengard, 1978; Green and Maayani, 1977), and the hallucinogenic drug D-lysergic acid diethylamide (Green et al., 1977) are potent inhibitors of the H_2-linked cyclase in broken cell preparations from mammalian brain. Many appear to act as competitive antagonists of the H_2-receptor in this system, although some of the neuroleptics, with the exception of chlorpromazine, inhibit cyclase activity in a noncompetitive fashion (Green, 1983). In guinea pig hippocampal brain slices and dissociated brain cell preparations, however, studies of the H_2-receptor-mediated accumulation of cyclic AMP showed that most of the neuroleptics and antidepressant drugs were approximately two orders of magnitude weaker as antagonists of the H_2-response in intact cellular systems (Tuong et al., 1980; Kanba and Richelson, 1983; Hill, 1987b). In contrast, the dissociation constants determined for classic H_2-receptor antagonists such as cimetidine, ranitidine, metiamide, and tiotidine from studies in intact and broken cell preparations were identical.

Anomalously high binding affinities for the H_2-receptor as determined from adenylate cyclase measurements have also been reported for the H_1-antagonists cyproheptadine and promethazine (Green et al., 1977; Kanof and Greengard, 1979a) and the inhibitors of imidazole-N-methyltransferase quinacrine, amodiaquine, and metoprine (Kanof and Greengard, 1979a). In the case of promethazine, this high H_2-antagonist potency is at variance with its low potency on peripheral H_2-receptors in guinea pig atrium (Johnson, 1982; Verma and McNeil, 1977). However, in intact cell systems these compounds are very weak H_2-antagonists (Tuong et al., 1980; Kanba and Richelson, 1983). The reason for the discrepancy in the discriminatory properties of H_2-receptors for non-H_2-ligands in homogenates and intact cellular systems is unclear. The most likely explanation is that drugs such as quinacrine and promethazine gain access to intracellular components of the receptor-effector system, which are not normally available to them in intact cell systems, through which they can inhibit H_2-receptor-stimulated adenylate cyclase activity in a noncompetitive manner (Hill, 1987b). Alternatively, the relatively high potency of certain compounds in the adenylate cyclase assay may reflect the fact that the H_2-receptor may adopt a different conformation in the presence of high concentrations of adenosine 5′-triphosphate, Mg^{2+}, and GTP or GppNHp required for measurment of cyclic AMP formation in broken cell preparations (Tuong et al., 1980; Kanba and Richelson, 1983). In this respect it is interesting that the efficacy of H_2-agonists can be markedly increased in the presence of GppNHp (Johnson et al., 1979a, Bristow et al., 1982).

b. PHOSPHOLIPID METHYLATION. Many cellular membranes contain enzymes, phosphatidylethanolamine-N-methyltransferases, that synthesize phosphatidylcholine by stepwise methylation of phosphatidylethanolamine using S-adenosyl-L-methionine as the methyl donor (Hirata et al., 1978; Ozawa and Segawa, 1988). In erythrocyte ghosts it has been shown that methylation of phosphatidylethanolamine, which is distributed within the lipid membrane facing the cytoplasm, begins on the cytoplasmic side of the membrane, but after successive methylations the final product, phosphatidylcholine, is translocated to the outer surface of the membrane (Crews et al., 1980; Hirata and Axelrod, 1980). Hirata et al. (1979) proposed that this translocation of phospholipids following N-methylation decreases the membrane microviscosity in the region of a cyclic AMP-stimulating receptor and increases its coupling to adenylate cyclase. In keeping with this hypothesis, recent work in rat brain synaptosomes has demonstrated that histamine H_2-receptor-stimulated adenylate cyclase activity is associated with increases in phospholipid methylation (Ozawa et al., 1987; Ozawa and Segawa, 1988). Indeed, the demonstration of an adenylate cyclase response in rat brain synaptosomes is dependent upon the presence of a methyl donor, namely, S-adenosyl-methionine, in the incubation medium (Ozawa and Segawa, 1988). There is a small delay of approximately 1 min in adenylate cyclase activation in this tissue which is consistent with the time course of the H_2-receptor-mediated N-methylation reaction (Ozawa and Segawa, 1988). However, it should be noted that S-adenosyl-methionine is not a requirement for the demonstration of H_2-mediated adenylate cyclase activity in all tissues, e.g., guinea pig brain (Hegstrand et al., 1976). At present the only other tissue in which an H_2-receptor-mediated stimulation of phospholipid methylation by histamine has been demonstrated is rat mast cells (Tolone et al., 1982).

c. SECOND-MESSENGER-MEDIATED CONTROL OF ION CHANNELS. The action of H_2-receptor stimulation on ion channels appears to be secondary to changes in the intracellular levels of cyclic AMP. In guinea pig and human ventricular muscle, H_2-receptor stimulation produces a positive inotropic effect which is accompanied by an increase in the height and the duration of the plateau phase of the action potential (Eckel et al., 1982; Levi and Alloatti, 1988). It has been proposed that H_2-

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receptor-mediated increases in intracellular cyclic AMP levels lead to an increase in the slow inward Ca^{2+} current (I_{Ca}) as a result of cyclic AMP-dependent phosphorylation of calcium channels which increases the number of channels that may open during depolarisation (Levi and Alloatti, 1988; Reuter, 1983; Reuter et al., 1986). Recent data obtained from whole-cell patch-clamp studies have confirmed that H_2-receptor stimulation increases the amplitude of I_{Ca} in guinea pig ventricular myocytes (Levi and Alloatti, 1988; Hescheler et al., 1987). Furthermore, the intermediacy of cyclic AMP is strongly indicated by the following findings: (*a*) the increased calcium current was mimicked by intracellular perfusion with cyclic AMP (Levi and Alloatti, 1988); (*b*) after the calcium current was increased with micromolar cyclic AMP, saturating concentrations of histamine were without effect (Levi and Alloatti, 1988); (*c*) the effect of histamine on I_{Ca} was inhibited by intracellular perfusion with the cyclic AMP antagonist R_p-adenosine-3′,5′-monothionophosphate (Hescheler et al., 1987); and (*d*) the effect of histamine was mimicked by 8-(4-chlorphenylthio)-cyclic AMP (Eckel et al., 1982) and depressed by the phosphodiesterase activator N-methylimidazole (Inui and Imamura, 1976).

In hippocampal pyramidal cells, H_2-receptor stimulation antagonises a calcium-mediated potassium conductance without affecting calcium currents (Haas and Greene, 1986). This has the effect of augmenting the neuronal excitation elicited by various excitatory stimuli such as excitatory amino acids, intracellular current injection, or synaptic stimulation (Haas, 1984; Haas and Konnerth, 1983; Haas and Greene, 1986). This is because bursts of spike activity in these cells are normally followed by a long-lasting after-hyperpolarisation (due to activation of calcium-dependent potassium channels) which tends to keep the cells away from their firing threshold for several seconds (Haas, 1984; Haas and Konnerth, 1983). Inhibition of these curents by H_2-receptor stimulation, therefore, leads to a profound potentiation of excitatory signals. As with the effect on I_{Ca} in cardiac myocytes, the effect of H_2-receptors on potassium currents can be mimicked by intracellular application of cyclic AMP or by bath application of 8-bromo-cyclic AMP (Madison and Nicholl, 1982; Haas, 1985). Furthermore, the effect of histamine on population spikes can be augmented and prolonged by phosphodiesterase inhibitors (Haas, 1985). It remains to be established, however, whether cyclic AMP inhibits these calcium-dependent potassium currents directly via protein phosphorylation of the potassium channels themselves or whether the primary effect is a cyclic AMP-mediated reduction in $[Ca^{2+}]_i$ in pyramidal cells.

d. H_2-RECEPTOR-MEDIATED RELEASE OF INTRACELLULAR CALCIUM. In isolated gastric mucosal parietal cells, histamine-stimulated secretion of HCl has been associated with increased intracellular levels of cyclic AMP (Soll and Berglindh, 1987) and is little altered by removal of extracellular Ca^{2+} (Chew, 1985, 1986). However, recent data indicate that H_2-receptor stimulation is associated with an increase in the intracellular free concentration of calcium ions as measured by the calcium indicators quin-2 and fura-2 (Chew, 1986; Chew and Brown, 1986; Malinowska et al., 1988). This effect of histamine is not inhibited by removal of extracellular calcium or by the calcium channel blocker nicardipine, suggesting that a release of calcium from intracellular calcium stores is involved (Chew, 1986; Chew and Brown, 1986). In contrast to the data obtained with both carbachol and cholecystokinin in these cells, the increased release of stored calcium by H_2-receptor stimulation is not associated with inositol phospholipid hydrolysis. The H_1-receptor is the histamine receptor normally associated with inositol phospholipid hydrolysis and calcium mobilisation (see above); however, it is clear that the effect of histamine in parietal cells is mediated by H_2-receptors because it can be completely inhibited by 100 μM cimetidine and not altered by a rather heroic concentration (200 μM) of the H_1-antagonist tripelennamine (Chew, 1986; Negulescu and Machen, 1988).

Studies in single parietal cells have confirmed that H_2-receptor stimulation can release calcium from intracellular stores (Negulescue and Machen, 1988). The increase in $[Ca^{2+}]_i$ in response to histamine is characterised by an initial spike followed by a sustained plateau that is dependent upon influx of extracellular calcium (Negulescue and Machen, 1988). Histamine, unlike carbachol, often caused two repeated increases in $[Ca^{2+}]_i$ which were less frequent in the absence of extracellular calcium. Dibutyryl-cyclic AMP and 3-isobutyl-1-methylxanthine did not trigger an increase in $[Ca^{2+}]_i$ by themselves but tended to produce a second increase in $[Ca^{2+}]_i$ after prior stimulation by histamine (Negulescue and Machen, 1988). It should be noted, however, that the adenylate cyclase activator forskolin did produce an initial calcium transient in isolated rabbit gastric glands (Chew, 1986). These data indicate that the initial H_2-receptor-induced release of intracellular calcium, which comes from the same intracellular store on which carbachol acts via inositol-trisphosphate (Negulescu and Machen, 1988), is through a different mechanism from that used by most calcium-mobilising receptors. Furthermore, there is some tentative evidence to suggest that this may not be secondary to raised intracellular cyclic AMP levels (Negulescu and Machan, 1988).

3. Major functional responses. a. GASTRIC ACID SECRETION. The potent effect of H_2-receptor stimulation on gastric acid secretion in vivo and the inhibitory effects of H_2-receptor antagonists on pentagastrin-stimulated acid secretion has indicated a physiological role for histamine in the control of gastric acid secretion (Black et al., 1982; Black and Shankley, 1987; Soll and Berglindh, 1987). There is, however, considerable debate over the

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exact role that histamine plays in excitation-secretion coupling in mammalian gastric mucosa (Black and Shankley, 1987). Two hypotheses have been put forward to explain the pivotal role of histamine H_2-receptor stimulation in the regulation of gastric acid secretion: (*a*) the transmission hypothesis in which histamine acts as the final common mediator of the actions of acetylcholine and gastrin and (*b*) the permissive hypothesis in which potentiating interactions occur among histamine, gastrin, and acetylcholine at the level of the parietal cell itself (Black and Shankley, 1987; Soll and Berglindh, 1987).

Evidence for the permissive hypothesis has largely accrued from studies of receptor function in isolated gastric glands or parietal cells where secretory function can be monitored indirectly by following oxygen consumption or the accumulation of weak bases such as aminopyrine (Soll and Berglindh, 1987). Thus, in canine parietal cells there is evidence of potentiating interactions between H_2-receptors and both muscarinic and gastrin receptors from measurements of oxygen consumption and aminopyrine accumulation (Soll and Berglindh, 1987; Soll, 1978, 1982). Furthermore, measurements of histamine release from mast cells within the canine fundic mucosa have failed to show any enhancement of histamine release by either cholinomimetics or gastrin (Soll and Berglindh, 1987).

However, studies of isolated cells in other species indicate that there may be considerable species variations in the mechanisms underlying the control of acid secretion. Thus, although there is evidence for positive interactions between H_2-receptor and muscarinic receptor stimulation in rabbit gastric glands, it has been difficult to show a similar interaction between histamine and gastrin (Berglindh, 1977; Chew and Hersey, 1982). Moreover, release of histamine from rabbit gastric glands can be stimulated by both gastrin and acetylcholine (Nylander et al., 1985), indicating that the transmission hypothesis may be involved in this species. Pharmacological studies in the mouse isolated stomach preparation also support the latter hypothesis (Black and Shankley, 1987).

It is well established that H_2-receptor stimulation activates adenylate cyclase leading to an increase in the intracellular levels of cyclic AMP (Batzri et al., 1982a,b; Chew et al., 1980; Gespach et al., 1982; Soll and Wollin, 1979). In contrast, gastrin and acetylcholine have been shown to elevate intracellular levels of calcium as a result of both inositol trisphosphate-induced release of calcium from intracellular stores and calcium influx accross the plasma membrane (Negulescu and Machen, 1988; Chew and Brown, 1986; Muallem and Sachs, 1984). These data suggest that there are at least two parallel intracellular pathways involved in the stimulation of acid secretion, which can potentially interact at the level of the parietal cell. For example, the potentiation observed between histamine and acetylcholine in canine parietal cells from measurments of oxygen uptake and aminopyrine accumulation (Soll, 1978, 1982) could be secondary to an indirect effect of calcium on adenylate cyclase activity, analogous to that seen with H_1-receptor stimulation in brain slices (Donaldson et al., 1988b). However, at present there is no evidence to suggest that there is a synergistic interaction between the intracellular signals in parietal cells under conditions in which potentiation of the secretory response occurs between histamine and carbachol (Soll and Berglindh, 1987). Indeed, the only interaction seen in isolated rat gastric mucosal cells is an inhibitory action of cyclic AMP-elevating agents on muscarinic receptor-mediated inositol phospholipid hydrolysis (Puurunen et al., 1987).

A striking feature of the effect of histamine H_2-receptor stimulation on intracellular second-messenger formation in parietal cells is that, in addition to raising cyclic AMP levels, histamine also releases calcium from intracellular stores (see above; Chew, 1986; Chew and Brown, 1986; Negulescu and Machen, 1988; Malinowska et al., 1988). The exact role that this calcium release plays remains to be established, but it is notable that a cyclic AMP-mediated accumulation of aminopyrine in response to histamine is still demonstrable following depletion of the intracellular calcium pool in cells buffered intracellularly with the calcium chelators quin-2 and fura-2 (Malinowska et al., 1988).

b. SMOOTH MUSCLE RELAXATION. H_2-receptor stimulation produces relaxation of smooth muscle in a number of tissues including airway (Eyre and Chand, 1982; Foreman et al., 1985b; Chand et al., 1980; Vincenc et al., 1984) and vascular (Reinhardt and Ritter, 1979; Edvinsson et al., 1983; Gross et al., 1981; Ottososon et al., 1988, 1989) smooth muscle. It seems likely that this effect of H_2-receptor stimulation is associated with an increase in the intracellular levels of cyclic AMP, but the data available concerning the effect of H_2-receptor stimulation on adenylate cyclase activity in smooth muscle cells are rather limited (Reinhardt and Ritter, 1979; Karnushina et al., 1980).

c. EFFECT ON CARDIAC MUSCLE. Histamine is present in high concentrations in cardiac tissues in most animal species (Cabanie and Godfraind, 1988; Bristow et al., 1982b; Levi et al., 1982). In guinea pig heart H_2-receptors mediate a positive chronotropic effect in right atria (Levi et al., 1982; Black et al., 1972) and a positive inotropic effect in ventricular muscle (Steinberg and Holland, 1975; Verma and McNeill, 1977; Eckel et al., 1982; Hattori and Kanno, 1985). Histamine is a potent stimulant of adenylate cyclase activity in guinea pig and human cardiac muscle (Johnson, 1982), and there is strong evidence that the cardiac effects of H_2-receptor stimulation are, like β_1-adrenoceptor responses, mediated via cyclic AMP (Bristow et al., 1982; Cabanie and Godfraind, 1988). Thus, it has been proposed that in ventricular

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muscle H_2-receptor stimulation increases I_{Ca} following cyclic AMP-dependent phosphorylation of voltage-sensitive calcium channels (Levi and Alloatti, 1988). Consistent with this hypothesis are the findings that H_2-receptor stimulation can restore Ca^{2+}-dependent electrical and mechanical responses in potassium-depolarised cardiac preparations (Inui and Imamura, 1976; Gristwood et al., 1981; Hattori et al., 1983; Hattori and Levi, 1984). Recent patch-clamp studies have confirmed that H_2-receptor stimulation increases the amplitude of I_{Ca} in single guinea pig ventricular myocytes (Levi and Alloatti, 1988; Hescheler et al., 1987; see section B, 2, c above).

d. H_2-RECEPTORS AND THE IMMUNE SYSTEM. Histamine is well known as a mediator of immediate hypersensitivity reactions, but recent work has suggested that it may have an important role as a modulator of the immune response (Plaut and Lichtenstein, 1982; Melmon and Khan, 1987). Histamine can inhibit the chemotactic responsiveness of basophils (Lett-Brown and Leonard, 1977) and release of histamine from basophils and mast cells via an action on H_2-receptors (Bourne et al., 1971; Lichtenstein and Gillespie, 1975; Ting et al., 1980; Plaut and Lichtenstein, 1982). However, much recent interest has centered around the effect of H_2-receptor stimulation on various lymphocyte subsets (Melmon and Khan, 1987).

Histamine, via an action on H_2-receptors, can inhibit a variety of lymphocyte functions, including the proliferative response to mitogens (Plaut and Lichenstein, 1982), antibody synthesis by antibody-secreting B cells (Melmon et al., 1974), cell-mediated cytolysis (Schwartz et al., 1980b; Melmon et al., 1981), and production of lymphokines (Bourne et al., 1976). Considerable work has been done on the inhibitory effect of raised intracellular cyclic AMP on the immune system (Plaut and Lichtenstein, 1982; Khan et al., 1985), and it seems likely that this second messenger is responsible for many of the effects of H_2-receptor stimulation.

Histamine has been shown to elevate cyclic AMP levels in neutrophils (Gespach and Abita, 1982), basophils (Lichtenstein and Gillespie, 1975), and subsets of T lymphocytes (Khan et al., 1985; Melmon and Khan, 1987). Large histamine H_2-receptor-mediated stimulations of cyclic AMP accumulation have been observed in human suppressor T cells , whereas helper/inducer T cells and cytotoxic T cells are much less responsive (Khan et al., 1985). However, after mitogenic stimulation with either concanavalan A or phytohaemagglutinin, there is a dramatic rise in the cyclic AMP response to H_2-stimulation in helper/inducer T and cytotoxic T cells but not in suppressor T cells (Khan et al., 1985). The increased responsiveness of both cytotoxic T and helper/inducer T cells can, however, be prevented by coincubation with suppressor T cells during mitogenic stimulation. This modulation of receptor expression/function by mitogens and supressor cells appears to be specific for the H_2-receptor because no change in responsiveness was observed with isoprenaline (Khan et al., 1985; Melmon and Khan, 1987).

Histamine (via H_2-receptor stimulation) can induce the suppressor capacity of suppressor T cells and these cells can then inhibit mitogen-induced helper/inducer T cell proliferation and B cell differentiation (Sansoni et al., 1985). These data suggest that histamine-inducible suppressor cells may be important for normal immunoregulation and raises the possibility for the use of H_2-selective and lymphocyte-selective agonists as immunosuppressant agents.

An exciting advance in this area of research has been provided by the development of lymphocyte-specific histamine derivatives (Melmon and Khan, 1987; Khan et al., 1986). A number of histamine congeners have now been produced (table 4) that contain spacer groups of varying length between the histamine moiety and various aromatic modifying groups (Melmon and Khan, 1987; Khan et al., 1986). A number of these compounds (table 4) are up to 40,000 times more potent than histamine on the cyclic AMP response in lymphocytes but inactive on the H_2-receptor in guinea pig myocardium. The presently available data suggest that the histamine receptor-mediating cyclic AMP accumulation in murine cloned cytolytic T cells and natural suppressor cells resembles the H_2-receptor in that the responses to histamine and dimaprit are competitively antagonised by cimetidine (K_i = 0.1 μM) (Khan et al., 1986). However, there were marked differences in the antagonist potencies of cimetidine against the different histamine congener agonists, although all responses were inhibited by 0.1 mM cimetidine (Khan et al., 1986). This observation, taken together with the markedly different agonist profile in lymphocytes and cardiac H_2-receptors, raises the possibility that the H_2-receptor on lymphocytes may be different from H_2-receptors in other tissues.

C. Histamine H_3-Receptor

1. Ligand-binding studies. Advantage has been taken of the high affinity of R-(α)-methylhistamine for the histamine H_3-receptor in mammalian brain in the development of a radioactive probe for this receptor subtype. Studies with [^{3}H]R-(α)-methylhistamine have revealed binding sites in rat cerebral cortex (30 fmol/mg protein) with the general characteristics of histamine H_3-receptors (Arrang et al., 1987a). The specific binding of [^{3}H] R-(α)-methylhistamine in rat cerebral cortex is displaceable by a range of H_3-receptor ligands, although at present the number of compounds tested is rather limited. There is an excellent agreement between the dissociation constant of the antagonist, thioperamide, determined in studies of ligand-binding and H_3-receptor function, but the K_i values determined for agonists are generally 5 to 10 times lower than their corresponding EC_{50} values in functional studies (Arrang et al., 1987a). The reason for this remains to be determined, but it is possible that the

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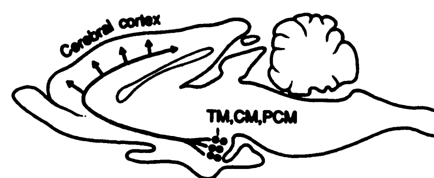
TABLE 4
Activity of histamine congeners on murine lymphocytes

	$\text{Imidazole-}CH_2\text{-}CH_2\text{-}NH\text{-}X$ (HN N ring)	Relative potencies: Natural suppressor (H_2)	Relative potencies: Cytolytic T cells (H_2)	Guinea pig heart (H_2)
(1)	H (Histamine)	1.0	1.0	1.0
(2)	$CH(CH_3)\text{-}(CH_2)_4\text{-}C(=O)\text{-}NH\text{-}C_6H_4\text{-}CF_3$	43,000	43,000	Inactive
(3)	$CH(CH_3)\text{-}(CH_2)_3\text{-}C(=O)\text{-}NH\text{-}C_6H_4\text{-}CH_3$	3,800	1,550	0.01
(4)	$CH(CH_3)\text{-}(CH_2)_4\text{-}C(=O)\text{-}NH\text{-}C_6H_4\text{-}CH_3$	3.0	4.6	7.0
(5)	$CH(CH_3)\text{-}(CH_2)_4\text{-}C(=O)\text{-}NH\text{-}(CH_2)_3\text{-}CH_3$	Inactive	Inactive	0.01

equilibrium binding of the ^{3}H-agonist may be to some high-affinity agonist-induced conformation of the H_3-receptor (Arrang et al., 1987a). This problem will only be resolved when radiolabeled antagonist probes for this receptor are available.

Autoradiographic studies with [^{3}H]*R*-(α)-methylhistamine have demonstrated the presence of thioperamide-displaceable binding in a number of rat brain regions, particularly the cerebral cortex, striatum, hippocampus, olfactory nuclei, and bed nucleus of the stri terminalis, which receive ascending histaminergic projections from the magnocellular nuclei of the posterior hypothalamus (Arrang et al., 1987a). Dense labeling is also observed in the premammilary area which contains the majority of the histamine-containing cell bodies (Arrang et al., 1987a). Very low density (approximately 5 fmol/mg protein) labeling has been observed in guinea pig lung parenchymal membranes (Arrang et al., 1987a), indicating the presence of H_3-receptors outside of the CNS (see below).

2. *Functional studies.* a. INHIBITION OF HISTAMINE RELEASE. The presence of H_3-receptors on histamine nerve terminals was first demonstrated by Arrang et al. (1983) using slices of rat cerebral cortex loaded with [^{3}H] histidine (fig. 4). In these assays a nonsuperfused system was used and the inhibitory action of H_3-agonists investigated against potassium- or veratridine-induced [^{3}H] histamine release (Arrang et al., 1983, 1985a,b, 1987a, 1988a,b; Hill and Straw, 1988). In this system, the maximum inhibitory effect (approximately 60% under optimal conditions) was progressively diminished as the strength of the displacing stimulus or the extracellular calcium concentration was increased (Arrang et al., 1985b). This suggests that H_3-receptors may act to restrict the influx of calcium ions, which is essential for histamine release (Arrang et al., 1983, 1985b; Hill and



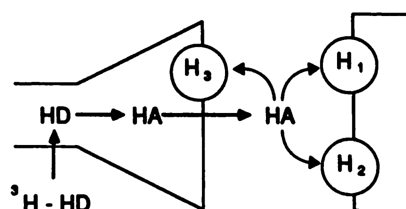


FIG. 4. Presynaptic histamine H_3-receptors control histamine release from ascending histaminergic fibres in rat cerebral cortex. The cell bodies are restricted to the tuberal magnocellular nucleus (TM), caudal magnocellular nucleus (CM), and postmamillary caudal magnocellular nucleus (PCM). Abbreviations: HD, histidine; HA, histamine.

Straw, 1988), into the histamine-containing nerve terminals. Furthermore, because there is a marked enhancement of depolarisation-induced release of [^{3}H]histamine by H_3-antagonists under these experimental conditions, it is likely that the overall response is influenced by the tonic action of endogenously released histamine (Arrang et al., 1983, 1985b, 1987a).

H_3-receptor-mediated inhibition of histamine release is not confined to rat cerebral cortex, and similar responses have been observed in rat striatum, hippocampus, and hypothalamus (Arrang et al., 1985b) and in human cerebral cortex (Arrang et al., 1988a). In this latter tissue, both *R*-(α)-methylhistamine and thioperamide were used to define the H_3-receptor with quantitatively similar results to those obtained in rat cerebral cortex (Arrang et al., 1988a).

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More recent studies have investigated the effect of H_3-receptor ligands on electrically stimulated [^{3}H]histamine release from superfused slices of rat cerebral cortex (Van der Werf et al., 1987; Van der Werf and Timmerman, 1989). In this system [^{3}H]histamine release varies with both stimulus frequency and duration (Van der Werf et al., 1987). The effectiveness of H_3-receptor stimulation is also sensitive to the frequency of electrical stimulation. Thus, in contrast to the nonperfused assay system, the release of [^{3}H]histamine can be completely prevented by 1 μM histamine at frequencies up to 10 Hz. At higher frequencies (20 to 30 Hz), however, the maximal inhibition of histamine release is markedly reduced, and the EC_{50} value is increased (Van der Werf et al., 1987). This latter result suggests that there may be a spare H_3-receptor reserve in this tissue (Van der Vliet et al., 1988). This conclusion is supported by studies with a partial H_3-agonist, VUF8621, in which only the maximal response, and not the EC_{50} value, varied with stimulus frequency (Vliet et al., 1988).

b. INHIBITION OF HISTAMINE SYNTHESIS. In addition to increasing [^{3}H]histamine release from rat cerebral cortical slices, potassium depolarisation is associated with an increased formation of [^{3}H]histamine from [^{3}H] histidine via the action of the specific histamine-synthesising enzyme L-histidine decarboxylase (Arrang et al., 1983; Hill and Straw, 1988). In a similar fashion to the H_3-receptor-mediated control of histamine release, the histamine synthesis induced by depolarising stimuli can be attenuated by exogenously applied histamine (Arrang et al., 1987b). This effect can be mimicked by R-(α)-methylhistamine and antagonised by burimamide, impromidine, and thioperamide, indicating the involvement of H_3-receptors (Arrang et al., 1987a,b). It is notable that the K_i values determined from inhibition of the H_3-receptor-induced inhibition of histamine synthesis consistently differ by a factor of 4 to 8 from the values similarly obtained from studies of histamine release (e.g., K_i = 4 nM and 31 nM for thioperamide from studies of release and synthesis, respectively). The reason for this is unclear, but it may be due to methodological differences in the measurement of the two parameters.

The effect of the two H_3-selective ligands, R-(α)-methylhistamine and thioperamide, on histamine synthesis and metabolism has been investigated in vivo (Arrang et al., 1987a; Oishi et al., 1989; Garbarg et al., 1989). In rat cerebral cortex, intravenous or oral administration of R-(α)-methylhistamine (10 to 30 mg/kg) produced a marked (up to 65%) inhibition of [^{3}H]histamine synthesis which could be reversed by intraperitoneal administration of thioperamide (10 mg/kg) (Arrang et al., 1987a; Garbarg et al., 1989). Interestingly, administration of thioperamide alone produced a marked increase in histamine synthesis indicative of the presence of a degree of tonic inhibitory H_3-receptor stimulation (Arrang et al., 1987a).

Effects of in vivo adminstration of both R-(α)-methylhistamine and thioperamide have also been observed in peripheral tissues, notably rat lung, abdominal skin, and spleen (Arrang et al., 1987a). In the case of rat lung, thioperamide significantly increased histamine synthesis. This is perhaps suggestive of an endogenous regulation by histamine. The cell types involved in these peripheral tissues are not known but may include mast cells or cells undergoing rapid tissue growth and regeneration (Hill, 1987b).

c. INHIBITION OF THE RELEASE OF OTHER NEUROTRANSMITTERS. Discrepancies in the distribution of [^{3}H] R-(α)-methylhistamine-binding sites and the levels of histidine decarboxylase suggest that H_3-receptors may not be confined to histamine-containing neurones in the mammalian CNS (Arrang et al., 1987a; Van der Werf and Timmerman, 1989). Support for this contention has been provided by Schlicker et al. (1988) who produced preliminary evidence that H_3-receptor stimulation can inhibit the electrically evoked release of [^{3}H]5-HT from rat cerebral cortical slices. Thus, the inhibitory effect of histamine (10 μM) on 5-HT release was antagonised by 32 μM burimamide and 1 μM impromidine but not by 10 μM pheniramine or 3.2 μM ranitidine (Schlicker et al., 1988). Recent studies have indicated that histamine release in mammalian brain can also be regulated by muscarinic (Gulat-Marnay et al., 1989a) and α_2-adrenoceptor stimulation (Hill and Straw, 1988; Gulat-Marnay et al., 1989b); thus, it is perhaps not surprising that H_3-receptors may regulate the release of other neurotransmitters. More quantitative studies of the effect of H_3-receptor ligands on other neurotransmitter systems have been obtained on peripheral tissues.

In guinea pig mesenteric artery, perivascular nerve stimulation produces an excitatory junction potential in vascular smooth muscle cells that can be inhibited by histamine presynatically (Ishikawa and Sperelakis, 1987). This effect is mimicked by N-α-methylhistamine and can be competitively antagonised by both impromidine (K_i = 48 nM) and burimamide (K_i = 330 nM), indicating that H_3-receptors may produce vasodilatation in this tissue by inhibiting the release of sympathetic neurotransmitters (Ishikawa and Sperelakis, 1987). Recent data also indicate that H_3-receptors in guinea pig ileum and trachealis may regulate the activity of the parasympathetic nervous system (Barnes and Ichinose, 1989; Ichinose et al., 1989; Ichinose and Barnes, 1989; Trzeciakowski, 1987; Tamura et al., 1988).

In guinea pig ileum, transmural stimulation of the myenteric plexus elicits a cholinergically mediated contraction that can be inhibited presynaptically by histamine and Nα-methylhistamine in the presence of the H_1-receptor antagonist mepyramine (Trzeciakowski, 1987; Fjalland, 1979). Impromidine antagonises this inhibitory effect with a K_B value (26 nM) very similar to that observed in other H_3-receptor systems (Trzecia-

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kowski, 1987). A similar observation has been made in guinea pig trachea and human bronchi where H_3-receptors modulate cholinergic neurotransmission at postganglionic vagal nerve endings (Ichinose et al., 1989; Barnes and Ichinose, 1989; Ichinose and Barnes, 1989). Electrophysiological studies in guinea pig ileum indicate that H_3-receptors may also regulate neurotransmission at nicotinic synapses of parasympathetic ganglia in the myenteric plexus (Tamura et al., 1988). There are also preliminary indications that H_3-receptors may be able to inhibit the release of tachykinins from nonadrenergic noncholinergic nerves in both of these tissues (Barnes and Ichinose, 1989; Ambache et al., 1973).

There is one report of a direct vasodilation of potassium-contracted rabbit middle cerebral artery produced by *R*-(α)-methylhistamine (Ea-Kim and Oudart, 1988). In this study the concentration-response curve was not affected by mepyramine or cimetidine but was competitively antagonised by 1 μM impromidine (K_B = approximately 59 nM, calculated from data of Ea-Kim and Oudart, 1988). These data indicate that this is an H_3-receptor-mediated effect and provides the first indication that these receptors may not be confined to presynaptic nerve endings.

3. Interactions with effector systems. The mechanism underlying the inhibitory effect of H_3-receptor stimulation on neurotransmitter release in central and peripheral tissues remains to be established. However, comparison with other receptor systems, known to have a similar effect on neurotransmitter release (e.g., adenosine A_1-receptor, opiate receptor, and α_2-adrenoceptor), suggests a number of possibilities for the effector systems linked to the H_3-receptor. The possibilities include inhibition of adenylate cyclase activity, activation of potassium channels, and inhibition of voltage-dependent calcium channels (Fredholm and Dunwiddie, 1988; North, 1989). Studies in slices of guinea pig hippocampus have shown that the H_3-agonist *R*-(α)-methylhistamine is not able to inhibit dimaprit-induced cyclic AMP accumulation (Garbarg et al., 1989), suggesting that H_3-receptors are not negatively linked to adenylate cyclase.

V. Other Histamine Receptors

A. A Role for Histamine in Tissue Growth and Repair

Although most studies of the physiological role of histamine have concentrated on the extracellular actions of the endogenous amine released from histaminergic nerve terminals or mast cells, there are indications that histamine may have a role in tissue growth and repair (Kahlson and Rosengren, 1971). The activity of the enzyme, histidine decarboxylase, which catalyses the formation of histamine from histidine, has been reported to be high in a number of rapidly growing tissues including rat foetal tissues, tissues involved in wound healing, certain tumour cells, and skin under the influence of tumour-producing phorbol esters (Ishikawa et al., 1970; Watanabe et al., 1981; Bartholeyns and Bouclier, 1984; Bartholeyns and Fozard, 1985). These observations led Kahlson and Rosengren (1971) to propose that newly synthesised (nascent) histamine could be involved in cell proliferation, perhaps via an intracellular action. Support for this hypothesis has been provided by the observations that the highly specific and irreversible histidine decarboxylase inhibitor, *S*-(α)-fluoromethylhistidine can slow tumour growth (Bartholeyns and Fozard, 1985; Bartholeyns and Bouclier, 1984).

Preliminary evidence supporting an intracellular second-messenger role for histamine has been obtained from measurements of platelet aggregation (Saxena et al., 1989). This study showed that the platelet aggregation induced by phorbol-12-myristate-13-acetate or collagen is accompanied by an elevation in intracellular levels of histamine and that both responses can be inhibited by *S*-(α)-fluoromethylhistidine. The inhibitory effect of the histidine decarboxylase inhibitor could, however, be reversed by adding histamine to platelets permeabilised with saponin (Saxena et al. 1989). It was notable, however, that histamine on its own was not able to induce aggregation in permeabilised platelets. Interestingly, platelet aggregation induced by phorbol-12-myristate-13-acetate was also inhibited by N,N,diethyl-2-[4-(phenylmethyl)phenoxy]ethamine in a manner that could be reversed (by approximately 40%) by histamine in permeabilised platelets (Saxena et al., 1989).

N,N,Diethyl-2-[4-(phenylmethyl)phenoxy]ethamine is a paradiphenylmethane derivative which like tamoxifen binds with high affinity to the microsomal antioestrogen-binding site in rat liver (Brandes and Hermonat, 1984). It is able to displace [^{3}H]histamine from rat cerebral cortical membranes with a K_i of 4 μM (Brandes et al., 1987). This is within the concentration range that N,N,diethyl-2-[4-(phenylmethyl)phenoxy]ethamine can inhibit growth of cultured MCF-7 human breast cancer cells, an effect that can be reversed by L-histidine administration (Brandes et al., 1987). However, although the evidence that N,N,diethyl-2-[4-(phenylmethyl) phenoxy]ethamine (and tamoxifen at high doses) can inhibit the actions of histamine at an intracellular receptor site is still very circumstantial, the attraction of the hypothesis should act as the stimulus for future research on the role of histamine in tissue growth and repair.

B. Invertebrate Histamine Receptors

A considerable amount of evidence has accumulated to suggest that histamine may function as a synaptic neurotransmitter in invertebrate nervous systems, particularly in the case of the mollusc *Aplysia* (Weinreich et al., 1975; Weinreich, 1977; Gruol and Weinreich, 1979) and the insect photoreceptor (Hardie, 1987, 1988; Nassael et al., 1988). However, there are only one or two reports in which attempts have been made to characterise the pharmacological properties of the histamine receptors mediating responses in these tissues.

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Two distinct hyperpolarising responses have been observed in response to histamine on the somal membranes of various identified *Aplysia* neurones (Gruol and Weinreich, 1979). These are a fast biphasic response and a slowly developing monophasic component which appear to be mediated by conductance increases to chloride and potassium ions, respectively (Gruol and Weinreich, 1979). Recent patch-clamp studies in identified neurons of the abdominal ganglion of *Aplysia* suggest that the histamine receptor coupled to potassium channels mediates its effect via a pertussis toxin-sensitive GTP-binding protein (Sasaki and Sato, 1987).

Several histamine analogues, most notably 2-methylhistamine and 4-methylhistamine, were able to mimick the effect of histamine on the slow potassium current which could be selectively and competitively antagonised by 10 μM cimetidine but not by other H_2-antagonists (Gruol and Weinreich, 1979). In contrast, neither 2-methyl- or 4-methylhistamine elicited a fast chloride-dependent response, and the response to histamine was not blocked by any H_1- or H_2-receptor antagonists (Gruol and Weinreich, 1979). The histamine-stimulated chloride current was, however, inhibited by tubocurarine and strychnine (Gruol and Weinreich, 1979). These data indicated that two pharmacologically distinct histamine receptors mediate responses to histamine in *Aplysia*, which are very different from vertebrate histamine receptors.

In large monopolar cells, which are postsynaptic to photoreceptors in the housefly *Musca domestica*, application of histamine produces a rapid, chloride-mediated, hyperpolarisation (Hardie, 1987). The effect of iono-phoresed histamine can be potently antagonised by hexamethonium, gallamine, and decamethonium and to a lesser extent by several H_2-antagonists (Hardie, 1988). There is also circumstantial evidence that the hyperpolarising response to histamine may also contain a potassium current similar to that observed in *Aplysia* neurons (Hardie, 1987). Thus, it is possible that the in vivo pharmacological characterisation (Hardie, 1988) of the response to histamine in large monopolar cells may be complicated by the presence of these two components and may actually resemble more closely that observed in *Aplysia* (Gruol and Weinreich, 1979).

Patch-clamp analysis of the chloride current in housefly large monopolar cells provides strong evidence that the histamine receptor mediating this effect is a ligand-gated chloride channel (Hardie, 1989). Thus, the presently available evidence supports the existence of two invertebrate histamine receptors, one of which is a ligand-gated chloride channel (which can be antagonised by strychnine, gallamine, and a number of other nicotinic ligands) and the other of which controls the opening of a potassium channel via a pertussis toxin-sensitive G protein (which can be competitively antagonised by cimetidine).

VI. Summary and Conclusions

It is clear from the preceding overview of histamine receptor pharmacology that research into the pharmacology of histamine receptors is at an exciting stage of development. The rapid advance of molecular biology should soon see the structural identification and cloning of all three of the major vertebrate histamine receptors. Further work will continue toward enhancing our understanding of the control by histamine of intracellular signaling via H_1-and H_2-receptors, and the rapid explosion of work on the H_3-receptor should begin to unravel the mechanisms underlying its actions, perhaps via effects on ionic channels. The potential role of histamine as an intracellular second messenger raises exciting possibilities, as does the search for a histamine receptor analogous to the ligand-gated ion channel in the invertebrate nervous system.

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REFERENCES

ABDEL-LATIF, A. A.: Calcium-mobilizing receptors, polyphosphoinositides and the generation of second messengers. Pharmacol. Rev. **38:** 227–272, 1986.

ACEVES, J., MARISCAL, S., MORRISON, K. E., AND YOUNG, J. M.: The binding of doxepin to histamine H_1-receptors in guinea-pig and rat brain. Br. J. Pharmacol. **84:** 417–424, 1985.

ADAM, H. M., AND HYE, H. K. A.: Concentration of histamine in different parts of brain and hypophysis of cat and its modification by drugs. Br. J. Pharmacol. **28:** 137–152, 1966.

ADAMSKI, S. W., SVENSJO, E., AND GREGA, G. J.: Effects of AVP and DDAVP on histamine-induced increases in macromolecular permeability in the hamster cheek pouch. Microcirc. Endothelial Lymphatics **2:** 41–53, 1985.

AIRAKSINEN, M. S., AND PANULA, P.: The histaminergic system in the guinea-pig brain. J. Comp. Neurol. **273:** 163–186, 1988.

ALEXANDER, S. P. H., GROUT, R. J., HILL, S. J., AND KENDALL, D. A.: The adenosine receptors modulating the accumulation of inositol phosphates and cyclic AMP in brain slices are different. Br. J. Pharmacol. **96:** 135P, 1989.

AL-GADI, M., AND HILL, S. J.: Characterization of histamine receptors mediating the stimulation of cyclic AMP accumulation in rabbit cerebral cortical slices. Br. J. Pharmacol. **85:** 877–888, 1985.

AL-GADI, M., AND HILL, S. J.: The role of calcium in the cyclic AMP response to histamine in rabbit cerebral cortical slices. Br. J. Pharmacol. **91:** 213–222, 1987.

AMBACHE, N., KILLICK, S. W., AND ABOO ZAR, M.: Antagonism by burimamide of inhibitions induced by histamine in plexus-containing longitudinal muscle preparations from guinea-pig ileum. Br. J. Pharmacol. **48:** 362–363P, 1973.

AMERININ, S., FRANCONI, F., LEDDA, F., MANTELLI, L., AND MUGELLI, A.: H_1- and H_2-receptors in the guinea-pig heart: an electrophysiological study. Agents Actions **12:** 10–18, 1982.

ANDO-YAMAMOTO, M., KIYAMA, H., HAYASHI, H., FUKUI, H., TOHYAMA, M., WATANABE, T., AND WADA, H.: Demonstration of histaminergic neurons in horizontal cells of guinea-pig retina. Brain Res. **410:** 269–274, 1987.

ARBONES, L., CLARO, E., PICATOSTE, F., AND GARCIA, A.: [^{3}H]-mepyramine binding to histamine H_1-receptors in bovine retina. Biochem. Biophys. Res. Commun. **135:** 445–450, 1986.

ARBONES, L., PICATOSTE, F., AND GARCIA, A.: Histamine H_1-receptors mediate phosphoinositide hydrolysis in astrocyte-enriched primary cultures. Brain Res. **450:** 144–152, 1988.

ARRANG, J. M., DEFONTAINE, N., AND SCHWARTZ, J. C.: Phencyclidine blocks histamine H_3-receptors in rat brain. Eur. J. Pharmacol. **157:** 31–35, 1988b.

ARRANG, J. M., DEVAUX, B., CHODKIEWICZ, J. P., AND SCHWARTZ, J. C.: H_3-receptors control histamine release in human brain. J. Neurochem. **51:** 105–108, 1988a.

ARRANG, J. M., GARBARG, M., LANCELOT, J. C., LECOMPTE, J. M., POLLARD, H., ROBBA, M., SCHUNACK, W., AND SCHWARTZ, J. C.: Highly potent and selective ligands for histamine H_3-receptors. Nature (Lond.) **327:** 117–123, 1987a.

ARRANG, J. M., GARBARG, M., QUACH, T. T., TUONG, M. D., YERAMIAN, E., AND SCHWARTZ, J. C.: Actions of betahistine at histamine receptors in the brain. Eur. J. Pharmacol. **111:** 73–84, 1985a.

ARRANG, J. M., GARBARG, M., AND SCHWARTZ, J. C.: Auto-inhibition of brain histamine release mediated by a novel class (H_3) of histamine receptor. Nature (Lond.) **302:** 832–837, 1983.

ARRANG, J. M., GARBARG, M., AND SCHWARTZ, J. C.: Autoregulation of histamine release in brain by presynaptic H_3-receptors. Neuroscience **15:** 553–562, 1985b.

ARRANG, J. M., GARBARG, M., AND SCHWARTZ, J. C.: Autoinhibition of histamine synthesis by presynaptic H_3-receptors. Neuroscience **23:** 149–157, 1987b.

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ARRANG, J. M., SCHWATZ, J. C., AND SCHUNACK, W.: STEREOSELECTIVITY OF THE HISTAMINE H_3-presynaptic autoreceptor. Eur. J. Pharmacol. 117: 109–114, 1985c.
ARUNLAKSHANA, O., AND SCHILD, H. O.: Some quantitative uses of drug antagonists. Br. J. Pharmacol. Chemother. 14: 153–161, 1959.
ASH, A. S. F., AND SCHILD, H. O.: Receptors mediating some actions of histamine. Br. J. Pharmacol. Chemother. 27: 427–439, 1966.
ASSIMOCOPOULOS-JEANNET, R. D., BLACKMORE, P. R., AND EXTON, J. H.: Studies on α-adrenergic activation of hepatic glucose output: studies on role of calcium in α-adrenergic activation of phosphorylase. J. Biol. Chem. 252: 2662–2669, 1977.
BAILEY, S. J., LIPPE, I. T., AND HOLZER, P.: Effect of the tachykinin antagonist, [D-Pro[4], D-Trp[7,9,10]] substance P-(4-11), on tachykinin- and histamine-induced inositol phosphate generation in intestinal smooth muscle. Naunyn-Schmiedebergs Arch. Pharmacol. 355: 296–300, 1987.
BARBIN, G., PALACIOS, J. M., RODERGAS, E., SCHWARTZ, J. C., AND GARBARG, M.: Characterization of the high-affinity binding sites of [^{3}H]-histamine in rat brain. Mol. Pharmacol. 18: 1–10, 1980.
BARKER, L. A., AND HOUGH, L. B.: Selectivity of 4-methylhistamine at H_1- and H_2-receptors in the guinea-pig isolated ileum. Br. J. Pharmacol. 80: 65–71, 1983.
BARNES, P. J., AND ICHINOSE, M.: H_3-receptors in airways. Trends Pharmacol. Sci. 10: 264, 1989.
BARTHOLEYNS, J., AND BOUCLIER, M.: Involvement of histamine in growth of mouse and rat tumors: antitumoral properties of monofluoromethylhistidine, an enzyme-activated irreversible inhibitor of histidine decarboxylase. Cancer Res. 44: 639–645, 1984.
BARTHOLEYNS, J., AND FOZARD, J. R.: Role of histamine in tumor development. Trends Pharmacol. Sci. 6: 123–125, 1985.
BATTY, I. R., NAHORSKI, S. R., AND IRVINE, R. F.: Rapid formation of inositol 1,3,4,5-tetrakisphosphate following muscarinic receptor stimulation of rat cerebral cortical slices. Biochem. J. 232: 211–215, 1985.
BATZRI, S., HARMON, J. W., AND THOMPSON, W. F.: Interaction of histamine with gastric mucosal cells: effect of histamine agonists on binding and biological response. Mol. Pharmacol. 22: 33–40, 1982a.
BATZRI, S., HARMON, J. W., AND THOMPSON, W. F.: Interaction of histamine with gastric mucosal cells: effect of histamine H_2-antagonists on binding and biological response. Mol. Pharmacol. 22: 41–47, 1982b.
BAUDRY, M., EVANS, J., AND LYNCH, G.: Excitatory amino acids inhibit stimulation of phosphatidylinositol metabolism by aminergic agonists in hippocampus. Nature (Lond.) 319: 329–331, 1986.
BEAVAN, M. A.: Anaphylactoid reactions to anesthetic drugs. Anesthesiology 55: 5–7, 1981.
BEAVAN, M. A.: Factors regulating availability of histamine at tissue receptors. *In* Pharmacology of Histamine Receptors, ed. by C. R. Ganellin and M. E. Parsons, pp. 103–145, Wright, Bristol, England, 1982.
BEAVAN, M. A., MOORE, J. P., SMITH, G. A., HESKETH, T. R., AND METCALF, J. C.: The calcium signal and phosphatidylinositol breakdown in 2H3 cells. J. Biol. Chem. 259: 7137–7142, 1984a.
BEAVAN, M. A., ROGERS, J., MOORE, J. P., HESKETH, T. R., SMITH, G. A., AND METCALF, J. C.: The mechanism of the calcium signal and correlation with histamine release in 2H3 cells. J. Biol. Chem. 259: 7129–7136, 1984b.
BECKER, C. G., AND NACHMAN, R. L.: Contractile proteins of endothelial cells, platelets and smooth muscle. Am. J. Pathol. 71: 1–20, 1973.
BERGLINDH, T.: Potentiation by carbachol and aminophylline of histamine and db-cyclic AMP-induced parietal cell activity in isolated gastric glands. Acta Physiol. Scand. 99: 75–84, 1977.
BERRIDGE, M. J.: Inositol trisphosphate and diacylglycerol as second messengers. Biochem. J. 220: 345–360, 1984.
BERRIDGE, M. J.: Inositol trisphosphate and diacylglycerol: two interacting second messengers. Annu. Rev. Biochem. 56: 159–193, 1987.
BERRIDGE, M. J., AND IRVINE, R. F.: Inositol trisphosphate, a novel second messenger in cellular signal transduction. Nature (Lond.) 312: 315–321, 1984.
BERRIDGE, M. J., AND IRVINE, R. F.: Inositol phosphates and cell signalling. Nature (Lond.) 341: 197–205, 1989.
BERRIDGE, M. J., DOWNES, C. P., AND HANLEY, M. R.: Lithium amplifies agonist-dependent phosphatidylinositol responses in brain and salivary glands. Biochem. J. 206: 587–595, 1982.
BERRIE, C. P., HAWKINS, P. T., STEPHENS, L. R., HARDEN, T. K., AND DOWNES, C. P.: Phosphatidylinositol-4,5-bisphosphate hydrolysis in turkey erythrocytes is regulated by p2y purinoceptors. Mol. Pharmacol. 35: 526–532, 1989.
BEST, L., BROOKS, K. J., AND BOLTON, T. B.: Relationship between stimulated inositol lipid hydrolysis and contractility in guinea-pig visceral longitudinal smooth muscle. Biochem. Pharmacol. 34: 2297–2301, 1985.
BIELKIEWICZ, B., AND COOK, D. A.: The binding of [^{3}H]-mepyramine to histamine H_1-receptors in monkey brain. Can. J. Physiol. Pharmacol. 63: 756–9, 1985.
BIELKIEWICZ-VOLLRATH, B., CARPENTER, J. R., SCHULZ, R., AND COOK, D. A.: Early production of 1,4,5-inositol trisphosphate and 1,3,4,5-inositol tetrakisphosphate by histamine and carbachol in ileal smooth muscle. Mol. Pharmacol. 31: 513–522, 1987.
BLACK, J., ARMOUR, C., JOHNSON, P., AND VINCENC, K.: The calcium dependence of histamine, carbachol and potassium chloride-induced contraction in human airways in vitro. Eur. J. Pharmacol. 125: 159–168, 1986.
BLACK, J. W., DUNCAN, W. A. M., DURANT, C. J., GANELLIN, C. R., AND PARSONS, M. E.: Definition and antagonism of histamine H_2-receptors. Nature (Lond.) 236: 385–390, 1972.
BLACK, J. W., GERSKOWITCH, V. P., AND LEFF, P.: Reflections on the classification of histamine receptors. *In* Pharmacology of Histamine Receptors, ed. by C. R. Ganellin and M. E. Parsons, pp 1–9, Wright, Bristol, England, 1982.
BLACK, J. W., AND SHANKLEY, N. P.: How does gastrin act to stimulate oxyntic cell secretion? Trends Pharmacol. Sci. 8: 486–490, 1987.
BLAKEMORE, R. C., BROWN, T. H., COOPER, D. G., DURANT, G. J., GANELLIN, C. R., IFE, R. J., PARSONS, M. E., RASMUSSEN, A. C., AND SACH, G. S.: SKF 93319: a specific antagonist of histamine at H_1- and H_2-receptors. Br. J. Pharmacol. 80: 437P, 1983.
BLAKEMORE, R. C., BROWN, T. H., DURANT, G. J., GANELLIN, C. R., PARSONS, M. E., RASMUSSEN, A. C., AND RAWLINGS, D. A.: SKF 93479, a potent and long acting histamine H_2-receptor antagonist. Br. J. Pharmacol. 74: 200P, 1981.
BOARDER, M. R., PLEVIN, R., AND MARRIOT, D. B.: Angiotensin II potentiates prostaglandin stimulation of cyclic AMP levels in intact bovine adrenal medulla cells but not adenylate cyclase in permeabilised cells. J. Biol. Chem. 263: 260–269, 1988.
BOLTON, T. B.: Mechanisms of action of transmitters and other substances on smooth muscle. Physiol. Rev. 59: 606–718, 1979.
BOLTON, T. B., AND CLARK, J. P.: Effects of histamine, high potassium and carbachol on ^{42}K efflux from longitudinal muscle of guinea-pig intestine. J. Physiol. 320: 347–361, 1981.
BOLTON, T. B., AND LIM, S. P.: Properties of calcium stores and transient outward currents in single smooth muscle cells of rabbit intestine. J. Physiol. 409: 385–401, 1989.
BOLTON, T. B., CLARK, J. P., KITMAURA, K., AND LANG, R. J.: Evidence that histamine and carbachol may open the same ion channels in longitudinal smooth muscle of guinea-pig ileum. J. Physiol. 320: 363–379, 1981.
BOMMER, M., LIEBISCH, D., KLEY, N., HERZ, A., AND NOBLE, E.: Histamine affects release and biosynthesis of opioid peptides primarily via H_1-receptors in bovine chromaffin cells. J. Neurochem. 49: 1688–1696, 1987.
BONNER, T. I., BUCKLEY, N. J., YOUNG, A. C., AND BRANN, M. R.: Identification of a family of muscarinic acetylcholine receptor genes. Science (Wash. DC) 237: 527–532, 1987.
BORCHAND, U., AND HAFNER, D.: Electrophysiological characterisation of histamine receptor subtypes in mammalian heart preparations. Nauyn-Schmiedebergs Arch. Pharmacol. 334: 294–302, 1986.
BOTTOMLEY, K. M. K., RISING, T. J., AND STEWARD, A.: Relative efficacies of H_2-receptor agonists in the guinea-pig right atrium. Br. J. Pharmacol. 84: 47P, 1985.
BOURNE, H. R., LICHTENSTEIN, L. M., MELMON, K. L., HENNEY, C. S., WEINSTEIN, Y., AND SHEARER, G. M.: Modulation of inflammation and immunity by cyclic AMP. Science (Wash. DC) 184: 19–28, 1976.
BOURNE, H. R., MELMON, K. L., AND LICHTENSTEIN, L. M.: Histamine augments leukocyte cyclic AMP and blocks antigenic histamine release. Science (Wash. DC) 173: 743–745, 1971.
BOUTHENET, M. L., RUAT, M., SALES, N., GARBARG, M., AND SCHWARTZ, J. C.: A detailed mapping of histamine H_1-receptors in guinea-pig central nervous system established by autoradiography with [^{125}I]-iodobolpyramine. Neuroscience 26: 553–600, 1988.
BRADSHAW, J., BRITTAIN, R. T., CLTHEROW, J. W., DALY, M. J., JACK, D. PRICE, B. J., AND STABLES, R.: Ranitidine: a new potent selective H_2-receptor antagonist. Br. J. Pharmacol. 66: 464P, 1979.
BRANDES, L. J., AND HERMONAT, M. W.: A diphenylmethane derivative specific for the antiestrogen binding site in rat liver microsomes. Biochem. Biophys. Res. Commun. 123: 724–728, 1984.
BRANDES, L. J., BOGDANOVIC, R. P., CAWKER, M. D., AND LABELLA, F. S.: Histamine and growth: interaction of antiestrogen binding site ligands with a novel histamine site that may be associated with calcium channels. Cancer Res. 47: 3025–4031, 1987.
BREGESTOVSKI, P., BAKHRAMOV, A., DANILOV, S., MOLDOBAEVA, A., AND TAKEDA, K.: Histamine-induced inward currents in cultured endothelial cells from human umbilical vein. Br. J. Pharmacol. 95: 429–436, 1988.
BREZENOFF, H. E., AND JENDEN, D. J.: Modification of arterial blood pressure in rats following microinjection of drugs into the posterior hypothalamus. Int. J. Neuropharmacol. 8: 593–600, 1969.
BREZENOFF, H. E., AND LOMAX, P.: Temperature changes following microinjection of histamine into thermoregulatory centres of the rat. Experientia 26: 51–52, 1970.
BRIMBLECOMBE, R. W., DUNCAN, W. A. M., DURANT, G. J., EMMETT, J. C., GANELLIN, C. R., AND PARSONS, M. E.: Cimetidine—a nonthiourea H_2-receptor antagonist. J. Int. Med. Res. 3: 86–92, 1975.
BRISTOW, D. R., HARE, J. R., HEARN, J. R., AND MARTIN, L. E.: Radioligand binding studies using ^{3}H-cimetidine and ^{3}H-ranitidine. Br. J. Pharmacol. 72: 547P–548P, 1981.
BRISTOW, L. J., AND BENNETT, G. W.: Biphasic effects of intra-accumbens histamine administration on spontaneous motor activity in the rat: a role for central histamine receptors. Br. J. Pharmacol. 95: 1292–1302, 1988.
BRISTOW, M. R., CUBICCIOTTI, R., GINSBURG, R., STINSON, E. R., AND JOHNSON, C. L.: Histamine-mediated adenylate cyclase stimulation in human myocardium. Mol. Pharmacol. 21: 671–679, 1982a.
BRISTOW, M. R., GINSBURG, R., AND HARRISON, D. C.: Histamine and the human heart: the other receptor system. Am. J. Cardiol. 49: 249–251, 1982b.

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BROTHERTON, A. F. A.: Induction of prostacyclin biosynthesis is closely associated with increased guanosine 3',5'-cyclic monophosphate accumulation in cultured human endothelium. J. Clin. Invest. 78: 1253–1260, 1986.
BROTHERTON, A. F. A., MACFARLANE, D. E., AND HOAK, J. C.: Prostacyclin biosynthesis in vascular endothelium is not inhibited by cyclic AMP: studies with 3-isobutyl-1-methylxanthine and forskolin. Thrombosis Res. 28: 637–647, 1982.
BROWN, E., KENDALL, D. A., AND NAHORSKI. S. R.: Inositol phospholipid hydrolysis in rat cerebral cortical slices: I. Receptor characterisation. J. Neurochem. 42; 1379–1387, 1984.
BROWN, E. A., GRIFFITHS, R., HARVEY, C. A., AND OWEN, D. A. A.: Pharmacological studies with SKF 93944 (temelestine), a novel histamine H_1-receptor antagonist with negligable ability to penetrate the central nervous system. Br. J. Pharmacol. 87: 569–578, 1986a.
BROWN, R. D., PRENDVILLE, P., AND CAIN, C.: α_1-adrenergic and H_1-histamine receptor control of intracellular Ca^{2+} in a muscle cell line: the influence of prior agonist exposure on receptor responsiveness. Mol. Pharmacol. 29: 531–539, 1986b.
BRUSCHI, G., BRUSCHI, M. E., REGOLISTI, G., AND BORGHETTI, A.: Myoplasmic Ca^{2+}-force relationship studied with fura-2 during stimulation of rat aortic smooth muscle. Am. J. Physiol. 254: H840–H854, 1988.
BULBRING, E., AND BURNSTOCK, G.: Membrane potential changes associated with tachyphylaxis and potentiation of the response to stimulating drugs in smooth muscle. Br. J. Pharmacol. Chemother. 15: 611–624, 1960.
BURGEN, A. S. V., AND HARBIRD, C. J.: The effect of sulphydryl block on the binding of H_1-antagonists to the muscarinic receptor. Br. J. Pharmacol. 80: 600–601, 1983.
BURKARD, W. P.: Histamine H_2-receptor binding with ^{3}H-cimetidine in brain. Eur. J. Pharmacol. 50: 449–450, 1978.
BUSSE, W. W., AND SOSMAN, J.: Decreased H_2 histamine response of granulocytes of asthmatic patients. J. Clin. Invest. 59: 1080–1087, 1977.
CABANIE, M., AND GODFRAIND, T.: The role of histamine in the cardiovascular system. Drugs Exp. Clin. Res. 14: 141–7, 1988.
CALCUTT, C. R., GANELLIN, C. R., GRIFFITHS, R., LEIGH, B. K., MAGUIRE, J. P., MITCHELL, R. C., MYLEK, M. E., PARSONS, M. E., SMITH, I. R., AND YOUNG, R. C.: Zolantidine (SKF 95282) is a potent selective brain-penetrating histamine H_2-receptor antagonist. Br. J. Pharmacol. 93: 69–78, 1988.
CAMERON, W., DOYLE, K., AND ROCKLIN, R. E.: Histamine type 1 (H1) receptor radioligand binding studies on normal T cell subsets, B cells and monocytes. J. Immunol. 136: 2116–2120, 1986.
CAMPOS, H. A.: A possible crossed histamine-containing pathway adjacent to the sympathetic system of rat vas deferens. J. Pharmacol. Exp. Ther. 244: 1121–1127, 1988.
CARMEN-KRZAN, M.: The effect of group selective reagents *N*-ethylmaleimide and dithiothreitol on histamine H_1-receptor binding sites in vascular smooth muscle membranes. Agents Actions 14: 561–565, 1984.
CARR, A. A., AND MEYER, D. R.: Synthesis of terfenadine. Arzneim Forsch. Drug Res. 32 (suppl. II): 1157–1159, 1982.
CARROLL, P. R., AND GLOVER, W. E.: Modification of cardiovascular responses to histamine by dithiothreitol. Br. J. Pharmacol. 59: 333–341, 1977.
CARSWELL, H., AND NAHORSKI, S. R.: Distribution and characteristics of histamine H_1-receptors in guinea-pig airways identified by [^{3}H]-mepyramine. Eur. J. Pharmacol. 81: 301–307, 1982.
CARSWELL, H., AND YOUNG, J. M.: Regional variation in the characteristics of histamine H_1-agonist-mediated breakdown of inositol phospholipids in guinea-pig brain. Br. J. Pharmacol. 89: 809–817, 1986.
CARSWELL, H., GALIONE, A. G., AND YOUNG, J. M.: Differential effect of temperature on histamine- and carbachol-stimulated inositol phospholipid breakdown in slices of guinea-pig cerebral cortex. Br. J. Pharmacol. 90: 175–182, 1987.
CARSWELL, H., GALIONE, A. G., AND YOUNG, J. M.: Histamine H_1-agonist stimulated breakdown of inositol phospholipids. *In* Frontiers in Histamine Research, Advances in the Biosciences, ed. by C. R. Ganellin and J. C. Schwartz, vol 51, pp. 27–38, Pergamon Press, London, 1985.
CARTER, T. D., HALLAM, T. J., CUSACK, N. J., AND PEARSON, J. D.: Regulation of P_{2y}-purinoceptor-mediated prostacyclin release from human endothelial cells by cytoplasmic calcium concentration. Br. J. Pharmacol. 95: 1181–1190, 1988.
CASALE, T. B., RODBARD, D., AND KALINGER, M.: Characterization of histamine H-1 receptors on human peripheral lung. Biochem. Pharmacol. 34: 3285–3292, 1985a.
CASALE, T. B., WESCOTT, S., RODBARD, D., AND KALINER, M.: Characterisation of histamine H-1 receptors on human mononuclear cells. Int. J. Immunopharmacol. 7: 639–645, 1985b.
CASY, A. F.: Chemistry of anti-H_1 histamine antagonists. In Handbook of Experimental Pharmacology, vol 18, part 2, ed. by M. Rocha e Silva, pp. 175–214, Springer-Verlag, Berlin, 1977.
CAVANAGH, R. L., USAKEWICZ, J. J., AND BUYNISKI, J. P.: A comparison of some of the pharmacological properties of etinidine, a new histamine H_2-receptor antagonist, with those of cimetidine, ranitidine and tiotidine. J. Pharmacol. Exp. Ther. 224: 171–179, 1983.
CHAND, N., AND EYRE, P.: Classification and biological distribution of histamine receptor sub-types. Agents Actions 5: 277–295, 1975.
CHAND, N., DHAWAN, B. N., SRIMAL, R. C., RAHAMANI, N. H., SHUKLA, R. K., AND ALTURA, B. M.: Reactivity of trachea, bronchi and lung strips to histamine and carbachol in rhesus monkeys. J. Appl. Physiol. 19: 729–734, 1980.
CHANG, R. S. L., AND SNYDER, S. H.: Histamine H_1-receptor binding sites in guinea-pig brain membranes: regulation of agonist interactions by guanine nucleotides and cations. J. Neurochem. 34: 916–922, 1980.
CHANG, R. S. L., TRAN, V. T., AND SNYDER, S. H.: Characteristics of histamine H_1-receptors in peripheral tissues labelled with [^{3}H]-mepyramine. J. Pharmacol. Exp. Ther. 209: 437–442, 1979a.
CHANG, R. S. L., TRAN, V. T., AND SNYDER, S. H.: Heterogeneity of histamine H_1-receptors: species variations in [^{3}H]-mepyramine binding in brain membranes. J. Neurochem. 32: 1653–1663, 1979b.
CHASIN, M., MAMRAK, F., AND SAMANIEGO, S. G.: Preparation and properties of a cell-free, hormonally responsive adenylate cyclase from guinea-pig brain. J. Neurochem. 22: 1031–1038, 1974.
CHENG, H. C., AND WOODWARD, J. K.: A kinetic study of the antihistamine effect of terfenadine. Arzneim Forsch. Drug Res. 32 (suppl. II): 1160–1166, 1982.
CHEW, C. S.: Differential effects of extracellular calcium removal and non-specific effects of Ca^{2+} antagonists on acid secretory activity in isolated gastric glands. Biochim. Biophys. Acta 846: 370–378, 1985.
CHEW, C. S.: Cholecystokinin, carbachol, gastrin, histamine and forskolin increase $[Ca^{2+}]_i$ in gastric glands. Am. J. Physiol. 250: G814–823, 1986.
CHEW, C. S., AND BROWN, M. R.: Release of intracellular Ca^{2+} and elevation of inositol trisphosphate by secretogogues in parietal and chief cells isolated from rabbit gastric mucosa. Biochim. Biophys. Acta 888: 116–125, 1986.
CHEW, C. S., AND HERSEY, S. J.: Gastrin stimulation of isolated gastric-glands. Am. J. Physiol. 242: G504–G512, 1982.
CHEW, C. S., HERSEY, S. J., SACHS, G., AND BERGLINDH, T.: Histamine responsiveness of isolated gastric glands. Am. J. Physiol. 238: G312–G320, 1980.
CHILVERS, E. R., CHALLISS, R. A. J., BARNES, P. J., AND NAHORSKI, S. R.: Mass changes of inositol (1,4,5)trisphosphate in trachealis muscle following agonist stimulation. Eur. J. Pharmacol. 164: 587–590, 1989.
CLARO, E., ARBONES, L., GARCIA, A., AND PICATOSTE, F.: Phosphoinositide hydrolysis mediated by histamine H_1-receptors in rat brain cortex. Eur. J. Pharmacol. 123: 187–196, 1986.
CLARO, E., GARCIA, A., AND PICATOSTE, F.: Histamine-stimulated phosphoinositide hydrolysis in developing rat brain. Mol. Pharmacol. 32: 384–390, 1987.
CLARO, E., GARCIA, A., AND PICATOSTE, F.: Carbachol and histamine stimulation of guanine-nucleotide-dependent phosphoinositide hydrolysis in rat brain cortical membranes. Biochem. J. 261: 29–35, 1989.
CLYMAN, R. I., BLACKSIN, A. S., SANDLER, J. A., MANGANIELLO, V. C., AND VAUGHAN, M.: The role of calcium in regulation of cyclic nucleotide content in human umbilical artery. J. Biol. Chem. 250: 4718–4721, 1976.
CLYMAN, R. I., SANDLER, J. A., MANGANIELLO, V. C., AND VAUGHAN, M.: Guanosine 3',5'-monophosphate and adenosine 3',5'-monophosphate content of human umbilical artery: possible role in perinatal arterial patency and closure. J. Clin. Invest. 55: 1020–1025, 1975.
CODE, C. F.: Histamine receptors and gastric secretion. *In* Pharmacology of Histamine Receptors, ed. by C. R. Ganellin and M. E. Parsons, pp. 217–235, Wright, Bristol, England, 1982.
COOK, D. A., KRUEGER, C. A., AND MICHALCHUK, A.: Temperature and histamine receptor function—what is really happening? Can J. Physiol. Pharmacol. 63: 751–755, 1985.
COSTA, E., AND GUIDOTTI, A.: Molecular mechanisms in the receptor action of benzodiazepines. Annu. Rev. Pharmacol. Toxicol. 19: 531–545, 1979.
COUPET, J., AND SZUCHS-MEYERS, V. A.: Brain histamine H_1- and H_2-receptors and histamine sensitive adenylate cyclase: effects of antipsychotics and antidepressants. Eur. J. Pharmacol. 74: 149–155, 1981.
COX, B., GREEN, M. D., AND LOMAX, P.: Thermoregulatory effects of histamine. Experientia 32: 498–500, 1976.
CRAWFORD, M. S. L., AND YOUNG, J. M.: $GABA_B$ receptor-mediated inhibition of histamine H_1-receptor-induced inositol phosphate formation in slices of rat cerebral cortex. J. Neurochem. 51: 1441–1447, 1988.
CREVELING, C. R., MCNEIL, E. T., MCCULLOH, D. H., AND DALY, J. W.: Membrane potentials in cell-free preparations from guinea-pig cerebral cortex: effect of depolarising agents and cyclic nucleotides. J. Neurochem. 35: 922–932, 1980.
CREWS, F. T., HIRATA, F., AND AXELROD, J.: Identification and properties of methyltransferases that synthesize phosphatidylcholine in rat brain synaptosomes. J. Neurochem. 34: 1491–1497, 1980.
CYBULSKY, D. L., KANDEL, S. I., WELLS, J. W., AND GORNALL, A. G.: Guanylylimidodiphosphate modulates [^{3}H]-histamine binding in a solubilised preparation from rat brain. Eur. J. Pharmacol. 72: 407–409, 1981.
DALE, M. M., AND OBIANIME, W.: Phorbol myristate acetate causes in guinea-pig lung parenchymal strip a maintained spasm which is relatively resistant to isoprenaline. FEBS LETT. 190: 6–10, 1985.
DALY, J. W.: Cyclic Nucleotides in the Nervous System, Raven Press, New York, 1977.
DALY, J. W., MCNEIL, E., PARTINGTON, C., NEUWIRTH, M., AND CREVELING, C. R.: Accumulation of cyclic AMP in adenine-labelled cell-free preparations from guinea-pig cerebral cortex: role of α-adrenergic and H_1-histaminergic receptors. J. Neurochem. 35: 326–337, 1980.
DALY, M. J., AND PRICE, B. J.: Ranitidine and other H_2-receptor antagonists: recent developments. *In* Progress in Medicinal Chemistry, vol 20, pp. 337-368, ed. by G. P. Ellis and G. B. West, Elsevier, Amsterdam, 1983.
DAMMANN, H. E., DREYER, M., KANGAH, R., MULLER, P., AND SIMON, B.:

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PHARM REV

PHARMACOLOGICAL REVIEWS

Optimal reduction of gastric acid secretion in the treatment of peptic ulceration. Drugs 35 (suppl. 3): 106–113, 1988.
DANOFF, S. K., AND YOUNG, J. M.: Is histamine potentiation of adenosine-stimulated cyclic AMP accumulation in guinea-pig cerebral cortical slices mediated by products of inositol phospholipid breakdown? Biochem Pharmacol. 36: 1177–1179, 1987.
DAUM, P. R., DOWNES, C. P., AND YOUNG, J. M.: Histamine-induced inositol phospholipid breakdown mirrors H_1-receptor density in brain. Eur. J. Pharmacol. 87: 497–498, 1983.
DAUM, P. R., DOWNES, C. P., AND YOUNG, J. M.: Histamine stimulation of inositol-1-phosphate accumulation in lithium-treated slices from regions of guinea-pig brain. J. Neurochem. 43: 25–32, 1984.
DAUM, P. R., HILL, S. J., AND YOUNG, J. M.: Histamine H_1-agonist potentiation of adenosine-stimulated cyclic AMP accumulation in slices of guinea-pig cerebral cortex: comparison of response and binding parameters. Br. J. Pharmacol. 77: 347–357, 1982.
DEVOTO, P., MARCHISIO, A. M., CARBONI, E., AND SPANO, P. F.: Detection of ^{3}H-cimetidine specific binding in rat anterior pituitary. Eur. J. Pharmacol. 63: 91–93, 1980.
DEWS, P. B., AND GRAHAM, J. D. P.: The antihistamine substance 2786 R.P. Br. J. Pharmacol. Chemother. 1: 278–286, 1946.
DILLON-CARTER, O., AND CHUANG, D. M.: Homologous desensitization of muscarinic cholinergic, histaminergic, adrenergic and serotonergic receptors coupled to phospholipase C in cerebellar granule cells. J. Neurochem. 52: 598–603, 1989.
DIXON, R. A. F., SIGAL, I. S., RANDS, E., REGISTER, R. B., CANDELORE, M. R., BLAKE, A. D., AND STRADER, C. D.: Ligand binding to the β-adrenergic receptor involves its rhodopsin-like core. Nature (Lond.) 326: 73–76, 1987.
DOHLMAN, H. G., CARON, M. G., AND LEFKOWITZ, R. J.: A family of receptors coupled to guanine nucleotide regulatory proteins. Biochemistry 26: 2655–2664, 1987.
DONALDSON, J., AND HILL, S. J.: Histamine-induced inositol phospholipid breakdown in the longitudinal smooth muscle of guinea-pig ileum. Br. J. Pharmacol. 85: 499–512, 1985.
DONALDSON, J., AND HILL, S. J.: 1,4-Dithiothreitol-induced alteration in histamine H_1-agonist binding in guinea-pig cerebellum and cerebral cortex. Eur. J. Pharmacol. 129: 25–31, 1986a.
DONALDSON, J., AND HILL, S. J.: Enhancement of histamine H_1-receptor agonist activity by 1,4-dithiothreitol in guinea-pig cerebellum and cerebral cortex. J. Neurochem. 47: 1476–1482, 1986b.
DONALDSON, J., AND HILL, S. J.: Histamine-induced hydrolysis of polyphosphoinositides in guinea-pig ileum and brain. Eur. J. Pharmacol. 124: 255–265, 1986c.
DONALDSON, J., AND HILL, S. J.: Selective enhancement of histamine H_1-receptor responses in guinea-pig ileal smooth muscle by 1,4-dithiothreitol. Br. J. Pharmacol. 87: 191–199, 1986d.
DONALDSON, J., AND HILL, S. J.: 1,4-Dithiothreitol-induced changes in histamine H_1-agonist efficacy and affinity in the longitudinal smooth muscle of guinea-pig ileum. Br. J. Pharmacol. 90: 263–271, 1987.
DONALDSON, J., BROWN, A. M., AND HILL, S. J.: Influence of rolipram on the cyclic-3',5'-monophosphate response to histamine and adenosine in slices of guinea-pig cerebral cortex. Biochem. Pharmacol. 37: 715–723, 1988a.
DONALDSON, J., BROWN, A. M., AND HILL, S. J.: Temporal changes in the calcium dependence of the histamine H_1-receptor-stimulation of cyclic AMP accumulation in guinea-pig cerebral cortex. Br. J. Pharmacol. 98: 1365–1375, 1989.
DONALDSON, J., HILL, S. J., AND BROWN, A. M.: Kinetic studies on the mechanism by which histamine H_1 receptors potentiate cyclic AMP accumulation in guinea-pig cerebral cortical slices. Mol. Pharmacol. 33: 626–633, 1988b.
DONETTI, A., CEREDA, E., BELLORA, E., GALLAZZI, A., BAZZANO, C., VANONI, P., DEL SOLDATO, P., MICHELETTI, R., PAGANO, F., AND GIACHETTI, A.: Imidazolylphenyl)formamidines: a structurally novel class of potent histamine H_2-receptor antagonists. J. Med. Chem. 27: 380–6, 1984.
DONOSO, A. O., AND ALVAREZ, E. O.: Brain histamine as a neuroendocrine transmitter. Trends Pharmacol. Sci. 6: 98–100, 1984.
DOWNES, C. P.: Agonist-stimulated phosphatidylinositol-4,5-bisphosphate metabolism in the nervous system. Neurochem. Int. 9: 211–230, 1986.
DRAZEN, J. M., FANTA, C. H., AND LACOUTURE, P. G.: Effect of nifedipine on constriction of human tracheal strips in vitro. Br. J. Pharmacol. 78: 687–691, 1983.
DRIVER, A. G., AND MUSTAFE, S. J.: Correlation of histamine H_1 receptor function and [^{3}H]-mepyramine binding in porcine tracheal tissue. Eur. J. Pharmacol. 139: 287–295, 1987.
DRIVER, A. G., KUKOLY, C. A., AND BENNETT, T. E.: Expression of histamine H_1-receptors on cultured histiocytic lymphoma cells. Biochem. Pharmacol. 38: 3083–3091, 1989.
DUNCAN, P. G., BRINK, C., ADOLPHSON, R. L., AND DOUGLAS, J. S.: Cyclic nucleotides and contraction/relaxation in airway muscle: H_1 and H_2 agonists and antagonists. J. Pharmacol. Exp. Ther. 215: 434–442, 1980.
DURANT, G. J., DUNCAN, W. A. M., GANELLIN, C. R., PARSONS, M. E., BLAKEMORE, R. C., AND RASMUSSEN, A. C.: Impromidine (SKF 92676) is a very potent and specific agonist for histamine H_2-receptors. Nature (Lond.) 276: 403–405, 1978.
DURANT, G. J., LOYNES, J. M., AND WRIGHT, H. B.: Potential histamine H_2-receptor antagonists. 1. Amino-thylimidazo (1,2-α) pyridines and imadazole (1,5-α) pyridines. J. Med. Hematol. 16: 1272–1276, 1973.
EA-KIM, L., AND OUDART, N.: A highly potent and selective H_2-agonist relaxes rabbit middle cerebral artery, in vitro. Eur. J. Pharmacol. 150: 393–396, 1988.
ECKEL, L., GRISTWOOD, R. W., NAWRATH, H., OWEN, D. A. A., AND SATTER, P.: Inotropic and electrophysiological effects of histamine on human ventricular heart muscle. J. Physiol. 330: 111–123, 1982.
EDVINSSON, L., CERVOS-NAVARRO, J., LARSSON, L. I., OWMAN, C., AND RONNBERG, A. L.: Regional distribution of mast cells containing histamine, dopamine or 5-hydroxytryptamine in the mammalian brain. Neurology 27: 878–883, 1977.
EDVINSSON, L., GROSS, P. M., AND MOHAMED, A.: Characterization of histamine receptors in cat cerebral arteries in vitro and in situ. J. Pharmacol. Exp. Ther. 225: 168–175, 1983.
EL-FAKAHANY, E., AND RICHELSON, E.: Phenoxybenzamine and dibenamine interactions with calcium channel effectors of the muscarinic receptor. Mol. Pharmacol. 20: 519–525, 1981.
EMMELIN, N., AND MUREN, A.: Effects of antihistamine compounds on the adrenaline liberation from suprarenals. Acta Physiol. Scand. 17: 345–355, 1949.
EVA, C., AND COSTA, E.: Potassium ion facilitation of phosphatidylinositol turnover activation by muscarinic receptor agonists in rat brain. J. Neurochem. 46: 1429–1435, 1986.
EVANS, T., SMITH, M. M., TANNER, L. I., AND HARDEN, T. K.: Muscarinic cholinergic receptors of two cell lines that regulate cyclic AMP metabolism by different molecular mechanisms. Mol. Pharmacol. 26: 395–404, 1984.
EYRE, P., AND CHAND, N.: Histamine receptor mechanism of the lung. *In* Pharmacology of Histamine Receptors, ed. by C. R. Ganellin and M. E. Parsons, pp. 298–322, Wright, Bristol, England, 1982.
FAINGOLD, C. L.: Antihistamines as central nervous system depressants. *In* Handbook of Experimental Pharmacology, ed. by M. Rocha e Silva, vol 18, part 2, pp. 567–573, Springer Verlag, New York, 1966.
FIGGE, J., LEONARD, P., AND RICHELSON, E.: Tricyclic antidepressants: potent blockade of histamine H_1-receptors of guinea-pig ileum. Eur. J. Pharmacol. 58: 479–483, 1979.
FINCH, L., AND HICKS, P. E.: The cardiovascular effects of intraventricularly administered histamine in the anaesthetised rat. Naunyn-Schmiedebergs Arch. Pharmacol. 293: 151–157, 1976.
FJALLAND, B.: Evidence for the existence of another type of histamine H_2-receptor in guinea-pig ileum. J. Pharm. Pharmacol. 31: 50–51, 1979.
FLEISCH, J. H., KRZAN, M. C., AND TITUS, E.: Pharmacological receptor activity of rabbit aorta. Effect of dithiothreitol and *N*-ethylmaleimide. Circ. Res. 33: 284–290, 1973.
FLEISCH, J. H., KRZAN, M. C., AND TITUS, E.: Alterations in pharmacologic receptor activity by dithiothreitol. Am. J. Physiol. 227: 1243–1248, 1974.
FOREMAN, J. C., NORRIS, D. B., RISING, T. J., AND WEBBER, S. E.: The binding of [^{3}H]-tiotidine to homogenates of guinea-pig lung parenchyma. Br. J. Pharmacol. 86: 475–482, 1985a.
FOREMAN, J. C., RISING, T. J., AND WEBBER, S. E.: A study of the histamine H_2-receptor mediating relaxation of the parenchymal lung strip preparation of the guinea-pig. Br. J. Pharmacol. 86: 465–473, 1985b.
FREDHOLM, B. B., AND DUNWIDDIE, T. V.: How does adenosine inhibit transmitter release? Trends Pharmacol. Sci. 9: 130–134, 1988.
FREDRICKSON, P. A., AND RICHELSON, E.: Hallucinogens antagonise histamine H_1-receptors of cultured mouse neuroblastoma cells. Eur. J. Pharmacol. 56: 261–264, 1979.
FRIEDEL, R. O., AND SCHANBERG, S. M.: Effects of histamine on phospholipid metabolism of rat brain in vivo. J. Neurochem. 24: 819–820, 1975.
FRIELLE, T., KOBILKA, B., LEFKOWITZ, R. J., AND CARON, M. G.: Human β_1- and β_2-adrenergic receptors: structurally and functionally related receptors derived from distinct genes. Trends Neurosci. 11: 321–324, 1988.
FUJIWARA, T., SUMINOTO, K., ITOH, T., SUZUKI, H., AND KURIYAMA, H.: Relaxing actions of protcaterol, a beta-2 adrenoceptor stimulant, on smooth muscle cells of the dog trachea. Br. J. Pharmacol. 93: 199–209, 1988.
FURCHGOTT, R. F., CHERRY, P. D., ZAWADZKI, J. V., AND JOTHIANANDAN, D.: Endothelial cells as mediators of vasodilatation of arteries. J. Cardiovasc. Pharmacol. 6: S336–S343, 1984.
GAJTKOWSKI, G. A., NORRIS, D. B., RISING, T. J., AND WOOD, T. P.: Specific binding of [^{3}H]-tiotidine to histamine H_2-receptors in guinea-pig cerebral cortex. Nature (Lond.) 304: 65–67, 1983.
GANELLIN, C. R.: Selectivity and the design of histamine H_2-receptor antagonists. J. Appl. Chem. Biotechnol. 28: 183–200, 1978.
GANELLIN, C. R.: Chemistry and structure-activity relationships of drugs acting at histamine receptors. *In* Pharmacology of Histamine Receptors, ed. by C. R. Ganellin and M. E. Parsons, pp. 10–102, Wright, Bristol, England, 1982.
GANELLIN, C. R.: A survey of recently described H_2-receptor histamine antagonists. *In* Frontiers in Histamine Research, Advances in the Biosciences, ed. by C. R. Ganellin and J. C. Schwartz, vol 51, pp. 47–59, Pergamon Press, London, 1985.
GANNON, M. N., AND HOUGH, L. B.: Histamine receptors coupled to [s3H]-cAMP accumulation in brain: pharmacological characterisation in a vesicular preparation of guinea-pig cortex. Mol. Pharmacol. 33: 44–50, 1988.
GANNON, M. N., HOUGH, L. B., AND WEINSTEIN, H.: A metacoid sensitization model to describe multiple receptors linked to a common response: application

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PHARM REV

PHARMACOLOGICAL REVIEWS

to histamine receptors coupled to [^{3}H]cyclic AMP accumulation in guinea-pig cortex. Mol. Pharmacol. **35:** 205–213, 1989.

GARBARG, M., AND SCHWARTZ, J. C.: Synergism between histamine H_1- and H_2-receptors in the cyclic AMP response in guinea-pig brain slices: effects of phorbol esters and calcium. Mol. Pharmacol. **33:** 38–43, 1988.

GARBARG, M., TRUNG TONG, M. D., GROS, C., AND SCHWARTZ, J. C.: Effects of histamine H_3-receptor ligands on various biochemical indices of histaminergic neuron activity in rat brain. Eur. J. Pharmacol. **164:** 1–11, 1989.

GARBARG, M., YERMANIAN, E., KORNER, M., AND SCHWARTZ, J. C.: Biochemical studies of cerebral H_1-receptors. *In* Frontiers in Histamine Research, Advances in the Biosciences, ed. by C. R. Ganellin and J. C. Schwartz, vol. 51, pp. 19–25, Pergamon Press, London, 1985.

GAVISH, M., CHANG, R. S. L., AND SNYDER, S. H.: Solubilization of histamine H-1, GABA and benzodiazepine receptors. Life Sci. **25:** 783–790, 1979.

GESPACH, C., AND ABITA, J.-P.: Human polymorphonuclear neutrophils: pharmacological characterization of histamine receptors mediating the elevation of cyclic AMP. Mol. Pharmacol. **21:** 78–85, 1982.

GESPACH, C., BOUHOURS, D., BOUHOURS, J. F., AND ROSSELIN, G.: Histamine interaction on surface recognition sites of H_2-type in parietal and non-parietal cells isolated from the guinea-pig stomach. FEBS Lett. **149:** 85–90, 1982.

GILMAN, A. G.: G proteins: transducers of receptor-generated signals. Annu. Rev. Biochem. **56:** 615–649, 1987..

GLOVER, W. E.: Effect of dithiothreitol of histamine receptors in rabbit colon and guinea-pig ileum. Clin. Exp. Pharmacol. Physiol. **6:** 151–157, 1979.

GOTH, A.: On the general problem of the release of histamine. *In* Handbook of Experimental Pharmacology, vol. 18, part 2, ed. by M. Rocha e Silva, pp. 58–74, Springer-Verlag, Berlin, 1978.

GOTH, A., AND JOHNSON, A. R.: Current concepts on the secretory function of mast cells. Life Sci. **16:** 1201–1214, 1975.

GRAHAM, H. T., LOWRY, O. H., WHEELWRIGHT, F., AND LENZ, M. A.: Distribution of histamine among leukocytes and platelets. Blood **10:** 467–481, 1955.

GRANDORY, B. M., CUSS, F. M., AND BARNES, P. J.: Breakdown of phosphoinositides in airway smooth muscle: lack of influence of anti-asthmatic drugs. Life Sci. **41:** 1621–1627, 1987.

GREEN, J. P.: Histamine receptors in brain. Handb. Psychopharmacol. **17:** 385–420, 1983.

GREEN, J. P., AND MAAYANI, S.: Tricyclic antidepressant drugs block histamine H_2-receptor in brain. Nature (Lond.) **269:** 163–165, 1977.

GREEN, J. P., JOHNSON, C. L., WEINSTEIN, H., AND MAAYANI, S.: Antagonism of histamine-activated adenylate cyclase in brain by D-lysergic acid diethylamide. Proc. Natl. Acad. Sci. USA **74:** 5697–5701, 1977.

GREGA, G. A.: Contractile elements in endothelial cells as potential targets for drug action. Trends. Pharmacol. Sci. **7:** 452–457, 1986.

GRISTWOOD, R. W., OWEN, D. A. A., ECKEL, L., SATTER, P., AND NAWRATH, H.: Response of human ventricular heart to histamine. J. Pharm. Pharmacol. **33:** 246–247, 1981.

GROSS, P. M., HARPER, A. M., AND TEASDALE, G. M.: Cerebral circulation and histamine. 1. Participation of vascular H_1- and H_2-receptors in vasodilatory responses to carotid arterial infusion. J. Cereb. Blood Flow Metab. **1:** 97–108, 1981.

GRUND, V. R., GOLDBERG, N. D., AND HUNNINGHAKE, D. B.: Histamine receptors in adipose tissue: involvement of cyclic adenosine monophosphate and the H_2-receptor in the lipolytic response to histamine in isolated canine fat cells. J. Pharmacol. Exp. Ther. **195:** 176–184, 1975.

GRUOL, D. L., AND WEIREICH, D.: Two pharmacologically distinct histamine receptors mediating hyperpolarization on identified neurons of *Aplysia Californica*. Brain Res. **162:** 281–301, 1979.

GRZANNA, R., AND SHULTZ, L. D.: The contribution of mast cells to the histamine content of the central nervous system: a regional analysis. Life Sci. **30:** 1959–1964, 1982.

GULAT-MARNAY, C., LAFITTE, A., ARRANG, J. M., AND SCHWARTZ, J. C.: Regulation of histamine release and synthesis in the brain by muscarinic receptors. J. Neurochem. **52:** 248–254, 1989a.

GULAT-MARNAY, C., LAFITTE, A., ARRANG, J. M., AND SCHWARTZ, J. C.: Regulation of histamine release and synthesis in the brain by α_2-adrenoceptors. J. Neurochem. **53:** 519–524, 1989b.

HAAS, H. L.: Histamine potentiates neuronal excitation by blocking a calcium-dependent potatssium conductance. Agents Action **14:** 534–537, 1984.

HAAS, H. L.: Histamine may act through cyclic AMP on hippocampal neurones. Agents Actions **16:** 234–235, 1985.

HAAS, H. L., AND GREENE, R. W.: Effect of histamine on hippocampal pyramidal cells of the rat in vitro. Exp. Brain Res. **62:** 123–130, 1986.

HAAS, H. L., AND KONNERTH, A.: Histamine and noradrenaline decrease calcium-activated potassium conductance in hippocampal pyramidal cells. Nature (Lond.) **302:** 432–434, 1983.

HADFIELD, A. J., ROBINSON, N. R., AND HILL, S. J.: The nature of the binding of [^{3}H]-mepyramine to homogenates of guinea-pig cerebral cortex at different [^{3}H]-ligand concentrations. Biochem. Pharmacol. **32:** 2449–2451, 1983.

HAKANSON, R., LARRSON, L. I., AND SUNDLER, F.: Endocrine-like cells in rat stomach: effects of 6-hydroxydopa on amine stores and amino acid decarboxylase activities: a chemical fluorescence histochemical and electron microscopic study. J. Pharmacol. Exp. Ther. **191:** 92–101, 1974.

HAKANSON, R., WAHLESTEDT, C., WETLIN, L., VALLGREN, S., AND SUNDER, F.: Neuronal histamine in the gut wall releasable by gastrin and cholecystokinin. Neurosci. Lett. **42:** 305–310, 1983.

HALL, I. P., AND CHILVERS, E. R.: Inositol phosphates and airway smooth muscle. Pulmonary Pharmacol. **2:** 113–120, 1989.

HALL, I. P., AND HILL, S. J.: β_2-Adrenoceptor stimulation inhibits histamine-stimulated inositol phospholipid hydrolysis in bovine tracheal smooth muscle. Br. J. Pharmacol. **95:** 1204–1212, 1988.

HALL, I. P., AND HILL, S. J.: Inhibition of the phosphoinositide response to low concentrations of carbachol by IMBX in bovine tracheal smooth muscle. Br. J. Pharmacol. **97:** 444P, 1989a.

HALL, I. P., AND HILL, S. J.: Inhibition of the phosphoinositide response to 5-HT in bovine tracheal smooth muscle by agents which increase cyclic AMP levels. Br. J. Pharmacol. **97:** 560P, 1989b.

HALL, I. P., AND HILL, S. J.: Inhibition of salbutamol, forskolin and IBMX of ALF_4-induced inositol phosphate formation in airway smooth muscle. Br. J. Pharmacol. **99:** 788P 1989c..

HALL, I. P., DONALDSON, J., AND HILL, S. J.: Inhibition of histamine-stimulated inositol phospholipid hydrolysis by agents which increase cyclic AMP levels in bovine tracheal smooth muscle. Br. J. Pharmacol. **97:** 603–613, 1989.

HALLAM, T. J., AND PEARSON, J. D.: Exogenous ATP raises cytoplasmic free calcium in fura-2 loaded piglet aortic endothelial cells. FEBS Lett. **207:** 95–99, 1986.

HALLAM, T. J., JACOB, R., AND MERRITT, J.: Stimulated influx of divalent cations into the cytoplasm of human endothelial cells can be independent of receptor occupation. Br. J. Pharmacol. **94:** 340P, 1988a.

HALLAM, T. J., JACOB, R., AND MERRITT, J.: Evidence that agonists stimulate bivalent-cation influx into human endothelial cells. Biochem. J. **255:** 179–184, 1988b.

HALLAM, T. J., PEARSON, J. D., AND NEEDHAM, L. A.: Thrombin-stimulated elevation of human endothelial-cell cytoplasmic free calcium concentration causes prostacyclin production. Biochem. J. **251:** 243–249, 1988c.

HALLAM, T. J., JACOB, R., AND MERRITT, J. E.: Influx of bivalent cations can be independent of receptor stimulation in human endothelial cells. Biochem. J. **259:** 125–129, 1989.

HAMILTON, K. K., AND SIMS, P. J.: Changes in cytosolic Ca^{2+} associated with von Willebrand Factor release in human endothelial cells exposed to histamine: study of microcarrier cell monolayers using the fluorescent probe indo-1. J. Clin. Invest. **79:** 600–608, 1987.

HARDIE, R. C.: Is histamine a neurotransmitter in insect photoreceptors? J. Comp. Physiol. A **161:** 201–213, 1987.

HARDIE, R. C.: Effects of antagonists on putative histamine receptors in the first visual neurophile of the housefly (*musca domestica*). J. Exp. Biol. **138:** 221–241, 1988.

HARDIE, R. C.: A histamine-activated chloride channel involved in neurotransmission at a photoreceptor synapse. Nature (Lond.), **339:** 704–706, 1989.

HARVEY, C. A., AND OWEN, D. A. A.: Cardiovascular studies with SKF 93319, an antagonist of histamine at both H_1- and H_2-receptors. Br. J. Pharmacol. **83:** 427–432, 1984.

HATTORI, Y., AND KANNO, M.: Effect of Ni^{2+} on the multiphasic positive inotropic responses to histamine mediated by H_1-receptors in left atria of guinea-pigs. Naunyn-Schmiedebergs Arch. Pharmacol. **329:** 188–194, 1985.

HATTORI, Y., AND LEVI, R.: Adenosine selectively attenuates H_2- and beta-mediated cardiac responses to histamine and norepinephrine: An unmasking of H_1- and alpha-mediated responses. J. Pharmacol. Exp. Ther. **231:** 215–233, 1984.

HATTORI, Y., ENDOU, M., SHIROTA, M., AND KANNO, M.: Dissociation of phosphoinositide hydrolysis and positive inotropic effect of histamine mediated by H_1-receptors in guinea-pig left atria. Naunyn-Schmiedebergs Arch. Pharmacol. **340:** 196–203, 1989.

HATTORI, Y., KIMURA, S., FUJII, S., AND KANNO, M.: Effects of mechanical performance and biochemical and electrical activity in the heart of monkeys (*Macaca fuscata*). Eur. J. Pharmacol. **91:** 11–19, 1983.

HATTORI, Y., NAKAYA, H., TOHSE, N., AND KANNO, M.: Effects of Ca^{2+} channel antagonists and ryanodine on H_1-receptor medaited electromechanical response to histamine in guinea-pig left atria. Naunyn-Schmiedebergs Arch. Pharmacol. **337:** 323–330, 1988a.

HATTORI, Y., SAKUMA, I., AND KANNO, M.: Differential effects of histmaine mediated H_1- and H_2-receptors on contractility spontaneous rate and cyclic nucleotides in the rabbit heart. Eur. J. Pharmacol. **153:** 221–229, 1988b.

HEGSTRAND, L. R., KANOF, P. D., AND GREENGARD, P.: Histamine sensitive adenylate cyclase in mammalian brain. Nature (Lond.) **260:** 163–165, 1976.

HELTIANU, C., SIMIONESCUE, M., AND SIMIONESCUE, N.: Histamine receptors of the microvascular endothelium revealed in situ with a histamine-ferritin conjugate: characteristic high-affinity binding sites in venules. J. Cell Biol. **93:** 357–364, 1982.

HEPLER, J. R., HUGHES, A. R., AND HARDEN, T. K.: Evidence that muscarinic cholinergic receptors selectively interact with either the cyclic AMP or the inositol phosphate second-messenger response systems. Biochem. J. **247:** 793–796, 1987.

HESCHELER, J., TANG, M., JASTORFF, B., AND TRAUTWEIN, W.: On the mechanism of histamine induced enhancement of the cardiac Ca^{2+} current. Pflugers Arch. **410:** 23–29, 1987.

HIDE, M., FUKUI, H., WATANABE, T., WADA, H., AND YAMAMOTO, S.: Histamine H_1-receptor in endothelial and smooth muscle cells of guinea-pig aorta. Eur. J. Pharmacol. **148:** 161–169, 1988.

HILL, S. J.: Histamine receptors branch out. Nature (Lond.) **327:** 104–105, 1987a.

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PHARM REV

HILL, S. J.: Histamine receptors in the mammalian central nervous system: biochemical studies. *In* Progress in Medicinal Chemistry, vol. 24, ed. by G. P. Ellis and G. B. West, pp. 29–84, Elsevier, Amsterdam, 1987b.

HILL, S. J., AND KENDALL, D. A.: Studies on the adenosine-receptor mediating the augmentation of histamine-induced inositol phospholipid hydrolysis in guinea-pig cerebral cortex. Br. J. Pharmacol. **91:** 661–669, 1987.

HILL, S. J., AND KENDALL, D. A.: Cross-talk between different receptor-effector systems in the CNS. Cell. Signal. **1:** 135–141, 1989.

HILL, S. J., AND STRAW, R. M.: α_2-Adrenoceptor-mediated inhibition of histamine release from rat cerebral cortical slices. Br. J. Pharmacol. **95:** 1213–1219, 1988.

HILL, S. J., AND YOUNG, J. M.: Histamine H_1-receptors in the brain of the guinea-pig and the rat: differences in ligand binding properties and regional distribution. Br. J. Pharmacol. **68:** 687–696, 1980.

HILL, S. J., AND YOUNG, J. M.: Characterization of [^{3}H]-mepyramine binding to the longitudinal muscle of guinea-pig small intestine. Mol. Pharmacol. **19:** 379–387, 1981.

HILL, S. J., DAUM, P., AND YOUNG, J. M.: Affinities of histamine H_1-antagonists in guinea-pig brain: similarity of values determined from [s;3H]mepyramine binding and from inhibition of a functional response. J. Neurochem. **37:** 1257–1360, 1981.

HILL, S. J., EMSON, P.C., AND YOUNG, J. M.: The binding of [^{3}H]-mepyramine to histamine H_1-receptors in guinea-pig brain. J. Neurochem. **31:** 997–1004, 1978.

HILL, S. J., YOUNG, J. M., AND MARRIAN, D. H.: Specific binding of ^{3}H-mepyramine to histamine H_1-receptors in intestinal smooth muscle. Nature (Lond.) **270:** 361–363, 1977.

HIRATA, F., AND AXELROD, J.: Phospholipid methylation and biological transmission. Science (Wash. DC) **209:** 1082–1090, 1980.

HIRATA, F., STRITTMATTER, W. J., AND AXELROD, J.: β-Adrenergic receptor agonists increase phospholipid methylation, membrane fluidity and β-adrenergic receptor-adenylate cyclase coupling. Proc. Natl. Acad. Sci. USA **76:** 368–372, 1979.

HIRATA, F., VIVEROS, O. H., DILIBERTO, E. J., JR., AND AXELROD, J.: Identification and properties of two methyltransferases in conversion of phosphatidylethanolamine to phosphatidylcholine. Proc. Natl. Acad. Sci. USA **75:** 1718–1721, 1978.

HISHINUMA, S., AND UCHIDA, M. K.: Short-term desensitization of guinea-pig taenia caecum induced by carbachol occurs at intracellular Ca stores and that by histamine at H_1-receptors. Br. J. Pharmacol. **94:** 882–889, 1988.

HOFMANN, F., NASTAINCZYK, W., ROHRASTEN, A., SCHNEIDER, T., AND SIEBER, M.: Regulation of the L-type calcium channel. Trends Pharmacol. Sci. **8:** 393–398, 1987.

HOLLINGSWORTH, E. B., AND DALY, J. W.: Accumulation of inositol phosphates and cyclic AMP in guinea-pig cerebral cortical preparations: effects of norepinephrine, histamine, carbamylcholine and 2-chloroadenosine. Biochim. Biophys. Acta **847:** 207–216, 1985.

HOLLINGSWORTH, E. B., DE LA CRUZ, R. A., AND DALY, J. W.: Accumulations of inositol phosphates and cyclic AMP in brain slices: synergistic interactions of histamine and 2-chloroadenosine. Eur. J. Pharmacol. **122:** 45–50, 1986.

HOLLINGSWORTH, E. B., SEARS, E. B., AND DALY, J. W.: An activator of protein kinase C (phorbol-12-myristate-13-acetate) augments 2-chloroadenosine-elicited accumulation of cyclic AMP on guinea-pig cerebral cortical particulate preparations. FEBS Lett. **184:** 339–342, 1985.

HONG, S. L.: Inhibition of prostacyclin synthesis in endothelial cells by methylisobutylxanthine is not mediated through elevated cAMP level. Biochim. Biophys. Acta **754:** 258–263, 1983.

HOPKINS, N. K., AND GORMAN, R. R.: Regulation of endothelial cell cyclic nucleotide metabolism by prostacyclin. J. Clin. Invest. **67:** 540–546, 1981.

HORIO, S., KOHROGI, H., ANDO, M., SUGIMOTO, M., AND ARAKI, S.: Preventive and reverse effects of nifedipine on human bronchoconstriction in vitro. Arch. Int. Pharmacodyn. Ther. **267:** 80–90, 1984.

HORSTEMEYER, D. L., ICE, K. S., HOGABOOM, G. K., O'DONNELL, J. P., SMITH, D. J., AND FEDAN, J. S.: Binding of 4(5)-[2-(4-azido-2-nitroanilino-ethyl] imidazole to histamine receptors in guinea-pig cerebral cortical membranes. Proc. Soc. Exp. Biol. Med. **181:** 486–491, 1986.

HOUGH, L. B., AND GREEN, J. P.: Histamine-activated adenylate cyclase in brain homogenates of several species. Brain Research, **219:** 363–370, 1981.

HOUGH, L. B., GOLDSCHMIDT, R. C., GLICK, S. D., AND PADAWER, J.: Mast cells in rat brain: characterisation, localisation and histamine content. *In* Frontiers in Histamine Research, Advances in the Biosciences, vol. 51, ed by C. R. Ganellin and J. C. Schwartz, pp. 131–140, Pergamon, London, 1985.

HOUGH, L. B., WEINSTEIN, H., AND GREEN, J. P.: One agonist and two receptors mediating the same effect: histamine receptors linked to adenylate cyclase in the brain. *In* Receptors for Neurotransmitters and peptide hormones ed. by G. Pepeu, M. J. Kuhar, and S. J. Enna, pp. 183–192, Raven Press, New York, 1980.

HUGHES, A. R., AND HARDEN, T. K.: Adenosine and muscarinic cholinergic receptors attenuate cyclic AMP accumulation by different mechanisms in 1321N1 astrocytoma cells. J. Pharmacol. Exp. Ther. **237:** 173–178, 1986.

IACOVOU, J. W., HILL, S. J., AND BIRMINGHAM, A. T.: Involvement of extracellular calcium in agonist-induced contraction of guinea-pig detrusor. Br. J. Pharmacol. **95:** 848P, 1988.

ICHINOSE, M., AND BARNES, P. J.: Inhibitory histamine H_3-receptors on cholinergic nerves in human airways. Eur. J. Pharmacol. **163:** 383–386, 1989.

ICHINOSE, M., STRETTON, C. D., SCHWARTZ, J. C., AND BARNES, P. J.: Histamine H_3-receptors inhibit cholinergic neurotransmission in guinea-pig airways. Br. J. Pharmacol. **97:** 13–15, 1989.

IMOTO, M., TSUCHIE, K., TANAKA, M., SUGIYAMA, S., AND OZAWA, T.: Predominance of histamine H_1-receptors on liver plasma membrane. Biochem. Biophys. Res. Commun. **127:** 885–889, 1985.

INAGAKI, N., YAMATODANI, A., ANDO-YAMAOTO, M., TOHYAMA, M., WATANABE, T., AND WADA, H.: Organisation of histaminergic fibres in the rat brain. J. Comp. Neurol. **273:** 283–300, 1988.

INUI, J., AND IMAMURA, H.: Restoration by histamine of the calcium-dependent electrical and mechanical response in the guinea-pig papillary muscle partially depolarised by potassium. Naunyn-Schmiedebergs Arch. Pharmacol. **294:** 261–269, 1976.

IRVINE, R. F., AND MOORE, R. M.: Micro-injection of inositol-1,3,4,5-tetrakisphosphate activates sea urchin eggs by a mechanism dependent on external Ca^{2+}. Biochem. J. **240:** 917–920, 1986.

ISHIKAWA, E., TOKI, A., MORIYAMA, T., MATSUOKA, Y., AIKAWA, T., AND SUDA, M. J.: Induction of histidine decarboxylase in tumor-bearing fat. Biochemistry **68:** 347–355, 1970.

ISHIKAWA, S., AND SPERELAKIS, N.: A novel class (H_3) of histamine receptors on perivascular nerve terminals. Nature (Lond.) **327:** 158–160, 1987.

ISON, R. B., FRANKS, F. M., AND SOH, K. S.: The binding of conformationally restricted antihistamines to histamine receptors. J. Pharm. Pharmacol. **25:** 887–894, 1973.

JACOB, R., MERRITT, J. E., HALLAM, T. J., AND RINK, T. J.: Repetitive spikes in cytoplasmic calcium evoked by histamine in human endothelial cells. Nature (Lond.) **335:** 40–45, 1988.

JAFFE, E. A.: Cell biology of endothelial cells. Hum. Pathol. **18:** 234–239, 1987.

JAFFERJI, S. S., AND MICHELL, R. H.: Effects of calcium-antagonistic drugs on the stimulation of carbamylcholine and histamine of phosphatidylinositol turnover in longitudinal smooth muscle of guinea-pig ileum. Biochem. J. **160:** 163–169, 1976a.

JAFFERJI, S. S., AND MICHELL, R. H.: Stimulation of phosphatidylinositol turnover by histamine, 5-hydroxytryptamine and adrenaline in the longitudinal smooth muscle of guinea-pig ileum. Biochem. Pharmacol. **25:** 1429–1430, 1976b.

JOHNSON, C. L.: Histamine receptors and cyclic nucleotides. *In* Pharmacology of Histamine Receptors, ed. by R. Ganellin and M. Parson, pp. 146–216, J. Wright and Sons, Ltd., London, 1982.

JOHNSON, C. L., AND MIZOGUCHI, H.: The interaction of histamine and guanylnucleotides with cardiac adenylate cyclase and its relationship to cardiac contractility. J. Pharmacol. Exp. Ther. **200:** 174–186, 1977.

JOHNSON, C. L., WEINSTEIN, H., AND GREEN, J. P.: Studies on the H_2-receptors coupled to cardiac adenylate cyclase: effects of guanyl nucleotides and structural requirements for agonist activity. Biochim. Biophys. Acta **587:** 155–168, 1979a.

JOHNSON, C. L., WEINSTEIN, H., AND GREEN, J. P.: Studies on the H_2-receptor coupled to cardiac adenylate cyclase: blockade by H_2- and H_1- receptor antagonists. Mol. Pharmacol. **16:** 417–428, 1979b.

KAHLSON, G., AND ROSENGREN, E.: New approaches to the physiology of histamine. Physiol. Rev. **48:** 155–196, 1968.

KAHLSON, G., AND ROSENGREN, E.: Biogenesis and Physiology of Histamine. Edward Arnold Ltd, London, 1971.

KAKIUCHI, S., AND RALL, T. W.: Studies on adenosine-3′,5′-phosphate in rabbit cerebral cortex. Mol. Pharmacol. **4:** 379–388, 1968.

KALINER, M. A.: The mast cell—a fascinating riddle. N. Engl. J. Med. **301:** 498–499, 1979.

KALIVAS, P. W.: Histamine-induced arousal in the conscious and pentobarbital pretreated rat. J. Pharmacol. Exp. Ther. **222:** 37–42, 1982.

KANBA, S., AND RICHELSON, E.: Antidepressants are weak competitive antagonists of histamine H_2-receptors in dissociated brain tissue. Eur. J. Pharmacol. **94:** 313–318, 1983.

KANBA, S., AND RICHELSON, E.: Histamine H_1-receptors in human brain labelled with [^{3}H]-doxepin. Brain Res. **304:** 1–7, 1984.

KANDEL, S. I., STEINBERG, G. H., WELLS, J. W., KANDEL, M., AND GORNALL, A. G.: Separate binding sites for histaminergic drugs in rat cerebral cortex. Biochem. Pharmacol. **29:** 2269–2272, 1980.

KANOF, P. D., AND GREENGARD, P.: Brain histamine receptors as targets for antidepressant drugs. Nature (Lond.) **272:** 329–333, 1978.

KANOF, P. D., AND GREENGARD, P.: Pharmacological properties of histamine-sensitive adenylate cyclase from mammalian brain. J. Pharmacol. Exp. Ther. **209:** 87–96, 1979a.

KANOF, P. D., AND GREENGARD, P.: Pharmacological properties of histamine-sensitive adenylate cyclase from guinea-pig cardiac ventricular muscle. Mol. Pharmacol. **15:** 445–461, 1979b.

KANOF, P. D., HEGSTRAND, L. R., AND GREENGARD, P.: Biochemical characterization of histamine-sensitive adenylate cyclase in mammalian brain. Arch. Biochem. Biophys. **182:** 321–334, 1977.

KARAKI, H.: Ca^{2+} localization and sensitivity in vascular smooth muscle. Trends Pharmacol. Sci. **10:** 320–325, 1989.

KARNUSHINA, I. L., PALACIOS, J. M., BARBIN, G., DUX, E., JOO, F., AND SCHWARTZ, J. C.: Studies on a capillary-rich fraction isolated from brain: histamine components and characterisation of the histamine receptors linked to adenylate cyclase. J. Neurochem. **34:** 1201–1208, 1980.

KARNUSHINA, I. L., SPATZ, M., AND BEMBRY, J.: Cerebral endothelial cell culture. II. Adenylate cyclase response to prostaglandins and their interaction with the adrenergic system. Life Sci. **32:** 1427–1435, 1983.

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KATSUKI, S., AND MURAD, F.: Regulation of adenosine cyclic 3',5'-monophosphate and guanosine 3',5'-monophosphate levels and contractility in bovine tracheal smooth muscle. Mol. Pharmacol. **13:** 330–341, 1977.

KATSUMATA, Y., AND YAGI, K.: Distribution of adenyl cyclase sensitive to histamine in rabbit gastric mucosa. Biochem. Pharmacol. **25:** 603–604, 1976.

KELLER, M. B., GRUND, V. R., AND JOHNSON, C. L.: Impromidine stimulated adenylate cyclase activity in canine fat cell ghosts. Pharmacologist **23:** 186, 1981.

KENAKIN, T. P., AND COOK, D. A.: Blockade of histamine-induced contractions of guinea-pig ileum by β-haloalkylamines. Can. J. Physiol. Pharmacol. **54:** 386–392, 1976.

KENAKIN, T. P., AND COOK, D. A.: *N,N,*-Diethyl-2-(1-pyridyl)ethylamine a partial agonist for the histamine receptor in guinea-pig ileum. Can J. Physiol. Pharmacol. **58:** 1307–1310, 1980a.

KENAKIN, T. P., AND COOK, D. A.: The effect of desensitization on the antagonism of the histamine response by phenoxybenzamine. Mol. Pharmacol. **17:** 309–313, 1980b.

KENDALL, D. A., AND FIRTH, J. L.: Adenosine inhibition of histamine-stimulated inositol phospholipid hydrolysis in human cerebral cortical slices. Br. J. Clin. Pharmacol. **27:** 109P, 1989.

KENDALL, D. A., AND HILL, S. J.: Adenosine inhibition of histamine-stimulated inositol phospholipid hydrolysis in mouse cerebral cortex. J. Neurochem. **50:** 497–502, 1988.

KENDALL, D. A., AND NAHORSKI, S. R.: Inositol phospholipid hydrolysis in rat cerebral cortical slices: II. Calcium requirement. J. Neurochem. **42:** 1388–1394, 1984.

KENDALL, D. A., FEKANY, J. W., AND ENNA, S. J.: Properties of ^{3}H-cimetidine binding in rat brain membrane fractions. Life Sci. **26:** 1293–1302, 1980.

KHAN, M. M., MARR-LEISY, D., VERLANDER, M. S., BRISTOW, M. R., STROBER, S., GOODMAN, M., AND MELMON, K. L.: The effects of derivatives of histamine on natural suppressor cells. J. Immunol. **137:** 308–314, 1986.

KHAN, M. M., SANSONI, P., ENGLEMAN, E. G., AND MELMON, K. L.: Pharmacological effects of autacoids on subsets of T cells: regulation of expression/function of histamine-2 receptors by a subset of suppressor cells. J. Clin. Invest. **75:** 1578–1583, 1985.

KILLACKEY, J. J. F., JOHNSTON, M. G., AND MOVAT, H. Z.: Increased permeability of microcarrier-cultured endothelial monolayers in response to histamine and thrombin. Am. J. Pathol. **122:** 50–61, 1986.

KIYONO, S., SEO, M. L., SHIBAGAKI, M., WATANABE, T., MAEYAMA, K., AND WADA, H.: Effects of α-fluoromethylhistidine on sleep-waking parameters in rats. Physiol. Behav. **34:** 615–617, 1985.

KLEIN, I., AND LEVEY, G. S.: Activation of myocardial adenyl cyclase by histamine in guinea-pig, cat and human heart. J. Clin. Invest. **50:** 1012–1015, 1971.

KLEIN, M. C., AND GERTNER, S. B.: Evidence for a role of endogenous histamine in central cardiovascular regulation: inhibition of histamine-N-methyltransferase by SKF 91488. J. Pharmacol. Exp. Ther. **216:** 315–320, 1981.

KLEY, N.: Multiple regulation of proenkephalin gene expression by protein kinase C. J. Biol. Chem. **263:** 2003–2008, 1988.

KLEY, N., LOEFFLER, J. P., PITTIUS, C. W., AND HOLLT, V.: Ca^{2+} dependent histaminergic stimulation of proenkephalin A gene expression in cultured adrenal chromaffin cells. Neuroendocrinology **46:** 89–92, 1987.

KOMORI, S., AND BOLTON, T. B.: Actions of guanine nucleotides and cyclic nucleotides on calcium stores in single patch-clamped smooth muscle cells from rabbit portal vein. Br. J. Pharmacol. **97:** 973–982, 1989.

KONDO, M., TANIYAMA, K., AND TANAKA, C.: Histamine H_1-receptors in the guinea-pig urinary bladder. Eur. J. Pharmacol. **114:** 89–92, 1985.

KORNER, M., BOUTHENET, M. L., GANELLIN, C. R., GARBARG, M., GROS, C., IFE, R. J., SALES, N., AND SCHWARTZ, J. C.: [^{125}I]-iodobolpyramine, a highly sensitive probe for histamine H_1-receptors in guinea-pig brain. Eur. J. Pharmacol. **120:** 151–160, 1986.

KOTLIKOFF, M. I., MURRAY, R. K., AND REYNOLDS, E. E.: Histamine-induced calcium release and phorbol antagonism in cultured airway smooth muscle cells. Am. J. Physiol. **253:** C561–C566, 1987.

KUME, H., TAKAI, A., TOKUNO, H., AND TOMITA, T.: Regulation of Ca^{2+} dependent K^+ channel activity in tracheal myocytes by phosphorylation. Nature (Lond.) **341:** 152–154, 1989.

KUNO, T., KUBO, N., AND TANAKA, C.: Molecular size of histamine H_1-receptors determined by target size analysis. Biochem. Biophys. Res. Commun. **129:** 639–644, 1985.

LADURON, P. M., JANSSEN, P. F. M., GOMMEREN, W., AND LEYSEN, J. E.: In vitro and in vivo binding characteristics of a new long-acting histamine H_1-antagonist, astemizole. Mol. Pharmacol. **21:** 294–300, 1982.

LANGLANDS, J. M., RODGER, I. W., AND DIAMOND, J.: The effect of M&B 22948 on methacholine- and histamine-induced contraction and inositol-1,4,5-trisphosphate levels in guinea-pig tracheal tissue. Br. J. Pharmacol. **98:** 336–338, 1989.

LEE, T. P., KUO, J. F., AND GREENGARD, P.: Role of muscarinic cholinergic receptors in regulation of guanosine-3',5'-cyclic monophosphate content in mammalian brain, heart, muscle and intestinal smooth muscle. Proc. Natl. Acad. Sci. USA **69:** 3287–3291, 1972.

LE FUR, G., MALGOURIS, C., AND UZAN, A.: Effect of mequitazine a non sedative antihistamine on brain H_1-receptors. Life Sci. **29:** 547–552, 1981.

LEITMAN, D. C., FISCUS, R. R., AND MURAD, F.: Forskolin phosphodiesterase inhibitors and cyclic AMP analogues inhibit proliferation of cultured bovine aortic endothelial cells. J. Cell. Physiol. **127:** 237–343, 1986.

LETT-BROWN, M. A., AND LEONARD, E. J.: Histamine-induced inhibition of normal human basophil chemotaxis to C5a. J. Immunol. **118:** 815–818, 1977.

LEVI, R., CAPURRO, N., AND LEE, C-H.: Pharmacological characterisation of cardiac histamine receptors: sensitivity to H_1- and H_2-receptor agonists and antagonists. Eur. J. Pharmacol. **27:** 330–338, 1975.

LEVI, R., OWEN, D. A. A., AND TRZECIAKOWSKI, J.: Action of histamine on the heart and vasculature. *In* Pharmacology of Histamine Receptors, ed. by R. Ganellin and M. Parson, pp. 236–297, J. Wright and Sons, Ltd., London, 1982.

LEVI, R. C., AND ALLOATTI, G.: Histamine modulates calcium current in guinea-pig ventricular myocytes. J. Pharmacol. Exp. Ther. **246:** 377–383, 1988.

LEWIS, G. P., AND MANGHAM, B. A.: The pharmacology of graft rejection. Trends Pharmacol. Sci. **1:** 18–21, 1979.

LICHTENSTEIN, L. M., AND GILLESPIE, E.: The effect of the H_1- and H_2-antihistamines on 'allergic' histamine release and its inhibition by histamine. J. Pharmacol. Exp. Ther. **192:** 441–450, 1975.

LIDDELL, R. H. A., SCOTT, A. R. W., AND SIMPSON, J. G.: Histamine-induced changes in the endothelium of post-capillary venules: effects of chelating agents and cytochalasin B. Bibl. Anat. **20:** 109–112, 1981.

LIM, S. P., AND BOLTON, T. B.: A calcium-dependent rather than a G-protein mechanism is involved in the inward current evoked by muscarinic receptor stimulation in dialysed single smooth cells of small intestine. Br. J. Pharmacol. **95:** 325–327, 1988.

LIN, T. M., EVANS, D. C., WARRIEK, M. W., PIOCH, R. P., AND RUFFULO, R. R.: NIZATIDINE, A NEW SPECIFIC H_2-receptor antagonist. Gastroenterology **84:** 1231, 1983.

LINDEN, J., AND DELAHUNTY, M.: Receptors that inhibit phosphoinositide breakdown. Trends Pharmacol. Sci. **10:** 114–120, 1989.

LIPINSKI, J. F., SCHAUMBERG, H. H., AND BALDESSANI, R. J.: Regional distribution of histamine in human brain. Brain Res. **52:** 403–408, 1973.

LITOSCH, I.: Guanine nucleotides mediate stimulatory and inhibitory effects on cerebro-cortical membrane phospholipase C activity. Biochem. J. **251:** 245–251, 1989.

LIVETT, B. G., AND MARLEY, P. D.: Effects of opioid peptides and morphine on histamine-induced catecholamine secretion from cultured, bovine adrenal chromaffin cells. Br. J. Pharmacol. **89:** 327–334, 1986.

LO, W. W. Y., AND FAN, T.-P. D.: Histamine stimulates inositol phosphate accumulation via the H_1-receptor in cultured human endothelial cells. Biochem. Biophys. Res. Commun. **148:** 47–53, 1987.

LONCHAMPT, M. O., MARCHE, P., DEMERLE, C., GIRARD, A., CABANIE, M., ESANU, A., CHABRIER, P. E., AND BRAQUET, P.: Histamine H_1-receptors mediate phosphoinositide and calcium response in cultured smooth muscle cells—interaction with cicletanine. Agents Actions **24:** 255–260, 1988.

MAAYANI, S., HOUGH, L. B., WEINSTEIN, H., AND GREEN, J. P.: Response of the histamine H_2-receptor in the brain to antidepressant drugs. *In* Typical and Atypical Antidepressants: Molecular Mechanisms, ed. by E. Costa and G. Racagni, pp. 133–147, Raven Press, New York, 1982.

MADISON, D. V., AND NICOLL, R. A.: Noradrenaline blocks accommodation of pyramidal cell discharge in the hippocampus. Nature (Lond.) **299:** 636–638, 1982.

MADISON, J. M., AND BROWN, J. K.: Differential inhibitory effects of forskolin, isoproterenol and dibutyryl cyclic adenosine monophosphate on phosphoinositide hydrolysis in canine tracheal smooth muscle. J. Clin. Invest. **82:** 1462–1465, 1988.

MAEYAMA, K., HOHMAN, R. J., METZGER, H., AND BEAVAN, M. A.: Quantitative relationships between aggregation of IgE receptors, generation of intracellular signals and histamine secretion in rat basophilic leukemia (2H3) cells. J. Biol. Chem. **261:** 2583–2592, 1986.

MAGISTETTI, P. J., AND SCHORDERET, M.: Norepinephrine and histamine potentiate the increase in 3',5'-monophosphate elicited by vasoactive intestinal polypeptide in mouse cerebral cortical slices: mediation by α_1-adrenergic and H_1-histaminergic receptors. J. Neurochem. **5:** 362–368, 1985.

MALINOWSKA, D. H., SACHS, G., AND CUPPOLETTI, J.: Gastric H^+ secretion: histamine (cAMP-mediated) activation of protein phosphorylation. Biochim. Biophys. Acta **972:** 95–109, 1988.

MALLOWS, R. S. E., AND BOLTON, T. B.: Relationship between stimulated phosphatidic acid production and inositol lipid hydrolysis in intestinal longitudinal smooth muscle from guineapig. Biochem. J. **244:** 763–768, 1987.

MAJNO, G., AND PALADE, G. E.: Studies on inflammation. I. The effect of histamine and serotonin on vascular permeability: an electron microscopy study. J. Biophys. Cytol. **11:** 571–606, 1961.

MAJNO, G., SHEA, S. M, AND LEVENTHAL, M.: Endothelium contraction induced by histamine-type mediators: an electron microscope study. J. Cell. Biol. **42:** 647–642, 1968.

MANTELLI, L., AMERININ, S., PICCHI, A., MUGELLI, A., AND LEDDA, F.: Some characteristics of the inotropic effects of histamine H_1- and H_2-receptor agonists in comparison with those of alpha- and beta-adrenoceptor agonsits. Agents Actions **12:** 1–9, 1982.

MARTHAN, M., ARMOUR, C. L., JOHNSON, P. R. A., AND BLACK, J. L.: The calcium channel agonist BAY K8644 enhances the responsiveness of human airway muscle to KCl and histamine but not to carbachol. Am. Rev. Respir. Dis. **135:** 185–189, 1987.

MASTERS, S. B., MARTIN, M. W., HARDEN, T. K., AND BROWN, J. H.: Pertussis toxin does not inhibit muscarinic-receptor mediated phosphoinositide hydrolysis and calcium mobilization. Biochem. J. **227:** 933–937, 1985.

MATSUMOTO, T., KANAIDE, H., NISHIMURA, J., SHOGAKIUCHI, Y., KOBAYASHI,

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S., AND NAKAMURA, M.: Histamine activates H_1-receptors to induce cytosolic free calcium transients in cultured vascular smooth muscle cells from rat aorta. Biochem. Biophys. Res. Commun. 135: 172–177, 1986.

MCDONOUGH, P. M., EUBANKS, J. H., AND BROWN, J. H.: Desensitization and recovery of muscarinic and histaminergic Ca^{2+} mobilization in 1321N1 astrocytoma cells. Biochem. J. 249: 135–141, 1988.

MCINTYRE, T. M., ZIMMERMAN, G. A., SATOH, K., AND PRESCOTT, S. M.: Cultured endothelial cells synthesize both platelet-activating factor and prostacyclin in response to histamine, bradykinin and adenosine triphosphate. J. Clin. Invest. 76: 271–280, 1985.

MCNEIL, E. T., CREVELING, C. R., AND DALY, J. W.: Cyclic AMP-generating systems in cell-free preparations from guinea-pig cerebral cortex: loss of adenosine and amine responsiveness due to low levels of endogenous adenosine. J. Neurochem. 35: 338–342, 1980.

MCNEILL, J. H., AND VERMA, S. C.: Blockade by burimamide of the effects of histamine and histamine analogues on cardiac contractility, phosphorylase activation and cyclic adenosine monophosphate. J. Pharmacol. Exp. Ther. 188: 180–188, 1974.

MELMON, K. L., AND KHAN, M. M.: Histamine and its lymphocyte-selective derivatives as immune modulators. Trends Pharmacol. Sci. 8: 437–441, 1987.

MELMON, K. L., BOURNE, H. R., WEINSTEIN, Y., SHEARER, G. M., KRAM, J., AND BAUMINGER, S.: Hemolytic plaque formation by leukocytes in vitro. J. Clin. Invest. 53: 13–21, 1974.

MELMON, K. L., ROCKLIN, R. E., AND ROSENKRANZ, R. P.: Autacoids as modulators of the inflammatory and immune response. Am. J. Med. 71: 100–106, 1981.

MEYRICK, B., AND BRIGHAM, K. I.: Increased permeability associated with dilation of endothelial cell junctions caused by histamine in intimal explants from bovine pulmonary artery. Exp. Lung Res. 6: 11–25, 1983.

MICHELL, R. H.: Inositol phospholipids and cell surface receptor function. Biochim. Biophys. Acta 415: 81–147, 1977.

MITSUHASHI, M., AND PAYAN, D. G.: Characterization of functional histamine H1 receptors on a cultured smooth muscle cell line. J. Cell. Physiol. 134: 367–375, 1988a.

MITSUHASHI, M., AND PAYAN, D. G.: Phorbol ester-mediated desensitization of histamine H1 receptors on a cultured smooth muscle cell line. Life Sci. 43: 1433–1440, 1988b.

MITSUHASHI, M., AND PAYAN, D. G.: Receptor glycosylation regulates the affinity of histamine H_1-receptors during smooth muscle cell differentiation. Mol. Pharmacol. 35: 311–318, 1989a.

MITSUHASHI, M., AND PAYAN, D. G.: Solubilization and characterization of the pyrilamine-binding protein from cultured smooth muscle cells. Mol. Pharmacol. 35: 751–759, 1989b.

MOREL, N., HARDY, J.-P., AND GODFRAIND, T.: Histamine-operated calcium channels in intestinal smooth muscle of the guinea-pig. Eur. J. Pharmacol. 135: 69–75, 1987.

MORRIS, A. P., GALLACHER, D. V., IRVINE, R. F., AND PETERSEN, O. H.: Synergism of inositol trisphosphate and tetrakisphosphate in activating Ca^{2+}-dependent K^+ Channels Nature (Lond.) 330: 653–655, 1987

MUALLEM, S., AND SACHS, G.: Changes in cytosolic free Ca^{2+} in isolated parietal cells: differential effects of secretogogues. Biochim. Biophys. Acta 805: 181–185, 1984.

MUELLER, E., AND VAN BREEMAN, C.: Role of intracellular Ca^{2+} sequestration in beta adrenergic relaxation of a smooth muscle. Nature (Lond.) 281: 682–683, 1979.

MURRAY, R. K., BENNETT, C. F., FLUHARTY, S. J., AND KOTLIKOFF, M. I.: Mechanism of phorbol ester inhibition of histamine-induced IP_3 formation in cultured airway smooth muscle. Am. J. Physiol. 257: L209–L216, 1989.

NAHORSKI, S. R., ROGERS, K. J., AND EDWARDS, C.: Cerebral glycogenolysis and stimulation of β-adrenoceptors and histamine H_2-receptors. Brain Res. 92: 529–533, 1975.

NAKAHATA, N., AND HARDEN, T. K.: Regulation of inositol trisphosphate accumulation by muscarinic cholinergic and H_1-histamine receptors on human astrocytoma cells: differential induction of desensitization by agonists. Biochem. J. 241: 337–344, 1987.

NAKAHATA, N., MARTIN, M. W., HUGHES, A. R., HEPLER, J. R., AND HARDEN, T. K.: H_1-histamine receptors on human astrocytoma cells. Mol. Pharmacol. 29: 188–195, 1986.

NASSAEL, D. R., HOLMQVIST, M. H., HARDIE, R. C., HAKANSON, R., AND SUNDLER, F.: Histamine-like immunoreactivity in photoreceptors of the compound eyes and ocelli of the flies *Calliphora erythrocephala* and *Musca domestica*. Cell Tissue Res. 253: 639–646, 1988.

NEGULESCU, P. A., AND MACHEN, T. E.: Intracellular Ca regulation during secretogogue stimulation of the parietal cell. Am. J. Physiol. 254: C130–C140, 1988.

NEWTON, M. V., HOUGH, L. B., AND AZIMITIA, E. C.: Histamine-sensitive adenylate cyclase in monkey brain. Brain Res. 239: 639–643, 1982.

NICKERSON, M.: Receptor occupancy and tissue response. Nature (Lond.) 178: 697–698, 1956.

NIELSEN, S. T.: Binding of [^{3}H]-ICIA 5165, an H_2-receptor antagonist to guinea-pig gastric mucosa. Agents Actions 18: 524–531, 1986.

NIEMEGEERS, C. J. E., AWOUTERS, F. H. L., AND JANSSEN, P. A. J.: The in vivo pharmacological profile of histamine (H_1) antagonists in the rat. Drug Dev. Res. 2: 559–566, 1982.

NINKOVIC, M., HUNT, S. P., AND GLEAVE, J. R. W.: Localisation of opiate and histamine H_1-receptors in the primate sensory ganglion and spinal cord. Brain Res. 241: 197–206, 1982.

NISHIZUKA, Y.: The role of protein kinase C in cell surface signal transduction and tumour promotion. Nature (Lond.) 308: 693–698, 1984.

NISHIZUKA, Y.: Studies and perspectives of protein kinase C. Science (Wash. DC) 233: 305–312, 1986.

NOBLE, E. P., BOMMER, M., LIEBISCH, D., AND HERZ, A.: H_1-histaminergic activation of catecholamine release by chromaffin cells. Biochem. Pharmacol. 37: 221–228, 1988.

NOBLE, E. P., BOMMER, M., SINCINI, E., COSTA, T., AND HERZ, A.: H_1-histaminergic activation stimulates inositol-1-phosphate accumulation in chromaffin cells. Biochem. Biophys. Res. Commun. 135: 566–573, 1986.

NORRIS, D. B., GAJTKOWSKI, G. A., AND RISING, T. J.: Histamine H_2-binding studies in the guinea-pig brain. Agents Actions 14: 543–545, 1984.

NORTH, R. A.: Drug receptors and the inhibition of nerve cells. Br. J. Pharmacol. 98: 13–28, 1989.

NORTHOVER, A. M.: Action of histamine in endothelial cells of guinea-pig isolated hepatic portal vein and its modification by indomethacin or removal of calcium. Br. J. Exp. Pathol. 56: 52–61, 1985.

NOSEK, T. M., WILLIAMS, M. F., ZEIGLER, S. T., AND GODT, R. E.: Inositol trisphosphate enhances calcium release in skinned cardiac and skeletal muscle. Am. J. Physiol. 250: C807–C811, 1986.

NOWAK, J. Z., BIELKIEWICZ, B., AND LEBRECHT, U.: Dimaprit induced hypothermia in normal rats: its attenuation by cimetidine and by tricyclic antidepressant drugs. Neuropharmacology 18: 783–789, 1979.

NYLANDER, O., BERGQVIST, E., AND OBRINK, K. J.: Dual inhibitory actions of somatostatin on isolated gastric glands. Acta Physiol. Scand. 125: 111–119, 1985.

OAKES, S. G., IAIZZO, P. A., RICHELSON, E., AND POWIS, G.: Histamine-induced intracellular free Ca^{2+}, inositol phosphates and electrical changes in murine N1E-115 neuroblastoma cells. J. Pharmacol. Exp. Ther. 247: 114–121, 1988.

O'DONNELL, J. P., HOGABOOM, G. K., AND FEDAN, J. S.: Specific irreversible antagonism of histamine receptors in the isolated guinea-pig vas deferens by 4(5)-[2-(4-azido-2-nitroanilino)ethyl]imidazole, a photoaffinity analog of histamine. Eur. J. Pharmacol. 73: 261–271, 1981.

OHSAKO, S., AND DEGUCHI, T.: Receptor-mediated regulation of calcium mobilization and cyclic GMP synthesis in neuroblastoma cells. Biochem. Biophys. Res. Commun. 122: 333–339, 1984.

OISHI, R., ITOH, Y., NISHIBORI, M., AND SAEKI, K.: Effects of the histamine H_3-agonist (R)-α-methylhistamine and the antagonist thioperamide on histamine metabolism in mouse and rat brain. J. Neurochem. 52: 1388–1392, 1989.

OLIANAS, M., OLIVER, A. P., AND NEFF, N. H.: Correlation between histamine-induced neuronal excitability and activation of adenylate cyclase in the guinea-pig hippocampus. Neuropharmacology 23: 1071–1074, 1984.

O'NEILL, P. J., AND PATIL, P. N.: Stereoisomers of an antihistamine and the pharacological receptors of rabbit aorta. Pharmacol. Res. Commun. 7: 273–279, 1975.

ORELLANO, S., SOLSKI, P. A., AND BROWN, J. H.: Guanosine-5'-o-(thiotriphosphate)-dependent inositol trisphosphate formation in membranes is inhibited by phorbol ester and protein kinase C. J. Biol. Chem. 262: 1638–1643, 1987.

OSBAND, M., AND MCCAFFREY, R.: Solubilisation, separation and partial characterisation of histamine H_1 and H_2 receptors from calf thymocyte membranes. J. Biol. Chem. 254: 9970–9972, 1979.

OTTOSON, A., JANSEN, I., AND EDVINSSON, L.: Characterisation of histamine receptors in isolated human cerebral arteries. Br. J. Pharmacol. 94: 901–907, 1988.

OTTOSSON, A., JANSEN, I., AND EDVINSSON, L.: Pharmacological characterisation of histamine receptors in human temporal artery. Br. J. Clin. Pharmacol. 27: 139–145, 1989.

OZAWA, E.: Activation of phosphorylase kinase from brain by small amounts of calcium ion. J. Neurochem. 20: 1487–1488, 1973.

OZAWA, K., NOMURA, Y., AND SEGAWA, T.: Mechanism of Cu^{2+}-induced elevation of [^{3}H]-cimetidine binding to membranes in rat brain. Neurochem. Int. 7: 435–440, 1985.

OZAWA, K., NOMURA, Y., AND SEGAWA, T.: Histamine acting on H_2-receptors stimulates phospholipid methylation in synaptic membranes of rat brain. J. Neurochem. 48: 1392–1398, 1987.

OZAWA, K., AND SEGAWA, T.: Histamine increases phospholipid methylation and H_2-receptor-adenylate cyclase coupling in rat brain. J. Neurochem. 50: 1551–1558, 1988.

PALACIOS, J. M., GARBARG, M., BARBIN, G., AND SCHWARTZ, J. C.: Pharmacological characterisation of histamine receptors mediating the stimulation of cyclic AMP accumulation in slices of guinea-pig hippocampus. Mol. Pharmacol. 14: 971–982, 1978a.

PALACIOS, J. M., SCHWARTZ, J. C., AND GARBARG, M.: High affinity binding of ^{3}H-histamine in rat brain. Eur. J. Pharmacol. 50: 443–444, 1978b.

PALACIOS, J. M., WARMSLEY, J. K., AND KUHAR, M. J.: GABA, benzodiazepine and histamine H_1-receptors in the guinea-pig cerebellum: effects of kainic acid injections studied by autoradiographic methods. Brain Res. 214: 155–162, 1981a.

PALACIOS, J. M., WARMSLEY, J. K., AND KUHAR, M. J.: The distribution of histamine H_1-receptors in the rat brain: an autoradiographic study. Neuroscience 6: 15–37, 1981b.

PALACIOS, J. M., YOUNG, W. S., AND KUHAR, M. J.: Autoradiographic localisa-

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PHARM REV

tion of H_1-histamine receptors in brain using [^{3}H]-mepyramine: preliminary studies. Eur. J. Pharmacol. **58:** 295–304, 1979.

PALMER, R. M. J., FERGIE, A. G., AND MONCADA, S.: Nitric oxide release accounts for the biological activity of endothelium-derived relaxing factor. Nature (Lond.) **327:** 524–526, 1987.

PANETTIERI, R. A., MURRAY, R. K., DEPALO, L. R., YADVISH, P. A., AND KOTLIKOFF, M. I.: A human airway smooth muscle cell line that retains physiological responsiveness. Am. J. Physiol. **256:** C329–C335, 1989.

PANULA, P., YANG, H. Y. T., AND COSTA, E.: Histamine-containing neurons in the rat hypothalamus. Proc. Natl. Acad. Sci. USA **81:** 2572–2576, 1984.

PARK, S., AND RASMUSSEN, H.: Activation of tracheal smooth muscle contraction: synergism between Ca^{2+} and activators of protein kinase C. Proc. Natl. Acad. Sci. USA **82:** 8835–8839, 1985.

PARSONS, M. E., OWEN, D. A. A., GANELLIN, C. R., AND DURANT, G. J.: Dimaprit - [S-[3-(*N,N*-dimetylamino)-propyl]-isothiourea]—a highly specific histamine H_2-receptor agonist: part 1, pharmacology. Agents Actions **7:** 31–37, 1977.

PEARCE, B., AND MURPHY, S.: Neurotransmitter receptors coupled to inositol phospholipid turnover and Ca^{2+} flux: consequences for astrocyte function. *In* Glial Cell Receptors, ed. by H. K. Kimelberg, pp. 197–221, Raven Press, New York, 1988.

PEROUTKA, S. J., AND SNYDER, S. H.: [^{3}H]-Mianserin: Differential labelling of serotonin$_2$ and histamine$_1$ receptors in rat brain. J. Pharmacol. Exp. Ther. **216:** 142–148, 1981.

PEROUTKA, S. J., MOSKOWITZ, M. A., AND SNYDER, S. H.: Neurotransmitter receptor binding in bovine cerebral microvessels. Science (Wash. DC) **208:** 610–612, 1980.

PETCOFF, D. W., AND COOPER, D. M. F.: Adenosine receptor agonists inhibit inositol phosphate accumulation in rat striatal slices. Eur. J. Pharmacol. **137:** 269–271, 1987.

PILC, A., AND NOWAK, J. Z.: The influence of 4-methylhistamine, an agonist of histamine H_2-receptors on body temperature in rats. Neuropharmacology **19:** 773–775, 1980.

PIOMELLI, D., VOLTERRA, A., DALE, N., SIEGELBAUM, S. A., KANDEL, E. R., SCHWARTZ, J. H., AND BALARDETTI, F.: Lipoxygenase metabolites of arachidonic acid as second messengers for presynaptic inhibition of *Aplysia* sensory cells. Nature (Lond.) **328:** 38–43, 1987.

PLAUT, M., AND LICHTENSTEIN, L. M.: Histamine and immune responses. *In* Pharmacology of Histamine Receptors, ed. by C. R. Ganellin and M. E. Parsons, pp. 392–435, J. Wright, Bristol, England, 1982.

PLEVIN, M., AND BOARDER, M. R.: Stimulation of formation of inositol phosphate in cultures of bovine adrenal chromaffin cells by angiotensin II, histamine, bradykinin and carbachol. J. Neurochem. **51:** 634–639, 1988.

POLLARD, H., AND SCHWARTZ, J. C.: Histamine neuronal pathways and their functions. Trends. Neurosci. **10:** 86–89, 1987.

POLLARD, H., PACHOT, I., AND SCHWARTZ, J. C.: Monoclonal antibody against l-histidine decarboxylase for localisation of histaminergic cells. Neurosci. Lett. **54:** 53–58, 1985.

POLLOCK, W. K., WREGGETT, K. A., AND IRVINE, R. F.: Inositol phosphate production and Ca^{2+} mobilization in human umbilical-vein endothelial cells stimulated by thrombin and histamine. Biochem. J. **256:** 371–376, 1988.

PRELL, G. D., AND GREEN, J. P.: Histamine as a neuroregulator. Annu. Rev. Neurosci. **9:** 209–254, 1986.

PUURUNEN, J., LOHSE, M. J., AND SCHWABE, U.: Interactions between intracellular cyclic AMP and agonist-induced inositol phospholipid breakdown in isolated gastric mucosal cells of the rat. Naunyn-Schmiedebergs Arch. Pharmacol. **336:** 471–477, 1987.

QUACH, T. T., DUCHEMIN, A. M., ROSE, C., AND SCHWARTZ, J. C.: In vivo occupation of cerebral histamine H_1-receptors evaluated with ^{3}H-mepyramine may predict sedative properties of psychotropic drugs. Eur. J. Pharmacol. **60:** 391–392, 1979.

QUACH, T. T., DUCHEMIN, A. M., ROSE, C., AND SCHWARTZ, J. C.: Labelling of histamine H_1-receptors in brain of the living mouse. Neurosci. Lett. **17:** 49–54, 1980a.

QUACH, T. T., DUCHEMIN, A. M., ROSE, C., AND SCHWARTZ, J. C.: ^{3}H-Glycogen hydrolysis elicited by histamine in mouse brain slices: selective involvement of H_1-receptors. Mol. Pharmacol. **17:** 301–308, 1980b.

QUACH, T. T., DUCHEMIN, A. M., ROSE, C., AND SCHWARTZ, J. C.: Specific desensitization of histamine H_1-receptor-mediated [^{3}H]glycogen hydrolysis in brain slices. Mol. Pharmacol. **20:** 331–338, 1981.

QUACH, T. T., ROSE, C., AND SCHWARTZ, J. C.: [^{3}H]-Glycogen hydrolysis in brain slices: responses to neurotransmitters and modulation of noradrenaline receptors. J. Neurochem. **30:** 1335–1341, 1978.

RAEBURN, D., ROBERTS, J. A., RODGER, I. W., AND THOMSON, N. C.: Agonist induced contractile responses of human bronchial muscle in vitro: effects of Ca^{2+} removal, La^{3+} and PY 108068. Eur. J. Pharmacol. **121:** 251–255, 1986.

REASBECK, P. G., AND YOUNG, J. M.: Interaction of benzilylcholine mustard, benzilycholine and lacheaine with the histamine receptor in the longitudinal muscle of guinea-pig ileum. Br. J. Pharmacol. **48:** 148–155, 1973.

REINHARDT, D., AND RITTER, E.: Hypothermia-induced potentiation of histamine H_2-receptor-mediated relaxation and cyclic AMP increase in the isoalted mesenteric artery of the rabbit. Agents Actions **9:** 9–14, 1979.

REINHARDT, D., SCHMIDT, U., BRODDE, O. E., AND SCHUMANN, H.: H_1- and H_2-receptor mediated responses to histamine on contractility and cyclic AMP of atrial and papillary muscles from guinea-pig hearts. Agents Actions **7:** 1–12, 1977.

REINHARDT, D., WAGNER, J., AND SCHUMANN, H. J.: Differentiation of H_1- and H_2-receptors mediating positive chrono- and inotropic responses to histamine on atrial preparations of the guinea-pig. Agents Actions **4:** 217–221, 1974.

REINHARDT, D., WIEMANN, H., AND SCHUMANN, H. J.: Effects of the H_1-antagonist promethazine and H_2-antagonist burimamide on chronotropic, inotropic and coronary vascular responses to histamine in isolated perfused guinea-pig hearts. Agents Actions **6:** 683–689, 1976.

RESINK, T. J., GRIGORIAN, G. Y., MOLDABAEVA, A. K., DANILOV, S. M., AND BUHLER, F. R.: Histamine-induced phosphoinositide metabolism in cultured human umbilical vein endothelial cells: association with thromboxane and prostacyclin release. Biochem. Biophys. Res. Commun. **144:** 438;3n446, 1987.

REUSE, J. J.: Comparison of various histamine antagonists. Br. J. Pharmacol. Chemother. **3:** 174–180, 1948.

REUTER, H.: Calcium channel modulation by neurotransmitters, enzymes and drugs. Nature (Lond.) **301:** 569–574, 1983.

REUTER, H., KOKUBUM, S., AND PROD'HOM, B.: Properties and modulation of cardiac calcium channels. J. Exp. Biol. **124:** 191–201, 1986.

RICHELSON, E.: Histamine H_1 receptor-mediated guanosine 3′,5′-monophosphate formation by cultured mouse neuroblastoma cells. Science (Wash. DC) **201:** 69–71, 1978.

RICHELSON, E.: Histamine receptors, cyclic nucleotides and psychotropic drugs. *In* Frontiers in Histamine Research, Advances in the Biosciences, vol. 51, ed. by C. R. Ganellin and J. C. Schwartz, pp. 131–140, Pergamon, New York, 1985.

RILEY, J. F., AND WEST, G. B.: The occurrence of histamine in mast cells. *In* Handbook of Experimental Pharmacology, vol. 18, part 1, ed. by M. Rocha e Silva, pp. 116–135, Springer-Verlag, Berlin, 1966.

RISING, T. J., AND NORRIS, D. B.: Histamine H_2-receptor radioligand binding studies. *In* Frontiers in Histamine Research, Advances in the Biosciences, ed. by C. R. Ganellin and J. C. Schwartz, vol. 51, pp. 61–67, Pergamon, New York, 1985.

RISING, T. J., NORRIS, D. B., WARRENDER, S. E., AND WOOD, T. P.: High affinity ^{3}H-cimetidine binding in guinea-pig tissues. Life Sci. **27:** 199–206, 1980.

ROBERTS, F., AND CALCUTT, C. R.: Histamine and the hypothalamus. Neuroscience **9:** 721–739, 1983.

ROBINSON, R. L.: Histamine-induced catecholamine secretion from the cat adrenal medulla is mediated primarily by the H_1-receptor. Fed. Proc. **41:** 1060, 1982.

ROSE, C., QUACH, T. T., LORENS, C., AND SCHWARTZ, J. C.: Relationship between occupation of cerebral H_1-receptors and sedative properties of antihistamines. Arzneim Forsch. Drug Res. **32** (suppl. II): 1171–1173, 1982.

ROSENFELD, G. C., THOMPSON, W. J., AND JACOBSEN, E. D.: Reevaluation of cAMP in histamine induced gastric acid secretion. Gastroenterology **70:** 832–835, 1976.

ROTH, F. E., AND GOVIER, W. M.: Comparative pharmacology of chloropheniramine (chlor-trimeton) and its optical isomers. J. Pharmacol. Exp. Ther. **124:** 347–349, 1958.

ROTROSEN, D., AND GALLIN, J. I.: Histamine type I receptor occupancy increases endothelial cytosolic calcium, reduces F-actin and promotes albumin diffusion across cultured endothelial monolayers. J. Cell Biol. **103:** 2379–2387, 1986.

ROTTER, A., AND FROSTHOLM, A.: Cerebellar histamine H_1-receptor distribution: an autoradiographic study of Purkinje cell degeneration, staggerer, weaver and reeler mutant mouse strains. Brain Res. Bull. **16:** 205–214, 1986.

RUAT, M., AND SCHWARTZ, J. C.: Photoaffinity labeling and electrophoretic identification of the H_1-receptor: comparison of several brain regions and animal species. J. Neurochem. **53:** 335–339, 1989.

RUAT, M., KORNER, M., GARBARG, M., GROS, C., SCHWARTZ, J. C., TERTIUK, W., AND GANELLIN, C. R.: Characterisation of histamine H_1-receptor binding peptides in guinea-pig brain using [^{125}I]iodoazidophenpyramine, an irreversible specific photoaffinity probe. Proc. Natl. Acad. Sci. USA **85:** 2743–2747, 1988.

SAKUMA, I., GROSS, S. S., AND LEVI, R.: Positive inotropic effect of histamine on guinea-pig left atrium: H_1-induced stimulation of phosphoinositide turnover. Fed. Proc. **46:** 962, 1987.

SAKUMA, I., GROSS, S. S., AND LEVI, R.: Positive inotropic effect of histamine on guinea-pig left atrium: H_1-receptor-induced stimulation of phosphoinositide turnover. J. Pharmacol. Exp. Ther. **247:** 466–472, 1988.

SANSONI, P., SILVERMAN, E. D., KHAN, M. M., MELMON, K. L., AND ENGLEMAN, E. G.: Immunoregulatory T cells in man: Histamine-induced suppressor T cells are derived from Leu 2+ (T+) subpopulation distinct from that which gives rise to cytotoxic T cells. J. Clin. Invest. **75:** 650–656, 1985.

SASAKI, K., AND SATO, M.: A single GTP-binding protein regulates K^+-channels coupled with dopamine, histamine and acetylcholine receptors. Nature (Lond.) **325:** 259–262, 1987.

SATOH, H., AND INUI, J.: Endothelial cell-dependent relaxation and contraction induced by histamine in isolated guinea-pig pulmonary artery. Eur. J. Pharmacol. **97:** 321–324, 1984.

SAUVE, R., SIMONEAU, C., PARENT, L., MONETTE, R., AND ROY, G.: Oscillatory activation of calcium-dependent potassium channels in Hela cells induced by histamine H_1-receptor stimulation: a single-channel study. J. Membr. Biol. **96:** 199–208, 1987.

SAWAI, S., WANG, N. P., FUKUI, H., FAKUDA, M., MANABE, R., AND WADA, H.: Histamine H_1-receptor in the retina: species differences. Biochem. Biophys. Res. Commun. **150:** 316–322, 1988.

SAXENA, S. P., BRANDES, L. J., BECKER, A. B., SIMONS, K. J., LABELLA, F. S.,

PHARMACOLOGICAL REVIEWS

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PHARM REV

AND GERRARD, J. M.: Histamine is an intracellular messenger mediating platelet aggregation. Science (Wash. DC) **243:** 1596–1599, 1989.

SCHLICKER, E., BETZ, R., AND GOTHERT, M.: Histamine H_3-receptor-mediated inhibition of serotonin release in the rat brain cortex. Naunyn-Schmiedebergs Arch. Pharmacol. **337:** 588–590, 1988.

SCHOTTE, A., AND LEYSEN, J. E.: Distinct autoradiographic labelling of serotonin 5-HT_2 receptors, α_1-adrenoceptors and histamine H_1-receptors and of tetrabenazine-displaceable ketanserin binding sites in rodent brain with [^{125}I]-7-amino-8-iodo-ketanserin. Eur. J. Pharmacol. **145:** 213–216, 1988.

SCHWABE, U., OHGA, Y., AND DALY, J. W.: The role of calcium in the regulation of cyclic nucleotide levels in brain slices of rat and guinea-pig. Naunyn-Schmiedebergs Arch. Pharmacol. **302:** 141–151, 1978.

SCHWARTZ, A., ASKENASE, P. W., AND GERSHON, R. K.: Histamine inhibition of the in vitro induction of cytotoxic T-cell responses. Immunopharmacology **2:** 179–190, 1980b.

SCHWARTZ, J. C.: Histaminergic mechanism in brain. Annu. Rev. Pharmacol. Toxicol. **17:** 325–339, 1977.

SCHWARTZ, J. C., ARRANG, J. M., AND GARBARG, M.: Three classes of histamine receptor in brain. Trends. Pharmacol. Sci., **7:** 24–28, 1986a.

SCHWARTZ, J. C., GARBARG, M., AND POLLARD, H.: Histaminergic transmission in the brain. *In* Handbook of Physiology: The Nervous System. IV Intrinsic Regulatory System of the Brain, ed. by F. E. Bloom and V. Mountcastle, pp. 257–316. American Physiological Society, Bethesda, MD, 1986b.

SCHWARTZ, J. C., POLLARD, H., AND QUACH, T. T.: Histamine as a neurotransmitter in mammalian brain: neurochemical evidence. J. Neurochem. **35:** 26–33, 1980a.

SEEMAN, P., AND WEINSTEIN, J.: Erythrocyte membrane stabilization by tranquilizers and antihistamines. Biochem. Pharmacol. **15:** 1737–1752, 1966.

SEWING, K. F., BEIL, W., AND HANNEMANN, H.: Comparative pharmacology of histamine H_2-receptor antagonists. Drugs **35** (suppl. 3): 25–28, 1988.

SHAW, G. G.: Hypothermia produced in mice by histamine acting on the central nervous system. Br. J. Pharmacol. **42:** 205–214, 1971.

SHONK, R. F., AND RALL, T. W.: Ontogeny of adenosine-3′,5′-monophosphate metabolism in guinea-pig cerebral cortex. I. Development of responses to histamine, norepinephrine and adenosine. Mol. Cell. Biochem. **73:** 141–155, 1987.

SILVER, P. J., AND STULL, J. T.: Regulation of myosin light chain kinase and phosphorylase phosphorylation in tracheal smooth muscle. J. Biol. Chem. **257:** 6145–6150, 1982.

SIMON, B., AND KATHER, H.: Histamine-sensitive adenylate cyclase of human gastric mucosa. Gastroenterology **73:** 429–431, 1977.

SINGER, H. A., AND PEACH, M. J.: Calcium and endothelial-mediated vascular smooth muscle relaxation in rabbit aorta. Hypertension **4** (suppl. II): 19–25, 1984.

SINHA, J. N., GUPTA, M. L., AND BHARGAVA, K. P.: Effect of histamine and antohistamines on central vasomotor loci. Eur. J. Pharmacol. **5:** 235–238, 1969.

SMITH, I. R., CLEVERLEY, M. T., GANELLIN, C. R., AND METTERS, K. M.: Binding of [^{3}H]-cimetidine to rat brain tissue. Agents Actions **10:** 422–426, 1980.

SMITH, I. R., LEIGH, B. K., AND MYLEK, M. E.: ^{3}H-tiotidine binding to guinea-pig cortical and striatal membranes. Agents Actions **19:** 169–173, 1986.

SNIDER, R. M., MCKINNEY, M., FORRAY, C., AND RICHELSON, E.: Neurotransmitter receptors mediate cyclic GMP formation by involvement of arachidonic acid and lypoxygenase. Proc. Natl. Acad. Sci. USA **81:** 3905–3909, 1984.

SOLL, A. H.: The interactions of histamine with gastrin and carbamylcholine on oxygen uptake by isolated mammalian parietal cells. J. Clin. Invest. **61:** 381–389, 1978.

SOLL, A. H.: Potentiating interactions of gastric stimulants on ^{14}C-aminopyrine accumulation by isolated canine parietal cells. Gastroenterology **83:** 216–223, 1982.

SOLL, A. H., AND BERGLINDH, T.: Physiology of isolated gastric glands and parietal cells: receptors and effectors regulating function. Physiology of the Gastrointestinal Tract, 2nd ed., ed. by L. R. Johnson, pp. 883–909, Raven Press, New York, 1987.

SOLL, A. H., AND WOLLIN, A.: Histamine and cyclic AMP in isolated canine parietal cells. Am. J. Physiol. **237:** E444–E450, 1979.

SOLL, A. H., LEWIN, K., AND BEAVAN, M. A.: Isolation of histamine-containing cells from canine fundic muscoa. Gastroenterology **77:** 1283–1290, 1979.

SOLL, A. H., LEWIN, K., AND BEAVAN, M. A.: Isolation of histamine-containing cells from rat gastric mucosa: biochemical and morphological difference from the mast cell. Gastroenterology **80:** 717–727, 1981.

SPIKER, M. D., PALMER, G. C., AND MANIAN, A. A.: Action of neuroleptic agents on histamine-sensitive adenylate cyclase in rabbit cerebral cortex. Brain Res. **104:** 401–406, 1976.

STANLEY, C., BROWN, A. M., AND HILL, S. J.: Effect of isozyme-selective inhibitors of phosphodiesterase on histamine-stimulated cyclic AMP accumulation in guinea-pig hippocampus. J. Neurochem. **52:** 671–676, 1989.

STASZEWSKA-BARCZAK, J., AND VANE, J. R.: The release of catecholamines from the adrenal medulla by histamine. Br. J. Pharmacol. Chemother. **25:** 728–742, 1965.

STEINBERG, G. H., EPPEL, J. G., KANDEL, M., KANDEL, S. I., AND WELLS, J. W.: H_2 histaminic receptors in rat cerebral cortex. 1. Binding of [^{3}H]-histamine. Biochemistry **24:** 6095–6107, 1985a.

STEINBERG, G. H., KANDEL, M., KANDEL, S. I., AND WELLS, J. W.: H_2 histaminic receptors in rat cerebral cortex. 2. Inhibition of [^{3}H]-histamine by H_2-antagonists. Biochemistry **24:** 6107–6115, 1985b.

STEINBERG, G. H., KANDEL, M., KANDEL, S. I., AND WELLS, J. W.: H_2 histaminic receptors in rat cerebral cortex. 3. Inhibition of [^{3}H]-histamine by H_2agonists. Biochemistry **24:** 6115–6125, 1985c.

STEINBERG, M. I., AND HOLLAND, D. R.: Seperate receptors mediating the positive inotropic and chronotropic effect of histamine in guinea-pig atria. Eur. J. Pharmacol. **34:** 95–104, 1975.

STEINBUSCH, H. W. M., SAUREN, Y., GROENWEGEN, H., WATANABE, T., AND MULDER, A. H.: Histaminergic projections from the premammilary and posterior hypothalamic region to the caudate-putamen complex in the rat. Brain Res. **368:** 389–393, 1986.

STRADER, C. D., SIGAL, I. S., REGISTER, R. B., CANDELORE, M. R., RANDS, E., AND DIXON, A. F.: Identification of residues required for ligand binding to the β-adrenergic receptor. Proc. Natl. Acad. Sci. USA **84:** 4384–4388, 1987.

STUDY, R. E., AND GREENGARD, P.: Regulation by histamine of cyclic nucleotide levels in sympathetic ganglia. J. Pharmacol. Exp. Ther. **207:** 767–778, 1978.

SUBRAMANIAN, N., SEIDLER, F. J., WHITMORE, W. L., AND SLOTKIN, T. A.: Histamine stimulates brain phospholipid turnover through a direct, H-1 receptor mediated mechanisms. Life Sci. **27:** 1315–1319, 1980.

SUBRAMANIAN, N., AND SLOTKIN, T. A.: Solubilization of a [^{3}H]-cimetidine binding site from rat brain: A clonidine-sensitive H-2 receptor subtype? Mol. Pharmacol. **20:** 240–243, 1981.

SUBRAMANIAN, N., WHITMORE, W. L., SEIDLER, F. J., AND SLOTKIN, T. A.: Ontogeny of histaminergic neurotransmission in the rat brain: concomitant development of neuronal histamine, H-1 receptors and H-1 receptor-mediated stimulation of phospholipid turnover. J. Neurochem. **36:** 1137–1141, 1981.

SUNG, C. P., JENKINS, B. C., BURNS, L. R., HACKNEY, V., SPENNEY, J. G., SACHS, G., AND WIEBELHAUS, V. D.: Adenyl and guanyl cyclase in rabbit gastric mucosa. Am. J. Physiol. **225:** 1359–1363, 1973.

SVENSJO, E., AND GREGA, G. J.: Evidence for endothelial cell-mediated regulation of macromolecular permeability by postcapillary venules. Fed. Proc. **45:** 89–95, 1986.

SVENSJO, E., AND ROEMPKE, K.: Dose-related antipermeability effect of terbutaline and its inhibition by a selective $_2$-receptor blocking agent. Agents Actions **16:** 1–2, 1985.

SWEATMAN, P., AND JELL, R. M.: Dopamine and histamine sensitivity of rostral hypothalamic neurones in the cat: possible involvement in thermoregulation. Brain Res. **127:** 173–178, 1977.

TAKEDA, M., TAKAGI, T., YASHIMA, Y., AND MAENO, H.: Effect of a new potent H_2-blocker, 3-[[[2-[diaminomethylene]-4-thiazolyl-methyl]thio]-N^2-sulfamoyl propionamidine (YM 11170), on gastric secretion, ulcer formation and weight of male accessory sex organs in rats. Arzneim-Forsch. Drug Res. **32:** 734–737, 1982.

TAKEDA, N., INAGAKI, S., TAGUCHI, Y., TOHYAMA, M., WATANABE, T., AND WADA, H.: Origins of histamine-containing fibres in the cerebral cortex of rats studied by immunohistochemistry with histidine decarboxylase as a marker and transection. Brain Res. **323:** 55–63, 1984.

TAKUWA, Y., TAKUWA, N., AND RASMUSSEN, H.: Measurement of cytoplasmic free Ca^{2+} concentration in bovine tracheal smooth muscle using aequorin. Am. J. Physiol. **253:** C817–C827, 1987.

TAMURA, K., PALMER, J. M., AND WOOD, J. D.: Presynaptic inhibition produced by histamine at nicotinic synapses in enteric ganglia. Neuroscience **25:** 171–179, 1988.

TANNER, L. I., HARDEN, T. K., WELLS, J. N., AND MARTIN, M. W.: Identification of the phosphodiesterase regulated by muscarinic cholinergic receptors of 1321N1 human astrocytoma cells. Mol. Pharmacol. **29:** 455–460, 1986.

TAYLOR, C. W., AND MERRITT, J. E.: Receptor coupling to polyphosphoinositide turnover: a parallel with the adenylate cyclase system. Trends Pharmacol. Sci. **7:** 238–242, 1986.

TAYLOR, J. E., AND RICHELSON, E.: Desensitization of histamine H_1-receptor-mediated cyclic GMP formation in mouse neuroblastoma cells. Mol. Pharmacol. **15:** 462–471, 1979.

TAYLOR, J. E., AND RICHELSON, E.: High affinity binding of tricyclic antidepressants to histamine H_1-receptors: fact or artifact. Eur. J. Pharmacol. **67:** 41–46, 1980.

TAYLOR, J. E., AND RICHELSON, E.: High affinity binding of [^{3}H]-doxepin to histamine H_1-receptors in rat brain: possible identification of a sub-class of histamine H_1-receptors. Eur. J. Pharmacol. **78:** 279–285, 1982.

TAYLOR, J. E., YAKSH, T. L., AND RICHELSON, E.: Histamine H_1-receptors in the brain and spinal cord of the cat. Brain Res. **243:** 391–394, 1982.

TAYLOR, K. M.: Comparison of the antihistamine effect of burimamide and mepyramine and their effect on the activity of histamine methyltransferase. Biochem. Pharmacol. **22:** 2775–2776, 1973.

TAYLOR, K. M., AND SNYDER, S. H.: Histamine in rat brain: sensitive assay of endogenous levels, formation *in vivo* and lowering by inhibitors of histidine decarboxylase. J. Pharmacol. Exp. Ther. **179:** 619–633, 1971.

TAYLOR, K. M., GFELLER, E. D., AND SNYDER, S. H.: Regional localisation of histamine and histidine in the brain of the rhesus monkey. Brain Res. **41:** 171–180, 1972.

TENNES, K. A., MCKINNEY, J. S., AND PUTNEY, J. W.: Metabolism of inositol-1,4,5-trisphosphate in guinea-pig hepatocytes. Biochem. J. **242:** 797–802, 1987.

THOMAS, G.: Mechanism of ionophore A23187 induction of plasma protein leakage and its inhibition by indomethacin. Eur. J. Pharmacol. **81:** 35–42, 1985.

PHARMACOLOGICAL REVIEWS

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PHARM REV

PHARMACOLOGICAL REVIEWS

TING, S., DUNSKY, E. H., AND ZWEIMAN, B.: Histamine suppression of eosinophilotaxis and histamine release in vivo. J. Allergy Clin. Immunol. 65: 196–197, 1980.

TODA, N.: Endothelium-dependent relaxation induced by angiotensin II and histamine in isolated arteries of dog. Br. J. Pharmacol. 81: 301–307, 1984.

TOHDA, M., AND NOMURA, Y.: Effects of histamine on polyphosphoinositide metabolism in NG108–15 cells. Neurochem. Int. 14: 73–78, 1989.

TOLL, L., AND SNYDER, S. H.: Solubilization and characterization of histamine H_1-receptors in brain. J. Biol. Chem. 257: 13593–13601, 1982.

TOLONE, G., BONSERA, L., AND POTIERI, G. M.: Histamine binding to H_2-receptors stimulates phospholipid methylation in mast cells. Experientia 38: 966–968, 1982.

TORCHIANA, M. L., PENDLETON, R. G., COOK, P. G., HANSON, C. A., AND CLINESCHMIDT, B. V.: Apparent irreversible H_2-receptor blocking and prolonged gastric antisecretory activities of 3-*N*-[3-[3-(1-prolonged gastric antisecretory activities of 3-*N*-[3-[3-(1-piperidino-methyl)phenoxy]propyl]amino-4–1,2,5-thiadazole-1-oxide (L-643,441). J. Pharmacol. Exp. Ther. 224: 514–519, 1983.

TORPHY, T. J., BURMAN, M., HUANG, L. B. F., HOROHONICH, S., AND CIELSINSKI, L. B.: Regulation of cAMP content and cAMP-dependent protein kinase activity in airway smooth muscle. Prog. Clin. Biol. Res. 245: 263–275, 1987.

TRAN, V. T., CHANG, R. S. L., AND SNYDER, S. H.: Histamine H_1-receptors identified in mammalian brain membranes with [^{3}H]-mepyramine. Proc. Natl. Acad. Sci. USA 75: 6290–6294, 1978.

TRAN, V. T., LEBOVITZ, R., TOLL, L., AND SNYDER, S. H.: [^{3}H]-doxepin interactions with histamine H_1-receptors and other sites in guinea-pig and rat brain homogenates. Eur. J. Pharmacol. 70: 501–509, 1981.

TREHERNE, J. M., AND YOUNG, J. M.: Digitonin-solubilized histamine H_1-receptors bind to polyethylenimine-treated glass-fibre filters. J. Pharm. Pharmacol. 40: 730–733, 1988a.

TREHERNE, J. M., AND YOUNG, J. M.: Temperature-dependence of the kinetics of the binding of [^{3}H]-(+)-*N*-methyl-4-methyldiphenhydramine to the histamine H_1-receptor: comparison with the kinetics of [^{3}H]-mepyramine. Br. J. Pharmacol. 94: 811–822, 1988b.

TREHERNE, J. M., AND YOUNG, J. M.: [^{3}H]-(+)-*N*-methyl-4-methyldiphenhydramine, a quarternary radioligand for the histamine H_1-receptor. Br. J. Pharmacol. 94: 797–810, 1988c.

TRENDELENBURG, U.: The action of histamine and pilocarpine on the superior cervical ganglion and the adrenal glands of the cat. Br. J. Pharmacol. Chemother. 9: 481–487, 1954.

TRENDELENBURG, U.: The action of histamine and 5-hydroxytryptamine on isolated mammalian atria. J. Pharmacol. Exp. Ther. 130: 450–460, 1960.

TRZECIAKOWSKI, J. P.: Inhibition of guinea-pig ileum contractions mediated by a class of histamine receptors resembling the H_3-subtype. J. Pharmacol. Exp. Ther. 243: 874–880, 1987.

TRZECIAKOWSKI, J. P., AND LEVI, R.: The cardiac pharmacology of tiotidine (ICI 125,211): a new histamine H_2-receptor antagonist. J. Pharmacol. Exp. Ther. 214: 629–634, 1980.

TSAI, B. S., AND YELLIN, T. O.: Regulation by monovalent cations of histamine H_2-receptors-coupled adenylate cyclase from guinea-pig fundic gastric mucosa. Life Sci. 33: 895–902, 1983.

TUONG, M. D. T., GARBARG, M., AND SCHWARTZ, J. C.: Pharmacological specificity of brain histamine H_2-receptors differs in intact cells and cell-free preparations. Nature (Lond.) 287: 548–551, 1980.

UZAN, A., AND LE FUR, G.: Are antihistamines sedative via a blockade of brain H_1-receptors? J. Pharm. Pharmacol. 31: 701–702, 1979.

VAN AMSTERDAM, R. G. M., MEURS, H., BROUVER, F., POSTEMA, J. B., TIMMERMANS, A., AND ZAAGSMA, J.: Role of phosphoinositide metabolism in functional antagonism of airway smooth muscle contraction by β-adrenoceptor agonists. Eur. J. Pharmacol. Mol. Pharmacol. 172: 175–183, 1989.

VAN DE VOORDE, J., AND LEUSEN, I.: Role of the endothelium in the vasodilator response of rat thoracic aorta to histamine. Eur. J. Pharmacol. 87: 113–120, 1983.

VAN DER VLIET, A., VAN DER WERF, J. F., BAST, A., AND TIMMERMAN, H.: Frequency-dependent autoinhibition of histamine release from rat cortical slices: a possible role for H_3 receptor reserve. J. Pharm. Pharmacol. 40: 577–579, 1988.

VAN DER WERF, J. F., AND TIMMERMAN, H.: The histamine H_3-receptor: a general presynaptic histaminergic regulatory system?: Trends Pharmacol. Sci. 10: 159–162, 1989.

VAN DER WERF, J. F., BAST, A., BIJLOO, G. J., VAN DER VLIET, A., AND TIMMERMAN, H.: HA autoreceptor assay with superfused slices of rat brain cortex and electrical stimulation. Eur. J. Pharmacol. 138: 199–206, 1987.

VAN WAUWE, J., JANSSENS, F., NIEMEGEERS, J. E., AWOUTERS, F., VAN NUETEN, J. M., AND JANSSEN, P. A. J.: In vitro pharmacology of astemizole, a new type of H_1-antihistaminic compound. Arch. Int. Pharmacodyn. Ther. 251: 39–51, 1981.

VANHOUTTE, P. M.: The end of the quest? Nature (Lond.) 327: 459–460, 1987.

VERMA, S., AND MCNEILL, J.: Cardiac histamine receptors: difference between left and right atria and right ventricle. J. Pharmacol. Exp. Ther. 200: 352–362, 1977.

VERMA, S. C., AND MCNEILL, J. H.: Blockade by burimamide of the effects of histamine and histamine analogues on cardiac adenylate cyclase. J. Pharm. Pharmacol. 26: 372–373, 1974.

VINCENC, K., BLACK, J., AND SHAW, J.: Relaxation and contraction responses to histamine in the human lung parenchymal strip. Eur. J. Pharmacol. 98: 201–210, 1984.

WAHLESTEDT, C., SKAGERBERG, G., HAKANSON, R., SUNDLER, F., WADA, H., AND WATENABE, T.: Spinal projections of hypothalamic histidine decarboxylase-immunoreactive neurons. Agents Actions 16: 231–233, 1985.

WALLACE, R. M., AND YOUNG, J. M.: Temperature dependence of the binding of [^{3}H]-mepyramine and related compounds to the histamine H_1-receptor. Mol. Pharmacol. 23: 60–66, 1983.

WAN, D. C. C., MARLEY, P. D., AND LIVETT, B. G.: Histamine activates proenkephalin A mRNA but not phenylethanolamine-N-methyltransferase mRNA expression in cultured bovine adrenal chromaffin cells. Eur. J. Pharmacol. Mol. Pharmacol. 172: 117–129, 1989.

WANG, N. P., FUKUI, H., MATSUOKA, H., AND WADA, H.: Determination of the molecular size of the hepatic H_1-receptor by target size analysis. Biochem. Biophys. Res. Commun. 137: 593–598, 1986.

WARBANOW, W., AND WOLLENBERGER, A.: Mechanical responses of cultured pre- and neonatal myocytes. J. Mol. Cell. Cardiol. 11 (suppl. 1): 64, 1979.

WARRENDER, S. E., NORRIS, D. B., RISING, T. J., AND WOOD, T. P.: ^{3}H-cimetidine and the H_2-receptor. Life Sci. 33: 1119–1126, 1983.

WATENABE, T., TAGUCHI, Y., HAYASHI, H., TANAKA, J., SHIOSAKA, S., TAHYAMA, M., KUBOTA, H., TERANO, Y., AND WADA, H.: Evidence for the presence of a histaminergic neuron system in the rat brain: an immunohistochemical analysis. Neurosci. Lett. 39: 249–254, 1983.

WATENABE, T., TAGUCHI, Y., SHIOSAKA, S., TANAKA, J., KUBOTA, H., TERANO, Y., TOHYAMA, M., AND WADA, H.: Distribution of the histaminergic neuron system in the central nervous system of rats: a fluorescent immunohistochemical analysis with histidine decarboxylase as a marker. Brain Res. 295: 13–25, 1984.

WATENABE, T., TAGUSHI, Y., SASAKI, K., AND KITAMURA, Y.: Increase in histidine decarboxylase activity in mouse skin after application of the tumor promoter tetradecanoylphorbol acetate. Biochem. Biophys. Res. Commun. 100: 427–432, 1981.

WEINER, R. I., AND GANONG, W. F.: Role of brain monoamines and histamine in regulation of anterior pituitary secretion? Physiol. Rev. 58: 905–976, 1978.

WEINREICH, D.: Synaptic responses mediated by identified histamine-containing neurons. Nature (Lond.) 267: 854–656, 1977.

WEINREICH, D., WEINER, C., AND MCCAMAN, R.: Endogenous levels of histamine in single neurons isolated from CNS of *Aplysia californica*. Brain Res. 84: 341–345, 1975.

WELLS, J. W., CYBULSKY, D. L., KANDEL, M., KANDEL, S. I., AND STEINBERG, G. H.: Cognitive properties of H_2-receptors revealed by [^{3}H]-histamine. *In* Frontiers in Histamine Research, Advances in the Biosciences, ed. by C. R. Ganellin and J. C. Schwartz, vol. 51, pp. 69–78, Pergamon, New York, 1985.

WHITE, T.: Peripheral vascular effects of histamine administered into the cerebral ventricles of anaesthetised cats. Experientia 21: 132–133, 1965.

WHITWORTH, P., AND KENDALL, D. A.: Lithium selectively inhibits muscarinic receptor-stimulated inositol tetrakisphosphate accumulation in mouse cerebral cortex slices. J. Neurochem. 51: 258–265, 1988.

WHORTON, A. R., COLLAWN, J. B., MONTGOMERY, M. E., YOUNG, S. L., AND KENT, R. S.: Arachidonic acid metabolism in cultured aortic endothelial cells: effect of cAMP and 3-isobutyl-1-methylxanthine. Biochem. Pharmacol. 34: 119–123, 1985.

WIECH, N. L., AND MARTIN, J. S.: Absence of an effect of terfenadine on guinea-pig brain histamine H_1-receptors in vivo determined by receptor binding techniques. Arzneim Forsch. Drug Res. 32 (suppl. II): 1167–1170, 1982.

WOLFF, A. A., AND LEVI, R.: Histamine and cardiac arrhythmias. Circ. Res. 58: 1–16, 1986.

WOUTERS, W. VAN DUN, J., LEYSEN, J. E., AND LADURON, P.: Differential photoaffinity labelling of serotonin S_2-receptors and histamine H_1-receptors using 7-azido-ketanserin. FEBS Lett. 182: 291–296, 1985a.

WOUTERS, W. VAN DUN, J., LEYSEN, J. E., AND LADURON, P.: Photoaffinity probes for serotonin and histamine receptors, synthesis and characterisation of two azide analogues of ketanserin. J. Biol. Chem. 260: 8423–8429, 1985b.

XU, J., AND CHUANG, D. M.: Serotonergic, adrenergic and histaminergic receptors coupled to phospholipase C in cultured cerebellar granule cells of rats. Biochem. Pharmacol. 36: 2353–2358, 1987.

YELLIN, T. O., BUCK, S. H., GILMAN, D. J., JONES, D. F., AND WARDLEWORTH, J. M.: ICI 125,211: A new gastric antisecretory agent acting on histamine H_2-receptors. Life Sci. 25: 2001–2009, 1979.

YERAMIAN, E., GARBARG, M., AND SCHWARTZ, J. C.: N-Ethylmaleimide-induced changes in agonist affinity for histamine H_1-receptors in the guinea-pig brain. Mol. Pharmacol. 28: 155–162, 1985.

YOSHIMASA, T., SIBLEY, D. R., BOUVIER, M., LEFKOWITZ, R. J., AND CARON, M. G.: Cross-talk between cellular signalling pathways suggested by phorbol ester-induced adenylate cyclase phosphorylation. Nature (Lond.) 327: 67–70, 1987.

YOSHIZAKI, T.: Effect of histamine, bradykinin and morphine on adrenaline release from rat adrenal glands. Jpn. J. Pharmacol. 23: 695–699, 1973.

YOUNG, C. S., MASON, R., AND HILL, S. J.: Inhibition by H_1-antihistamines of the uptake of noradrenaline and 5-hydroxytryptamine into rat brain synaptosomes. Biochem. Pharmacol. 37: 976–978, 1988a.

YOUNG, C. S., MASON, R., AND HILL, S. J.: Studies on the mechanism of histamine-induced release of noradrenaline and 5-hydroxytryptamine from slices of rat cerebral cortex. Biochem. Pharmacol. 37: 2799–2805, 1988b.

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