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# Antihistamines

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**Abstract**

The discovery of histamine, its physiological role and reversal of its pharmacological effects by antihistamines takes us on a journey through the origins of modern physiology and the rising understanding of pharmacology at the end of the 19th and the early part of the 20th centuries. This journey, which has been traced in the excellent historical review by Michael Emanuel [Clin Exp Allergy 1999;29:1–11], is populated by some of the greatest scientists of the era, including six Nobel laureates – Bovet, Dale, Ehrlich, Richet, Windaus and Black. In addition, it laid the basis of medicinal chemistry not only for antihistamines, but also for the discovery of a plethora of drugs still in use today.



At the beginning of the 20th century, scientists had a reasonably clear idea of the anatomy of the nervous system and that individual nerve cells formed the basis of the system. They also knew that nerve messages travelled in the form of minute electrical currents along the length of a neuron and then passed from the axon of one cell to the dendrites of a nearby cell. It was suggested that this transmission involved biologically active amines. Indeed, epinephrine (adrenaline) had already been discovered [1, 2]. Then, in 1910, Dale [3] published his studies on β-iminazolylethylamine, a putrefaction product of histidine. Believing this amine, which was later to be named histamine, to be a transmitter in the autonomic nervous system, Dale performed detailed comparisons with adrenaline. In his discussion, Dale concluded:

> The action of β-iminazolylethylamine appears a somewhat complicated one. It cannot be summarised with reference to any division of the autonomic system, like that of some other amines.

Although Dale was also studying anaphylaxis [4], it was not until his paper in 1919 on histamine shock [5] that he finally tied histamine and anaphylaxis together, and it was another 8 years [6] before histamine was extracted from tissues. In that paper, Dale concluded that histamine 'must have some important function in the control and adjustment of the circulation through the small blood vessels'.

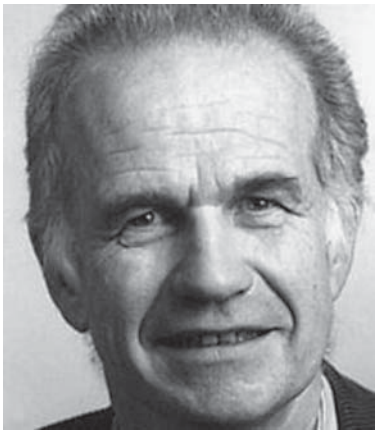

**Fig. 1.** Daniel Bovet.

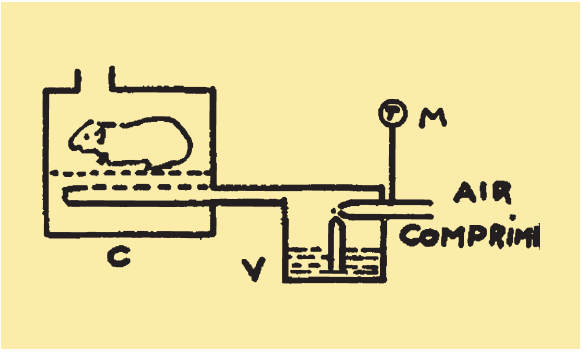


**Fig. 2.** Diagram of an apparatus in which bronchospasm in guinea pigs is produced by inhalation of histamine aerosol. C = Closed box in which the animal is observed; V = aerosolizer containing a solution of histamine hydrochloride; M = manometer.

**Fig. 3.** Bernard Halpern.

## The Discovery of Antihistamines

It was against this background that Daniel Bovet (fig. 1) started his quest to find an antihistamine. In his 1950 review of his quest to discover an antihistamine [7], Bovet wrote:

> Three naturally occurring amines, acetylcholine, epinephrine, and histamine, may be grouped together because they have a similar chemical structure, are all present in the body fluids, and exert characteristically strong pharmacologic activities. There are alkaloids which interfere with the effects of acetylcholine. Similarly, there are sympathicolytic poisons which neutralize or reverse the effects of epinephrine. It seemed possible to me, therefore, that some substance might exist which exerts a specific antagonism toward histamine. With this hypothesis in mind, I began an investigation in 1937 to determine the effect upon the susceptibility toward histamine of various substances of known activity on the autonomic nervous system.

Bovet, together with Anne-Marie Staub, who was preparing her doctorate thesis in his laboratory, used three types of laboratory methods for the evaluation of the degree of activity of the various compounds [7]. In the first test, they determined the action against the lethal effects of histamine in guinea pigs. This test they believed to be 'perfectly specific'. In the second test (fig. 2, reproduced together with its original legend), they determined the protection against histamine administered in the form of an aerosol.

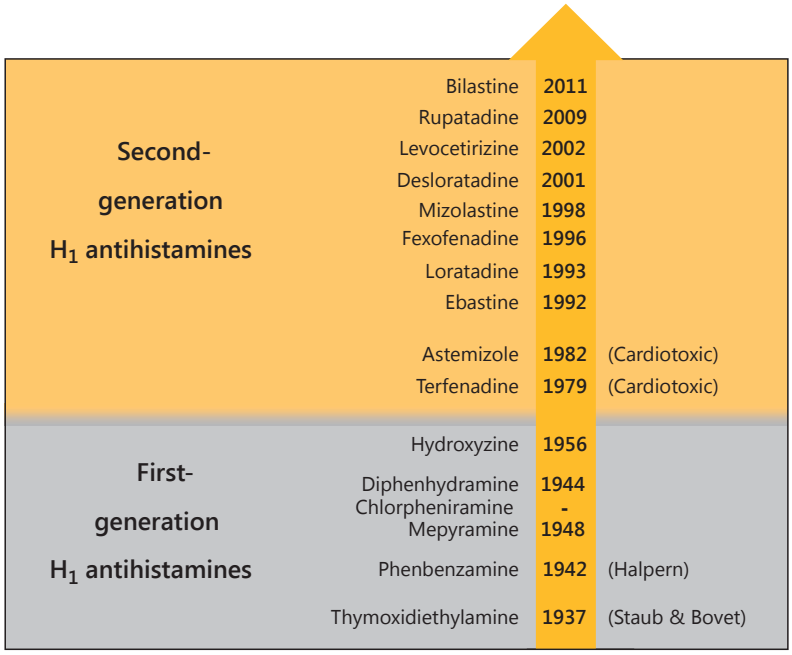


**Fig. 4.** The dates of introduction of the most common $H_1$ antihistamines.

Here, they believed that symptoms similar to asthma were produced. In the third test for determining antihistaminic activity, which they believed to be the least specific one, they ascertained the effect of compounds on histamine-induced spasm of the isolated guinea pig ileum.

Thymoxyethyldiethylamine (929 F) was the first of the substances in which antihistamine properties were recognized [8, 9]. From the chemical standpoint, compound 929 F belonged to a series of amines with a phenolic ether function which included substances that possessed either anti-epinephrine or antihistaminic activity. Another group of compounds in which sympathomimetic, sympatholytic and antihistaminic amines were found side by side were aniline compounds. It was the study of one of this group that led to the discovery of diethylaminoethyl-N-ethylaniline (1571 F) [10]. A derivative of 1571 F, N-diethylaminoethyl-N-benzylaniline (Antergan), was the first antihistamine to be introduced clinically in 1942 by Bernard Halpern from the Institute Pasteur in Paris [11] (fig. 3). This was followed by diphenhydramine in 1945 [12] and chlorpheniramine, brompheniramine and promethazine [13] later in the same decade (fig. 4).

## The Discovery of $H_2$, $H_3$ and $H_4$ Antihistamines

While the classical antihistamines discovered in the 1940s and 1950s, such as mepyramine, suppressed the effects of histamine in contracting the smooth muscle of various organs, such as the gut and bronchi, actions such as increased gastric acid secretion, increased heart rate and contraction of the rat uterus were 'mepyramine resistant'. This observation led Ash and Schild [14] to hypothesize that histamine exerted its effects through more than one receptor and led them to define the classical 'mepyramine-sensitive' receptor as the histamine $H_1$ receptor.

In order to find drugs which antagonized the 'mepyramine-resistant' effects of histamine, particularly its stimulation of gastric acid secretion, in 1964 Sir James Black and his colleagues at The Research Institute of Smith Kline and French Laboratories began to synthesize and test over 700 compounds which were closely related to the structure of histamine [15]. This work led to the definition of the histamine $H_2$ receptor and the discovery of burimamide and cimetidine [16], the forerunners of the $H_2$ antihistamines for the treatment of gastric ulcers.

Work by Jean-Charles Schwartz et al. [17] in Paris in the early 1980s demonstrated that histamine was not only a transmitter in the periphery, but also in the brain. Furthermore, they showed that the postsynaptic effects were mediated primarily by histamine. However, they also realized that histamine, like other neurotransmitters, may modulate its own release through a presynaptic receptor, an action they suggested to be mediated by a class of receptor, designated as $H_3$, which was pharmacologically distinct from the previously characterized histamine $H_1$ and $H_2$ receptors [18]. This discovery and the realization that histamine $H_3$ receptors are located almost exclusively in the brain led to the investigation of $H_3$ antihistamines for the treatment of cognitive disorders and Alzheimer's disease [19].

Using the DNA sequence of the histamine $H_3$ receptor, several research groups independently identified a previously unexplored G-protein-coupled receptor sequence in the human genome as a new histamine receptor, the histamine $H_4$ receptor [20]. The identification of histamine $H_4$ receptors on hematopoietic cells, eosinophils, mast cells and dendritic cells, and its potential role in chemotaxis and activation of these cells has stimulated widespread research into the possible use of $H_4$ antihistamines in allergic disease [21].

## First- and Second-Generation $H_1$ Antihistamines

While the earliest antihistamines resembled histamine in their basic chemical structure consisting of an ethylamine group linking aromatic and aliphatic substituents, similar or greater activities have been found in compounds of many different chemical series, including ethanolamines, ethylene diamines, alkylamines, piperazines, piperidines and phenothiazines.

While all these groups of compounds contain drugs with $H_1$ antihistaminic activity, they also contain compounds with other 'anti-amine' actions, either as antagonists or interfering with their re-uptake mechanisms. Not only does this explain the diverse adverse effects of first-generation $H_1$ antihistamines, but it also provided the pharmaceutical industry with a platform to search for other drugs. Two examples are given. First, a systematic chemical synthesis of phenothiazine derivatives in an attempt to find a substance resembling promethazine, but with a more marked antipsychotic action, led to the discovery of chlorpromazine, a drug with many actions in the central nervous system, including antidopaminergic, anticholinergic and anti-α-adrenergic activity [22]. Second, following the discovery of chlorpromazine another antihistaminic agent, imipramine, was investigated for its potential antipsychotic activity. However, while it was noted that imipramine had little antipsychotic action, elevation of the mood of depressed patients was evident. This observation led to the introduction of tricyclic antidepressants [23]. It is hardly surprising, therefore, that these first-generation antihistamines had poor receptor selectivity and significant unwanted side effects.

A major advance in antihistamine development occurred in the 1980s with the introduction of second-generation $H_1$ antihistamines [24], which are minimally or non-sedating because of their limited penetration of the blood-brain barrier. In addition, these drugs are highly selective for the histamine $H_1$ receptor and have no anticholinergic effects (fig. 4).

## $H_1$ Antihistamines and the Central Nervous System

Perhaps the greatest drawback of first-generation $H_1$ antihistamines is their ability to cross the blood-brain barrier and interfere with histaminergic transmission. Histamine is an important neuromediator in the human brain which contains approximately 64,000 histamine-producing neurons, located in the tuberomamillary nucleus. When activated these neurons stimulate $H_1$ receptors in all of the major parts of the cerebrum, cerebellum, posterior pituitary and spinal cord [25] where they increase arousal in the circadian sleep/wake cycle, reinforce learning and memory, and have roles in fluid balance, suppression of feeding, control of body temperature, control of the cardiovascular system and mediation of stress-triggered release of ACTH and δ-endorphin from the pituitary gland [26]. It is not surprising

then that antihistamines crossing the blood-brain barrier interfere with all of these processes.

Physiologically, the release of histamine during the day causes arousal whereas its decreased production at night results in a passive reduction of the arousal response. When taken during the day, first-generation $H_1$ antihistamines, even in the manufacturers' recommended doses, frequently cause daytime somnolence, sedation, drowsiness, fatigue, and impaired concentration and memory [27, 28]. When taken at night, first-generation $H_1$ antihistamines increase the latency to the onset of rapid eye movement (REM) sleep and reduce the duration of REM sleep [29–31]. The residual effects of poor sleep, including impairment of attention, vigilance, working memory and sensorimotor performance, are still present the next morning [30, 32]. The detrimental central nervous system effects of first-generation $H_1$ antihistamines on learning and examination performance in children, and on the impairment of the ability of adults to work, drive and fly aircraft, have been reviewed in detail in a recent review [33].

In contrast to first-generation $H_1$ antihistamines, second-generation $H_1$ antihistamines have a reduced penetration of the brain. The major reason for this is because their translocation across the blood-brain barrier is under the control of active transporter proteins, of which the ATP-dependent efflux pump, P-glycoprotein, is the best known [34, 35]. It has also become apparent that antihistamines differ in their substrate specificity for P-glycoprotein, with fexofenadine being a particularly good substrate [36]. In the brain, the $H_1$ receptor occupancy of fexofenadine assessed using positron emission tomography (PET) scanning is negligible at <0.1%, and, in psychomotor tests, fexofenadine is not significantly different from placebo [37]. Furthermore, fexofenadine has been shown to be devoid of central nervous effects even at supraclinical doses of up to 360 mg [38].

While fexofenadine is devoid of central nervous system effects, many other second-generation $H_1$ antihistamines still penetrate the brain to a small extent where they have the potential to cause some degree of drowsiness or somnolence, particularly when used in higher doses. For example, PET scanning of the human brain has shown that single oral doses of 10 and 20 mg of cetirizine caused 12.5 and 25.2% occupancy of the $H_1$ receptors in prefrontal and cingulate cortices, respectively [39]. These results would explain the repeated clinical findings that the incidence of drowsiness or fatigue is greater with cetirizine than with placebo [40–43]. Recent publications have suggested that, at the manufacturer's recommended doses, levocetirizine is less sedative than cetirizine [44] and desloratadine causes negligible somnolence [45, 46]. However, it should be pointed out that 'mean results' do not reveal everything as some patients may show considerable somnolence whereas others are unaffected.

## $H_1$ Antihistamines and Cardiotoxicity

The introduction of the first non-sedating $H_1$ antihistamines in the late 1970s and 1980s brought new and unexpected problems, with an increasing number of reports showing an association between the consumption of astemizole and terfenadine and cardiotoxicity. Both of these are essentially prodrugs which are metabolized by the cytochrome P450 enzyme, CYP3A4, to their active form. However, it was soon realized that if this metabolism was blocked by the concomitant use of inhibitors of CYP3A4, such as ketoconazole, itraconazole and macrolide antibiotics, or by grapefruit juice, which causes post-translational downregulation of CYP3A4, then this could cause the prolongation of the QT interval, leading to the appearance of polymorphic ventricular arrhythmias, syncope and even cardiac arrest in susceptible individuals [47]. The main mechanism underlying this acquired QT syndrome and a potentially fatal torsade de pointes arrhythmia is the inhibition of the potassium channel encoded by hERG (the human ether-a-go-go-related gene).

Astemizole and terfenadine are no longer approved by regulatory agencies in most countries. However, some first-generation $H_1$ antihistamines, such as promethazine [48], brompheniramine [49] and chlorpheniramine [50], may also be associated with a prolonged QTc and cardiac arrhythmias when taken in large doses or overdoses. Today, the concentration of a drug to produce a half-maximal block of the hERG potassium current ($IC_{50}$) is used

as a surrogate marker for proarrhythmic properties of compounds and is the primary test for cardiac safety of drugs [51]. No clinically significant cardiac effects have been reported for the second-generation $H_1$ antihistamines fexofenadine, the metabolite of terfenadine, desloratadine, loratadine, cetirizine, levocetirizine, azelastine, ebastine, mizolastine, rupatadine or bilastine [52–56].

## The Anti-Inflammatory Properties of $H_1$ Antihistamines

The potential of $H_1$ antihistamines to exert anti-inflammatory properties has been debated for over half a century ever since Arunlakshana and Schild [57] in 1953 demonstrated their ability to inhibit histamine release from mast cells. With the advancing knowledge about the molecular mechanisms underlying the effects of $H_1$ antihistamines, it is pertinent to reassess this possibility and comment on its possible clinical relevance. In order to put these comments on a scientific basis, we have postulated that some anti-inflammatory effects of $H_1$ antihistamines are subsequent to their interaction with $H_1$ receptors while others are receptor independent.

*Receptor-Independent Mechanisms*

The early studies of Mota and Dias de Silva [58] in 1960 using guinea pig and rat mast cells showed clearly that not only do antihistamines have the capacity to inhibit histamine release, but at higher concentrations they may also stimulate a drug-induced release of histamine. From the many studies done with first-generation and some early second-generation $H_1$ antihistamines to explore the mechanisms of this biphasic effect, the following conclusions may be drawn [47]. First, there is no correlation between the concentrations of drugs which inhibit histamine release and their $H_1$ antihistaminic potency. The most likely mechanism lies in their lipophilic cationic structure which allows them to exert a direct inhibitory effect on calcium ion channels, reducing the inward $Ca^{2+}$ current activated by intracellular $Ca^{2+}$ store depletion. Second, the concentrations of drugs required to prevent mast cell and basophil histamine release in vitro are in the order of 1–10 μM, much higher than those likely to occur systemically in vivo following oral dosage.

To test the clinical significance of this effect, two $H_1$ antihistamines, cetirizine and loratadine, were administered at a dose of 10 mg orally, 4 h before the provocation of histamine release by intradermal injections of 3 and 10 mg/ml of codeine [59]. The results showed a clear inhibition of the ensuing weal and flare responses, demonstrating that the drugs had been absorbed and were bioactive. However, the use of dermal microdialysis to recover histamine release from the extracellular fluid showed that neither drug reduced histamine release. Thus, it is unlikely that inhibition of mast cell histamine release by $H_1$ antihistamines contributes to their beneficial therapeutic effects following systemic administration in the treatment of allergic and inflammatory reactions. Similar results have been obtained with fexofenadine following nasal allergen challenge [60]. However, these effects may be clinically relevant following the topical administration of drugs which enables higher concentrations to be achieved locally. An example of this is the administration of olopatadine eyedrops which significantly reduce histamine release into tears [61].

*Receptor-Dependent Mechanisms*

The first clue that $H_1$ antihistamines may have receptor-dependent anti-inflammatory effects came in 1987 from the observation that cetirizine reduced the influx of eosinophils into the sites of allergic reactions [62]. Initially this was claimed to be an 'additional' effect of cetirizine which was not related to the histamine $H_1$ receptor, but it soon became apparent that these anti-inflammatory effects were not solely confined to cetirizine but were shared by other $H_1$ antihistamines [63]. Subsequent studies have shown the anti-inflammatory effect to result from the ability of $H_1$ antihistamines to downregulate the activation of NF-κB [64], an ubiquitous transcription factor which binds to promoter/enhancer regions of many genes regulating the production of a number of pro-inflammatory cytokines and adhesion proteins, including IL-1β, IL-6, IL-8, TNF-α and GM-CSF. Because this effect is mediated by $H_1$ receptors it will occur with all clinically used $H_1$ antihistamines, the degree of effect being dependent on

their $H_1$ antihistaminic potency and the dose at which the drugs are used [47].

### $H_1$ Antihistamines Are Not Receptor Antagonists but Are Inverse Agonists

The human histamine $H_1$ receptor is a member of the superfamily of G-protein-coupled receptors. This superfamily represents at least 500 individual membrane proteins that share a common structural motif of seven transmembrane α-helical segments. The histamine $H_1$ receptor gene encodes a 487-amino-acid protein with a molecular mass of 55.8 kDa [65]. The histamine $H_1$ receptor, like other G-protein-coupled receptors, may be viewed as 'cellular switch' which exists as an equilibrium between the inactive or 'off' state and the active or 'on' state. In the case of the histamine $H_1$ receptor, histamine cross-links sites on transmembrane domains III and V to stabilize the receptor in its active conformation, thus causing the equilibrium to swing to the 'on' position. $H_1$ antihistamines, which are not structurally related to histamine, do not antagonize the binding of histamine but bind to different sites on the receptor to produce the opposite effect [47]. For example, cetirizine cross-links sites on transmembrane domains IV and VI to stabilize the receptor in the inactive state and swing the equilibrium to the 'off' position. Thus, $H_1$ antihistamines are not receptor antagonists but are inverse agonists in that they produce the opposite effect on the receptor to histamine. Consequently, the preferred term to define these drugs is '$H_1$ antihistamines' rather than 'histamine antagonists'.

### Conclusions

Clearly, the last 70 years have seen great advances in the development of antihistamines; but what of the future? The further development of $H_1$ antihistamines for the treatment of allergic diseases appears to be limited to completely preventing penetration into the brain so that higher doses can be used in absolute safety in conditions such as severe urticaria. Research into $H_4$ antihistamines is still in its infancy and the efficacy of these is yet to be established. Finally, it is now becoming apparent that many histamine-induced events may be caused by the activation of multiple histamine receptor subtypes and, thus, the development of drugs with activity at more than one receptor subtype may offer a new approach to antihistamine therapy.

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