

EDITORIAL

H₁-antihistamines and inflammation

Do H₁-antihistamines possess anti-inflammatory properties which contribute to their clinical efficacy in the treatment of allergic disease? This is a question which has been raging since Arunlakshana [1], almost half a century ago, demonstrated the ability of the drugs to inhibit histamine release from mast cells. Since that time, countless papers, including that by Schroeder and colleagues [2] in this issue of *Clinical and Experimental Allergy*, have been published detailing *in vitro* studies which illustrate that H₁-antihistamines clearly have the potential to inhibit many aspects of the migration and activation of diverse inflammatory cells. What is still not clear, however, is how they exert their effects and whether or not the effects are clinically relevant.

Antihistamines are often viewed as selective antagonists of the histamine H₁-receptor which have relatively few other actions. However, the basic structure of antihistaminic drugs is very similar to that of antagonists of muscarinic cholinergic, α -adrenergic, β -adrenergic, dopaminergic and serotonergic receptors, as well as local anaesthetics and calcium antagonists. Thus, many drugs which share this common backbone have diverse actions, e.g. the major tranquilliser chlorpromazine and the tricyclic antidepressant, amitriptyline, are also potent antihistamines [3], while many antihistamines, including mepyramine, also possess marked anti-cholinergic activity. The evolution of the newer antihistamines, which carry less central sedative actions and fewer antagonistic effects at receptors for other amines, has led to a series of drugs which are more selective in their actions. It must be emphasized, however, that they are only selective, not specific. Thus, when examining the possible mechanisms by which antihistamines exert their anti-inflammatory effects, both receptor-independent and receptor-dependent mechanisms need to be considered.

Early studies examining the effects of H₁-antihistamines on mediator secretion from mast cells and basophils suggested that the physical nature of these drugs, namely positively charged lipophilic molecules, allows them to associate with the cell membrane and inhibit the binding of calcium, thereby reducing the activity of calcium-dependent enzymes, such as calmodulin [4–6]. More recent studies have proposed effects on calcium mobilization [7] and the discharge of intracellular calcium stores [8] as being responsible for a diverse spectrum of effects, including histamine secretion, eicosanoid generation and oxygen free radical production. However, the accumulated

evidence indicates that there is no clear relationship between the effects of H₁-antihistamines on calcium fluxes and the modulation of inflammatory cell function [9,10]. In other studies, antihistamines have been suggested to have a direct effect on the activity of membrane-associated enzymes, inhibition of protein kinase C [11] and NADPH oxidase [12,13], for example, purportedly being responsible for the effects of the drugs on oxygen free radical production. However, the clinical relevance of these non-receptor-mediated effects is questionable as they require concentrations of antihistamines higher than those achieved *in vivo* [5,14–16].

The possibility that H₁-antihistamines may exert anti-inflammatory effects as a direct result of their interaction with histamine receptors has recently gained credence with new knowledge gained about their mechanisms of action at the molecular level. All histamine receptors identified so far are G-protein-coupled receptors (GPCR), a super family of integral membrane proteins consisting of seven membrane spanning helices and a cytosolic G-protein-coupled C-terminal domain. Activation of the H₁-receptor and consequential G_{αq}-protein activation leads to phospholipase C catalysed hydrolysis of membrane inositide phospholipids [17,18] and initiation of a biochemical cascade involving inositoltrisphosphate (IP₃) generation, protein kinase C activation and calcium mobilization.

While it has been known for several years that histamine may initiate this biochemical cascade, it has been shown recently that transient expression of the human histamine H₁-receptor in SV40-immortalized African green monkey kidney cells results in an agonist-independent elevation of the basal levels of the second messenger inositoltrisphosphate [19]. Furthermore, several histamine H₁-antihistamines, including cetirizine, loratadine and epinastine, reduced this constitutive histamine H₁-receptor activity [19]. These data have two profound implications. First, they indicate that the histamine H₁-receptor exists as an equilibrium between its inactive and active forms. Even in the absence of stimulation by histamine, there is constitutive receptor-mediated activation G_{αq}-protein and consequential phospholipase C catalysed inositide phosphate hydrolysis. Secondly, the ability of H₁-antihistamines to downregulate constitutive histamine H₁-receptor activity demonstrates that they are not, as previously believed, H₁-receptor antagonists, but are inverse agonists. According to theory, agonists combine with the active conformation of

the receptor to stabilise it and, thus, shift the equilibrium between the active and inactive conformations towards the active one. In contrast, inverse agonists combine with the inactive form of the receptor to shift the equilibrium the opposite way.

A possible site at which histamine H_1 -receptor inverse agonists may exert anti-inflammatory activity is at the level of the transcription factor, NF- κ B. Bakker and colleagues [20] demonstrated that cloning the human histamine H_1 -receptor into SV40 cells resulted in an agonist-independent activation NF- κ B. In other studies, low concentrations of the antihistamines cetirizine and azelastine downregulate NF- κ B expression in parallel with inhibiting the generation of IL-1 β , IL-6, IL-8, TNF α and GM-CSF, the synthesis of all of which is stimulated by NF- κ B [21–23]. As NF- κ B activation is also a necessary requirement for adhesion protein expression, these data may also explain the downregulation of ICAM-1 expression on conjunctival blood vessels *in vivo* by a spectrum of antihistamines, including loratadine [24], cetirizine [25], azelastine [26,27] and levocabastine [28,29].

Before summarizing, it is pertinent to review briefly the current knowledge about histamine receptors. To date it has been assumed that antihistamines, such as cetirizine, fexofenadine and desloratadine, interact primarily with the H_1 -receptor (a Gq-coupled receptor encoded on chromosome 3) to exert their protective effects in allergic and inflammatory disease. These drugs interact poorly with the H_2 -receptor (a Gs-coupled receptor encoded on chromosome 5) and the H_3 -receptor (a Gi-coupled receptor encoded on chromosome 20). However, a fourth histamine receptor has recently been identified (the H_4 -receptor, a Gi-coupled receptor encoded on chromosome 18) which is associated with bone marrow, peripheral blood mononuclear cells and eosinophils [30–32]. Although functional studies on this receptor are in their infancy, it has been suggested that the unique expression profile and physiological role of the H_4 -receptor may make it a therapeutic target for the regulation of immune function, particularly with respect to allergy and asthma [30].

Thus, it appears likely that antihistamines exert anti-inflammatory effects by both receptor-dependent and receptor-independent mechanisms.

The receptor-dependent mechanisms involve the stabilization by the inverse agonist drugs of the histamine receptor in its inactive conformation. Preliminary data suggest that this is the mechanism underlying the inhibition of the generation of NF- κ B-dependent cytokines and adhesion proteins. If other transcription factors, such as GATA-3 which is involved in the production of Th2-like cytokines [33], are similarly coupled to the histamine H_1 -receptor, then this would explain the findings of Schroeder and colleagues in this issue of *Clinical and Experimental*

Allergy that the production of IL-4 and IL-13 is inhibited by low concentrations of desloratadine [2]. This explanation would also mean that, because inhibition of cytokine production is an H_1 -receptor-mediated effect, all H_1 -antihistamines would have similar properties, as would certainly appear to be the case for the inhibition of ICAM-1 expression [24–29].

The receptor-independent mechanisms, which require higher drug concentrations, appear to include the release from inflammatory cells of pre-formed mediators, such as histamine and eosinophil proteins, eicosanoid generation and oxygen free radical production. Such an hypothesis would be consistent with the observation by Schroeder and colleagues that inhibition of the generation of basophil histamine and LTC₄ requires concentrations of desloratadine in the micromolar region [2]. It is also consistent with the report by Nielsen and colleagues [34], also in this issue of *Clinical and Experimental Allergy*, that the allergen-induced release of histamine, tryptase, prostaglandin D₂ and eosinophil cationic protein in the skin *in vivo* was not inhibited by cetirizine.

The final question is whether or not the anti-inflammatory effects of H_1 -antihistamines are clinically relevant. The receptor-independent effects, which require higher concentrations of drug than those achieved *in vivo*, are almost certainly not. However, it is less easy to be categorical about the receptor-dependent effects. Certainly such anti-inflammatory effects can be demonstrated *in vivo*, as evidenced by the reduction of ICAM-1 expression [24–29]. Also, the report [35] that, compared with placebo, treatment of infants sensitized to grass pollen or house dust mite with cetirizine for 18 months significantly reduced the incidence of asthma suggests that H_1 -antihistamines may have clinically relevant effects. It should be stressed, however, that such effects are weak in comparison with conventional anti-inflammatory drugs such as corticosteroids.

References

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