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REVIEW

Modulation of neutrophil oxidative burst via histamine receptors

M Číž and A Lojek

Department of Free Radical Pathophysiology, Institute of Biophysics, Academy of Sciences of the Czech Republic, Brno, Czech Republic

Correspondence
M. Číž, Department of Free Radical Pathophysiology, Institute of Biophysics, Academy of Sciences of the Czech Republic, Královopolská 135, 612 65 Brno, Czech Republic.
E-mail: milanciz@ibp.cz

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Histamine has the ability to influence the activity of immune cells including neutrophils and plays a pivotal role in inflammatory processes, which are a complex network of cellular and humoral events. One of the main functions manifested by activated neutrophils is oxidative burst, which is linked to the production of reactive oxygen species; therefore, the effects of histamine receptor agonists and antagonists on the oxidative burst of neutrophils is reviewed. A role for the well-characterized histamine H_1 and H_2 receptors in this process is discussed and compared to that of the recently discovered H_4 receptor.

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Abbreviations
CaI, calcium ionophore A23187; N-fMLP, N-formyl-methionyl-leucyl-phenylalanine; OZP, opsonized zymosan particle; PMA, phorbol myristate acetate; ROS, reactive oxygen species; TLR, toll-like receptor

Oxidative burst of neutrophils

Neutrophils are the most abundant type of white blood cells, comprising about 50–70% of all leukocytes. One of the most important defence mechanisms of neutrophils is associated with their ability to mediate a strong oxidative burst through the formation of reactive oxygen species (ROS). While oxidative burst is important for the elimination of invading microorganisms, the overproduction of ROS or the impairment of endogenous antioxidant defences may result in detrimental effects on the host's own cells and tissues (Freitas *et al.*, 2009). Neutrophil oxidative burst is accompanied by the production of NADPH oxidase, which reduces oxygen to a superoxide anion radical. It is generally assumed that the NADPH oxidase is activated exclusively in the plasma membrane. However, in neutrophils, this assumption does not fit with the subcellular localization of the membrane components of the NADPH oxidase, which are stored in the granular compartments, and it has become increasingly evident that oxidants are also produced in an intracellular compartment, identified as specific granules. Myeloperoxidase is stored in another subset of granules, the azurophil granules, and participates in the processing of the ROS. In fact, it has been suggested that neutrophil activation is accompanied by the fusion of azurophil with specific granules, allowing these peroxidase-dependent reactions to take place (Karlsson and Dahlgren, 2002). PKC-δ is required for full production of NADPH oxidase and activation of the respiratory burst. Neutrophils also express PKC-α and β, which may be involved in adhesion, degranulation and phagocytosis, but the evidence for this is not yet conclusive (Bertram and Ley, 2011). Although the complex mechanisms that coordinate the membrane traffic, oxidative burst and release of granule contents required for the microbicidal activities of neutrophils are not completely understood, it is evident that they are unique and differ from those in macrophages (Nordenfelt and Tapper, 2011). Neutrophils exhibit more rapid rates of phagocytosis and a more intense oxidative respiratory response than macrophages. The phagosome maturation pathway in macrophages, which is linked to the endocytic pathway, is substituted in neutrophils by the rapid delivery of preformed granules to non-acidic phagosomes.

The nature and extent of ROS production by neutrophils in response to different stimuli are a matter of extensive research. The modulation of neutrophil function by histamine is applicable to a variety of disease models. This review

summarizes the relevant research in order to provide a framework for understanding how histamine regulates the oxidative burst of neutrophils.

Effects of histamine on the immune system

Histamine is one of the most versatile biogenic amines with multiple roles during the immune response and in allergic disorders. With four distinct GPCRs (histamine H_1–H_4 receptors), intracellular binding sites (most likely members of the cytochrome P450 family) as well as a membrane transporter (organic cation transporter) expressed in various immunocompetent cells, histamine can induce a complex network of interactions (Schneider *et al.*, 2010). These signalling pathways are expressed differently, depending on the stage of differentiation or activation of target cells, thus adding a further degree of complexity to the system. For this reason, the published data are sometimes conflicting and vary according to the particular cell type or responses analysed and the experimental approaches used. Histamine is generated by several cells during the immune response not only through the release of intracellular stores in mast cells or basophils in response to IgE-dependent or -independent stimuli, but also through *de novo* synthesis, catalysed by histidine decarboxylase, in a number of haemapoietic cells that secrete the amine immediately without prior storage. These features enable histamine to finely tune the delicate balance between immunity and tolerance by affecting the polarization and cytokine production of dendritic cells, immunoregulatory cells, natural killer cells, epithelial cells, B-lymphocytes and T-lymphocytes, so providing new pharmacological strategies to control immune reactivity during immune disorders, such as autoimmunity (O'Mahony *et al.*, 2011). Histamine and its four receptors represent a complex system of immunoregulation with distinct effects dependent on receptor subtype and their differential expression. These are influenced by the stage of cell differentiation, as well as the microenvironment, leading to the selective recruitment of effector cells into tissue sites accompanied by effects on cellular maturation, activation, polarization and effector functions, which can lead to tolerogenic or pro-inflammatory responses. It is clear that the effects of histamine on the homeostasis of the immune system are dependent on the expression and activity of the four currently known histamine receptors (O'Mahony *et al.*, 2011; Ferstl *et al.*, 2012). However, 100 years after the original identification of histamine, the complex regulatory interactions between histamine and the host immune response to everyday microbial and environmental challenges are still not fully understood.

The discovery (Liu *et al.*, 2001; Nguyen *et al.*, 2001; Oda *et al.*, 2002), at the turn of the millennium, that the histamine H_4 receptor is largely expressed in haemapoietic cells as well as its chemotactic properties suggest that it has a regulatory role in the immune system (Jutel *et al.*, 2009; Zampeli and Tiligada, 2009). Histamine H_4 receptors modulate eosinophil migration and selective recruitment of mast cells, leading to an amplification of histamine-mediated immune responses and eventually to chronic inflammation. The involvement of histamine H_4 receptors in dendritic cell activation and T cell differentiation demonstrate that it has an immunomodulatory function. The characterization of the histamine H_4 receptor as the histamine receptor involved in modulating the immune system has provoked its therapeutic exploitation in inflammatory disorders, such as allergy, asthma, chronic pruritus and autoimmune diseases. The efficacy of a number of histamine H_4 receptor ligands has been evaluated in both *in vivo* and *in vitro* animal models of disease and in human biological samples. Despite a number of variations in the findings reported, the available data strongly point to the histamine H_4 receptor as a novel target for the pharmacological modulation of histamine-transmitted immune signals and provide an optimistic perspective for the therapeutic exploitation of this promising new drug target in inflammatory disorders.

Effects of histamine receptor agonists and antagonists on the oxidative burst of neutrophils

Oxidative burst in animal neutrophils

The *in vitro* effects of histamine on the chemiluminescence response of bovine neutrophils were determined by Phillips *et al.* (1987); the addition of histamine was found to significantly suppress the chemiluminescence response of these neutrophils. This suppression was dependent on the continuous presence of histamine in the culture media. Hydrogen peroxide-generated chemiluminescence was also suppressed by high concentrations of histamine. The results of this study suggest that histamine has a pharmacological or regulatory role in the control of the oxidative burst reaction of bovine neutrophils.

The concentrations of histamine that are released locally at sites of inflammation can be very high. Hence, Benbarek *et al.* (1999) investigated the effects of supraphysiological doses (from 10^{-5} to 5×10^{-3} M) of histamine on the production of ROS by equine neutrophils *in vitro*. In their model of histamine-stimulated neutrophils, the authors investigated the effects of both histamine H_1 and H_2 receptor antagonists, the role of calcium and magnesium ions, the role of staurosporine and pertussis toxin (inhibitors of PKC and G proteins), and the effects of superoxide dismutase, catalase and hydroxyl radical scavengers (phenylalanine and mannitol). Surprisingly, histamine (from 10^{-5} to 10^{-3} M) stimulated the neutrophils to produce chemiluminescence and electron spin resonance signals, characterized by spin adducts of superoxide anion and/or hydroxyl radicals. The chemiluminescence response of these neutrophils was inhibited by 10^{-4} and 10^{-3} M of the histamine H_1 receptor antagonists, promethazine, pyrilamine and diphenhydramine, by calcium and magnesium depletion, and by 10 nmol of staurosporine. The chemiluminescence signal of neutrophils was also partially inhibited by pertussis toxin (4 $\mu g \cdot mL^{-1}$). The electron spin resonance signals were suppressed by pyrilamine (H_1 receptor antagonist) and superoxide dismutase, and partially inhibited by catalase and hydroxyl radical scavengers. The authors concluded that high concentrations of histamine stimulated the

neutrophils to produce ROS via histamine H_1 receptors and the NADPH oxidase pathway.

In another study (Kralova *et al.*, 2006), the inhibitory effects of dithiaden (a first-generation H_1-antihistamine, concentration range 10^{-6}–5×10^{-4} M) on the production of ROS by rat neutrophils were compared with those of four second-generation H_1-antihistamines (10^{-6}–5×10^{-4} M) – loratadine, acrivastine, astemizole and ketotifen-fumarate. In general, the second-generation H_1 antihistamines exerted different effects on the chemiluminescence response of rat neutrophils depending on their chemical structure, selectivity and affinity for histamine H_1 receptors. The differences in the responsiveness between human and rat neutrophils could be explained by an inverse ratio between neutrophils and lymphocytes in rat and human blood. Moreover, rat neutrophils contain less myeloperoxidase, the compound responsible for the generation of hypochlorous acid and the related chemiluminescence signal.

Oxidative burst in human neutrophils

Using the chemoattractant *N*-formyl-methionyl-leucyl-phenylalanine (N-fMLP) as a stimulus, Seligmann *et al.* (1983) demonstrated that histamine and histamine H_1/H_2 receptor agonists inhibited N-fMLP-stimulated changes in membrane potential, superoxide anion radical production, hydrogen peroxide formation and degranulation of human neutrophils in a dose-dependent manner. In contrast, neither histamine nor the histamine H_1/H_2 receptor agonists had any effects on the neutrophil functions stimulated by phorbol myristate acetate (PMA) or calcium ionophore A23187 (CaI). All the inhibitory effects of histamine and the histamine H_1/H_2 receptor agonists were reversed in a competitive manner by the histamine H_2 receptor antagonist cimetidine. Kinetic studies demonstrated that the inhibitory effects of histamine on neutrophil function were only observed when histamine was added before N-fMLP and that inhibition occurred early in the sequence of neutrophil activation, did not persist after its removal and was reversed by the addition of cimetidine 10–20 s before stimulation with N-fMLP.

Akamatsu *et al.* (1991) studied the effects of azelastine (0.05, 0.5 or 5 $\mu g \cdot mL^{-1}$), an orally-active, selective histamine H_1 receptor antagonist of the second-generation, on the production of ROS by human neutrophils. The ROS investigated were superoxide anion radical, hydrogen peroxide and hydroxyl radical. They found that azelastine significantly inhibited the generation of all three ROS.

Mikawa *et al.* (1999) studied the effects of the histamine H_2 receptor antagonists cimetidine, ranitidine and famotidine, at clinically relevant concentrations and at 10 and 100 times this concentration, on human neutrophil function *in vitro*. Both cimetidine and famotidine inhibited superoxide anion radical and hydrogen peroxide production of the neutrophils in a dose-dependent manner, although the inhibitory effects were minimal. In contrast, ranitidine failed to change superoxide anion radical or hydrogen peroxide production of neutrophils. However, the increase in intracellular calcium concentration in neutrophils induced by a stimulant was dose-dependently attenuated by both cimetidine and famotidine. This inhibitory effect on the calcium intracellular concentration in neutrophils may represent one of the mechanisms responsible for inhibition of ROS generation by these drugs.

Ching *et al.* (1995) found that 10^{-3} M histamine inhibited the N-fMLP-induced superoxide anion radical production by dibutyryl cAMP-differentiated HL60 cells, a model of human neutrophils. They also showed that this effect was partly mediated via histamine H_2 receptors; the histamine H_2 receptor antagonists famotidine, mifentidine and ranitidine partially antagonized the inhibitory effect of histamine.

In an *ex situ* clinical trial study, Donskov *et al.* (2006) demonstrated that histamine has protective effects on natural killer cells and T lymphocytes against oxidative damage. Their results were based on the inhibition of formation and release of neutrophil-derived ROS. In this study, 1.0 mg histamine dihydrochloride (Ceplene™, Maxim Pharmaceuticals Inc., San Diego, CA, USA) was administered to the patients twice daily for 3 weeks.

Intra- and extracellular component of the oxidative burst of human neutrophils

A large study on the effects of histamine on the oxidative burst of neutrophils has been carried out by Nosal and co-workers. They started by investigating the effects of histamine (10^{-7}–10^{-4} M) and the histamine H_1 receptor antagonist dithiaden (10^{-7}–10^{-4} M) on the generation of ROS by human neutrophils (Nosal *et al.*, 2002). Depending on the concentration used, dithiaden was markedly more effective at inhibiting activated chemiluminescence of whole blood neutrophils than histamine. In isolated neutrophils, both histamine and dithiaden dose-dependently inhibited opsonized zymosan particle (OZP)- and CaI-stimulated chemiluminescence. However, in contrast, with PMA and N-fMLP as the stimulating agents, these authors observed a potentiation of the chemiluminescence response of isolated neutrophils by both histamine and dithiaden. Subsequently, they showed that both histamine (10^{-7}–10^{-4} M) and dithiaden (10^{-6}–10^{-4} M) significantly decreased both the extra- and intracellular-mediated chemiluminescence response of isolated human neutrophils stimulated with OZP (Drabikova *et al.*, 2002). While dithiaden decreased the chemiluminescence signal induced by both the extra- and intracellular components with the same potency, histamine preferentially decreased the extracellular-mediated chemiluminescence signal. The finding that histamine as well as the histamine H_1 receptor antagonist dithiaden decreased the respiratory burst of neutrophils indicated that not only histamine receptors but also non-receptor mechanisms are involved in the reduction of the chemiluminescence signal. Effects on enzymes (NADPH oxidase, myeloperoxidase or PLA_2) or on the neutrophil membrane structure are possible mechanisms that would induce a reduction in the chemiluminescence signal. These possible mechanisms were further partially confirmed when the effects of three histamine H_1 receptor antagonists (pheniramine, chlorpheniramine and brompheniramine in the concentration range of 0.1–100 μM) on ROS formation outside and inside human neutrophils were evaluated (Jancinova *et al.*, 2006). The antihistamines tested displayed dual activity – they inhibited the extracellular- and potentiated the intracellular-mediated chemiluminescence of PMA-activated neutrophils; chlorpheniramine and brompheniramine were found to be more effective than pheniramine.

Compared with other H_1 antihistamines, such as dithiaden or loratadine, that are active both extra- and intracellularly, the observed inhibition caused by the pheniramines (10–100 μM) tested is unique in that it occurred selectively outside neutrophils (Nosal *et al.*, 2009). This finding might indicate that these drugs have the ability to minimize the toxic effects of extracellular ROS without affecting intracellular ROS production, which is involved in the regulation of neutrophil functions and in microbial killing. It was also observed that dithiaden and loratadine (both at concentrations of 10–100 μM) dose-dependently inhibited the chemiluminescence response of whole blood and significantly decreased oxidative burst at both extra- and intracellular sites of PMA-stimulated, isolated neutrophils (Nosal *et al.*, 2006). Both these antihistamines decreased the release of myeloperoxidase at concentrations 10 times lower than those needed to inhibit the generation of the superoxide anion radical. When compared with the antihistamines investigated, histamine was much less effective at inhibiting the parameters evaluated.

Expression of histamine receptors in neutrophils and signalling pathways associated with the oxidative burst

The effects of histamine are mediated by four types of receptor, which belong to the GPCR family. Three of these receptors (H_1, H_2 and H_4 receptors) have been reported to be expressed in neutrophils (for a review, see Akdis and Simons, 2006; Marson, 2011). Activation of the H_1 receptor results in the stimulation of PLC via $G\alpha_{q/11}$, which then leads to an increase in inositol-1,4,5-triphosphate and 1,2-DAG and thereby an increase in intracellular Ca^{2+} concentration and cAMP formation that produces its physiological effects (Stark, 2007). The histamine H_2 receptor couples to $G\alpha_s$ proteins and induces AC-mediated cAMP accumulation. (Burde and Seifert, 1996; Reher *et al.*, 2012) The signalling mechanisms for H_4 receptors are much less well understood but it seems that their activation via $G\alpha_i/G\alpha_0$ leads to inhibition of AC and an increase in intracellular Ca^{2+} concentration (Stark, 2007; Marson, 2011).

The recently identified histamine H_4 receptor is primarily expressed on leukocytes and has been implicated in the activation of lymphocytes, eosinophils and mast cells *in vitro*. Although some studies and reviews have asserted that histamine H_4 receptors are expressed on neutrophils or have described histamine H_4 receptor-mediated effects on neutrophils (e.g. Fogel *et al.*, 2005; Varga *et al.*, 2005), the expression of histamine H_4 receptors on neutrophils is still not conclusive. It seems that at least some, if not all, of the histamine H_4 receptor-specific effects observed in neutrophils could be mediated by other cell types. For example, Takeshita *et al.* (2003; 2004) presented evidence for a critical role of histamine H_4 receptors in the mast cell-dependent, recruitment of neutrophils. Similarly, Thurmond *et al.* (2004) reported that a selective antagonist of the histamine H_4 receptor, compound JNJ 7777120, significantly blocked neutrophil infiltration in a mouse model of zymosan-induced peritonitis. This model was also reported to be mast cell-dependent, which suggests that the effect of this compound might also be mediated by mast cells.

Direct scavenging effects of antihistamines

When studying the effects of antihistamines on the production of ROS by neutrophils, one also has to take into account any direct scavenging effects of the drugs being investigated. In 1994, Ching *et al.* (1994) showed that the histamine H_2 receptor antagonists cimetidine, ranitidine and famotidine, besides affecting hydroxyl radicals, were also good hypochlorous acid scavengers. Akamatsu *et al.* (1991) assessed the scavenging effects of azelastine on the ROS generated in a cell-free, xanthine–xanthine oxidase system. While azelastine significantly inhibited the generation of individual ROS, it did not markedly affect the ROS levels generated in this xanthine–xanthine oxidase system. Similarly, neither were the three histamine H_2 receptor antagonists cimetidine, ranitidine and famotidine found to scavenge the ROS generated by this cell-free xanthine–xanthine oxidase system (Mikawa *et al.*, 1999).

The effects of activated neutrophils on histamine release

Coble *et al.* (1984) showed that when mast cells are exposed to immune complexes and PMA-activated neutrophils they degranulate and release histamine. This release of histamine was not dependent on myeloperoxidase, but on other ROS, as myeloperoxidase-deficient neutrophils also induced histamine release. Furthermore, human neutrophils activated by the chemotactic peptide N-fMLP have been reported to evoke histamine release from rat serosal mast cells (Fantozzi *et al.*, 1986). The histamine release was dependent on N-fMLP concentration and could be dose-dependently inhibited by a flavonoid silymarin, which is known for its ROS scavenging properties. These results further stress the concept of a neutrophil-mast cell interaction, which may be involved in inflammatory processes.

Despite the fact that histamine is predominantly preformed and stored in mast cells and basophils, recently evidence has been obtained indicating that other cell types produce histamine in an inducible fashion. It has been suggested that neutrophils may also produce and release histamine during inflammatory reactions. Smuda *et al.* (2011) observed that bone marrow-derived neutrophils stimulated with a range of toll-like receptor (TLR) agonists secreted histamine in response to LPS or compound R837, suggesting an important role for TLR4 or TLR7 in this effect. LPS-stimulated histamine release was enhanced by co-culture with granulocyte-macrophage colony-stimulating factor; this release of histamine was transient and peaked 8 h after stimulation. This was dependent on *de novo* synthesis of histamine as cells derived from histidine decarboxylase-deficient mice were unable to produce histamine but did generate ROS upon

stimulation. Using pharmacological inhibitors, the authors further showed that PI3K, which has been shown to regulate other neutrophil functions, was needed for this production of histamine.

Conclusion

Histamine has been clearly shown to modify a variety of neutrophil responses including their oxidative burst and release of ROS. There is abundant evidence to suggest an important and direct role for histamine in the regulation of neutrophil-dominant inflammatory reactions. However, the data on the effects of histamine and histamine receptor agonist/antagonist on neutrophils are controversial. In particular, the data published with regard to the inhibitory effects of both histamine and histamine antagonists vary and are often conflicting. Some of these discrepancies can be explained by variations in the concentrations of compounds used, type of cell activation, etc.

Histamine receptors, particularly H_1 receptors, have been important drug targets for many decades. The recently discovered H_4 receptor opens a new window of pharmacological treatment for affecting the activity of immune cells including neutrophils. A number of selective H_4 receptor ligands have been proposed, which may provide new insights into the molecular mechanisms of histamine effects and could lead to the discovery of exciting new potential drug targets for treating inflammatory disorders.

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Conflicts of interest

The authors state no conflict of interests.

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