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Role of histamine receptors in the effects of histamine on the production of reactive oxygen species by whole blood phagocytes

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ABSTRACT

Aims: The diverse physiological functions of histamine are mediated through distinct histamine receptors. In this study we investigated the role of H_2R and H_4R in the effects of histamine on the production of reactive oxygen species by phagocytes in whole blood.

Main methods: Changes in reactive oxygen species (ROS) production by whole blood phagocytes after treatment with histamine, H_4R agonists (4-methylhistamine, VUF8430), H_2R agonist (dimaprit) and their combinations with H_4R antagonist (JNJ10191584) and H_2R antagonist (ranitidine) were determined using the chemiluminescence (CL) assay. To exclude the direct scavenging effects of the studied compounds on the CL response, the antioxidant properties of all compounds were measured using several methods (TRAP, ORAC, and luminol–HRP–H_2O_2 based CL).

Key findings: Histamine, 4-methylhistamine, VUF8430 and dimaprit inhibited the spontaneous and OZP-activated whole blood CL in a dose-dependent manner. On the other hand, only VUF8430 was able to inhibit PMA-activated whole blood CL. Ranitidine, but not JNJ10191584, completely reduced the effects of histamine, 4-methylhistamine and dimaprit. The direct scavenging ability of tested compounds was negligible.

Significance: Our results demonstrate that the inhibitory effects of histamine on ROS production in whole blood phagocytes were caused by H_2R. Our results also suggest that H_4R agonists in concentrations higher than 10^{-6} M may also influence ROS production via binding to H_2R.

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Introduction

Histamine, an endogenous biogenic amine, is an important chemical messenger which has numerous (patho)physiological effects in central and peripheral tissues (Hill et al., 1997; Shahid et al., 2009; Zampeli and Tiligada, 2009; Zhang et al., 2007). These effects are mediated via four histamine receptors (H_1R, H_2R, H_3R, and H_4R), which belong to the superfamily of G protein-coupled receptors (GPCRs). The H_1R is involved in most of the acute inflammatory responses and antagonists for this receptor have been used as successful drugs to treat allergy (Huang and Thurmond, 2008; Shahid et al., 2009). The H_2R is involved mainly in gastric acid secretion, heart contraction or it regulates various functions such as cell proliferation, differentiation and immune response (Bury et al., 1992; O'Reilly et al., 2002). The H_3R is localized primarily to the central nervous system and modulates neurotransmitter level (Shahid et al., 2009). H_4R is the latest identified histamine receptor and is preferentially, but not exclusively, identified in hematopoietic cells, especially in basophils, mast cells, eosinophils, T lymphocytes, and dendritic cells. Some authors have reported H_4R on neutrophils and monocytes (Morse et al., 2001; Oda et al., 2000; Zhu et al., 2001). Binding of histamine to H_4R may lead to the activation of phospholipase C (PLC), which, in turn, further affects the calcium mobilization of mast cells and eosinophils via inositol triphosphate production (Buckland et al., 2003; Hofstra et al., 2003). Histamine may also inhibit forskolin-induced cAMP formation (Nakamura et al., 2000) and activates the mitogen-activated protein kinase pathway (Morse et al., 2001) or induces the chemotaxis of eosinophils, mast cells or dendritic cells (Baumer et al., 2008; Clark et al., 1975; Hofstra et al., 2003; Ling et al., 2004; O'Reilly et al., 2002).

Histamine secreted from various cells following challenge by pathogens, modulates the function of neutrophils and other phagocytes mainly through the activation of H_1R and H_2R (Lojek et al., 2011; Melmon and Khan, 1987). One of the most important microbicidal tools of phagocytes is the production of reactive oxygen species (ROS) (Ciz et al., 2012). Some groups confirmed that histamine inhibits ROS production by isolated neutrophils or macrophages through H_2R (Azuma et al., 2001; Betten et al., 2003). To our knowledge, results which describe the effect of H_4R on the production of ROS by phagocytes in whole blood or isolated phagocytes have not yet been published. Therefore, in this study we investigated the role of H_4R in the effect of

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histamine on the production of ROS by phagocytes in whole blood. Specific histamine H_2R and H_4R agonists and antagonists were used for determining which type of receptor was responsible for the effects observed. H_1R and H_3R were not tested because H_3R was not described on hematopoietic cells and H_1R is involved in other signaling pathways (Shahid et al., 2009). Opsonized zymosan particles (OZP, as the typical receptor binding stimulus) and phorbol myristate acetate (PMA, as the typical receptor bypassing stimulus) were used as activators with different effects on the activation of NADPH oxidase. OZP triggers the signaling during phagocytosis via complement and/or Fc receptors, whereas PMA directly activates protein kinase C (PKC).

Materials and methods

Histamine and H_2R, H_4R agonists and antagonists

Histamine dihydrochloride was purchased from Sigma-Aldrich (United States). To determine which type of histamine receptor is involved in signal transduction leading to the activation of phagocyte NADPH oxidase, the following H_2R, H_4R agonists and antagonists were used: 4-methylhistamine (H_4R agonist; TOCRIS Bioscience, United Kingdom), VUF8430 (H_4R agonist; TOCRIS Bioscience, United Kingdom), JNJ10191584 maleate (H_4R antagonist; TOCRIS Bioscience, United Kingdom), Dimaprit dihydrochloride (H_2R agonist; Sigma-Aldrich, United States) and Ranitidine hydrochloride (H_2R antagonist; Sigma-Aldrich, United States). These tested compounds were selected based on literature (Azuma et al., 2001; Betten et al., 2003; Lim et al., 2006, 2009; Shahid et al., 2009; Varga et al., 2005). The compounds studied were not toxic for cells in concentrations used as proven by ATP tests (data not shown).

Blood collection

Heparinized (50 IU/ml) blood samples were obtained by venipuncture from healthy male volunteers with their informed consent. The sampling procedure was in accordance with the ethical standards of the responsible committee of the Institute of Biophysics on human experimentation and with the Helsinki Declaration of 1975, as revised in 1983.

Chemiluminescence (CL) assay of whole blood

The CL of human whole blood was evaluated in a microtiter plate luminometer Orion II (Berthold Detection Systems GmbH, Germany). The principle of the method has previously been described (Ciz et al., 2007). Briefly: each reaction mixture consisted of 100× diluted whole blood, 1 mM luminol, and histamine or its H_2R/H_4R agonists or antagonists in various concentrations between 10^{-8} M and 10^{-4} M. Hank's balanced salt solution (HBSS) was used to adjust the total reaction volume to 225 μl. The reaction was started by 25 μl of one of the activators (OZP in a concentration of 62.5 μM, PMA in a concentration of 0.81 μM) and the samples were immediately measured.

For determining changes in ROS production by a combination of histamine agonists and antagonists, the following incubation conditions were used: After 10 min incubation (in the dark, 37 °C) of antagonist with whole blood and luminol, histamine or one of the tested agonists (10^{-8}–10^{-4} M) was added. Finally after 5 min incubation (in the dark, 37 °C) one of the activators was added and the samples were immediately measured.

The data were based on integral values of CL over 90 min and converted to a percentage of the respective control (without histamine or its receptor agonist or antagonists).

Total peroxyl radical-trapping antioxidant parameter (TRAP) analysis

Luminol-enhanced chemiluminescence was used to follow up the peroxyl radical reaction. The chemiluminescence signal is driven by the production of luminol-derived radicals from the thermal decomposition of 2,2-azo-bis-2-amidinopropane hydrochloride (ABAP, Polysciences, Inc., Warrington, USA). This method has been described previously (Cizova et al., 2004). Briefly: The reaction mixture contained 160 μl of phosphate buffered saline (PBS; pH 7.4), 16.8 μl of 10 mM luminol, and 6.7 μl of a tested compound. The samples were incubated at 37 °C in a temperature-controlled carrousel of the luminometer for 10 min. To start peroxyl radical generation, 16.8 μl of 400 mM ABAP were added. Trolox (6-hydroxy-2,5,7,8-tetramethyl-chroman-2-carboxylic acid; Aldrich, USA) was used as a reference inhibitor, in a concentration of 400 μM. The TRAP value was determined from the duration of the period of time when the CL signal was diminished by the tested compounds.

Oxygen radical absorbance capacity (ORAC) assay

The ORAC method measures the antioxidant scavenging activity against the peroxyl radical generated by the thermal decomposition of 2,2-azo-bis-(2-amidino-propane) dihydrochloride (AAPH) at 37 °C. Fluorescein (FL) was used as the fluorescent probe. The ORAC was measured according to the method described previously (Denev et al., 2010). Solutions of AAPH, fluorescein, Trolox and samples were prepared in a phosphate buffer (75 mM, pH 7.4). The reaction mixture contained 170 μl of FL (final concentration 5.36×10^{-8} M), 20 μl of AAPH (final concentration 51.51 mM), and 10 μl of the tested compound. The FL solution and the sample were incubated at 37 °C for 20 min, directly in a microplate reader, and AAPH (dissolved in buffer at 37 °C) was added. The mixture was incubated for 30 s before the initial fluorescence was measured. After that, fluorescence readings were taken at the end of every cycle (1 min) after shaking. For the blank, 10 μl of phosphate buffer was used instead of the tested compounds. Trolox solutions (6.25; 12.5; 25; 50; 100 μM) were used for defining the standard curve. The antioxidant activity was expressed in Trolox equivalence.

ROS scavenging in luminol–HRP–H_2O_2 cell-free system

H_2O_2 and horseradish peroxidase (HRP) were used as a source of CL signal. Aliquots of 50 μl of tested compounds (final concentrations 10^{-4}–10^{-8} M), HRP (final concentration 2 U/ml) and luminol (final concentration 10 μM) were mixed in a 96-well luminescence plate. The reaction was started by adding hydrogen peroxide to a final concentration of 100 μmol/l. The final volume of the sample was adjusted to 200 μl by HBSS. CL was measured for 10 min at 37 °C by Luminometer Immunotech LM-01T (Beckman Coulter). The results were expressed as integral values of CL over 10 min and converted to a percentage of the control.

Statistical analysis

All samples were measured in duplicates. The results are expressed as the mean ± standard error of the mean (SEM), $n = 5$. Data were statistically analyzed using a one-way analysis of variance (ANOVA), which was followed by Dunnett's multiple comparison test. $P < 0.05$ was taken to indicate significant differences between data mean values.

Results

Antioxidative properties of histamine and agonists/antagonists of H_2R and H_4R

To exclude the direct scavenging effects of the studied compounds on the CL response, the antioxidant properties of all compounds were

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