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Review

Histamine increases the level of IFN γ produced by HIV-1 specific CTLs and this production depends on total IgE levelJ. Hanzlikova^a, D. Sedlacek^{b,*}, M. Liska^a, J. Goricikova^a, T. Vlas^a, S. Amiramini^b, P. Panzner^a, M. Maly^c^a Department of Immunology and Allergy in Faculty Hospital Pilsen, Alej Svobody 80, 30460 Pilsen, Czech Republic^b Department of Infectious Diseases in Faculty Hospital Pilsen, Dr. E. Benese 13, 30599 Pilsen, Czech Republic^c Department of Biostatistics in National Department of Health, 10042 Prague, Czech Republic

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ABSTRACT

Background: The HIV (human immunodeficiency virus) population remains a global concern whose treatment is effective, though not yet optimal. Immune based therapies have thus far been disappointing and still need to be explored further. Based on published data suggesting that the functions of cytotoxic CD8 + T lymphocytes (CTL) can be improved by histamine, we investigated the effect of histamine *in vitro* on HIV-1 specific CD8 + T lymphocytes in HIV + subjects.

Results: 60 HIV + subjects were included in the study. We evaluated CTL function by IFN γ (interferon gamma) production (using the enzyme-linked immunospot assay (Elispot), BD Bioscience). Changes in the production of IFN γ after incubation with histamine were compared with the levels of total IgE (immunoglobulin E, measured using a Dade Behring analyzer), because histamine is endogenously released through IgE. Activation of HIV-specific CTL by histamine occurs via H2R (histamine receptors). Thus we attempted to block this activation using cimetidine (antagonist H2R).

Conclusions: We found an increase in IFN γ production after the activation of HIV-1 specific CD8 + T lymphocytes by histamine (this elevation was blocked by cimetidine), furthermore, we demonstrated a negative correlation between the production of IFN γ and levels of total IgE.

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Abbreviations: AIDS, acquired immunodeficiency syndrome; CTL, cytotoxic T lymphocytes; cART, combined antiretroviral therapy; ELISPOT, enzyme-linked immunospot assay; HIV, human immunodeficiency virus; HR, histamine receptors; HIV, human immunodeficiency virus; Ig, immunoglobulin; IFN, interferon; IL, interleukin; PB, peripheral blood; PHA, phytohemagglutinin; NK cells, natural killer cells; Th, T helper lymphocytes.

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1. Introduction

Human immunodeficiency virus (HIV) infection is the cause of the global acquired immunodeficiency syndrome (AIDS) epidemic and remains a fatal disease despite concerted efforts (Baltimore, 2008). Unfortunately, in recent years there has been an increase in new infections globally. In particular this has been in heterosexual transmission (Sedlacek et al., 2007). The standard treatment for HIV+ subjects with advanced AIDS is combined antiretroviral therapy (cART). Immune therapy has been used to supplement cART, usually in the form of cytokines (e.g. IL-2, IL-12, IFN γ), though with little effect. One strategy would be to enhance the activity of CD8+ cytotoxic T lymphocytes or NK cells, and destroy HIV-affected CD4+ lymphocytes in patients (Hess et al., 2004; Jansen et al., 2004). Based on the positive impact of histamine on CD8+ T lymphocytes in oncological diseases and hepatitis C (Asemisen et al., 2005; Donskov et al., 2002; Lurie et al., 2002; Perz and Ho, 2008; Schmidt et al., 2002; Tedaldi, 2005), we examined the effect of histamine on the activation of HIV-1 specific CD8+ T lymphocytes from HIV+ subjects.

Histamine is the main mediator of atopic reactions facilitated by H1R (Histamine-1-Receptor); it is released by mast cells and basophils after allergen bridging of IgE antibodies bound on their surface. Excessive release of histamine and the development of allergic reactions can be suppressed with H1 antihistamines.

Histamine has, thanks to its additional receptors (H2R–H4R), many other effects. H2R in parietal cells has an impact on hypersecretion of gastric acid but it is well known that H2R is also expressed in the gastrointestinal tract (Sander et al., 2006).

Upregulation of H2R depends on H2R expression or H2R internalization and/or H2R recycling (Osawa et al., 2005).

Through H2R and other histamine receptors histamine plays not only a very important role in regulation of immunity and in antigen specific immune responses (Jutel et al., 2002) but also in tumor immunity (Gricco et al., 2006; Horváth et al., 2006).

H2R antagonist also plays a very important role (Fernandez et al., 2008). Takahashi describes that cimetidine induced the production of an antitumoral cytokine in gastrointestinal cancer through the activation of caspase-1, which is reported to modify immature IL-18 to mature/active IL-18, and to elevate the intracellular cAMP (Takahashi et al., 2006). Similarly Fukuda describes the role of cimetidine in salivary gland tumors (Fukuda et al., 2007).

Generally speaking: binding histamine blocks the production of reactive oxygen species by monocytes/macrophages. Histamine thus prevents reactive oxygen species-mediated damage, optimizing NK and T cell function and facilitating immune response to viral infection.

These effects can be ameliorated using H2 antihistamines (Huang and Thurmond, 2008; Lurie et al., 2002).

The last two types of histamine receptors are H3R and H4R: Histamine H3-type receptors are located mainly in the CNS as well as in peripheral tissues. These receptors facilitate a reduction of the release of neurotransmitters: histamine, acetylcholine, norepinephrine and serotonin (Huang and Thurmond, 2008; Medina et al., 2008). H4R histamine also effects the release of inflammatory mediators and chemotactic functions (Huang and Thurmond, 2008; Laberge et al., 1995; Medina et al., 2008).

Recent data has demonstrated the effects of histamine in connection with regulatory T lymphocytes or Th17 T lymphocytes that control the response of the immune system to exogenous and endogenous antigens (Brenchley et al., 2008; Gaardbo et al., 2008; Gri et al., 2008).

In this study, histamine was added *in vitro* to HIV-1 specific CTLs and its impact on the production of IFN γ monitored.

Based on other data we expected that histamine would effect on CTLs via H2R (Lurie et al., 2002). At the same time, we monitored the levels of total IgE in response to the release of endogenous histamine from mastocytes and basophils. On the basis of published data in patients with hepatitis C and defined malignancies, we expected similar increases of IFN γ after *in vitro* incubation CTLs with histamine. Production of the IFN γ was monitored in HIV-1 specific CTLs.

Production of IFN γ by HIV-1 specific CTLs after incubation with histamine was attempted to be blocked by H2R blocker (cimetidine).

Given that histamine is released from mast cells and basophils of atopic subjects following their response to an interaction of specific IgE with allergen, we compared changes in the production of IFN γ by HIV-1 specific CTLs with the levels of total IgE.

Hypothesis. Histamine increases the production of IFN γ by HIV-1 specific CTLs and these changes in production depend on the level of total IgE. Increase in the production of IFN γ by HIV-1 specific CTLs after incubation with histamine should be blocked by cimetidine.

2. Materials and methods

2.1. Blood sampling

8 ml PB were investigated, after signing informed consent form in accordance with the Helsinki Declaration, approved by the Ethics Committee of University Hospital Plzen.

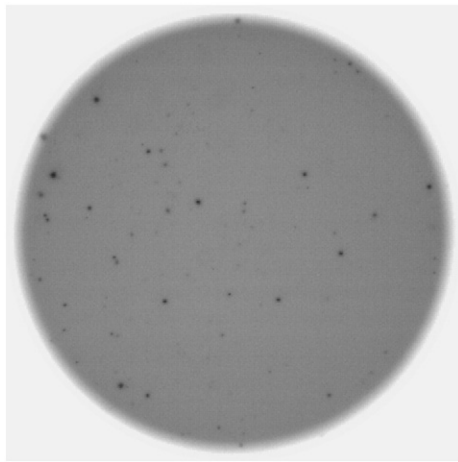


Fig. 1. ELISPOT: the number of colored stain-spots at the bottom of microplate corresponds to the number of HIV-1 specific CTL.

2.2. Reference groups

60 HIV-positive patients were investigated, after signing the informed consent form. HIV-1 positive subjects included 37 men and 23 women, average age 38.3 ± 11.6 years. Patients with atopy: 22 (36.7%). The final number of evaluated patients was decreased by 1 pregnant woman, who had significantly different results, and by 4 patients who did not have complete results.

2.3. Determination of HIV-specific CD8 + T lymphocytes using the ELISPOT IFN γ kit precoated with primary anti-human anti-IFN γ antibody (6 ml heparinized peripheral blood)

We identified HIV-specific CD8 + T lymphocytes, *in vitro* using a standard technique ELISPOT (BD Bioscience, USA). HIV-specific antigens used were recombinant peptides gp120 and gag (at a concentration of $2 \mu\text{g/ml}$, Sigma, Germany, GenBank/DNA/HIV Peptide 1. Peptide HIV-1 GP120 fragment 30: MDL number: MFCD00133404, sequence Ala-Phe-Val-Thr-Ile-Gly-Lys-Ile-Gly. Peptide content 70%. 2. Peptide HIV-1 GAG, recombinant: amino acid residues (from 77 to 436). Purity is $>95\%$). The concentration of histamine we chose respects the work of A. M. Assemissen, where the author cites as an optimal concentration of histamine, $0.1 \mu\text{mol/ml}$. We tried various concentrations and finally we used concentration of histamine 0.1 nmol/ml .

Peripheral blood mononuclear cells were isolated by means of centrifugation on a density gradient using Ficoll (Ficoll-Hypaque, Sigma, 106 cells/ml). We added to the wells with the primary antibody $100 \mu\text{l}$ separated lymphocytes, HIV peptides gp120 and gag ($2 \mu\text{g/ml}$) alone or HIV peptides and

histamine (0.1 nmol/ml , i.e. 18.4 ng/ml , Sigma) or HIV peptides, histamine and cimetidine (0.03 nmol/ml , i.e. 7.6 ng/ml , Sigma). As a positive control we used cells stimulated with phytohemagglutinin (PHA, 0.1 mg/ml , Sigma) and as a negative control we used cells without stimulation.

We followed this by incubating in the thermostat in a $5\% \text{ CO}_2$, enriched atmosphere at 37°C for 18 h. Biotynylated secondary human anti-IFN γ antibody ($100 \mu\text{l/well}$) was used to detect the captured IFN γ .

Spots were visualized using enzyme-conjugate with streptavidin and chromogenic substrate solution with alkaline phosphatase. The number of colored spots corresponded to each HIV-1 specific CTL producing IFN γ (Fig. 1). The quantity of created spots in all the holes were analyzed using an automatic analyzer ImmunoSpot CTL Reader Version 4.0 (CTL, Germany), equipped with appropriate software, with subsequent processing software for image analysis (Olympus Micromage analysis, Version 4.0, for Windows 95/98 NT 4.0 Olympus, Japan). We did not measure secreted IFN γ by ELISA.

2.4. Measurement of serum total IgE

Immediately after, 2 ml of peripheral blood was collected serum was separated and stored at -20°C until testing. Total IgE was measured with a latex nephelometry analyzer (Dade-Behring, Marburg, Germany). Levels above 100 IU/ml were considered as elevated. Border value of IgE 100 IU/ml was set according to the publication on the response and risk of atopy in infertile women (Hanzlikova et al., 2009) where she used the experience of authors that atopic genesis is considered highly probable when the IgE level exceeds 100 IU/ml (Harrison and Unwin, 1989).

3. Theory/calculation

3.1. Statistical analyses

Calculations were carried out using Poisson's regression and Spearman's correlation coefficient.

4. Results and conclusions

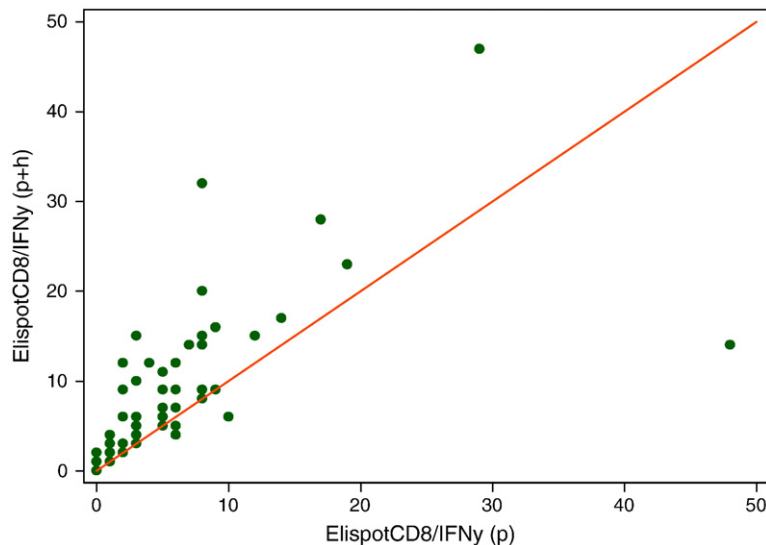
4.1. Production of IFN γ by HIV-1 specific CTLs after incubation with HIV peptides and histamine was compared to activation with HIV peptides only

There was a significantly higher production of IFN γ by HIV-1 specific CTL after activation with the HIV peptides in combination with histamine, compared to the activation by HIV peptides alone ($p < 0.001$). (Table 1, Graph 1).

Table 1

Stimulation of HIV-1 specific CD8 + CTL. Correlation between parameters after the stimulation with HIV-1 peptides alone (p), HIV-1 peptides together with histamine (p + h), and HIV-1 peptides with histamine and cimetidine (p + h + c).

	Patients	Mean (spots)	St. deviat.	Median	Minim. value	Maxim. value	St. error
HIV pept (p).	55	5.64	7.98	3	0	48	0.31
P + histamine (h)	55	8.56	9.01	6	0	47	0.38
P + h + cimetidine	55	5.15	7.24	3	0	40	0.31



Graph 1. Correlation of the number of HIV-1 specific CTL producing IFN γ (number of spots) after stimulation of HIV peptides and HIV peptides with histamine ($p < 0.001$).

4.2. Production of IFN γ by HIV-1 specific CTLs after incubation with HIV peptides and histamine is blocked by cimetidine

There was a significant reduced production of IFN γ by HIV-1 specific CD8 + T lymphocytes after the addition of cimetidine to the combination of HIV peptides and histamine, compared to combination of HIV peptides and histamine without cimetidine ($p < 0.001$) (Tables 1 and 2, Graph 2).

4.3. Production of IFN γ by HIV-1 specific CTLs after activation by HIV peptides and histamine has a negative correlation with total IgE level

Patients were divided according to levels of total IgE above or below a cut off of 100 IU/l. Compared to patients with total IgE above 100 IU/l, patients with total IgE below 100 IU/l had a higher production of IFN γ by HIV-1 specific CTLs after activation with the HIV peptides and histamine ($p < 0.001$) (Table 3a, b).

5. Discussion

AIDS is primarily characterized by CD4 + cell decline, but also by chronic activation of the immune system. In response to HIV infection CTLs have an important role (Appay et al., 2002). HIV-1 specific CTLs are able to identify CD4 + cells affected by HIV. A gradual decrease in the number and function of CD4 + T lymphocytes leads to the reduction of cytokines (e.g. IL-2, IFN γ), which are produced by a definite subtype of lymphocytes. These cytokines are necessary for proper

functions of not only the CTL, but also the NK, macrophages and other immune cells (Gandhi et al., 2002). The subsequent course of HIV infection involves the failure of CTLs function and leads to severe infections that the defective immune system cannot prevent. Preserved function of HIV-1 specific cytotoxic CD8 + T lymphocytes is reflected *inter alia*, the production of IFN γ (Lichterfeld et al., 2004).

Many patients with human immunodeficiency virus (HIV) have increased levels of IgE. Elevations of IgE are attributed to polyclonal stimulation of B cells, or as a response to allergens, viruses, fungi and bacteria.

However, in non-atopic HIV + patients serum IgE levels increase with disease progression (Bowser et al., 2007). Corominas investigated the mechanism of stimulating the CD23 receptor in HIV + patients, and in this work demonstrated the prevalence of atopy in 28% HIV + (Corominas et al., 2000). It was also suggested that IgE levels could be useful as a marker of disease progression (Park et al., 2002).

The aim of this study was to demonstrate the stimulating effect of histamine on HIV-1 specific CTLs. For lymphocytes *in vitro*, we measured the activation of HIV-1 specific CTLs using IFN γ production after the addition of histamine. We compared these results with the levels of total IgE.

Table 3

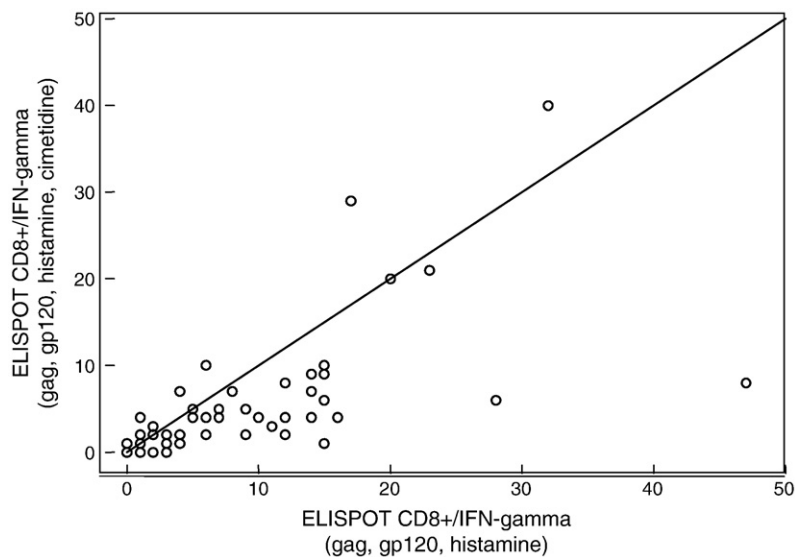
Production of spots (IFN γ producing HIV-specific CTL) in the patients with total IgE < 100 IU/l.

Activation	Mean (spots)	St. deviation	Min. (spots)	Max. (spots)
(a)				
HIV peptides (p)	7.17	10.10	0.00	48.00
p + histamine (h)	11.10	10.69	0.00	47.00
p + h + cimetidine	6.80	9.08	0.00	40.00
(b)				
HIV peptides (p)	3.83	3.46	0.00	10.00
p + histamine (h)	5.67	5.03	0.00	15.00
p + h + cimetidine	3.25	3.25	0.00	10.00

Table 2

Descriptive statistics of basic monitored parameters.

	Poisson's regr. coeff.	Number of pat.	p
Histamine	0.4183	55	<0.001
Histamine + cimetidine	−0.5094	55	<0.001



Graph 2. Lower than average number of spots in the measurements with histamine + cimetidine compared to measurements of histamine alone ($p < 0.001$).

IFN γ production in HIV + subjects after stimulation of HIV peptides and histamine were statistically significantly higher when compared to stimulation by HIV peptides alone, and depended on the level of total IgE.

Increased production of IFN γ by HIV-specific CTLs after stimulation with a combination of HIV peptides and histamine was found in patients with low total IgE (below 100 IU/ml).

We can only speculate on the possible effect of endogenous histamine on the reduced reactivity of cells to histamine *in vitro*.

This potential influence of endogenous histamine can be put into context as some authors suggest that HIV peptides act as allergens and that histamine is released during HIV infection through the links between HIV peptides gp120 and IgE on the surface of basophils and mastocytes (Becker, 2004; Marone et al., 2001; Pedersen et al., 1991). We recognize that the optimum in this context would be to determine the current levels of endogenous histamine and correlate them with the levels of endogenous cytokines. Due to the instability of histamine released, and the difficulty of its identification and evaluation, this idea was dropped.

In our study we demonstrated a correlation between IFN γ production and also the length of antiretroviral treatment. Following histamine stimulation, the production of IFN γ was higher in the two groups of patients with HIV, those treated 1–3 years and those over 3 years, in contrast to untreated persons ($p = 0.002$, $p = 0.044$).

We are the first group to show that histamine positively impacts on the function of HIV-1 specific CTLs and to demonstrate an increase of functions of HIV-1 specific CTLs after activation with histamine improving the function of cytotoxic T lymphocytes *in vivo* could contribute to solving one of the currently most important problems in AIDS therapy.

In the latent virus pool, the use of histamine together with standard antiretroviral therapy could improve the cytotoxic effect of CTLs in HIV + individuals who have a significantly disturbed function of this cell population.

This project has demonstrated the dependence of improved function of HIV + CTL on histamine. In the course of standard treatment, our future work will focus on identifying an optimal profile of the recipient of the histamine treatment (according to levels of total IgE, endogenous histamine or new cell populations Th17, Treg, etc.) in the course of standard treatment.

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Competing interests

The authors declare that they have no conflict of interests.

Authors's contributions

All authors have read and approved the final version of the manuscript.

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