Summary of Ph.D. Thesis

HISTAMINE IN ALLERGIC DISEASES:
AN OLD MOLECULE IN NEW CONCEPTS

Edina Garaczi M.D.

Supervisor:
Prof. Lajos Kemény M.D., D.Sc.

Department of Dermatology and Allergology
Albert Szent-Györgyi Clinical Center
University of Szeged

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1. INTRODUCTION

Histamine has been established to play a pathophysiological regulatory role in various immunological reactions. The main functions of histamine include H1 receptor (H1R) mediated actions on smooth muscle, vascular permeability and modulation of allergic response, and gastric acid secretion basically via H2 receptors (H2R). H3 receptor (H3R) is expressed in the nervous system, where it serves as a presynaptic feedback receptor on histaminergic neurons. H4 receptor (H4R), the last receptor discovered, is largely expressed in haemopoietic cells and its chemotactic properties designate its regulatory role in immunomodulation. Highly selective blockers and agonists suitable for *in vitro* and *in vivo* use have been developed for these histamine receptors. These include clinically established H1R and H2R blockers, as well as novel investigational drugs directed toward H4R.

Histamine is a diamine derivate of histidine that is produced under the control of a single enzyme, histidine decarboxylase (HDC). HDC deficient (HDC-/-) mice were generated by Ohtsu and his co-workers about a decade ago. Destruction of the HDC gene results in a marked reduction of the tissue histamine content. These HDC-/- mice represent a suitable experimental model to assess the role of histamine in allergic diseases.

In the first part of our present work, we investigated the immunoregulatory role of histamine using HDC-/- mice in a highly prevalent allergic disease, in contact dermatitis.

Allergic rhinitis is a common inflammatory disease that causes major illness and disability worldwide. The prevalence of AR was found to be around 25% in a study on the general population in Europe. The central role of histamine in the pathophysiology of allergic rhinitis is well established.

In the second part of this work we compared the efficacy of a second generation antihistamine, fexofenadine HCl with a newly developed phototherapeutic modality in patients with allergic rhinitis.

2. AIMS

2.1. To investigate the role of histamine in contact hypersensitivity

1. We compared the CHS response in HDC-/- mice with that of in wild type mice

2. We measured the cell composition of the axillary and inguinal lymph nodes

3. We measured the composition of infiltrating cells in the ear skin

4. We measured the expression of IL-2, IFN-γ, TNF-α and IL-4 genes in the ear skin

2.2. To compare the efficacy of fexofenadine HCl, a second generation antihistamine with that of a new intranasal phototherapeutic device in patients with seasonal allergic rhinitis

1. A randomized open study was conducted in patients with a history of at least 2 years of moderate-to-severe ragweed-induced allergic rhinitis.

2. Thirty-one patients were randomly assigned to receive either intranasal phototherapy or fexofenadine HCl for 2 weeks.

3. Each patient kept a daily diary of symptoms. Total nasal score (TNS), a sum of scores for nasal symptoms (nasal obstruction, itching, rhinorrhea and sneezing) was also calculated.

3. HISTAMINE IN CONTACT HYPERSENSITIVITY

3.1. INTRODUCTION

Histamine, synthesized by histidine decarboxylase (HDC), is produced mainly in mast cells, basophils and histaminerg neurons, but macrophages, dendritic cells and T lymphocytes also synthesize histamine. The production and release of histamine are modulated by various cytokines such as IL-1, IL-3, IL-5 and IL-8. Histamine plays a regulatory role in Th1/Th2 balance at multiple points; however, the majority of histamine actions seem to promote Th2 responses.

Contact hypersensitivity (CHS) response develops in two distinct phases: sensitization and elicitation. In the sensitization phase, mice exposed to contact allergen showed an increase in the percentage of antigen (Ag) specific $Thy1^+/CD5^+/CD3^-/TCR^-/B220^+$ cells in the skin-draining lymph nodes (DLN). These $B220^+$ ($CD45R^+$) B cells produce IgM/IgG type antibodies that pass into the circulation and the extravascular tissues. These antibodies bind to receptors on the surface of mast cells and platelets and play a role in the increase of vascular permeability. Cytokines produced by Tc1 cells (IFN-γ), Th1 cells (IL-2, IFN-γ and TNF-α), Th2 cells (IL-4 and IL-10) and Langerhans cells (IL-12 and IL-18) are important for the optimal induction and initiation of CHS in DLN.

The elicitation phase is characterized by two distinct phases. In the early phase of elicitation, the antigen bound by IgM/IgG type antibodies produced by $B220^+$ B cells leads to mast cell and platelet activation. Release of serotonin and TNF-α from these cells results in an increased vascular permeability. Geba *et al* found that delayed type hypersensitivity reaction (DTH) was either intact or only partially decreased in mast–cell deficient mice, and severe depletion of platelets with anti-platelet antibody strongly inhibited the contact hypersensitivity, especially in mast-cell deficient mice. These data suggest that serotonin and TNF-α are important mediators in the early phase of DTH.

In the later phase of elicitation (48-72 hours after challenge), antigen–specific T cells ($\alpha\beta$T cells) are activated, resulting in the production of various cytokines. It is known that in the CHS reaction the main effector cells are IFN-γ-producing $CD8^+$ Tc1 cells. The CHS responses are also regulated by IL-2, IFN-γ and TNF-α-producing $CD4^+$ Th1 cells, as well as by IL-4 and IL-10-producing $CD4^+$ Th2 cells.

In the present study, we examined the CHS response in HDC knockout (HDC-/-) histamine deficient mice. These mice were generated using a gene targeting method by Ohtsu *et al*. HDC-/- mice exhibit a decreased number of mast cells. The lack of histamine leeds to a large reduction in the overall contents of mast cell secretory granules, including proteases MMCP4, MMCP5 (chymases) and MMCP6 (tryptase). In HDC-/- mice, plasma extravasation could not be observed after passive cutaneous anaphylaxis test, suggesting that histamine plays a significant role not only in the anaphylactic increase of vascular permeability but also in the negative regulation of neutrophil infiltration.

The purpose of the present study was to determine the immunoregulatory role of histamine in dinitrofluorobenzene (DNFB)-induced delayed type hypersensitivity. We found, that the lack of histamine caused an intense Th1 type response, suggesting that histamine plays a negative regulatory role in contact dermatitis

3.2. RESULTS AND DISCUSSION

HDC-/- mice demonstrated increased contact hypersensitivity to DNFB
The abdominal skin of the mice was shaved and sensitized with 25 µl 0.5% 2,4-dinitrofluorobenzene in acetone/olive oil (4/1) for 2 consecutive days (days 0 and 1). Five days later, the dorsal surface of both ears was challenged with 15 µl 0.2% DNFB (n=6). The control mice were also sensitized with DNFB, but their ears were treated with acetone/olive oil (n=4).Twenty-four hours after challenge, the DNFB induced increase of the ear thickness was significantly higher in the HDC-/- mice than in wild type mice. Fourty-eight hours after challenge the ear thickness was still higher in HDC-/- mice compared to wild type mice, but the difference was not significant between the two groups.

The percentages of CD4$^+$ Th and CD8$^+$ Tc cells were lower, those of CD45R$^+$ B cells were higher in the DLNs of HDC-/- mice

No significant difference was observed between the total number of the DLN cells in the DNFB treated HDC-/- and wild type mice. The percentages of CD3$^+$ T, CD4$^+$ Th and CD8$^+$ Tc were significantly lower in the HDC-/- mice. In contrast, the percentage of B220$^+$ (CD45R$^+$) B cells was significantly higher in the HDC-/- mice than in the wild type mice. The percentages of granulocytes and macrophages did not differ in the two groups.

Similar differences were seen in the cell composition of the axillary and inguinal lymph nodes of untreated HDC-/- and wild type mice. The percentages of the different cell subpopulations did not differ significantly from those found in the appropriate DNFB treated groups. Consequently these differences do not seem to be due to the DNFB treatment, but they are rather associated with the lack of histamine in HDC-/- mice.

The number of infiltrating cells was higher in the ear specimens of HDC-/- mice

Histologic sections were made from the ears 24 and 48 hours after challenge. In contrast to the acetone/olive-treated ear specimens, in the DNFB painted ears of both HDC-/- and wild type mice a cellular infiltrate and edema was seen. The majority of the infiltrating cells were neutrophil granulocytes and mononuclear cells in both DNFB treated groups at 24 and 48 hours after challenge, but the number of infiltrating cells and the degree of edema was higher in the HDC-/- mice.

Using HDC-/- mice Hirasawa *et al* found that histamine plays a negative regulatory role for the neutrophil infiltration *via* H2R receptor in allergic inflammation. It has been reported that in the skin of HDC-/- mice the expression of H1R and H2R receptors is very sensitive to histamine levels and both receptors are downregulated in the skin of HDC-/- mice. These results suggest that histamine might inhibit neutrophil infiltration in wild-type mice *via* H2R receptors and the lack of histamine favors a strong granulocyte and macrophage infiltration in HDC-/- mice

Strong CD45$^+$ leukocyte infiltration was observed in the ears of HDC-/-mice

We observed a significantly higher percentage of CD45$^+$ leukocytes in the dermis of the ears of the HDC-/- mice than in that of wild type mice, using immunohistochemistry. The number of CD3$^+$ T cells was not increased in the DNFB-painted ears compared to the acetone treated ones in either group.

IL-2, IFN-γ, TNF-α and IL-4 mRNA expression was examined by real-time RT-PCR

The expression of IL-2, IFN-γ, TNF-α and IL-4 genes was examined by optimized real-time RT-PCR reactions in the ear samples obtained at 24 and 48 hours after challenge.

In wild type mice, IL-2 mRNA was undetectable, in contrast with this HDC-/- mice constitutively expressed a detectable level of IL-2 mRNA. In the HDC-/- mice, DNFB treatment caused a more than 8-fold increase in the level of IL-2 mRNA 24 hours after challenge, however, the quantity of IL-2 mRNA decreased 48 hours after challenge. In contrast with this, in wild type mice, IL-2 mRNA was not detected 24 hours after challenge and it reached a detectable level only 48 hours after challenge.

The IFN-γ mRNA level showed a significantly higher increase in HDC-/- mice than in wild type mice 24 hours after challenge. 48 hours after challenge, the IFN-γ mRNA level decreased in HDC-/- mice, while increased in wild type mice.

The HDC-/- mice constitutively expressed a detectable level of TNF-α, while in wild type mice TNF-α was undetectable. The increase in TNF-α expression was 7-fold in HDC-/- mice 24 hours after the DNFB treatment, and approximately 3.5-fold higher 48 hours after challenge. In the wild type mice, TNF-α mRNA was not detected 24 hours after the treatment, and showed an increase 48 hours after challenge.

The expression of IL-4 mRNA reached a detectable level in HDC-/- mice but not in wild type mice. The DNFB treatment of HDC-/- mice produced a moderate increase of IL-4 mRNA expression 24 hours after challenge, and the increase in IL-4 mRNA expression was 5-fold 48 hours after the treatment compared to the 24-hour data. In the wild type mice, IL-4 mRNA was not demonstrated 24 hours after challenge, but a detectable amount of mRNA appeared 48 hours after the DNFB treatment.

We observed a very early Th1 cytokine response in HDC-/- mice, followed by the increased levels of IL-2, IFN-γ and TNF-α mRNAs 24 hours after DNFB challenge. In these mice, the high levels of Th1 cytokines might contribute to the very early increase of the ear thickness and the inflammatory response demonstrated by immunohistology.

Histamine is known to inhibit Th1 lymphocyte functions such as production of IL-2, IFN-γ *via* H2R receptors, and to enhance Th1-type responses by triggering the H1R receptors. Fitzsimons *et al* demonstrated that in the skin of HDC-/- mice the H1R and H2R receptors are downregulated which might be due to the prolonged histamine deficiency. We found a very early and high Th1 cytokine response after antigen challenge that might be caused by histamine deficiency. These data indicate that endogenous histamine can downregulate the CHS reaction *via* H2R receptor in wild type mice. The lack of histamine causes a downregulation of the H2R receptors in HDC-/- mice thereby leading to a higher Th1 cytokine response compared to wild type mice. These results suggest that in the histamine deficient mice, the Th1/Th2 balance is modulated towards Th1 dominancy.

In our study, we demonstrated that histamine is involved in the regulation of delayed type hypersensitivity. Using histamine deficient mice we showed, that histamine plays a suppressive immunoregulatory role in the DNFB induced CHS response.

4. INTRANASAL PHOTOTHERAPY
IN SEASONAL ALLERGIC RHINITIS

4.1. INTRODUCTION

Allergic rhinitis is a common inflammatory disease that causes major illness and disability worldwide. The prevalence of AR was found to be around 25% in a study on the general population in Europe.

We recently showed that intranasal phototherapy is an effective treatment for allergic rhinitis (AR). Rhinophototherapy with low doses of mixed ultraviolet and visible light significantly improve the clinical symptoms of AR by acting at multiple points such as induction of T-cell and eosinophil apoptosis and suppression of release of mediators like eosinophil cationic protein and interleukin 5.

Guidelines issued by the Allergic Rhinitis and its Impact on Asthma (ARIA) group recommend the use of second generation antihistamines as first-line treatment for AR. The newer-generation oral antihistamines such as desloratadine, fexofenadine and levocetirizine have demonstrated efficacy in reducing the symptoms of AR, including rhinorrhea, nasal itching and sneezing, and in some clinical studies nasal congestion. Fexofenadine is a non-sedating antihistamine, has a rapid onset and a long duration of action. In addition to blocking H1 receptors, it has been shown to reduce allergic inflammatory responses mediated by mast cells, basophils, epithelial cells, eosinophils and lymphocytes.

The use of second-generation antihistamines in the treatment of seasonal allergic rhinitis (SAR) is well established. However, in clinical practice, SAR symptoms are not always satisfactory controlled by medication and some patients fail to respond to treatment. A new phototherapeutic device has been developed at the University of Szeged, emitting a combination of low dose UVB, UVA and visible light for the treatment of allergic rhinitis. The aim of this pilot study was to compare the efficacy of intranasal phototherapy with that of the new generation antihistamine, fexofenadine HCl in seasonal allergic rhinitis.

4.2. MATERIALS AND METHODS
Patients and study design
A randomized open study was conducted in patients with a history of at least 2 years of moderate to severe ragweed-induced allergic rhinitis. Positive skin prick test results and an elevated level of ragweed-specific IgE antibody confirmed the diagnosis. The Ethical Committee of University of Szeged approved the protocol. All patients gave their written informed consent.

The patients were enrolled after the beginning of the ragweed season, when the pollen counts were higher than $50/m^3$ in the Szeged area. Thirty-one patients with moderate-to-severe symptoms were randomly assigned to receive either intranasal phototherapy (5% UVB, 25% UVA and 70% visible light) 3 times a week for 2 weeks (n=18), or 180 mg fexofenadine HCl per day for 2 weeks (n=13), with a randomization ratio of 3 to 2. Each intranasal cavity was treated with gradually increasing doses (starting dose: 1.08 J/cm^2, maximal dose: 1.62 J/cm^2), the irradiations were performed with the Rhinolight 180 mW lamp (Rhinolight Ltd, Szeged, Hungary). The dose was raised by 0.27 J/cm^2 at every second treatment.

Each patient kept a daily diary of symptoms on a scale of 0 to 3 (0 indicating no symptoms and 1, 2, 3 indicating mild, moderate and severe symptoms, respectively) for nasal obstruction, nasal itching, rhinorrhea, sneezing and palate itching during the treatment. Total nasal score (TNS), a sum of scores for nasal symptoms (nasal obstruction, itching, rhinorrhea and sneezing) was also calculated.

Statistical analysis
Repeated measures ANOVA test was used to assess the statistical significance of clinical symptom changes and the overall efficacy. The *post hoc* analysis (Dunnett test) revealed the differences between the time points in each treatment group. The percentage changes from baseline in TNS were compared using Fisher exact two tailed test. Value of $P<0.05$ was considered statistically significant.

4.3. RESULTS
Eighteen patients (12 women, 6 men; ages ranged from 18 to 58 years, mean age: 40.67) received intranasal phototherapy and thirteen patients (8 women, 5 men; ages ranged from 18 to 55 years, mean age: 40.00) received 180 mg fexofenadine HCl per day. The 2 groups did not differ significantly in TNS at the beginning of treatment period ($P=0.236$). The baseline TNS

(mean±SD) was 8.61±2.64 in the rhinophototherapy group, and 7.46±2.57 in the fexofenadine HCl group.

In all of the parameters the scores decreased significantly at the end of treatment compared with day 1 for all of the parameters: sneezing ($P=0.0002$), rhinorrhea ($P=0.0004$), nasal itching ($P=0.0003$), nasal obstruction ($P=0.0014$) and palate itching ($P=0.00002$). In the fexofenadine HCl group none of the symptoms improved significantly ($P> 0.05$) at the end of the study except sneezing ($P=0.007$). TNS was significantly decreased in the rhinophototherapy group ($P<0.0001$), but no significant difference was observed in the fexofenadine HCl group after 2 weeks of treatment compared to the baseline ($P=0.35$).

When we compared the two treatment groups, we did not find significant differences in any of the parameters between the rhinophototherapy group and the fexofenadine HCl group. However, the improvement in the rhinitis symptoms was more pronounced in the rhinophototherapy group compared to the fexofenadine HCl group, but this difference was not statistically significant at the end of the study.

We assessed the changes from baseline in TNS at the end of the study. TNS-25, TNS-50 and TNS-75 correspond to the percentages of responders at day 14 with TNS improvement of more than 25%, 50% and 75%, respectively. If the patient's TNS was reduced by less than 25%, the patient was classified as nonresponder.

After 2 weeks of intranasal phototherapy, there were 15 patients (83.3%) with more than 25% improvement in TNS and 11 patients (61.1%) with more than 50% improvement in TNS compared to the baseline. In contrast to this only 4 patients (30.8%) exhibited more than 25% improvement in TNS and 2 patients (15.4%) showed more than 50% improvement in TNS in the fexofenadine HCl group after last treatment. We found that the ratio of patients with both TNS-25 ($P=0.0075$) and TNS-50 ($P=0.025$) were significantly higher in the rhinophototherapy group compared to the fexofenadine HCl group. There was no significant difference in TNS-75 between the two groups.

Intranasal phototherapy was overall well tolerated. The only side effect was dryness of the nasal mucosa, which occurred in all patients in the rhinophototherapy group and in two patients in the fexofenadine HCl group. All patients scored the dryness as mild except one in the rhinophototherapy group, and were controlled by emollients. In the case of this patient in the rhinophototherapy group one treatment was skipped. All patients completed the study.

4.4. DISCUSSION

In this pilot study, we found that intranasal phototherapy is more effective than fexofenadine HCl in reducing clinical symptoms in patients with moderate-to-severe SAR. In the rhinophototherapy group, all symptoms improved significantly, in contrast to this none of the scores decreased significantly in the fexofenadine HCl group at the end of the 2 weeks of treatment, except sneezing.

Second generation antihistamines are recommended as first-line therapy for seasonal allergic rhinitis. In randomized studies with great number of patients fexofenadine HCl exhibited significant improvement in SAR. The low number of patients involved in our study may account for the results obtained for the fexofenadine HCl group. However, the efficacy of rhinophototherapy in reducing majority of symptoms associated with SAR suggests a more powerful treatment effect.

The mechanism of action involved in the therapeutic effect of rhinophototherapy was investigated in previous studies. We have also published that nasal mucosa exposed to UV light possess the capacity to repair DNA damage. Nasal dryness induced by allergic inflammation occurs in patients with active symptoms of rhinitis. However, higher number of patients with mild dryness of the nasal mucosa was observed after rhinophototherapy compared to the fexofenadine HCl treatment. We are currently investigating the drying effect of UV with different wavelength on the nasal mucosa. Further studies are needed to define the therapeutic potential of intranasal phototherapy and to determine its application as chronic treatment for perennial allergic rhinitis and possibly to other inflammatory diseases.

5. CONCLUSION

Since its discovery at the beginning of the 20th century, histamine has been established to play a key pathophysiological regulatory role in various immunological functions. However, the precise role of histamine is still uncertain. In the last couple of years the role of endogenous histamine has been extensively studied in allergy, asthma, and various autoimmune diseases using histamine deficient mice.

Histidine decarboxylase deficient (HDC-/-) mice were developed about a decade ago by Ohtsu *et al*. In these mice the levels of histamine in various tissues are much lower than those in wild type mice. We at first expected that the contact hypersensitivity response would be suppressed in HDC-/- mice. Surprisingly we found that the DNFB induced CHS is more intense in histamine deficient mice than in wild type mice. We provided here the first evidence that histamine can regulate negatively the immunologic response in contact dermatitis. In accordance with our results, the negative regulatory functions of endogenous histamine have been recently reported by other research groups using experimental animal models with various allergic and autoimmune diseases.

In our study we used HDC-/- mice and we demonstrated that histamine plays a negative regulatory role in contact hypersensitivity response.

Allergic rhinitis is the most frequent allergic disease affecting 10-20% of the population worldwide. Second generation antihistamines are the first-line treatments in AR, however the treatment of allergic rhinitis is occasionally unsatisfactory and some patients fail to respond to the treatment. Using experimental mouse models, it has been shown that H1R antagonists failed to completely suppress nasal allergic symptoms.

In our present work, we compared the efficacy of a second generation antihistamine with that of a new therapeutic device intranasal phototherapy in seasonal allergic rhinitis. Intranasal phototherapy or rhinophototherapy has been recently developed emitting combined UVA, UVB and visible light at the University of Szeged. Previously, rhinophototherapy has been shown to be effective in controlling rhinitis symptoms in moderate-to-severe SAR. Here we showed that intranasal phototherapy may be an alternative treatment for patients with allergic rhinitis not controlled by antihistamines.

In summary, the pathophysiological role of histamine in immunoregulation is a much more complex story than expected. New evidences about the diverse functions of endogenous histamine and its receptors can offer an optimistic perspective for novel therapeutics.

ACKNOWLEDGEMENTS

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