

CHAPTER 3

Histamine Synthesis and Lessons Learned from Histidine Decarboxylase Deficient Mice

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Abstract

This chapter summarizes the information about the transcriptional regulation of histidine decarboxylase (HDC), which is the catabolic enzyme of histamine synthesis, and the activity of histamine *in vivo* as clarified using HDC gene deficient mice (HDC-KO). The research of the regulatory mechanism of histamine synthesis has been focused on transcriptional and posttranslational aspects. The generation of HDC-KO mice clarified several new pathophysiological functions of histamine. It is now recognized that the activity of histamine is not limited to allergic, peptic and neurological functions as in the old paradigm, but extends to other fields such as cardiology, immunology and infectious diseases. Therefore, this chapter will focus on these newly revealed functions of histamine. For example, histamine was known to be involved in the effector phase of allergic responses, but a role has now been shown in the sensitization phases and in innate immunity. In the allergic bronchial asthma model using HDC-KO mice it was found that histamine positively controls eosinophilia, but not bronchial hypersensitivity. The effect on eosinophils was afterwards shown to be mediated through the activity of the histamine H₄ receptor. The recent advances in the understanding of histamine synthesis and the activity of HDC have dramatically expanded our understanding of the scope of histamine function.

Introduction

Histamine, 2-(4-imidazole)-ethylamine, has been regarded as one of the most important biogenic amines since the original pharmacological studies in 1910 and 1911.^{1,2} Histamine regulates smooth muscle contraction, immune responses, vascular permeability, neurotransmission and the stimulation of gastric acid secretion. Histamine is synthesized from histidine through oxidative decarboxylation by histidine-decarboxylase (HDC; EC 4.1.1.22), a pyridoxal 5'-phosphate (PLP)-dependent enzyme.³ HDC is expressed in the liver of developing fetuses and in the stomach, brain, thymus, kidney, spleen and bones. Restricted and cell-specific expression of HDC in peripheral tissues is controlled both transcriptionally by processes such as DNA methylation^{4,5} and posttranslationally where levels can be controlled by the ubiquitin-proteasome system,^{6,7} caspases⁸ and other mechanisms. At the transcriptional level, expression of HDC is regulated by various kinds of stimuli including gastrin,⁹ phorbol esters like phorbol 12-myristate-13-acetate (PMA),⁹⁻¹² oxidative stress¹³ and thrombopoietin.¹⁴

Histamine exerts its activity through four different G-protein-coupled receptors.¹⁵⁻¹⁸ The histamine H₁ receptor (H₁R) couples to G_q G-proteins and leads to the phosphoinositol hydrolysis pathway. The H₁R is known to be responsible for the acute inflammatory responses. Antagonists

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of the H₁R are used for treatment of allergic states. The H₂ receptor (H₂R) links to Gs G-proteins to activate adenylate cyclase, H₃ receptors (H₃R) couple to Gi G-proteins to inhibit the adenylate cyclase pathway and the H₄ receptor (H₄R) couples to Gi/o G-proteins and leads to increases in calcium. The representative function of H₂R pathway is gastric acid secretion. H₃R are responsible for the inhibition of neuronal histamine release. The functional role of the H₄R is an emerging field that has been energetically investigated in recent years.¹⁹

It has been 15 years since the cloning of HDC and much new information on its transcriptional regulation has accumulated. This chapter will compile all of this information and review the function and regulation of HDC. Moreover, this new data has also led to a better understanding of the role of histamine and this too will be reviewed.

HDC Transcriptional Regulation

HDC are PLP-dependent enzymes in mammals and Gram-negative bacteria. It was deduced that the mammalian native enzyme catalyzed its activity in the form of homodimer (53-54 kDa/subunit).^{20,21} However, the mammalian cDNAs were found to encode 74 kDa peptides²² and therefore it became clear that different active HDC peptides (53-74 kDa/subunit) exist *in vivo*.^{23,24} After cloning of HDC gene it was found that the human gene was unique per haploid genome.²⁵ Many studies on mammalian HDC transcriptional regulation have been devoted to characterize the mechanisms operating in gastric cells under different stimuli and circumstances (gastrin, *Helicobacter pylori* infection, oxidative stress, etc).²⁶ Although one may expect tissue-specific and time-specific transcriptional regulation in the HDC gene, this information is still very limited.⁵

Epigenetic Regulation of HDC Gene Expression

In hematopoietic cell lineages, HDC gene expression has been reported in mast cells and basophils. In an attempt to discover how HDC gene expression is regulated in these cells, we found that the human HDC-promoter region in HDC-expressing cell lines is selectively unmethylated.⁵ A correlation between HDC expression and hypomethylation was also found in primary mast cells and methylation of a HDC promoter-luciferase reporter construct resulted in decreased luciferase activity in a transient expression system. Later on we confirmed the importance of methylation in regulating the activity of the mouse promoter.⁴ HDC gene expression is strongly induced in the mouse immature mast cell line P815 after incubation in the peritoneal cavity.²⁷ The induction of gene expression is correlated with the demethylation of the promoter. Consistently, forced demethylation by 5-azacytidine treatment induced high expression of HDC mRNA in P815 cells. These data suggest that DNA methylation may be one of the major mechanisms that regulate HDC gene expression and may be of functional importance in the development of mast cells.

In addition to DNA methylation, there is also evidence that histone acetyltransferases (HATs) and histone deacetylases (HDACs) regulate HDC gene expression. After the demonstration that KLF4 represses the HDC gene promoter,²⁶ Tip60 was identified as a KLF4-interacting protein. Transfection experiments suggest that Tip60 inhibits HDC-promoter activity. The data also suggests that Tip60 functions as a corepressor of KLF4 in the regulation of HDC promoter activity.²⁸

Histamine production in enterochromaffin-like cells in the stomach is controlled by gastrin²⁹ and, in turn, histamine controls gastric acid secretion by activating the proton pump in parietal cells through H₂R activation.³⁰ This is the rationale for the use of H₂R antagonists for treating peptic ulcer disease. Studies in HDC-KO mice that are therefore histamine-deficient have confirmed that *de novo* histamine synthesis is essential for gastric acid secretion induced by gastrin, but does not play a role in vagal release of acetylcholine that also participates in acid production.³¹ Since gastrin treatment decreased the association of KLF4, Tip60 and HDAC7 with HDC promoter, the decrease of repressive complexes formed by these factors might suppress HDC transcription.²⁸ In this report a new technology, chromatin immunoprecipitation (ChIP), was used that allows the *in vivo* identification of direct transcription factor-binding sites in the context of chromatin and, therefore, avoids many of the previous problems. In theory, ChIP could be used to investigate any target on chromatin against which an antibody can be raised and, consequently, it has successfully

been used to identify regions of the genome associated with specific transcription factors, cofactors, histone modifications and DNA methylation. By using ChIP analysis it was found that transcription factors bind the promoter region of HDC and not to the first or second intron. The binding was disrupted by gastrin treatment suggesting that Tip60 and HDAC7 act as corepressors of KLF4 in the regulation of HDC gene expression.²⁸ It has also been reported that the promoter of the HDC gene was activated by hypoxia inducible factor-1 in a human mast cell line and this activation seems to occur during hypoxic stress.³²

L-Histidine Decarboxylase Gene Knockout Mice

HDC-KO mice lack the ability to synthesize histamine and, therefore, cannot undergo histamine-dependent activation through any of the four known histamine receptors.³³ These mice have been used to clarify the role of histamine in various conditions including anaphylactic responses and allergic inflammation,³⁴⁻³⁶ as well as several neurophysiologic functions.^{37,38} Because it is difficult to achieve complete and long-lasting elimination of the effects of histamine *in vivo* by pharmacological approaches, HDC-KO mice provide an excellent tool for studying the effect of chronic deprivation of histamine in disease models.

Histamine and Immunity

Histamine is well known for its role in immunological reactions. The development of H₁R and H₂R knockout mice has clarified the role of histamine in T cells.^{39,40} Histamine has been proved to be important as a regulator in Th1 and Th2 cells.³⁹ Gutzmer et al. have reported that human dendritic cells express all four histamine receptors (H₁R to H₄R). H₂R and H₄R stimulation suppresses IL-12p70 production and mediates chemotaxis in human dendritic cells.⁴¹

It is also clear that histamine functions in innate immunity since it mediates NK cell chemotaxis⁴² and cytokine release from invariant natural killer T cells (iNKT) through the H₄R.⁴³ Histamine-free HDC-KO mice have a numerical and functional deficit in iNKT cells as evidenced by a drastic decrease in IL-4 and IFN- γ production by these cells. This deficiency was established both by measuring cytokine levels in the serum and intracellularly in gated iNKT cells. The defect was due to the lack of histamine since a single injection of histamine into HDC-KO mice sufficed to restore normal IL-4 and IFN- γ production. Histamine-induced functional recovery was mediated mainly through the H₄R since it could be abrogated by a selective H₄R antagonist and by the demonstration of a similar iNKT cell deficit in H₄R-deficient (H₄R-KO) mice. These findings identify a novel function of histamine through the H₄R in modulating iNKT cell functions and, therefore, may contribute the initial host defense mechanism. Furthermore since the production of IL-4 is important for antibody class switching to produce IgE, it is possible that histamine is not only a canonical allergic effector molecule, but can also regulate the afferent phase of the allergic state as well.

Histamine in Wound Healing

The absence of histamine in HDC-KO mice resulted in delayed cutaneous wound healing and exogenously administered histamine was able to restore this response.⁴⁴ Furthermore, overproduction of histamine in HDC gene-transgenic mice lead to accelerate healing compared to wild-type mice (Fig. 1). These results indicate that histamine accelerates cutaneous wound healing. Macrophage recruitment and angiogenesis at the wound edge were specifically impaired in HDC-KO mice and histamine treated wounds in HDC-KO mice demonstrated increased macrophage recruitment and angiogenesis. Since macrophages are an important cellular component for the wound healing process, it was postulated that histamine, whether directly or indirectly, accelerates the recruitment of macrophage to the wound. The protein levels of basic fibroblast growth factor (bFGF) at the wound edge was higher in wild-type mice, especially on the 3rd and 5th day of wound healing, compared to HDC-KO mice. Topically administered SU5402, a specific antagonist to fibroblast growth factor receptor-1 (FGFR1) tyrosine kinase, to the wound surface suppressed the wound healing in wild-type mice, but not in HDC-KO mice. Moreover, SU5402 reduced macrophage recruitment and angiogenesis in wild-type mice. From these observations it was concluded that the accelerated

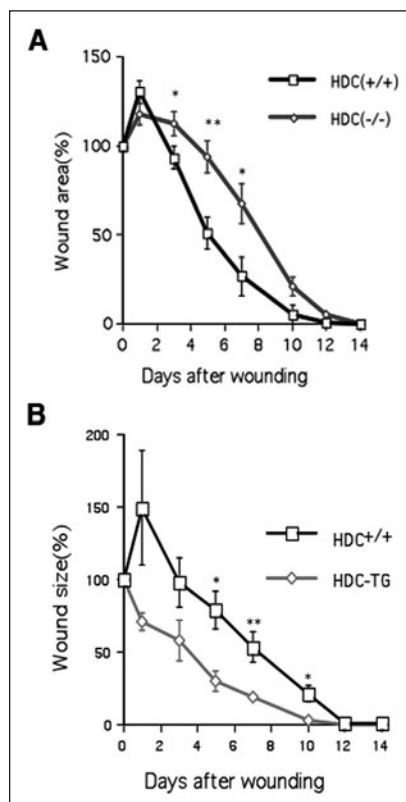


Figure 1. Histamine affects on the wound healing process. A) Wound areas in HDC-KO (HDC+/-) and wild-type (HDC-/-) mice were determined by tracing the wound margin using a transparent sheet. Results are means $\pm$ SEM, $n = 8$, for each time point and group. * $P < 0.05$, ** $P < 0.01$ compared with wild-type mice. B) Wound area of wild-type and HDC transgenic (HDC-Tg) mice. Results are means $\pm$ SEM, $n = 6$ for the wild-type, $n = 5$ for the HDC-Tg mice. * $P < 0.05$, ** $P < 0.01$ compared with wild-type mice. The figure is modified from reference 44.

wound healing activity of histamine was mediated by the activity of bFGF, which leads to angiogenesis and macrophage recruitment in the wound healing process.

Histamine in Malaria

There are several lines of evidence suggesting that the existence of histamine is beneficial for parasites to spread through the vasculature, perhaps due to its vasodilatory effects.⁴⁵ Furthermore, histamine can increase endothelial expression of thrombomodulin through the H_1R .⁴⁶ Thrombomodulin is important for the sequestration of the parasitized erythrocyte through its binding to anticoagulants. From the inoculation of *Plasmodium* sporozoites via *Anopheles* mosquito bites to the development of blood-stage parasites, a hallmark of the host response is an inflammatory reaction characterized by elevated histamine levels in the serum and tissues. After consideration of the proinflammatory and immunosuppressive activities associated with histamine, it can be postulated that histamine participates in malaria pathogenesis. Combined genetic and pharmacological approaches demonstrated that histamine binding to H_1R and H_2R , but not H_3R and H_4R increases the susceptibility of mice to infection with *Plasmodium*.⁴⁷ To further understand the role of histamine in malaria pathogenesis, HDC-KO mice were used. HDC-KO mice were highly resistant to severe malaria whether infected

by mosquito bites or via injection of infected erythrocytes.⁴⁷ HDC-KO mice displayed resistance to two lethal strains: *Plasmodium berghei* (Pb) ANKA, which triggers cerebral malaria (CM) and Pb NK65, which causes death without neurological symptoms. The resistance of HDC-KO mice to CM was associated with a preserved blood-brain barrier integrity. Also the resistance seemed to be associated with the absence of infected erythrocyte aggregation in the brain vessels. No infiltration of CD4 and CD8 T cells was observed in the brains of infected HDC-KO mice, although this was observed in wild-type mice after infection. These results suggest that histamine-mediated signaling contributes to malaria pathogenesis and that understanding the basis for these biological effects may lead to novel therapeutic strategies to alleviate the severity of malaria.

Histamine in Crohn's Disease

Crohn's disease (CD), one of the two major types of inflammatory bowel disease, is a chronic inflammatory disorder of unknown etiology that affects any part of the gastrointestinal tract from the mouth to anus, however, the small intestine and colon are most commonly involved. It has been considered that CD is a multifactorial disease with genetic background, environmental factors and immunological responses all contributing.

Although historically CD is rare in Asian countries, the number of patients with CD has increased during the past decade. One of the reasons for the change is thought to be due to changes in diet and exposure to new dietary antigens that may stimulate the mucosal immune response. Patients with active CD respond to bowel rest along with total parenteral nutrition (TPN). In addition, enteral nutrition in the form of elemental or peptide-based preparations is as effective as glucocorticoids or TPN. Although the therapeutic mechanisms of elemental diets (ED) remain unclear, some possibilities have been suggested: (1) a low-antigenic diet reduces the mucosal immune response; (2) a low-fat diet is less pro-inflammatory; and (3) that ED alters the enteric flora population.

Since ED may have mechanisms to suppress intestinal inflammation directly, the effect of amino acids that are the main component of ED was assessed. Histidine reduced histologic damage in a model of CD.⁴⁸ Furthermore, histidine, but not lysine or alanine, inhibited the production of TNF α and IL-6 by LPS-stimulated peritoneal macrophages in a concentration-dependent manner. Since intracellular histidine is metabolized to histamine by HDC, we hypothesized that histamine might be the substance which ameliorates CD in histidine supplemented ED. However, histidine was still able to reduce production of TNF α and IL-6 in LPS-stimulated HDC-deficient peritoneal macrophages.⁴⁸ Thus, the anti-inflammatory effect of histidine seemed to be independent of histamine synthesis.

Histamine in Allergic Bronchial Asthma

Histamine is a major mediator that elicits a number of the acute physiologic responses in allergic asthma.⁴⁹ Its role in asthma is supported by several pieces of evidence including the release of histamine from cells participating in allergic responses, the reproduction of the features of allergic inflammation by application of histamine, the reduction of allergic inflammation by histamine receptor antagonists and the reduced eosinophilia in mice genetically modified not to synthesize histamine.³⁵ Mast cells, basophils, enterochromaffin-like cells in gastric wall and neurons in tubero-mammillary nucleus in hypothalamus are major sources of histamine at the cellular level. Mast cells and basophils are the postulated major sources of histamine in allergic reaction. Histamine release from these cells is triggered by the interaction of an allergen with specific immunoglobulin E (IgE) bound to the high-affinity IgE receptor on the cell membrane or by nonspecific stimuli including exercise or cold, dry air. The actions of histamine in allergic asthma may be rather complicated since it not only has the direct actions on smooth muscle and sensory nerves, but also can have indirect activity on vagal reflexes that cause cough.

The role of histamine in immunology has been a major topic of study over the past few years. Previous studies have suggested that histamine enhances Th2 responses through modulation of dendritic cell function and regulation of IL-10 and IL-12 production. Dendritic cells express H₁R, H₂R and H₄R⁵⁰ and their exposure to histamine induces a shift toward the DC2 phenotype with regard to the expression of cytokines and chemokines that promote Th2 immune responses.^{51,52}

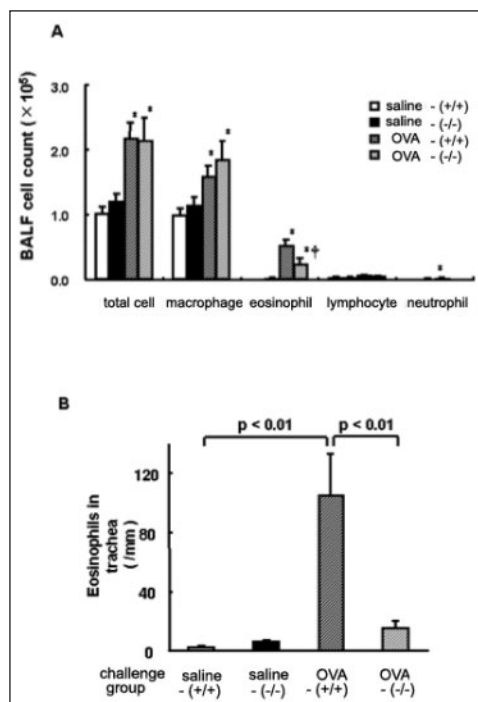


Figure 2. A) Total cell and differential leukocyte counts in the bronchoalveolar lavage fluid BALF in a mouse allergic asthma model. On the 3rd day after the ovalbumin (OVA) inhalation challenge, the mice were anesthetized and the recovered fluid from bronchial tract was analyzed. Each value indicates mean $\pm$ SEM in 1 ml BALF of 8 to 11 mice (Mann-Whitney U test). HDC-KO are designated as (-/-) and wild-type mice as (+/+). B) Eosinophil counts in the submucosal area of the trachea. Eosinophil number within the submucosal area encircling the trachea was counted and expressed as number/mm basement membrane. Each value indicates mean $\pm$ SEM of five to six animals (Mann-Shitney U test). Modified with permission from reference 35, ©2003 American Thoracic Society.

Histamine inhibits IL-12 production, while enhancing IL-10 synthesis in lipopolysaccharide-treated leukocytes.^{53,54} These observations suggest a Th2-promoting influence of histamine. In contrast, studies with mice bearing a targeted deletion of the H_1R show reduced production of IFN γ and increased IL-4 and IL-13 secretion, results more consistent with the Th1-polarizing function of this receptor.³⁹ Recently, the H_4R was shown to play an important role in allergic lung inflammation with effects on Th2 responses and the recruitment of lung eosinophils and lymphocytes.⁵⁵ Blockade of the H_4R on dendritic cells leads to decreases in cytokine and chemokine production and limits their ability to induce Th2 responses in T cells. In addition effects on innate immune responses such as those on iNKT cells already mentioned indicate that histamine plays important role not only during the efferent phase but also for the afferent phase of allergic responses.

We previously examined the role of endogenous histamine on eosinophilic recruitment and hyperresponsiveness in allergic bronchial asthma mouse model using HDC-KO mice.³⁵ Histamine levels in the airways in HDC-KO mice were largely diminished compared with wild-type mice. Inhalation challenge with ovalbumin (OVA) in OVA-sensitized wild-type mice caused total cell, macrophage and eosinophil accumulation in the lung as well as airway hyper-responsiveness to methacholine three days after the challenge. The eosinophil recruitment to the lung was significantly reduced in HDC-KO mice compared with wild-type mice (Fig. 2).

In the bone marrow proliferation of eosinophils was induced after OVA challenge in wild-type mice; however, the proliferation was significantly suppressed in HDC-KO mice. In contrast, airway hyper-responsiveness was not suppressed in HDC-KO mice. These results suggest that endogenous histamine is involved in the accumulation of eosinophils into the airways after allergic challenge, possibly via effects in the bone marrow. Since histamine has eosinophil chemotactic activity via H_4R ,⁵⁶ reduced eosinophilia in HDC-KO mice could be explained through the activity via H_4R . However, allergen-induced airway hyper-responsiveness occurred independently of airway eosinophilia in this model.

Histamine in Systemic Anaphylaxis Model

Compared with other allergic disorders, such as asthma, allergic dermatitis and allergic rhinitis, the pathophysiology of anaphylaxis seems relatively simple. Antigen cross-links antibody molecules, activating immunoglobulin receptors on inflammatory cells and causing them to release mediators that increase vascular permeability and cause smooth muscle contractions that produce urticaria, hypotension, dyspnea, abdominal cramping and diarrhea.⁵⁷ Mouse systemic anaphylaxis reaction is IgE-dependent and manifested by hypotension, airway obstruction and hypothermia.³⁶ The $Fc\epsilon$ receptor is expressed on the plasma membrane of mast cells and is bound to IgE antibodies.⁵⁸⁻⁶² Antigen binding to IgE molecules leads to cross-linking of the $Fc\epsilon$ receptor, which in turn leads to the secretion of the intragranular content into the environmental fluid, leading to the symptoms observed in systemic anaphylaxis. The reaction starts from a few minutes to 30 minutes after the allergen challenge and it leads to an increase in vascular permeability, contraction of smooth muscle and an increase in mucin secretion. The final results are circulatory collapse, which is observed as hypotension, an increase in heart rate and a decrease in peripheral blood resistance, sometimes leading to death.

To elucidate the role of histamine in each of these symptoms, we induced a passive systemic anaphylaxis reaction in HDC-KO mice and wild-type mice and compared the changes in body temperature, blood pressure and respiratory function.³⁶ Blood pressure dropped in both HDC-KO and wild-type mice. However, decreases in respiratory frequency, body temperature and elongation of expiratory respiration time occurred only in wild-type mice (Fig. 3). Therefore, in this model of passive systemic anaphylaxis reaction via the $Fc\epsilon$ receptor, respiratory frequency, expiratory time and body temperature were shown to be controlled by the activity of histamine, but its contribution to blood pressure was small. Since mast cell deficient W/W^v mice did not show any decrease in body temperature compared to control mice, it can be concluded that histamine derived from mast cells contributes to the change of body temperature.

Histamine in Atherosclerosis

HDC mRNA levels increase during the progression of atherosclerosis in the human aorta. HDC protein localized to macrophage-derived foam cells and mononuclear cells including lymphocytes.⁶³ The effect of histamine depends on the vascular size and localization. In capillaries, histamine distends the vessel wall and exerts an inflammatory reaction such as extravasation of blood. In contrast the muscular arteries, including coronary and mesenteric arteries, are constricted by histamine, owing to the contraction of medial smooth muscle cell (SMC). Histamine also has effects on the proliferation of SMC.⁶⁴ To clarify the role of histamine-producing cells and its origin in atherosclerosis, we investigated HDC expression in atherosclerotic arteries after the mouse had received a bone marrow transfusion from green fluorescent protein (GFP)-transgenic mice.⁶⁵ Two different atherosclerosis models were investigated—a ligation-induced vascular injury model and a cuff-induced vascular injury model. In the ligation model, the neointima of atherosclerotic carotid arteries contained bone marrow-derived HDC+/+ cells expressing macrophage or smooth muscle antigens. In contrast in the cuff replacement model, the HDC+/+ bone marrow-derived cells, which were positive for Mac-3, were mainly located in the adventitia. After inducing atherosclerotic lesions, HDC-KO mice showed reduced neointimal thickening and a decreased intima-to-media ratio in comparison to wild-type mice. These results indicate that histamine produced from bone

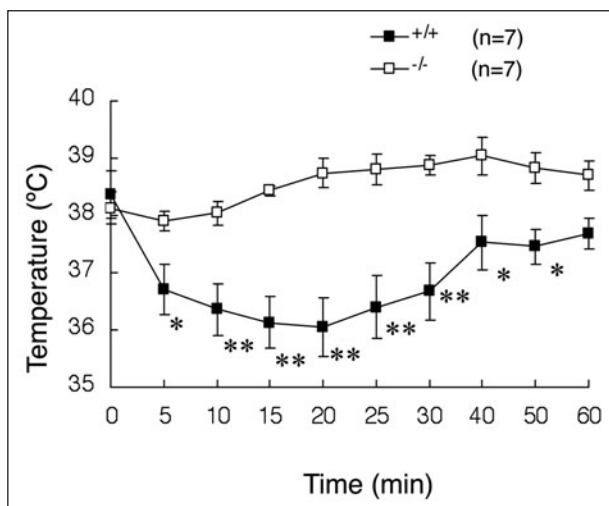


Figure 3. Change of body temperature in HDC-KO (-/-) and wild-type (+/+) mice after the passive systemic anaphylaxis reaction. Body temperature was monitored using thermometer probe situated in anal. * $P < 0.05$ and ** $P < 0.01$ in comparison with HDC-KO mice. Reproduced with permission from reference 36, ©2002 from Elsevier.

marrow-derived progenitor cells, which could transdifferentiate into SMC- or macrophage-like cells, are important for the formation of neointima and atheromatous plaques.

Histamine Uptake into and Release from Histamine Producing Cells

A number of cells have been shown to take up histamine. For example a medullary population of basophils containing few granules have been shown to take up histamine from the environment.⁶⁶ Mast cells from HDC-KO mice were also demonstrated to store exogenous histamine immediately after incubation with histamine and release the stored histamine after anti-DNP IgE and DNP-HSA treatment.⁶⁷

The uptake of the histamine into the basophil/mast cell granules involves transport through two distinct membranes—the plasma membrane and the vesicular membrane. It was shown that the bidirectional organic cation transporter 3 (OCT3/Slc22a3) has a role in histamine uptake.⁶⁸ In addition the vesicular monoamine transporter 2 (VMAT2) is involved in the vesicular membrane transport system, since mast cells prepared from VMAT2-deficient mice showed reduced release of histamine.⁶⁹ The vesicular membrane transport system appeared to be more efficient than plasma membrane transport, because the amount of histamine in the granular fraction was much higher than in cytosolic fraction. Therefore, once histamine has been absorbed by the mast cell, it is transported into the secretory granules quite rapidly.⁶⁷ OCT3 also participates in the control of basophil function since exogenous histamine inhibits not only its own synthesis, but also that of IL-4, IL-6 and IL-13.⁶⁸

Conclusion

This chapter has summarized the recently clarified mechanisms of histidine decarboxylase regulation and the insights gained using histidine decarboxylase gene knockout mice on the varied roles of histamine *in vivo*. Since *in vivo* the synthesis of histamine from histidine is catalyzed solely by histidine decarboxylase, the amount of histamine is suppressed closely to null levels by knocking out the gene and hence the HDC-KO have been a useful tool for observing altered phenotypes in the absence of histamine. The availability of the gene-manipulated mice along with the aid of

selective pharmacological agents have been powerful tools for uncovering and clarifying the various phenomena mediated by histamine *in vivo*. The information gained by using such approaches can provide basic knowledge that can be used for exploring the direction of clinical studies.

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