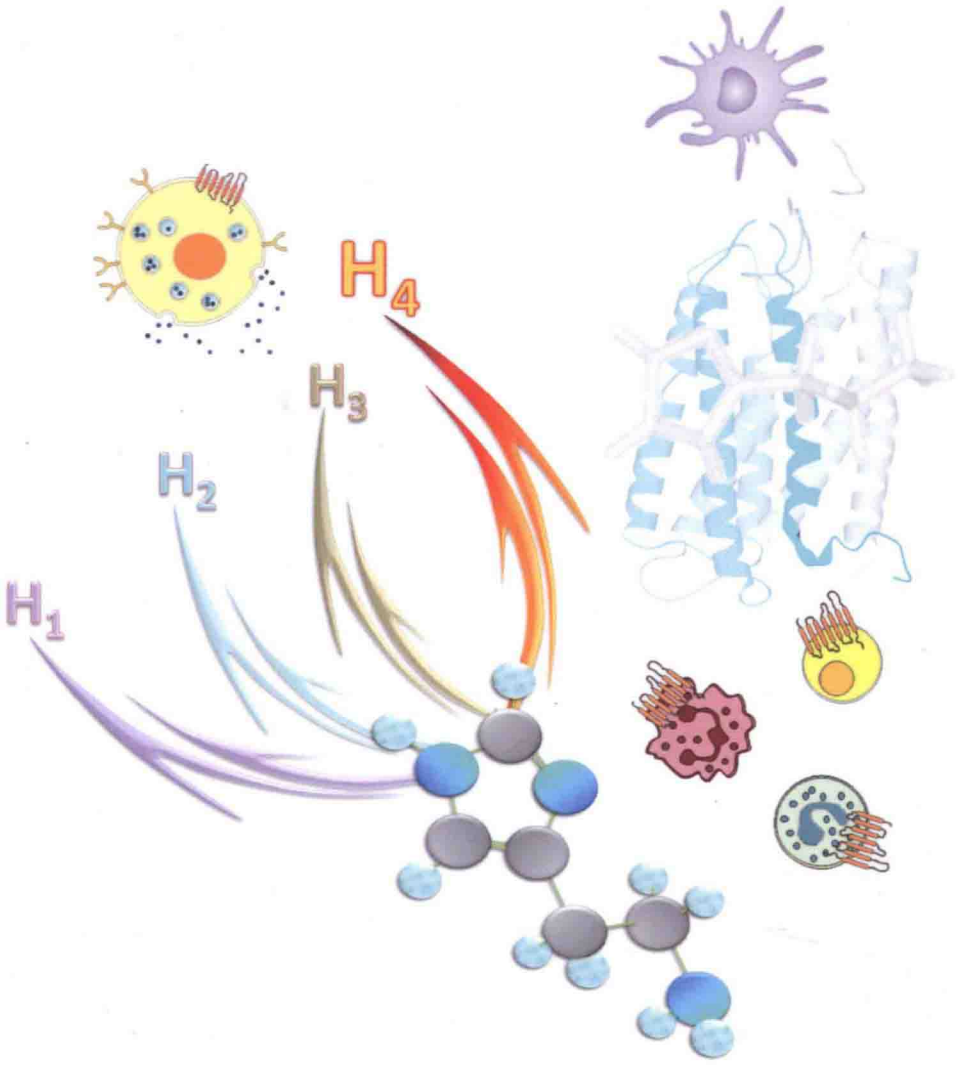
Histamine H_4 Receptor: A Novel Drug Target in Immunoregulation and Inflammation

edited by Holger Stark



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Histamine H_4 Receptor:
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Preface

Some fields of research are tremendously growing within a few years due to high scientific interest. The histamine H_4 receptor field is such a scientific area with huge input from various sources due to high therapeutical interest and unmet medical need in many related diseases. To cover many of these aspects we have put together this book covering a variety of research approaches surrounding the histamine H_4 receptor. One of the main intentions was to attract young researchers going into this field with enhanced background knowledge. Therefore, we have put together some basic aspects for the beginners, some more advanced material for the advanced researchers as well as some more detailed aspects on points of discussion for the experts. The following nine chapters are the result of decades of research on the histamine area as well as of the recent COST Action of the European Union BM0806 "Recent advances in histamine receptor H_4R research" from 2009 to 2013 having Ekaterini Tiligada, Athens/Greece, as Chair. This COST Action succeeded in putting together different research groups of different topics and different countries to join and to work together. I deeply thank all authors from all over the world for their highly valuable contributions.

I also deeply thank Versita with Anna Rulka and co-workers for the continuous support during the publication process as well as the extraordinary possibility to make this book available for everyone by the open access publication form.

It is our hope that the visibility and the use of this book may support and accelerate the introduction of new histamine H_4 receptor-based drugs for the patients.

Holger Stark, Germany

Chapter 1

The histamine H_4 receptor story

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The long-lasting story of histamine and the receptors of this biogenic amine started in the beginning of the last century with the detection of the biological activity of the decarboxylation product of L-histidine and followed later with the introduction of the so-called "anti-histamines". The story has been refreshed several times with the innovation of histamine H_2 receptor blockers giving the classical pharmacological characterization of this new receptor subtype, with the neurotransmitter function based on the histamine H_3 receptor and soon after its cloning the detection of the histamine H_4 receptor subtype by molecular biology methods.

In different chapters of this book, the authors go into some details on the historic importance of the "old" histamine. These historic views may explain some of the blind alleys and one-ways that have been followed during different steps of knowledge as well as some new and very recent findings. Due to the medicinal chemistry background of the editor, this book has not started with the detection of the receptor but with the identification and development of some early lead compounds used for the characterization of function and cross-actions of the histamine H_4 receptor (Figure 1.1).

Schreeb et al. (2013) gave a general description of the structural relationships on agonist and antagonist of the different histamine receptor subtypes. They went into further details with the narrative of structure-affinity and structure-activity relationships of different lead structures on histamine H_4 receptor. Based on some histamine-related imidazole-containing compounds they transiently went over to benzimidazoles and pyrimidine derivates. With the structural descriptions, they show the overlap of pharmacophoric moieties within the different classes stressing the possibilities as well as the limitations for chemical modifications in these developments. It is interesting to see in which way the position of some ring nitrogen moieties or amino substituents can greatly change or maintain the binding properties within highly related scaffolds.

The formation and fate of histamine is the topic of the chapter by Schwelberger et al. (2013). Recent X-ray studies on the human L-histidine

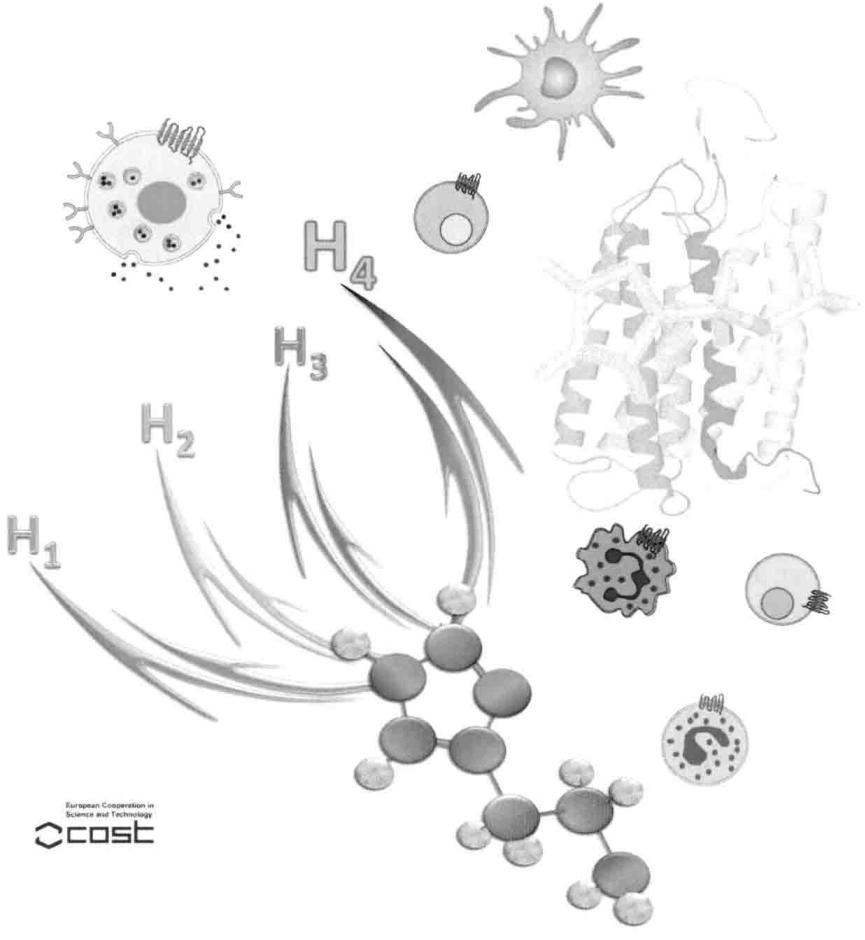

Figure 1.1 Illustration from the COST Action BM8006 hinting the transition from molecules to function and the complex network in histamine H_4 receptor research.

decarboxylase greatly contributed to the understanding of the binding domains. The not fully understood transport mechanisms are mainly organized by organic cation transporters with different tissue distribution and membrane localization. Other monoamine transporters of different families with related influences on the transport in different cells, e.g. neuronal and endocrine cells, make these uptake and secretion processes even more complex. Beyond storage and release, the metabolic pathway highlights large differences depending on the localization in the periphery or the central nervous system. The central histamine *N*-methyltransferase leads to a different product than the peripherally localized diamine oxidase, which products can then undergo