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## Molecular pharmacology of the human histamine H4 receptor

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## Summary

### **Molecular pharmacology of the histamine H<sub>4</sub> receptor**

The aim of this thesis is to obtain a better understanding of how the histamine H<sub>4</sub> receptor functions. The research has been focused at the molecular level. The histamine H<sub>4</sub> receptor is a G protein-coupled receptor (GPCR). This type of receptor plays an important role in our body, and are the binding site of several stimuli such as light, smell, endorphins, adrenaline and histamine. Approximately 50% of all medicine currently on the market bind to GPCRs. The GPCRs can be subdivided in smaller subpopulations/families. One of these subpopulations are the family of histamine receptors. The histamine family consists of 4 members. The histamine H<sub>1</sub> receptor is the oldest known member and plays a role in allergies. The histamine H<sub>2</sub> receptor is important in the secretion of stomach acid. The histamine H<sub>3</sub> receptor is predominantly localized in the brain and is potentially involved in several processes, such as food intake, sleep/wake cycle. The histamine H<sub>4</sub> receptor is the latest member of histamine receptors. The DNA encoding the H<sub>4</sub> receptor was discovered and cloned close to the year 2000.

During the start of this Ph.D. program only little was known about the role of the histamine H<sub>4</sub> receptor. In order to get a better picture of what type of ligands bind well to the receptor several ligands, known to have affinity for histamine receptors, were tested for their ability to bind to the histamine H<sub>4</sub> receptor. The discovery that 4-methylhistamine, a ligand with moderate affinity for the H<sub>2</sub> receptor, has high affinity for the H<sub>4</sub>R is described in chapter 2

Various proteins in our body have a tendency to aggregate with other proteins. This phenomenon is known as oligomerization. When two identical proteins aggregate, this is called homo-oligomerization, whereas the connection between two different proteins is termed

hetero-oligomerization. Even though oligomerization of proteins has been known for a long time, it was generally assumed that GPCRs function as monomers.

It was not until the end of the 20th century that convincing evidence emerged suggesting that GPCRs also form oligomers. Several different techniques were used to determine that the H<sub>4</sub>R can also form homo-oligomers. This is described in more detail in chapter 3.

Proteins are encoded by genes within our body. Every gene is a piece of DNA with a specific start and ending. For some proteins, including the H<sub>3</sub>R and the H<sub>4</sub>R, the gene that encodes the receptor protein is not one single uninterrupted strand of DNA, but fragments of DNA separated from each other. In general our body removes the DNA between these fragments and pastes them together to create one uninterrupted gene. However, sometimes our body makes a mistake and too much or too little DNA is removed, which then results in a gene that does not encode the normal receptor anymore. It is known that this occurs for the H<sub>3</sub>R, leading to the existence of at least 20 different varieties of the H<sub>3</sub>R.

Chapter 4 describes the identification of smaller variants of the H<sub>4</sub>R. These smaller H<sub>4</sub>R can form hetero-oligomers with the full length H<sub>4</sub>R and can have a negative influence on the function of the H<sub>4</sub>R by doing so.

The histamine receptors belong to the class of aminergic GPCRs. The GPCRs within this class bind small ligands, that are derived from amino acids. In chapter 5 an overview is presented of published data, concerning oligomerization of aminergic receptors.

The chemokine receptors are a specific class of GPCRs, that play an important role in inflammation. Recent research has indicated that the histamine H<sub>4</sub> receptor also plays a role in inflammation. Several commonly known herpesviruses, such as Kaposi's sarcoma virus and

the human cytomegalovirus, contain genes that encode for chemokine receptors. An extensively studied viral chemokine receptor is US28. Chapter 6 describes how the H<sub>4</sub>R and US28 receptors form hetero-oligomers and how this affects their signal transduction

For the development of new drugs, it is very useful to know the structure of the GPCR in great detail. To obtain such detailed information, it is necessary to have relatively large and pure quantities of the receptor protein. Chapter 7 describes how large quantities of H<sub>4</sub>R protein can be obtained by employing genetically modified viruses.

Finally, in chapter 8 an attempt is made to place the findings that have been made within this research project into a broadened perspective. Additionally, suggestions are made for future experiments to continue research on the function and role of the H<sub>4</sub>R.

Although, since the discovery of the H<sub>4</sub>R significant progress has been made in obtaining a better understanding in the role of the H<sub>4</sub>R, many questions remain unanswered. Up till now it is not known whether the H<sub>4</sub>R plays a crucial role in any disease, even though suggestions for a role in arthritis and breast cancer have been put forward. If it turns out that the H<sub>4</sub>R is an important drug target, this would undoubtedly speed up the search for ligands that bind selectively and with high affinity to the H<sub>4</sub>R. With regard to the formation of hetero-oligomers it may be necessary or therapeutically more efficient to develop drugs that bind selectively to a hetero-oligomer.