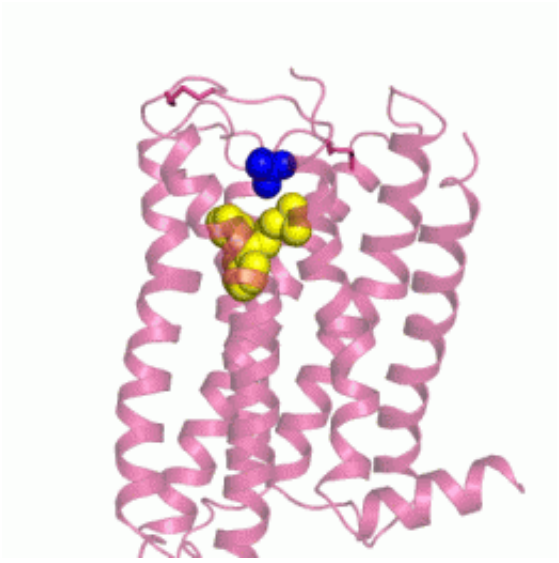
Histamine H1 receptor breakthrough heralds improved allergy treatments

June 23 2011



New 3D picture of human membrane protein enables development of targeted anti-histamines without side-effects.

An international team of scientists using Diamond Light Source, the UK's national synchrotron facility, has successfully solved the complex 3D structure of the human Histamine H_1 receptor protein. Published in the journal *Nature* this week, their discovery opens the way for the development of 'third generation' anti-histamines, specific drugs effective against various allergies without causing adverse side-effects.

The team, comprising leading experts from the USA (The Scripps Research Institute in California), Japan (Kyoto University), and the UK (Imperial College London and Diamond), worked across three continents for 16 months on the project.

“It took a considerable team effort but we were finally able to elucidate the molecular structure of the Histamine H1 receptor protein and also see how it interacts with anti-histamines. This detailed structural information is a great starting point for exploring exactly how histamine triggers allergic reactions and how drugs act to prevent this reaction,” said Professor So Iwata, David Blow Chair of Biophysics at Imperial College London.

H_1 receptor protein is found in the cell membranes of various human tissues including airways, vascular and intestinal muscles, and the brain. It binds to histamine, an important function of the immune system, but in susceptible individuals this can cause allergic reactions such as hay fever, food and pet allergies. Anti-histamine drugs work because they prevent histamine attaching to H1 receptors.

“First generation anti-histamines such as Doxepin are effective, but not very selective, and because of penetration across the blood-brain barrier, they can cause side effects including sedation, dry mouth and arrhythmia. By showing exactly how histamines bind to the H1 receptor at the molecular level, we can design and develop much more targeted treatments.” said Dr Simone Weyand, post-doctoral scientist at Imperial College London.

The research was technically challenging because membrane proteins are notoriously difficult to crystallise – a step that is vital in solving protein structures using a synchrotron. The proteins were grown in cells at Kyoto University in Japan, then processed cell material was flown to Professor Raymond Stevens at The Scripps Research Institute in La Jolla,

California, who leads the GPCR Network of the National Institute of General Medical Sciences' Protein Structure Initiative, and has developed powerful techniques to analyse membrane proteins and crystallise G-protein coupled receptors (GPCRs) funded by the National Institutes of Health Common Fund.

The crystals took around two months to grow and when each batch of around 100 was ready, they were frozen and flown to the UK. Here, Prof Iwata and Dr Weyand (pictured left on I24) worked with Diamond's scientists to analyse a total of over 700 samples using the Microfocus Macromolecular Crystallography (MX) beamline I24, a unique instrument capable of studying tiny micro-crystals using an X-ray beam a few microns wide.

Prof Stevens said: "A key aspect of our program is to collaborate with the leading researchers in the world so that we can uncover the mysteries of how GPCRs work. To fully understand this large and important human protein family will take a global community effort and the study of multiple receptors with different techniques and approaches. The collaboration with the Iwata lab is a great example of success made possible by joining forces; in this case, our work on histamine H_1 receptor helps to advance the field as quickly and efficiently as possible."

Prof Iwata added: "The fact that we've managed to solve this structure in 16 months starting from pure protein is very exciting as it shows what can be achieved when a team of experts pool skills and experience in sample preparation, experimental techniques and data analysis. Having the Membrane Protein Laboratory situated inside the Diamond synchrotron itself is a major advantage for projects like this. We've benefited from rapid-access to the beamline and round the clock support for our experiments and data analysis work."

More information: 'Structure of the human histamine H1 receptor complex with doxepin' Tatsuro Shimamura, Mitsunori Shiroishi, SimoneWeyand, Hirokazu Tsujimoto, GraemeWinter, Vsevolod Katritch, Ruben Abagyan, Vadim Cherezov, Wei Liu, GyeWon Han, Takuya Kobayashi, Raymond C. Stevens & So Iwata. *Nature*, 22 June 2011. dx.doi.org/10.1038/nature10236

Provided by Diamond Light Source