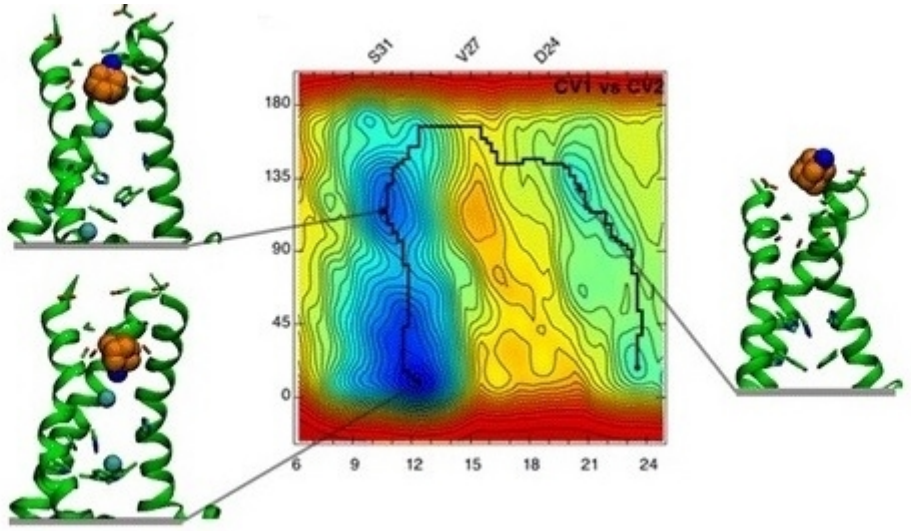
A team of the UB describes the action mechanism of a drug which inhibits influenza A virus



(via UB)

To cover the high complexity of the studied system, they also applied advanced simulation techniques and resources given by the BSC through the Marenostrum supercomputer and the support from a Partnership for Advanced Computing in Europe (PRACE) project.

A research team of the University of Barcelona has identified the action mechanism of amantadine –an antiviral drug- to block the M2 channel and stop the viral infection process. The new study, published in the *Journal of the American Chemical Society*, is carried out by a team supervised by the professors F. Javier Luque and Santiago Vázquez, together with Salomé Llabrés and Jordi Juárez-Jiménez, from the Faculty of Pharmacy and Food Sciences and The Institute of Biomedicine of the University of Barcelona (IBUB).

Influenza A is a viral infection which can be highly contagious among animals and humans. The infection outbreaks, which caused diseases worldwide, provoke symptoms such as acute respiratory infections, temperature and muscle pain, but with a different morbidity and death pattern than the one in common influenza.

During the virus infection, the M2 protein acts as a proton channel which enables the entrance of protons (H+) inside the virus and the following replication of the viral genome in the infected cell. Amantadine, which targets the M2 channel of the virus, blocks the ionic flow of protons and stops the infection process and influenza A virus reproduction. However, the apparition of mutant viruses which are drug-resistant has gradually reduced the efficacy of anti-viral drugs.

Amantadine changes its orientation inside M2 channel

In the article, the scientific team describes the binding mechanism of the drug in the wild type and the mutant V27A of M2 channel in influenza A virus. “The new study identifies the binding mechanism in amantadine to the M2 channel, a process with an amantadine orientation change as the main trait, inside the channel, and the adoption of a binding mode that prevents M2 channel from acting: transporting protons to the inside of the virus” says Professor F. Javier Luque, from the Department of Nutrition, Food Sciences and Gastronomy at the Food and Nutrition Torribera Campus.

This process of interaction with the drug is a sensitive process in V27A, amantadine-resistant. “The results show that the V27A mutation completely changes the process of interaction of the amantadine, which adopts a binding different to the wild type. This creates a decrease in the drug’s affinity and shows why there is a loss of its inhibiting capacity” says Professor Luque, director of the Computational Biology and Drug Design Group of the University of Barcelona, within the platform Bioinformatics Barcelona (BIB).

The study also explains that counter-ions are key elements to stabilize the kind of amantadine binding inside M2 channel. The participation of counter-ions in the binding confers an additional electrostatic stabilization, which complicates the drug exit from the channel and it increases its inhibiting activity.

M2 channel, therapeutic target against influenza A virus

In previous studies, the UB team had pharmacologically designed, synthetized and assessed compounds in order to block the mutant V27A channel, but with a different efficacy. The action mechanism which is now described in the Journal of the American Chemical Society adds an explanation for this diversity in the pharmacological response and spreads perspectives to design drugs with antiviral activity for the resistant type –for example, compounds with a bigger hydrophobic surface than the ones used in the wild type-, a line of work spread by the team of Professor Santiago Vázquez, from the Department of Pharmacology, Toxicology and Therapeutic Chemistry.

The experimental protocol of the new work combined methods of molecular simulation (to identify the molecular determinants of drug action) with the pharmacological synthesis and assessment of new compounds designed out of the binding mechanism. To cover the high complexity of the studied system, they also applied advanced simulation techniques and resources given by the Barcelona Supercomputing Center (BSC), through the Marenostrum supercomputer and the support from a Partnership for Advanced Computing in Europe (PRACE) project.

In an immediate future, the scientific team will focus their work lines on the study of the amantadine binding mechanism to the mutant S31N channel –the prevalent channel in current types of influenza virus- and the exploration of possibilities to design multi-target compounds, which should be more effective in their anti-viral activity.

(Caption: The new study identifies the binding mechanism of amantadine –antiviral drug- with the ionic channel M2 of viral coverage, an essential process in the infection and reproduction of the influenza A virus.)

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