MedicalXpress

# Research team describes the action mechanism of a drug inhibiting influenza A virus

December 13 2016

A research team at 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*, was 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 that can be highly contagious among animals and humans. The infection outbreaks provoke symptoms such as acute respiratory infections, fever and muscle pain, but with a different morbidity and death pattern than the one in common influenza.

During virus infection, the M2 protein acts as a proton channel that 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 that 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.

"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 for influenza A virus

In previous studies, the UB team had pharmacologically designed, synthesized and assessed compounds in order to block the mutant V27A channel, but with a different efficacy. The action mechanism described in the *Journal of the American Chemical Society* adds an explanation for

this diversity in the pharmacological response 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.

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 the immediate future, the scientific team will focus 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.

**More information:** Salomé Llabrés et al. Mechanism of the Pseudoirreversible Binding of Amantadine to the M2 Proton Channel, *Journal of the American Chemical Society* (2016). DOI: 10.1021/jacs.6b07096

Provided by University of Barcelona