Scientists achieve highest resolution ever for human protein

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Never has a crystal structure of a human protein molecule in a cell wall been so crystal clear. Leiden researchers Ad IJzerman and Laura Heitman, together with American colleagues, have achieved the most detailed crystal structure ever of a target protein for medicines. The findings have been reported in *Science*.

The protein in question is the adenosine A2A receptor, the main receptor for caffeine in the human body. This receptor is also linked to Parkinson's disease. The class of around 800 proteins to which the adenosine A2A receptor belongs forms the target for roughly half of all medicines. "No wonder that researchers across the globe have been trying for decades to find out more about these proteins," comments IJzerman.

To find out whether medicines are effective, you need to understand how the receptors in the cell wall work. An important means of achieving this is to crystallize the protein, so that it can be examined with X-rays. IJzerman and his research team had already managed in 2008 to determine the crystal structure of the adenosine A2A receptor, but at a lower resolution. IJzerman: 'Since then, a handful of structures of other receptors have appeared in the scientific literature, but at such a low resolution that in some cases it was even difficult to determine how medicines bind to such receptors.' Heitman continues: 'With our new structure, we have achieved the highest resolution ever for any protein in the human cell wall.'

The degree of detail of the new high-resolution crystal structure makes it possible to see things that were previously not discernible. "It is like comparing what Galileo saw with his primitive telescope with the images made by the Hubble telescope," IJzerman explains. It is now possible to see, for instance, how water molecules play a vital role in activating the adenosine A2A receptor. A water channel in the inactive receptor appears to be disrupted once it has been activated. The teams also discovered a hidden site where a natrium ion is located, away from the receptor's drug-binding cavity. This gives an insight into the way natrium ions affect the working of hormones and neurotransmitters in the body, something that was previously a mystery.

The high-resolution structure was the result of a clever strategy by the collaborators at the Scripps Institute in La Jolla (California). By binding the receptor protein, that is oily and therefore does not easily crystallize, to another protein that crystallizes readily, the researchers were able to produce minuscule crystals of the fusion product. Previously, they had used the protein lysozyme for this process, but this time they used proteins that crystallize even more easily and that are a better match for the receptor. This then yielded the high resolution structure that gives so much more information than any other receptor structure previously elucidated.

Research indicates that coffee drinkers are less susceptible to developing Parkinson's disease. Caffeine has been shown to inhibit the effect of the receptor, adenosine A2A, associated with this disorder.

Provided by Leiden University

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