Many receptor models used in drug design may not be useful after all

October 2 2008

It may very well be that models used for the design of new drugs have to be regarded as impractical. This is the sobering though important conclusion of the work of two Leiden University scientists published in *Science* this week. The editorial board of the renowned journal even decided to accelerate the publication on the crystal structure of the adenosine A2A receptor via *Science Express*.

Together with an expert team at the Scripps Institute (La Jolla) led by crystallographer Ray Stevens, Ad IJzerman, head of the division of medicinal chemistry at the Leiden/Amsterdam Center for Drug Research, and postdoctoral fellow Rob Lane worked on the structure elucidation of this protein, which is one of caffeine's main targets in the human body, and a key player in Parkinson's disease.

Obtaining a crystal structure of a receptor bound to a drug is by far the best way to learn and appreciate how drugs actually work. "For decades scientists from all over the world have struggled to get the crystal structure of this type of G protein-coupled receptor", IJzerman explains. "These arduous attempts are easily understood when one takes into account that the whole family of these proteins are the targets for almost half of the medicines that are available in the pharmacy shop. It seemed an impossible task, since these proteins are in the cell wall, which means they are in a fatty environment, and are fatty themselves. We all know that fat does not crystallize easily."

The scientists in California had found an elegant solution for this

problem though. They coupled the receptor protein to another protein that, in contrast, crystallizes easily, and managed to obtain tiny crystals of the fusion product. That was sufficient to crack the architectural code of the protein, for which very advanced crystallization equipment was used. In fact, something similar had worked for yet another receptor, but this time it was an adenosine receptor's turn. These receptors are at the core of the research in the division of medicinal chemistry of the Leiden/Amsterdam Center for Drug Research, and that's exactly why the American colleagues turned to the Leiden group. Forces were joined, and that's how the receptor constructs were characterized biochemically and pharmacologically, while at the same time the crystallization trials were ongoing across the Atlantic.

By the end of June 2008 the first crystals of suitable quality had been obtained and analyzed. That led to a big surprise that will undoubtedly have tremendous implications for the pharmaceutical industry. "The binding site for drugs on this receptor is very different from the one that had been found on two other receptors that we currently know the crystal structure of", says Rob Lane, asked for comments. "In the adenosine A2A receptor a small molecule, prosaically called ZM241385, is co-crystallized. This compound has high affinity for the receptor, and therefore it is best described as some sort of 'supercaffeine', a type of molecule that we had worked on in Leiden before." With some degree of understatement, Lane continues: "The drug is in a very different position than was expected on the basis of the other crystal structures. And there's the rub; almost everybody in the world of drug design has so far used receptor models that may not be so useful at all. That is the sobering and at the same time important discovery we made."

Source: Leiden University