Scientists unlock structure of elusive 'stress' protein (w/ Video)

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Newly discovered structure of the protein receptor that controls our response to stress

Scientists working to design advanced medicines that are perfectly targeted to control the body's natural receptors have made a major discovery using Diamond's Microfocus Macromolecular Crystallography beamline (I24). For the first time, they have been able to visualise and study the structure of CRF1, the protein receptor in the brain which controls our response to stress.

Heptares Therapeutics, a leading UK-based drug discovery and development company, was responsible for identifying the 3D structure of the 'stress' receptor, and their results are published today in the journal *Nature*. This discovery will help scientists to develop improved treatments for depression and anxiety. Furthermore, having identified the architecture of CRF1, scientists now have a template that can be used to accelerate research into other protein receptors that are known to be in the same 'family', including those that can be targeted to treat Type 2 diabetes and osteoporosis.

Stress-related diseases such as depression and anxiety are now commonplace. 1 in 4 people experience some kind of mental health problem in the course of a year. Over 105 million work days are lost to stress each year, costing UK employers £1.2 billion.

The UK also faces a major health challenge from diabetes. In the past 20 years, the number of people in the country suffering from diabetes has more than doubled to 2.9 million. By 2025 it is estimated that 5 million people will have diabetes, and that most of these cases will be Type 2 diabetes.

Heptares is a leader in the development of drugs targeting certain protein receptors, called G protein-coupled receptors. Currently 30% of drugs for a variety of diseases target these receptors, making them the largest and most important family of drug targets in the human body.

In the past, drug design has been largely the product of trial and error. Drugs would be developed and then tested until they had the desired effect. Because scientists lacked a comprehensive understanding of why and how the drugs were working, this approach could lead to unwanted side-effects.

A new way of making medicines, known as rational drug design, produces drugs that are specifically targeted to protein receptors in the body. By visualising the stress protein receptor at the atomic level, they were able, for the first time, to identify a 'pocket' in the structure. Computer technology will allow scientists to design a drug to fit precisely into this pocket, inhibiting the response of the 'stress' receptor. Such focused targeting will only affect the receptor they are aiming for and reduce the chance of unexpected side effects. The level of detail required for this work could only be achieved using the intense synchrotron light produced at Diamond Light Source, the UK's synchrotron science facility in Oxfordshire. The synchrotron speeds electrons to near light speed, producing a light 10 billion times brighter than the sun. Around 2,500 scientists a year use this light to study samples, and its intensity allows them to visualise on a scale that is unobtainable in their home laboratories. Heptares is currently the biggest annual industrial user of the synchrotron.

Provided by Diamond Light Source

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