# Discovery offers new understanding of diabetes drug target

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Scientists at the University of Leicester have published findings about a new advance in the study of major diabetes drug target.

The advance - described by the researchers as 'very significant' - could lead to new drugs being developed to target a protein that plays a critical role in controlling the way the body breaks down sugar.

Professor John Schwabe and his team from the University of Leicester Department of Biochemistry (together with teams from Japan and Hungary) have been studying the protein, PPAR gamma. PPAR gamma is a major drug target for the treatment of type 2 diabetes. Although it was known how drugs are able to activate this protein, until this study, using the sophisticated technique of X-ray Crystallography, it was not clear how PPAR gamma is naturally activated in the body.

X-ray Crystallography is the principal method by which the detailed 3-dimensional structures of molecules - especially the molecules of living systems - have been discovered. It is achieved by firing X-rays at the target and creating its structures by analysing how the x-rays scatter into many different directions.

Through this method, the Leicester team have shown how PPAR gamma binds to eight different fatty acids, derived in part from what we eat. They found that many of these acids joined irreversibly with the protein and led to its long term activation. They have also shown that sometimes two fatty acids bind simultaneously, which might mean that PPAR

gamma could be targeted by a mixture of drugs.

Professor John Schwabe, who led the Leicester project with his team, including Dr Toshimasa Itoh and Dr Louise Fairall, said: "The finding that natural activators for PPAR gamma couple irreversibly to the PPAR gamma receptor dramatically changes our understanding of how this receptor is activated.

"It may also allow for the design of novel pharmaceuticals that give longer term activation of PPAR gamma, at lower doses, without some of the side effects of the current generation of drugs."

Professor Schwabe said: "PPAR gamma is a critical player in the increasingly prevalent metabolic disease of type 2 diabetes which affects more than 180 million people worldwide (World Health Organisisation) and in the UK alone costs the NHS £9.6 million every day.

"PPARgamma is activated by two widely prescribed anti-diabetic insulin- sensitising drugs, Actos and Avandia. However the identity of the natural activators for PPAR gamma has remained unclear.

"Our breakthrough is important because it reveals for the first time that how this protein is activated by naturally-occuring fatty acids. This knowledge will help in the design of future novel pharmaceutical agents."

The research has been published in the journal Nature Structural and Molecular Biology. The paper will also be featured as a Highlight in the journal Nature Chemical Biology and has been designated a "Must Read" by the Faculty of 1000.

Source: University of Leicester

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