A new molecule to combat diabetes and obesity

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Type 2 diabetes, the most common form of diabetes, is increasing at an alarming state with more than 180 million people affected worldwide. With the rising incidence of obesity, a major risk factor for the onset of type 2 diabetes, this metabolic disorder represents a major health concern. A group from the Ecole Polytechnique Fédérale de Lausanne, Switzerland, now shows that there may exist new ways to fight these disorders.

The study, published in the current issue of the scientific journal Cell Metabolism (September 2, 2009), demonstrates that activation of the protein -TGR5- can treat type 2 diabetes and reduce weight gain. In collaboration with Prof. Roberto Pellicciari and his team at the University of Perugia (Italy), and Intercept Pharmaceuticals (New York, USA; Perugia, Italy), the group at the EPFL, led by Dr Kristina Schoonjans and Prof. Johan Auwerx, have characterized the metabolic properties of a selective TGR5 activator (INT-777), a drug with a promising future for the treatment of diabetes and obesity.

Earlier work from the same group showed that bile acids (endogenous molecules involved in digestion), via the activation of TGR5 in muscle and brown adipose tissue, are able to boost energy expenditure and to prevent or reverse diet-induced obesity in mice.

In the present study, the group of Dr Kristina Schoonjans and Prof. Johan Auwerx went further in studying the role of TGR5 in the gut where TGR5 is expressed in cells specialized in the production of gut-

derived hormones. The authors found that in these so-called enteroendocrine cells TGR5 controls the secretion of the hormone Glucagon-Like Peptide 1 (GLP-1), which plays a critical role in the control of pancreatic function and the regulation of blood sugar levels. In addition to this discovery and in collaboration with Prof. Roberto Pellicciari, who designed the novel potent and selective TGR5 activator, INT-777, under a longstanding collaboration with Intercept Pharmaceuticals, the group at the EPFL has shown that under laboratory conditions this compound can effectively treat diabetes and reduce fat mass. The authors have furthermore demonstrated that these effects were related to the increase in both GLP-1 secretion and energy expenditure.

This work is of great interest since it could herald a new approach in the treatment of type 2 diabetes and obesity. "Recently, two classes of drugs exploiting the properties of the hormone GLP-1 have been marketed for the treatment of type 2 diabetes. The first strategy aims to increase the blood levels of GLP-1 by limiting its degradation in the body. The second is to mimic the effects of GLP-1 using drugs activating the GLP-1 receptor (GLP-1R) ", explains Charles Thomas, first author of the study. In this study, the authors propose a third therapeutic option based on increasing GLP-1 secretion via administration of TGR5 agonist therapy. The results obtained by the authors are even more spectacular since in addition to stimulating the secretion of GLP-1, INT-777 activation of TGR5 in other tissues leads to an increase in energy expenditure responsible for a reduction in fat mass and obesity.

Source: Ecole Polytechnique Fédérale de Lausanne