Micro-RNA blocks the effect of insulin in obesity

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(PhysOrg.com) -- German researchers have discovered a new mechanism that leads to the development of type 2 diabetes in obesity.

Body weight influences the risk of developing diabetes: between 80 and 90 percent of patients with type 2 diabetes are overweight or obese. According to scientists at the Max Planck Institute for Neurological Research in Cologne and the Cologne Cluster of Excellence in Cellular Stress Responses in Aging-associated Diseases (CECAD), short ribonucleic acid molecules, known as micro-RNAs, appear to play an important role in this mechanism. The researchers discovered that the obese mice form increased levels of the regulatory RNA molecule miRNA-143. miRNA-143 inhibits the insulin-stimulated activation of the enzyme AKT. Without active AKT, insulin cannot unfold its blood-sugar-reducing effect and the blood sugar level is thrown out of kilter. This newly discovered mechanism could provide the starting point for the development of new drugs for the treatment of diabetes.

The hormone insulin plays a key role in the regulation of blood sugar levels. If there is too much glucose in the blood, insulin opens the glucose transport channels in the cell membrane of muscles and fat cells. Glucose then reaches the body's cells and the blood's sugar content sinks. Additionally, the insulin inhibits the production of new sugar in the liver. Type 2 diabetics are able to produce sufficient volumes of insulin; however, their cells are resistant to it - and the hormone is unable to fulfil its task. If untreated, this disease damages the blood vessels due to the raised blood sugar levels, which can lead to a heart attack or stroke.

The molecular processes in the body's cells responsible for the connection between body weight and diabetes are largely unknown. However, in all tissues that respond to insulin, Micro-RNAs can be found. The Cologne-based scientists working with Jens Brüning, Director at the Max Planck Institute for Neurological Research and scientific coordinator of the Cologne Cluster of Excellence in Cellular Stress Responses in Aging-associated Diseases at the University of Cologne assume, therefore, that micro-RNAs may also play a role in type 2 diabetes. These short ribonucleic acid molecules can regulate the activity of genes and thus control protein production.

The research group in Cologne has now discovered a new mechanism that leads to insulin resistance of the cells. Accordingly, obese mice form excess miRNA-143 in their livers. This RNA molecule silences genes that are responsible for the activation of the enzyme AKT and therefore inhibits insulin from activating AKT. "AKT is important for glucose transport in the cell and for the inhibition of glucose synthesis in the liver. When the enzyme is inhibited, insulin fails to take effect and the blood sugar remains elevated," explains Jens Brüning.

For their research study, the researchers compared normal weight mice with obese mice with type 2 diabetes. They discovered that the diseased animals produce more than twice as much miRNA-143 in their livers than the normal ones. Moreover, the researchers found only a low concentration of the protein ORP8 in the obese mice which formed large quantities of miRNA-143. ORP8 stimulates insulin to activate AKT and therefore reduces the sugar content of the blood. If ORP8 is lacking, insulin is unable to take effect and the AKT remains inactive.

The researchers do not yet know why obese mice form more miRNA-143 than their normal weight counterparts. "If we succeed in explaining the signalling paths in the cell that lead to the production of miRNA-143, we will have a starting point for the development of new

drugs for the treatment of type 2 diabetes," explains Jens Brüning in reference to future research plans.

More information: Sabine D. Jordan, Markus Krüger, Diana M. Willmes, Nora Redemann, F. Thomas Wunderlich, Hella S. Brönneke, Carsten Merkwirth, Hamid Kashkar, Vesa M. Olkkonen, Thomas Böttger, Thomas Braun, Jost Seibler, Jens C. Brüning, Obesity-induced overexpression of miRNA-143 inhibits insulin-stimulated AKT activation and impairs glucose metabolism, *Nature Cell Biology*, Published online March 27, 2011, DOI: 10.1038/ncb2211