The pig and its pancreas

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The increasing prevalence of type 2 diabetes places a huge burden on its victims and poses a tremendous challenge to healthcare systems. Half of all heart attacks and stroke cases, but also many other deleterious conditions, can be ascribed to the effects of this metabolic syndrome. In Germany alone, some seven million people currently suffer from the disease, and the number of cases worldwide is projected to reach 370 million by the year 2030. Type 2 diabetes results from a combination of genetic and environmental factors which cause the organism to become resistant to the action of insulin. This hormone controls the level of glucose in the blood, so insulin resistance leads to a chronic rise in glucose concentrations.

A team of LMU researchers led by Professor Eckhard Wolf and Professor Rüdiger Wanke has now introduced a new model system for the study of the disease. They have created a genetically modified strain of pigs that consistently develop the essential symptoms of type 2 diabetes. "The physiology of the pig is actually very similar to that of humans", says Wolf. "Our model therefore provides a unique tool for the development and testing of new approaches to the diagnosis and therapy of diabetes."

After a meal, the concentration of glucose in the blood rises, causing the beta-cells of the pancreas to secrete a correlated amount of insulin. The hormone in turn stimulates uptake of glucose by several tissues, including the skeletal muscles. In cases of type 2 diabetes, this regulatory circuit is disturbed. Cells exposed to insulin fail to respond, and the consequent failure to remove the glucose causes its level to remain high.

This state of chronic hyperglycemia has deleterious effects on many organ systems, leading to cardiovascular disease, kidney failure and blindness, for example. Up until a few decades ago, the disease, which remains incurable, was largely confined to the elderly, but it has since become more and more prevalent among young adults, adolescents and even children. The younger the age of onset, the greater the chance that increasingly severe conditions will develop as time passes.

The so-called incretin hormones, GIP (short for glucose-dependent insulin-releasing polypeptide) and GLP-1 (glucagon-like peptide 1), are produced in the intestine after ingestion of a meal, and are transported via the circulation to the pancreas. There they stimulate the synthesis and secretion of insulin by binding to specific receptor molecules on the beta cells. GLP-1 has already proven effective in the treatment of diabetes. GIP, on the other hand, has shown very limited efficacy in patients with diabetes, and whether this lack of responsiveness is a cause or a consequence of the diabetic condition itself remains controversial. "In our genetically modified (transgenic) pigs, which produce a partially defective GIP receptor, the response to GIP is also very weak", reports Dr. Simone Renner, who is first author on the new publication and research associate at the chair for Molecular Animal Breeding and Biotechnology. "Our results suggest that inability to respond to GIP leads not only to a fall in glucose utilization and insulin secretion, but is also associated with a reduction in the mass of beta cells in the pancreas. This would argue that impaired response to GIP is more likely to be a cause rather than a consequence of diabetes. We hope that our model will help to accelerate the translation of the latest research findings into clinical applications."

The pig is a particularly suitable model, because its metabolism and physiology closely resemble our own. The transgenic pigs not only display a weak response to GIP, they also display other traits that are typical of type 2 diabetes in humans. For instance, the efficiency of both

glucose utilization and insulin secretion falls off with increasing age, as in humans. The number of insulin-producing beta cells in the pancreas is also lower than normal, due to the fact that the cells divide less frequently. Thus, the new model system provides a variety of oppurtunities for innovative research on diabetes. Among other things, the system should be ideal for testing and improving therapeutic regimes based on incretins, which already represent an important treatment option. One might also be able to utilize the system in the development of imaging techniques for direct measurement of beta cell mass in patients. Indeed, the Munich team have now established a total of four different genetic models that are relevant to diabetes, and therefore provided researchers with a unique and invaluable research resource.

More information: Glucose intolerance and reduced proliferation of pancreatic _-cells in transgenic pigs with impaired GIP function", Simone Renner, et al., Diabetes Online Ahead of Print, 26 Februar 2010, doi:10.2337/db09-0519

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