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Novel mechanisms controlling insulin release and fat deposition discovered

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Scientists at the Swedish medical university Karolinska Institutet have in two recent studies shown that a receptor called ALK7 plays important roles in the regulation of body fat deposition as well as the release of insulin from beta-cells in the pancreas. These findings have implications for the development of treatments against diabetes and obesity.

“We have shown in animal studies that removing the ALK7 receptor improves insulin release by beta-cells in the pancreas, and at the same time decreases fat deposition in situations of high caloric intake”, says Professor Carlos Ibáñez, who lead the two studies that are now published as back-to-back papers in the *PNAS*. “The well-known connections between diabetes and obesity make our combined findings quite exciting.”

Up to 6 per cent of the world population is estimated to suffer from some form of diabetes, either due to a reduced ability to produce insulin, or to insulin resistance. Insulin is a hormone required by cells in the body to absorb glucose from the blood, thereby providing them with energy. Obesity has been shown to increase the risk of developing diabetes, and as overweight becomes more prevalent in the human population, so do the cases of diabetes.

The research group led by Carlos Ibáñez studies how signaling by growth factors and their receptors regulate different physiological functions in the body. They have recently investigated the functions of one of these receptors, called ALK7, using mutant mice (knock-out mice) lacking

this receptor. They found that in the absence of ALK7, mice developed abnormally high levels of insulin in the blood, which with age led to insulin resistance and liver steatosis, a pathological condition in which the liver enlarges and accumulates abnormally high levels of fat.

In collaboration with another research group at Karolinska Institutet, led by Professor Per-Olof Berggren, they also found that Calcium signaling in pancreatic beta-cells was reduced by the actions of the growth factor Activin B through the ALK7 receptor, and that blood glucose levels regulates the expression of both Activin B and ALK7. In agreement with these results, mice lacking Activin B also developed hyperinsulinemia to a similar extent as ALK7 mutants.

“In other words, our data revealed an unexpected negative feedback loop in the control of glucose-dependent insulin release, mediated the actions of Activin B on the ALK7 receptor”, says Carlos Ibáñez.

In the second study, the scientists found that mice lacking ALK7 accumulated less fat and gained less weight than their normal counterparts when fed on a high-fat diet. They discovered that another growth factor called GDF3 could also signal via the ALK7 receptor, and that mice lacking GDF3 showed similar defects in fat deposition and weight gain as the ALK7 mutants. Intriguingly, however, mutant mice consumed equal amounts of food as their normal counterparts during the experiment.

“These results show that lack of ALK7 or GDF3 improves energy balance in the body under regimes of high caloric intake”, says Carlos Ibáñez.

Source: Karolinska Institutet