Antibody injection promising for diabetes and obesity

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(Medical Xpress) -- Researchers at Genetech Inc. in South San Francisco, California, led by molecular biologist Junichiro Sonoda, have discovered that a single injection of antibodies into obese diabetic mice provided a marked and sustained improvement in their condition and a reduction in their weight.

The research by Genetech, which is part of the Roche Group, targeted "brown fat," and the injections resulted in greater energy expenditure, lowered blood sugar, and reduced fat in the livers of the mice. Researcher Dr. Sonoda said the results were unprecedented, with the drug removing liver fat, which improves the disease conditions.

Brown fat is a specialized kind of fat (adipose tissue) that burns energy to keep the body warm, rather than storing it for future energy needs. Independent studies by three groups of scientists in 2009 found that adult bodies have small amounts of brown fat, primarily around the shoulder blades, the spine, and in the neck. Until this research it had been assumed that brown fat was only found in babies.

The finding of brown adipose tissue in adults led to the idea that if the brown fat could be activated, people might lose weight through burning more calories, and this could reduce the levels of obesity and associated conditions such as type 2 diabetes.

Studies have shown that the hormone fibroblast growth factor 21 (FGF21) activates brown fat, and it has been shown to reduce blood

triglycerides and to normalize blood sugar levels in mice. Early attempts to use recombinant FGF21 as a drug failed because it is cleared from the bloodstream in only a few hours, giving it little chance to operate.

The new study began by making antibodies to bind to the FGF21 receptors. Dr Sonoda said that one of these receptors was FGFR1, which increased the expression of a number of genes involved in energy expenditure. FGFR1 is found in fat tissues and in the pancreas.

In other cases where antibodies are used as drugs they inhibit the receptors, but in this case the aim was to stimulate the receptors instead to make them mimic the effects of FGF21. Dr Sonoda said the results obtained in mice were better than expected, with one injection into the diabetic, obese mice normalizing blood sugar levels after a week, and the levels remained low for up to a month, with no apparent side effects. The mice also lost around 10% of their body weight during the period.

In type 2 diabetes there is insufficient insulin in the bloodstream to extract sugar and deliver it to cells where its energy is required. This leads to increased blood sugar levels, which can damage various organs in the body. A link between the fibroblast growth factor and diabetes had been identified in mice previously, but so far tests in humans have been unsuccessful.

A drug based on the research is not expected to be available for many years, and no date has been announced for the beginning of clinical trials.

The paper was published in the journal *Science Translational Medicine* on December 14th.

More information: Amelioration of Type 2 Diabetes by Antibody-Mediated Activation of Fibroblast Growth Factor Receptor 1, *Sci Transl*

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ABSTRACT

Clinical use of recombinant fibroblast growth factor 21 (FGF21) for the treatment of type 2 diabetes and other disorders linked to obesity has been proposed; however, its clinical development has been challenging owing to its poor pharmacokinetics. Here, we describe an alternative antidiabetic strategy using agonistic anti-FGFR1 (FGF receptor 1) antibodies (R1MAbs) that mimic the metabolic effects of FGF21. A single injection of R1MAb into obese diabetic mice induced acute and sustained amelioration of hyperglycemia, along with marked improvement in hyperinsulinemia, hyperlipidemia, and hepatosteatosis. R1MAb activated the mitogen-activated protein kinase pathway in adipose tissues, but not in liver, and neither FGF21 nor R1MAb improved glucose clearance in lipoatrophic mice, which suggests that adipose tissues played a central role in the observed metabolic effects. In brown adipose tissues, both FGF21 and R1MAb induced phosphorylation of CREB (cyclic adenosine 5′-monophosphate response element–binding protein), and mRNA expression of PGC-1α (peroxisome proliferator–activated receptor-γ coactivator 1α) and the downstream genes associated with oxidative metabolism. Collectively, we propose FGFR1 in adipose tissues as a major functional receptor for FGF21, as an upstream regulator of PGC-1α, and as a compelling target for antibody-based therapy for type 2 diabetes and other obesity-associated disorders.