

FOCUS ON RESEARCH

AN ANALYSIS OF THE MOLECULAR AND BIOCHEMICAL DEFECTS IN INSULIN ACTION THAT CORRELATE WITH THE DEVELOPMENT OF OBESITY-INDUCED INSULIN RESISTANCE

Researchers

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Aim

To find out if obesity alters the activity of one or more important molecules inside human muscle cells, leading to health problems later in life.

Project Outline/Methodology

Obesity is the single greatest risk factor for the development of diabetes. This is currently thought to be largely due to the development of 'insulin resistance'. This is a condition where cells in the body don't respond correctly to the hormone insulin. The molecular reasons for the reduced response to insulin are not known, however the insulin and the receptor for insulin appear functional. Therefore we hypothesised that the defect must lie inside cells, on one or more of the insulin signalling pathways required for control of glucose metabolism. We recruited male volunteers, under the age of 45, with no family history of diabetes. We focussed on young males with no diabetes in order to find out what molecular problems were occurring before they developed diabetes, but were associated with obesity. We assessed whole body insulin sensitivity, Body Mass Index (BMI), fat distribution and general health. We collected a small piece of muscle before and after exposure to insulin. The proteins in these muscle biopsies were isolated and we specifically measured the level of 15 proteins, 12 of which should be regulated by insulin. In this way we would see if the level of any of these important insulin molecules changed as body fat increased, or if one or more of the molecules had a reduced response to insulin.

Key Results

We found that there is a direct relationship between body mass index (BMI) and whole body insulin sensitivity in young male adults with no diabetes. In other words as fat content of the body increases the ability of insulin to regulate glucose in the blood is reduced. Indeed for every 5 BMI units there is nearly a 50% reduction in the efficacy of insulin. We found that at least one of the molecules investigated was defective in all of the most obese individuals. So increasing obesity reduces molecular insulin action

but there is not a single molecular defect responsible, suggesting different causes of the insulin resistance. However the regulation of one specific molecule was reduced in more volunteers than any other. In addition, defects could be observed even in the mildly overweight volunteers, while those with no problems were the leanest.

Conclusions

Whole body insulin sensitivity is directly related to body fat content, even in the young male population without Diabetes. Small increases in body fat above normal reduce insulin sensitivity, so a small reduction in body fat in the overweight will have beneficial effects on insulin action and metabolic health. A single defect in intracellular insulin action is not responsible for all insulin resistance. Instead, there are several molecules that can be affected by obesity although it appears that there is not a continuous decline in a molecule as body fat increases, but rather a threshold of adiposity that affects signalling.

What does this study add to the field?

Our work suggests that Type 2 Diabetes can be subdivided into different molecular diseases. Surprisingly, the molecule most affected is not the one we would have predicted, and further work is needed to establish if this contributes to disease progression or complications.

Implications for Practice or Policy

We need to realise that not all people with Diabetes can be treated with a single therapy, and that establishing personal defects in insulin regulation of molecules could help identify the best treatment.

Where to next?

Further work will be needed to characterise the potential of each molecule in diagnosis and treatment, prior to development of diabetes.

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