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Mechanisms of insulin resistance caused by nutrient toxicity

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Abstract

Insulin resistance, the impaired action of insulin, has been linked to many important consequences, including Type 2 diabetes, hypertension, dyslipidemia, acanthosis nigricans and polycystic ovarian syndrome. Although there are some genetic causes for insulin resistance, the most common cause is an excess of nutrition a condition called "Nutrient Toxicity". Both excess glucose and excess fat can cause insulin resistance in muscle and fat tissues and excess fat can cause insulin resistance in the liver. High fat feeding and fat infusion rapidly lead to the development of insulin resistance caused by impairment in glucose transport. Other studies have shown defects in insulin signaling possibly secondary to activation of Protein Kinase C resulting from the accumulation of active fatty acyl CoA's. Glucose toxicity has been studied both in vivo and in vitro. In vivo it has been shown that rats over-expressing the gluconeogenic enzyme Phosphoenol Pyruvate Carboxykinase (PEPCK) develop insulin resistance in fat and muscle tissues and some features of the metabolic syndrome including mild obesity and dyslipidemia. Excess glucose entry in fat cells results in increased flux through the hexosamine biosynthesis pathway leading to activation of protein kinase C and impairment of glucose transport. Obesity resulting from excess nutrient intake can also cause insulin resistance by an increase in the production of agents that impair insulin action such as TNFα and resistin and a decrease in the production of an insulin sensitizing compound adiponectin.

Both glucose and free fatty acids acutely stimulate insulin secretion but chronic exposure to high levels of either nutrient leads to impairment of beta cell function. The combination of insulin resistance and beta cell failure leads to diabetes. Nutrient toxicity is thus the driving cause of the diabetes epidemic that is being recorded around the world.

Keywords: Lipotoxicity; Glucotoxicity; Protein kinase C; Hexosamine biosynthesis pathway; Cytokines

1. Introduction

Insulin resistance, the reduction in the ability of insulin to perform its functions, is a key feature of type 2 diabetes. Several other clinical situations are associated with insulin resistance including, cushing's syndrome, acromegaly, the third trimester of pregnancy, cirrhosis of the liver, and most commonly, obesity. There are many mechanisms of insulin resistance but this paper will focus on insulin resistance caused by excess nutrition.

2. Fat-induced insulin resistance

Many mechanisms have been proposed for fat-induced insulin resistance. Of great interest has been the recent discovery that fat cells make and secrete compounds that impact on insulin action. These include tumor necrosis factor alpha (TNFα), resistin and adiponectin. These will be mentioned only very briefly because adipokines are not the topic of this article although excess nutrition can result in changes in their levels. TNFα is produced by fat cells [1], and causes insulin resistance by impairing the function of the insulin receptor by altering its phosphorylation state [2]. Resistin, has had a checkered career in terms of its significance in insulin resistance, but the consensus appears to be that it can impair insulin action [3]. Adiponectin on the other hand is a product of the fat cell that not only enhances insulin sensitivity but also reduces vascular disease [4]. In obese individuals, adipose tissue overproduces TNFα [5] and under-produces adiponectin [6].

Many years ago it was proposed that if a muscle is burning fat it will not burn glucose, and so insulin will appear not to lower glucose effectively (Randle hypothesis) [7]. Thiebaud et al. infused free fatty acids in humans together

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with heparin to increase free fatty acid levels and then measured whole body glucose uptake, glucose oxidation and non-oxidative glucose disposal during an hyperinsulinemic euglycemic clamp. In this procedure insulin is infused at different levels in order to measure its action. To prevent plasma glucose from falling, glucose is infused at a variable rate to maintain euglycemia. Clearly, under these circumstances, the more glucose that is needed to be infused to keep euglycemia the more sensitive the animal or the person is to insulin. The infusion of free fatty acids caused the insulin dose-response curve on glucose uptake to be shifted to the right [8]. In other words, free fatty acid infusion caused insulin insensitivity. More insulin was needed to achieve the same level of glucose uptake than when saline was infused. This was also shown in glucose oxidation and non-oxidative glucose disposal [8].

More recently, in a more elegant study, Roden et al. [9] maintained elevated free fatty acid levels for 6 h. In the control group, free fatty acid levels were allowed to fall. Insulin action was assessed by increasing insulin levels up to 400 pmol/l, achieving the same insulin levels in both groups. Plasma glucose was maintained constant using the hyperinsulinemic euglycemic clamp approach. In the first few hours there was no difference in the amount of glucose that had to be infused to maintain euglycemia. But with time, in the group that had the elevated free fatty acids, the amount of glucose required to keep the plasma glucose constant was reduced, suggesting that these people were developing insulin resistance. Glucose oxidation was reduced from an even earlier time point (Fig. 1).

Using another approach to increase the rate of fatty acid entry into cells, Kim et al. produced two types of transgenic mice over-expressing lipoprotein lipase. This enzyme cleaves the triglyceride in chylomicrons and VLDL particles releasing free fatty acids which are taken up into the adjacent tissue. Two different transgenic mice were produced, one in

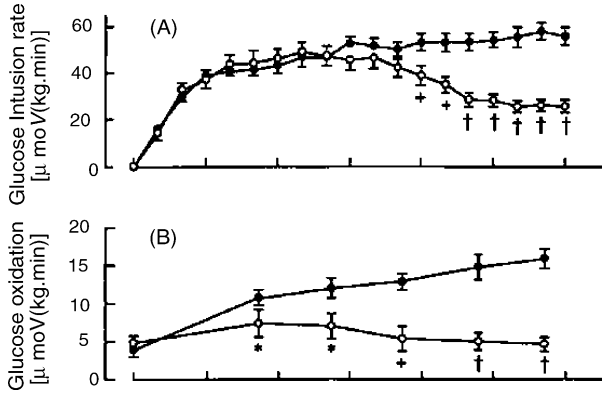

Fig. 1. Glucose infusion rate (A) and glucose oxidation (B) over a 6 h infusion of either FFA or saline. In (A) it is shown that after the third hour, the rate of glucose infusion needed to maintain euglycemia declined showing a reduction in insulin sensitivity. Glucose oxidation (B) was impaired from an earlier time point by the elevated FFA's (from Roden et. al. from ref. [9] with permission).

which the lipoprotein lipase was over-expressed in muscle, and the other model in which the lipoprotein lipase was over-expressed in the liver. The mice over-expressing lipoprotein lipase in muscle had mildly impaired glucose tolerance but did not have hyperinsulinemia. In the liver-specific lipoprotein lipase over-expressing mice, there was a more marked impairment of glucose tolerance [10].

In the muscle-specific lipoprotein lipase over-expressing animals there was an increase in intramuscular but not hepatic triglyceride levels (Fig. 2A). Glucose infusion rate was lower in these animals suggesting that they had insulin resistance. There was no difference in endogenous glucose production (Fig. 2B). Whole-body glucose uptake, glycolysis and glycogen and lipid synthesis were reduced (Fig. 2C). Muscle glucose uptake, glycolysis and muscle glycogen synthesis were reduced (Fig. 2D).

How does excess fat in muscle cause insulin resistance? The insulin receptor is a dimer of two alpha and two beta chains. When insulin binds to one of the alpha chains it activates the tyrosine kinase in the beta chain, which firstly cross-phosphorylates the other chain and then becomes an even more active tyrosine kinase and phosphorylates an intracellular protein, IRS-1. IRS-1 is tyrosine phosphorylated on many sites but can also be phosphorylated on serine and threonine. Serine/threonine phosphorylation prevents the tyrosine phosphorylation of IRS-1 and therefore impairs the action of IRS-1. When IRS-1 is tyrosine phosphorylated it attracts PI-3 kinase which when activated, eventually causes the activation of Akt, as well as PKCζ. By mechanisms that are still not fully clear, the activation of Akt then causes the translocation of the glucose transporter GLUT 4 to the surface, thus increasing glucose entry. LPL over-expressing animals were shown to have a reduction in PI-3 kinase activity. However the tyrosine phosphorylation of the insulin receptor was not reduced.

In the liver-specific LPL over-expressing mice the excess triglyceride is in the liver and not in the muscle. These animals were also insulin resistant. It was shown that, whereas in the control animal, insulin suppressed endogenous glucose production (EGP) by 80%, in the animals that had excess fat entry into the liver EGP was only suppressed by just over 20%, showing profound hepatic insulin resistance. As expected, whole body and muscle glucose clearance and glucose uptake were normal in these animals.

Kin et al. went on to show that there is accumulation of fatty acyl CoA concentration in these two models. In addition they showed that in the muscle-specific LPL mice there was also increased ceramide in skeletal muscle. It is known that fatty acyl CoA's can activate protein kinase C. An important kinase that was discovered in Japan. There are many isoforms of PKC now known, and the one that has been shown to be activated by fat inside tissues is PKC-θ. PKC-θ knock out mice are protected from Free fatty acid infusion-induced insulin resistance [11]. It was found that free fatty acid infusion reduced IRS-1 tyrosine phosphorylation in the wild-type animals but this did not occur in the PKC-θ knockout animals.