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Pathogenesis of Diabetes Mellitus type 2

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In the natural history of type 2 diabetes (T2DM), individuals progress from normal glucose tolerance (NGT) to impaired glucose tolerance (IGT) to overt T2DM and this progression has been demonstrated in populations of diverse ethnic background[1]. It is widely recognised that both insulin resistance and beta-cell dysfunction are important in the pathogenesis of glucose intolerance. In populations with a high prevalence of T2DM, insulin resistance is well established long before the development of any impairment in glucose homeostasis but as long as the beta-cell is able to secrete sufficient amounts of insulin to offset the severity of insulin resistance, glucose tolerance remains normal.[1] This dynamic interaction between insulin secretion and insulin resistance is essential to the maintenance of NGT and interruption of this cross-talk between the beta-cell and peripheral tissues results in the progressive deterioration of glucose homeostasis.[2]

Early in the development of T2DM, the initial burst of insulin release in response to food intake is compromised, allowing postprandial hyperglycemia to develop. Meal-associated hyperglycemia further contributes to increase insulin resistance and decrease insulin production.

Why is Glucose Control so Important?

In the fasting state, the suppression of insulin and stimulation of glucagon production control the concentration of blood glucose. These processes allow the liver to mobilize glucose from its glycogen stores and synthesize glucose from amino acids and pyruvate (gluconeogenesis). In addition, when insulin levels are low, the uptake of glucose by muscle is minimized, and adipocytes release free fatty acids (FFA).

In the fed state, insulin is released in two phases. The first phase, a short, small burst released on food intake or an increase in plasma glucose concentration, preempts and decreases the postprandial glucose elevation.[3] Later, a more sustained, second-phase insulin release directly proportional to the plasma glucose elevation occurs. In response to this biphasic release of insulin, the liver and muscle take up glucose, converting it to glycogen, and adipose tissues also take up glucose, storing it as triglycerides.[3]

Other effects of insulin

Insulin exerts its action not only toward glucose but also promotes fatty acids re-esterification into triglyceride, and inhibits triglyceride hydrolysis and release of FFA into the circulation (lipolysis). Thus, insulin resistance at the level of adipose tissue results in excess release of free fatty acids (FFA) into the circulation. Several studies have shown that elevated FFA concentrations are linked with the onset of peripheral and hepatic insulin resistance. Elevated FFA and intracellular lipid appear to inhibit insulin signaling, leading to a reduction in insulin-stimulated muscle glucose transport that may be mediated by a decrease in GLUT-4 translocation. The resulting suppression of muscle glucose transport leads to reduced muscle glycogen synthesis and glycolysis. In the liver, elevated FFA may contribute to hyperglycaemia by antagonizing the effects of insulin on endogenous glucose production.[4]

Role of incretins

Incretins are compounds that potentiate insulin secretion; Glucagon like peptide -1 (GLP-1) is one of these. GLP-1 is secreted by the L-cell of the intestine in response to a meal.[5] It has been shown that GLP-1 secretion is blunted in diabetic or obese patients. In consequence of that also the beta cell function, ie the amount and mode of insulin secreted in response to the meal is inadequate and contribute to excess postprandial hyperglycemia.

Also FFA have *per se* a direct effect on insulin secretion and beta-cell function[6]. Increased plasma FFA levels after 2-4h and 24h of lipid infusion have been shown to enhance both basal and glucose-stimulated insulin secretion. It has been shown that in healthy humans, acute and chronic lipid infusion determines peripheral and hepatic IR, induces hyperinsulinemia by increasing both fasting and glucose-stimulated insulin secretion.[7,8] On the other hand, an overnight reduction of plasma FFA results in improvement of glucose tolerance despite reduction in circulating insulin levels. Thus, excess release of FFA into the circulation, as occurs in obesity or abdominal fat accumulation, has the double effect to promote insulin secretion and insulin resistance.

The loss of first-phase insulin release has adverse metabolic and physiologic consequences, ie hyperglycemia on insulin-producing beta-cells and insulin-sensitive tissues (glucotoxicity), even if the second-phase release is adequate or even excessive. At the same time lipolysis is not inhibited while FFA uptake is promoted, thus resulting in cell lipotoxicity.[9]

In summary

Both insulin resistance and beta-cell dysfunction play a role in the transition from normal glucose tolerance to hyperglycemia. Excess FFA release and lack of inhibition of lipolysis (hyperlipemia) worsen this state.

References

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