Impaired insulin clearance as a cause rather than a consequence of insulin resistance

Impaired insulin sensitivity and reduced β-cell function have been regarded as the two major physiological defects in type 2 diabetes mellitus. It is generally accepted that the initial defect in this disease is insulin resistance, which is typically elicited by overeating and decreased physical activity, both of which are tightly linked with obesity. β-Cells then compensate for insulin resistance by enhancing insulin secretion. However, the various cellular stresses caused by the insulin-resistant state reduce the ability of β-cells to secrete insulin and eventually lead to rising blood glucose levels. Whereas decreased insulin clearance is also observed very early in the development of type 2 diabetes mellitus, this change has generally been regarded as a mechanism for compensating for impaired insulin sensitivity by increasing serum insulin levels.

However, if decreased insulin clearance is a compensatory mechanism for impaired insulin sensitivity, insulin resistance should appear earlier than decreased insulin clearance during the transition from a metabolically normal state to the onset of impaired glucose metabolism. Although no studies have evaluated serial changes in insulin sensitivity and clearance during the development of moderate insulin resistance, cross-sectional data regarding the relationship between insulin resistance and clearance have provided useful information on this issue. Insulin clearance is known to be lower in obese than non-obese individuals; however, it was also found to be lower in metabolically unhealthy obese individuals than those who were healthy. In addition, we recently investigated insulin sensitivity in muscles and liver, and insulin clearance using a two-step hyperinsulinemic euglycemic clamp in healthy, non-obese Japanese men. After dividing these individuals into two groups according to insulin clearance, we investigated the clinical features of the individuals with lower insulin clearance and identified decreased insulin sensitivity in muscles, but not in the liver. Furthermore, in these healthy individuals, decreased insulin clearance was correlated with decreased insulin sensitivity in muscles. These data show that even in a relatively healthy population, there are variations in insulin clearance, and individuals with decreased insulin clearance show moderate insulin resistance. This evidence suggests that reverse dynamics are plausible: impaired insulin clearance could precede and induce insulin resistance. If this is true, then insulin clearance might be genetically defined.

The onset of type 2 diabetes mellitus is highly affected by genetic factors. Genome-wide association studies identified several single nucleotide polymorphisms associated with susceptibility to type 2 diabetes mellitus. One of these is located in an exon of the Slc30A8 gene, which encodes ZnT8. ZnT8 is a Zn transporter that is characteristically expressed in the membranes of insulin-containing granules, and transports Zn from the cytosol to the intragranular space. Zn is essential in the formation of insulin hexamers, which crystallize within the granule lumens because of their low solubility and form the dense-core granules observed in electron microscopy. Mice with β-cell-specific Slc30A8 deficiency show loss of the translucent halo space around the dense cores, suggesting that ZnT8 is essential for the accumulation of Zn in the secretory granules. Indeed, the disruption of Slc30A8 in β-cells resulted in reduced Zn secretion from these cells. Hence, the analysis of mice with β-cell-specific Slc30A8 deficiency revealed roles of β-cell-secreted Zn. Consequently, we found at least two roles of the Zn in blood insulin levels. First, these mice showed enhanced insulin secretion, probably as a result of mitigation of the activating effect of Zn on adenosine triphosphate-sensitive potassium channels. Second, these mice showed enhanced insulin clearance, because Zn inhibits insulin clearance in the liver. The findings of enhanced insulin secretion and clearance in mice with β-cell-specific Slc30A8 deficiency are the opposite of those in humans with a high susceptibility to type 2 diabetes mellitus. Indeed, individuals with loss-of-function mutations in ZnT8 were protected against the onset of type 2 diabetes mellitus. Although the mechanism of this phenomenon is still unknown, these results suggest that a genetic factor related to insulin clearance could contribute to the susceptibility to type 2 diabetes mellitus.

Insulin enhances glucose uptake in muscles and suppresses gluconeogenesis in the liver to reduce blood glucose levels. Also, insulin enhances fat storage in adipose tissues and the liver, but chronic accumulation of fat in these locations impairs the ability of insulin to lower blood glucose levels. A specific feature of metabolically abnormal individuals is selective insulin resistance, characterized by resistance to insulin-mediated glucose uptake in muscles and suppression of gluconeogenesis, but not to enhanced fat storage in adipose tissues and the liver. The accumulated evidence suggests that sustained hyperinsulinemia reduces the expression of insulin receptor substrate (IRS)-2, but not IRS-1. Accordingly, hyperinsulinemia induces resistance to insulin effects that are highly dependent on IRS-2, such as increasing glucose uptake in muscles via enhanced transporta-
clearance could cause selective insulin resistance through hyperinsulinemia. Supporting evidence for this model exists in the case of decreased carcinoembryonic antigen-related cell adhesion molecule (CEACAM)-1 function. On its phosphorylation, CEACAM-1 promotes the receptor-mediated uptake of insulin in the liver, and thus plays a key role in regulating liver insulin clearance. Although CEACAM-1 might have other effects, the inactivation of CEACAM-1 in mice causes not only reduced insulin clearance with hyperinsulinemia, but also insulin resistance.

If this model is applicable to the general human population, there could be at least two major etiologies for selective insulin resistance: (i) obesity; and (ii) impaired insulin clearance (Figure 1). Theoretically, individuals with insulin resistance as a result of impaired insulin clearance would be less obese than those with insulin resistance as a result of obesity. This pattern can be seen in Asian people with insulin resistance. In particular, South Asian people are known to be susceptible to developing insulin resistance with less obesity.

In summary, the accumulated evidence suggests that impaired insulin clearance and obesity could be two major and independent causes of insulin resistance. Both of these probably contribute to insulin resistance in most individuals, but the degree of each contribution is highly variable. However, it is possible that in typical Asians, impaired insulin clearance might play a more important role than in Caucasians. Confirming this hypothesis could provide important clues regarding the pathophysiology of type 2 diabetes mellitus.

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DISCLOSURE
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