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Activation of glucose transporter type 2 isoform transcription by PPARγ may contribute to glucose disposal in the hyperglycemia caused by type 2 diabetes

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The principal pathology in the type 2 diabetes may be insulin resistance. This metabolic disorder includes impaired glucose tolerance, dyslipidemia, vascular disorders, and impaired insulin secretion. Of these, glucose intolerance may be arisen from impaired glucose transport into muscle/fat or inappropriate glucose disposal in the liver. In the muscle/adipocyte, glucose transporter type 4 isoform (GLUT4) plays major role, whereas type 2 isoform of glucose transporter (GLUT2) is predominant form in the liver. Thus, the major strategies to control blood glucose level in the management of type 2 diabetes have been focused on normalizing or activating the GLUT4 in the muscle/adipocyte or the GLUT2 in the liver.

Recently, peroxisomal proliferator activator receptor γ (PPARγ) agonists, thiazolidinediones (TZDs) have been drawn much attentions. These drugs act as ligands for the nuclear receptor PPARg and enhance the sensitivity of skeletal muclse, adipose tissue, liver, and pancreatic b-cells. In addition to their effects on blood glucose regulation, they have known to improve the syndromes associated with insulin resistance. Currently, studies on the mechanisms how glucose could be disposed in the muscle/adipcoytes have been reported by many investigators, mostly emphasizing in terms of GLUT4 translocation or transcriptional control in those tissues. However, in spite of its important role in the blood glucose regulation, the effect of TZDs on the liver is not well understood to date.

GLUT2, which is also known as liver/pancreas type glucose transporter isoform, could be a target of TZDs action, if the drugs sensitize the liver to control blood glucose level. Together with glucokinase, GLUT2 is also known as glucose sensor. From this

background, we were able to localize peroxisomal proliferator-activator response element (PPRE) in the promoter regions of rat GLUT2 and glucokinase gene and reported their physiological implications in the insulin secretion in response to changing blood glucose level in type 2 diabetic Zucker diabetic fatty (ZDF) rats.

To understand how liver plays a role in controlling blood glucose level by trglitazone (TGZ), one of TZDs, we have cloned mouse GLUT2 promoter (GenBank accession number AY064392) by polymerase chain reaction (PCR) and dissected the promoter region to localize TZD responsive element. Through this study, we were able to localize the PPRE in the -197/-184 region of mouse GLUT2 promoter and characterized the cis-element in detail.