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Small fragment (GSP) derived from intestinal harmone glucose-dependent insulinotropic polypeptide (GIP) improves glucose transport and exerts beneficial lipid metabolic effects in 3T3-L1 adipoctyes

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The epidemic of type 2 diabetes and impaired glucose tolerance is one of the main causes of morbidity and mortality worldwide. In this disorder, tissues such as muscle, fat and liver become less responsive or resistant to insulin. The present work was undertaken to investigate the effects and the molecular mechanism of a fragment derived from Glucose-dependent insulinotropic polypeptide (GIP) on the glucose transport for controlling diabetes mellitus. Small fragment of peptide derived from GIP, named as GSP. GSP stimulates glucose uptake by the rat skeletal muscle cells (L6myotubes). This effect was shown to be mediated by the increased translocation of glucose transporter type4 (GLUT4) protein from the cytoplasm to the plasma membrane as well as the synthesis of GLUT4 protein. The effect of GSP on glucose transport was stymied by wortmannin, HNMP-(AM)^3, AI½ and indinavir. In vitro phosphorylation analysis revealed that, like insulin, GSP also enhances the tyrosine phosphorylation of the insulin receptor-β, insulin receptor substrate-1, and the serine phosphorylation of Akt under both basal and insulin-stimulated conditions without affecting the total amount of these proteins. To determine the exact site of action and binding of GSP we performed si-RNA based knockdown assay and found out that knockdown of Insulin receptor-alpha subunit gene stymied the effect of GSP on glucose uptake by rat skeletal muscle cells (L6 myotubes). GSP also increases the tyrosine phosphorylation of both IR-β and IRS-1, and the IRS-1 associated PI-3 kinase activity in TNF-α-treated L6 myotubes (insulin resistance model). In-vivo activity of GSP also showed significant decrease in glucose intolerance in db/db mice by oral glucose tolerance test (OGTT). Apart from its anti-hyperglyceimic activity GSP also showed beneficial lipid metabolic effect by inhibhiting the lipid globules formation in mouse 3T3-L1 adipocytes. To determine the interacting proteins associated with activation of insulin signalling pathway by GSP, we will plan to do pulldown assay. We also do RAC-1 assay to find out the role of small GTPase protein in phosphorylation of the said proteins. Taken together, these findings provide ample evidence that the small peptide derived from glucose dependent insulin tropic polypeptide (GSP) stimulates glucose transporter typ 4 translocation-mediated glucose uptake by the activation of the phosphatidylinositol- 4,5-bisphosphate 3-kinase/Akt dependent pathway and hence showed anti-diabetic/antihyperglyceimic activity and also have lipid lowering effect.

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