Insulin receptor binding motif tagged with IgG4 Fc (Yiminsu) works as an insulin sensitizer to activate Akt signaling in hepatocytes

J. Wang1,2, T. Zou3, H.X. Yang1,2, Y.Z. Gong4, X.J. Xie4, H.Y. Liu5* and D.F. Liao4*

1Institute of Cardiovascular Research, Key Laboratory for Atherosclerology of Hunan Province, University of South China, Hengyang, Hunan, China
2School of Public Health, University of South China, Hengyang, Hunan, China
3Department of Cardiovascular Medicine, First Affiliated Hospital of the University of South China, Hengyang, Hunan, China
4Division of Stem Cell Regulation and Application, State Key Laboratory of Chinese Medicine Powder and Medicine Innovation in Hunan (Incubation), Hunan University of Chinese Medicine, Changsha, Hunan, China
5Metammune LLC and Moldepot Inc., Morrisville, NC, USA

*These authors contributed equally to this study.
Corresponding authors: H.Y. Liu / D.F. Liao
E-mail: dkbio@qq.com / dfliao66@aliyun.com

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ABSTRACT. Insulin resistance is a key feature of obesity and type 2 diabetes mellitus (T2DM). Interaction of insulin with the insulin receptor (IR) leads to both its auto-phosphorylation and phosphorylation of tyrosine residues on the IR substrate (IRS) proteins, initiating the activation of intracellular signaling cascades. The metabolic effects of IRS are known to be mediated through pathways involving phosphatidyl-
inositol 3-kinase (PI-3K), which result in the activation of Akt signaling. The C-terminal region of the IR ectodomain is required to facilitate the conformational changes that are required for high-affinity binding to insulin. Furthermore, the CH2 and CH3 domains in the Fc fragments of immunoglobulins are responsible for their binding to the Fc receptor, which triggers transcytosis. In this study, we created a fusion peptide of the C-terminal end of the human IR ectodomain with the IgG4 Fc fragment, including an intervening polyG fragment to ensure enough space for insulin binding. We named this new peptide “Yiminsu”, meaning an insulin sensitizer. The results of our analyses show that Yiminsu significantly facilitates insulin signaling via the activation of Akt in hepatocytes in a dose- and time-dependent manner. Further studies are required to determine whether Yiminsu can act as an insulin sensitizer.

Key words: Yiminsu; Insulin sensitizer; Type 2 diabetes; IgG4 Fc