S32-3 Generation of Novel Long-acting Glucagon-like Peptide 1Mimetics by Sugar Modification

◯Kohji HANASAKI[1], Kenji ASAKURA[1], Kazuyoshi TOMITA[1], Taichi UEDA[1], Takeo OSHIMA[1], Takanori IWASAKI[1], Takaomi ITO[1], Hirofumi NAGATOME[1], Akio TAKIMOTO[1], ShinIchi MIHARA[1], Hiroko TOGAME[1], ShinIchiro NISHIMURA[2], Hirosato KONDO[1]

[1]Shionogi & Co. Ltd. Shionogi Res. Lab., [2]Hokkaido Univ. Grad. Sch. of Adv. Life Sci.

【Aim】As shown in the studies of erythropoietin, glycosylation affects on the metabolism and physical properties of proteins/peptides. Therefore, introduction of specific sugars into appropriate position of known biologics may lead to novel types of bio-drugs with improved characteristics. In the present study, we examined the effects of glycosylation of postprandial gastrointestinal peptide, glucagon-like peptide 1 (GLP-1), on its pharmacological activity. Although GLP-1 is expected as an anti-diabetic agent, it is rapidly degraded by dipeptidyl peptidase IV (DPP-IV) resulting in its plasma instability. 【Methods】Various types of glycosylated GLP-1, such as GlcNAc-, LacNAc- and Sialyl LacNAc-modified GLP-1, were synthesized by chemical and enzymatic modifications. 【Results】Glycosylation of GLP-1 resulted in significant increase in stability against the degradation by DPP-IV with sufficient receptor-binding property and functional agonistic activity. Interestingly, the biological properties of glycosylated GLP-1 extremely varied according to the conditions of glyco-modification (e.g. types of sugar-chain, the position and number of glycosylation etc.). In *db/db* mice, glycosylated GLP-1 exerted significantly prolonged (e.g. 0.5 h vs. 6 h for control and glycosylated GLP-1, respectively) and approximately 100-fold potent glucose-lowering effect compared with native GLP-1. 【Conclusion】Glycosylated GLP-1 exerted improved biological stability and prolonged and potent glucose-lowering effect *in vivo* and might be suitable for the next generation of the incretin mimetics.