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DA-1241, a novel GPR119 Agonist, Improves Hyperglycaemia via Inhibition of Hepatic Gluconeogenesis and Enhancing Glucose Stimulated Insulin Secretion via Stimulation of GLP-1 Secretion

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Objective: Unlike other G protein-coupled receptor (GPR) 119 agonists, DA-1241 has shown long-term beneficial effects on glucose and lipid metabolism in previous studies. We examined the antidiabetic effects of DA-1241 in vitro and in vivo. We investigated the effects of DA-1241 on insulin secretion from pancreatic β-cells, serum glucagon-like peptide-1 (GLP-1) levels, gluconeogenesis and hepatic autophagy. In addition, we evaluated the effects of DA-1241 on fatty liver disease and lipid profile.

Methods:

The effects of DA-1241 on gluconeogenic enzyme expression and autophagic flow were evaluated in HepG2 cells and livers isolated from LC3-GFP-transgenic mice. DA-1241 was administered to high-fat diet (HFD)-fed C57BL/6J mice for 12 weeks, and serum insulin and GLP-1 levels were measured by oral glucose tolerance tests at week 8.

Results:

DA-1241 reduced gluconeogenic enzyme expression in HepG2 cells. DA-1241 initially induced autophagic activation then blocked autophagic flow in HepG2 cells and livers from LC3-GFP mice. DA-1241 improved glucose tolerance with an increased serum GLP-1 and insulin levels. However, intraperitoneal glucose tolerance

and insulin tolerance tests were not improved with DA-1241 treatment. In line with the results of diminished lipid accumulation, DA-1241 significantly reduced hepatic triglyceride contents.

Conclusion: DA-1241 resulted in improved glycaemic control by increasing glucose-dependent insulin release via improvement of GLP-1 secretion and reduced hepatic gluconeogenesis, which might be associated with autophagic blockade. Chronic administration of DA-1241 attenuated lipid accumulation and reduced hepatic TG contents, which might be related to SREBP-1C-mediated lipogenic enzyme inhibition.

Key Words: DA-1241, GPR119 agonist, GLP-1, gluconeogenesis, autophagy