Yi Huan et al., J Diabetes Metab 2018, Volume 9
DOI: 10.4172/2155-6156-C4-087

27th European Diabetes Congress

June 20-21, 2018 | Rome, Italy

A discovery of GPR119/DPP4 dual-target compounds as anti-diabetic candidates

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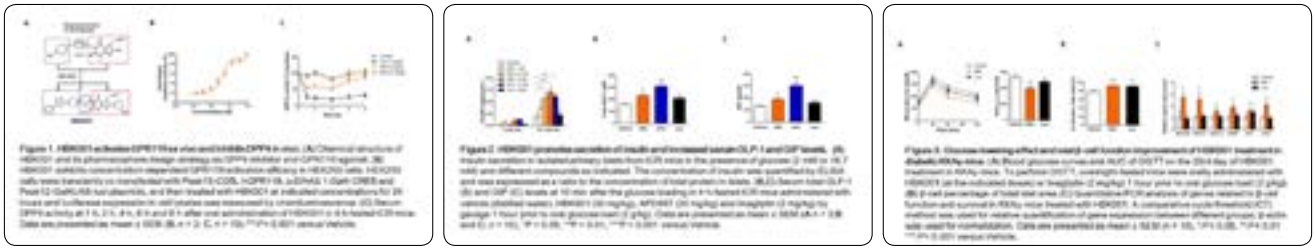
Glucagon like peptide-1 (GLP-1) plays a vital role in glucose homeostasis and sustaining β-cell function. Currently there are two major methods to enhance endogenous GLP-1 activity; inhibiting dipeptidyl peptidase-4 (DPP4) or activating G protein-coupled receptor 119 (GPR119). Here we designed and synthesized a series of xanthine derivatives as potent dual ligands targeting DPP-IV and GPR119 through an approach of the merged pharmacophores of GPR119 agonists and DPP-IV inhibitor linagliptin. Among these derivatives, we validate a compound, HBK001 which can both inhibit DPP4 and activate GPR119 *ex* and *in vivo*. We show that HBK001 can promote glucose-stimulated insulin secretion in mouse primary islets in a concentration-dependent manner. A single administration of HBK001 in ICR mice can increase plasma incretins (GLP-1 and GIP) levels much more efficiently than DPP4 inhibitor linagliptin. Long-term treatment of HBK001 in KKAy mice can ameliorate hyperglycemia as well as improve glucose tolerance, while linagliptin fails to achieve such glucose-lowing effects despite inhibiting 95% of serum DPP4 activity. Furthermore, HBK001 can improve islet morphology in diabetic KKAy mice, increase β-cell mass by promoting proliferation and up-regulating genes involved in β-cell proliferation and function. Thus, we have identified, designed and synthesized a novel GPR119/DPP4 dual-target compound, HBK001, which represents a promising therapeutic candidate for type 2 diabetes, especially for patients who are insensitive to current DPP4 inhibitors..



Recent Publications

1. Huan Y, Jiang Q, Li G, Bai G, Zhou T, Liu S, Li C, Liu Q, Sun S, Yang M, Guo N, Wang X, Wang S, Liu Y, Wang G, Huang H and Shen Z (2017) The dual DPP4 inhibitor and GPR119 agonist HBK001 regulates glycemic control and beta cell function ex and *in vivo*. Sci Rep. 7(1):4351.
2. Gang Li, Yi Huan, Baokun Yuan, Jin Wang, Qian Jiang, Ziyun Lin, Zhufang Shen and Haihong Huang (2016) Discovery of novel xanthine compounds targeting DPP-IV and GPR119 as anti-diabetic agents. European Journal of Medicinal Chemistry 124:103-116.

Biography

Yi Huan has her expertise in discovery and development of novel anti-diabetic drugs. She established a variety of pharmacological methods and technologies to screen compounds, evaluate the activities of anti-diabetic agents. Now she is focusing on the discovery of novel anti-diabetic candidates, such as SGLT2 inhibitors, GPR119/40/120 agonists, FXR agonists and selective PPAR activators. Some of the anti-diabetic candidates she found have been developed into pre-clinical research up to date. She is interested in pharmacological mechanism research and devotes into elucidation of the anti-diabetic effect of new drugs.

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