Acta Pharmaceutica Sinica B 2025;15(1):667−668

Chinese Pharmaceutical Association
Institute of Materia Medica, Chinese Academy of Medical Sciences

Acta Pharmaceutica Sinica B

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EDITORIAL

The homotherapy for heteropathy: GCGR/GLP1R pathway in fibrotic diseases

Peptide hormones act through its receptors to regulate a various of physiological processes, including energy metabolism, growth and sleep. The famous helical peptides with important role in maintaining energy metabolic balance are glucagon (GCG) and glucagon-like peptide-1 (GLP1), which bind to and activate their receptor the G-protein-coupled receptors (GPCR) GCGR and GLP1R, respectively to regulate blood sugar, food intake and finally body weight. GCG is a gastrointestinal hormone produced in the pancreas, mainly acting opposite to insulin. In response to fasting or acute hypoglycemia, it increases blood glucose by stimulating hepatic gluconeogenesis and glycogen breakdown[1]. Meanwhile, GCG can affect the energy metabolism and thermogenesis processes of the body[2]. Studies have shown that exogenous administration of GCG can reduce hepatic triglyceride synthesis and promote hepatic lipolysis[3]. GLP1 is a hormone primarily produced by intestinal L cells, it binds to its receptor GLP1R expressed mainly on pancreas to enhance insulin secretion in a glucose concentration dependent manner, inhibiting glucagon secretion, and delaying gastric emptying and reduce food intake through central appetite suppression. Thereby, activation of GLP1-GLP1R achieves effects such as lowering blood sugar and weight loss[4,5]. The two signaling pathways have opposite effects on blood glucose, so it seems to be confusing that why we combine these dual receptor agonists of GCGR/GLP1R together in some diseases.

Compared with co administration of a single agonist, single molecule multi receptor agonists have the advantages of maximizing therapeutic efficacy, reducing side effects, and more stable pharmacokinetic properties due to the simultaneous activation of different signaling pathways. Therefore, single molecule with multi receptor agonists based on GLP1R are expected to integrate the beneficial effects of several gastrointestinal hormones into the same molecule to improve metabolic disorders and related diseases. The dual receptor agonists of GCGR/GLP1R combine the thermogenic and lipolytic effects of GCG with the delayed gastric emptying effect of GLP1 to produce significant weight reduction, and weaken the hyperglycemic effect of GCG through the insulinotropic effect of GLP1, thereby effectively controlling blood glucose. GCGR and GLP1R signaling pathway has its irrefutable role in many diseases including type 2 diabetes, obesity and non-alcoholic steatohepatitis[4,6,7]. Besides, dual activation of GCGR/GLP1R by their dual target agonist has a role in fibrosis[8]. Hence, there is a rising question: why targeting activation of the same GCGR/GLP1R signaling could treat different diseases, known as the homotherapy for heteropathy?

Recently, Liu et al.[9] now revealed an additional dimension of the GCGR/GLP1R co-agonist peptide, 1907B, which exerted anti-intestinal fibrosis effect through inhibiting glycolysis-driven histone lactylation to decrease the H3K9 lactylation in epithelial cells and ameliorated epithelial-to-mesenchymal transition. In this study, the authors first found the downregulation of both GCGR and GLP1R in the stenotic ileum of patients and in the fibrotic colon of mice with DSS-induced colitis. The key cytokine TGFβ1 in inflammatory and fibrotic intestine led to decreased expression of GCGR and GLP1R, which disrupted the energy metabolism in epithelial cells to glycolysis. As a product of glycolysis, increased lactate promoted the histone H3K9 lactylation on Vimentin, *Tgfb* and other profibrotic genes, which mediated the EMT process of intestinal fibrosis. This mechanism shed light on the role of epigenetic change in intestinal fibrosis.

Interestingly, as a good example of homotherapy for heteropathy, the same team had published two papers titled with *Design of a highly potent GLP1R and GCGR dual-agonist for recovering hepatic fibrosis* and *Design and discovery of a highly potent ultralong-acting GLP-1 and glucagon co-agonist for attenuating renal fibrosis* in *Acta Pharm Sin B* before[10,11]. The findings of GLP1R and GCGR dual-agonist in hepatic fibrosis were consistent with other reports that another GLP1R and GCGR dual-agonist, TB001, attenuated liver fibrosis through decreasing extracellular matrix accumulation during hepatic injury, inhibiting activation of hepatic stellate cells *via* suppression of TGF-β/Smad in CCl_4-and *S. japonicum*-induced liver fibrosis and blocking pro-inflammatory NF-κB−IKBα/JNK signaling axis. As for the function of the GLP-1R and GCGR dual-agonist, 1907B, in attenuating renal fibrosis, 1907B reduced kidney inflammation and fibrosis *via* multiple mechanisms. First, it protected kidney against inflammation through inhibiting IKBα−NF-

Peer review under the responsibility of Chinese Pharmaceutical Association and Institute of Materia Medica, Chinese Academy of Medical Sciences.

https://doi.org/10.1016/j.apsb.2025.01.012

κB and TGF-β1−Smad signaling pathways. Besides, 1907B attenuated kidney oxidative stress, increased the expression of antioxidant factors *via* GLP-1 signaling and mitochondrial turnover *via* glucagon signaling, which both improve mitochondrial function and energy metabolism.

Taken these three works by the team of Prof. Jiang together, it is not difficult to find that the key nodes of GLP1R and GCGR dual-agonist in three different fibrosis diseases includes TGFβ signaling, pro-inflammatory signaling and the regulation of energy balance through glycolysis, mitochondrial homeostasis. So, the three same key nodes in various fibrosis diseases may be the reasons of why dual-activation of GCGR/GLP1R signaling exerts therapeutic effect in different fibrosis diseases. Furthermore, because the clinical trials of many GCGR/GLP1R co-agonists including 1907B are in different stage for the treatment of diabetes, obesity, hyperuricemia, cirrhosis, liver fibrosis and nonalcoholic steatohepatitis, the safety of the agonists in human is verified. Therefore, GCGR/GLP1R co-agonist is a promising drug candidate in future clinical use of various fibrosis diseases.

All these studies by the team of Prof. Jiang opens a new avenue of the application of GCGR/GLP1R co-agonist in a chronic metabolism-associated inflammatory diseases including fibrosis diseases, which is a typical example of the homotherapy for heteropathy.

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