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Small molecule allosteric agonists of glucagon-like peptide 1 receptor for treatment of type 2 diabetes

Lead University of the Sciences Inventor

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Unmet Need

Over the past 40 years, the number of overweight people world-wide has increased six-fold; this disturbing trend is projected to continue in the foreseen future. Obesity can cause a number of health problems including cardiovascular diseases and diabetes, with type-2 diabetes representing 90 - 95% of diabetes patients.

The Glucagon-Like Peptide 1 Receptor (GLP-1R), a member of Class B family of G-protein coupled receptors (GPCRs), is an effective target for the treatment of type-2 diabetes, and its incretin peptide and varied peptide mimetics are adopted drugs. Despite remarkable anti-diabetic effects, GLP-1R peptide-based agonists are limited by several disadvantages. They are available only as an injection, they lack effective long-term glucose control capability, and they can cause serious side effects such as nausea and vomiting in some patients. Conversely, although considerable progress has been made in developing small molecule, nonpeptide drugs targeting GLP-1R, no small molecule drugs are available currently.

Therefore, novel approaches in developing small molecule drugs targeting GLP-1R are needed in the treatment of type-2 diabetes.

Opportunity

Given the allosteric nature of GPCRs, targeting the allosteric sites on GPCRs for small molecule therapeutic intervention represents an alternative and promising approach for drug discovery. Compared to ligands acting at orthosteric sites, allosteric ligands demonstrate several potential benefits. For example, allosteric agonists may benefit the development of orally delivered GLP-1 analogs. Limited bioavailability is a big obstacle of oral peptide drug delivery. Without increasing bioavailability, allosteric agonists can augment the efficacy of endogenous and exogenous GLP-1 and its analogs. Hence, targeting the allosteric sites of GLP-1R for small molecule drug discovery represents a promising alternative for overcoming shortcomings related to GLP-1R peptide-based treatment.

Unique Attributes

For Class B GPCRs, the allosteric binding sites are found either at the intracellular loop region or inside the transmembrane (TM) domain. However, until last year, the effort of targeting these allosteric sites for small-molecule drug discovery was hindered by the lack of TM structure of GLP-1R.

The USciences team carried out structure-based molecule design studies by first constructing a 3D structural model of the TM domain of GLP-1R in its active conformation. In silico screenings of commercially-available, drug-like compounds against the allosteric site on this TM domain, as well as on the ECD domain of GLP-1R have identified two compounds as potential GLP-1R PAM-agonist. Their agonistic and modulating activities were subsequently confirmed using a cAMP response element (CRE)-based reporting system and another assay.

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Based on these results, we believe that these compounds can be exploited for developing small molecule drugs targeting GLP-1R for the treatment of diabetes. This novel and successful approach can also be applied to design and screen other essential GPCR protein allosteric agonist or antagonist for cardiovascular and immune diseases.

Clinical Applications

With further development, for treatment of type-2 diabetes.

Stage of Development

Preclinical Studies.

Intellectual Property

Provisional patent in force.

Collaboration Opportunity

Actively seeking licensee for commercialization or collaboration to complete preclinical studies.

References and Publications

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