G-PROTEIN-COUPLED RECEPTORS

New switch to activate class B GPCRs

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The glucagon-like peptide 1 (GLP1) receptor belongs to a group of G-protein-coupled receptors (GPCRs) that is difficult to target with small-molecule drugs. Now, Bjerre-Knudsen and colleagues have identified a small-molecule agonist of the GLP1 receptor that stimulates glucose-dependent insulin release, which could aid the search for orally active GLP1 agonists for the treatment of diabetes.

GLP1 potentiates insulin secretion in response to food intake, and also has actions that can reduce weight, and so has attracted considerable interest as a potential anti-diabetic agent. However, GLP1 is rapidly degraded *in vivo*, which limits its therapeutic application. Degradation-resistant peptide agonists of GLP1 have been developed, including exenatide (Byetta; Amylin, Eli Lilly), which was approved for the treatment of diabetes in 2005. However, exenatide needs to be administered by injection and so orally available GLP1 agonists would therefore be desirable.

In a step towards this goal, the authors identified several small-molecule agonists of the GLP1 receptor using competition binding assays and functional cyclic AMP (cAMP) screens. Interestingly, compounds were not antagonized by the selective GLP1-receptor antagonist exendin, which binds to the peptide-binding site on the receptor. Furthermore, the agonists augmented the binding of the endogenous ligand GLP1 to the receptor in a concentration-dependent manner. Although the most potent of these compounds displayed bell-shaped concentration-response curves in cAMP assays, the inhibitory effect of the agonists at high concentrations was shown to be nonspecific.

The pharmacological properties of these GLP1 agonists were further investigated with the most potent compound identified, known as compound 2. In binding assays, there was an apparent increase in the affinity of GLP1 for its receptor in the presence of the compound, but this was not accompanied by an increase in efficacy or potency of GLP1 in the presence of compound 2 in functional cAMP assays. The lack of competition of compound 2 with GLP1 is consistent with the existence of an allosteric binding site for the compound on the GLP1 receptor. This, combined with the observation that compound 2 is also an agonist, suggests that it could act as an ago-allosteric modulator, a newly described group of agonists with a novel mechanism of action.

Next, the authors examined the effect of compound 2 on insulin release. Compound 2 potentiated glucose-induced insulin release from islets isolated from wild-type mice but not those from GLP1-receptor-deficient mice. Similar to GLP1, compound 2 was strongly glucose-dependent in its potentiation of insulin secretion, with neither GLP1 nor compound 2 influencing insulin release at low glucose concentrations.

In studies using the perfused rat pancreas, compound 2 potentiated glucose-induced insulin release, and again a higher stimulation of insulin secretion was observed at higher glucose concentrations.

Although this study did not result in the identification of potent drug-like compounds, it could aid the search for small-molecule GLP1 receptor agonists. Furthermore, it provides encouragement for efforts to identify small-molecule modulators of other potential drug targets in the same family of GPCRs as GLP1.

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ORIGINAL RESEARCH PAPER Bjerre-Knudsen, L. B. *et al.* Small-molecule agonists for the glucagon-like peptide 1 receptor. *Proc. Natl Acad. Sci. USA* **104**, 937–942 (2007)