Pharmacokinetics and Pharmacodynamics of GLP-1-GIP Receptor Dual Agonist Peptides: From Once-Daily to Once-Weekly

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Background

Glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP) are two major hormones that are released from the intestinal tract in response to food intake. Both hormones stimulate glucose-dependent insulin secretion. Analogs of the insulin hormone GLP-1 are being used for the management of type 2 diabetes and are often accompanied by modest weight loss. Evidence from animal studies suggests that anti-obesity efficacy of GLP-1 can be enhanced by co-administration with the incretin hormone GIP.

We here present data for novel balanced GLP-1/GIP receptor dual agonist DIs with varied pharmacokinetic properties. The pharmacodynamic effects of the DIs were characterized in normal, diabetic, and diet-induced obese mice.

The designed compounds are full dual agonists with EC₅₀ values of 4-35 pM and 11-40 PM for the GLP-1 and GIP receptors, respectively (Table 1).

By adjusting the linker, the length of fatty acid chain, functional group at the end of the fatty acid chain and a limited number of amino acids in the peptide sequence, it was possible to vary the terminal half-lives of the DI compounds in mice from 2 to 20 hours (after s.c. administration).

The acute effects of dual agonists on glucose tolerance in normal and diabetic mice

Selected DIs with extended half-lives were evaluated for their acute effects in intraperitoneal glucose tolerance tests (IPGTT) in normal and diabetic db/db mice. Most of the DIs dose-dependently and significantly improved glucose tolerance in both mouse models when compared to vehicle. The DIs affected glucose tolerance 22 h after s.c. injection which is in accordance with their long systemic half-lives in mice.

Conclusions

Co-activation of GLP-1 and GIP receptors are considered as a promising new strategy for the treatment of obesity type 2 diabetic patients. The presented pharmacokinetic and pharmacodynamic results demonstrate the possibility to prolong the activity of GLP-1/GIP dual agonists. The data show promise for the future development of a possible once-weekly GLP-1/GIP agonist drug candidate for the treatment of type 2 diabetes.