The Molecular Basis for the Delayed Absorption of the Once-Daily Human GLP-1 Analogue, Liraglutide

Abstract

Background and aims: The human GLP-1 analogue liraglutide is designed for once-daily administration. Liraglutide is a long acting GLP-1 analogue with a single (C14 fatty acid) attached. Liraglutide has a much prolonged half-life and action compared to endogenous GLP-1. The actions of Liraglutide include increased satiety and decreased food intake and reduced modelled subcutaneous liraglutide for the prolonged plasma half-life, while self association has been speculated to be the main mechanisms behind the delayed absorption, which is allosterically different from GLP-1 (1-37; 10–12; 11–13; 12–11). In addition, the prolonged plasma half-life of liraglutide and the self-associated properties of liraglutide has made the product suitable for once-daily self-administration.

Introduction

The incretin hormone GLP-1 has physiological properties well suited for treating type 2 diabetes; however, native GLP-1 is inappropriate for exogenous therapy due to its very short half-life (1–2 minutes, in vivo administration), caused by rapid degradation by the DPP-IV enzyme and clearance by the kidney.

Liraglutide, an analog of human GLP-1 in clinical development, has 97% amino acid sequence identity to GLP-1, but it is acylated with a hexadecanoyl-glutamyl side chain on lysine at position 26 (Figure 1). Its half-life in human plasma following intravenous administration and 13 hours following subcutaneous administration. Therefore, subcutaneous injection is 10–12 hours (at 1 hour for native GLP-1).

The prolonged plasma half-life of liraglutide is due to reversible albumin binding and resistance to DPP-IV. The prolonged subcutaneous absorption involves self-association.

This study investigate liraglutide self association and evaluates the influence of its side chain by comparison to the non-acylated precursor molecule, 34R,GLP-1(7-37). Self-association may have important implications for stability and RPRD properties. The authors determined the molecular mass observed in plasma, binding to human serum albumin and the non-acylated precursor 34R,GLP-1(7-37) provided further evidence on the oligomeric status of the hormone. The authors use analytical ultracentrifugation and circular dichroism and circular dichroism spectroscopy, 1H NMR, and analytical ultracentrifugation technique were used to study oligomer size and conformation of the oligomers present in solution. These data provide extensive insights into the molecular basis for the delayed absorption of liraglutide within the clinical timeframes as defined by the Food and Drug Administration (FDA).

Methods

Circular dichroism spectroscopy, 1H NMR, and analytical ultracentrifugation technique were used to study oligomer size and conformation of the oligomers present in solution. These data provide extensive insights into the molecular basis for the delayed absorption of liraglutide within the clinical timeframes as defined by the FDA.

Conclusions

Liraglutide remained in a predominantly self-associated state in concentrations ranging from 0.001–1.2 mM, whereas GLP-1(7-37) was monomeric at µM concentrations.

The difference is attributed to the liraglutide fatty acid side chain and its hydrophobic interactions being much stronger than peptide-peptide interactions of 34R,GLP-1(7-37).

The tendency to form strongly self-associated oligomers is probably important for the protracted absorption of liraglutide after subcutaneous injection. Previous reports of acylated insulin and GLP-1 analogs suggest that both allomeric binding and peptide self-association at the injection site contribute to prolonged absorption; however, the oligomer size for liraglutide and its propensity to stay self-associated to sub-µM concentrations appear to be the most important factors in the mechanism of prolongation.

This property is unique for the acylated GLP-1 analog liraglutide, and results in PK profiles not only directly dependent on viscosity but also suitable for administration using needle sizes as small as 31G.

References