Glucose Responsive Insulin: An Unprecedented Cleavable Linker Concept

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INTRODUCTION

Achieving the optimal combination of multiple glucose measurements and insulin injections provides a complex daily situation for most insulin-dependent diabetes patients with currently available insulin products. To date, several fast-acting and long-acting insulins have been developed. However, while the pharmacokinetic profiles have been optimized, it has remained an elusive goal for decades to develop a Glucose Responsive Insulin (GRI), which can be responsive to the fluctuations in blood glucose concentrations during the day. Here we present an unprecedented GRI concept.

CONCEPT

The concept is based on the hydrolysis of a cleavable Linker that is covalently bound to insulin. The chemical nature of this central Linker is designed to rapidly release active insulin when glucose rises above euglycemia, and this release of active insulin will increase with increasing blood glucose concentration. The second element of the concept is an albumin-mediated inactivation of the GRI by lipolysis. After injection, the GRI will bind to albumin and circulate as a depot, resulting in a slow release of insulin like seen with other basal insulins such as insulin Detemir.

RESULTS

Non-cellular glucose testing of linkers

Figure 3 | Linkers were incubated with glucose at different equivalents or without glucose. The remaining substrate was quantified at different time points by UPLC and the half-life was calculated. Examples of a glucose-responsive Linker (left panel) and non-responsive Linker (right panel) are shown.

In vivo efficacy of GRIs

Figure 4 | GUB130164 was incubated at a range of glucose (left panel) and/or compounds (right panel) concentrations for 24 hours before added to CHO cells overexpressing the human insulin receptor (CHO-IR). Phosphorylated Akt (pAkt) was quantified by ELISA as potency read-out, n=3.

CONCLUSIONS

We present a novel linker-based GRI concept and demonstrate the feasibility of a GRI approach that combines the properties of a both basal and bolus insulin. Specifically, we have:

○ Demonstrated glucose response on Linkers and full GRIs
○ Validated glyceroldehyde as a valuable screening tool in vitro
○ Addressed the importance of the level of equivalents
○ Demonstrated significant and prolonged glucose lowering effects in a Pa rat model of Type 1 diabetes