A Feasibility Study of Bihormonal Closed-Loop Blood Glucose Control Using Dual Subcutaneous Infusion of Insulin and Glucagon in Ambulatory Diabetic Swine

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Abstract

Background:

We sought to test the feasibility and efficacy of bihormonal closed-loop blood glucose (BG) control that utilizes subcutaneous (SC) infusion of insulin and glucagon, a model-predictive control algorithm for determining insulin dosing, and a proportional-derivative control algorithm for determining glucagon dosing.

Methods:

Thirteen closed-loop experiments (~7–27 h in length) were conducted in six ambulatory diabetic pigs weighing 26–50 kg. In all experiments, venous BG was sampled through a central line in the vena cava. Efficacy was evaluated in terms of the controller's ability to regulate BG in response to large meal disturbances (~5 g of carbohydrate per kilogram of body mass per meal) based only on regular frequent venous BG sampling and requiring only the subject's weight for initialization.

Results:

Closed-loop results demonstrated successful BG regulation to normoglycemic range, with average insulin-to-carbohydrate ratios between ~1:20 and 1:40 U/g. The total insulin bolus doses averaged ~6 U for a meal containing ~6 g per kilogram body mass. Mean BG values in two 24 h experiments were ~142 and ~155 mg/dl, with the total daily dose (TDD) of insulin being ~0.8–1.0 U per kilogram of body mass and the TDD of glucagon being ~0.02–0.05 mg. Results also affirmed the efficacy of SC doses of glucagon in staving off episodic hypoglycemia.

Conclusions:

We demonstrate the feasibility of bihormonal closed-loop BG regulation using a control system that employs SC infusion of insulin and glucagon as governed by an algorithm that reacts only to BG without any feedforward information regarding carbohydrate consumption or physical activity. As such, this study can reasonably be regarded as the first practical implementation of an artificial endocrine pancreas that has a hormonally derived counterregulatory capability.

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