The Effect of C-Peptide on Hypoglycemic Counterregulation in Healthy Individuals

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Introduction: Individuals with Type 1 diabetes (T1D) must rely on exogenous insulin to maintain euglycemia which leads to frequent bouts of hypoglycemia. In patients with T1D, hypoglycemia accounts for 4-10% of deaths, either directly or indirectly, and results in hypoglycemia being considered the number one barrier to glycemic control. Progress in the technologic development of insulin delivery devices have made the process of insulin delivery safer but has not been able to eliminate hypoglycemia. C-peptide, a naturally occurring byproduct of insulin synthesis, is not included in current insulin regimens. The alpha cells of the pancreas, which are responsible for glucagon production, contain a C-peptide receptor making it conceivable that C-peptide could serve a clinical role in times of hypoglycemia. This study sought to determine the effect of C-peptide on glucagon secretion and endogenous glucose production (EGP) during insulin-induced hypoglycemia.

Methods: Healthy adults, aged 18-40 years old, who were non-obese and not pregnant participated in the study. Each subject underwent two metabolic studies in random order; one in which C-peptide was infused intravenously during insulin-induced hypoglycemia and one where saline was infused. Each study was divided into two periods: a 2.5-hour Basal Period followed by a 2-hour Hypoglycemic Period. Blood samples were taken throughout the study to measure glucose homeostasis and counterregulatory hormone levels. Each study visit took place 2-4 weeks apart. Repeated measures ANOVA was used to compare glucose turnover, the glucose infusion rate, and counterregulatory hormone and substrate levels. All tests are two-tailed with a significance of 5%.

Results: A total of 4 individuals have completed the study, allowing for an initial evaluation of a human response to the co-infusion of C-peptide during hypoglycemia. The levels of glucose, insulin, and C-peptide were measured and demonstrated expected responses. The mean ending glucagon level in the control studies was 145.5 pg/mL and in the C-peptide studies was 170.2 pg/mL with area under the curve being 13134.24 and 13839.32, respectively. Cortisol, epinephrine, and norepinephrine were lower in the C-peptide trials (24.8 ug/dL, 309.5 pg/mL, and 372.8 pg/mL, respectively) compared to the control studies (31.0 ug/dL, 572.6 pg/mL, and 461.6 pg/mL, respectively). Glucose infusion rate appears to be lower overall in the control studies (0.00, 0.21, 1.18, 1.79, 1.04, 0.98, 1.67, and 1.09 mg/kg/min) when compared to the C-peptide studies (0.00, 0.51, 1.47, 3.01, 1.54, 2.21, 1.71, and 1.71 mg/kg/min). No p-value has yet shown significance.

Conclusions: This study suggests a possible pattern of increased glucagon secretion due to the presence of C-peptide under hypoglycemic conditions based on glucagon levels, sympathetic responses, and exogenous glucose demand. While the p-values do not yet show significance, an increased sample size will increase the power of the study and allow a definitive conclusion to be drawn.

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