RESTORATION OF DEFECTIVE GLUCAGON SECRETION DURING HYPOGLYCEMIA IN AUTOIMMUNE DIABETES.

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Type 1 diabetic patients lose the ability to secrete glucagon during insulin-induced hypoglycemia. A leading theory to explain this loss is that alpha cells require a “switch-off” signal from neighboring beta cells to release glucagon in response to hypoglycemia. The “switch-off” hypothesis has been tested in diabetic streptozotocin (STZ)-treated rats by regionally reinsulinizing the alpha cell \textit{in vivo} prior to the hypoglycemic challenge. To ascertain the relevance of these findings to autoimmune diabetes, we examined diabetes prone (BBDP) BB rats for alpha cell responsiveness to hypoglycemia. In control studies an intravenous insulin injection caused sudden hypoglycemia (blood glucose ≤ 40mg/dl); the plasma glucagon response was greatly diminished in diabetic BBDP rats compared to non-diabetic BBDP rats (57+/−14 vs. 872±36 pg/ml respectively; p<0.001). To evaluate the “switch-off” hypothesis, diabetic BBDP rats were divided into 2 groups: Group A. Insulin switch-off group: we provided an insulin signal by regionally infusing 0.5u/ml insulin (0.025u/min) directly into the superior pancreaticoduodenal artery of diabetic BBDP rats, a rate that did not alter systemic venous glucose levels. The arterial insulin infusion was switched off when the animals became hypoglycemic due to provision of a peripheral venous insulin injection. Group B. Saline control group: In this group, saline was infused into the pancreaticoduodenal artery instead of insulin. This combined maneuver restored the glucagon response to hypoglycemia in group A only (Group A: 203 ± 33 vs. Group B: 58± 7ng/ml, p<0.001). There was no significant difference between group A and a group of age-matched adult non-diabetic BB rats (203 ± 33 vs. 183± 17ng/ml, p=ns). These data indicate that the beta cell “switch-off” hypothesis can be extended to explain the alpha cell secretory defect in autoimmune diabetes.