

Carvedilol Improves Hypoglycemia Awareness in Rats

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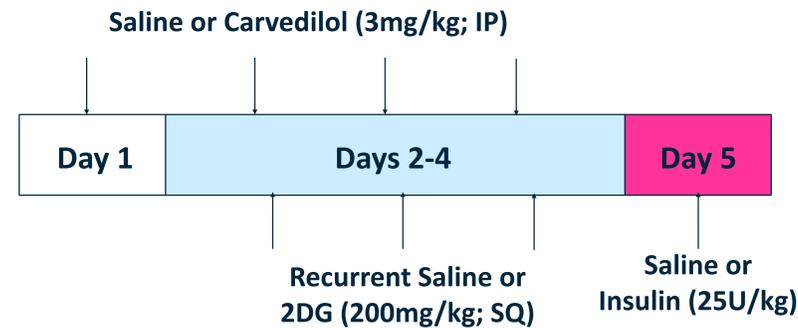
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II. Methods



III. Results

Figure 1 – Left Panel: Plasma glucose concentrations were significantly lower in the animals receiving an insulin injection on day 5 compared to those receiving a saline injection. Importantly, the level of hypoglycemia was well matched between insulin-treated animals. **Right Panel:** Food consumption data on day 5 shows that the induction of hypoglycemia in saline-treated animals (■) increased food consumption significantly compared to saline-treated animals that were injected with saline (□) (*P<0.01 vs Saline). When the animals were made hypoglycemia unaware with 2DG (■), food consumption in response to hypoglycemia was reduced significantly compared to the insulin group (**P<0.04 vs Saline+Insulin), suggesting that the 2DG animals were less aware of hypoglycemia compared to animals treated with insulin. Finally, treatment of 2DG-treated animals with Carvedilol (▨) increased food consumption in response to hypoglycemia compared to the 2DG+Insulin animals (#P<0.01 vs 2DG+Insulin).

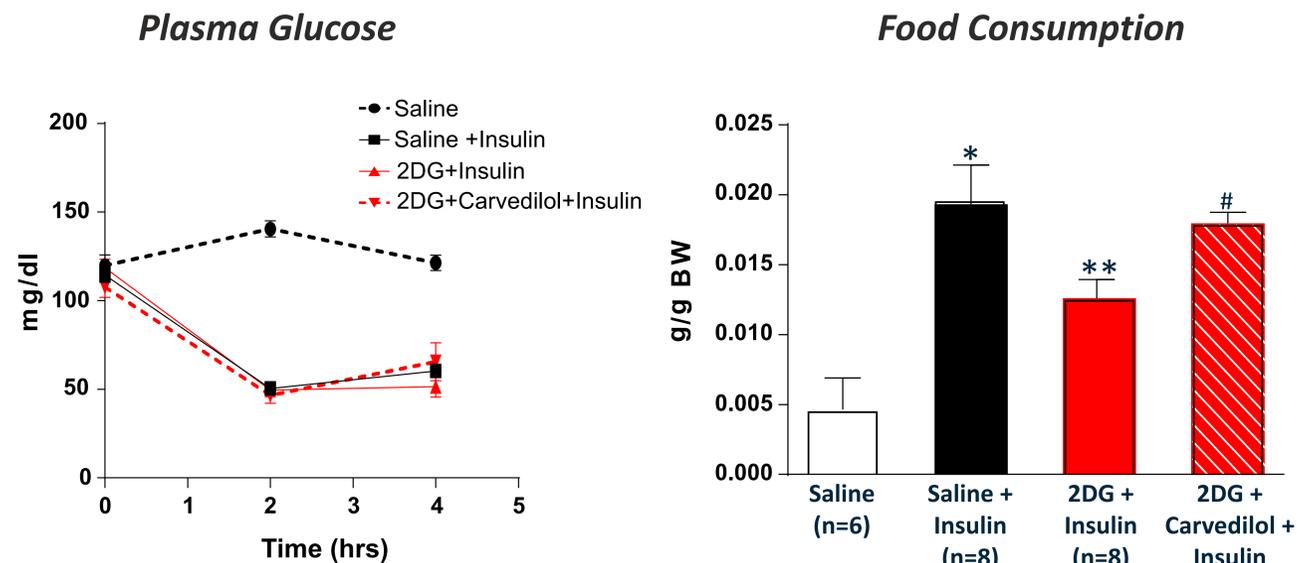
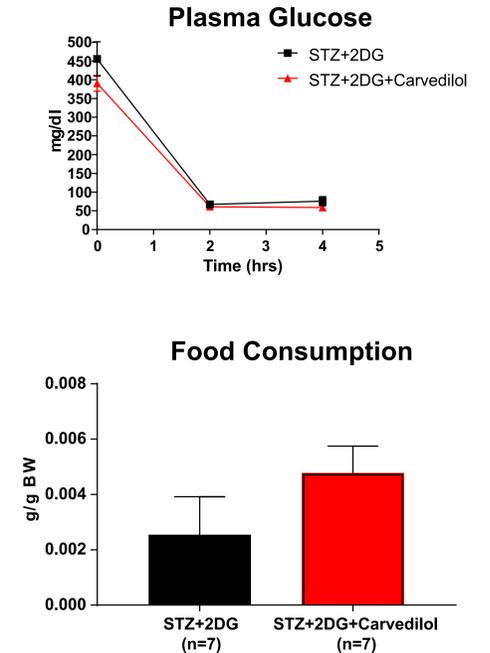


Figure 2 – We repeated the same study in streptozotocin-induced diabetic animals (STZ) that were made hypoglycemia unaware with 2DG and found that Carvedilol increased food consumption in response to hypoglycemia, although the improvement just failed to reach statistical significance.



I. Introduction

Type 1 and severe Type 2 diabetics rely on intensive insulin therapy to improve metabolic control and reduce long-term diabetic complications. However, this treatment also increases the risk of hypoglycemia by 3-6 fold. Recurrent hypoglycemia (RH) diminishes the sympathoadrenal response, which reduces awareness of hypoglycemia and increases morbidity. Finding therapeutic treatments to prevent hypoglycemia and/or improve hypoglycemia awareness (HA) in patients with diabetes is of great importance. We and others have shown that repeated activation of the central adrenergic system may initiate downstream events that result in hypoglycemia unawareness, hence, β -blockers may be a useful therapy to help improve HA.

Carvedilol is an FDA approved non-specific β -blocker that is lipophilic and has a good safety profile. This study seeks to determine if Carvedilol can improve awareness of hypoglycemia in a rodent model of hypoglycemia unawareness.

Hypoglycemia unawareness is evaluated in humans using a questionnaire that rates the intensity of hypoglycemia symptoms. Rodents are unable to use a questionnaire, therefore hunger or food seeking behavior may be used as a surrogate indicator of hypoglycemia unawareness in rodents.

IV. Conclusions

- Treatment with Carvedilol improved hypoglycemia awareness in rats made hypoglycemia unaware with 2-deoxyglucose.
- Carvedilol may be a useful therapy to prevent the development of counterregulatory failure and improve hypoglycemia awareness in patients with diabetes.
- In order to investigate a more clinically applicable model, we began to repeat this study using a diabetic rat model. While the results do not yet have enough power to demonstrate statistical significance, the trend points toward similar results (Figure 2). The studies in the diabetic rodent model are currently ongoing.

V. Acknowledgements

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