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A protective role of hydrogen sulfide from obesity-associated metabolic stress in GLP-1 regulation

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Abstract:
Introduction: Obesity is a risk factor in the development of a variety of diseases including cardiovascular disease and diabetes. Part of this disease develops from reduced levels of the glucoregulatory gut hormone GLP-1. The precise mechanism of why GLP-1 is reduced in obesity is not known. Importantly, obese individuals tend to have increased levels of circulating glucose, glycated proteins, and fatty acids including palmitate. These factors cause damaging stressors in cells known as reactive oxygen species (ROS). We hypothesize that palmitate impairs GLP-1 regulation and causes glucose intolerance through the production of cellular ROS. We also hypothesize that we can block ROS induction using the antioxidant hydrogen sulfide (H_2S) and restore GLP-1 and normoglycemia.

Approach: GLP-1 cells (both mouse and human) were treated with varying doses of palmitate with or without H_2S. Cellular ROS generation was determined using a fluorescent dye, and GLP-1 secretion was assessed using a hormone ELISA. Mice were fed a high palmitate, high sugar diet (known as Western diet) for 16 weeks to induce obesity and glucose intolerance. GLP-1, glucose tolerance, ROS were assessed after a single injection of H_2S or saline.

Results: Palmitate caused a 4-fold increase in ROS in both mouse and human GLP-1 cells. This was significantly reduced by co-incubating with H_2S. In obese mice, 16 weeks of Western diet caused a significant impairment in glucose tolerance and reduced GLP-1 secretion. These effects were reversed by a H_2S injection.

Conclusions: This ongoing work provides evidence on how the antioxidant gas H_2S can play a protective role in the obesity-induced diabetes through the enhancement of GLP-1 secretion.

The microbial gas H_2S reduces metabolic stress in GLP-1 cells. This study will lay the foundation for H_2S as a novel treatment for complications associated with obesity.