Use of Electrical Stimulation of Hepatic Neurons to Improve Glucose Homeostasis

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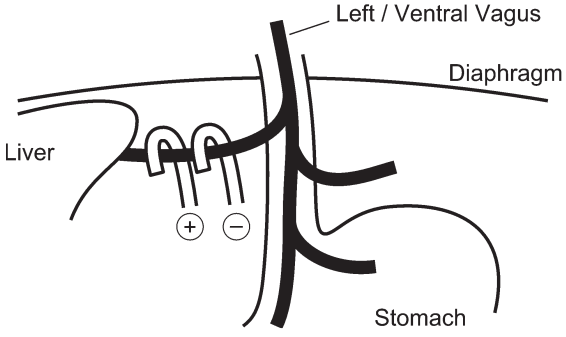
Overall glucose homeostasis is maintained by regulating liver glucose production and peripheral glucose uptake. Insulin, a hormone secreted from the pancreas, has historically thought to be the major regulator in this process.
Type 2 diabetes mellitus (T2DM) is a disease characterized by insulin resistance which leads to increases in glucose levels.

However, the genesis of this disease is multifactorial and indeed, accumulating evidence suggest that the brain's ability to regulate hepatic glucose production is also a key player in the dysregulation of glucose homeostasis in T2DM.
The textbook description of the central nervous system regulating blood glucose has historically focused on the sympathetic innervation of the liver. It has been shown that electrical stimulation of the hepatic sympathetic nerves does lead to an increase in glucose. The role of the parasympathetic innervation in glucoregulation has been mostly established via denervation studies. Here we hypothesized, that electrical stimulation of parasympathetic nerves to the liver will improve glucose homeostasis. The aim of this thesis was to verify this assumption, by stimulating the common hepatic branch in rats and simultaneously observing the blood glucose level.

Materials and Methods

Study 1. Acute electrical stimulation was performed for 1 hour in anesthetized lean and obese rats. Together with the initiation of the electrical stimulation, 1.5 ml of 50% dextrose or saline was injected into the stomach, in order to mimic postprandial conditions. Blood samples were taken prior to and during the study for glucose, insulin, and assessment of gastric emptying rate.



Placement of the electrode around the common hepatic branch of the vagus nerve.

Study 2. In 4 rats an electrode was implanted to study the impact of acute electrical stimulation on glucose tolerance in conscious chow-fed rats. The glucose tolerance test involved an intraperitoneal dextrose injection, followed by 2 hours of electrical stimulation while the animal remained unrestrained in their home cage. The same study was repeated after one week of 60% high-fat diet feeding.
The lean animals were used to study the impact of the electrical stimulus in the healthy animal. Obese rats were used to discover the possible influence of the stimulation in diabetic patients. Rodents unlikely develop T2DM, however they become glucose intolerant when put on a high-fat diet over a certain amount of time.
A signal with 0.3 ms wide 4 mA peaks every 71 ms, an on-time of 0.1 s and off-time of 4.9 s was applied to all animals that received stimulation, except for 5 animals, on which different frequencies and currents were tested.

Results & Discussion

The results from the studies in lean unconscious or conscious animals did not show any significant change in blood glucose levels, insulin secretion or gastric emptying. However obese animals had significantly increased glucose and insulin levels after a dextrose injection and 30 minutes of stimulation under anesthesia. These data suggest that the used stimulation paradigm would not be effective as a therapy for T2DM. Further studies are needed to determine if different stimulation signal may alter glucose homeostasis in a positive manner.

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