Research Days Abstract Submission

Abstract Title:
Therapeutic Ultrasound-Induced Insulin Release as a Potential Treatment for Type 2 Diabetes

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Abstract Text (should not exceed 400 words):

Objectives

Type 2 diabetes mellitus is a complicated and chronic metabolic disease resulting from the interplay of systemic insulin resistance of peripheral tissues, insufficient secretion from pancreatic beta cells, and insufficient beta cells due to genetic and environmental factors. The aim of this work is to study the calcium-dependent mechanisms of ultrasound-mediated insulin release and the translational potential of therapeutic ultrasound as a novel treatment for type 2 diabetes.

Methods

INS 832/13 cells were exposed to 800 kHz 0.5 W/cm² ultrasound and 5 mM EGTA, an extracellular calcium chelator. The cells were loaded with Ca²⁺ dye Quest Rhod4AM and voltage-sensitive Di-4-ANBDQS to measure real-time changes in intracellular Ca²⁺ and membrane potential in response to ultrasound stimulation.

A two-dimensional finite-element model of an axial slice of the human abdomen was constructed in PZFlex based on anatomy from a reference atlas. Maximum temperature was calculated for a five minute application of continuous 800 kHz ultrasound for both an empty and full (of water) stomach.

Studies with transgenic mice include terminal and survival studies to investigate the short term response to ultrasound application, including insulin, glucagon, and alpha-amylase release. In currently ongoing studies, the treatment group is exposed to 5 minutes of continuous 1 MHz 1.0 W/cm² ultrasound twice per week with blood samples being collected just before treatment, just after treatment, and thirty minutes after treatment.

Results

Ca²⁺ imaging studies showed an increase in fluorescence intensity approximately 5 seconds after the stimulus begins (n=3). Elevations in Ca²⁺ dye fluorescence intensity were accompanied by a decline in membrane potential, which is indicative of membrane depolarization. Initial modeling results indicated that the stomach must be filled with fluid to avoid significant burning of the skin. The highest temperature observed was 41.2°C.
with a water-filled stomach. Survival and terminal studies with transgenic mice are currently ongoing. Preliminary terminal studies indicated no gross damage from 1 MHz ultrasound application at 1 W/cm².

**Conclusions**

Fluorescence imaging studies suggested a transient calcium mobilization shortly after ultrasound application begins that is inhibited by EGTA. This suggests that the release mechanism involves an influx of extracellular calcium, possibly through ultrasound-induced micropores. The initial results from finite element analysis and animal studies show promise in the translational potential of therapeutic ultrasound in the treatment of type 2 diabetes. In future studies, models will be based on abdominal computer tomography (CT) images of normal and obese patients.