Metabolic Adaptations Induced by Medium Chain Triglycerides in a Rat model of Diabetes Measured by in vivo Magnetic Resonance Spectroscopy

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Targeted audience: Neuroscientists interested in the metabolic of diabetes.

Purpose: Diabetes is a metabolic disorder that can be controlled by intensive insulin therapy in order to prevent or delay complications. However, this therapy is limited by higher rates of severe hypoglycemia and often results in cognitive impairment and even death. A previous study had shown that medium chain triglycerides (MCTs) diet improves cognition without affecting adrenergic or symptomatic responses to hypoglycemia in type 1 diabetes (1). Our goal of this study is to identify the metabolic adaptations of MCT diet and to find alternative therapies in managing T1DM.

Methods: Sprague-Dawley rats were injected with 65 mg/kg streptozotocin (STZ) to induce four weeks of hyperglycemia. Rats were treated with long-acting insulin to maintain glycemia level of 300mg/dL and to avoid ketosis. After one week of hyperglycemia, rats were put on either MCT diet or control diet for three weeks. On the experiment day, rats were anaesthetized with isofluroane 1%, and ventilated with 70% N_2O/29% O_2. Blood glucose was reduced to ~50mg/dL with hyperinsulinemic hypoglycemic clamp. Proton–observed ^{13}C-edited (POCE) magnetic resonance spectra were acquired *in vivo* on 9.4 T Varian VNMRJ system during the infusion of [2,4-$^{13}C_2$]BHB. The time courses of brain ^{13}C-labeled Glu and Gln were recorded during the infusion. Metabolic rates were obtained by fitting the ^{13}C-time courses of Glu and Gln into two –compartment (neuron-astrocyte) model (2) using CWave software package (3).

Results: ^{13}C-labeling of Glu4 and Gln4 showed significant decrease in the MCT diet treated rats p=0.004 and P=0.002 for Gln4 and Gln4 respectively (Figure 1a, and 1b). Metabolic modeling showed that MCT diet induced significant drop in astrocytic uptake of BHB (VkbA) (P=0.01), and increase in neuronal glucose oxidation rates P=0.04 (pyruvate dedyhrogenase:PDH)(Figure 1c and 1d). These results were supported by a qPCR study that showed a decrease in mRNA of monocarboxylate transporter (Mct1)(Figure 1e).

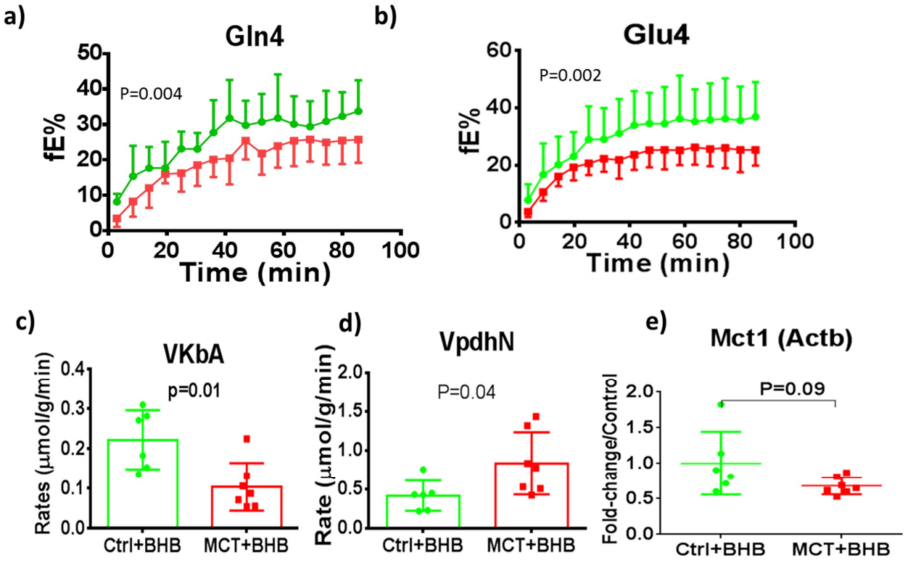

Figure 1. a) and b), ^{13}C-enrichment of Gln4 and Glu4 during infusion of 2,4-$^{13}C_2$-BHB. c) MCT diet decreases the astrocyte BHB uptake. d) MCT diet increases neuronal glucose oxidation. e) qPCR results shows decrease mRNA of monocarboxylate transporter (Mct1) in MCT diet treated rats. Green markers represent data from control diet group, red markers represent data from MCT diet group.

Discussion: The decrease in BHB uptake may due to the fact that BHB shares the same monocarboxylic transporter with the products of MCT diet on the blood brain barrier. Pretreatment of MCT diet reduced expression of Mct1 on the blood brain barrier, thus reduced brain uptake of labeled BHB during the hypoglycemic clamp.

Conclusions: Our results identified the metabolic changes of MCT diet under acute hypoglycemia in STZ-induced diabetic rats. While MCT diet does increase in insulin sensitivity under hyperglycemia condition it may not help under acute hypoglycemia conditions, by reducing the uptake of alternative energy substrate in astrocytes and increase the neuronal glucose oxidation

References: (1) Page et al. Diabetes, 2009 58(5)1237-44. (2) Jiang et al. Jcereb Blood Flow Metab. 2011 31(12:2313-23. (3) Mason et al. Brain Res Protoc 2003;10:181–190.

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