

Effects of chronic uncontrolled diabetes on neurochemical profile and glucose transport in the rat brain *in vivo* by 1H MRS at 9.4 T

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INTRODUCTION

The chronic hyperglycemia may cause neuropathologic conditions such as cognitive deficits as prevailing evidence suggests an increased risk of patients with diabetes to develop Alzheimer's disease ([1] and refs therein). Type 1 diabetes is associated with hyperglycemia and insulin deficiency, and cognitive dysfunction can occur in relation to duration of the disease and degree of glycemic control. In this study, we use streptozotocin (STZ)-induced diabetic rats as an experimental model of uncontrolled type 1 diabetes to characterize metabolic alterations in the brain. We have measured the neurochemical profile in chronic uncontrolled hyperglycemic conditions and normalized glycemic conditions via insulin as well as the glucose transport kinetics using *in vivo* ultra-short echo time ¹H MRS at 9.4 T.

METHODS

Thirteen Sprague-Dawley rats (2 months old) were injected with STZ (Sigma, 65mg/kg) to induce type-1 diabetes, and were subject to MR experiments. During the experiments, the rat was anesthetized by a gas mixture (air:oxygen = 1:1), containing 1-2 % isoflurane. The MRS data acquired before the STZ injection served as control (CTL). Upon completion of MR scans on 73 days (DM73) after the induction of diabetes, five rats were subject to glucose transport studies with concurrent infusion of insulin and glucose to achieve steady-state target glycemic levels. All experiments were performed on a 9.4 T MR system (Varian/Magnex Scientific). A two-loop quadrature RF surface coil was placed on animal head for transmitting and receiving at 400 MHz. Short echo-time STEAM (TE=2ms, TR=5s, TM=20ms) sequence [2] was used to acquire spectra from a voxel (90 μ l) in the neocortex. The spectral phase and frequency drift were corrected prior to the LCMoDel [3] analysis.

RESULTS AND DISCUSSION

As we have previously demonstrated [4], uncontrolled hyperglycemia resulted in significant elevation in the levels of several neurochemicals such as beta-hydroxybutyrate (bHB), glycerophosphoryl-choline (GPC), *myo*-inositol (Ins), and taurine (Tau) as soon as animals develop hyperglycemia, i.e., 3 days after diabetes induction. Over one month after the induction, prolonged uncontrolled hyperglycemia, led to significant decreases in alanine (Ala), aspartate (Asp), glutathione (GSH), N-acetylaspartate (NAA) levels. Upon normalization of glycemic levels via insulin infusion, the levels of most metabolites were normalized (Fig. 1). Ins levels remained lower, which is consistent with a previous study measured at 4 weeks of the STZ injection [5]. Significant decreases of Ala and NAA were measured only in chronic hyperglycemia (31 days and thereafter, data not shown), and failed to recover after normalization of glycemic levels. The lower levels of NAA after the glycemic normalization indicate that the potential neuronal damage or compromised integrity caused by prolonged hyperglycemia cannot be reversed by the acute glycemic normalization. Further, significant increases of PCr and decreases of Cr may indicate changes in cerebral energy status.

The relationship between plasma and brain glucose concentrations from the STZ-induced DM animals as well as control animals we have reported previously [6] is shown in Fig. 2. The apparent linear relation between plasma and brain over a wide range of plasma glucose concentration agrees well with the reversible Michaelis-Menten (MM) model for glucose transport across the blood brain barrier (BBB). The best fit to the data resulted in an apparent MM constant K_t of 0.72 ± 1.7 mM and the ratio of the maximal transport rate relative to cerebral metabolic rate of glucose, T_{max}/CMR_{glc} , was 2.1 ± 0.11 . Current values of K_t and T_{max}/CMR_{glc} were within the error range compared to those reported previously in control and STZ-treated rats [5]. Our data support the notion that glucose transport capacity across BBB was not altered in STZ-induced diabetes.

In summary, osmolar dysregulation due to chronic uncontrolled hyperglycemia leads to significant alterations in major osmolytes, and significant reduction in Ala, Asp, GSH, and NAA. Acute glycemic normalization restores levels of all metabolite except Ins, Ala and NAA. While chronic uncontrolled hyperglycemia results in irreversible degradation of neuronal health, it does not change brain glucose transport.

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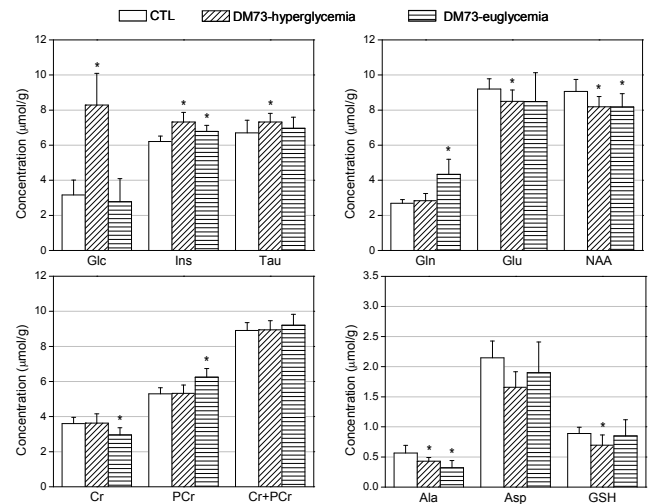


Fig. 1. Quantitative comparison of the metabolite levels obtained from the rat brain on CTL, on DM73 (DM73-hyperglycemia), and after glycemic normalization (DM73-euglycemia): * $p < 0.05$.

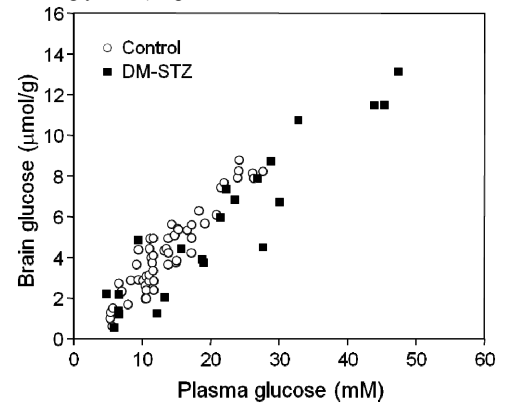


Fig. 2. The relationship between brain and plasma glucose concentration in STZ-induced diabetic animals (this study) and controls (Choi et al, 2001).