Neurochemical changes in the rat brain with STZ-induced diabetes using *in vivo* ^{1}H MR spectroscopy at 9.4 T

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INTRODUCTION

Recently, the neurological consequences of diabetes mellitus received increasing interests in both clinical and experimental settings. *In vivo* ^{1}H MRS at high magnetic fields provides an opportunity to examine neurochemical changes in diabetes in a completely noninvasive manner, so that diagnosis and early identification of the disease can be improved in addition to characterization of the disease progression. The purpose of this study was to obtain neurochemical profiles from streptozotocin (STZ)-induced diabetic rats to investigate early changes in the brain due to hyperglycemia in diabetes using the combination of ultra-short echo time ^{1}H MRS [1]and LCModel analysis for quantification [2] at 9.4 T.

METHODS

Ten Sprague-Dawley rats (mean ± SD = 304 ± 29 g) were injected with STZ (Sigma, 65mg/kg) to induce diabetes. before and after the injection. The rats were anesthetized (N_2O:O_2 = 1:1 with 1.4-1.8% isoflurane) during the measurements. The first scan was performed before the injection (control) and subsequent scans were performed on the third day (DM-1) and the second week after injection (DM-2). Therefore, each animal served as its own control. Blood glucose levels were measured right before the scans using a glucometer.

All experiments were performed on a Varian 9.4 T MR system. First- and second-order shims were adjusted using FASTMAP [3]. Ultra-short echo-time STEAM (TE=2ms, TR=5s, TM=20ms) [1] was used to localize a voxel (6×3×5 mm^3) in the neocortex region. The water signal was efficiently suppressed using variable power RF pulses with optimized relaxation delays (VAPOR) technique [1]. The acquired spectra from the rat brain were analyzed using LCModel [2]. Paired T-test was performed between control and DM-1 (3 days after diabetes induction), and control and DM-2 (2 weeks after diabetes induction).

RESULTS AND DISCUSSION

Figure 1 illustrates the spectra of the rat brain (A) before (n = 11), (B) DM-1 (n = 9) and (C) DM-2 (n = 5). Excellent water suppression allowed measuring the brain glucose signal at 5.23 ppm that shows linear increase over time after STZ-injection. The concentration of glucose (Glc) was significantly increased by 149% on the third day and 266% on the second week. The results show *in vivo* evidence of increased brain glucose in hyperglycemia [5,6]. Figure 2 shows changes of β-hydroxybutyrate (bHB), *myo*-inosital (Ins), glycerophosphocholine (GPC), phosphocholine (PCho), phosphorcreatine (PCr) and total creatine (Cr+PCr). These concentration changes occurred as early as three days after STZ injection. The concentration of bHB was increased by 103% at DM-1 and 113% at Dm-2. The elevated levels of bHB indicate ketoacidosis in the diabetic brain accompanied by hyperglycemia, and it is also known that bHB inhibits glucose metabolism, leading to further accumulation of glucose in the diabetic brain [7]. Some of changes such as GPC and PCr were not significant at DM-2, possibly due to lack of statistical power (n = 5) at this point.

In conclusion, we have demonstrated highly resolved *in vivo* ^{1}H MRS from diabetic rat brains over 18 metabolites. Analysis of the longitudinal neurochemical profiles provided potential of ^{1}H MRS to measure early yet subtle changes of metabolites in diabetes, indicating its use in clinical studies of diabetes.

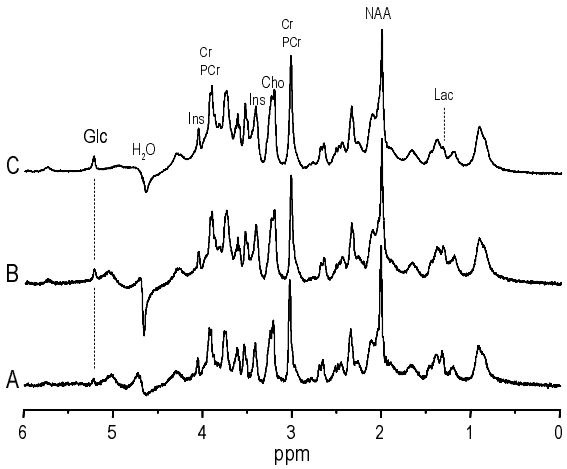

Fig. 1. ^{1}H MR spectra of the rat brain *in vivo* were measured before (A: control) and after STZ injection (B: DM-1, C: DM-2) at 9.4 T. A few neurochemicals such as bHB and *myo*-inositol started to show concentration changes only three days after STZ injection, providing the sensitivity of *in vivo* ^{1}H MRS at 9.4 T.

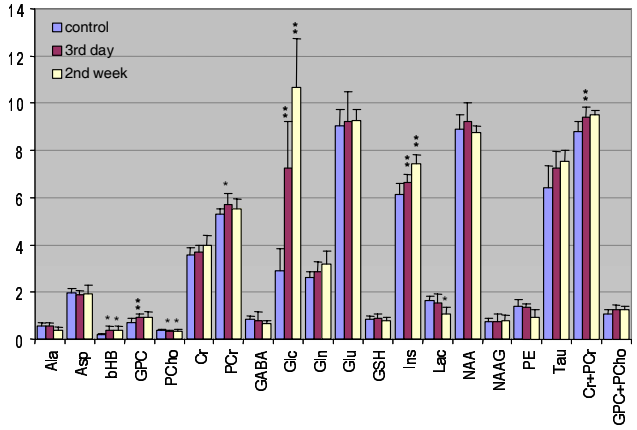

Fig. 2. Neurochemical changes in the rat brain *in vivo* in control and in diabetes. Significant level: *p<0.05, **p<0.005.

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