Detection of the cerebral acetone signal elevated in the STZ-induced diabetic rats measured by in vivo 1H MRS at 9.4 T

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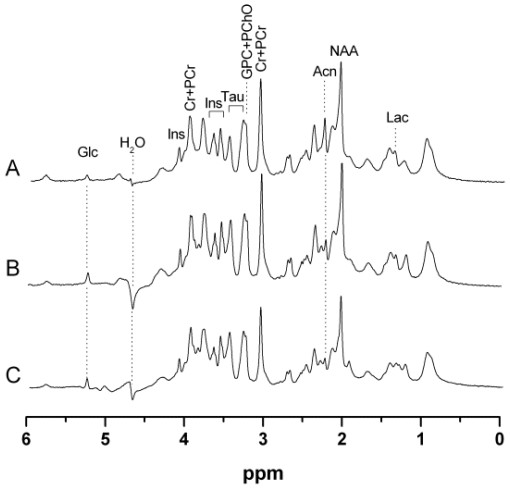
INTRODUCTION

Ketoacidosis is a pathological metabolic state in which levels of ketone bodies are elevated by breaking down of fatty acids and amino acids. For diabetic patients, particularly in poorly controlled type-1 diabetes, insulin deficiency may accompany ketoacidosis, leading to the presence of high concentrations of ketone bodies [1]. Thus, noninvasive study of changes in neurochemicals for diabetes is beneficial to characterize the disease progression and diagnosis in early stages, which can be accessed through the use of *in vivo* ^{1}H MRS, particularly at high magnetic fields. In this study, we identified increases of ketone bodies such as acetone and β-hydroxybutyrate (bHB), which are known to be produced from acetoacetate in humans, associated with hyperglycemia in the brain of streptozotocin (STZ)-induced diabetic rats.

METHODS

Seven sprague-Dawley rats (304 ± 29 g) expressing experimentally-induced type-1 diabetes via intra-venous injection of 65mg/kg of STZ (Sigma, St. Louis, MO). The ^{1}H MRS study of the STZ-induced diabetic rats was performed on the 9.4T Varian system (Magnex Sceintific, Abingdon, UK). A two-decoupled-loop quadrature surface RF coil was positioned on a rat head as a transceiver. The rats were anesthetized with isoflurane, and their core body temperature was maintained at 37˚C during MR measurements. The MR data were acquired about 10 weeks after STZ injection using short echo-time STEAM (TE/TM/TR = 2/20/5000 ms) [3] from a voxel size of 90 µl localized in the neocrotex. First- and second-order shims were adjusted using FASTMAP [4]. The creatine (Cr+PCr) signal at 3.03 ppm was used for phase and frequency drift corrections before LCModel [2] analysis for metabolite quantifications. A threshold of 20% to the Cramer-Rao lower bound was used before processing statistical analysis.



Fg 1. Consistent detection of the acetone (Acn) peak at 2.22 ppm in the brain of STZ-induced diabetic rats using *in vivo* ^{1}H MRS. Spectra were acquired from three different animals after over 10 weeks of the development of hyperglycemia induced by STZ-injection.

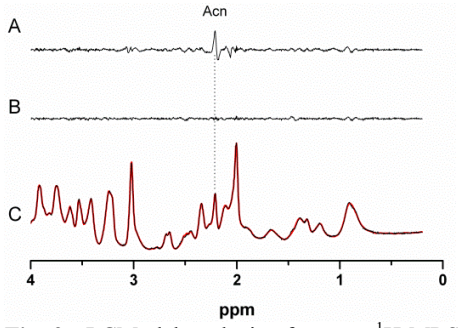


Fig. 2. LCModel analysis of *in vivo* ^{1}H MRS in a diabetic rat brain. Residual plots obtained from LCModel analysis using a basis set (A) without acetone and (B) with acetone; (C) Overlay of the LCModel fit (red) using a basis with acetone on the original spectrum.

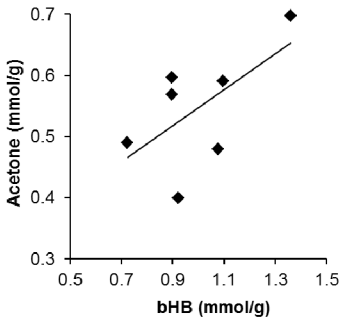


Fig. 3. Scatter plot of bHB vs. acetone levels quantified using LCModel analysis of *in vivo* ^{1}H MRS in the STZ-induced diabetic rats.

RESULTS AND DISCUSSION

Figure 1 exhibits ^{1}H MR spectra detected in the neocortex of rat brain after STZ-injection using ^{1}H MRS. Highly effective water suppression was achieved using a variable power RF pulses with optimized relaxation delays technique [3]. As shown in Fig.1, the animals with STZ-induced diabetes developed hyperglycemia and showed higher levels of glucose peaks in ^{1}H MR spectra [6, 7]. Figure 2 illustrates the curve fitting outcome for the ^{1}H MRS based on the LCModel analysis. In Fig. 2A, the fit residuals generated from the LCModel with the metabolite basis set without acetone exhibited a marked residual at 2.22 ppm. The identity of this unfit peak was confirmed as the character of acetone by examination of a model solution [8]. When a simulated acetone spectrum was included in the basis set, the analysis outcome demonstrated complete elimination of the fit residuals at 2.22 ppm (Fig. 2B), and the optimal LCModel curve fit (Fig. 2C). The inclusion of acetone (Acn) in the LCModel basis showed a very minor impact on the concentrations of the other metabolites. For these rats expressing high acetone concentration in the neocortex (n = 7), the average of glucose levels was 9.51 ± 0.90 μmol/g, compared with that of 2.88 ± 0.85 μmol/g in the control group (n = 7). Significant elevation of bHB was also observed in the same rats with the averaged value of 0.99 ± 0.20 μmol/g, while the bHB level in the control group was 0.22 ± 0.33 μmol/g in average, indicating ketoacidosis in these rat brains [5]. Furthermore, the moderate correlation between bHB and acetone (r^2 = 0.38) shown in Fig. 3 indicates that estimation of acetoacetate levels may be required to clarify the relationships between these ketone bodies and its metabolism under hyperglycemia. In summary, localized ^{1}H MRS provides a capability of detecting alterations in ketone body levels in diabetes mellitus.

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