High glutamine C57BL/6 mice

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PURPOSE

C57BL/6 is the most widely used mouse strain used in different research areas including developmental biology, neurobiology, cardiovascular biology, immunology, genetics, diabetes, obesity, etc. In addition, C57BL/6 mice are commonly used as a background strain in the production of transgenic, knock-in and knock-out mouse model of human diseases. At the ISMRM 2011 meeting we reported that while studying Q140 knock-in mouse model of Huntington's disease (HD) we found mice with abnormally high glutamine (Gln) in the brain[1]. This mouse model was generated on C57BL/6 mouse background strain and high Gln mice were observed in HD as well as in control group. The similar high Gln mice were later observed in the mouse model of spinocerebellar ataxia when C57BL/6 mice were used as a background strain[2]. A detailed study of these high Gln mice revealed that this defect is caused by a sporadic congenital portosystemic shunt[3]. The purpose of this study was not aimed to investigate these high Gln mice, but once again we observed them when C57BL/6 mouse strain was used. Therefore, the purpose of this abstract is to demonstrate how different the neurochemical profile of these high Gln mice is from normal healthy mice and to remind researchers using C57BL/6 mouse strain that neglecting this fact may result in significant bias in their results.

METHODS

Twenty-five C57BL/6 mice were scanned at 2 months age. All measurements were performed at 9.4T (Agilent/Varian) using FASTMAP shimming[4] and ultra-short TE STEAM (TE = 2 ms) localization sequence combined with VAPOR water suppression[5]. Metabolites were quantified using LCModel with the spectrum of fast relaxing macromolecules included in the basis set. The multi-slice FSE imaging (slice thickness = 0.8 mm) in coronal and sagittal orientations were used for a precise VOI selection.

RESULTS

In vivo ^{1}H MR spectra were acquired from the mouse hippocampus. The spectral quality consistently achieved in this study (Fig. 1) enabled reliable quantification of 15 brain metabolites. The difference between the neurochemical profiles of the high Gln mouse and the group of normal healthy mice of the same C57BL/6 strain was enormous (Fig. 2). The neurochemical profile of the high Gln mouse is characterized by an abnormally high Gln (+142%), low inositol (-43%) and taurine (-18%). In addition, other brain metabolites are altered, such as alanine, ascorbate, glutamate, lactate, total choline and total creatine (Fig. 2). Abnormally increased level of Gln is not specific for the hippocampus, but was also observed in other brain areas.

DISCUSSION

The pattern of metabolite changes in high Gln C57BL mice, most importantly the increase of Gln and the decrease of inositol and taurine are typical for hepatic encephalopathy[6]. The congenital portosystemic shunt discovered in C57BL/6 mice[3] is in agreement with this liver failure pattern. Increased levels of plasma ammonia were not detected in these mice. Therefore, ^{1}H MRS is probably the only non-invasive method to detect this deviation. The high Glu mice are definitely not normal and their inclusion in the genetically modified or control group of mice may cause a significant bias. This fact has to be seriously taken into consideration when C57BL/6 mouse strain is used for different neuroscience projects. ^{1}H MRS can be used for the mouse screening in order to eliminate these high Gln mice from the study.

CONCLUSION

The high Gln mice randomly appear in C57BL mouse colonies and have to be identified and eliminated from the further experiments.

REFERENCES: 1. Tkac et al., *Proc ISMRM* 2011, p 2288; **2.** Emir et al., *J Neurochem* 2013: 127, 660; **3.** Cudalbu et al., *PlosOne* 2013; 8, e69782; **4.** Gruetter et al., *Magn Reson Med* 2000:43,319; **5.** Tkac et al., *Magn Reson Med* 1999:41,649; **6.** Verma et al., *Liver Int* 2008; 28, 1095.

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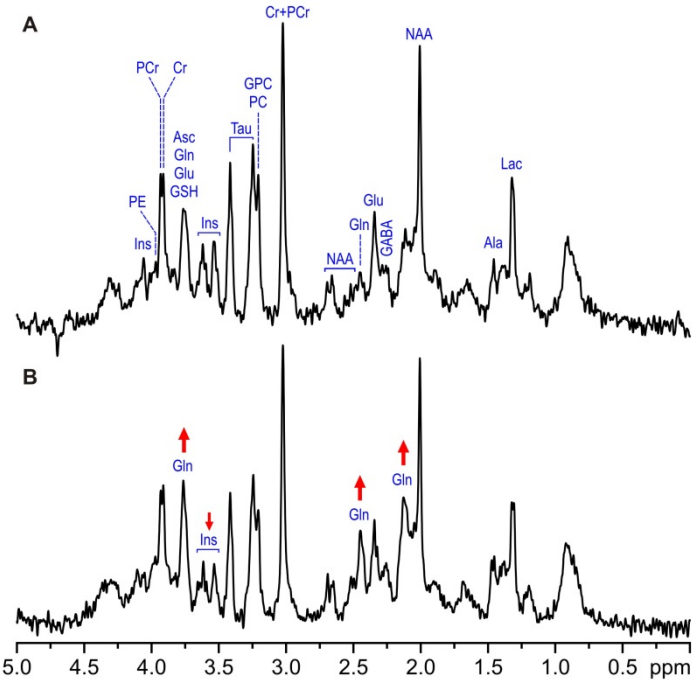

Figure 1 In vivo ^{1}H MR spectra acquired from the hippocampus of two months C57BL/6 mice. (A) Normal mice (N = 24), (B) high glutamine mouse. STEAM, TE = 2 ms, TR = 5 s, VOI = 4 µL, NT = 320.

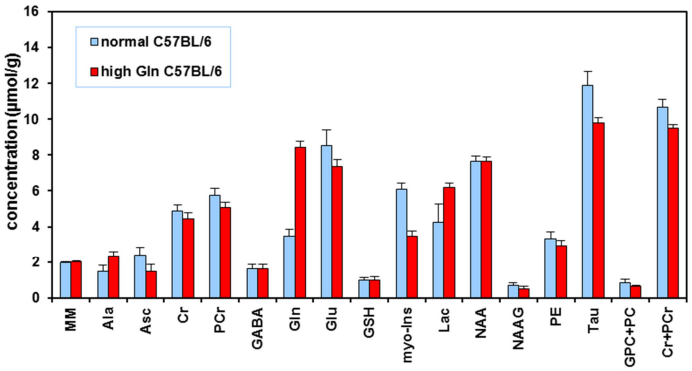

Figure 2 Comparison of the hippocampal neurochemical profile of the high glutamine C57BL/6 mouse to the profile of healthy C57BL/6 mice (N = 24). Error bars: SD (normal group), CRLB (high Gln).