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^{13}C and ^{1}H Magnetic Resonance Spectroscopy Using Cryogenically Cooled ^{1}H and ^{13}C Resonators to Investigate Brain Biochemistry in Mice at a 9.4 Tesla Small Animal MR Tomograph

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The superior aim of the present work was to advance methods for in vivo MRS for the quantification of brain biochemistry in mice at the 9.4 Tesla MR high field animal scanner (Bruker, Ettlingen, Germany) with the use of cryogenically cooled resonators (CryoProbes) at the Central Institute of Mental Health. This scanner is equipped with two different CryoProbes. One is designed for ^{1}H MR measurements and the other is a prototype of a ^{13}C MR CryoProbe system consisting of a cooled ^{13}C coil and an additional non-cooled ^{1}H saddle coil. With each CryoProbe specific developments and in vivo studies have been conducted.

The first aim was to use the ^{1}H MRS CryoProbe to investigate the effects of voluntary running and a cafeteria diet in the in vivo mouse brain. An empirical cross-sectional study was conducted to elucidate the biochemical and histological effects of a free choice cafeteria diet on the brain and to explore whether voluntary running would counteract the effects of such a diet. Additionally, we checked for correlations between biochemical changes found by means of ^{1}H MR spectroscopy and histological results in the hippocampal region. We demonstrated that our free choice cafeteria diet caused hyperglycemia and hyperinsulinemia. It also led to metabolic changes mainly in the hippocampal area without neuroinflammatory effects as shown by the absence of any histological or spectroscopic inflammatory markers. Furthermore, voluntary running counteracted the effect of diet in terms of altered metabolite levels so that there were no differences between the sedentary animal group receiving standard food and the exercising animals on a cafeteria diet.

Our second aim was to establish a ^{13}C channel at the magnetic resonance animal scanner using a prototype of a ^{13}C CryoProbe. This included both the experimental evaluation of Signal-to-Noise ratio gain of the CryoProbe compared to conventional room temperature coils and the creation of necessary methods to conduct hyperglycemic clamp experiments in mice. For the latter, appropriate pulse sequences, study designs and post-processing had to be developed in order to calculate metabolic flux rates.

As a first step in establishing a ^{13}C channel and conducting ^{13}C experiments we evaluated the performance of the prototype ^{13}C CryoProbe compared to room temperature coils. The ^{13}C CryoProbe reached an about four times higher Signal-to-Noise ratio than the best performing room temperature resonator. To complete the establishing of a ^{13}C channel, several techniques and methods had to be developed anew. First we programmed and implemented an appropriate polarization transfer pulse sequence, which allows to enhance the measured signal and to simultaneously reduce the chemical shift displacement. Together with a feasible infusion protocol and measurement design it could be shown that a voxelsize of 68 µL is enough to obtain ^{13}C as well as ^{1}H spectra with sufficient SNR to detect label incorporation of the most important metabolites in the living mouse brain, such as glutamate, glutamine, and lactate. Additionally, a working post-processing chain of obtained ^{13}C spectra using jMRUI was implemented. The developed Matlab application proved to be capable of determining metabolic fluxes in several tests with artificial and also with measured in vivo data. Taken all together, the establishing of a ^{13}C channel at the 9.4 T animal scanner was successful and a variety of necessary techniques, routines, and methods were developed and implemented. Considering the good performance of the ^{13}C CryoProbe it might be possible to investigate specific distinct brain areas, e.g. hippocampus, thalamus, and cortex, in mouse models in vivo a regimen that was so far restricted to ex vivo experiments only.