Ketone bodies and glucose in human brain during ketogenic diet and fasting

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Purpose

The ketone bodies beta-hydroxybutyric acid (bHb), acetoacetic acid (AcAc) and acetone (Ac) are products of fatty acid breakdown for energy supply in the liver and kidney. They are transported to other tissues where AcAc and bHb can be reconverted to acetyl-CoA to produce energy, via the citric acid cycle. In the brain, they are a vital source of energy during fasting and low-carbohydrate conditions[1] and have been shown to mediate neuroprotection in neurodegenerative diseases, stroke and traumatic brain injury. When investigating the capacity of ketone bodies to spare glucose and support neural function it has been found in rat brain that their oxidation is compensated by an equal reduction in glucose oxidation.[2] The appearance of different ketone bodies in brain was observed using 1H-MRS during fasting[3], in diabetes[4,5] and, under ketogenic diet, in epilepsy[6] and Ohtahara syndrome[7]. As ketogenic diet in neurological disorders is of increasing therapeutic interest, we set out to study its effect in healthy human brain by quantifying ketone bodies together with other metabolites by MRS at 3 T during ketogenic diet and fasting in two cortical volumes of interest.

Methods

Three healthy male volunteers participated in the study. Magnetic resonance measurements were performed under mixed diet (M), ketogenic diet (K) for 7 days and after 7 days of controlled fasting (F). They were conducted on a 3 T Verio MR scanner (Siemens Medical Systems, Erlangen, Germany) using a 32-channel receive head coil. Subsequent to MPRAGE imaging and shimming using FAST(EST)MAP, MR spectra were acquired from voxels in the anterior cingulate (ACC, 25 x 35 x 20 mm^3) and the central occipital cortex (25 x 25 x 25 mm^3) using SPECIAL[8] with TR = 3 s, TE = 8.5 ms and 256 averages. Spectra were analyzed using LCModel with a simulated basis set containing 21 metabolites including the ketone bodies, and referenced to an unsuppressed water scan. To supply LCModel with most realistic prior knowledge, bHb, AcAc and Ac were excluded from the basis set for analysis of the spectra at baseline since during mixed diet the cortical ratio of glucose:ketone bodies of 97:3 suggests virtual absence of the latter[9]. Apart from the ketone bodies and glucose (Glc), only metabolite amplitudes with LCModel Cramér-Rao lower bounds (CRLB) below 20 % were used for further analysis. Amplitudes were corrected for relaxation and for the amount of cerebrospinal fluid in the voxels from the segmented T1-weighted images using SPM8. Blood bHb was assayed using a commercial test kit.

Results

Since there were no principal differences in the metabolite time courses for the two voxels studied they were combined in the further analysis. Fig. 1 illustrates a SPECIAL spectrum from ACC under fasting, together with the fits for the ketone bodies. At ketogenic diet, CRLB for the ketone bodies were between 20 % and 50 % for 8 (of the 18) values, which decreased to well below 20 % with increasing substance levels at fasting. Of the 6 glucose levels at fasting, 3 had CRLB between 20 % and 50 %. However, as we expected very low metabolite levels to occur, all values were taken into consideration. The concentration of ketone bodies in brain increases during ketogenic diet and is highest at fasting (Fig. 2), which is accompanied by a decrease in Glc concentration in the same order of magnitude. T-tests gave $p < 0.05$ for changes in Glc (M > F, K > F) and bHb, AcAc and Ac (K < F), although the low number of measurements demands care at using statistical analyses. Of all other metabolites the only significant changes observed were decreases in glutathione and total choline from K to F.

Discussion and conclusion

The enhancement of the ensemble of 3 ketone bodies, paralleled by a drop in glucose level, was observed in healthy adult brain during ketogenic diet and fasting. This finding, which was not reported before, was facilitated by using very short echo time MRS and an LCModel basis set including simulated ketone body resonances. The parallel increases of bHb in brain and blood confirm former observations.[3] Failure to detect a previously shown lactate increase[3] was most likely due to adaption during the long time periods of ketogenic diet and fasting. Studies with more subjects are under way to verify our results and test the method to stratify patients in terms of response to ketogenic diet in diseases like epilepsy and multiple sclerosis.

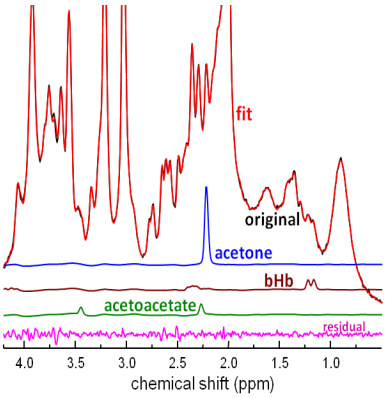

Fig. 1. Spectrum (clipped) from ACC during fasting and some LCModel fits.

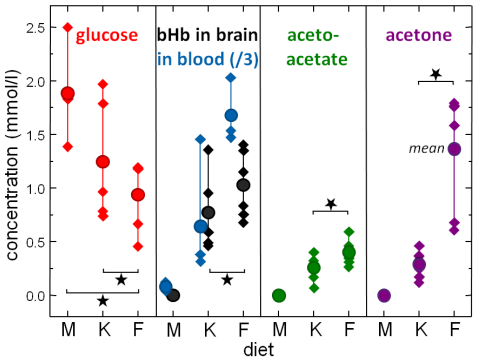

Fig. 2. Metabolite concentrations in both voxels and bHb in blood under mixed (M) and ketogenic (K) diet and fasting (F). ★ $p < 0.05$. Note that for brain ketone bodies zero was assumed at M.

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