Dynamic metabolic changes in liver and muscle tissue under glucose administration detected by ^{31}P MRS

T. Wokrina[1], M. Ulrich[1], M. Gilles[1], D. Kopf[1], G. Ende[1]

[1]NMR Research in Psychiatry, Central Institute of Mental Health, Mannheim, Germany

Introduction

Consequences from the metabolic syndrome and type-2 diabetes like weight gain and dyslipidemia are often assigned to insuline resistance. Aditionally, some antipsychotic drugs such as olanzapine tend to induce hepatic insulin resistance. However, drug-induced hepatic insulin resistance is not necessarily paralleled by peripheral (muscular) insulin resistance. With the use of a hyperinsulinemic euglycemic clamp it is not easily possible to determine where the glucose turnover takes place. The primary objectives of this study were 1) to determine wether phosphorous MRS is capable of measuring dynamic changes in metabolite concentrations under glucose and saline administration in healthy controls and 2) to differentiate between different tissue types of interest. Two tissue types were examined, namely liver and muscle tissue.

Methods

A group of 11 healthy, young male volunteers (mean age 26, SD 2 years) participated in this study. All of them gave written consent to the procedures applied. Firstly, after an overnight fast a hyperinsulinemic euglycemic clamp condition was prepared by a constant insulin infusion at 0.1 mU/kg BW/min. Glucose turnover rates were assessed before with a primed (3.4 mg/m^2/min) glucose infusion. Plasma concentrations were held at the baseline level. After two hours, the MRS examination was performed under clamp conditions. As blood glucose measurements are not feasible during MRS, the rate of glucose infusion was switched to a 110% of the average rate required during the previous 30 minutes in order to prevent hypoglycaemia during MRS. Secondly, the same experiment was performed with saline instead of glucose solution. Both experiments were carried out in a randomized, double blind design.

All MRS measurements were performed on a Siemens Magnetom Vision 1.5 T scanner with a double resonant ^{31}P-^{1}H surface coil (Siemens Medical Solutions, Erlangen, Germany). The 2D phosphorous MRSI measurement parameters included 8 x 8 encoding, TR 522 ms, NEX 32, slice thickness 40 mm and FOV 500 mm. In each examination two ^{31}P MRSI transversal slices were measured (acquisition time 18 minutes / slice). One slice was centered axially within the liver and the other one contained both left and right calf muscles (after repositioning of the volunteer). NOE enhancement and proton decoupling during acquisition was achieved by an independent transmit channel operating at the proton frequency.

The spectra were fitted in the time domain with jMRUI using the AMARES algorithm [1]. The following metabolites were determined: phosphocreatine (PCr), inorganic phosphate (Pi), adenosine 5'-triphosphate (ATP), phosphomono- and phosphodiesters (PME/PDE). Additionally, in the liver spectra a broad unspecified membrane phospholipid (MP) signal was added. Data analysis was done by the use of SPSS for WINDOWS release 12.0.1. In the paired samples T test values of $p < 0.05$ (uncorrected for multiple comparisons) were considered statistically significant.

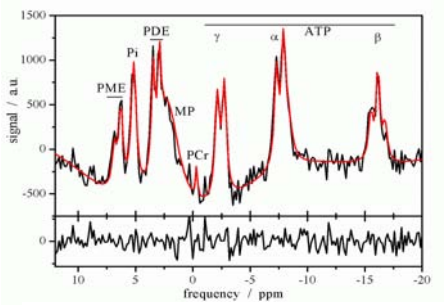

Figure 1: Liver spectrum and residual.

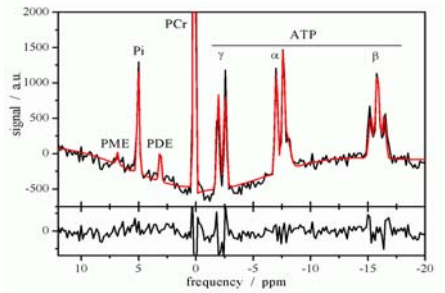

Figure 2: Calf muscle spectrum and residual. Note that the PCr peak maximum is suppressed by a factor of 10.

Results

Representative fitted ^{31}P spectra of liver and calf muscle tissue are shown in Figure 1 and 2 respectively. The absence (or at least strong suppression) of the residual PCr singlet in the liver spectra indicated the correct position of the selected voxel within the liver.

Figure 3 shows that the Pi / γATP and the PME / γATP metabolite ratios increase significantly under glucose adminstration in liver tissue. The values of the Pi / γATP ratio remarkably differ between subjects by up to a factor of 3 under both saline and glucose conditions. However, all subjects showed the same clear trend of an increase of the Pi / γATP ratio when glucose was administered.

The results in the calf muscle tissue are shown in Figure 4. The ratio Pi / Ptotal increases while the ratio PCr / Ptotal decreases under glucose administration. Voxels from left and right calf muscles did not significantly differ. Therefore, the average of left and right metabolite ratios was used. The increase of the ratio Pi / PCr under glucose administration exhibits the lowest $p = 0.002$. This result indicates that the net balance of the creatine-kinase reaction PCr → Cr + Pi is shifted towards the right side. It can be hypothesized that the energy cost of glycogen storage buildup in the calf muscle tissue is brought up by the use of PCr [2].

In conclusion, with ^{31}P MRS we were able to determine dynamic changes of phosphorous metabolite ratios under glucose compared to saline administration in healthy volunteers. Changes could be detected in two different types of tissue, namely liver and calf muscle. Further studies will be needed to further investigate the underlying processes and to better understand the large inter-subject variabilities especially in the liver data.

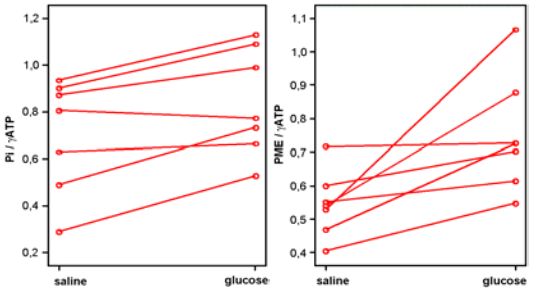

Figure 3: Pi / γATP (left, $p = 0.013$) and PME / γATP (right, $p = 0.025$) ratios under saline and glucose administration in liver tissue (N = 7).

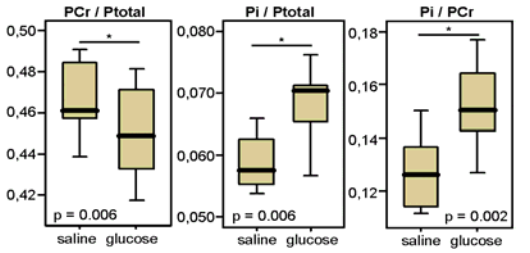

Figure 4: PCr / Ptotal, Pi / Ptotal and Pi / PCr ratios under saline and glucose administration in calf muscle (N = 8).

References

[1] Naressi A, et al., MAGMA 2001;12:141-52, available at www.mrui.uab.es./mrui.

[2] Felig P, Bergman M, The endocrine pancreas: Diabetes mellitus. In: Felig P, Baxter JD, Frohman LA: Endocrinology and Metabolism. Third Edition 1995; McGraw-Hill, New York,1107-1250.