Changes of myocardial lipid content and left ventricular function in the course of acute hypoglycemia and inhibition of lipolysis.

Martin Krssak[1,2], Yvonne Winnhofer[1], Peter Wolf[1], Drazenka Jankovic[1], Sabina Baumgartner-Parzer[1], Rodrig Marculescu[3], Michael Wolzt[4], Siegfried Trattnig[2], Anton Luger[1], and Michael Krebs[1]

[1]Division of Endocrinology and Metabolism, Department of Intrenal Medicine III, Medical University of Vienna, Wien, Austria, [2]Centre of Excellence High Field MR, Department of Radiology, Medical University of Vienna, Wien, Austria, [3]Department of Laboratory Diagnostics, Medical University of Vienna, Wien, Austria, [4]Department of Clinical Pharmacology, Medical University of Vienna, Wien, Austria

Purpose

Tight glycemic control is the most important action to prevent secondary complications in patients with diabetes. This has been repeatedly confirmed for microvascular and neuropathic complications. On the other hand recently published large, randomized prospective clinical trials reported that tight glycemic control, probably due to hypoglycemic episodes, increased cardiovascular mortality in patients with diabetes [1]. At the same time, evidence emerged that heart failure in diabetes is also linked to alterations of myocardial substrate metabolism. It is suggested that hypoglycemia counter-regulation relates to the development of heart failure in patients with diabetes by the action of counter-regulatory hormones as well as free fatty acids (FFA) on myocardial lipid metabolism and cardiac function. Which mechanism mainly contributes to, remains subject of investigation. Myocardial lipid content (MYCL) can be non-invasively measured by magnetic resonance (MR) spectroscopy [2] and it was shown to be elevated in patients with diabetes and associated with left ventricular diastolic dysfunction [3]. Studies on mechanism of MYCL accumulation pointed to the dynamic nature of this compartment and revealed the effects of increased plasma FFA, hyperglycemia and hyperinsulinemia [4,5]. Hence we aimed to study the acute effects of hypoglycemic episode and associated counter-regulation on myocardial function and lipid accumulation. Possible effects of increased lipolysis from adipose tissue caused by hypoglycemia associated counter-regulation were assessed by alternative inhibition of lipolysis. Second aim was the examination of possible changes in hepatocellular lipid content (HCL) which is another co-factor in development of diabetes mellitus.

Methods

Up to now eight healthy young male volunteers (age: 24.7±2.3a, BMI:23.6±3.3kg/m²) underwent 4 study days (SD, summarized in figure) each: SD1: placebo, SD2: hypoglycemia plus placebo, SD3: hypoglycemia plus Acipimox® 250 mg (lipolysis inhibitor) at the time point of 0 and 180 minutes, SD4: Acipimox® only. Hypoglycemia was induced by single dose Insulin Aspart® 1 IU/kgbw i.v. at the time point of 60 min. MYCL, HCL and left ventricular ejection fraction (LVEF) were measured by MR (described bellow) at 0, 180 and 420 min and 24 h.

Figure Time line of individual study days. Time points of MR, hypoglycaemia induction (insulin) and distribution of lipolysis inhibitor (Acipimox®) are noted.

MR measurements of heart and liver were performed at 3T TimTrio/SyngoVB17 MR System (Siemens, Erlangen, Germany). Combination of body-array and spine-multi channel coils was used for signal detection. All scans were performed in the inhale breath-hold position and triggered on ECG signal. Visualization of cardiac function was performed by prospective ECG-gated cine true fast imaging with steady-state precession (TrueFISP) in 2-chamber, 4-chamber and short axes (SA) orientation. SA images were used to quantify left ventricular global (end-diastolic and end-systolic volume, stroke volume, ejection fraction and myocardial mass) via ARGUS software (Siemens). Ejection fraction was used as primary index of LV function. For the MRS (PRESS, TE= 30 ms, individual TR= 750 – 1250 ms according heart beat frequency, dummy scans= 2) of myocardium VOI (15 x 10 x 30 mm^3) was positioned within the inter-ventricular septum in the midway between base and apex. Automatic shimming on adjustment volume avoiding pericardial fat was based on gradient recalled double echo field map acquisition (GRE-SHIM, WIP_452, Siemens). This sequence allows adjustment of the field of view, resolution and acquisition timing. B0 field mapping and frequency adjustment were performed in separate breath holds. Data acquisition was repeated twice for water signal (NS=4) and water suppressed signal (NS= 8) each. For the measurement of HCL similar short echo sequence (PRESS, TE= 30 ms, TR= 2000 ms, NS= 4, ND= 2) was used. VOI (3x3x3 cm^3) was placed in right lateral lobe of the liver and no water suppression was applied. Total experiment time did not exceed 50 minutes for one MR session. Data were processed off line by AMARES algorithm within jMRUI software package. MYCL and HCL were determined as a ratio of the intensities of CH_2 (1.25 ppm) and CH_3 (0.8-0.9 ppm) group resonances to the intensity of the water resonance. Relaxation (T_1 and T_2) correction was performed using values from literature [6-8]. Data are given as mean ± standard error of the mean and ANOVA was used to analyse differences during the time course.

Results

Insulin bolus induced substantial hypoglycaemia in all volunteers (mean minimal plasma glucose concentration: 36.6±4.7mg/dl). In the course of hypoglycemia associated counter-regulation we could observe transient increase of LV EF (SD2: +10.7 % of baseline, p=0.02) without changes in MYCL. Twenty-four hours later decrease of MYCL (SD2: -34% of baseline, p=0.06) could be detected. Suppression of adipose tissue lipolysis (Acipimox, SD3 and SD4) yielded acute reduction (240 min) of MYCL (~45% of baseline, p=0.03) and decrease of LVEF (-9.5% of baseline, p=0.01). HCL did not significantly change on any study day.

Conclusion

Hypoglycemic counter-regulation induced lipolysis from adipose tissue can overcome shortage of glucoce substrate and supply sufficient energy for myocardium, which uses MYCL stores in course of next 24 hours. Specific inhibition of adipose tissue lipolysis leads to acute decrease of MYCL stores and reduction in left ventricular function. This leads to the conclusion, that MYCL pool plays a major role for the maintenance of myocardial function.

References

[1] Patel et al. N Engl J Med 358:2560-72. (2008) [2] Szczepaniak et al. Magnetic Resonance in Medicine 49:417–423 (2003) [3] Rijzewijk et al. J Amer Col Cardiol 52: 1793–9 (2008) [4] van der Meer et al. J Clin Endocrinol Metab. 93(7):2702–2708 (2008) [5] Winhofer et al. Diabetes 61(5):1210-6 (2012) [6] Krssak et al. Magn Reson Mater Phys. 16: 155–159 (2004) [7] Gambarota et al. Magn Reson Mater Phys 24(6):339-45 [8] de Bazelaire et al. Radiology 230:652–659 (2004)