Intranasal insulin improves energy metabolism in humans

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Target audience: General audience and those dealing with metabolism and MR spectroscopy.

Purpose: Intranasal insulin (INI) is known to modulate food intake and food related activity in the central nervous system. It has been recently shown that INI suppresses endogenous glucose production (1). Further changes of the hepatic energy metabolism in humans have not been studied yet. This study investigates the acute effects of central and peripheral insulin on hepatic adenosine triphosphate (ATP) and inorganic phosphate (Pi) content in healthy humans.

Methods: Eight lean humans (age 26±2 yrs, BMI 23±1 kg/m^2) received intranasal insulin to mimic central insulin delivery (160 IU; Actrapid, Novo-Nordisk, Denmark) or placebo in a randomized, single-blinded, cross-over trial. In an additional intervention intravenous insulin (IVI) was adminstered mimicking the increased serum insulin concentrations after intranasal insulin without the central effect on the brain. Adenosine triphosphate (ATP) concentrations were determined at baseline and 3 hours after intervention by ^{31}P magnetic resonance spectroscopy on a 3T clinical MR scanner (Philips, Best). Liver fat (HCL) was measured at baseline to correct for fat infiltration in the liver in the ^{31}P absolute quantification.

For the acquisition of ^{31}P spectra a volume of interest of 6x6x6 cm^3 was positioned within the liver and 3-D localized liver spectra were obtained using image selected MRS (TR = 4 s, NSA = 192, spectral width: 3000 Hz, data points: 2K). Absolute quantification of liver phosphorus metabolites (γ-ATP and P_i) was performed as described (2) using the AMARES algorithm in jMRUI.

For intraday reposition the position of the coil was marked on the skin of the volunteers after the first measurement.

For assessment of liver fat content, a set of non-water suppressed ^{1}H spectra were acquired using stimulated echo acquisition mode (TR/TE/TM=4000/10/16 ms, NSA=32, VOI=3x3x2 cm^3). Data from ^{1}H MRS was analyzed to assess fat content as described by (3) and absolute concentrations were expressed as percent hepatocellular lipids relative to water content (HCL).

Results: The liver ATP concentration is increased by 25.7 ± 23.5% after intranasal insulin (p = .02, paired t-test), while it remains constant in the range of the COV of the measurement after intravenous insulin (+1.4 ± 13.7%) and in control subjects (+ 8.7 ± 14.3%). Inorganic phosphate slightly increased after INI (+ 13.5 ± 27.7%, non-significant) and placebo (+19.3 ± 17.6%, non-significant) and decreased after IVI (-11.1 ± 12.7%, non-significant). Liver fat content was below 2% for all subjects.

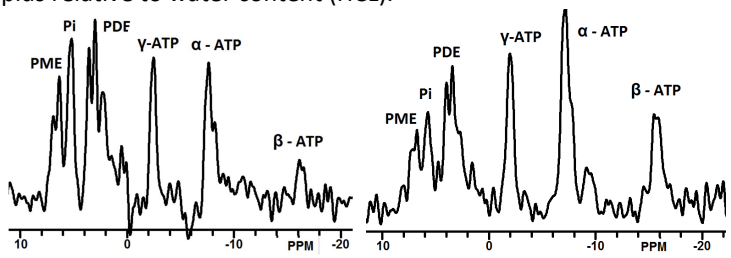

Fig. 1 31P liver spectrum of a healthy subject before and after INI administration

Discussion:

The novel finding of the present study was the rise in hepatic γ-ATP after intranasal insulin administration. It has been shown that insulin can acutely increase adenine nucleotide content in hepatocytes (4) and maintain liver ATP flux (5) and that intranasal insulin can enhance energy levels in brain (6). Therefore we suggest that brain insulin signaling contributes to regulation of liver energy homeostasis.

This study uncovered the spill-over of intranasal insulin into the systemic circulation. Based on the comparison between INI and IVI we have shown that the effect of intranasal insulin does not arise solely from the spill-over of insulin into the peripheral tissue.

In conclusion, intranasal insulin application can improve hepatic energy metabolism in healthy humans.

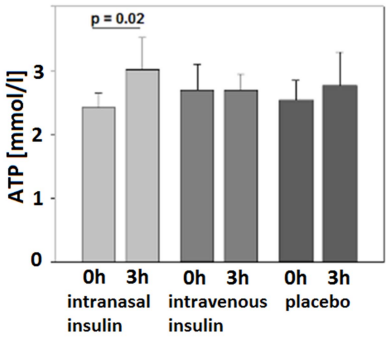

Fig. 2 ATP concentration before and after placebo, intranasal and intravenous insulin

References: 1. Dash S, et al. Diabetes 2014. published ahead of print 2. Laufs A, et al. Magn Reson Med 2014. 3. Hamilton G, et al. NMR Biomed, 2011. 24(7): p. 784-90. 4. Obici S, et al. Nat Med, 2002. 8(12): p. 1376-82. 5. Pocai A, et al. Nature, 2005. 434(7036): p. 1026-31. 6. Jauch-Chara K, et al. Diabetes, 2012. 61(9): p. 2261-8.

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