Flow and metabolism remain coupled in acute insulin induced hypoglycemia in human brain

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Introduction: How the brain functions under conditions of acute hypoglycemia remains a complex question, by virtue of the potential simultaneous shifts in processes of perfusion, metabolism and changing demand. Human studies by FDG PET are limited since deoxyglucose itself is known to increase cerebral perfusion (1). In the present study we examined this issue by measuring cerebral blood flow and oxidative metabolism in insulin induced hypoglycemic (HG) and euglycemic (EG) conditions at rest and during sensorimotor activation in normal human subjects.

Methods: **Infusion** Experiments were performed on 6 subjects (5M, 1F). The overall protocol was comprised of an insulin induced hypoglycemia (targeting a HG of 60mg/dl) followed by euglycemia, each phase lasting approximately 1.5hrs. The hypoglycemia was achieved using an insulin bolus of 1.6mU/kg/minx10min followed by a maintenance rate of 0.8mU/kg/min with variable glucose infusion rates. This protocol achieved hypoglycemia within 30min. Euglycemia was performed with the same insulin infusion rate so as to match the hypoglycemic phase. MR data were acquired 30min after the target plasma glucose was achieved so as to minimize any acute effects. After the HG phase the subject was removed from the magnet to ensure comfort and was then repositioned for the EG phase. Heart rate was monitored continuously and blood glucose was monitored at q5min intervals. **Activation** BOLD fMRI was performed in 2 blocks during EG and HG. Each block consisted of paced sequential finger tapping (~2Hz) on both hands for alternating between 30sec of rest and activity for 2 cycles. Multislice imaging data were motion corrected and convolved with a 3D gaussian filter. Statistical maps were created in E and H conditions with a Bonferroni-corrected p value of 0.01. Activation was characterized in terms of number of pixels above statistical threshold as well as the change in signal intensity within a fixed ROI (~100 pixels) in sensorimotor cortex. **MR** All data were acquired using a 4T Varian Inova whole body system with a 1H TEM head coil. ASL perfusion was measured using the FAIR technique in conjunction with single shot EPI with in plane saturation (TI=1.8s, TR=4s, res=64x64, FOV=19.2cm, thk=4mm). CBF was evaluated from 20 pairs of control and label images. At each glucose level, two CBF measurements were done during rest and during motor activation. R2/R2* relaxation rates were determined in EG and HG by a hybrid multi gradient echo/spin echo sequence (TR=1.2s, res 128x128, FOV 19.2, 16 gradient echoes 2.5msec/echo, TE=50msec and 80msec) with static field inhomogeneity correction (2). The BOLD relaxation rate is given by R2'=R2*-R2.
Model: The ratio of CMRO2 values during EG and HG was evaluated from the CBF and relaxation data as (2-4); $CMRO2(E)/CMRO2(H) = [(R2'(E)/R2'(H))^{1/\beta}]*[(CBF(E)/CBF(H))^{(1-\alpha/\beta)}]$, where α is the coupling exponent between flow and volume (α =0.38) and β is the coupling exponent between deoxyhemglobin concentration and transverse relaxation rate (β =1.5) (3,4). CBF and CMRO2 were evaluated for gray and white matter across the entire imaging slice as well as ROI analysis in sensorimotor cortex.

Results: There was variability in the provoked blood flow changes with the mild hypoglycemia; however in 5 of 6 subjects, blood flow (sensorimotor cortex) increased by +18±10 percent ($p<0.05$). However, the absolute CBF response during activation was not significantly different between EG and HG conditions, with ΔCBF_{EG} = 12±3, ΔCBF_{HG} = 12±3 (ml/100g/min). There was a general correlation between CBF and CMRO2 changes in EG and HG (Fig 1), implying that basal flow and metabolism remain coupled under varying conditions of plasma glucose. Fig. 2 shows the changes in BOLD response (% signal change) during EG and HG were inversely correlated with the changes in resting metabolism.

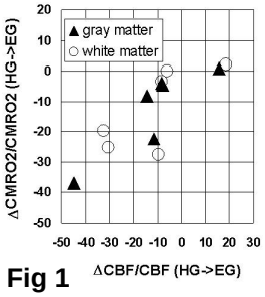

Fig 1

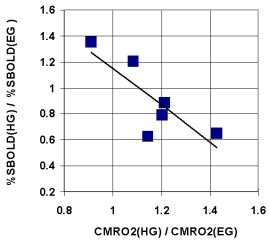

Fig 2

Conclusions: These data are consistent with the known variability in hypoglycemia induced perfusion changes, although still finding an increase in blood flow. Analysis of the R2/R2* data in EG and HG conditions suggests that although there is variability in the blood flow response, that CMRO2 remains coupled to CBF (Fig 1). The consistency of sensorimotor activation induced blood flow changes in either EG or HG suggest that the activation responses in mild hypoglycemia are primarily determined by blood glucose driven changes in basal flow and metabolism with minimal changes on activation induced neuro-vascular response. Thus, there appears to be increased oxygen consumption in spite of the acute mild hypoglycemia, and neurovascular coupling does not appear perturbed.

References: 1 Breier A et al Brain Res 618:277 1993 2) An H. et al, Mag Res Med 47:958-966, 2002 3) Hoge et al., Mag Res Med, 42, 849-863, 1999, 4) Lawrence et al Mag Res Med 50,99-106, 2003. **This work is supported by NIH DK64565 and M01 RR12248**.