Acute and chronic effects of glucose on brain metabolism: findings from healthy subjects and diseased conditions

Feng Xu[1], Peiying Liu[1], Juan Pascual[2], Xuchen Zhang[2], and Hanzhang Lu[1]

[1]*Advanced Imaging Research Center, University of Texas Southwestern Medical Center, Dallas, TX, United States,* [2]*Department of Neurology, University of Texas Southwestern Medical Center, Dallas, TX, United States*

INTRODUCTION: Glucose is the primary source of energy for the brain. However, the effect of glucose availability on brain metabolic rate is poorly understood. This is mainly due to a lack of suitable techniques. Recently, we have developed an MR method that can provide a non-invasive (no exogenous agent), fast (<5 min), and reliable (coefficient of variation, CoV<3%) measurement of global cerebral metabolic rate of oxygen ($CMRO_2$) on a standard 3T system (1,2). In the present study, we applied this new $CMRO_2$ technique to examine the impact of glucose availability on brain metabolism. We sought to answer three questions: 1) how might an acute increase in blood glucose level alter $CMRO_2$ in healthy controls? 2) how a chronic deprivation of glucose could influence the brain's $CMRO_2$ level and this was conducted in a group of patients with an inborn metabolic disease, genetic deficiency of glucose transporter protein type I, "Glut-1 DS". 3) how could an acute increase of blood glucose level in these patients transiently alter their $CMRO_2$?

METHODS: ***Experiments:*** All experiments were performed on a 3T Philips system. Nine healthy subjects (age 25.1±4.6yrd, 4F 5M) were enrolled for the acute glucose challenge. The subjects arrived at the imaging Center around 7:30am after overnight fasting and their blood glucose levels were measured. After being positioned on the magnet table and immediately before entering the bore, the subjects drank liquid containing 50g glucose. MR imaging started promptly and a series of 9 $CMRO_2$ measurements were made continuously (total duration 40 min). While not measured in the present study, previous literature has established that the blood glucose level during this period should increase continuously (3). The first $CMRO_2$ time point, which was completed within 10 min after the glucose consumption, is expected to reflect fasting $CMRO_2$ level. Blood glucose levels were measured again after the MRI experiment was completed.

Glut-1 DS is a rare genetic disease in which a protein called glucose transporter is mutated (one of two copies is muted) and these patients only have half the capacity for glucose transport in the brain. This creates a scenario that, although there is abundant glucose in the blood stream, the brain is "starving" for fuel. This condition provides an ideal model for our investigation of the effect of glucose availability on brain metabolism. We studied 5 Glut-1 DS patients (age 19.8±4.8 y, 2 F 3 M, 4 patients flew in from out-of-town) with protocols similar to those used for the healthy group. The only difference was that, instead of 9 points of dynamic measurements of $CMRO_2$, we only performed 2 $CMRO_2$ measurements in these patients as some of them were not able to stay still for a long period of time. One $CMRO_2$ was measured before the glucose intake and the other was performed 40min after the intake.

Data analysis: Global $CMRO_2$ (in unit of μmol O_2/min/100g brain tissue) was quantified by a method described previously (3) and was based on the Fick principle, i.e. $CMRO_2=CBF \times C_h \times OEF$, where OEF (oxygen extraction fraction) $=Y_a-Y_v$, CBF (ml/min/100g) is cerebral blood flow, C_h (μmol O_2/100ml blood) is a constant representing the capacity of blood to carry O_2, Y_a (%) and Y_v (%) are arterial and venous oxygenation, respectively. Y_a, Y_v, and CBF were measured with pulse Oximetry, TRUST MRI (4), and Phase-contrast MRI (3), respectively, and were used to calculate $CMRO_2$ based on the above equation. For the dynamic $CMRO_2$ data from the healthy controls, a mixed effect linear model was used to evaluate possible changes of $CMRO_2$, CBF, and OEF with post-ingestion time. For data from the Glut-1 DS patents, t tests were used to compare parameters before and after the glucose intake.

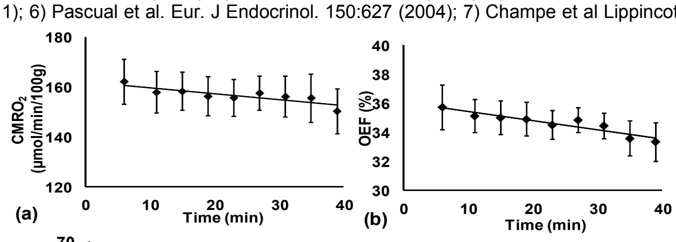
RESULTS and DISCUSSION: ***Healthy control data:*** As expected, blood glucose levels increased after the glucose intake (from 91±6 mg/dL to 138±24 mg/dL, P<0.001). Interestingly, $CMRO_2$ showed a significant reduction with time (P=0.002, Fig. 1a). This appears to be attributed to a decrease in OEF (P=0.026, Fig. 1b) while CBF is unchanged (P=0.89, Fig. 1c). Comparing $CMRO_2$ at the end to the beginning of the experiment, the healthy subjects demonstrated a 6.3±4.7% $CMRO_2$ reduction (P=0.007, Fig. 2b). Note that this $CMRO_2$ change is not likely due to the subject becoming drowsy or asleep after being inside the magnet for a while, because we have previously conducted a sham control study and the $CMRO_2$ (as well as OEF and CBF) was unchanged within 60 minutes (5). As a side note, $CMRO_2$ in females were 10% (P=0.007) higher than male subjects.

Glut-1 DS patient data: Blood glucose levels in Glut-1 DS patients were 87±7 mg/dL and 149±28mg/dL for fasting and fed states, respectively, confirming that their glucose digestion system and blood concentration were normal. Cross-sectional comparison between the patients and controls at baseline showed that $CMRO_2$ of the Glut-1 DS patients was 6% lower (P=0.03, Fig. 2a), suggesting that these patients suffered from glucose deprivation (in the brain, but not in the blood). This was found to be attributed to a lower OEF (P=0.007) in the patient group.

In Glut-1 DS patients, ingestion of glucose increased $CMRO_2$ by 4.7±3.9% (P=0.03, Fig. 2b), a pattern opposite to that in healthy controls. This finding is consistent with clinical findings in these patients that brain EEG signals typically become normalized after a meal (6).

The present study used a novel $CMRO_2$ technique to understand the acute and chronic effects of glucose on brain metabolism. In healthy subjects, acute increase in blood glucose level (e.g. after a meal) resulted in a reduction in $CMRO_2$. There are two possible explanations that are not mutually exclusive. One is that the brain's arousal level is decreased by the surging glucose level due to hormonal effects (e.g. insulin release) and this is consistent with the common perception of drowsiness after a meal. A second mechanism is that, in fasting state, the brain starts to use small amount of ketone bodies for fuel source when the blood glucose level is low, and ketone metabolism consumes more O_2 for the same amount of ATP (7), which is why the fasting $CMRO_2$ was higher. This possibility was supported by blood ketone data measured in the present study, which was significantly higher (P=0.03) in the fasting state compared to the fed state. Our study also showed that patients who have impaired glucose transport in the brain manifested reduced $CMRO_2$ and this is partly normalized after the glucose ingestion, which presumably increased blood-brain glucose gradient and therefore augments the net glucose transfer.

REFERENCES: 1) Liu et al. ISMRM (2012); 2) Xu et al. MRM 62:141 (2009); 3) Messier et al Eur J Pharmacol 490:33 (2004); 4) Lu and Ge MRM, 60:357 (2008); 5) Xu et al. JCBFM 31:58 (2011); 6) Pascual et al. Eur. J Endocrinol. 150:627 (2004); 7) Champe et al Lippincott's illustrated Reviews Biochemistry 4th ed. Wolters Kluwer and Lippincott Williams & Wilkins.



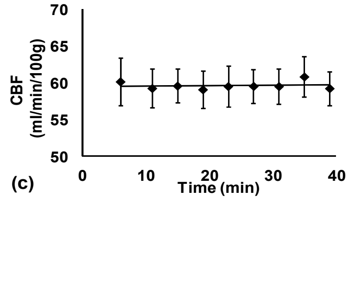


Fig. 1: Time courses of (a) $CMRO_2$, (b) OEF and (c) CBF after glucose ingestion. There was a significant time-dependent change in $CMRO_2$ (P=0.002) and OEF (P=0.026), but not in CBF (P=0.89). The error bar indicates standard error.

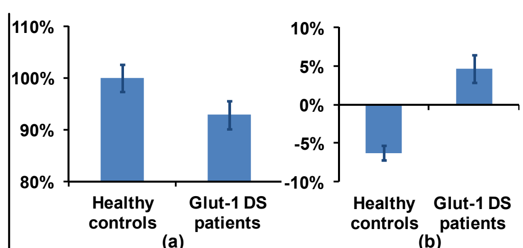


Fig. 2: (a) Differences in baseline $CMRO_2$ comparing patients to healthy controls. (b) Acute effects of glucose on $CMRO_2$. Note that $CMRO_2$ was decreased by glucose ingestion in controls, but the effect was opposite in Glut-1 DS patients.