Acute and chronic effects of glucose on brain metabolism: findings from healthy subjects and diseased conditions
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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, CV<3%) measurement of global cerebral metabolic rate of oxygen (CMRO2) on a standard 3T system (1,2). In the present study, we applied this new CMRO2 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 CMRO2 in healthy controls? 2) how a chronic deprivation of glucose could influence the brain’s CMRO2 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 CMRO2?

METHODS: Experiments: All experiments were performed on a 3T Philips system. Nine healthy subjects (age 25.1±4.6 y, 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 CMRO2 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 CMRO2 time point, which was completed within 10 min after the glucose consumption, is expected to reflect fasting CMRO2 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 mutated) 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 impact 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 CMRO2, we only performed 2 CMRO2 measurements in these patients as some of them were not able to stay still for a long period of time. One CMRO2 was measured before the glucose intake and the other was performed 40 min after the intake.

Data analysis: Global CMRO2 (in unit of µmol O2/min/100g brain tissue) was quantified by a method described previously (3) and was based on the Fick principle. i.e. CMRO2 = CBF·XOEF, where OEF (oxygen extraction fraction) = Yv / Yw. CBF (ml/min/100g) is cerebral blood flow, C (µmol O2/100ml blood) is a constant representing the capacity of blood to carry O2. Yv (%) and Yw (%) are arterial and venous oxygenation, respectively. Yv, Yw, and CBF were measured with pulse Oximetry, TRUST MRI (4), and Phase-contrast MRI (3), respectively, and were used to calculate CMRO2 based on the above equation. For the dynamic CMRO2 data from the healthy controls, a mixed effect linear model was used to evaluate possible changes of CMRO2, CBF, and OEF with post-ingestion time. For data from the Glut-1 DS patients, 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, CMRO2 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 CMRO2 at the end to the beginning of the experiment, the healthy subjects demonstrated a 6.3±4.7% CMRO2 reduction (P=0.007, Fig. 2b). Note that this CMRO2 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 CMRO2 (as well as OEF and CBF) was unchanged within 60 minutes (5).

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 CMRO2 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 CMRO2 by 4.7±3.9% (P=0.03, Fig. 2b), a pattern opposite to that in healthy controls. This 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 CMRO2 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 CMRO2. 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 O2 for the same amount of ATP (7), which is why the fasting CMRO2 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 improved glucose transport in the brain manifested reduced CMRO2 and this is partly normalized after the glucose ingestion, which presumably increased blood glucose gradient and therefore augments the net glucose transfer.


**Fig. 1.** Time courses of (a) CMRO2, (b) OEF and (c) CBF after glucose ingestion. The CMRO2 technique can depict time-dependent change in CMRO2 (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 CMRO2 comparing patients to healthy controls. (b) Acute effects of glucose on CMRO2. Note that CMRO2 was decreased by glucose ingestion in controls, but the effect was opposite in Glut-1 DS patients.