

Cerebral blood flow response to hypoglycemia in type 1 diabetes

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Introduction

Patients with type 1 diabetes and hypoglycemia unawareness have a reduction in the hormonal counterregulatory response to decreasing blood glucose (BG) levels and are unable to detect hypoglycemia before they become neuroglycopenic. A critical brain region for BG sensing is the hypothalamus. PET studies (Teves et al., 2004) as well as MRI studies (Page et al., 2009) have shown increased cerebral blood flow (CBF) in the hypothalamus and thalamus of healthy controls during insulin-induced hypoglycemia. In particular, the hypothalamic perfusion was found to increase before the counterregulatory hormones response in healthy controls (Page et al. 2009). The hypothalamic activation to hypoglycemia has been investigated in a population of type 1 diabetic patients not noted to have hypoglycemia unawareness with the blood oxygenation level (BOLD) contrast (Musen et al., 2008); interestingly, the glucose threshold for hypothalamic activation as measured by BOLD was found not to differ between these patients and controls. In this study, we tested the hypothesis that subjects with type 1 diabetes and hypoglycemia unawareness will have reduced activation of cerebral areas involved in glucose sensing during experimental hypoglycemia as compared to health controls. To make quantitative comparisons between these groups, we measured the hemodynamic response using arterial spin labeling techniques at 3 Tesla.

Methods

Fourteen subjects between 18 and 65 years of age participated to the study. Seven subjects had type 1 diabetes with hypoglycemia unawareness verified by Cox questionnaire (Clarke et al., 1995). The remaining subjects were healthy controls matched for age, gender, and body mass index. Cerebral blood flow measurements were performed on a 3 T scanner, using a protocol of pulsed arterial spin labeling technique (Luh et al., 1999). A slab of 15 slices 3.5 mm thick, with 1 mm interslice gap was positioned around the midbrain regions. High resolution 3D T1-weighted acquisitions were also performed for anatomical references. Glycemic levels were controlled by a two-step hyperinsulinemic clamp in which blood glucose was first maintained at 100 mg/dL and then dropped to 50 mg/dL. Perfusion measurements were performed as soon as the desired levels of glucose concentration became stable. Blood was collected for subsequent measurement of counterregulatory hormones and a questionnaire aimed at rating the typical symptoms associated with hypoglycemia was conducted under the hypoglycemic condition. Maps of t-test values were generated to compare CBF of controls vs patients, in conditions of both normoglycemia and hypoglycemia, and to compare the CBF variations induced by hypoglycemia (Δ CBF) of controls vs patients. Prior to the group analysis, CBF data were superimposed to the anatomical references, and standardized to the Talairach space.

Results and discussion

CBF of healthy controls was found to be generally lower as compared to patients in normoglycemia, whereas several brain regions of controls manifested higher CBF than patients during hypoglycemia. Overall, highly significant differences in the variations of CBF induced by hypoglycemia were found to occur between controls vs patients mainly in the thalamic region. Specifically, while the CBF increased significantly in the thalamus and hypothalamus of healthy controls, this hemodynamic response was largely absent in patients (Figure 1), implying that a BG threshold of 50 mg/dL was still not sufficient to induce a physiological hypothalamic CBF increase in type 1 diabetes unaware patients. This finding is consistent with a lack of counterregulatory response in these patients, which was confirmed by a significant reduction in the hormonal counterregulatory response and symptom scores compared to controls.

Conclusion

Arterial spin labeling techniques can successfully characterize the hemodynamic response to hypoglycemia. Critical differences in the thalamic regions were identified between controls and type 1 diabetes unaware patients, consistent with reduced glucose sensing and impaired counterregulation to hypoglycemia in these patients.

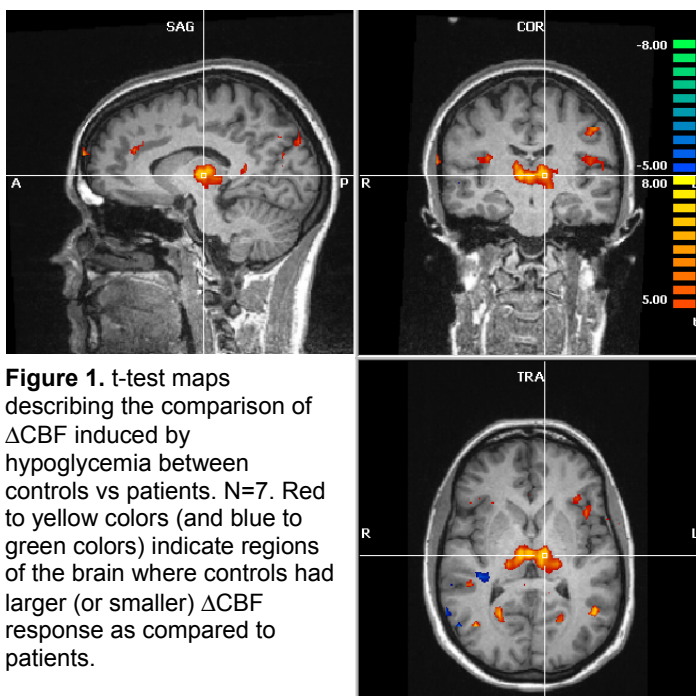


Figure 1. t-test maps describing the comparison of Δ CBF induced by hypoglycemia between controls vs patients. N=7. Red to yellow colors (and blue to green colors) indicate regions of the brain where controls had larger (or smaller) Δ CBF response as compared to patients.

References: Clarke WL et al (1995) Diabetes care 18:517-22; Luh WM et al (1999) Magnetic Resonance in Medicine 41:1246-54; Musen G et al (2008) The Journal of Clinical Endocrinology and Metabolism 93:1450-7; Page KA et al (2009) Diabetes 58:448-52; Teves D et al (2004) Proceedings of the National Academy of Sciences of the United States of America 101:6217-21.

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