Hypoglycemia activation of cerebral blood flow is mediated by glucose transporter isoform 2: an in vivo CASL study

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PURPOSE
Recent studies suggested that glucose transporter isoform 2 (GLUT2) could facilitate hypoglycemia-induced hormonal secretions1 and might play an important role in other hypoglycemia-related responses. For example, the underneath mechanism of hypoglycemia activation of cerebral blood flow (CBF) remained not well understood2. Thus, we aimed to study the roles of GLUT2 in hypoglycemia-induced CBF increase. In this study, we applied the continuous arterial spin labeling MRI technique on GLUT2−/− mice and their counterparts at euglycemia and insulin-induced hypoglycemia.

METHODS
Animals: GLUT2−/− mice were derived along with transgenic re-expression of GLUT1 in the pancreatic β− cells as previously described (RIPGLUT1GLUT2−/−)1. At age of 16-20th weeks, animals were prepared and well maintained under 1-2% isoflurane thereafter to maintain breathing rates >100bpm, which had been shown capable of maintaining mice under physiological conditions, such as PaCO2 in the range of 35-45mmHg. Tail bleeds were sampled and measured for glucose levels (Breeze glucose meter) immediately before and right after MR measurements, which were approximately one hour. An adjusted insulin infusion protocol, i.e. a bolus followed by a continuous rate, induced hypoglycemia in all mice. Once tail bleed glucose levels were reached less than 2mM, as hypoglycemic condition, the animals were scanned again. MR measurements: All MR measurements were performed at 9.4T (26cm diameter). CBF was measured using a well-established continuous arterial spin labeling (CASL) technique in combination with a home-built actively-detuned system. Four segmented semi-adiabatic EPI sequence was adopted with a labeling module to implement the CASL sequence (3 consecutive 2mm-thick slices, 23×15mm2, 128×64 data matrix). Cerebral blood flow (CBF) was assessed at euglycemia and hypoglycemia. Data Analysis: CBF maps were calculated from 16 paired labeled and controlled images with a labeling efficiency 0.83. Significant difference was when p<0.05.

RESULTS AND DISCUSSION
Glucose levels before insulin infusion were 10.1±1.4mM (mean±SDs, 8.6-12.4mM) in WT mice and 7.8±2.9mM (mean±SDs, 4.3-12.4mM) in RIPGLUT1GLUT2−/− mice, both of which were beyond hypoglycemia. While at euglycemia, CBF was globally higher in RIPGLUT1GLUT2−/− mice and significant in hippocampus (Figure 1, Table 1). When administrating 25.2±5.9UI/kg insulin in the WT mice and 15.1±1.6UI/kg insulin in those RIPGLUT1GLUT2−/− mice, hypoglycemia condition was reached, i.e. 1.6±0.2mM (mean±SDs, 1.2-2.3mM) in the WT mice and 1.2±0.1mM (0.9-1.6mM) in the knockout mice, respectively. While at hypoglycemia, CBF changes of WT mice were beyond 30% and however CBF changes in RIPGLUT1GLUT2−/− mice were diminished (Figure 2).

The observed CBF increases upon hypoglycemia in the WT mice were consistent, but with a less degree, with previous study in other rodents2,4, which might due to the effects of isoflurane5.

CONCLUSION
In conclusion, our results in the RIPGLUT1GLUT2−/− mice suggested that hypoglycemia activation of cerebral blood flow could be mediated by GLUT-2 glucose transporter.

REFERENCES
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