

Effect of lactate on fMRI responses under hypoglycemia

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INTRODUCTION

Diabetes complications can be reduced by tight control of blood glucose using insulin, increasing the chance for severe and potentially lethal hypoglycemic episodes. Hypoglycemia can impair performance during a variety of cognitive tasks and electrophysiologic measurements of cortical and brainstem function in humans (1). Previous studies have shown that during hypoglycemia, the brain is able to utilize alternative fuel sources other than glucose to support brain function, such as lactate and ketone bodies. ¹³C-MRS studies using [3-¹³C]-lactate suggest that lactate can support neuronal energetics (2, 3), however the effect of lactate on brain function itself is not well understood. The goal of the current work was to investigate BOLD response to forepaw stimulation during different glycemic states that may serve as signatures of functional impairment caused by decrements in glucose delivery to the brain and the effect that lactate itself may have on brain function under hypoglycemic condition.

MATERIALS and METHODS: Animal preparation: Sprague-Dawley rats were anesthetized with isoflurane, tracheotomized and ventilated (70% N₂O, 30% O₂). After surgery rats were administered α -chloralose (~40 mg/kg/hr, I.P.) and isoflurane was discontinued. D-tubocurarine chloride (1 mg/kg/hr) was administered as a muscle relaxant. The femoral artery was cannulated for continuous blood pressure assessment and physiology measurements (blood pH, pO₂, pCO₂). Two femoral veins were cannulated for infusion of insulin, glucose, and lactate. **Forepaw stimulation:** Electrical stimulation (0.3 ms square wave pulses, 2 mA amplitude at 3 Hz) was delivered through thin needle copper electrodes inserted beneath the skin of the forepaw. The stimulus was controlled with a computer by custom written scripts with a 30s-off, 30s-on block design. **fMRI (n=5):** All fMRI data were obtained on a modified 11.7T Bruker horizontal-bore spectrometer (Billerica, MA) using a ¹H surface coil ($\varnothing = 1.4$ cm). The images were acquired with gradient-echo EPI sequence (TR/TE = 1000/15). **Hypoglycemic clamp and lactate infusion:** A gradual fall in glucose level was achieved using a steady infusion of regular insulin (50mU/kg/min) with a variable infusion of 20% glucose. After reaching a steady state plasma glucose level (40 \pm 5 mg/dL) for 1 hour, a lactate infusion was initiated. A bolus of 0.35 M lactate (1370ul/kg in 15 s) was immediately followed by a step down infusion of 428 ul/min/kg, then decreased to 162.8 ul/min/kg over 20min which was then maintained for the rest of the experiment. This infusion protocol resulted in a steady plasma lactate level of ~3mM.

RESULTS and DISCUSSION:

We evaluated forepaw stimulation-induced fMRI activity patterns in rat somatosensory area under different glycemic conditions. Electrical stimulation of the forepaw (2 mA, 0.3 ms duration pulses, 30 s) evoked a strong positive BOLD signal change in the contralateral primary somatosensory area of the forelimb (S_{1FL}) under euglycemia, as well as during mild hypoglycemia (plasma glucose 60-50mg/dL for <1 h) (Fig. 1A,B). The magnitude of the BOLD response was significantly reduced in S_{1FL} during hypoglycemia (plasma glucose <50 mg/dL for >1 h). The mean BOLD signal changes during forepaw stimulation under euglycemia, mild hypoglycemia and hypoglycemia were 4.6 \pm 1.7%, 2.0 \pm 0.6% and 0.6 \pm 0.2% respectively (Fig. 1 A-C). Infusion of lactate for 30 min under hypoglycemic condition helped to recover the functional response at the S_{1FL} region up to 1.3 \pm 0.4%, but lactate can only support a short period (~70 minutes) of functional response. In addition, there were significant BOLD responses in other regions beyond S_{1FL} upon lactate infusion (Fig. 1D), suggesting that lactate supports greater delocalization of activity during hypoglycemia compared to the highly focal response at euglycemia. Electrophysiological studies are underway to test whether the delocalized BOLD responses to lactate elevation reflect neuronal activity or altered blood flow.

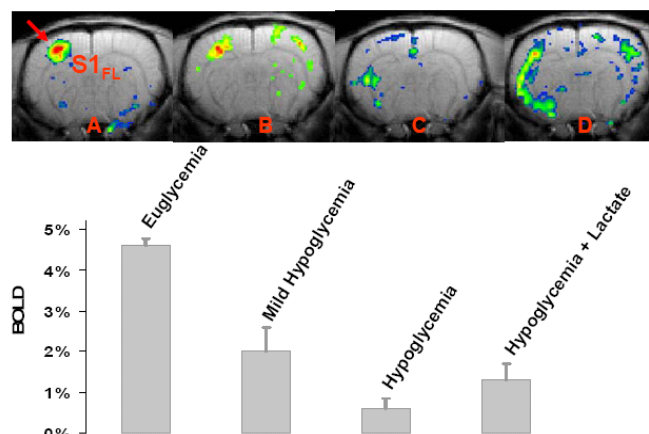


Fig.1 BOLD activations (11.7T) during forepaw stimulation (2 mA, 3Hz): fMRI data using a single run scan of block design paradigm (stimulus duration 30s). Top panel: Single trial response during euglycemia (glucose: 117 mg/dL) (A), mild hypoglycemia (glucose 57mg/dL) (B), hypoglycemia (glucose 37 mg/dL)(C), and Lactate+hypoglycemia (glucose 37mg/dL)(D). Bottom panel: Averaged data from S_{1FL} from five subjects.

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