

Functional MRI of Hypothalamic Responses to Circulating Glucose and Fatty Acids

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Introduction:

Hypothalamic sensing of circulating nutrients, such as glucose or fatty acids, has recently been implicated in the regulation of glucose homeostasis [1,2]. The mechanism(s) by which the hypothalamus responds to physiological increases in the plasma glucose or fatty acids levels has not been established. Hypothalamic activation via glucose intake has been examined using fMRI and PET in both humans and animal models [3,4]. After glucose loading/ingestion, fMRI has shown that BOLD signal intensities decrease. However, none of the previous reports have addressed the relative contribution of hypothalamic glucose sensing and the associated increase in plasma insulin that occurs during hyperglycemia. Therefore, the purpose of this study is, 1) to test whether glucose sensing, isolated from changes in insulin levels, can induce a decrease in BOLD signal as detected by fMRI, and 2) to compare those results with the effect of fatty acids sensing in the hypothalamus, specifically by measuring $R2^*(1/T2^*)$ changes.

Methods:

Infusion Protocol: Rats (Sprague-Dawley, 250 –300g) were anesthetized using 2% isoflurane and a femoral vein was catheterized for infusion. A total of 9 overnight-fasted rats were studied (N=5 for glucose infusion; N=4 for lipid infusion with 20% Intralipid® [Baxter, Deerfield, IL]; plasma fatty acids levels elevated ~ 2.5 fold). To induce and maintain high plasma glucose level (~400mg/dl), 0.5 ml of 50% glucose was bolus injected, followed by a maintenance infusion of 33 % glucose. To remove the effect of insulin secretion due to glucose increase, somatostatin was co-infused intravenously. Saline and somatostatin were infused prior to hyperglycemia induction and MRI measurements were taken as control studies against the subsequent hyperglycemia (or hyperlipidemia) period.

MR Imaging: All experiments were performed on a 9.4T Varian imager/spectrometer. To minimize head motion artifact, the rat head was secured using ear and bite bars. MR studies were performed using a head volume coil or volume transmit (i.d.6.5 cm)/surface receive (2.5cm *2.0 cm ellipsoid) coils. Rat body temperature was maintained at $37.0^{\circ}\text{C} \pm 0.5^{\circ}\text{C}$ with circulating heated water.

The slice of interest (bregma ~ -2.5 to -3.5 mm) was determined using anatomical images. On the selected axial slice, B_0 homogeneity was optimized using an automated non-iterative shimming program [5] resulting in a typical linewidth of ~ 30-40 Hz at 9.4T. Gradient echo images were continuously acquired with multiple echoes (5, 10, 15, 20, 25 msec). Other imaging parameters include: 128*128 resolution, 30mm FOV, 1 mm slice thickness, with two averages per image. All images were transferred to a PC and processed with home-written programs in Matlab®(Mathworks, Natick, MA).

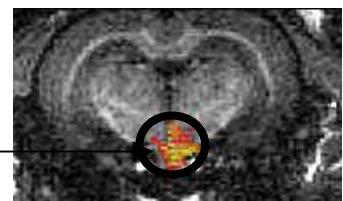
Results and Discussion:

Systemic glucose infusion in the presence of basal insulin results in a localized $R2^*$ increase ($T2^*$ decrease) in the medial hypothalamic area as shown in Figure 1. This is consistent with previous invasive studies using gold-thio-glucose [6]. Interestingly, in contrast to the response to hyperglycemia, no significant localized activation was detected during systemic lipid infusion. In light of the fact that hypothalamic sensing of both circulating glucose and fatty acids regulates glucose homeostasis [1,2], the results of this study suggest that hypothalamic glucose sensing requires a higher oxygen consumption than that of fatty acids sensing in order to have an impact on glucose homeostasis.

Figure 1. $R2^*$ activation map (positive t-map, $P<0.05$) after infusion of glucose (overlaid on the corresponding anatomical image).

Fig 1 $R2^*$ t-map (+)

Hypothalamic activation



References

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