Human hypothalamic responses following glucose ingestion

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Introduction

The hypothalamus is intimately involved in the regulation of food intake. Many of its nuclei contain glucose-sensitive neurons, which are thought to play an important role in long-term body weight regulation as well as in acute feeding behaviour [1]. The small size of the hypothalamus and its nuclei and the small signal changes in fMRI make it difficult and technically demanding to image the effects of food stimuli in this part of the brain. Still, a few fMRI studies have shown transient changes of the BOLD signal in the human hypothalamus after glucose administration [2,3]. Although the signal changes reported in these studies are not entirely consistent with each other, it is clear that glucose administration somehow results in a response in the hypothalamus. Likely, the rise in blood glucose concentration that follows the administration of glucose is an important factor mediating this response. The purpose of our study was twofold. First, to try and replicate the kind of BOLD measurements performed in earlier studies to examine the temporal profile of the hypothalamic response to a glucose load. Second, to investigate whether the amount of glucose ingested affects the hypothalamic response.

Subjects and methods

Fifteen healthy normal weight male volunteers participated (mean age 21.9 ± 3.1 years, BMI 21.5 ± 1.9 kg/m^2). Subjects were instructed to fast overnight from 10 pm (no food or beverages, except water). They were randomly assigned to one of three experimental conditions: 300ml of orange-flavoured water in which 25g or 75g of D-dextrose was dissolved (n=5 and n=6 resp.), or 300ml plain tap water (n=4). The functional scan was a T_2^*-weighted gradient-echo segmented EPI sequence (TR/TE=120/40ms, flip=30º, FOV=208×208 mm, 12 signal averages per scan, 10 mm midsagittal slice). Subjects were scanned for 37 minutes (256 scans). After a baseline of 7.2 min (50 scans), subjects ingested one of the test solutions through a peroral tube. Every subject's hypothalamus was manually segmented and divided into four regions of interest using a T1-weighted image: the upper and lower anterior hypothalamus, and the upper and lower posterior hypothalamus [2]. Also, a square reference area (10×10 pixels) in the frontal cortex was delineated. After registration of the functional scans, the mean gray value in the hypothalamus as a whole, and for each ROI, was calculated at every time point. Next, the percentage signal change from the mean baseline was calculated. For statistical analysis the data were pooled per minute (37 time points) and Student's t-tests were used to compare the mean signal changes between the two glucose conditions and the water condition at every time point.

Results

The mean signal changes in the hypothalamus and the reference area as a function of time are shown in Fig. 1A. At the start of drinking (t=0 min) large signal decreases occur for all treatments. These result from artifacts caused by the drinking and last for about 3 minutes, obscuring possible BOLD signal changes. After that, both glucose treatments show a prolonged significant signal decrease (1 - 2.5%)(Fig. 1B), whereas the water treatment returns to baseline. Moreover, the 75g glucose solution induces a larger decrease in signal than the 25g glucose solution. In the reference area there are no significant signal changes after drinking for any of the treatments (Fig. 1B).

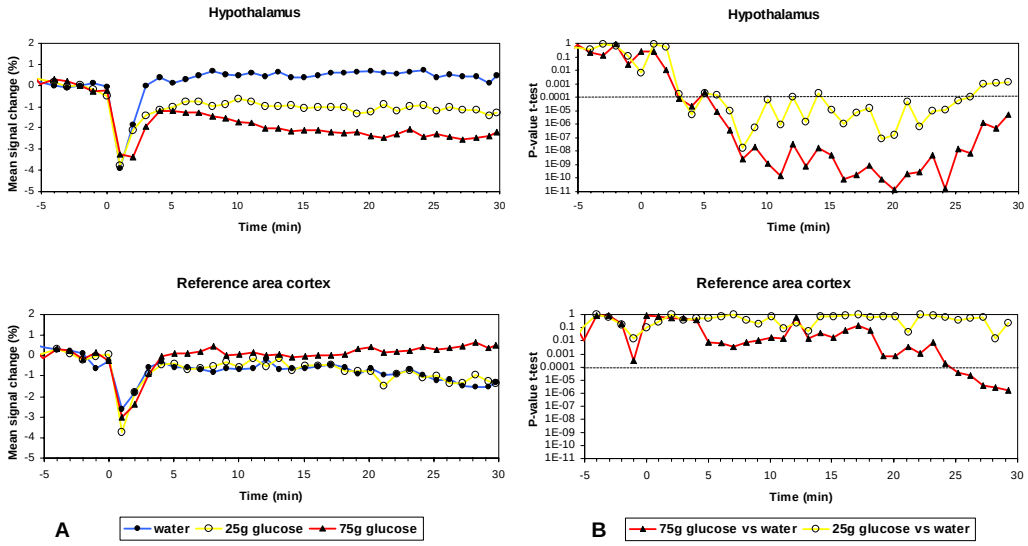

Figure 1. A: Mean signal change from the mean baseline in time under three conditions for the hypothalamus as a whole and a reference area of comparable size. Time t=0 min corresponds to the onset of drinking. B: P-values of the Student's t-tests comparing the mean signal change from the mean baseline of the two glucose conditions with that of the water condition at every time point. The dashed line indicates the Bonferroni corrected threshold of P=0.0001.

Conclusion and discussion

This is the first study showing a prolonged and dose-dependent decrease of the BOLD signal in the hypothalamus after glucose ingestion. Other studies have reported larger but shorter-lasting (±10 min) signal decreases, peaking around 10 minutes after the onset of drinking [2,3]. However, they have not investigated the effect of a different dose on these signal changes. Further analysis of subdivisions of the hypothalamus showed that the dose-dependency of the hypothalamic response was exclusively present in the upper anterior hypothalamus. The time course and dose-dependency of the hypothalamic response suggest that it is associated with changes in blood glucose and insulin levels. This will require further investigation.

References

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