Hypothalamic functional MRI response after glucose ingestion is diminished in patients with type 2 diabetes mellitus

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Introduction

Obesity is known to be one of the most important risk factors for development of type 2 diabetes (insulin-insensitivity). Since the hypothalamus plays an important role in glucose regulation, we hypothesized that the hypothalamic response to glucose might be disturbed in patients with type 2 diabetes. Previously, a prolonged decrease in the hypothalamic fMRI signal after ingestion of a glucose solution has been reported in healthy men [1]. Therefore, the aim of this study was to investigate whether the hypothalamic response to glucose ingestion differed between patients with type 2 diabetes and age-matched control subjects.

Subjects and methods

In a randomized, single-blind, case-controlled observational study, suitable fMRI data were obtained from 7 male patients with type 2 diabetes mellitus (mean age 55.8 ± 3.6 y, BMI 27.9 ± 2.0 kg/m^2) and from 10 healthy, age-matched men (mean age 52.3 ± 4.7 y, BMI 26.1 ± 3.2 kg/m^2). Subjects were scanned twice for 38 min on separate days, after fasting overnight. After an 8-min baseline, they ingested either a glucose solution (75 g in 300 mL water) or water (300 mL). For the functional scan, a 12-mm midsagittal slice was scanned with a T_2^*-weighted gradient-echo segmented EPI sequence (TR/TE = 120/30 ms, flip = 30°, FOV = 208 × 208 mm, 12 signal averages/scan) using a 3.0 T Philips Achieva system. Every subject's hypothalamus was manually segmented and 2 regions of interest (ROI) were delineated with the use of a T_1-weighted image of the same slice [2]. Also, a square reference area of 10 × 10 pixels was delineated in the thalamus. After registration of the functional scans, the mean gray value in the hypothalamus was calculated at every time point. Next, the percentage signal change from the mean baseline was calculated. To correct for global signal changes the signal in the reference area was subtracted from that in the hypothalamus at every timepoint. For statistical comparison the data were pooled per minute, yielding 38 one-minute time slots. Differences between the two treatments were tested for by comparing the mean fMRI signal changes per minute between glucose and water ingestion with a Student's t-test. Also, the mean fMRI signal changes after glucose ingestion were compared for every one-minute time slot between healthy controls and patients with diabetes.

Results

FMRI signal changes are shown in Figure 1. Stimulus ingestion caused strong signal decreases (movement artefacts) and took 5.5 min on average. Compared with water, glucose ingestion resulted in a prolonged significant signal decrease in the upper hypothalamus in healthy men ($P < 0.05$, not shown), but not in patients with type 2 diabetes. This decrease started ~15 min after glucose ingestion and lasted till the end of the scan. The fMRI signal change after glucose ingestion in healthy men was significantly greater than that in diabetics from 15 min onwards in the upper anterior hypothalamus (Figure 2).

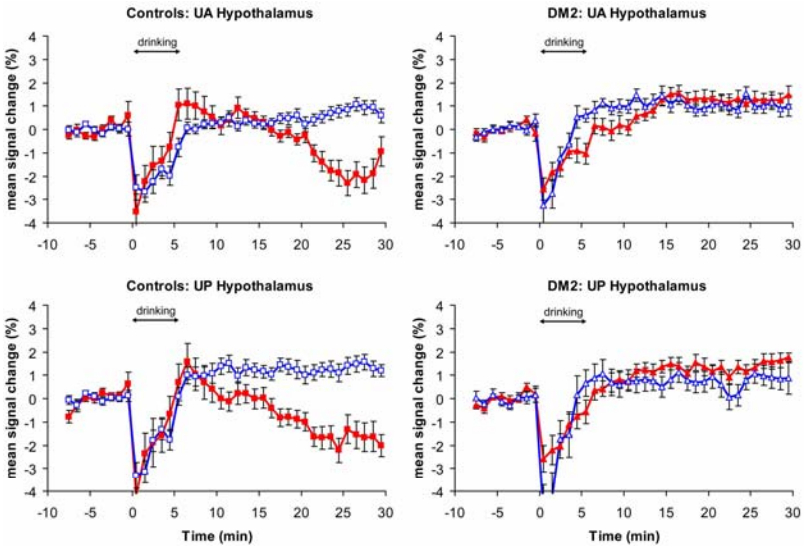

Figure 1. Mean ± SEM fMRI signal changes per minute in the upper anterior (UA, top) and upper posterior (UP, bottom) hypothalamus in controls (left pane) and in patients with diabetes (DM2, right pane), after ingestion of 300 mL 75-g glucose solution (red lines) or water (blue lines). The duration of drinking was ~5 min (horizontal arrows). *Legend*: Controls: ■ glucose, □ water, DM2: ▲ glucose, Δ water. T = 0 min is the onset of treatment.

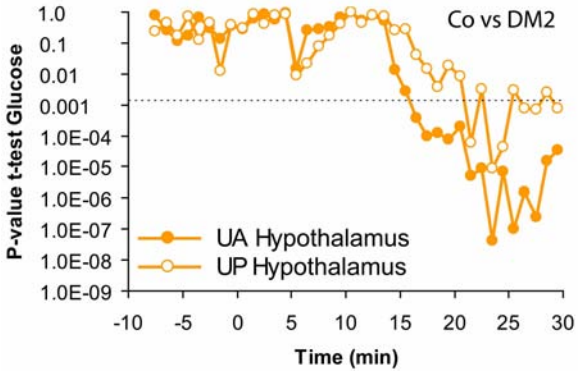

Figure 2. P-values of the t-tests comparing the mean fMRI signal changes per minute after glucose ingestion between healthy controls (Co) and patients with type 2 diabetes (DM2) in the upper anterior hypothalamus (●) and the upper posterior hypothalamus (○). T = 0 min is the onset of stimulus ingestion. The dotted line indicates the Bonferroni-corrected threshold of P = 0.0013.

Discussion and Conclusion

We observed a diminished hypothalamic response to glucose ingestion in patients with type 2 diabetes. Previously, it has been found that the hypothalamic fMRI signal decrease in response to glucose ingestion was attenuated and delayed in obese subjects [2]. The lack of a decreased hypothalamic fMRI signal observed in diabetic patients has several non-exclusive explanations. First, it could relate to the severely impaired incretin effect (i.e., the augmentation of postprandial insulin secretion by gastrointestinal hormones) observed in type 2 diabetics [3]. Second, it could relate to the brain's impaired glucose-sensing mechanisms seen in diabetics [4]. Third, functional alterations in the cerebral microvasculature due to microangiopathy could affect local cerebral blood flow (CBF), which in turn affects the BOLD signal [5]. The prolonged signal decrease in response to glucose ingestion which we found in the control group are similar to those reported earlier [1, 6]. However, in the present study the fMRI signal returned to baseline for a short duration before it decreased again, while the inhibition of the fMRI signal was present directly after drinking in previous studies [1, 6]. The most likely explanation for this difference is that our subjects were ~30 years older than the subjects in previous studies. This suggests that the hypothalamic response to glucose is delayed in older subjects. In conclusion, our findings suggest that the hypothalamic response to glucose ingestion is impaired in patients with type 2 diabetes.

References

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