Ingestion versus infusion: contribution of preabsorptive mechanisms to the hypothalamic response to glucose

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Introduction

The hypothalamus plays a central role in the regulation of food intake and is involved in the homeostasis of the plasma glucose concentration. Preabsorptive signals, which are defined here as hormonal and neural signals which are triggered prior to and during absorption (i.e., before nutrients reach the blood stream), are important for adaptive responses to food intake. Previously, a prolonged decrease in the hypothalamic BOLD signal after ingestion of a glucose solution was reported [1]. The rapid onset of this response, before absorption of glucose into the blood stream, suggested a contribution of some preabsorptive mechanism to the hypothalamic response to glucose [1]. Here, we investigated the contributions of preabsorptive mechanisms to the hypothalamic response to glucose. In addition, blood glucose and insulin concentrations were determined.

Subjects and methods

Seven healthy, normal-weight men participated in a randomized crossover design. Subjects were scanned 4 times for 38 min on separate days, after fasting overnight. After an 8-min baseline, they received one of 4 treatments: oral ingestion of glucose, intravenous (i.v.) infusion of glucose, oral ingestion of water or i.v. infusion of saline. For the oral treatments, subjects ingested a 300-mL glucose solution (75 g glucose) or tap water. For the i.v. treatments, 40% glucose solution or saline were infused into an antecubital vein. Subjects received 0.5 g glucose per kg body weight with a maximum of 35 g [2], i.e., a maximum of 87.5 mL 40% glucose solution. 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. Also, on every test day 6 blood samples were drawn: before scanning (fasted) and during scanning at -3 min (before treatment) and at 15, 30, 45, and 60 min after the onset of treatment. Samples were collected in serum separation tubes for determination of serum glucose and insulin concentrations. Every subject's hypothalamus was manually segmented with the use of a T_1-weighted image of the same slice [3]. Also, a square reference area (10 × 10 pixels) was delineated in the thalamus. After registration of the functional scans, the mean gray value in the hypothalamus 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 analysis, the data obtained after stimulus ingestion were pooled per minute (30 time points) and Student's t-tests were used to compare the mean signal change at every time point after treatment with that before treatment (the 8 min baseline).

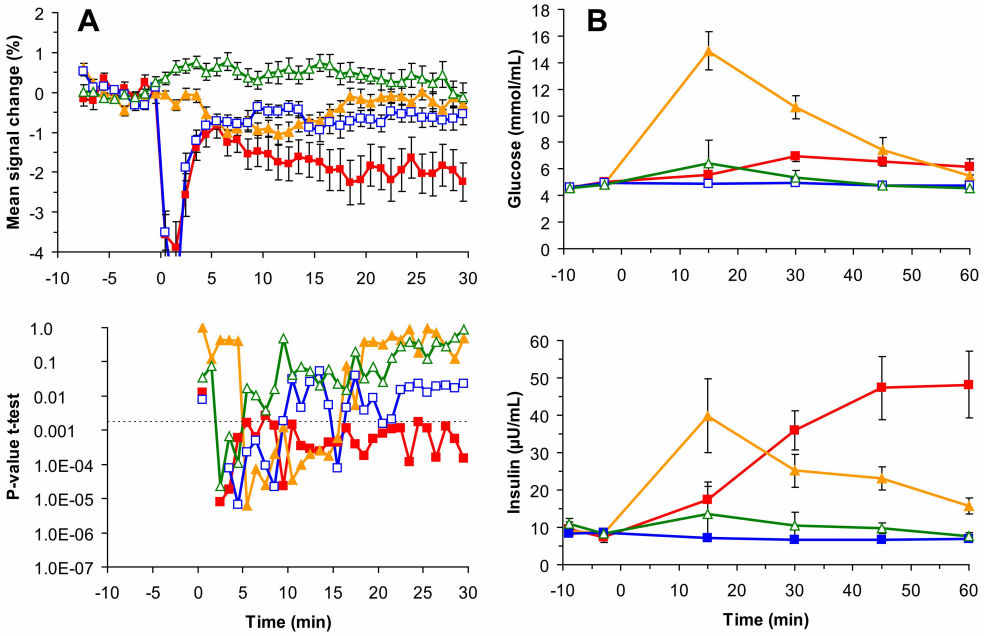

Figure 1. **A**: Mean ± SEM fMRI signal changes per minute in the hypothalamus (top) and P-values of the t-tests comparing the mean signal per minute with the mean signal before treatment (the 8-min baseline) (bottom). For clarity and because of artefacts in the data due to the drinking, the first two data points after stimulus ingestion have been omitted. The dotted line indicates the Bonferroni-corrected threshold of P = 0.0017. The approximate duration of drinking was 2 min. Intravenous treatments took 3 min to complete. **B**: Mean ± SEM glucose (top) and insulin (bottom) responses for the 4 treatments. *Legend*: ■ oral glucose, ▲ i.v. glucose, □ oral water, Δ i.v. saline. T = 0 min is the onset of treatment.

Results

Glucose ingestion resulted in a prolonged significant signal decrease in the hypothalamus, whereas glucose infusion was associated with a smaller and transient signal decrease (Fig. **1A**). Glucose and insulin responses are shown in Fig. **1B**. Glucose ingestion caused a slow rise in glucose concentration up to ~7 mmol/L, along with a strong rise in insulin concentration. In contrast, glucose infusion resulted in rapid rises in glucose and insulin concentrations up to ~15 mmol/L and ~40 µU/mL, respectively, followed by decline. At 60 min, the glucose concentration was approximately back at baseline.

Discussion and Conclusion

We investigated the effects of oral glucose and i.v. infusion of glucose on the hypothalamic fMRI signal and on blood glucose and insulin concentrations. The better glucoregulation observed after oral glucose is due to the 'incretin effect': the insulin response to i.v. glucose is smaller than that to oral glucose [4] because oral glucose induces the release of insulinotropic gut hormones. The prolonged fMRI signal decrease seen after oral glucose is in line with previous findings [1, 5]. Intravenous glucose resulted in a shorter and attenuated hypothalamic response, which started ~5 min after the onset of treatment and lasted for ~10 min, until 15 min. At 5 min the oral glucose fMRI signal has recovered from the drinking artefacts, but has not risen back to baseline. At 15 min, when the hypothalamic response to i.v. glucose ends, the insulin concentration starts declining. In the case of oral glucose, the insulin concentration is still rising at 30 min, and the fMRI signal is still below baseline. This suggests that preabsorptive mechanisms not only cause the early onset of the hypothalamic response, but are also crucial for the prolonged signal decrease after oral glucose. More in particular, this suggests that the hypothalamic response to glucose is associated with the blood insulin concentration. The oral dose was 75 g of glucose, while the i.v. dose was 35 g, however, the changes in the blood glucose after i.v. glucose were greater. Previously, we found a smaller, but still prolonged, hypothalamic response to a 25-g dose of glucose [1]. This suggests that the transient nature of the hypothalamic response to i.v. glucose is due to the absence of preabsorptive signals rather than the lower dose. In conclusion, we found that preabsorptive signals contribute substantially to the hypothalamic response to glucose.

References

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