Effect of dietary composition on the neuronal activation following peripheral injection of cholecystokinin in mice detected by manganese-enhanced magnetic resonance imaging

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Introduction

Obesity is an increasingly prevalent disease and much research is being carried out to understand the many factors that contribute to its development. Structural and functional changes in the neuronal circuits controlling food intake may be responsible for an alteration of energy intake and thus be involved in the onset of overeating and obesity. Evidence now exists that dietary conditions can alter the neuronal networks controlling food intake and more particularly their response to peripheral anorectic signals such as cholecystokinin (CCK). CCK is an anorexigenic hormone normally secreted by enteroendocrine cells in the upper gastrointestinal tract in response to mechanical and chemical stimuli including fat in the duodenum. In this study, we looked at the effect of long-term nutrient intake on the central response to CCK. Our hypothesis is that the localization and intensity of CCK-induced activity in specific brain areas may be dependent on the nature of the dietary regimen.

Methods

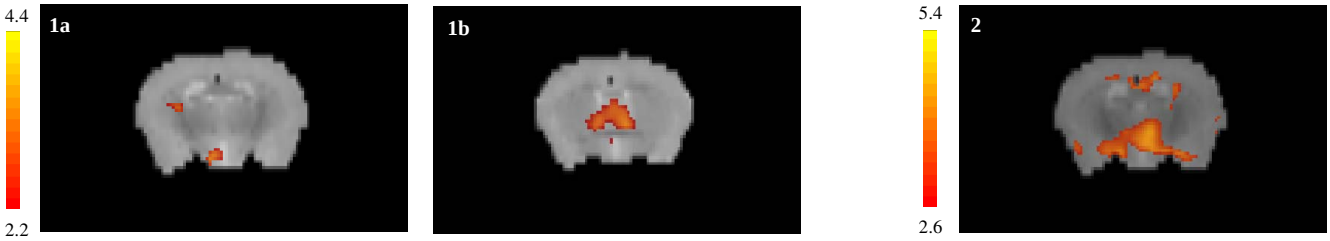
Animals and Treatment

Male C57BL/6 mice initially 6-8 weeks old were maintained on a standard high-carbohydrate (HC), high-fat (HF) or high-protein (HP) diet. Diets were given for a period of 6 weeks, during which body weights and food intake were recorded.

Study of dietary intake patterns: 15 mice (n=5 per dietary group) were placed in special metabolic cages with a computerized data acquisition system designed to continuously record and study food and water ingestions patterns of small animals (every second). The cumulative food intake was recorded during 24 h over 4 days. The last two 24-h recordings (considered the most stable) were kept for micro and macro-analyses of food intake patterns.

Manganese Enhanced MRI (MEMRI) was performed on 36 mice (n=12 from each dietary group) using a 7T Bruker Pharmascan MRI system. A timecourse of 150 volumes was acquired using a T1-weighted RARE sequence with the following parameters: TR=1300ms, TEeff=5ms, matrix=192x96, field of view= 38.4x19.2mm, 27 contiguous 0.33mm thick transverse slices and 2 averages (acquisition time per volume 46s, total 1hr 55mins). Infusion of $MnCl_2$ was commenced after six initial baseline acquisitions. Each mouse received 5 µl/g of body weight of 100 mM MnCl2 at a rate of 0.2 ml/h. Simultaneously each mouse received an i.p. injection of CCK (2nmol/kg) or an equivalent volume of 0.9% saline. Image timecourses were motion corrected with SPM5 [1] and coregistered to a mouse brain template [2] using AFNI [3] before GLM analysis in FSL [4].

Results and Discussion



Figures: statistical maps of differential Mn uptake for 1) saline vs CCK and 2) HC vs HP. Mice injected with CCK demonstrated significantly reduced Mn uptake in the ventromedial nucleus of the hypothalamus (1a), nucleus accumbens (1b) and striatum (1b). The HP group had lower activation in the paraventricular nucleus (PVN) of the hypothalamus compared to the HC group (2). Results are presented as colour-coded z-scores thresholded using clusters to a (corrected) significance level of $p < 0.05$.

Dietary intake. There were no significant differences in energy intake between the different dietary groups. Mice fed the HP diet had a larger number of meals (10.3±0.9 vs. 7.7±0.5, p=0.04) but that were of smaller size (33.8±3 vs. 48±3.5 kJ, p=0.03) compared to mice fed the HF diet. Mice fed the HF diet had larger inter-meal intervals than the HC animals during the day only (p=0.006). HP-fed mice had a shorter delay to consume their first meal (58.6 min compared to 72±0.8 for the HF and 152.2±0.3 min for the HC, p=0.04) as well as a lower ingestion speed (7.7±0.5 kJ/min compared to 10.3±0.8 for the HF and 8.9±0.3 kJ/min for the HC, p=0.04). These results reveal an effect of long term diets on altering eating patterns.

MEMRI. Assessment of the response to CCK by MEMRI showed a significant reduction in neuronal activity in appetite centers (fig 1a) as well as in the reward centers (fig 1b). These results are in accordance with findings that cholecystokinin inhibits expression of orexigenic peptides in the hypothalamus and prevents stimulation of specialized neurons by ghrelin (reviewed by [5]). When comparing the effects of the different diets, while the HF diet didn't induce any significantly different activity patterns when compared to the other two, some fairly large reductions in Mn uptake were found when comparing the HP to the HC diet (fig 2). These findings are in line with previous immunohistological findings where a high-protein diet resulted in a decrease in fos-positive neurons in the ventromedial hypothalamus and amygdala of rats [6].

Conclusion

These two complementary methodological approaches suggest that there is a significant relation between long-term dietary intake and eating behavior. Our results also suggest that habituation to a high protein diet leads to modifications in CCK-induced anorectic effects in the hypothalamus, possibly through modulations of brain plasticity.

References

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