Satiety dysfunction in Prader-Willi syndrome demonstrated by fMRI

N A Shapira, M C Lessig, A G He, G A James, D J Driscoll, Y Liu


The neurobiology relating to the insatiable appetite observed in Prader-Willi syndrome (PWS) has not been fully characterised. Two functional magnetic resonance imaging (fMRI) scans were performed on each of three adults with PWS. The scans were carried out pre- and post-treatment with the antiepileptic topiramate, which had little effect on body weight and appetite in these subjects. Subjects fasted overnight and drank a 75 g dextrose solution prior to fMRI scans for measurement of brain activation levels during/after glucose ingestion. Following glucose administration, there was a significant delay in activation at the hypothalamus and other brain regions associated with satiety compared with previous data on obese volunteers. These regions include the insula, ventromedial prefrontal cortex, and nucleus accumbens. Individuals with PWS showed a mean latency of 24 min while in a previous study obese volunteers had shown a latency of 15 min and lean volunteers a latency of 10 min in the hypothalamus. Our results provide evidence towards a satiety dysfunction in the central nervous system of PWS patients.

Prader-Willi syndrome (PWS) is a neurogenetic disorder characterised by hyperphagia that develops within the first 6 years of life following a period of failure to thrive. The insatiable appetite exhibited often leads to uncontrollable obesity in this population. Van Hooren et al have promoted control of obesity with preventative learning measures; however, token economies and the use of regulated antiepileptic topiramate, which had little effect on body mass index of 31.8, 30.4, and 37.8 respectively at enrolment. Participants had been confirmed as having PWS through chromosomal and DNA molecular analyses. Concomitant psychotropic medications at the time of enrolment included fluoxetine and valproic acid in the male subject and venlafaxine in the two female subjects. In addition to these medications, the subjects were taking vitamin and mineral supplements such as calcium. None of these individuals had been prescribed human growth hormone previously and they did not have a history of appetite suppressant use. These individuals provided full informed consent prior to study procedures in accordance with the institutional review board of the University of Florida Health Science Center. All three subjects were concurrently enrolled in an 8 week open label trial of the anticonvulsant topiramate for appetite regulation. No effect on food intake and appetite change was shown in this 8 week trial.

MRI procedures

For the reported fMRI study, the subjects were scanned in a 3.0 T MRI scanner (GE/Signa) with an fMRI protocol described previously. Briefly, functional images were obtained before (5 minutes for baseline) and after (for 37 minutes) a subject consumed a beverage containing 75 g dextrose, as in an oral glucose tolerance test. An echo planar imaging (EPI) sequence was used (echo time 25 ms, repetition time 5000 ms, flip angle 90°, matrix size 128×128; field of view 240×240 mm²), with 24 axial slices (thickness 6 mm) covering the whole brain. T1 weighted structural MR images were acquired before or after each functional scan with the same field of view and slice profile for the image co-registration with the EPI images and a conventional three-dimensional MRI. Subjects were given the glucose solution and scanned both prior to (scan 1) and post (scan 2) the 8 week open label trial with topiramate.

Biochemical and appetite measurement

Serial blood draws were carried out before, during, and after functional scans to measure glucose and insulin on all subjects. The measured blood glucose and insulin levels were within the normal range.

Abbreviations: EPI, echo planar imaging; fMRI, functional magnetic resonance imaging; PWS, Prader-Willi syndrome; ROI, region of interest; TCA, temporal clustering analysis
Image processing and data analysis

For each subject, the EPI images were analysed using TCA to identify the temporal maxima of the fMRI signal. The TCA method was used to extract the time course of individual brain response, which is independent of the variance of individual anatomy. TCA measures the magnitude of the dynamic fMRI signal by forming a high density histogram of the image voxels that reach the maximum change at the time of imaging. After creating a time window in TCA, the EPI images acquired during this time window were compared with those acquired during the 5 min baseline using group t tests. For each functional scan, the imaging data were then averaged over the three PWS subjects and a t threshold applied based on a spatial clustering technique. Given the small sample size in the study, we chose a t threshold reflecting statistical significance at p<0.01 (uncorrected) for the voxel-wise changes in fMRI signal following glucose administration. The resulting statistic parametric maps were co-registered with the T1 weighted images for Talairach normalisation and localisation. The regions of interest (ROIs) were identified as those above threshold areas of functional activations. These ROIs were used for further analysis of the time courses of the local fMRI signal.

RESULTS

Dynamic analysis using TCA demonstrated that maximum changes in brain activity appeared approximately 24 minutes (23.8 (4.3) min for scan 1; 24.04 (3.7) min for scan 2) after oral glucose administration. Fig 1 shows that a 5 min time window centred at the 24th min was generated for mapping the fMRI signal change compared with the baseline. For both times (i.e., pre- and post-topiramate treatment), the ROI analysis showed negative changes in the ventromedial prefrontal cortex, the nucleus accumbens, and the hypothalamus, and positive changes in the dorsolateral prefrontal cortex and insula (Fig 1A). Given the small number of subjects, it should be noted that the ventromedial prefrontal cortex is the only region remaining on the activation map if a corrected statistical threshold is used for multiple comparisons. The time course of fMRI signal changes was extracted from this region and averaged across the six scans performed on the three subjects (Fig 1B).

There was no significant difference in the delays and magnitudes of brain activity changes before and after topiramate treatment based on direct comparisons between scans 1 and 2 (images not shown), except for a trend towards increase of insular activation after treatment. Topiramate therapy did not significantly alter body mass index or appetite as measured by a “feelings of hunger” visual scale, which was consistent with the imaging data.

DISCUSSION

Our preliminary data demonstrate a delay of 24 min for PWS brain activity after glucose administration. In a previous fMRI study using a single sagittal slice, healthy lean subjects showed changes around 10 minutes and obese subjects around 15 minutes in the hypothalamus, with a consistent delay in response to glucose ingestion. These brain regions consist of a distributed functional network, which has been implicated in the regulation of hunger and satiation. With imaging of the whole brain, the current study has identified the brain regions, including the insular cortex, the prefrontal cortex, the ventral basal ganglia, and the hypothalamus, which have a consistent delay in response to glucose ingestion. These brain regions consist of a distributed functional network, which has been implicated in the regulation of hunger and satiation. We also observed that the delay time in brain response in PWS to glucose ingestion was not altered by topiramate.

Limitations of this study are the small number of subjects, and, as previous fMRI studies acquired only a single sagittal slice, PWS and obese subjects might show a similar brain activation pattern in areas outside of the hypothalamus.

In conclusion, our results provide further evidence towards a satiety dysfunction in the central nervous system of PWS patients. Future studies will be needed to fully characterise this dysfunction and the endocrine contribution to it.

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