Connectivity increase in reward-related brain regions in patients with congenital lipodystrophy: A longitudinal study with leptin-substitution treatment

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Target audience: Researchers interested in central nervous effects of leptin and in functional MRI.

Purpose: Leptin is an adipocytokine derived hormone. Its serum concentrations correlate with the body fat content. Leptin is an important factor in insulin signaling, but also central-nervous effects are known. Disturbed leptin signaling, caused by a leptin deficiency or, by dysfunctions in the leptin signaling cascade, causes overeating mainly via hypothalamic activations of orexigenic neuron populations, resulting in obesity1. In congenital lipodystrophy (LD), a paucity of subcutaneous adipocytes causes reduced leptin serum concentrations. Patients suffer from high serum-triglycerides and accordant co-morbidities, and can develop severe diabetes with high insulin demands due to an increase in insulin resistance. Also, patients often develop a disturbed eating behavior with reduced satiety after food consumption, leading to an increase in meal frequency. This altered eating behavior can be restored by leptin substitution. Data from previous functional magnetic resonance imaging (fMRI) studies revealed task-dependent acute changes in brain activity in reward- and eating behavior-related brain areas after cessation of leptin substitution in leptin deficient patients2. To assess long term effects of leptin substitution on resting-state brain connectivity in treatment naive patients with congenital LD, we performed task-free resting-state fMRI in LD patients before and during the initial 52 weeks of treatment.

Methods: Eight LD patients (6 female, age 36 ± 4 y SEM, BMI 27 ± 2 kg/m² SEM) participated in the MRI study. All patients were leptin-treatment naïve, fulfilled the inclusion criteria for receiving leptin treatment and consented in participating in the MRI study. Behavioral tests and MRI scanning were performed at 6 different time points: before the leptin supplementation, and after 1, 4, 12, 26, and 52 weeks of leptin treatment. On each measurement day, a blood draw was made. Thereafter, patients consumed a standard meal consisting of 20% of their daily energy requirements. Before and after the meal, patients filled in visual analog scales (VAS) to assess their hunger and satiety feelings (100 mm bar, very left 0 mm=no hunger, satiety, respectively, to very right 100 mm=extreme hunger, satiety, respectively).

At each of the 6 time points, resting-state fMRI data were acquired on a whole-body 3T TIM Trio scanner (Siemens, Erlangen, Germany) with a 32-channel head coil using a gradient-echo echo-planar imaging (EPI) sequence. Patients were asked to stay awake, relax, and look at a fixation cross. The following parameters were used: 300 whole brain volumes, acquisition matrix=64x64, slice thickness=4 mm (1 mm gap), resulting in a nominal voxel size of 3x3x5 mm³. Further imaging parameters: 30 axial slices, TR=2300 ms, TE=30 ms, flip angle=90° and bandwidth=1817 Hz/pixel. The total scanning time was 11.5 minutes.

Data pre-processing was performed using SPM8. To identify treatment-related connectivity changes, eigenvector centrality (EC) mapping3 was computed using the LIPSIA software package4. EC provides a measure for detecting central hubs within a brain network using an algorithm similar to Google’s PageRank algorithm5. For all voxels, a similarity matrix was generated including the components of this eigenvector to determine the EC of all voxels.

Finally, across all resulting EC maps, a statistical analysis was performed using SPM8 with a flexible factorial design in order to test for repeated measurements including a session and a subject factor. Parameter estimates were assessed to test for a linear EC increase over time. The resulting statistical parametric map was processed using a voxel-wise threshold of p<.001. In order to correct for multiple comparisons, significant clusters were obtained with a family-wise error (FWE) corrected p<.01.

Results: Glycated haemoglobin (A1c) as a measure for severity of diabetes, decreased by 17.1 % after 52 weeks of leptin treatment (before leptin treatment 8.3 ± 0.6 % SEM, after 52 weeks 6.7 ± 0.5 % SEM, p=.13, 6 patients completed 52 weeks treatment at time of analysis). Fasting hunger ratings decreased from 59 ± 7 mm on a 100 mm VAS before beginning of leptin treatment to 16 ± 4 mm, p=.01 after 26 weeks and 38 ± 12, p=.21 after 52 weeks (6 patients completed). Satiety ratings after the standard meal increased from 65 ± 10 mm to 93 ± 2 mm, p=.04 after 26 weeks and 71 ± 11, p=.55 after 52 weeks. In MRI-scanning, highest increases in connectivity were found in nucleus accumbens bilaterally (T3=5.64) in the medial frontal gyrus (T3=4.81), and in the hypothalamus (T3=5.52) (Fig. 1).

Discussion: In a leptin deficient state, i.e. before leptin substitution, patients with congenital lipodystrophy anecdotally described an addiction-like appetite to food. A large part of their free daytime revolved around preparation of food and consumption of food. After a meal, satiety only persisted for a short time and already after approximately one hour patients reported to experience hunger again and crave for food. After leptin substitution, patients experienced longer periods of satiety after a meal, reduced meal frequencies and lost interest in thoughts about food. In accordance with these observations, leptin treated patients showed reduced hunger ratings when fasting and increased satiety ratings after the standard meal. The long-term strengthening of functional connectivity of the nucleus accumbens we found under leptin substitution is located in the same brain region, where previous findings showed alterations in activity in patients with leptin deficiency, receiving leptin substitution. Data from previous fMRI studies revealed task-dependent acute changes in brain activity in reward- and eating behavior-related brain areas after cessation of leptin substitution in leptin deficient patients2. To assess long term effects of leptin substitution on resting-state brain connectivity in treatment naive patients with congenital LD, we performed task-free resting-state fMRI in LD patients before and during the initial 52 weeks of treatment.

Conclusion: Our results demonstrate leptin substitution related long term changes in resting-state connectivity in hedonic (i.e., nucleus accumbens and medial prefrontal cortex) and homeostatic brain structures (i.e., hypothalamus) involved in the control of eating behavior.

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