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Fat-mass-related hormone, plasma leptin, predicts brain volumes in the elderly

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Abstract

Leptin, a hormone produced by body fat tissue, acts on hypothalamic receptors in the brain to regulate appetite and energy expenditure, and on neurons in the arcuate nucleus to signal that a individual has had enough to eat. Leptin enters the central nervous system at levels that depend on a individual's body fat. Obese people, on average, show greater brain atrophy in old age, so it is valuable to know whether brain atrophy relates to leptin levels, which can be targeted by interventions. We therefore determined how plasma leptin levels, and BMI, relate to brain structure, and whether leptin levels might account for BMI's effect on the brain. We measured regional brain volumes using tensor-based morphometry, in MRI scans of 517 elderly individuals with plasma leptin measured (mean: 13.3±0.6 ng/ml; mean age: 75.2±7.3 years; 321 men/196 women). We related plasma leptin levels to brain volumes at every location in the brain after adjusting for age, sex, and diagnosis and, later, also BMI. Plasma leptin levels were significantly higher (a) in women than men, and (b) in obese versus overweight, normal or underweight individuals. People with higher leptin levels showed deficits in frontal, parietal, temporal and occipital lobes, brainstem, and the cerebellum, irrespective of age, sex, or diagnosis. These associations persisted after controlling for BMI. Greater brain atrophy may occur in people with central leptin insufficiency, a marker of obesity. Therapeutic manipulation of leptin may be a promising direction for slowing brain decline.

Keywords

Alzheimer's disease; BMI; brain structure; leptin; MRI; obesity

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Conflicts of interest

There are no conflicts of interest.

Introduction

Leptin is a crucially important hormone, produced by body fat, or adipose tissue [1,2]. It regulates appetite and energy expenditure, and communicates information on fat mass and nutritional status to the brain. It acts on the hypothalamus to signal when a individual has had enough to eat, and this in turn helps to lower food intake [3] and regulate body weight [4]. Leptin also facilitates hippocampal long-term potentiation and plays a key role in learning and memory [5]. Leptin levels can be manipulated, offering a basis for some new therapeutic approaches to treat Alzheimer's disease (AD) [6–8].

Leptin circulates in the plasma in proportion to a individual's body fat mass, or adiposity [1], so a natural correlation arises between plasma levels of leptin and a individual's BMI [4]. Plasma leptin enters the brain through a saturable transport system [9], so cerebrospinal fluid (CSF) levels of leptin do not always rise in proportion to plasma levels [4]. Elevated plasma levels of leptin may also be a sign of leptin resistance, in obese people [10].

We and others have shown that higher BMI – associated with being overweight and obese – is associated with a distributed pattern of lower brain volumes in healthy elderly, and in people diagnosed with AD and mild cognitive impairment (MCI) [11–13]. There is a tendency for some people to lose weight when they become severely ill, but in the earlier stages of MCI and AD, and in normal aging, more overweight people tend to show greater brain atrophy.

A small proportion of this brain atrophy is explained by carrying a very common variant in the obesity risk gene, *FTO* [14], however, it is vital to identify other influential factors, as potential targets for interventions. As plasma leptin levels are associated with BMI, we decided to use three-dimensional (3D) brain morphometry to relate plasma leptin levels to regional volumes at every location in the brain. We discovered a detailed 3D anatomical pattern of structural brain differences associated with leptin levels, and we tested if any effects persisted after accounting for BMI.

Materials and methods

Individuals

We studied 517 elderly individuals (53 healthy controls, 354 with MCI, 110 with AD; mean age: 75.2±7.3 years) who received a 1.5Tanatomical brain MRI scan and were genotyped for ApoE (the major risk allele for late-onset AD) as part of the Alzheimer's Disease Neuroimaging Initiative (ADNI) study. All ADNI data are publicly available at http://www.loni.ucla.edu/ADNI. Inclusion and exclusion criteria are detailed in the ADNI protocol [15].

Plasma leptin

For 517 Caucasian individuals, plasma leptin (ng/ml) was assessed at the time of their baseline brain MRI scans, after an overnight fast. Leptin was measured using the 'Human Discovery Multi-Analyte Profile' platform by Rules-Based Medicine (RBM, Austin, Texas, USA, http://www.rulesbasedmedicine.com). The quantification methods are described in the document 'Biomarkers Consortium ADNI Plasma Targeted Proteomics Project – Data Primer' (http://adni.loni.ucla.edu).

Image acquisition and processing

High-resolution structural MRI scans were acquired on 1.5T scanners from General Electric (Milwaukee, Wisconsin, USA), Siemens (Germany), or Philips (the Netherlands) with a

standardized MRI protocol [16]. Each scan involved a 3D sagittal magnetization-prepared rapid gradient-echo sequence (MP-RAGE) with the following parameters: repetition time (2400 ms), flip angle (8°), inversion time (1000 ms), 24 cm field of view, a 192×192×166 acquisition matrix, and a voxel size of $1.25\times1.25\times1.2mm^3$, later reconstructed to 1mm isotropic voxels. To adjust for global differences in brain positioning and size, all scans were first linearly aligned to the International Consortium for Brain Mapping template [17] through a nine-parameter transformation using the Minctracc algorithm [18]. Globally aligned images were resampled in an isotropic space of 220 voxels along each axis (*x*, *y*, and *z*) with a final voxel size of 1 mm^3.

Tensor-based morphometry analysis

As part of our tensor-based morphometry analysis, an average brain template – also known as the 'minimal deformation template' (MDT) – was first created from the MRI scans of 40 cognitively healthy ADNI individuals, to serve as an unbiased target to align other brain scans [19]. All preprocessed MR images were nonlinearly aligned to the study-specific template so that they would all share a common coordinate system defined by the MDT. The local expansion or compression factor of the 3D elastic warping transform [20] (sometimes called the 'Jacobian determinant'), was plotted for each individual. These 3D maps reveal areas of structural volume excess or deficits in each individual, relative to the normal elderly group average anatomy.

Statistical correlations

The distribution of plasma leptin, our primary predictor, was somewhat skewed (Fig. 1a) in our population. To adjust its distribution to be closer to Normal, we used a logarithm transformation of the measured values for leptin (Fig. 1b).

At each image voxel within the brain, a multiple regression analysis was run to test for statistical associations between regional brain volumes and $\log_{10}$ (leptin) levels across all the individuals, after adjusting for age, sex, and diagnosis (Fig. 2a); we also subsequently tested for effects within each of the AD, MCI, and control groups (Fig. 2b–d). In the same regression model, we also analyzed statistical associations after covarying for BMI, to test the hypothesis that associations were being driven solely by BMI.

In addition to adiposity, insulin and sex differences – including sex hormone levels – affect plasma leptin concentrations [21]. So we also analyzed associations after adjusting for insulin and testosterone levels, in addition to age, sex, diagnosis, and BMI.

We created 3D statistical brain maps to show regions where brain volume associations were significantly associated with leptin. To control for false positives, we enforced a standard false discovery rate correction for multiple statistical comparisons across voxels in the brain, using the conventionally accepted false positive rate of 5% (q=0.05).

Results

Demographic characteristics

The average morning plasma leptin levels in the ADNI cohort were 13.3±0.6 ng/ml. Mean levels in AD, MCI, and control groups were 14.4±1.5, 12.3±0.7, and 17.5±2.0 ng/ml, respectively. As in prior studies [22,23], women (n=196; 20.5±1.5 ng/ml) showed higher average leptin levels than men (n=321; 8.9±0.5 ng/ml; P<0.0001). Obese individuals [24] (n=116; 22.7± 1.6 ng/ml) showed greater leptin levels than groups of overweight (n=236; 13.9±0.8 ng/ml), normal (n=190; 7.8±0.5 ng/ml), or underweight individuals (n=3; 2.8±0.5

ng/ml). As expected, plasma leptin levels were positively correlated with BMI, after controlling for age and sex ($P<0.0001$).

Leptin and brain volumes

In a linear regression analysis across all individuals, covarying for age, sex, and diagnostic group, regional brain volumes were associated with leptin levels, with deficits detected in the frontal, parietal, temporal and occipital lobes, brainstem, and the cerebellum. Some volume excess relative to the MDT was noted in the peripheral CSF spaces with an increase in leptin levels (Fig. 2a). This is expected, as CSF spaces expand with greater brain atrophy.

A subgroup analysis revealed similar significant leptin-associated regional brain volume deficits in AD, MCI, and control groups individually (Fig. 2b–d). The larger MCI group showed deficits over a broad region of the brain, relative to the MDT.

The above-described leptin–brain volume associations continued to exist after adjusting for BMI, insulin, testosterone, in the full ADNI group – and in the MCI group alone – but not in the AD and the control groups, although they showed a similar trend.

We found no significant effect of carrying the *APOE*4 genotype on leptin levels, suggesting that the leptin effects were not tracking a latent genotypic difference in the major AD risk gene, *APOE*.

Discussion

The higher plasma leptin concentrations in women than men are most likely due to sex differences in body fat, sex hormones, and insulin levels [22,23].

Automated whole brain volumetric analysis of brain MRI revealed a 3D pattern of strong associations between plasma leptin levels and regional brain volume deficits in the frontal, parietal, temporal and occipital lobes, brainstem, and the cerebellum. These links with leptin levels were found (a) across all individuals (Fig. 2a and b) in separate analyses of each diagnostic group specifically (Fig. 2b–d). These very regions were shown earlier to be associated with obesity and higher BMI [11–13]. Among the subgroups, MCI individuals showed larger areas of association between leptin levels and brain, and continued to show significant associations with brain volumes after controlling for BMI, unlike the AD or the control groups. This is most likely due to the larger sample size for the MCI group (MCI, $n=354$ versus AD, $n=110$ and controls, $n=53$); ADNI enrolls over twice as many MCI individuals as people with AD or elderly controls, so the larger available MCI sample offered greater power to detect associations.

In normal individuals, some studies have reported that elevated plasma leptin is associated with reduced incidence of AD and with larger total cerebral brain volume. This paradoxical effect is thought to be due to some beneficial effects of leptin on the brain, in nonobese individuals [25]. However, our results showing significant brain deficits associated with plasma leptin in the full ADNI group and the MCI group of individuals, regardless of their diagnosis or BMI, possibly track the effects of leptin resistance or inefficiency, a marker of obesity.

The findings from our study may improve understanding of the consequences of having elevated leptin levels in the plasma, and the potential benefits of therapies [6–8] targeted to improve CSF/plasma leptin ratios [9].

Even though ADNI is not the most ideal sample to carry out this analysis, it is a good test bed because of the availability of data for plasma leptin, high-resolution MRI scans of the

brain, and well-validated computational methods for volume quantification in a large and well-defined cohort. A minor weakness was that we did not manipulate leptin levels, so it is impossible to say whether leptin caused the brain differences, or whether leptin measures are correlated with other factors that damage the brain; importantly, however, the leptin effect persists after adjusting for BMI, and high BMI is associated with greater brain atrophy. A larger interventional design is needed to resolve this.

Conclusion

The relationship between leptin and brain volumes is an intriguing one with central leptin being neuroprotective in some circumstances; chronically elevated plasma levels of leptin, perhaps due to leptin resistance, may be associated with brain volume deficits. As leptin and brain volumes appear to be linked, it may be of interest to use these 3D brain structure profiles to test for neuroprotective effects of therapeutic strategies targeting central leptin levels, specifically to slow the onset of dementia and cognitive decline [6–8].

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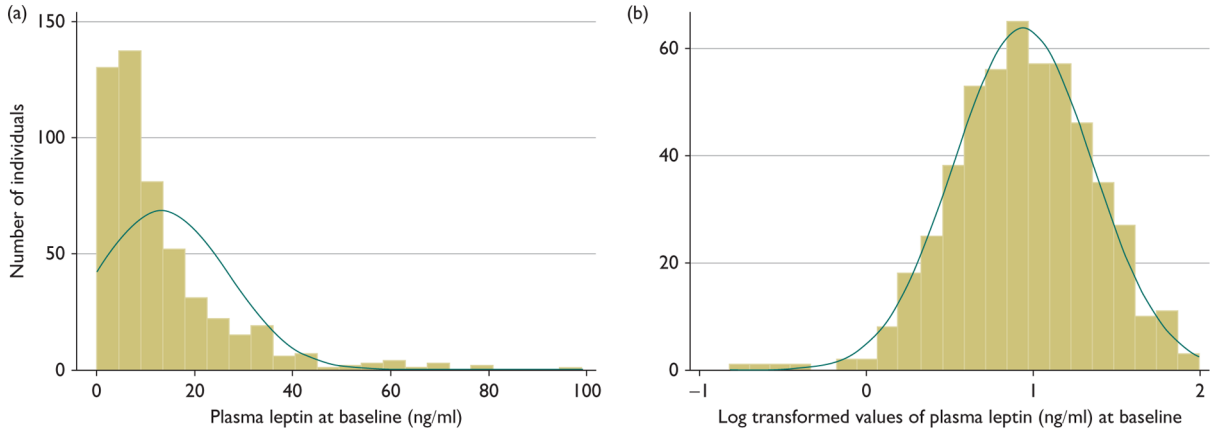

Fig. 1.

(a) The distribution of plasma leptin (ng/ml) in the ADNI population. (b) The logarithmically transformed (log_{10}) leptin values, which better conform to a Normal distribution; these were used in our analysis. All MRI figures are displayed in radiological convention (the left side of the brain is shown on the right). ADNI, Alzheimer's Disease Neuroimaging Initiative.

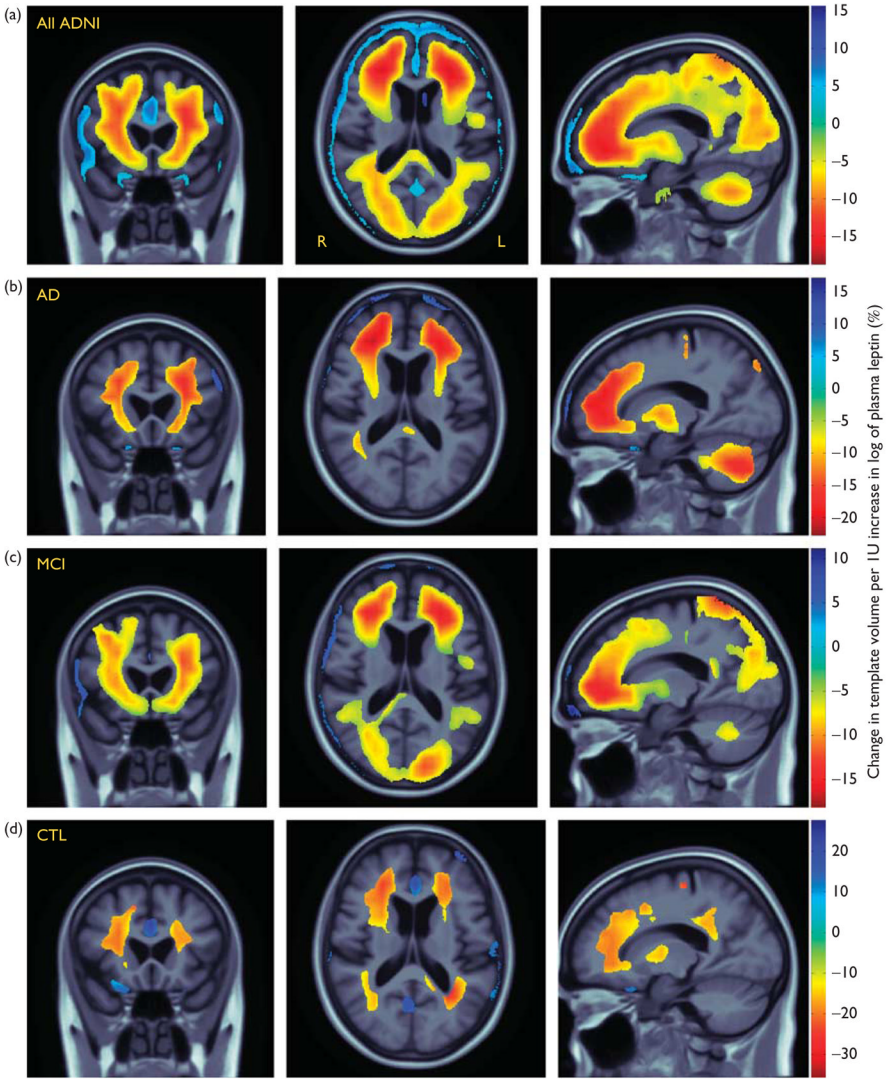

Fig. 2.

Brain deficits were detected in people with higher levels of the fat-mass-associated hormone, leptin. Three-dimensional β-value maps show at each nominally significant voxel across the whole brain, the estimated regional brain differences (% relative to mean template), per every 1U increase in the logarithm of plasma leptin levels [$\log_{10}$ (ng/ml)], in (a) all ADNI individuals (n=517; FDR critical P-value, 0.02); (b) individuals diagnosed with AD (n =110; FDR critical P-value, 0.007); (c) individuals diagnosed with MCI (n=110; FDR critical P-value, 0.01); and (d) healthy control individuals (CTL; n=53; FDR critical P-value, 0.002). These associations have been adjusted for age and sex. AD, Alzheimer's disease; ADNI, Alzheimer's Disease Neuroimaging Initiative; CTL, control; FDR, false discovery rate; MCI, mild cognitive impairment.