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Relationships between plasma leptin concentrations and human brain structure: a voxel-based morphometric study

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Abstract

We have previously demonstrated that obese people have reduced grey matter (GM) in several brain areas, including regions implicated in the regulation of taste (i.e., inferior frontal operculum and postcentral gyrus), reward (i.e., putamen), and behavioral processing (i.e., middle frontal gyrus), compared with their lean counterparts. It is well established that the brain may serve as a direct target for adiposity signals, one of the most important being leptin. We investigated the relationships between fasting plasma leptin concentrations and brain tissue composition in a group of 32 young adult Caucasians (12M/20F, age 32±1 y, body fat 29±1%, mean ± SE) with normal glucose tolerance by using voxel-based morphometry of magnetic resonance imaging scans. Fasting plasma leptin concentrations were positively correlated with grey matter (GM) volumes of the left cerebellum and left inferior temporal gyrus and negatively associated with GM volumes of the left inferior frontal operculum, left postcentral gyrus, and right putamen ($P<0.001$, uncorrected for multiple comparisons) after adjustment for sex, percent body fat, age, fasting plasma insulin concentrations (i.e., the major determinants of plasma leptin), and global GM volume (thus allowing for an assessment of regional effects only). This study showed an independent, negative correlation between fasting plasma leptin concentrations, which are increased in obesity, and the volumes of GM in brain areas where obese people have reduced GM compared to their lean counterparts. These relationships may explain some of the abnormalities in brain morphology recently found to be associated with excess body fatness.

Keywords

grey matter volume; leptin; obesity

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Introduction

An epidemic of overweight and obesity has developed in the United States over the past 20 years, with nearly two thirds of US adults now overweight or obese [1]. Excess body fat is accompanied by damage to several target organs, i.e., heart, skeletal muscle, pancreas, liver, and kidney [2]. The brain can be affected by obesity, too. In fact, prospective studies have demonstrated that overweight is a risk factor for neurodegenerative disorders [3;4]. We have recently reported that human obesity is characterized by morphological abnormalities of the brain [5], by using voxel-based morphometry (VBM) [6]. In particular, obese people had reduced grey matter (GM) in several brain areas implicated in the regulation of taste (i.e., inferior frontal operculum and postcentral gyrus), reward (i.e., putamen), and behavioral processing (i.e., middle frontal gyrus), compared with their lean counterparts [5]. This study, however, could not address the possible mechanisms responsible for these brain abnormalities.

It is well established that the brain may serve as a direct target for adiposity signals [7], one of the most important being leptin. Leptin is an adipocyte-derived hormone that acts as a major regulator of food intake and energy homeostasis [8] and is produced in proportion to the amount of body fat [9]. Both the lack of leptin action and resistance to leptin effects are associated with obesity in animals and humans [8;10]. The lack of leptin effects in the genetically-obese ob/ob mouse is also accompanied by brain structural abnormalities including reduced brain weight and cortical brain volume, delayed maturation of neurones and glial cells, and increased susceptibility to neurodegeneration [11;12]. Significant increases of regional GM after leptin replacement has been reported in a VBM study of three human adults with a recessive mutation in the ob gene associated with leptin deficiency and morbid obesity [13]. These trophic effects of leptin on brain tissue composition, however, have been demonstrated in both animals and humans on a milieu of absolute leptin deficiency. It is not known what the effects of leptin on brain morphology are in conditions of normal or high plasma concentrations, as occur in lean and obese subjects.

Therefore, we sought to investigate the relationships between fasting plasma leptin concentrations and brain tissue composition in a group of 32 young adult Caucasians with normal glucose tolerance by using VBM of MRI data.

Subjects and Methods

Subjects

Thirty-two right-handed lean (body mass index [BMI] <25 kg/m^2, n=16) and obese (BMI ≥35 kg/m^2, n=16) Caucasian subjects (Table 1), 12 males and 20 females, were recruited from the greater Phoenix area by newspaper advertisement, as part of a larger study of neurofunctional and neurostructural correlates of eating behaviour and body weight [5;14–16]. These subjects had been included in a previously performed VBM study of morphological differences in brain tissue composition between lean and obese individuals [5]. The present analysis was limited to those individuals for whom fasting plasma samples for measuring leptin concentrations were available. All volunteers were in good health, as determined by medical history, physical examination, and laboratory screening tests, and reported that they were non-smokers and not taking any medications. The female volunteers were studied while in the follicular phase of the menstrual cycle. Subjects were admitted for 1 week to the Clinical Research Section of the NIH in Phoenix, AZ, restricted to the metabolic ward, placed on a weight maintaining diet (50% carbohydrate, 30% fat, 20% protein), and limited to sedentary activity for the duration of the study. Subjects underwent a 2-h 75-g oral glucose tolerance test to exclude impaired glucose tolerance and diabetes 3 days after admission and following a 12-h overnight fast. Alcohol and drug abuse (and/or history of substance abuse or addiction), endocrine disorders (including abnormal thyroid function and type 2 diabetes), hypertension, and pulmonary,

cardiovascular, gastrointestinal, hepatic, renal, and central nervous system (CNS) disorders were excluded at screening. Behavioural or psychiatric conditions (such as claustrophobia, major depression, presence of psychotic symptoms, bulimia nervosa) were screened for using the Structured Clinical Interview for DSM-IV-R (SCID) [17]. None of the study subjects had current psychiatric disorders, as assessed using the SCID, or was taking any psychotropic medications. The protocol was approved by the Institutional Review Boards of the National Institute of Diabetes and Digestive and Kidney Diseases and Banner Good Samaritan Regional Medical Center, and informed written consent was obtained from all subjects before participation. All experiments were conducted in accordance with the Declaration of Helsinki (http://www.wma.net).

Analytical measurements

Plasma leptin concentrations were determined by a commercially available radioimmunoassay (Linco Research, Inc., St. Charles, MO). Its specificity for human leptin was 100% and its cross-reactivity with insulin, C-peptide, glucagon, and insulin-like growth factor-I was not detectable. The intra- and inter-assay CVs were 5% and 4.5%, respectively. Plasma glucose and insulin concentrations were determined by the glucose oxidase method (Beckman Instruments, Fullerton, CA) and by an automated radioimmunoassay (Concept 4; ICN, Costa Mesa, CA), respectively.

Body composition

Percent body fat was measured by dual-energy x-ray absorptiometry (DPX-L, Lunar Corp., Madison, WI), as previously described [18].

MRI acquisition

Magnetic resonance imaging was performed on a 1.5 Tesla Signa system (General Electric, Milwaukee, WI). A set of high-resolution T1-weighted images was acquired with a fast spoiled gradient echo (FSPGR) 3d sequence (repetition time [TR]/ echo time [TE] = 12/5.2; TI 300, 1 nex; field-of-view [FOV] = 24 × 24 cm; 256 × 256 matrix); the whole-brain data were acquired in an axial plane yielding 120 contiguous slices with slice thickness of 1 mm. Gross anatomical abnormalities were ruled out by an experienced neuroradiologist who evaluated MRI scans for each subject.

VBM procedure

VBM is a technique for whole-brain, voxel-wise analysis of local changes in brain tissue content [6]. Optimized VBM in Statistical Parametric Mapping 5 (SPM5, Wellcome Department of Imaging Neuroscience, London, UK; www.fil.ion.ucl.ac.uk/spm) software was used for data processing. In brief, the T1-weighted images were corrected for intensity inhomogeneities, stereotactically transformed into standard Montreal Neurological Institute space using an automated spatial normalization algorithm, segmented into grey matter (GM), white matter (WM), and cerebrospinal fluid component images, modulated by multiplying the voxel densities with the Jacobian determinants to incorporate volume changes during normalization into the analysis, and smoothed by convolving with a 12-mm full-width at half-maximum isotropic Gaussian kernel. The 12-mm kernel used here is one of the most commonly used kernels for VBM since it ensures the residuals conform to the normality assumption by central limit theorem [19] and minimizes the risk of false positive findings [20].

Statistics

To avoid possible edge effects around the border between GM and WM and to include only relatively homogeneous voxels, all voxels with a GM value of <0.1 (of a maximum value of 1) were excluded. Linear regression analyses for the GM and WM maps with fasting plasma

leptin concentrations were performed in SPM5. Statistical inferences were made at each voxel using sex, percent body fat, age, and fasting plasma insulin concentrations as independent variables. Global GM and WM volumes were used as covariates in the GM and WM analyses, respectively, thus allowing assessment of regional effects only. The results of these analyses were thresholded at $P < 0.001$ (uncorrected for multiple comparisons), due to the exploratory nature of this investigation, and only clusters larger than 20 contiguous voxels were considered in the analysis. Effects of interest were examined using linear contrasts of parameter estimates and are presented as statistical parametric maps of the t statistic. Since a previous study showed reduced GM in the inferior frontal operculum, postcentral gyrus, and putamen of obese subjects compared to lean individuals [5], the small volume correction (SVC) function for these areas was used. These small volumes were determined by using standard anatomical masks obtained from the automated anatomical labelling (AAL) map [21]. For the post-hoc analysis, individual local GM volume data, extracted from the areas where significant correlations were found and adjusted for global GM volume (by general linear model), was plotted against fasting plasma leptin concentrations, adjusted for sex, percent body fat, age, and fasting plasma insulin concentrations (by general linear model). Simple and multiple regression analyses between fasting plasma leptin concentrations and the other study variables were performed using SAS statistical package 8.2 (SAS Institute, Cary, NC). Fasting plasma concentrations of leptin and insulin were logarithmically-transformed before statistical analyses to approximate normal distribution. Data are presented as mean ± SD throughout the text and tables.

Results

General, anthropometric, and metabolic characteristics of the study population are shown in Table 1. Fasting plasma leptin concentrations were positively correlated with percent body fat (r: 0.97, P<0.0001) and fasting plasma insulin concentrations (r: 0.70, P<0.0001), as expected. Compared to men, women had higher fasting plasma concentrations of leptin (23.1 ± 21.9 vs. 4.3 ± 4.8 ng/ml, P=0.002) and insulin (35 ± 15 vs. 25 ± 10 μU/ml, P=0.04), as well as greater percent body fat (32 ± 8 vs. 23 ± 12 %, P=0.0005), as previously reported [22].

Based on these results, the relationship between fasting plasma leptin concentration and GM volume was adjusted for sex, percent body fat, age, and fasting plasma insulin concentrations, as well as global GM volume, to ascertain the independent effects of leptin on regional GM volume. Results of this correlation analysis, with the stereotactic coordinates of the local maxima and the corresponding t values, are shown in Table 2. Fasting plasma leptin concentrations were positively correlated with GM volume in the left cerebellum and left inferior temporal gyrus and negatively associated with GM volume in the left inferior frontal operculum, left postcentral gyrus and right putamen. Notably, these associations were in the same direction in the obese (left cerebellum: partial r: 0.57, P=0.02; left inferior temporal gyrus: partial r: 0.61, P=0.01; left inferior frontal operculum: partial r: −0.81, P=0.0002; left postcentral gyrus: partial r: −0.58, P=0.02; right putamen: partial r: −0.65, P=0.006) and the lean subgroups (left cerebellum: partial r: 0.45, P=0.08; left inferior temporal gyrus: partial r: 0.48, P=0.06; left inferior frontal operculum: partial r: −0.38, P=0.15; left postcentral gyrus: partial r: −0.51, P=0.04; right putamen: partial r: −0.46, P=0.07)..

By using SVC, the negative association between fasting plasma leptin concentrations and the volume of GM in the left inferior frontal operculum survived the correction for multiple comparisons (P=0.03). A similar trend to survive the correction for multiple comparisons after SVC was also found for the correlations of fasting plasma leptin concentrations with the GM volumes in the left postcentral gyrus and right putamen, even though these associations did not reach statistical significance (P=0.10 and P=0.07, respectively, corrected for multiple comparisons).

No significant associations, either positive or negative, were found between fasting plasma leptin concentrations and WM volume, after adjustment for sex, age, percent body fat, fasting plasma insulin concentrations, and global WM volume.

Discussion

This study of lean and obese subjects demonstrates an association between higher fasting plasma leptin concentrations and reduced GM in brain regions previously shown to have reduced GM in obese persons, including the inferior frontal operculum, postcentral gyrus, and putamen [5]. These associations were independent of body fat, the major determinant of leptin concentrations, and other known confounders, such as sex, age, insulin, and global GM volume. When the study population was divided by BMI, the above correlations were stronger in the obese compared to the lean subgroup. Hence, since plasma leptin concentration is higher in obese than lean subjects [9], we suggest that leptin may have contributed in some way, directly or indirectly, to the GM reductions in obese individuals [5].

Even though the coordinates of the brain areas where fasting plasma leptin concentrations were negatively associated with GM volume in the present analysis were not perfectly overlapping with those where GM was reduced in obese compared to lean individuals in the previous study [5], they were nonetheless in close proximity, except for the inferior frontal operculum, in which the association was on the left side, as opposed to the previous report showing reduced GM in the right inferior frontal operculum of obese individuals [5]. However, it should be noted that reduced GM was observed in the left inferior frontal operculum of obese subjects, but this difference was not reported due to the strict significance threshold that was used. In the present study, a more lenient threshold was employed due to the smaller number of subjects.

The association between fasting plasma leptin concentrations and reduced GM volumes of some cortical (i.e., inferior frontal operculum and postcentral gyrus) and striatal (i.e., putamen) areas may be unexpected, given the reported neurotrophic action of leptin on the brains of ob/ob mice [23–25]. These mice, however, have complete leptin deficiency [23–25]. It is not known if the neurotrophic effects of leptin on mice with leptin deficiency are relevant to the neuronal effects of leptin in lean or obese persons, who have normal or high leptin concentrations, respectively [9]. Furthermore, while favourable actions of leptin on brain tissue have been reported in neonate or young mice or even mouse embryos [23;25], leptin treatment in adulthood does not reverse the neuroanatomical defects [24]. In addition, leptin did not alter the proportion of astrocyte/oligodendrocyte progenitor colonies when high, as opposed to low, doses were used [25]. Moreover, the role of leptin in apoptosis is somewhat controversial, with both proapoptotic [26;27] and antiapoptotic [28;29] activities being reported. The only human study addressing the effects of leptin on brain tissue composition, performed on three adults with a recessive mutation in the ob gene homologous to the mutation in the ob/ob mice who were treated with leptin for 18 months, did report significant increases in the density of regional GM, as evaluated by VBM [13]. In this study, however, only one-sided contrasts to evaluate increased GM density after therapy were performed [13], and so whether leptin decreased GM density in any brain regions was not tested.

The design of this exploratory analysis does not provide indications about mechanisms responsible for the negative association between plasma leptin and GM volumes in the above brain areas. Several hypotheses, however, may be formulated. In particular, it is not known to what extent the negative associations reported here reflect a direct action of leptin on those brain areas, or are secondary to the effects of leptin on other central-signalling molecules, such as neuropeptide Y (NPY), agouti-related protein, proopiomelanocortin, and cocaine- and amphetamine-related transcript, whose expression is affected by leptin [30]. Interestingly, leptin inhibits the expression of NPY [30], which is known to promote neuronal differentiation

[31], thus providing a possible substrate for the associations reported here. In addition, previous studies [32] have shown a positive association between glucocorticoids, whose hyper-secretion is associated with brain atrophy [33], and leptin, thus indicating that the negative correlation between plasma leptin and GM volumes might be somehow mediated by cortisol. Finally, the negative correlation between plasma leptin concentrations and GM volumes of some brain areas may just reflect the negative effect that excess food intake, which stimulates leptin production [34], exerts on brain tissue composition [35]. Further studies are needed to address this important issue.

Fasting plasma leptin concentrations also were positively correlated with GM volumes in the inferior temporal gyrus and the cerebellum. An area of the cerebellum located only a few millimetres apart from this was shown to have increased GM density after leptin replacement therapy in leptin-deficient humans [13], an observation that is consistent with the present finding. Why leptin might have both a negative and a positive influence on GM volume in different brain regions is not clear. These findings may indicate a global reorganization of tissue composition throughout the brain, rather than isolated increases or decreases in regional GM volumes. This is supported by previous VBM-based studies demonstrating that both increases and decreases of GM coexist in several conditions, such as heavy marijuana use [36], adult strabismus [37], obsessive compulsive disorder [38], bipolar disorder [39], dyslexia [40], Down's syndrome [41], schizophrenia [42], and obesity [5].

It is important to consider this preliminary study in the context of some limitations. First, this was a post-hoc analysis of a previously performed VBM study of differences in brain tissue composition between lean and obese individuals, and it was conducted on those subjects for whom fasting plasma samples were available for measuring leptin concentrations. Therefore, the distribution of body fat and plasma leptin was somewhat skewed due the composition of the study population. Nonetheless, the persistence of the above associations reported in the whole population also in the lean and, even more significantly, obese groups, separately reinforces the present findings. Second, VBM does not have the anatomical precision of classic region-of-interest-based volumetric studies, since it uses a relatively simple warping method, which only attempts to register the brain images "globally". This limitation, however, should not detract from the considerable advantages of the voxel-based approach in terms of efficiency, comprehensiveness, and freedom from observer bias [43]. In addition, the algorithms for the normalization and segmentation routines have been improved substantially in the latest SPM release, which was used for the present study (i.e., SPM5), thus making the VBM analysis more accurate and reliable.

In conclusion, the present study demonstrates that higher fasting plasma leptin concentrations are correlated with less GM in brain areas that had previously been implicated in obesity. This relationship may explain some of the abnormalities in brain morphology associated with excess body fat. Additional studies are needed to ascertain whether there is a causal association between higher leptin and lower GM in the above brain areas and whether this association reflects direct or indirect effects of leptin on the morphology of the human brain.

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Table 1

General, anthropometric, and metabolic characteristics of the study population.

Sex (M/F)	12/20	-
Age (y)	32 ± 9	18–49
Body weight (kg)	89 ± 27	50–140
Body fat (%)	29 ± 11	7–44
Fasting glucose (mg/dl)	85 ± 7	63–97
Fasting insulin (μU/ml)	31 ± 14	13–83
Fasting leptin (ng/ml)	16 ± 20	0.5–65

Data are mean ± SD and min-max, except for sex (n).

Table 2

Correlations between fasting plasma leptin concentrations and grey matter (GM) volume in the study population.

		MNI Coordinates			t	Spatial extent (voxels)
		x	*y*	*z*		
Positive correlations	L Inferior temporal gyrus	−52	−58	−22	4.0	67
	L Cerebellum	−38	−46	−30	3.9	52
Negative correlations	L Inferior frontal operculum	−46	4	8	4.3	30
	L Postcentral gyrus	−54	−10	16	4.0	26
		−50	−16	20	3.7	
	R Putamen	32	−16	0	3.6	22

* Coordinates are from the Montreal Neurological Institute brain atlas, such that x is the distance in millimetres to the right (+) or left (−) of midline, y is the distance in millimetres anterior (+) or posterior (−) to the anterior commissure, and z is the distance in millimetres superior (+) or inferior (−) to a horizontal plane through the anterior and posterior commissures.