Leptin and Cognition

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Key Words

Alzheimer's disease • Leptin levels • Cognition

Abstract

Background: Leptin has been reported to have positive effects on cognition but has not been studied in a population-based sample or stratified by race or gender. **Methods:** Leptin and fat mass were measured in 2,731 subjects, including 50% African Americans. Eight years later, subjects were administered the Montreal Cognitive Assessment (MoCA). Demographic factors and baseline measures, including a deficiency in leptin or levels in excess of what was predicted by fat, were investigated to see which predicted cognitive performance. **Results:** There was a statistical trend for lower leptin levels to be associated with higher cognitive scores. Once stratified by race and gender, excessive leptin was associated with lower MoCA total scores and delayed recall domain score for black men, but white men demonstrated a reverse relationship. **Conclusion:** Excess leptin appears to have differential effects on delayed recall in black and white men.

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Introduction

Based on a number of observations, Alzheimer's disease (AD) has been proposed to be a generalized metabolic disorder. For example, some studies have suggested that being overweight or obese in middle age is a risk for the later development of cognitive decline [1–3]. In addition, it has been observed that people with AD begin

to lose weight several years prior to the onset of clinical symptoms, suggesting a link with adipose tissue metabolism [4, 5]. On the other hand, both obesity and underweight have been found to coincide in AD patients [6]. If the onset of AD is related to changes in a single metabolic process, a simple replacement therapy might be possible.

Adipokines have been studied for their relationship to AD. Specifically, leptin is a hormone, secreted by adipose tissue, which suppresses appetite and regulates energy expenditure. Excessive body fat accumulation is associated with increased levels of leptin [7]. Mice with leptin receptor disruption show impaired long-term potentiation, synaptic plasticity and spatial learning [8]. Leptin introduced by viral vector in the hippocampus of mice results in an increased proliferation of neuronal precursors and a decreased neurodegeneration [9]. Also in rodents, leptin has been shown to modulate production and clearance of beta amyloid (A β) [10], and such clearance in the hippocampus has been associated with improved performance in object recognition [11]. Additionally, leptin-treated gerbils showed greater hippocampal neuron survival after ischemic challenge [12]. Furthermore, leptin injected into the hippocampus of SAMP8 mice with impaired learning and memory showed improved retention after administration [13]. However, in one study, leptin administered directly into the hippocampus of rodents suppressed memory consolidation, specifically for the spatial location of food [14].

Similar observations have been made in humans, where higher levels of leptin are associated with increased hippocampal and whole brain volume and studies have suggested an association between higher leptin levels

and a reduced incidence of AD [15]. Low leptin levels in older adults have been associated with the development of AD and other dementias [15]. However, other studies were unable to show a difference in leptin between AD patients and controls, unless an ApoE4 allele was present [16]. In addition, decreased leptin in AD patients with inappropriately low weight suggests a malfunction on the hypothalamic level [17]. With regard to cognition, one study showed leptin to have a modest protective quality against cognitive decline [18], using the Modified Mini Mental State Exam [19].

The greater prevalence of AD among women may be related to greater relative loss of adipokines in women than men. For example, C-reactive protein (CRP) levels are highly correlated with leptin and remain so after adjusting for several measures of adiposity in obese women, but not in men, suggesting a higher level of CRP and inflammation per unit of adipose burden in women [20], although one study found no association between mild cognitive impairment and abdominal fat in older Japanese women as opposed to men [21]. If there is a relationship between adipokines and neurodegeneration, it would be reasonable to assume that those effects would become evident before the detection of cognitive dysfunction. This project examines the relationship between body fat mass, leptin levels and cognitive performance in a multiracial cohort of middle-aged men and women.

Materials and Methods

The Dallas Heart Study (DHS), funded by the Donald W. Reynolds Foundation, is a population-based investigation initiated in 1998 employing biochemical, imaging and cognitive measures to study the development of cardiovascular disease [22]. The first stage included subjects ranging in age from 30 to 65 years, of whom 50% were African American. Data collected included demographic information, measures of body fat using dual energy X-ray absorptiometry (DEXA) and leptin among other measures. The second stage, initiated 8 years later, repeated most of the measures from the first stage and included new measures, including the Montreal Cognitive Assessment (MoCA) [23], a measure of global cognitive function. The MoCA assesses a wide range of cognitive abilities including attention, orientation, language, verbal memory, praxis and executive function. To be included in this project, for all subjects, a valid MoCA score and body fat mass, waist-to-hip ratio and levels of leptin were required. Age, gender, education and ethnicity were also recorded.

MoCA scores were investigated using multiple linear regressions to see which factors, if any, predicted cognitive function. In addition, since leptin concentration increases with body fat mass and varies according to race and gender, we performed a

multiple linear regression to confirm this was the case in our data set [24]. Since the effects of leptin on MoCA were subtle and outweighed by race and gender, the dataset was then divided into 6 subgroups for further investigation: black female, Hispanic female, white female, black male, Hispanic male and white male.

As the relationship of leptin to fat mass is nearly linear on a log-log scale, a log10 leptin regression model included body fat as a predictor for each subgroup. Residual leptin, defined as the departure of predicted leptin from the actual leptin value, has been used previously to assess the relationships of body composition, energy and metabolism [25]. Using the entire dataset, a stepwise multiple regression model predicting log leptin found the following factors significantly related: higher log body fat ($p < 0.001$), gender ($p < 0.001$) and race ($p < 0.001$). The R^2 of the model was 0.80 (results not shown). Log body fat remained predictive of log leptin in each gender-race subgroup. Subjects in each subgroup had predicted log leptin calculated from their body fat and the excess or deficient leptin recorded as residual leptin. Residual leptin was defined as a variable representing leptin levels out of proportion to fat mass.

The MoCA items were totaled for all cognitive domains (a maximum of 30 points) and separately for executive function and memory. The executive domain was defined as the sum of scores from the trail, cube, clock, abstraction and verbal fluency items (a maximum of 8 points). Memory was defined as the total score from the delayed recall items (a maximum of 5 points). A 2-way ANOVA (3 levels for race and 2 levels for gender) with Bonferroni post hoc testing for race was performed for the following measures: age, education, BMI, fat mass, log percent body fat, waist-to-hip ratio, log leptin and MoCA.

For each gender-race subgroup and the entire dataset, the MoCA total, executive and memory scores were investigated with multiple linear regression to ascertain which factors predicted performance. Finally, Pearson product moment correlations were used to examine the relationship between residual leptin and cognitive scores. Statistical analyses were conducted using IBM® SPSS Statistics V19 (SPSS, Inc., IBM, Chicago, Ill., USA). Assumptions of all statistical tests were reviewed; variables were investigated for normality by examining measures of skewness and kurtosis as well as the distribution of each (results not shown). All measures were judged to be approximately normally distributed, with the exception of leptin, which normalized upon transformation with a log10 function. Statistical significance was set at $p < 0.05$ using 2-tailed tests unless otherwise specified.

Results

There were 2,731 subjects with complete data. Table 1 presents the baseline characteristics of the subjects by race and gender at DHS visit 1 including the number of subjects, mean age, education, BMI, total fat mass, percent fat, waist-to-hip ratio and leptin concentration. The mean MoCA scores from DHS visit 2 are also included. A 2-way

Table 1. Baseline characteristics of DHS subjects at visit 1

Variable	Black women	Hispanic women	White women	Black men	Hispanic men	White men
n	927	242	485	517	166	394
Age, years	42.9±10.5	38.6±9.73	44.9±11.0	43.4±10.7	39.8±10.0	44.0±9.77
Education, years	13.0±2.1	10.7±4.0	14.5±2.6	13.2±2.1	11.4±3.9	15.1±2.8
BMI	31.9±7.9	30.0±7.6	28.3±7.6	28.7±6.4	29.1±5.2	28.0±5.1
Fat mass, kg	34.8±12.7	30.3±12.0	29.8±12.3	21.8±10.2	21.5±7.3	22.9±8.9
Percent fat	39.0±6.7	39.5±6.6	38.1±7.4	23.1±6.9	25.4±5.1	25.5±6.2
Waist-to-hip ratio	0.87±0.07	0.85±0.07	0.83±0.07	0.95±0.06	0.97±0.05	0.96±0.06
Leptin, ng/dl	32.3±20.4	23.5±15.1	22.7±15.5	10.1±10.3	7.12±5.9	8.13±6.6
MoCA ^a	22.1±4.1	22.9±3.9	25.8±2.8	21.7±3.9	22.5±3.9	25.4±3.0

Statistics are mean ± standard deviation. A 2-way ANOVA with Bonferroni post hoc testing showed significant differences among groups with $p < 0.05$ for age (by race and between all race groups), education (by gender, race and between all race groups), BMI (by gender, race, gender by race and between black vs. white and Hispanic vs. white), fat mass (by gender, race, gender by race and between black vs. white and black vs. Hispanic), percent fat (by gender, race, gender by race and between black vs. white), waist-hip ratio (by gender, race, gender by race and between Hispanic vs. white), leptin (by gender, race, gender by race and between black vs. white and black vs. Hispanic) and MoCA (by gender, race and between all race groups).

^a MoCA scores were recorded at DHS visit 2, approximately 8 years later.

ANOVA with Bonferroni post hoc pairwise comparisons for race showed significant group differences with $p < 0.05$ for age (race and between all pairwise race groups), education (gender, race and between all pairwise race groups), BMI (gender, race, gender by race interaction and pairwise between the race groups black vs. white and Hispanic vs. white), fat mass (by gender, race, gender by race and between black vs. white and black vs. Hispanic), percent body fat (gender, race, gender by race interaction and pairwise between black vs. white), waist-to-hip ratio (gender, race, gender by race interaction and pairwise between Hispanic vs. white), log leptin (gender, race, gender by race interaction and pairwise between black vs. white and black vs. Hispanic) and total MoCA (gender, race and pairwise between all race groups).

A stepwise multiple regression model predicting the total MoCA score for the entire dataset resulted in the following significant factors: greater years of education ($p < 0.001$), race ($p < 0.001$), younger age ($p < 0.001$), lower waist-to-hip ratio ($p < 0.001$) and higher log body fat ($p = 0.011$). Log leptin was the next variable that entered the model with $p = 0.089$. The R^2 of the model, including log leptin, was 0.30 (results not shown).

Table 2 presents the results of the stepwise multiple regression models for each race-gender subgroup to examine the demographic and clinical factors which predict total MoCA score, executive function or delayed recall (memory) among the gender-race subgroups. Among black women, higher education and younger age positively pre-

dicted all 3 measures. For Hispanic women, higher years of education were positively predictive for all measures, but younger age was only predictive of MoCA total score and executive function. Among white women, higher education positively predicted MoCA total score and executive function, but age was not a significant predictor and there were no significant predictors of delayed recall. For black men, higher education, younger age and lower waist-to-hip ratio positively predicted the MoCA total score and executive function. Smaller residual leptin levels were positive predictors of MoCA total score and delayed recall. Among Hispanic men, higher education and younger age positively predicted MoCA total score, executive function and delayed recall. Higher percent fat positively predicted increased MoCA total score and delayed recall. For white men, higher education positively predicted MoCA total score, executive function and delayed recall. Younger age predicted higher MoCA total scores and delayed recall, but not executive function. Lower waist-to-hip ratio positively predicted MoCA total scores and executive function, but not delayed recall. Higher residual leptin positively predicted MoCA total scores and delayed recall.

Table 3 presents the Pearson product moment correlations of residual leptin with cognitive measures among each gender-race subgroup. Residual leptin was negatively associated with memory in black men and positively associated in white men. Women and Hispanics showed no correlation and there was no correlation for total score or executive function in any subgroup.

Table 2. Multiple regressions of cognition by gender and race

Model/Variable	Black women	Hispanic women	White women	Black men	Hispanic men	White men
<i>MoCA</i>						
Age	-0.13 (-0.16/-0.10) p < 0.001	-0.11 (-0.18/-0.04) p = 0.002	–	-0.06 (-0.11/-0.01) p = 0.013	-0.09 (-0.15/-0.02) p = 0.010	-0.05 (-0.08/-0.01) p = 0.007
Education	0.82 (0.67/0.97) p < 0.001	0.47 (0.32/0.62) p < 0.001	0.40 (0.29/0.52) p < 0.001	0.46 (0.27/0.65) p < 0.001	0.43 (0.27/0.58) p < 0.001	0.34 (0.23/0.45) p < 0.001
Waist-to-hip ratio	–	–	–	-9.8 (-16.9/-2.8) p = 0.006	–	-8.3 (-15.0/-1.7) p = 0.014
Percent fat	–	–	–	–	0.14 (0.01/0.27) p = 0.032	–
Residual leptin	–	–	–	-2.07 (-4.10/-0.04) p = 0.045	–	1.61 (0.00/3.22) p = 0.050
R ²	R ² = 0.26	R ² = 0.33	R ² = 0.15	R ² = 0.18	R ² = 0.28	R ² = 0.22
<i>Executive Function</i>						
Age	-0.05 (-0.06/-0.03) p < 0.001	-0.04 (-0.07/-0.01) p = 0.017	–	-0.03 (-0.05/-0.01) p = 0.010	-0.04 (-0.07/-0.01) p = 0.009	–
Education	0.32 (0.25/0.39) p < 0.001	0.21 (0.14/0.28) p < 0.001	0.20 (0.14/0.25) p < 0.001	0.24 (0.15/0.33) p < 0.001	0.18 (0.11/0.25) p < 0.001	0.18 (0.12/0.24) p < 0.001
Waist-to-hip ratio	–	–	–	-3.78 (-7.22/-0.35) p = 0.031	–	-4.87 (-8.41/-1.32) p = 0.007
Percent fat	–	–	–	–	–	–
Residual leptin	–	–	–	–	–	–
R ²	R ² = 0.19	R ² = 0.31	R ² = 0.15	R ² = 0.17	R ² = 0.24	R ² = 0.17
<i>Delayed Recall</i>						
Age	-0.04 (-0.05/-0.02) p < 0.001	–	–	–	-0.04 (-0.07/-0.01) p = 0.011	-0.02 (-0.04/-0.00) p = 0.026
Education	0.15 (0.10/0.21) p < 0.001	0.06 (0.01/0.12) p = 0.033	–	–	0.10 (0.03/0.17) p = 0.005	0.07 (0.02/0.13) p = 0.008
Waist-to-hip ratio	–	–	–	–	–	–
Percent fat	–	–	–	–	0.06 (0.00/0.12) p = 0.037	–
Residual leptin	–	–	–	-0.81 (-1.64/0.03) p = 0.058	–	0.98 (0.18/1.78) p = 0.017
R ²	R ² = 0.11	R ² = 0.08	R ² = 0.01	R ² = 0.03	R ² = 0.15	R ² = 0.07

Statistics are B-statistic (lower/upper bound of 95% CI) and p values of variables entered at the last step of the regression.

Table 3. Pearson product moment correlation of residual leptin with cognition

Cognitive measure	Black women	Hispanic women	White women	Black men	Hispanic men	White men
MoCA	-0.016, p = 0.721	0.023, p = 0.797	0.024, p = 0.682	-0.086, p = 0.163	-0.047, p = 0.628	0.102, p = 0.111
Executive function	0.012, p = 0.788	-0.038, p = 0.669	0.009, p = 0.878	-0.019, p = 0.759	-0.116, p = 0.233	0.013, p = 0.845
Delayed recall	-0.077, p = 0.090	0.047, p = 0.593	-0.019, p = 0.746	-0.124, p = 0.045	0.023, p = 0.816	0.141, p = 0.027

Statistics are Pearson correlation (R) and p values.

Discussion

This large, prospective study fails to find a robust effect of absolute leptin levels on middle-aged performances of cognition as measured by the MoCA. In fact, a lower

log of leptin indicated a trend towards significance in an effect opposite to those reported in the previous studies of elderly patients using other cognitive measures. This suggests the possibility that the function of leptin, or leptin receptors, may be altered with aging. Also of note,

the seemingly incompatible combination of lower waist-to-hip ratio but higher total fat mass also had significant positive effects on cognitive performance. This may point to the specific location and distribution of excess fat as being more contributory than the amount alone, as has been found in studies of fat mass and cognition [21, 26].

Once stratified by race and gender, the level of leptin out of proportion to that expected by the fat mass became a predictor of cognition for some subgroups. The effect occurred in opposite directions in black and white men. Excessive leptin per unit of fat was associated with a lower total MoCA score and memory in black men and with higher MoCA scores in white men. This finding for delayed recall held true even after the more conservative Pearson product moment correlation was used. Higher waist-to-hip ratios were negatively associated with MoCA score in both groups. Previous studies have shown that blacks produce more leptin per measure of fat than whites [24]. This subordinate analysis could suggest a functional difference in leptin or its receptors between whites and blacks. Of note, increased percent fat was suggested to be protective only in Hispanic men. Women in the study did not show any relationship between cognitive performance and measures of fat or leptin. Indeed, education and age largely explained performances within each subgroup.

There are several limitations to this study. The mean age of the subgroups ranged from 38 to 44 years at the time of biological measurements with an average 8-year interval until cognitive testing. Although there is no reported association between leptin levels and age, we do not know leptin levels at the time the MoCA was administered. Thus, no change in cognitive function can be

inferred. Our findings might have been different in an older cohort if the action of leptin is cumulative because of increased leptin levels or a change in the sensitivity of leptin receptors. Our study provides an adjunctive look at the effect of leptin on cognition at a period before cognitive decline would be expected. Furthermore, the large sample size may produce statistically significant findings with little clinical relevance. Finally, while several variables were found to be significant predictors of cognition in this study, the coefficients of determination for the models were weak to moderate.

In conclusion, this study of middle aged people fails to replicate the protective effect reported for leptin in older individuals. Higher leptin levels seem to have different effects on cognition in men, detrimental effects in black men and protective effects in white men. Further study should be conducted on the relationship between leptin levels and the change in leptin levels as these groups age. This project underscores the need for future biological studies to take ethnicity into account [27].

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