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Leptin and Cognition

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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 2731 subjects, including 50% African Americans. Eight years later, subjects completed a cognitive assessment. Demographic factors and baseline measures, including leptin deficient or 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 scores and word recall for black men but white men demonstrated an opposite effect.

Conclusion—Excess leptin appears to have differential effects on recall in black and white men.

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 later development of cognitive decline [1–3]. Additionally, it has been observed that persons 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 coincident in AD patients [6]. If 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 increased proliferation of neuronal precursors and decreased neurodegeneration [9]. Also in rodents, leptin has been shown to modulate production and clearance of beta amyloid (Aβ) [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

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hippocampus of SAMP8 mice with impaired learning and memory showed improved retention after administration [13]. However, in one study, leptin administrated 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 later 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]. Additionally, 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 measure 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 eight 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, all subjects were required to have available a valid MoCA score and body fat mass, waist to hip ratio and levels of leptin. 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. Additionally, since leptin concentration increases with body fat mass and varies by 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 by these into six groups for further investigation: black female, Hispanic female, white female, black male, Hispanic male and white male.

The relationship of leptin to fat mass is nearly linear on a log-log scale, thus a log base ten of leptin model was calculated based on body fat for each subset. Residual leptin, defined as

the departure from predicted leptin based on the data predictive variables, has been used previously to assess relationships of body composition, energy and metabolism [25]. In establishing a residual leptin variable here, a multiple regression for the log of leptin with the entire dataset selected the following factors as having a positive impact on the level at the final iteration: higher log of 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 of body fat remained independently predictive of log of leptin in each gender-race subset. Subjects here had predicted log of leptin calculated from their body fat and the excess or deficient leptin recorded as residual leptin. Residual leptin was thus defined as a variable representing leptin levels out of proportion to fat mass.

The MoCA items were totaled for all cognitive domains (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 questions (maximum of 8 points). Memory was defined as the score from the delayed recall section (maximum of 5 points). A two-way ANOVA (race by gender) with Bonferroni post-hoc testing was performed for the measures age, education, BMI, fat mass, percent fat, waist to hip ratio, leptin or log of leptin and MoCA.

For each gender-race subset and entire data set, 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 see specifically if residual leptin correlated with cognitive scores. Statistical analyses were conducted using IBM© SPSS Statistics V19 (SPSS, Inc., IBM© SPSS Statistics V19, Chicago, IL, 2010). Assumptions of all statistical tests were reviewed; variables were investigated for normality by calculations of skewness and kurtosis (results not shown). Variables were judged to be approximately normally distributed, with the exception of leptin, which normalized upon transformation with a log base ten function. Statistical significance was set at $p<0.05$ using 2-tailed tests unless otherwise specified.

Results

There were 2731 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-hip ratio and leptin concentration. Also included are the mean MoCA scores from DHS visit 2. A two-way ANOVA with Bonferroni post-hoc testing for race 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 to hip ratio (by gender, race, gender by race and between Hispanic vs. white), leptin or log of 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 multiple regression for the total MoCA score with the entire dataset selected the following factors as having a positive impact on score at the final iteration: greater years of education ($p<0.001$), race ($p<0.001$), younger age ($p<0.001$), lower waist-hip ratio ($p<0.001$) and higher log of body fat ($p=0.011$). A statistical trend was found for lower log of leptin levels related to increased MoCA scores ($p=0.089$). The R^2 of the model was 0.30 (results not shown).

Table 2 presents the results of the multiple regressions to determine which factors predict total MoCA score, executive function or recall among the gender-race subsets. Among black women, higher education and younger age positively impacted scores in all three measures. For Hispanic women, higher years of education had a positive impact for all measures, but younger age only affected total score and executive function. Among white women, higher education positively impacted total score and executive function, but age was not a factor and there were no significant predictors of recall. For black men, higher education, younger age and lower waist-hip ratio positively impacted total score and executive function. Smaller residual leptin levels positively impacted total score and recall. Among Hispanic men, higher education and younger age positively impacted total score, executive function and recall. Higher percent fat positively increased total score and recall. For white men, higher education positively impacted total score, executive function and recall. Younger age positively increased total score and memory, but not executive function. Lower waist-hip ratio positively increased total score and executive function, but not memory. Higher residual leptin positively impacted total score and memory.

Table 3 presents the Pearson product moment correlations of residual leptin with cognitive measures among each gender-race subset. 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.

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, lower log of leptin trended towards significance in an effect opposite of those reported in 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-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 more contributory than amount alone, as 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 fat mass became a predictor of cognition for some subgroups. The effect occurred in opposite directions in black men and white men. Excessive leptin per unit of fat was associated with lower total MoCA score and memory in black men and with higher MoCA scores in white men. This finding for 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 time of biological measurements with an average eight-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 change in sensitivity

of leptin receptors. Our study provides an adjunctive look at leptin's effect 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 persons fails to replicate the protective effect reported for leptin in older persons. Higher leptin levels seem to have different effects on cognition in men, detrimental in black men and protective in white men. Further study should be conducted on the relationship between leptin levels, and 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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Table 1

Baseline Characteristics of DHS Subjects at Visit 1[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 (kg/m^2)	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-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[2]	22.1 ± 4.1	22.9 ± 3.9	25.8 ± 2.8	21.7 ± 3.9	22.5 ± 3.9	25.4 ± 3.0

[1] Statistics are mean ± standard deviation. A two-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*race and between black vs white and Hispanic vs white), Fat Mass (by gender, race, gender*race and between black vs white and black vs Hispanic), Percent Fat (by gender, race, gender*race and between black vs white), Waist-Hip ratio (by gender, race, gender*race and between Hispanic vs white), Leptin (by gender, race, gender*race and between black vs white and black vs Hispanic) and MoCA (by gender, race and between all race groups).

[2] MoCA scores were recorded at DHS visit 2, approximately eight years later.

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Table 2

Multiple Regressions of Cognition by Gender and Race[1].

Model	Variable	Black Women	Hispanic Women	White Women	Black Men	Hispanic Men	White Men
MoCA	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-Hip	-	-	-	−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
Executive Function	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-Hip	-	-	-	−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
Recall	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-Hip	-	-	-	-	-	-
	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

[1]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[1].

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
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**

[1]Statistics are Pearson correlation (R) and p-values.

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