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Putative neuroprotective role of visfatin against cognitive dysfunction in obese patients

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ABSTRACT

Objectives: Visfatin (adipokine) is thought to have neuroprotective properties. The aims of to determine the type and extent of prefrontal cortical dysfunction and to evaluate the potential neuroprotective role of visfatin.
Methods: Sixty-one obese patients were included. A diagnosis of primary obesity was made on the basis of a BMI > 30. Visfatin serum levels were determined by enzyme immunoassay. The Wisconsin Card Sorting Test (WCST) was used to assess prefrontal cortex-mediated cognitive function.
Results: Visfatin levels were not correlated with age or BMI. However, patients with higher visfatin levels tended to show an overall improvement in WCST scores. Nonetheless, a significant positive correlation (P = 0.032) was found only between high serum visfatin levels and the number of correctly completed categories in the WCST.
Discussion: The results described herein indicate a possible neuroprotective effect of visfatin against obesity-related cognition dysfunction, particularly in regard to the categorizing capacity associated with executive function.

KEYWORDS	cognition, obesity, visfatin

Introduction

Visfatin and metabolism

An intensive body of research on fatty tissue metabolism has revealed the adipocyte as a key player in the regulation of lipid and energy metabolism, as well as in the production and secretion of hormones and cytokines. These adipocyte-derived modulatory factors are collectively termed adipokines. Adipokines can exert both local and global hormonal actions, and include proteins such as adiponectin, interleukin-6, leptin, resistin, tumour necrosis factor-alpha, and visfatin. Adipokines also play major roles in the pathogenesis of insulin-resistant and cardiovascular diseases (Sommer et al. 2008).

Visfatin is a 52-kDa protein encoded by a gene contained

within the long arm of chromosome 7 between 7q21.1 and 7q31.33 (Jia et al. 2004). Visfatin was initially known as pre-B-cell colony-enhancing factor (PBEF), because of its ability to induce the maturation of B lymphocytes, or nicotinamide phosphoribosyltransferase (Nampt), because of its activity during the biosynthesis of nicotinamide adenine dinucleotide (NAD) (Kamińska et al. 2010). The production of nicotinamide adenine mononucleotide (NMN) by PBEF/Nampt/visfatin is the rate-limiting step in the salvage pathway for the subsequent biosynthesis of NAD by NMN adenylyltransferase. NAD is in turn an essential coenzyme involved in redox reactions during intracellular energy metabolism (Revollo et al. 2007).

In addition to its participation in energy metabolism, visfatin can reportedly mimic the actions of insulin by binding to and activating the insulin receptor. Indeed, visfatin lowered plasma glucose levels in mice, presumably by substituting for insulin (Fukuhara el a. 2005). These findings suggest the potential therapeutic utility of visfatin in the management of diabetes and other metabolic disorders.

Regulation of visfatin production is dependent on the stimulation of macrophages in fatty tissue (Mayi et al. 2010). Therefore, inflammatory processes are crucial for normal visfatin metabolism. At the same time, visfatin contributes to vascular inflammation by mediating pro-inflammatory signalling in the blood vessel wall (Romacho et al. 2009). The adipokine also affects vascular reactivity by triggering endothelium-dependent, nitric oxide-related vasodilatation (Yamawaki et al. 2009). Accordingly, visfatin could theoretically modify the course of metabolic syndrome.

Visfatin and neuroprotection

Several lines of evidence suggest that visfatin operates in the central nervous system as a neuroprotective factor. For example, genetically altered mice with reduced visfatin/PBEF/Nampt expression had a significantly larger infarct volume and a higher number of degenerating neurons than age-matched, wild-type controls in a photothrombosis-provoked model of cerebral ischemia (Zhang et al. 2010). These observations indicate that visfatin limited neuronal damage after stroke, probably by enhancing energy metabolism (Zhang et al. 2010) and promoting blood vessel relaxation (Yamawaki et al. 2009). Furthermore, a significantly higher serum visfatin level was observed among human patients with ischemic stroke relative to control subjects without stroke. The elevated visfatin levels were independently associated with stroke occurrence, implying that the adipokine was upregulated in an attempt to protect the brain from further injury (Lu et al. 2009).

Cognitive dysfunction in obesity, and putative neuroprotective effect of visfatin

Several reports have suggested that cognitive abilities can be adversely affected in obese subjects, especially in terms of working memory and executive function (Chelune et al. 1986; Gunstad et al. 2007; Lokken et al. 2009). Executive function refers to a set of mental processes utilized in goal achievement that allow the individual to integrate past experiences with present actions. Executive function and working memory are thought to be regulated by the prefrontal cortex. Conversely, executive dysfunction and cognitive defects in working memory are linked to abnormalities in prefrontal metabolic activity and decreased local blood flow in the prefrontal cortex (Volkow et al. 2009; Willeumier et al. 2011).

Whitmer and Kivipelto observed numerous groups of obese and overweight patients over a period of more than 20 years and found that a body mass index (BMI) of > 25 was an independentrisk factor for dementia (Kivipelto et al. 2005; Whitmer et al. 2005). Moreover, a study by Gustafson and colleagues indicated that elderly women with a BMI of > 25 were more likely to develop Alzheimer's disease than age-matched, normal-weight women, likely due to the unfavourable impact of obesity on vascular health (Gustafson et al. 2003).

In light of these findings, the current study sought to validate the relationship between cognitive dysfunction and obesity. We also explored the hypothesis that visfatin might confer neuroprotection against cognitive dysfunction in an obese patient population.

Methods

Patients

Sixty-one Caucasian patients (48 women and 13 men; mean age, 39.9 ± 12.6 years) of Polish nationality with primary obesity were enrolled in this study. Primary obesity was defined as a BMI of > 30, where secondary causes of obesity were excluded based on medical history, physical examination, and biochemical results (e.g., cortisol, prolactin, and thyroid-stimulating hormone levels). Biometric analyses were performed to measure the weight (kg), height (m), waist and hip circumferences (cm), BMI, and waist-to-hip ratio (WHR) for each patient. Subjects with a severe somatic or psychiatric disorder, any neurological abnormality, or any addiction to drugs or alcohol were excluded from the study. The demographic and clinical characteristics of the study participants are shown in Table 1. The Bioethics Committees of Collegium Medicum (Bydgoszcz, Poland) and Nicolaus Copernicus University (Toruń, Poland) approved this study (agreement No. 533/2008). This study conformed to the guidelines of the Helsinki Declaration of 1975, as revised in 2000.

Table 1. Demographic and clinical characteristics of the study participants.

Group	N	Median BMI (range)	Median age, years (range)	Median visfatin level, ng/ml (range)
Women	48	38.0 (30.8–59.4)	37 (18–68)	45.6 (4.1–331.5)
Men	13	38.4 (30.7–63.2)	36 (21–69)	36.6 (9.6–130.2)

BMI, body mass index.

Measurement of serum visfatin content

Serum visfatin levels were determined via an enzyme immunoassay that employed a primary antibody against the C-terminal region of human visfatin (Phoenix Pharmaceuticals, Inc., St. Joseph, MO, USA). Spearman's rank-order correlation analysis was used to investigate the associations between serum visfatin levels and demographic and clinical factors.

Neuropsychological assessment

A neuropsychological assessment was conducted for each study participant by using the computerized version of the Wisconsin Card Sorting Test (WCST). The WCST evaluates working memory and execution function connected with prefrontal cortical activity (Heaton et al. 1993). The original version of the test was created by Berg and Grat in 1948 (Berg 1948) to gauge abstract thinking and perseveration, the ability to change or maintain logical conceptions, and the capacity to properly use feedback information from the environment to make decisions. Five automatically calculated WCST parameters were used for neuropsychological assessment in the present investigation: 1) the percentage of perseverative errors (WCST_P), also known as A-not-B errors, reflecting an inability to change a reaction when confronted with relevant stimuli; 2) the percentage of non-perseverative errors (WCST_NP), reflecting random or accidental errors resulting from an attention deficit or the failure to inhibit distracting stimuli; 3) the percentage of conceptual level responses (WCST_CLR), reflecting the ability to carry out conceptual thinking and strategic planning; 4) the number of correctly completed categories (WCST_CC), reflecting the ability to utilize new information along with previous experiences to achieve a goal; and 5) the number of cards required to complete the first category (WCST_1st), reflecting the capacity to formulate a logical conception.

Statistical analysis
The Shapiro-Wilk test was initially used to assess the normality of the distribution of the study variables. Because the Shapiro-Wilk test revealed a lack of normal distribution, the median and the range (minimum and maximum values) were instead used to compare study variables. The significance of differences between two groups was verified by using the non-parametric Mann-Whitney U test, and the significance of differences among three groups was verified by using the Kruskal Wallis analysis of variance (ANOVA) test. In all cases, a P value of < 0.05 was considered statistically significant. All calculations were performed by using the STATISTICA 9.0 Suite of Analytics Software Products and Solutions (StatSoft, Tulsa, OK, USA).

Results
Serum visfatin levels among the study participants were measured via an enzyme immunoassay with a primary antibody against the C-terminal region of visfatin. Median visfatin levels were similar in age-matched women (45.6 ng/ml) and men (36.6 ng/ml) (Table 1). Correlations between serum visfatin concentrations and various demographic and clinical factors are shown in Table 2. Visfatin content was negatively, albeit insignificantly, associated with the age, waist circumference, and WHR of the subjects. However, visfatin content was not significantly correlated with BMI (Table 2).

Table 2. Spearman's rank-order correlation analysis of associations between serum visfatin levels and demographic/clinical factors.

Parameter	R	P value
Age	–0.199	0.14
BMI	0.082	0.53
Waist circumference	–0.058	0.65
WHR	–0.193	0.14

R, Spearman's correlation coefficient.
WHR, Waist-to-hip ratio.

In addition, serum visfatin levels were not significantly different in patients with central (abdominal) vs. generalized (uniformly distributed) obesity, as assessed by the Mann Whitman U test (Table 3).

Table 3. Serum visfatin levels in patients with central vs. generalized obesity.

Obesity type	N	Median visfatin level, ng/ml (range)
Central	34	40.3 (4.1–331.5)
Generalized	27	48.2 (7.9–133.1)

Furthermore, no significant differences were found among patient groups with obesity grades I, II, and III, as determined by the Kruskal Wallis ANOVA test (Table 4).

Table 4. Serum visfatin levels in study participants according to obesity grade.

Obesity grade	N	Median visfatin level, ng/ml (range)
I	13	38.2 (11.9–130.2)
II	25	45.0 (4.1–331.5)
III	23	41,1 (7.9–133.1)

Neuropsychological assessments were conducted for the entire study group via the WCST with the five parameters described above (WCST_P, WCST_NP, WCST_CLR, WCST_CC, and WCST_1st). The relationship between serum visfatin levels and the five WCST parameters was then explored via Spearman's rank-order correlation analysis (Table 5). A significant correlation (P = 0.032) was found only between visfatin content and the number of correctly completed categories (regarded as a determinant of effective thinking and the ability to integrate previous experiences and environmental cues into appropriate actions), but not between visfatin content and the other WCST parameters (Table 5).

Table 5. Spearman rank-order correlation analysis of associations between serum visfatin levels and WCST scores.

Parameter	R	P value
WCST_P	–0.211917	0.10
WCST_NP	–0.157753	0.22
WCST_CLR	0.194755	0.13
WCST_CC	0.273806	0.032
WCST_1st	–0.029200	0.82

R, Spearman's correlation coefficient.
WCST, Wisconsin Card Sorting Test.
WCST_P, percentage of perseverative errors.
WCST_NP, percentage of non-perseverative errors.
WCST_CLR, percentage of conceptual level responses.
WCST_CC, number of correctly completed categories.
WCST_1st, number of cards needed to complete first category.

Patients were then stratified into two subgroups according to visfatin levels, low (< the median serum visfatin level for all subjects) vs. high (> the median serum visfatin level for all subjects) (Table 6). Patients in the high-visfatin subgroup tended to show an overall improvement in WCST scores. Nevertheless, a significant correlation (P = 0.039) was again found only between serum visfatin content and the number of correctly completed categories (Table 6).

Table 6. WCST scores in subgroups stratified by low and high serum visfatin levels.

WCST parameter	Low visfatin level (< 51.6 ng/ml) N = 40 median (range)	High visfatin level (> 51.6 ng/ml) N = 21 median (range)	P value
WCST_P	9.0 (5–58)	9.0 (5–17)	0.57
WCST_NP	12.5 (3–51)	8.0 (4–27)	0.22
WCST_CLR	73.0 (9–91)	79.0 (50–90)	0.29
WCST_CC	6.0 (0–6)	6.0 (2–6)	0.039
WCST_1st	11.5 (10–129)	11.0 (10–63)	0.72

WCST, Wisconsin Card Sorting Test.
WCST_P, percentage of perseverative errors.
WCST_NP, percentage of non-perseverative errors.
WCST_CLR, percentage of conceptual level responses.
WCST_CC, number of correctly completed categories.
WCST_1st, number of cards needed to complete first category.

Discussion
Roles of visfatin
Visfatin is an adipocyte-derived enzyme that can reduce serum glucose levels in mice by binding to the insulin receptor and mimicking the actions of insulin (Fukuhara et al. 2005). Visfatin is also implicated in nitric oxide-related vasodilatation in endothelium-intact rat aorta through actions on endothelial nitric oxide synthase Yamawaki et al. 2009). Moreover, recent publications have underscored a potential neuroprotective role of visfatin during ischemic responses in the central nervous system, which apparently stems from the capacity of the adipokine to enhance energy metabolism and to induce endothelium-dependent blood vessel relaxation (Yamawaki et al. 2009; Zhang et al. 2010).

Visfatin and inflammation

A recent study scrutinized the connection between circulating visfatin levels and gene expression in visceral and subcutaneous fat. The investigators found that visfatin levels were higher in obese compared with normal subjects, and that the elevated visfatin content was strongly associated with the expression of pro-inflammatory factors in fatty tissue (Terra et al. 2011; Conde et al. 2011). Along the same lines, a recent review highlighted the role of adipose tissue as an endocrine/paracrine/autocrine organ, and stressed the role of visfatin and other adipokines in the physiopathology of a number of inflammatory diseases (Conde et al. 2011). Therefore, these reports imply that high visfatin levels in obese subjects may contribute to the development of harmful inflammatory conditions Terra et al. 2011; Conde et al. 2011), such as alterations in immunity and chronic low-grade inflammation.

Visfatin and cognitive function

The analyses performed in the current investigation revealed a significant positive correlation between serum visfatin levels and the number of correctly completed categories in the WCST, which is widely used to assess prefrontal cortex-dependent cognitive function. The number of correctly completed categories in the WCST (the WCST_CC score) provides an index of thinking effectiveness, suggesting a neuroprotective advantage of high visfatin levels in obese subjects. The relationship between visfatin levels and the WCST_CC score was confirmed in a subgroup analysis of patients with low and high serum visfatin content.

Conclusions

In conclusion, the current study suggests that visfatin might have a protective effect on nervous tissue in the prefrontal cortex of obese individuals. However, obesity is a complex medical condition with a multi-faceted etiology, and many abnormal processes can affect the prefrontal cortex. Moreover, visfatin may contribute to both detrimental and beneficial biological processes in obese subjects. Further investigation is required to clarify the neuroprotective role of visfatin.

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