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Research paper

Decreased plasma adiponectin among male firefighters with symptoms of post-traumatic stress disorder

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ABSTRACT

Background: Recent studies have reported that adiponectin-mediated neuromolecular pathways are involved in fear extinction, implying that adiponectin may be an important biological marker for posttraumatic stress disorder (PTSD). However, no study has investigated the association between adiponectin and patients with PTSD.
Methods: We examined plasma adiponectin levels, high-sensitivity C-reactive protein (hs-CRP), and psychopathological factors using the Korean version of the Impact Event Scale-Revised (IES-R-K) and the Center for Epidemiologic Studies Depression Scale in 507 male firefighters. The PTSD symptom group was defined as those with a score of 25 or higher on the IES-R-K. Multiple logistic regression analysis was conducted to examine the covariates for the PTSD symptom group.
Results: Out of 507 male firefighters, 139 (27.4%) had a score of 25 or more on the IES-R-K. The PTSD symptom group had lower plasma adiponectin levels than the controls. There was an inverse correlation between plasma adiponectin levels and PTSD severity. There was no correlation between adiponectin levels and depression. The adiponectin level was associated with the presence of PTSD symptom (odds ratio = 0.955, 95% CI = 0.920–0.991).
Limitations: A cross-sectional design and using self-rated instruments.
Conclusions: To the best of our knowledge, the results showed that decreased adiponectin-mediated activity is associated with PTSD. Future studies are necessary to identify the causative role of adiponectin for PTSD as well as any possible covariates.

1. Introduction

Posttraumatic stress disorder is a relatively common mental disorder with an approximate prevalence rate of 3.0–5.6% (Stein et al., 2014). Patients with posttraumatic stress disorder (PTSD) experience substantial psychiatric distress, such as persistent re-experiencing of traumatic events, avoidance of stimuli, marked arousal, and depression (Greenberg et al., 2015). Additionally, PTSD is associated with metabolic diseases such as obesity (Bartoli et al., 2015) and type 2 diabetes mellitus (DM) (Roberts et al., 2015). Although lifestyle factors accompanied by psychiatric symptoms have some influence on the high incidence of metabolic diseases, recent studies have investigated the role of underlying neurobiological factors, particularly adiponectin (Castaneda et al., 2011; Zhang et al., 2016).

Adiponectin, which was first discovered two decades ago, is a 30-kDa adipocyte-derived adipokine (Scherer et al., 1995). The main function of adiponectin for humans is to promote insulin sensitivity (Ruan and Dong, 2016), which is closely associated with obesity and type 2 DM. However, adiponectin also plays an important role in the central nervous system (CNS). Peripherally infused adiponectin is detected in the cerebrospinal fluid (CSF) (Qi et al., 2004), which suggests that peripheral adiponectin crosses the blood-brain barrier (BBB). Initially, the central role of adiponectin was considered from the perspective of food intake and body weight based on the insulin sensitivity-related activity (Pannacciulli et al., 2003).

However, subsequent studies have suggested that adiponectin has pleiotropic activity in the CNS through the adiponectin receptors (Thundyil et al., 2012). The adiponectin receptors, adiponectin receptor 1 (AdipoR1) and adiponectin receptor 2 (AdipoR2), are mainly distributed in the hippocampus and hypothalamus (Kubota et al., 2007; Liu et al., 2012), which are closely associated with PTSD via modulation of the hypothalamus-pituitary-adrenal (HPA) axis (Gunnar and Quevedo, 2008; Mehta and Binder, 2012). One of the mechanisms that lead to psychiatric symptoms of PTSD is abnormal fear extinction

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(Garfinkel et al., 2014), which is primarily modulated in the hippocampus (Corcoran and Maren, 2001; Ji and Maren, 2007).

A recent study suggested that adiponectin is closely associated with fear extinction in the animal model of PTSD (Zhang et al., 2016). Although several human studies reported low peripheral adiponectin in anxiety (Rebelo et al., 2015) and depression (Diniz et al., 2012), to the best of our knowledge, no study has examined the association between adiponectin and the PTSD-affected population.

In this study, we aimed to investigate plasma adiponectin levels among people with symptoms of PTSD. Based on evidence from previous animal and human studies, we hypothesized that adiponectin levels may be lower in the PTSD symptom group compared with controls. Additionally, we hypothesized that adiponectin levels would have inverse correlations with PTSD severity.

2. Methods

2.1. Participants

This study was conducted between December 2012 and March 2013. A total of 545 male firefighters were recruited. Among them, 507 (93.0%) participants completed the self-rated questionnaires, laboratory tests, and anthropometric tests. All participants had been working normally. All participants were provided full explanations of the study protocol, and they gave written informed consent. The study was approved by the Institutional Review Board of the Korea University Ansan Hospital.

2.2. Laboratory measures

Peripheral blood was drawn from the antecubital region into a lithium-heparinized tube. Adiponectin levels were measured using a sandwich ELISA kit with a TMB microwell peroxidase substrate solution. hs-CRP levels were measured using a particle-enhanced immunoturbidimetric assay using Cobas, a novel Roche-Hitachi 8000 c702-I Chemistry Autoanalyzer (Roche Diagnostics System, Switzerland).

2.3. Waist circumference

The waist circumference was measured using a measuring tape at the narrowest region around the naval with minimal respiration at exhalation. In the case of some obese subjects, in which it was not possible to detect the narrowest region around the naval, the shortest circumference between the iliac crest and the costal bone was measured.

2.4. Self-rated assessments

2.4.1. IES-R -K

The Impact of the Event Scale-Revised Korean version (IES-R-K) (Eun et al., 2005) is the Korean-translated version of the Impact of Event Scale-Revised (IES-R) (Weiss and Marmar, 1997). The IES-R-K is a five-point Likert scale ranging from 0 (not at all) to 4 (extremely). The IES-R-K items are divided into three domains: hyperarousal (six items; e.g., “I was jumpy and easily startled”), avoidance (six items; e.g., “I tried not to talk about it.”), intrusive thoughts (five items; i.e., “I thought about it when I didn’t want to”), and others, including sleep, dissociation, and emotional numbness (five items; e.g., “I had trouble staying asleep”).

A high score indicates severe PTSD symptom. Based on a previous study (Asukai et al., 2002), the cut-off for the PTSD symptom group was set at 25, which means that subjects who scored at least 25 were categorized into the PTSD symptom group.

2.4.2. CES-D

The current level of depression was measured using the Korean version of the Center for Epidemiological Studies-Depression Scale (CES-D) (Cho and Kim, 1993; Radloff, 1977). The CES-D is a Likert scale that consists of 20 items. Each item's score ranges from 0 (rarely or never) to 3 (most or all of the time), and the highest possible total score is 60. For most items, higher scores denote more severe depressive symptoms, except items 5, 10, and 15, which are inversely computed.

2.5. Statistical analyses

All sociodemographic, clinical, and laboratory data between the PTSD symptom group and controls were compared using a chi square test for dichotomous variables and an independent *t*-test for continuous variables. The correlations between adiponectin levels and PTSD symptom, a partial correlation analysis adjusted for age, and the waist circumference were calculated. To test the influence of adiponectin levels for the presence of PTSD symptom, multiple logistic regression analysis was conducted. The unadjusted odds ratio (OR) and 95% confidence interval (CI) were calculated to compare with the adjusted OR and 95% CI. The linearity of the continuous variables with respect to the logit of the dependent variable was assessed via the Box-Tidwell test. Based on this assessment, all continuous independent variables were found to be linearly related to the logit of the dependent variable. The statistical significance was set at $p < 0.05$ with a two-tailed test. All statistical analyses were performed with IBM SPSS Statistics ver. 20.0 (IBM Corp., Armonk, NY, USA).

3. Results

3.1. Participants

The sociodemographic, laboratory, and clinical data of the participants are presented in Table 1. The PTSD symptom group experienced longer working periods than the controls. The proportion of participants who were married was lower in the PTSD group, although the mean age of the PTSD group was higher than that of the controls. The PTSD symptom group had higher BMI levels, waist circumferences, and plasma adiponectin levels than the controls. There was no difference in the hs-CRP between the two groups.

3.2. Relationship between plasma adiponectin levels and PTSD symptom

The plasma adiponectin level was inversely correlated with the IES-R-K scores after adjusting for age and waist circumference (Fig. 1). In the multiple logistic regression analysis, the adiponectin level was associated with a decreased odds ratio for the presence of PTSD symptom (Table 2). The unadjusted OR (95% CI) was 0.942 (0.908–0.978, $p = 0.002$), reflecting a more inverse relationship between adiponectin level and the presence of PTSD symptom than that reflected in the adjusted OR.

However, adiponectin had no relationship with depression. There were no significant differences in the plasma adiponectin levels in depressive symptoms group. There was also no correlation between adiponectin levels and CES-D total scores.

4. Discussion

In this study, we measured the peripheral adiponectin levels in firefighters, who are particularly vulnerable to PTSD (Wagner et al., 1998). One of the primary findings of this study was that plasma adiponectin levels were associated with the presence of PTSD symptom. Additionally, there was an inverse correlation between adiponectin levels and PTSD severity. To the best of our knowledge, this study is the first to show the association between the peripheral adiponectin levels and the PTSD-affected population. Our results are in line with previous