Psychoneuroendocrinology 86 (2017) 209–217

Contents lists available at ScienceDirect

Psychoneuroendocrinology

journal homepage: www.elsevier.com/locate/psyneuen

Plasma lipoproteins in posttraumatic stress disorder patients compared to healthy controls and their associations with the HPA- and HPT-axis

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ARTICLE INFO

Keywords:
Stress
PTSD
Cardiovascular disease
Low-density lipoprotein cholesterol
Cortisol
DHEA

ABSTRACT

Background: Based on studies among primarily male veteran subjects, lipoproteins are thought to mediate the association of posttraumatic stress disorder (PTSD) with cardiovascular disease (CVD). However, recent civilian studies with female samples or samples with both sexes represented provide little evidence for this association. Gender, diet and sex-specific effects of stress hormones on lipoproteins may explain this dissociation in findings.
Method: Cross-sectional analysis of plasma concentrations of total cholesterol (TC), low-density lipoprotein (LDL), high-density lipoprotein (HDL) and triglycerides (TG) in a male and female sample of 49 PTSD-patients due to civilian trauma and 45 healthy controls. Second, we related these lipoproteins to several stress hormones (prolactin, cortisol, DHEA(S), TSH, T4).
Results: Patients showed lower LDL ($p = 0.033$) and LDL:HDL ratio ($p = 0.038$) compared to controls, also when adjusting for diet. Sex influenced the effect of having PTSD on LDL with only male patients having lower values than male controls ($p = 0.012$). All stress hormones were associated with several lipoproteins, mostly in a sex-dependent manner. For LDL, a significant sex-by-cortisol effect ($p < 0.001$), having PTSD-by-sex-by-DHEA ($p < 0.001$), having PTSD-by-sex-by-DHEAS ($p = 0.016$) and having PTSD-by-sex-by-prolactin ($p = 0.003$) was found.
Conclusion: In this male and female civilian sample we found a somewhat more favorable lipoprotein profile in PTSD-patients in contrast to evidence from strictly male veteran samples exhibiting a less favorable lipoprotein profile. Male patients did not exhibit a worse lipoprotein profile than female patients and therefore gender cannot explain the contradiction in evidence. Additionally, we found that PTSD-related stress hormones are associated with lipoproteins levels in patients in a sex-specific manner. Specific configurations of stress hormones may contribute to CVD in male patients or protect in female patients. Further research on these configurations could indicate which PTSD-patients are especially at risk for CVD and which are not. This could guide future precision medicine efforts to prevent and treat the still growing burden of CVD morbidity and mortality in PTSD.

1. Introduction

Posttraumatic stress disorder (PTSD) is a mental disorder characterized by recurrent recollections of earlier experienced horrifying events (i.e. combat experiences, natural disasters, sexual assault), avoidance of these memories, and a state of chronic hypervigilance. PTSD is a major health problem with an estimated lifetime prevalence of about 7% in the general population (de Vries and Olff, 2009), approximately twice as prevalent in women compared to men (Olff et al., 2007), and responsible for an invalidating disease burden worldwide (Baxter et al., 2014; Wittchen et al., 2011).

PTSD has been found to contribute to the development of cardiovascular disease (CVD) (Kubzansky et al., 2009; Kubzansky et al., 2007; Paulus et al., 2013), independently from comorbidity with other mental disorders such as depression (Scott et al., 2013). PTSD adversely impacts cardiovascular outcomes after surviving myocardial infarction (von Kanel et al., 2011). CVD is an important cause of reduced life expectancy among PTSD-patients (Ahmadi et al., 2011; Boscarino, 2008).

Lipoprotein particle metabolism is suggested to partly explain the association between PTSD and CVD (Dedert et al., 2010; Wentworth et al., 2013). Lipoproteins are biochemical assemblies containing both

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http://dx.doi.org/10.1016/j.psyneuen.2017.09.020
Received 19 March 2017; Received in revised form 25 September 2017; Accepted 26 September 2017

proteins and lipids. Their structure allows insoluble lipids (i.e. cholesterol and triglycerides) to be transported. Free fatty acids that are an essential fuel source and indispensable for cell membrane synthesis can be esterified into triglycerides and packaged in lipoprotein particles for transport in the circulation. Large-scale population studies indicate that increased levels of triglycerides (TG), low-density lipoprotein cholesterol (LDL) and total cholesterol (TC), and decreased levels of high-density lipoprotein cholesterol (HDL) are robust risk factors for CVD (Castelli et al., 1986; Toth et al., 2013).

Because this typical unfavorable lipid profile was initially found in PTSD-patients compared to healthy controls (Dzubur Kulenovic et al., 2008; Kagan et al., 1999; Karlovic et al., 2004a; Karlovic et al., 2004b; Maia et al., 2008; Solter et al., 2002), lipoproteins were assumed to underlie the greater incidence of CVD in PTSD-patients. Contradictory evidence arose as later studies only partly confirmed (Dennis et al., 2014; Heppner et al., 2009) or failed to demonstrate this unfavorable lipid profile (Gill et al., 2013; Jendricko et al., 2009; Tochigi et al., 2005). Moreover, conflicting findings also emerged such as those of Maia et al. (2008) who did not find decreased HDL, while Dennis et al. (2014) found only HDL to be decreased. Thus, questions remain despite the initial evidence for a role of lipoprotein metabolism in PTSD.

First, it must be noted that initial studies were primarily based on male veteran samples, while later studies with less clear and negative findings were based on male and female data (Heppner et al., 2009; Tochigi et al., 2005) or only female (Gill et al., 2013) samples, and included civilians instead of veterans (Dennis et al., 2014; Gill et al., 2013; Tochigi et al., 2005). This suggests that sex and veteran/civilian status might influence lipoprotein profile in PTSD-patients. Dedert et al. (2010) argue that the evidence should therefore be completed with more and broader sociodemographic groups. Sex differences in lipoprotein profile generally exist as women tend to have lower TG, lower LDL and higher HDL than men (Freedman et al., 2004; Pascot et al., 2002). Second, it was recently found that lifestyle factors like smoking and poor sleep quality unfavorably influence lipid values in PTSD-patients (Dennis et al., 2014; Talbot et al., 2015). Third, biological mechanisms through which PTSD may impact lipoprotein metabolism remain largely unclear. For instance, one-carbon metabolism has been found altered in PTSD-patients (de Vries et al., 2015), while one-carbon metabolism interacts with lipid metabolism (Assies et al., 2015; da Silva et al., 2014; Momin et al., 2017; Xiao et al., 2011).

To our knowledge, one important lifestyle factor – diet – was never controlled for. Lipoprotein concentrations, however, greatly depend on diet (Berger et al., 2015; Lamarche and Couture, 2015; Ooi et al., 2015). Diet might explain the differences found between veteran and civilian samples as for instance, veterans have lower intakes of vitamins and a higher intake of total fat as a percentage of energy (Park et al., 2011).

Furthermore, an important potential mechanism through which PTSD can influence lipoprotein metabolism, a disbalance in stress hormones, was also never investigated. Ample evidence exists for hypothalamic–pituitary–adrenal (HPA) axis dysregulation in PTSD with decreased cortisol and enhanced sensitivity to negative feedback (Meewisse et al., 2007; Morris et al., 2012). Cortisol not only affects glucose metabolism, but also fatty acid metabolism and development of lipid abnormalities (Di Dalmazi et al., 2015; Macfarlane et al., 2008; Mocking et al., 2015; Peckett et al., 2011). Additionally, dehydroepiandrosterone (DHEA) and its sulphate ester (DHEAS), as well as adrenal gland hormones beside cortisol, are mainly found to be increased in PTSD-patients (Bremner et al., 2007; Kellner et al., 2010). Both favorable, neutral and even negative effects of DHEA(S) on lipoproteins have been found, with most differences being sex-dependent (Porsova-Dutoit et al., 2000; Srinivasan et al., 2010). Prolactin, a pituitary gland hormone, is generally decreased in PTSD-patients (Jergovic et al., 2015; Olff et al., 2006) and has been found to influence lipogenesis, lipolysis, adipogenesis and adipokine release (Ben-Jonathan and Hugo, 2015; Carre and Binart, 2014). Finally, some evidence exists for hypothalamus-pituitary-thyroid (HPT) axis dysregulation in PTSD with decreased thyroid-stimulating hormone (TSH) in patients (Olff et al., 2006). The thyroid hormones triiodothyronine and its prohormone thyroxine (T4) significantly affect lipoprotein metabolism (Angelin and Rudling, 2010) even within the normal-range of TSH-values (Rizos et al., 2011). In sum, evidence exists that PTSD-associated stress hormones may affect lipoprotein metabolism, often in a sex-dependent manner. Sample sex composition and alterations in stress hormones found among PTSD-patients might thus be responsible for the discrepancy in findings between strictly male or female samples, or samples with both sexes represented.

We therefore investigated the role of lipoproteins in PTSD by comparing fasting plasma concentrations of TG, LDL, HDL and TC between male and female patients with PTSD due to civilian trauma and healthy controls. We hypothesized (1) elevated TG, LDL and TC, and decreased HDL in patients (the unfavorable profile), and (2) differences to vary by sex with the expectation of a more favorable lipid profile in women. Differences were assumed to be influenced by dietary factors. Finally, we exploratively related plasma concentrations of the stress hormones cortisol, DHEA(S), prolactin, TSH and T4 to the measured lipoproteins.

2. Material and methods

2.1. Participants

We included 49 outpatients with PTSD due to a civilian trauma (e.g. accident, loss of loved one, sexual violence) and 45 healthy controls. We assessed the DSM-IV PTSD diagnosis using the Structured Interview for Posttraumatic Stress Disorder and coexisting clinical disorders with the Structured Clinical Interview for DSM-IV (SCID-I) using trained clinical professionals (psychologists, psychiatrist). The Biomarker studýs methodology, such as inclusion and exclusion criteria, clinical assessment and dietary assessment have been described in more detail previously (de Vries et al., 2015).

2.2. Biological measures

We measured height, weight and waist circumference and calculated the body mass index (BMI). We collected blood samples in heparinized tubes by venipuncture between 08:00 and 10:00 after an overnight fast. We analyzed the blood samples immediately after blood was taken in our Medical Research Laboratories and determined plasma TC, HDL, and TG concentrations using a Roche/Hitachi Modular P800 chemistry analyzer through standard enzymatic methods. We applied the Friedewald formula to determine LDL concentration. Stress hormone values were assessed using commercially available kits with inter- and intra-essay coefficients of variation $< 10\%$. Details about these measures can be found in our article on HPA- and HPT-axis alterations in PTSD (Olff et al., 2006).

2.3. Dietary assessment

We instructed participants to record all foods and beverages they consumed over the 24-h preceding the morning we collected the blood samples. Each participant was instructed to adequately register the foods and amounts consumed, the preparation methods, and portion sizes using both close-ended and open-ended questions (Thompson and Subar, 2013). We then calculated relevant nutritional values such as the amount of proteins, carbohydrates, saturated, mono- and poly-unsaturated fats, and caloric intake using information from the Dutch Food Composition Database (Voedingscentrum, 2006). Several sources provided data for this food composition database. A standard procedure was used to check whether the data were fit-for-purpose. Most food composition data came from chemical analyses by accredited laboratories. Quality criteria were applied for food identification, sampling, and methods of analysis. Supplementary information was collected