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Reductions in circulating endocannabinoid levels in individuals with post-traumatic stress disorder following exposure to the world trade center attacks

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Summary Endocannabinoid (eCB) signaling has been identified as a modulator of adaptation to stress, and is integral to basal and stress-induced glucocorticoid regulation. Furthermore, interactions between eCBs and glucocorticoids have been shown to be necessary for the regulation of emotional memories, suggesting that eCB function may relate to the development of post-traumatic stress disorder (PTSD). To examine this, plasma eCBs were measured in a sample (n = 46) drawn from a population-based cohort selected for physical proximity to the World Trade Center (WTC) at the time of the 9/11 attacks. Participants received a structured diagnostic interview and were grouped according to whether they met diagnostic criteria for PTSD (no PTSD, n = 22; lifetime diagnosis of PTSD = 24). eCB content (2-arachidonoylglycerol (2-AG) and anandamide (AEA)) and cortisol were measured from 8 a.m. plasma samples. Circulating 2-AG content was significantly reduced among individuals meeting diagnostic criteria for PTSD. The effect of reduced 2-AG content in PTSD remained significant after controlling for the stress of exposure to the WTC collapse, gender, depression and alcohol abuse. There were no significant group differences for AEA or cortisol levels;

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however, across the whole sample AEA levels positively correlated with circulating cortisol, and AEA levels exhibited a negative relationship with the degree of intrusive symptoms within the PTSD sample. This report shows that PTSD is associated with a reduction in circulating levels of the eCB 2-AG. Given the role of 2-AG in the regulation of the stress response, these data support the hypothesis that deficient eCB signaling may be a component of the glucocorticoid dysregulation associated with PTSD. The negative association between AEA levels and intrusive symptoms is consistent with animal data indicating that reductions in AEA promote retention of aversive emotional memories. Future work will aim to replicate these findings and extend their relevance to clinical pathophysiology, as well as to neuroendocrine and molecular markers of PTSD.

1. Introduction

The development of post-traumatic stress disorder (PTSD) is related to abnormalities in the regulation of biological stress response systems, specifically the hypothalamic–pituitary–adrenal (HPA) axis and sympathetic nervous system (Krystal and Neumeister, 2009; Yehuda, 2009). Current theories suggest that increased responsivity of glucocorticoid receptors resulting in reduced cortisol levels at the time of a traumatic exposure, or immediately thereafter, will result in increased noradrenergic transmission associated with a prolonged state of distress (Pervanidou and Chrousos, 2010). This state of arousal will result in the 'hyperconsolidation' of emotional memories, and ultimately, could lead to the development of PTSD. However, since not all persons exposed to trauma develop PTSD, it has also been of interest to identify hormones or signaling molecules that could be responsible for either increasing the probability of PTSD or for promoting resistance to PTSD development. By examining a population-based cohort of individuals exposed to the World Trade Center (WTC) collapse, we have recently identified genetic markers related to glucocorticoid signaling in individuals who developed PTSD (Yehuda et al., 2009; Sarapas et al., 2011). Accordingly, further investigation of systems involved in the regulation and actions of glucocorticoid hormones was undertaken to explore the underlying biological mechanisms specific to the development of PTSD.

The endocannabinoid (eCB) system represents an ideal candidate system to investigate with respect to the pathophysiology of PTSD (Hill and Gorzalka, 2009; Neumeister, 2013). The eCB system is primarily composed of a central CB_1 receptor and two endogenous ligands (*N*-arachidonylethanolamine [anandamide; AEA] and 2-arachidonoylglycerol [2-AG]). In addition, there are also CB_2 receptors, whose expression is primarily restricted to immune cells of macrophage lineage but may also be expressed in the CNS, as well as a family of fatty acid ethanolamides, such as palmitoylethanolamide and oleoylethanolamide, which share biosynthetic and catabolic pathways with AEA, but are not ligands for the CB receptors. The eCB system is known to constrain activation of the stress response through distributed actions in limbic and hypothalamic circuits in the brain (Riebe and Wotjak, 2011; Hill and Tasker, 2012). More so, eCB signaling is responsive to glucocorticoid hormones (Di et al., 2003; Hill et al., 2010a), and the recruitment of eCB signaling by glucocorticoids has been found to mediate many of the physiological actions of these hormones, including negative feedback termination of HPA axis activity (Evanson et al., 2010; Hill et al., 2011) and modulation of emotionally salient cognitive processes (Campolongo et al., 2009; Atsak et al., 2012). In addition to the role of eCBs in mediating the actions of glucocorticoids, eCB signaling is involved in many processes which are dysregulated in PTSD, such as the extinction of emotionally aversive memories (Marsicano et al., 2002; Plendl and Wotjak, 2010; Gunduz-Cinar et al., 2013), habituation and adaptation to stress (Patel et al., 2005b; Hill et al., 2010b) and release of catecholamines from sympathetic nerve terminals (Ishac et al., 1996; Bellocchio et al., 2013).

Based on these converging lines of evidence and the neurobiology of PTSD, we hypothesize that reductions in circulating concentrations of eCB represent a biomarker of stress vulnerability, and that deficient eCB signaling is involved in the biological processes related to PTSD. To examine these hypotheses, we evaluated circulating concentrations of the eCBs AEA and 2-AG in a sample derived from a population-based cohort selected for physical proximity to the WTC at the time of the 9/11 attacks. A sub-sample of this cohort was previously selected for a genome-wide association study of PTSD (Yehuda et al., 2009). This is an ideal cohort in which to search for biological identifiers of PTSD, as risk for exposure was based on proximity to the WTC, and was uncomplicated by the confound that exposure often introduces to genetic association studies (e.g., familial risk for exposure to interpersonal violence). Furthermore, circulating eCB concentrations are elevated in response to acute stress (Hill et al., 2009b; Dlugos et al., 2012), whereas deficient recruitment of eCB signaling in response to acute stress, or low basal eCB contents in the circulation, have been related to excessive stress-induced activation of the HPA axis (Chouker et al., 2010; Dlugos et al., 2012) and negative long-term outcomes following exposure to stressful events, such as cardiac surgery (Hauer et al., 2012). Our data indicate that PTSD is associated with reduced concentrations of 2-AG in the circulation and that both 2-AG and AEA concentrations associate with specific symptom clusters within PTSD.

2. Methods

2.1. Participants

Subjects were 46 participants who comprised a subset of a population based sample ($n = 109$) evaluated at the Mount Sinai School of Medicine (MSSM) four to six years following the 9/11 attacks (Yehuda et al., 2009). The subjects studied at the MSSM were those who responded positively to a mailing asking participants to have an in-person diagnostic