



Altered hair endocannabinoid levels in mothers with childhood maltreatment and their newborns

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ARTICLE INFO

Keywords:

Endocannabinoids
N-oleoylethanolamide
N-stearoylethanolamide
N-palmitoylethanolamide
1-Arachidonoylglycerol
Childhood maltreatment

ABSTRACT

The endocannabinoid (EC) system possesses anti-inflammatory properties and seems to be altered in trauma-exposed individuals. In an intergenerational approach, this study investigated the link between childhood maltreatment (CM) experiences and alterations in the EC system. Hair samples of $N = 142$ mothers and $N = 91$ newborns were analyzed, retrospectively assessing EC regulation during the last trimester of pregnancy with four ECs: 1-arachidonoylglycerol (1-AG), N-oleoylethanolamide (OEA), N-stearoylethanolamide (SEA), and N-palmitoylethanolamide (PEA). Compared to mothers without CM, hair of mothers with CM showed significantly higher levels of 1-AG and lower levels of SEA. Newborns of mothers with CM exhibited higher levels of 1-AG and OEA. Furthermore, the higher the severity of maternal CM, the lower were maternal SEA levels and the higher neonatal OEA levels. Findings indicate altered EC levels during the last trimester of pregnancy in mothers with CM and their developing fetus, highlighting potential intergenerational effects from one generation to the other.

1. Introduction

As an early and frequently chronic stressor, childhood maltreatment (CM), including abuse and neglect, exerts its adverse impact in a highly sensitive period of development. Thereby, it affects the maturation, the functionality, and the integrity of various biological systems such as the endocrine stress response, the immune system and their interplay. The resulting alterations contribute to an increased risk for physical and mental disorders over the life span (Nemeroff, 2016). Parents with a history of CM are more stressed in the postnatal period (Schury et al., 2017) and exhibit more psychosocial risk factors for a healthy development of their child in the puerperium compared to non-CM parents (Koenig et al., 2016). Thus, they are at risk to transmit health risks to their offspring via biological pathways.

To investigate the effects of traumatic experiences on the human stress response system, particularly on the hypothalamus-pituitary-adrenal (HPA) axis, the steroid hormone cortisol is most commonly utilized as a biomarker (e.g., Kalmakis, Meyer, Chiodo, & Leung, 2015). Another important regulator is the endocannabinoid (EC) system since

it can buffer the basal activity of the glucocorticoid system and mediates its feedback mechanisms promoting HPA axis homeostasis (Riebe & Wotjak, 2011). Its bioactive signaling lipids, the ECs, are synthesized on-demand from cell membrane components (glycerophospholipids) in the brain and the periphery (for more information about the EC metabolism see Ueda, Tsuboi, and Uyama (2013)). The EC system possesses regulatory functions in stress-induced anxiety, modulation of memory, regulation of pain or reward, and also synaptic plasticity (Morena, Patel, Bains, & Hill, 2015). Furthermore, the EC system represents a major target of drugs and therapies due to its homeostatic role in many other physiological regulation pathways (Aizpurua-Olaizola et al., 2016). For example, it is also involved in the regulation of energy metabolism, including energy balance and glucose homeostasis. In providing a positive energy balance, the EC system potentially modulates, among others, the biogenesis, integrity, and oxidative capacity of mitochondria (Lipina, Irving, & Hundal, 2014), has protective effects against oxidative stress (Zolese et al., 2008), and acts immune-modulatorily (Hillard, Weinlander, & Stuhr, 2012).

The two most intensively investigated ECs in psychiatric and

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neurological disorders are anandamide (AEA) and 2-arachidonoylglycerol (2-AG; see reviews: Hillard et al., 2012; Iannotti, Di Marzo, & Petrosino, 2016). To unravel further mechanisms of the EC system important for health and disease, the class of *N*-acylethanolamines seems to be a promising target for future investigations (Hansen, 2010) as these EC congeners are chemically similar to AEA and potentiate the effects of AEA (Ho, Barrett, & Randall, 2008). *N*-acylethanolamines are composed of fatty acids linked to an ethanolamine and encompass the saturated acyl chains *N*-stearoylethanolamide (SEA) and *N*-palmitoylethanolamide (PEA) as well as the unsaturated acyl chain *N*-oleoylethanolamide (OEA).

The biological functions of SEA and PEA have been described as anti-inflammatory, with SEA downregulating allergic inflammation in the skin (Dalle Carbonare et al., 2008) as well as suppressing pro-inflammatory cytokine production (Berdyshev et al., 2015), and PEA representing a therapeutic agent for influenza and common cold (Keppel Hesselink, de Boer, & Witkamp, 2013). PEA was further characterized as neuroprotective in neurological disorders and showed analgesic properties by modulating pain and inflammation (Mattace Raso, Russo, Calignano, & Meli, 2014). In this role, PEA is discussed as pharmacologically effective in the symptom treatment of physical (e.g. Petrosino & Di Marzo, 2017), and psychological disorders (e.g. Coppola & Mondola, 2014). While PEA has been intensively studied, the investigation of SEA has been rather neglected (Dalle Carbonare et al., 2008). The third *N*-acylethanolamine OEA acts as a regulator for appetite and body weight as its release reduces food intake and induces satiety (see review of Thabuis et al., 2008). In a recent metabolite profiling study, elevated plasma levels of OEA were related to obesity (Zhao et al., 2016).

The EC system might be important in the etiology and treatment of stress-related psychiatric disorders as EC signaling influences the consolidation, retrieval and extinction of traumatic memories (Lutz, Marsicano, Maldonado, & Hillard, 2015). Furthermore, the on-demand biosynthesis and release of ECs allows an expeditious adaptation to changing conditions (Lutz, Marsicano, Maldonado, & Hillard, 2015). Under acute psychosocial stress, healthy humans showed significantly increased serum concentrations of OEA, SEA, and PEA (Dlugos, Childs, Stuhr, Hillard, & de Wit, 2012). With regard to trauma spectrum disorders, such as Posttraumatic Stress Disorder (PTSD), most studies assessed EC levels in blood with mixed results. Compared to healthy controls, patients with a current PTSD showed higher plasma levels of AEA, 2-AG, OEA, SEA, and PEA (Hauer et al., 2013) and complex PTSD patients higher serum levels of OEA (Schaefer et al., 2014), whereas lifetime PTSD patients exhibited a lower plasma level of 2-AG (Hill et al., 2013). Additionally, PEA was identified as the second most important metabolite in the separation of PTSD cases and controls in a recent metabolite fingerprinting study (Karabatsiakakis et al., 2015). Whereas the assessment in blood only mirrors circulating EC levels at the moment of blood sampling, the measurement of EC levels in hair allows a more cumulative and retrospective assessment of EC levels and was demonstrated to be rather stable with respect to wash-out effects (Krumbholz, Anielski, Reisch, Schelling, & Thieme, 2013). Measuring EC levels in hair, a recently published study (Wilker et al., 2016) reported reduced OEA, SEA, and PEA levels linked with a higher traumatic load (number of lifetime traumatic event types experienced) in patients with acute PTSD and mentally healthy, but trauma-exposed controls. Wilker et al. (2016) assumed that the observed reductions in EC levels could indicate an increased inflammatory state in the aftermath of trauma exposure (Wilker et al., 2016). Indeed, in a recent study, we could show a comparable pro-inflammatory phenotype with a higher inflammasome activation in CM-exposed individuals in adulthood (Boeck et al., 2016; see also meta-analysis of Baumeister, Akhtar, Ciufolini, Pariante, and Mondelli (2016)).

To our knowledge, no other study so far surveyed the EC system in the context of CM. For this reason, we aimed at investigating alterations in ECs (OEA, SEA, PEA, 1-arachidonoylglycerol (1-AG)) in mothers with

or without CM experiences and corresponding alterations in the EC system of the developing fetus. In accordance with the assumption of a pro-inflammatory phenotype following CM (cf. Boeck et al., 2016), we hypothesized that CM-exposed mothers would show reduced EC levels in hair compared to non-exposed mothers. As an additional aim, this study allows to explore potential intergenerational effects by investigating whether maternal CM experiences were associated with EC level alterations in hair collected from newborns. Since in the puerperium intergenerational biological effects of maternal CM experiences on the EC system of newborns can be investigated in a “pure” way without potential behavioral influences (e.g., traumatic experiences of the offspring itself or parenting behaviors), the measurement point was set right after birth.

2. Materials and methods

2.1. Participants, procedure, and study design

The data were collected within the project “My Childhood – Your Childhood”, which aimed at investigating psychobiological risk and resilience factors in the transgenerational transmission of CM in a community sample and was conducted from October 2013 to December 2015. All procedures were approved by the Ethics Committee of Ulm University. Study exclusion criteria were insufficient knowledge of the German language, severe complications during parturition, any severe health problems of either mother or child, and maternal age under 18 years. Mother-infant-dyads were recruited at the Department of Obstetrics and Gynecology of the University Hospital Ulm shortly after parturition ($M = 2.7$ days [$SD = 4.8$]), provided written informed consent before participating in the study and took part in a screening interview. Besides asking for demographic, clinical, and hair-related characteristics (see Table 1), the German version of the *Childhood Trauma Questionnaire* (CTQ; Bader, Hänny, Schäfer, Neuckel, & Kuhl, 2009) was used to assess maternal CM experiences. In addition, hair samples of mothers and newborns were collected. For an overview of the recruitment process, see Fig. 1.

2.2. Sociodemographic and psychological measures

Maternal CM experiences were assessed in an interview with the German short version of the CTQ (Bader et al., 2009) covering the five subscales emotional, physical and sexual abuse as well as emotional and physical neglect with five items each. The CTQ sum score provides a cumulative measure for the severity of CM experiences, also called “maltreatment load” (Schury & Kolassa, 2012). Established cut-off criteria (Bernstein & Fink, 1998) subdivide the severity of each CTQ subscale into the categories “none”, “mild”, “moderate”, and “severe”. Women without any CM experiences were classified as CM-, whereas women with at least mild CM experiences in at least one CTQ subscale were categorized as CM+.

In addition, several potential covariates were assessed: self-reported lifetime psychiatric diagnoses (“Have you ever been diagnosed with a psychiatric disorder, such as depression, anxiety disorder, or other psychiatric disorder by a physician or psychologist? If yes, which?”), perceived stress in the last four weeks using the 4-item *Perceived Stress Scale* (PSS4; Cohen, Kamarck, & Mermelstein, 1983) as well as gender and birth weight of the newborns. In addition, women were questioned about hair-related characteristics (hair treatment: coloration, bleaching, permanent wave; hair washing frequency per week).

2.3. Hair endocannabinoid analyses

Hair sampling took place directly after the women had given written informed consent ($M = 2.07$ days [$SD = 0.95$; Range = [0;5]] after parturition). For the hair sampling in mothers, three hair strands (~3 mm diameter each) were cut close to the scalp from the posterior

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