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Relationship of childhood adversity and neighborhood violence to a proinflammatory phenotype in emerging adult African American men: An epigenetic link

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ABSTRACT

African American men (AAM) who are exposed to trauma and adversity during their early life are at greater risk for poor health over their lifespan. Exposure to adversity during critical developmental windows may embed an epigenetic signature that alters expression of genes that regulate stress response systems, including those genes that regulate the inflammatory response to stress. Such an epigenetic signature may increase risk for diseases exacerbated by inflammation, and may contribute to health disparity. The purpose of this study was to evaluate the extent to which exposure to early life adversity influences the psychological, cortisol, and proinflammatory response to acute stress (Trier Social Stress Test – TSST) in emerging adult AAM, ages 18–25 years (N = 34). Hierarchical linear modeling was used to examine the cortisol and IL-6 pattern of response to the TSST with respect to childhood adversity factors and DNA methylation of the IL-6 promoter. Findings revealed that in response to the TSST, greater levels of childhood trauma and indirect exposure to neighborhood violence were associated with a greater TSST-induced IL-6 response, and a blunted cortisol response. Reduced methylation of the *IL6* promoter was related to increased exposure to childhood trauma and greater TSST-induced IL-6 levels. These results support the concept that exposure to childhood adversity amplifies the adult proinflammatory response to stress, which is related to epigenetic signature.

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1. Introduction

Increasing evidence demonstrates that childhood adversity subsequent to neglect, abuse, poverty, or disturbed family relations exerts a strong and enduring influence on adult health (Brent and Silverstein, 2013; Danese et al., 2009). A feature common to those raised in an adverse environment is chronic exposure to high levels of psychosocial stress (Evans, 2004), which is known to increase levels of inflammatory mediators and the potential risk for diseases exacerbated by inflammation (Rohleder, 2014). Stress exposure may be especially intense for individuals who grow up in impoverished neighborhoods with few resources and high levels of violence and crime (Landis et al., 2007). Both stress exposure and inflammatory processes play an important role in the pathogenesis of cardiovascular disease (Lu et al., 2013). This is particularly relevant for African American men (AAM) who suffer a disproportionate death rate from cardiovascular disease, as compared to both African American women and non-Hispanic whites (Center for Disease Control, 2013). Despite the clear impact on health, the biological pathways linking childhood adversity to inflammation-related disease risk remains unknown. Such knowledge can offer insight into the relationships between exposure to adversity early in life and disparity in health throughout the lifespan.

Childhood adversity is known to disrupt the development of stress-response systems (Danese and McEwen, 2012; Danese et al., 2007; Heim et al., 2010; McCrory et al., 2011; Nemeroff, 2004), contributing to a stress-vulnerable adult phenotype characterized by dysregulated HPA stress reactivity (Heim et al., 2010; Nemeroff, 2004) and chronic low grade inflammation (Danese et al., 2007). Additionally, in response to acute stress challenge, individuals who experienced adversity during their childhood exhibit an exaggerated release of proinflammatory cytokines (Carpenter et al., 2010) and a reduced release of the anti-inflammatory hormone, cortisol (Carpenter et al., 2007, 2011, 2009; Elzinga et al., 2008; Lovallo et al., 2012). Such a proinflammatory phenotype may connect the stress of childhood adversity with increased disease burden and premature death in AAM; since adversity predicts higher levels of inflammatory markers in AA than in whites (Slopen et al., 2010). Moreover, inflammatory risk

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associated with early life adversity has been observed in children (Diez Roux and Mair, 2010; Slopen et al., 2013), and in healthy adolescents, who were found to exhibit an increasingly proinflammatory phenotype based on the extent to which they were reared in a harsh family environment (Miller and Chen, 2010).

However, it remains to be determined what molecular pathway links adverse early life experiences with an adult proinflammatory response to stress. During early life, including childhood and adolescence, developing biological systems are more plastic and thus, more sensitive to environmental influence (Hochberg et al., 2011), and this plasticity includes those cells that regulate the inflammatory response (McDade, 2012). For example, the experience of childhood traumatic events has been shown to be to be associated with increased levels of transcription of peripheral blood proinflammatory genes (*IL1B*, *IL8*, *PTGS2*) in late life (Levine et al., 2015). It is possible that persistence of such a proinflammatory phenotype may result from early life epigenetic embedding, which primes these individuals to have a greater stress-induced inflammatory response over their lifespan. Exposure to adversity during critical developmental windows can induce stable changes in epigenetic states that modulate gene expression levels without alteration of nucleotide sequence; however, the evidence in humans has focused on epigenetic changes related to regulation of the hypothalamic pituitary adrenocortical axis (Vaiserman, 2015), rather than epigenetic embedding of cells that regulate the inflammatory response. Nevertheless, a theoretical model has been put forth, which posits that exposure to early life adversity epigenetically imprints monocytes/macrophages in a manner that gives rise to a durable adult proinflammatory phenotype characterized by a greater inflammatory response to stress challenge (Miller et al., 2011). Consistent with this theory, epigenetic effects of stress on cells of the human innate immune system have been demonstrated (Mathews et al., 2011), while others show that exposure to stress hormones (i.e., glucocorticoids) may prime immune cells to produce a greater inflammatory response to subsequent stress exposure (Frank et al., 2010; Mathews et al., 2011; Wohleb et al., 2012).

Thus, for this investigation we enrolled emerging adult AAM (18–25 years of age) to evaluate the extent to which exposure to childhood adversity, including neighborhood violence, predicts the psychological, cortisol, and peripheral blood mononuclear cell proinflammatory (IL-6) response to acute stress (Trier Social Stress Test – TSST). A second objective was to evaluate the relationship between exposure to childhood adversity and a proinflammatory epigenetic signature. To accomplish the latter objective, the level of *IL6* promoter methylation was measured in peripheral blood mononuclear cells of AAM with regard to childhood adversity and the salivary IL-6 response to the TSST. Salivary IL-6 was measured as it has been associated with greater cardiovascular disease risk (Out et al., 2012) and increased levels of salivary proinflammatory cytokines (TNF-alpha and IL-6) have been found to be related to increased risk for carotid atherosclerosis, as measured by intima-media thickness (Kosaka et al., 2014). The expectation was that childhood adversity imprints an epigenetic signature (DNA methylation) at the *IL6* promoter, which heightens the proinflammatory response to stress challenge during emerging adulthood. Understanding the contribution of promoter DNA methylation to a proinflammatory phenotype has potential to explain individual differences in inflammatory stress reactivity and future disease risk and severity.

2. Methods

2.1. Participants and procedure

African American men (AAM) between 18 and 25 years of age were recruited from two Chicago metropolitan low income neighborhoods. A portion of the sample was referred to the study by community centers that provide programs for low income AA families. Participants' health and medical history was assessed by self-report. For eligibility, all participants were to be without acute illness in the 2 weeks preceding the study protocol, without a history of medical, psychiatric disorders, drug and alcohol abuse and were not taking psychotropic or anti-inflammatory medications. This study was approved by the Loyola University Chicago Institutional Review Board for the Protection of Human Subjects and informed consent was obtained from all participants.

Participants were scheduled to undergo the Trier Social Stress Test (TSST) between 11:00 am – 12:00 pm. Prior to testing, participants were instructed to avoid caffeine for 4 h, alcohol and exercise for 12 h, smoking and over-the-counter medications for 24 h; this was confirmed upon their arrival for undergoing the TSST. The TSST protocol is established to induce psychological stress and elevations in stress hormones and IL-6 (Kirschbaum et al., 1993; Larson et al., 2001). A standardized procedure for the TSST was followed in which participants were instructed to deliver a 4-min impromptu speech simulating a job interview, followed by a mental arithmetic task in the presence of two evaluative judges (Kirschbaum et al., 1993; Larson et al., 2001). The TSST was conducted in a quiet setting within the University (i.e., standard conference room). Evaluative judges were male. They wore white lab coats, and were seated behind a table. One judge remained silent during the procedure, while the other directed the stress testing; both maintained neutral facial expressions. The participant prepared his speech while seated, but stood to undergo the speech and math tasks. A scripted procedure was used to introduce the participant to the TSST, and to instruct the participant about the speech and mathematics testing protocol. The procedure was videotaped.

Prior to testing, participants were seated for 15 min before providing a blood sample (20 ml) for epigenetic analysis, and a saliva sample for baseline (T0) cortisol and IL-6. After conclusion of the TSST, saliva samples were collected at 15 min (T1), 30 min (T2), 45 min (T3), and 60 min (T4) post TSST (Pace et al., 2009). Participants also completed pre- and post-TSST measures of anxiety and positive/negative affect (Marsland et al., 2006), as well as a post-TSST packet of questionnaires, as described below. After completion of their role in the study, the participants were debriefed about the goals of the study and compensated with a gift card to a local food store.

2.2. Questionnaires

2.2.1. Demographic childhood socioeconomic status (SES) and health behaviors

Demographic information, including participant's age, marital status, education, and employment status was obtained using a self-report questionnaire. Childhood SES was evaluated by assessing parental occupation, education, household income, and whether the participant's parents were home owners when participants were in kindergarten. Health behaviors were assessed by self-report and included: physical activity, sleep, smoking, use of street drugs, and daily consumption of alcoholic and caffeinated beverages. For physical activity participants completed a questionnaire that asked them to indicate the types and frequency of physical activity (exercise/sports) they engaged in during the past month, and also during the past three days. They also rated the intensity of physical activity based on the question: *If you exercised in the past month, how many times did you* "work up a sweat"?

2.2.2. Childhood trauma questionnaire (CTQ)

To assess childhood adversity, the CTQ-Version 3 was administered. This instrument measures the nature and extent of exposure

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