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Research Article

Early Life Stress Alters Adult Inflammatory Responses in a Mouse Model for Depression

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Abstract

Increased levels of pro-inflammatory cytokines and hypothalamic pituitary axis (HPA) activity are strongly associated with depression. Childhood stress and trauma predispose individuals for increased inflammatory tone and major depression in later life, suggesting that early life reprogramming of the stress/immune axis may be involved in the pathogenesis of depression. In this study, we are using a short duration neonatal maternal separation stress (MS) paradigm in mice to test if early life stress can impact plasma and brain inflammatory tone into adulthood. We use ELISA assays to investigate levels of the pro-inflammatory cytokines IL-1beta, IL-2, IL-6 and TNF-alpha, in both plasma and brain tissue of mice exposed to MS (STR), their unseparated littermates (LMC) and unhandled age matched controls (AMC). Cytokine levels are assessed in male and female adult mice with and without a bacterial lipopolysaccharide (LPS) induced immune challenge. We present evidence that stress exposure, during the first week of life, predisposes both male and female mice for increased inflammatory cytokine secretion, peripherally and in brain tissue, upon adult exposure to lipopolysaccharide (LPS).

ABBREVIATIONS

HPA: Hypothalamic Pituitary Axis; IL-1beta: Interleukin-1-Beta; IL-2: Interleukin-2; IL-6: Interleukin-6; TNF-Alpha: Tumor Necrosis Factor-Alpha; MS: Maternal Separation Stress; PND: Postnatal Day; STR: Stressed Mice; LMC: Litter Mate Controls; AMC: Age Matched Controls; LPS: Lipopolysaccharide; ANOVA: Analysis of Variance; Cort: Corticosterone (Also Corticosteroid); CNS: Central Nervous System

INTRODUCTION

Increased inflammatory tone is a frequent correlate of mental health disorders and has been hypothesized to play a role in their genesis [1-6]. Increased levels of inflammatory cytokines, foremost IL-1 beta, IL-6 and TNF-alpha, have been demonstrated in blood/serum/plasma as well as in cerebrospinal fluid and brain tissue of individuals with major depressive disorder [6-9] and correlate with an increased risk of suicide [10]. Altered glia responses and morphology in brain samples provide corroboration of altered neuroinflammatory responses in depression [11-13].

A plethora of research has linked depression to stressful early life events [14-17]. Traumatic events, which include psychological and physical stressors such as abuse and neglect along with illness and malnutrition, result in an increased risk for depressive disorders [16-19]. Early childhood stress and trauma is associated with reprogramming of the hypothalamic pituitary axis (HPA) and later life increased stress responsiveness [19-24]. Moreover, children who have experienced neglect and abuse are known to have alterations in brain structure and plasticity, increased inflammatory cytokines and high levels of anxiety, cognitive deficits and behavioral problems, even in the absence of a psychiatric diagnosis [9, 22, 25]. Rodent studies have supported a causal relationship between early life stress exposure and the emergence of endocrine and behavioral alterations consistent with those seen in depression [23, 26, 27]. Typically, such rodent models have employed the paradigms of maternal separation stress (MS) to induce symptoms in the offspring [22,23]. MS rodent models have consistently shown that pups, as they mature, have disruptions of HPA responsiveness, increased anxiety, increased locomotion and altered cognition [22,23,28]. The severity of HPA axis disruption and behavioral alterations reported by different studies varies substantially, and a confounding factor in many past studies has been that the length of maternal separation induces metabolic deprivation, which also can precipitate brain, behavior and inflammatory changes [29].

In our mouse model for MS, the pups are removed from the nest for only one hour each day, over a six-day period following

birth [day of birth is defined as postnatal day 1(PND1). Moreover, half of each litter removed for MS is counterbalanced with the other half of the litter which remains with the dam (LMC) throughout the MS period. We have shown previously that this brief stress exposure is sufficient to elicit an increase in corticosterone release in the pups by postnatal day [PND] seven, the end of the stress exposure [30]. As adults, these mice show increased anxiety and aggression along with structural changes in cerebral cortex and altered plasticity [30,31]. Thus, our maternally separated, stressed [STR] mice have a behavioral and morphological phenotype that is consistent with the sequellae of depression. Non-stressed LMC also are affected behaviorally and morphologically, albeit differently compared to untouched AMC mice [30,31].

The purpose of the present study is to test the hypothesis that early life stress in our mouse model can alter pro-inflammatory cytokine levels in the brain by adulthood. The experimental literature suggests that innate immune and neuroinflammatory responses can be re-programmed by early life stress [21,32], but to our knowledge this has not been directly tested in a brief exposure MS paradigm. Based on this and the above reviewed findings in depression, we hypothesize that pro-inflammatory cytokine levels will be increased in brain tissue of our STR and perhaps also LMC mice.

MATERIALS AND METHODS

Animals

All studies were performed on offspring of Balb/CByJ mice purchased from Jackson Laboratories and raised in our own breeding colony at Morgan State University. Mice were housed in clear polycarbonate cages in temperature- and humidity-controlled rooms with a timed 12 light-/dark cycle, in accordance with the guidelines of the American Association of Veterinary Medicine. All protocols were approved by the Institutional Animal Care and Use Committee at Morgan State University and carried out in accordance with NIH Guide for the Care and Use of Laboratory Animals and the guidelines of the American Veterinary association. For stress exposure, male and female Balb/CByJ pups were subjected to maternal separation for one hour daily between PND 2 and PND 7 [with the day of birth defined as PND 1, as previously described [30,31]. Briefly, we employed a split litter design, removing half the male and female pups daily, for 6 days, from the dam for one hour [STR group]; the other half of the litter remained with the dam [LMC group]. During the stress procedure, pups were exposed, on alternating days, to 30 min. of a warm environment or cold stress, subsequently allowed to re-acclimatize to room temperature for 30 minutes and then returned to the dam in the home cage. Following the stress exposure, pups remained with the dam until weaning at PND 30. At weaning, mice were separated by sex and group housed according to their litter of origin. Additional litters born during the same time as the STR/LMC mice were used as age matched, colony reared, controls (AMC). Apart from weekly cage changes, which did not commence until the pups were one week old, these mice were not handled at all until weaning. For the LPS administration, mice received 5 µg of LPS [Sigma Aldrich: E. coli 0111: B4 [L3012]] in 250 µl of saline into the peritoneal cavity; controls received comparable volumes of physiological saline solution only. LPS and saline control injections were performed 2 hours prior to sacrifice of the mice for brain tissue and blood collections. All mice were sacrificed as adults, using cervical dislocation followed by decapitation. Trunk blood was collected for plasma corticosterone [Cort] and cytokine analysis. Brains were removed and dissected on an ice cooled metal plate. Injections and tissue [blood, brain] collections were performed between approximately 12 noon and 3 PM for all mice. This time-period falls into the middle of the “sleep” period for these nocturnal animals. Cortical tissue was collected and flash frozen for cytokine analysis. Samples were stored at -80° C. Our experiments utilized a total of 116 male and female adult Balb/CByJ young adult mice, aged 3 to 5 months. Mice in each of the two cohorts described below originated from 6 or more different litters. For measurements of baseline cytokine levels a total of 48 mice were used [n=8 male/female each for STR, LMC, and AMC]. An additional 58 mice [21 STR, 19 LMC and 18 AMC, approximately half of each sex] were used for immune stimulation experiments with LPS. Half of the mice in each group were injected with LPS and the other half received saline.

Cytokine analysis

The cytokines IL-1β, IL-2 IL-6, and TNF-alpha were measured using ELISA assays [eBioscience, San Diego, CA], per the protocol enclosed in the kit. Briefly, cerebral cortex was homogenized using sonication [60 Sonic Dismembrator, Fisher Scientific, Pittsburg, PA] on crushed ice for approximately 3-5 seconds in ice-cold assay buffer [eBioscience kit]. A protease inhibitor cocktail containing 104 mM AEBSF, 80 µM aprotinin, 4µM bestatin, 2mM leupeptin and 1.5mM pepstatin A, was added into the assay solution. 100µl samples were run in triplicate with a 1:10 dilution factor. Optic density of the samples was read using a microplate reader SpectraMax PLUS384 [Molecular Devices, Sunnyvale, CA] at 450nm.

Corticosterone Analysis

Corticosterone [Cort] was measured using Immunodiagnostic corticosterone HSEIA kits [catalog # AC15F1], according to the manufacturer’s protocol. Briefly, serum samples were diluted at 1:20 by adding 100 µl of serum sample to 400 µl of phosphate buffered saline [PBS]. All samples were analyzed in triplicate. Optic density of the samples was measured as described above.

Data Analysis

Microsoft Excel software was used to plot a log to log corticosterone graph for the standard curve and calculate cytokine concentrations [pg/ml]. ANOVA [one way and 2-way] was performed using GraphPad Prism [GraphPad Software, La Jolla, CA].

RESULTS

Baseline corticosterone levels were assessed only in the plasma of non-injected mice of all conditions, since in saline and LPS injected mice plasma volumes only allowed for analysis of TNF-alpha and IL-6. As illustrated in Figure (1), ANOVA [2-way, sex by condition] did not show significant differences in corticosterone levels when STR,LMC and AMC mice were

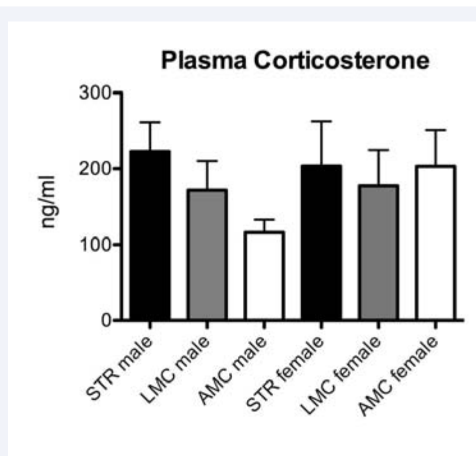

Figure 1 Shows baseline corticosterone levels measured in the plasma of mice not subjected to any injections prior to tissue collection at about 3 months postnatal. Statistical analysis does not reveal significant differences between conditions. We show here levels in both males and females because there were interesting albeit nonsignificant [at the p=0.05 level] group differences in males.

compared with each other [P= 0.42 for condition and 0.047 for sex, df=5, residual 35].

For cytokine levels, initial 2-way ANOVA did not reveal significant sex differences by treatment group [no injection, saline, LPS injection]. Thus, male and female samples were combined for subsequent analyses. Plasma cytokine levels in saline injected mice fell below the detection levels indicated by the manufacturer [8 pmol/ml for TNF-alpha and 4 pmol/ml for IL-6, data not shown]. Significant TNF-alpha and IL-6 increases, 150-300 fold respectively, followed the LPS injections across all conditions. Furthermore, as illustrated in Figure (2A), plasma IL-6 was significantly increased in STR and LMC mice compared to AMC [P=0.02, F=4.3, df 33]. In contrast, as shown in Figure (2B), TNF-alpha levels in both STR and LMC mice were significantly decreased compared to AMC mice [P= 0.048, F=3.33, df=33]. Comparison of cytokine levels in cerebral cortex, between LPS injected mice, saline injected mice and mice that did not receive any injections revealed unique patterns for each of the cytokines we measured [see Figure (3)]. Highly significant differences by treatment were seen in two-way ANOVA for IL-1beta, IL-2 and IL-6 [P< 0.0001 for all three] but not for TNF-alpha. LPS and saline injections resulted in increased levels of IL-1beta and IL-6. Both LPS and saline injections resulted in lowered IL-2 release in cortex. Condition differences were not statistically significant for either IL-1beta or IL-2. Only for IL-6 release did we see a significant condition dependent pattern. Both STR and LMC mice showed significantly increased levels of IL-6 following LPS and saline injections compared to AMC [P=0.04, Df=2, F=3.3] and a significant treatment by condition interaction [P=0.02, Df=4, F=3.0]. Bonferroni post-hoc analysis indicated that the condition differences were carried by LPS injections in the LMC mice [P<0.01] but by saline injections for the STR mice [P<0.05].

DISCUSSION AND CONCLUSION

Our data show that neonatal stress significantly alters inflammatory cytokine responses to LPS injections in both plasma and cerebral cortex of Balb/CByJ mice. This supports the hypothesis that pro-inflammatory cytokine responses can be altered by early life stressful experiences and that increased inflammatory tone may play a critical role in the pathogenesis of depression. The robust cytokine response in plasma for both IL-6 and TNF-alpha, within 2 hours after LPS injection, is consistent with prior studies involving this immune stimulant. Our data for plasma level elevations in IL-6, following LPS stimulation, were in the same range or exceeded levels measured in previous studies in mice [33-37]. Plasma cytokine levels differed significantly between AMC vs. STR and LMC mice for both IL-6 and TGF-alpha, strongly suggesting that STR and LMC mice both experienced immune re-programming, in response to their early life

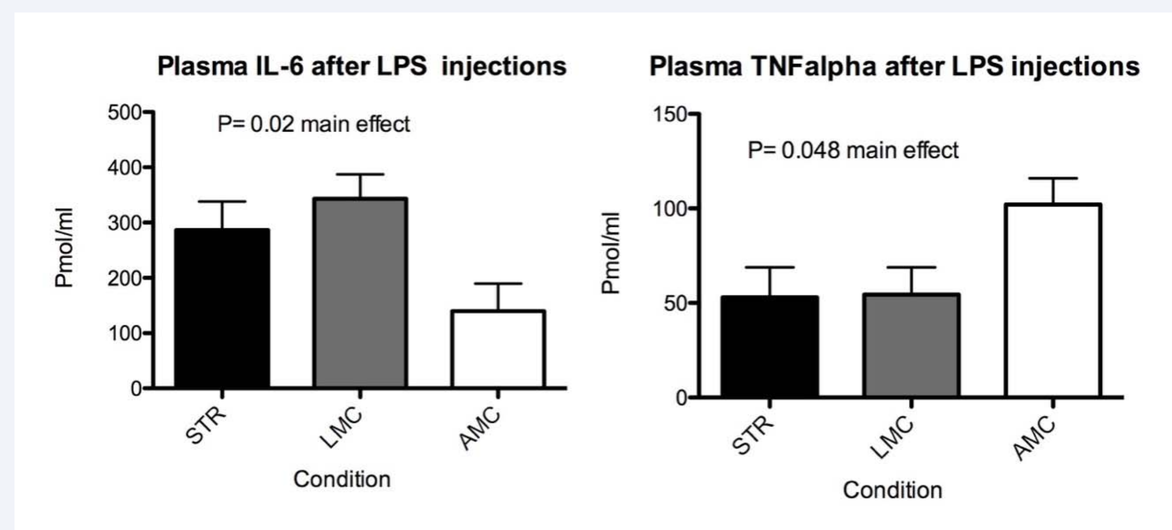

Figure 2 Illustrates plasma levels for IL-6 and TNF alpha in mice injected with LPS, 2 hours prior to blood collection. Note that for both cytokines, STR and LMC mice showed significantly altered levels compared to AMC. However, while IL-6 increases in STR and LMC mice of both sexes, TNF-alpha decreases compared to AMC.

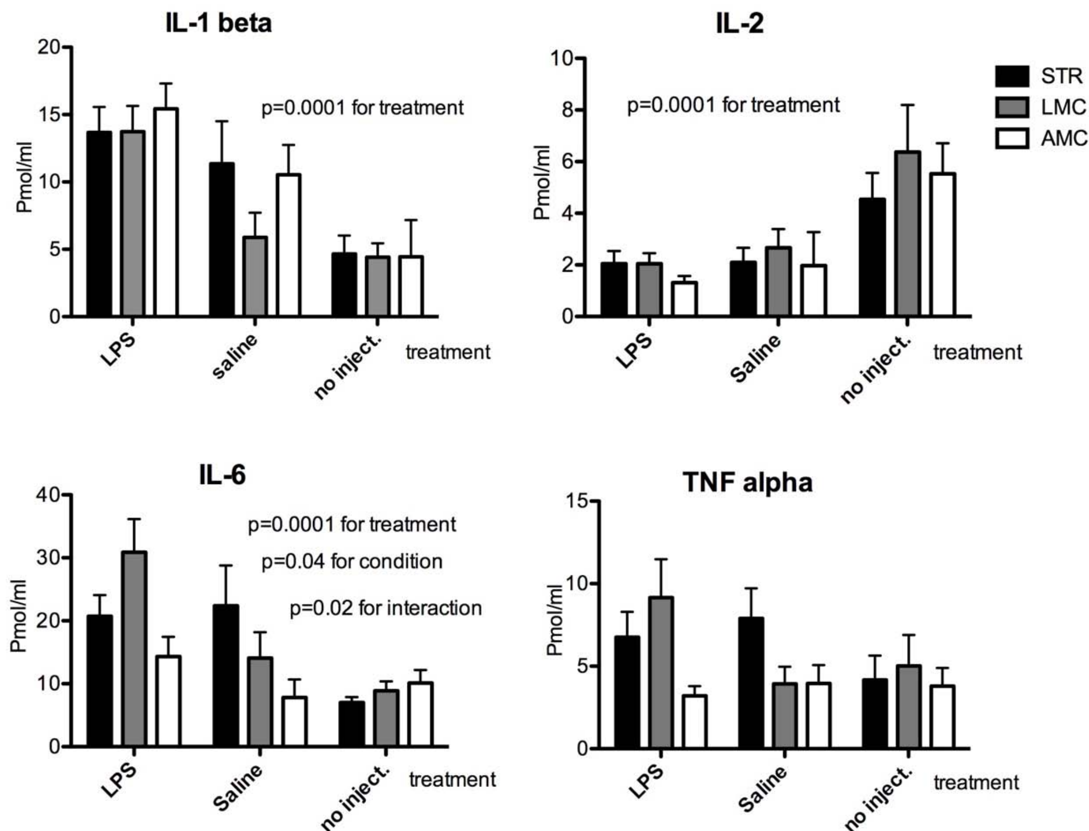

Figure 3 Compares levels of inflammatory cytokines in cerebral cortex across all conditions and the three different treatments groups [no injection, saline, LPS injection]. Both LPS and saline injections increased cortical IL-1beta and IL-6 levels, compared to baseline levels [mice with no injections], in highly significant manner; in contrast, IL-2 levels were significantly decreased by both saline and LPS injections. Only IL-6 showed significant condition dependent changes [P=0.04], with STR and LMC mice showing significantly more IL-6 level increases compared to AMC. TNF alpha in cortex barely reached levels of reliable detectability in any condition or with any treatment.

experience [20,21]. The near 50% reduction in TNF-alpha levels in STR and LMC mice compared to AMC mice was surprising. Previous examinations of this cytokine, in response to LPS, other innate immune system stimulation and adult stress exposure typically have reported plasma and brain level increases [33-37]. Comparisons of cortical cytokine levels between un-injected and saline injected mice suggest, that the restraint stress associated with the administration of intra-peritoneal injections is sufficient to alter brain cytokine levels for IL-1 beta and IL-6, albeit the immune stress associated with LPS injections further increases the response across all conditions [AMC, LMC and STR]. For cortical samples, a significant difference between STR and LMC, compared to AMC mice was only apparent for IL-6. LPS is known to trigger neuroinflammatory responses in brain tissue via activation of microglia, astrocytes and some neurons [21,38-40]. Peripheral LPS injections typically result in rapid increases of brain levels, including cerebral cortical levels, of IL-1beta, IL-6 and TNF-alpha [33,35,39]. We do show comparable level increases in cerebral cortex for IL-1-beta and IL-6. On the other hand, TNF-alpha levels were barely in the detectable range after LPS injections and did not show significant elevations compared to un-injected or saline injected mice. A possible explanation is that the TNF-alpha response to LPS stimulation may occur slightly later then the response of IL-6, thus harvesting the tissue after just 2 hours might not have shown a peak response for TNF-alpha [39]. It is possible that measuring TNF-alpha later after LPS injections might reveal significant differences between STR, LMC and AMC conditions. Level of IL-2 are not commonly measured following LPS stimulation but changes in this cytokine are not without precedence. Increased levels of IL-2 have been reported previously in the hypothalamus, following infection induced immune stimulation [38] and in plasma following acute stress in adult rodents [41]. On the other hand, decreases in cortical IL-2 levels have been reported in association with suicidal behavior [7] and our lab previously observed decreased IL-2 levels in cortex of mice with cortical serotonin depletions at birth [42]. Thus, a cortical decrease in IL-2 levels is consistent with a phenotype of depression. It is not entirely surprising that LMC mice are equally affected as STR mice by LPS and for cortical cytokine measures also saline injections. We previously described that LMC mice display significant behavioral changes including increased aggression and novelty seeking [31]. The behavioral phenotype of STR mice,

in contrast, included increased locomotion and anxiety along with increased aggression, but decreased exploratory behavior [31]. We hypothesize that the observed behavioral and cytokine effects are consequences of altered maternal care [licking and grooming] experienced by SRT and LMC mice compared to AMC. In conclusion, our data show, that altered neuroinflammatory responses, specifically decreased TNF-alpha in the peripheral circulations and increased IL-6 release peripherally as well as in cortex, are a direct consequence of early life stress and trauma. It is well established that the HPA axis and inflammatory responses constitute a mutually regulated system [20,38,43,44]. It has been hypothesized previously that in depression, increased inflammation might trigger increased cortisol. We show here that at least for IL-6 and TNF-alpha, early life stress predates altered levels of cytokine release in adulthood, therewith suggesting that stress is the primary event which in turn precipitates altered inflammatory responsiveness when an immune trigger occurs. This is supported by the absence of significant alterations in baseline Cort levels in our adult STR and LMC mice. However, a shortcoming of the current study is that we only were able to measure baseline Cort levels and not Cort levels after LPS and saline injections. Based on our observations in STR and LMC mice, an early life experience induced altered inflammatory response is not associated with a single behavioral phenotype and can be observed following both direct stress [STR] as well as disruptions of the normal rearing environment [LMC] [31]. Immune system dysregulation and altered inflammatory cytokine release is associated with a phenotypically diverse range of mental health disorders including autism and schizophrenia as well as with depression [3,21,45]. Thus, it is intriguing to speculate how the physical and psychosocial quality of early life trauma and different timing of early life experiences might trigger the shared symptom of immune system dysregulation but lead to altered behavioral disruptions in maturity.

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