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Socioeconomic status moderates associations between CNS serotonin and expression of β_2 -integrins CD11b and CD11c

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Abstract

One of the first steps in the development of atherogenesis is adhesion of circulating monocytes to the vascular endothelium that is stimulated by β_2 -integrins. Stress has been associated with enhanced expression of β_2 -integrins on monocyte cell surface (Greeson et al. 2008). Central nervous system (CNS) serotonin regulates aspects of the stress response that can influence inflammatory processes that increase risk for atherosclerosis. This study examines effects of an environmental stressor (indexed by socioeconomic status (SES)) and CNS serotonin (indexed by CSF 5HIAA level), on the expression of β_2 -integrins (CD11a, CD11b, CD11c) on circulating monocytes in 131 volunteers. Participants completed a protocol consisting of a lumbar puncture for assessment of CSF 5HIAA levels (day 1) followed by an experimental protocol (day 2). Blood samples for the present analyses were obtained at baseline on day 2. The interaction of SES $\times$ 5HIAA was a significant predictor of levels of CD11b and CD11c expression ($p=.02$, and $p=.05$, respectively); the mean CD11b difference between Hi and Lo SES subjects was significant ($p=.003$) only in those with Lo levels of 5HIAA, while SES differences in CD11b among those with Mid and Hi levels of 5HIAA did not vary statistically. The pattern of findings was similar for CD11c. The present results suggest that the combination of high environmental stress and low CNS serotonin function could contribute to atherogenesis through processes that lead to increased expression of the β_2 -integrins CD11b and CD11c on monocyte cell surfaces.

Keywords

Cardiovascular disease; biobehavioral mechanisms; serotonin; socioeconomic status

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Drs. Williams and Siegler designed the study and wrote the protocol. Dr. Brummett wrote the first draft of the manuscript and did the statistical analyses. Dr. Boyle helped edit the manuscript. Dr. Kuhn provided methodological support and proof read the manuscript. All authors have contributed to and have approved the final version of the manuscript.

Introduction

The neurotransmitter serotonin is involved in the regulation of psychological, behavioral, and biological functions that influence the development and course of both mood and medical disorders. Low central nervous system (CNS) serotonergic function has been associated for example, with anger, increased use of nicotine, increased sympathetic and decreased parasympathetic nervous system outflow, and altered neuroendocrine function (Williams, 1994, , 1998). It has been noted that altered CNS serotonergic function--through its association with association associated negative moods, risky health behaviors, and altered biological functions--may lead to increased disease risk in certain individuals, such as those with lower socioeconomic status (SES) (Williams, 1998, , 2008).

Low SES is an environmental risk factor that is associated with increased risk of disease and death (Adler et al. , 1993; Marmot et al. , 1987). Increased psychosocial stress that often accompanies low SES is likely an important contributor to the increased risk for illness (Baum et al. , 1999). Lower family SES during childhood is associated with increased cardiovascular response to stress (Williams et al. , 2008) and increased mortality in adulthood, independently of adult SES, suggesting an enduring impact of adverse social and physical circumstances on health (Davey et al. , 1998). Importantly, environmental stressors have marked immediate repercussions, but also affect responses to later challenges; and repeated stressful events may sensitize neuronal systems so that stress experienced at a later date may cause heightened neurochemical alterations (Anisman, 2009; Anisman et al. , 2003; Anisman and Merali, 1999). Thus, the stress associated with low SES may have a lasting effect on psychosocial and behavioral risk factors throughout life (Lynch et al. , 1997).

Both chronic and acute psychological stress significantly effect immune system function (Anisman, 2009; Segerstrom and Miller, 2004; Steptoe et al. , 2007). A review of the relation between psychological stress and the human immune system examined over 300 studies that were conducted over the past 30 years, and concluded that psychological challenges modify numerous aspects of immune responding (Segerstrom and Miller, 2004). One of the first steps in the development of atherogenesis is adhesion of circulating monocytes to the vascular endothelium stimulated by α_2 -integrins (Ross, 1999). Integrins are heterodimeric integral membrane proteins composed of an alpha chain and a beta chain, and the adherence of circulating monocytes to endothelial cells is mediated by a group of cell surface receptors-- α_2 -integrins (CD11a, -b, -c). Activation and expression of α_2 -integrins promote migration of activated monocytes that, in turn, leads to secretion of proinflammatory cytokines (Gahmberg et al. , 1997). It has been shown that emotional stress results in enhanced expression of α_2 -integrins on the monocyte cell surface (Greeson et al. , 2008).

CNS serotonin regulates aspects of the stress response that may influence inflammatory processes, suggesting that individuals who experience heightened stress may be vulnerable with regard to altered immune function (Schiepers et al. , 2005). This study examined effects of and environmental stressor, indexed by low SES, and low CNS serotonin, indexed by CSF 5HIAA level (Ballenger et al. , 1979; Higley and Linnoila, 1997; Roy et al. , 1988), on the expression of α_2 -integrins (CD11a, CD11b, CD11c) on circulating monocytes in 131 healthy volunteers.

Methods

Subjects

Subjects were recruited during the period 1998–2001 via advertisements in the public media, inclusion in the community newsletter sent with the county water bill, flyers posted throughout the community, via outreach screening events at civic organizations and other public events,

and in paid advertisements such as the back of supermarket tapes. This protocol required that subjects not be at risk due to the study procedures and that subject characteristics not hamper interpretation of the findings, making it important to ensure a sample population in good current health. Therefore, all subjects underwent a comprehensive examination using a modified SCID as well as medical history, physical exam, electrocardiogram, chest radiograph, hemoglobin, hematocrit, white cell count, and blood chemistries to rule out current psychiatric and medical disorders. Specifically, participants were excluded for the following: 1) DSM-IV criteria for a current axis I disorder or the report of prior diagnosis and/or hospitalization for severe psychiatric illness 2) major psychiatric impairment via SCID assessment, 3) less severe psychiatric history (e.g., anxiety disorder) within the past 6 months, 4) alcohol abuse or dependence, or use of any prescription drugs, as well as use of illegal drugs (as detected by a urine screen prior to entry into study), 5) chronic use of aspirin or NASID's, and 6) positive past or current medical history of significant chronic debilitating disease (e.g., AIDS, cardiovascular disease, seizure disorder, cerebral vascular disease, hypertension, diabetes, history of stroke, cancer, kidney disease, emphysema). This study was approved by the Duke University Medical Center Institutional Review Board, and an IRB-approved form was used to obtain written informed consent from all subjects.

As part of the study design, participants were recruited according to their current education and household income levels in order to have approximately equal groups of low and high SES. Thus, two categories of income were used—below or equal to \$24,900 and above \$24,900, based on the 40th percentile rank of household incomes in Durham County according to the 1990 Census (Burroughs et al. , 2003). The low SES category includes those who had income of less than or equal to \$24,900 and who had less than a college degree. The high SES group included those who had income greater than \$24,900, regardless of education, or those with a college degree. The present study sample consisted of 131 subjects with data available for CSF 5HIAA, and α -integrins (CD11a, -b, or -c). Of the 131 subjects, 76 (58.0%) were African American and 55 (42.0%) were Caucasian.

Procedures

All subjects were admitted to the General Clinical Research Center (GCRC) at Duke University Medical Center for an inpatient protocol consisting of a lumbar puncture for the assessment of CSF 5HIAA levels on day 1, followed by an experimental protocol on day 2. Subjects reported to the GCRC during the early afternoon. After completing admission procedures, and without a period of bed rest, lumbar puncture was performed by a board-certified anesthesiologist. Initially, as in published studies (Ballenger et al. , 1979; Higley and Linnoila, 1997), we obtained 10–12 ml of CSF, which was mixed (to abolish the expected gradient across successive samples during the collection) and then separated into 2-ml aliquots and frozen for later assay of monoamine metabolites. The unsurprising 10–15% incidence of post-tap headaches among the first female subjects led us to determine whether there was a gradient of 5HIAA levels across aliquots in the next two subjects. There was no gradient, with 5-HIAA concentrations in 11–12 ml being virtually identical to those in 1–2 ml. A previous study (Nordin et al. , 1996) showed that without strict bed rest prior to the lumbar puncture, body height is unrelated to CSF 5HIAA levels. Since our subjects had been ambulatory prior to lumbar puncture, it appears that CSF in the lumbar column had been mixed by their movements, thereby abolishing any gradient because of height. Therefore, we used a smaller needle to obtain only 3–4 ml of CSF, thereby preventing post-tap headaches. At 8 a.m. the following morning blood was obtained for assay of inflammatory markers.

CSF 5-HIAA

5-HIAA was measured by high-pressure liquid chromatography (HPLC) with electrochemical detection. The method used is a trace-enrichment method that utilized sequential C-18 columns

for sample cleanup and analytical separation (Doudet et al. , 1995). Samples were diluted in 0.2 N PCA containing 0.5 mM EDTA and 0.5 mM sodium metabisulfite, and injected directly onto the HPLC. The sample is enriched on a C-18 precolumn using an aqueous mobile phase composed of 0.05 M citrate, 0.05 M dibasic sodium phosphate, 0.5 mM EDTA at pH 3.5. Then the sample is eluted onto a Waters Spherisorb 3 μ M ODS2 C-18 column with a mobile phase containing 4–8% acetonitrile in addition to the components of the enrichment mobile phase. Samples are detected by electrochemical detection, with a detector potential set at +0.55 mV vs Ag/AgCl reference electrode. Data are collected with a computer-based data collection system, and quantitated with the use of internal standard and external standard curves. The sensitivity of the assay is 0.5 ng/sample, and values are reported as ng/ml.

α_2 -integrins (CD11a, CD11b, and CD11c)

Following placement of an intravenous catheter and a 45-minute waiting period, a blood sample was drawn to determine expression of α_2 -integrins CD11a -b, and -c on monocyte cell surfaces. Dual color flow cytometry was used to quantify expression of α_2 -integrins. One ml of whole blood was used for each measurement and each control. Phycoerythrin-conjugated CD 14 antibody was used as a specific marker for monocytes. After a 10-minute incubation at room temperature, samples were centrifuged and red cells were lysed by resuspension of the pellet in a commercial product, BD-lyse (Becton Dickinson), as per manufacture's directions. Samples were then washed twice in phosphate buffered saline (PBS) and fixed in 1% formaldehyde in PBS. Identically-conjugated same isotype myeloma antibodies are used as controls. All samples were analyzed using a Becton Dickinson FACS SCAN flow cytometer. Monocytes were gated based on forward scatter and wide scatter. Data are presented as mean fluorescence of the antibody studies in the monocyte populations, in arbitrary units, after subtracting the fluorescence of values of samples stained with the same isotype control myeloma proteins.

SES

Participants were a priori categorized as Hi or Lo SES according to study assignment as described above. This study was focused in large part on the health effects of SES and consultants from the Research Technology Institute (RTI, Durham NC) were consulted to assure that assessment of SES was representative of Durham County. Assessment of income and education level occurred at two points in the study. First, during the participant's initial screening their income and education levels were ascertained in categories. Next, following enrollment in the study, these measures were verified and refined for each participant.

Analyses

Using the general linear model (PROC GLM; SAS, Cary NC) separate analyses were conducted to examine the main effects of SES and 5HIAA, and the interaction of SES and 5-HIAA levels as predictors of CD11a, CD11b, and CD11c levels. Thus, three initial models included SES, 5HIAA, and a product term representing SES $\times$ 5HIAA as a predictor of CD11a, -b, or -c. In instances where the product term was nonsignificant this term was eliminated and the model was recalculated to examine main effects. Values for α_2 -integrins were log-transformed in all analyses.

Results

Descriptive data

Sample characteristics, by SES, are provided in Table 1. As expected according to the study design, the sample was fairly balanced with regard to SES and gender. The relation between 5HIAA and SES was non-significant ($p = .44$). In support of our assertion that low SES is

accompanied by higher levels of stress, we included examination of SES group means for each of the measures of stress that were available in the present study. Individuals in the Lo SES group had significantly higher ratings on the stress vulnerability facet scores (Costa and McCrae, 1992) ($p = .001$); higher personality anxiety subscale scores from the Activity Preference Questionnaire (Lykken et al. , 1973) ($p = .001$); and higher Spielberger State Anxiety scores (Spielberger, 1983) ($p = .001$). In addition, it is known that glucose and lipid levels may contribute to monocyte activation. Thus, it is important to note that in the present sample levels of serum glucose (fasting) and lipids (HDL, LDL, triglycerides) did not vary significantly by SES nor 5HIAA group.

In regression analyses, the interaction of SES $\times$ 5HIAA was a significant predictor of levels of CD11b ($p = .02$); and the variance explained by the inclusion of interaction term was 6% (i.e., partial R^2 0.06). Similarly, the interaction of SES and 5HIAA predicted CD11c ($p = .05$) expression; and the variance explained by the inclusion of interaction term was 5% (i.e., partial R^2 0.05). Figure 1 and Figure 2 graphically depict the significant SES $\times$ 5HIAA interactions. The form of the interaction for CD11b was such that the mean difference between Hi and Lo SES subjects was significant ($p = .003$) in those with Lo levels of 5HIAA, whereas, SES differences in CD11b among those with Mid and Hi levels of 5HIAA were not statistically different. The pattern of findings was similar for CD11c. Specifically, the mean CD11c difference between Hi and Lo SES subjects was only significant ($p = .009$) in those with Lo levels of 5HIAA. The interaction of SES $\times$ 5HIAA was not significantly associated with CD11a ($p = .28$), therefore this product term was dropped from the model and main effects were examined. Recalculation of the models with 5HIAA treated as a continuous variable did not meaningfully alter the findings. Neither SES, nor 5HIAA were significantly related to CD11a ($p = .10$; and $p = .94$, respectively).

Discussion

The role of serotonin as a neurotransmitter in the CNS has been extensively studied with respect to a broad range of psychological and biological functions, whereas simultaneous investigation of CNS serotonin function and immune system processes has received far less attention. The present study examined SES as a moderator of the associations among a measure of CNS serotonin and three inflammatory biomarkers that have been implicated in atherosclerosis. The interactive effects of SES and serotonin level were significantly associated with two of the three biomarkers examined, such that low SES subjects with low serotonin levels had significantly higher expression of α_2 -integrins as compared to their counterparts with higher serotonin levels--a pattern observed only in those with low SES.

Low CNS serotonergic responsivity has been associated with preclinical carotid artery atherosclerosis, the metabolic syndrome, and physical activity (Muldoon et al. , 2005; Muldoon et al. , 2007; Muldoon et al. , 2004). Serotonin vulnerability is defined as increased sensitivity to factors, such as environmental stress, that may disrupt the serotonergic system (Jans et al. , 2007). In the present sample individuals who have low serotonin in conjunction with higher stress (low SES) appear more vulnerable to disruptions in the inflammatory process. Inflammation has been significantly implicated in the pathogenesis of atherosclerotic cardiovascular disease (Ross, 1999), and studies have demonstrated associations between biomarkers of inflammation and current or future overt CAD e.g. (Alexander, 1994; Libby et al. , 2002; Ross, 1999). Individuals in the present study with low serotonin levels and higher levels of environmental stress may be at particular risk for CAD via heightened α_2 -integrin responding.

Moreover, low SES--a known risk factor for CAD--has been associated with altered immune responding in both observational and experimental research, e.g. (Brydon et al. , 2004; Petersen

et al. , 2008). Individual and community assessments of SES were inversely associated with inflammatory biomarkers in a midlife community sample (Petersen et al. , 2008); and low SES, defined by grade of employment, was associated with increased immune activation in participants from the Whitehall II cohort (Owen et al. , 2003). In a sample of civil servants low SES subjects had prolonged stress-induced increases in inflammatory biomarkers, as compared to high SES subjects (Brydon et al. , 2004). Results of these and other studies e.g., (Jousilahti et al. , 2003; Panagiotakos et al. , 2004) suggest that low SES individuals may be less able to adapt to stress and that increased inflammatory responses in individuals with low SES may help explain the increased risk of CAD morbidity and mortality conferred by this environmental stressor.

Each of the measures in the present study--low central nervous system (CNS) serotonergic function, low socioeconomic status (SES), and heightened immune responding--have been associated with increased risk development of coronary artery disease (CAD). Psychophysiological stress processes are thought to be a major underlying mechanism through which serotonin, SES, and inflammation contribute to risk for disease. It appears that relations among the CNS, immune, endocrine, and autonomic systems function in a complex reciprocal fashion, such that activation of the immune system affects neuroendocrine and central neurotransmitter processes and vice versa (Anisman, 2009; Dantzer et al. , 2008; Maier and Watkins, 1998). Data from the present study demonstrates that the combination of low serotonin and low SES is associated with increased inflammatory responses, suggesting that in vulnerable individuals (those with low serotonin) the chronic stress experienced due to low SES may lead to heightened inflammatory responding; and this may be one route by which SES and serotonin ultimately lead to increased risk for CAD.

The present study is not without limitations. The findings are based on a relatively small number of subjects. However, that it was not feasible to acquire the physiological measures of interest (i.e., CNS 5HIAA available in the present study) in a large sample. Thus the quality of the study measures must be weighed against the drawback of limited sample size. The size of the sample also restricted our ability to examine potentially relevant interactions, such as those for gender. The present sample was healthy and middle aged, thus our findings may not generalize to older and/or clinical populations. It should be emphasized that because monocyte activation is a highly labile measure that can be influenced by numerous factors, some of which are likely not included in this study, appropriate caution should be taken when interpreting the present findings. Also, these data are cross-sectional in nature and therefore inferences to causality can not be made. Indeed, the manner in which SES, low serotonin, and inflammatory processes confer increased risk for disease is certain to be complex and multifaceted.

In the present manuscript we refer to SES as an environmental stressor. SES, of course, is used here as a proxy measure of stress, as opposed to a more direct measure such as that gathered during an experimental stress protocol. We chose to focus on SES, rather than alternative measures of self-reported stress, for two fundamental reasons. First, examination of SES as an environmental stressor was a central focus of the grant that funded the present study. Great care was taken to ensure the accuracy and meaningful nature of this measure in the present sample—contributing, we hope, to the validity of the present findings. Second, there is an abundant literature that indicates SES is not associated with just one type of “stress”, but rather, is linked to multiple stress-related constructs (e.g., depressive symptoms, anxiety, and hostility). Testing their hypothesis that stressful emotions are the mechanism underlying the relationship between SES and health, Gallo and Matthews’s (1999) review of the literature demonstrates quite clearly that SES is associated with depression, hopelessness, anxiety, and hostile affect and cognition. They further showed that negative emotions are significantly associated with disease. They conclude that the data provide evidence, albeit indirect, that stressful emotions are a very likely mediator of the often demonstrated association between

SES and health. Further, in later work Gallo and Matthews (2003) suggest that the psychological environment associated with low SES is stressful in nature and that this stress in turn leads to reductions in an individual's reserve ability to manage psychological demands. Furthermore, this reduction in reserve capacity increases vulnerability to further negative emotions and cognitions.

In conclusion, one of the first steps in the development of atherogenesis is adhesion of circulating monocytes to the vascular endothelium stimulated by α -integrins. The present findings suggest that the combination of low SES and low CNS serotonin function could contribute to atherogenesis through processes that lead to increased expression of the α -integrins CD11b and CD11c on monocyte cell surfaces.

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Figure 1.
Association of CSF 5HIAA (tertile split) and α_2 -integrin CD11b: Moderation by SES

Figure 2.
Association of CSF 5HIAA (tertile split) and α_2 -integrin CD11c: Moderation by SES

Table 1

Sample Characteristics: By Hi and Lo SES

Characteristic	Total Sample N = 131	Hi SES N = 80	Lo SES N = 51
Gender, n (%) Male	73 (55.7)	44 (55.0)	29 (56.9)
Age, mean (SD)	34.5 (8.3)	35.4 (7.6)	33.1 (9.0)
Current Smoker, n (%)	31 (23.7)	18 (22.5)	13 (25.4)
CSF 5HIAA ng/ml, mean (SD)	18.5 (8.2)	18.3 (8.4)	19.0 (7.8)
α_2 -integrins, mean fluorescent intensity (SD) ^a			
CD11a	326.1(268.9)	302.7 (256.2)	362.4 (283.5)
CD11b	240.1(224.4)	233.4 (254.0)	250.7 (169.5)
CD11c	149.6 (123.0)	143.1 (128.8)	159.3 (141.1)

^a raw, non-log transformed values

* indicates significant difference between Hi and Lo SES groups