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Associations between Central Nervous System Serotonin, Fasting Glucose and Hostility in African American Females

Stephen H. Boyle, Ph.D.¹, Anastasia Georgiades, Ph.D.¹, Beverly H. Brummett, Ph.D.¹, John C. Barefoot, PhD¹, Ilene C. Siegler, Ph.D. MPH¹, Wayne R. Matson, PhD², Cynthia M. Kuhn, Ph.D.³, Katherine Grichnik, M.D.⁴, Mark Stafford-Smith, M.D.⁴, Redford B. Williams, M.D.¹, Rima Kaddurah-Daouk, PhD¹, and Richard S. Surwit, Ph.D.¹

¹Department of Psychiatry and Behavioral Sciences, Duke University Medical Center, Durham, N.C., 27710, USA

²Department of Systems Biochemistry, Bedford VA Medical Center, Bedford, MA, USA

³Department of Pharmacology and Cancer Biology, Duke University Medical Center, USA

⁴Department of Anesthesiology, Duke University Medical Center, USA

Abstract

Background—Previous research has shown an association between hostility and fasting glucose in African American women. Central nervous system serotonin activity is implicated both in metabolic processes and in hostility related traits.

Purpose—To determine whether central nervous system serotonin influences the association between hostility and fasting glucose in African American women.

Methods—The study consisted of 119 healthy volunteers (36 African American women, 27 white women, 21 white males, and 35 African American males, mean age 34±8.5 years). Serotonin metabolites were measured in cerebrospinal fluid. Hostility was measured by the Cook-Medley Hostility Scale.

Results—Hostility was associated with fasting glucose and central nervous system serotonin metabolites in African American women only. Controlling for the serotonin metabolites significantly reduced the association of hostility to glucose.

Conclusions—The positive correlation between hostility and fasting glucose in African American women can partly be explained by central nervous system serotonin function.

Corresponding author: Stephen H. Boyle PhD, BOX 3366 Duke University Medical Center, Durham, North Carolina, 27710. Phone: 919 (668 - 3647), FAX: 919 (688-5271), shboyle@duke.edu.

Author's Conflict of interest : The other authors have not disclosed any potential conflicts of interest.

Adherence to Ethical Standards: Dr. Redford B. Williams reports holding a U.S. patent on the 5HTTLPR L allele for use as a marker of increased cardiovascular risk in stressed persons and is a founder and major stockholder of Williams LifeSkills, Inc. Dr. Wayne Matson is currently Chief Scientist at Counterpoint Health Solutions and is involved in developing patents in disease risk factors based on metabolomics. Dr Kaddurah-Daouk is an equity holder in Metabolon, a biotechnology company in the metabolomics domain, and also an inventor on patents in the metabolomics field. She has received funding or consultancy fees for BMS, Pfizer, AstraZeneca and Lundbeck. All procedures, including the informed consent process, were conducted in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2000.

Keywords

Hostility; glucose; central nervous system serotonin; African American women

INTRODUCTION

African American women have increased risk of developing impaired glucose metabolism and type 2 diabetes mellitus relative to their white counterparts and African American and white men (1, 2). This health disparity does not appear to be completely accounted for by differences in traditional risk factors for type 2 diabetes such as obesity, suggesting that other factors may contribute. The psychological trait hostility has consistently been associated with coronary artery disease risk factors, including elevated adiposity and insulin resistance (3). Recent studies by our group have shown that African American women show a stronger association between hostility and fasting glucose (4), as well as with early signs of glucose dysregulation during an intravenous glucose tolerance test (5) compared to African American men and white men and women. The mechanisms responsible for the association of hostility with fasting glucose in the African American women have not yet been identified. Central nervous system serotonin activity may provide a plausible explanation for the relationship of between hostility and glucose metabolism due to its documented involvement in regulating both metabolic processes and psychological functioning (6).

Central nervous system serotonin is believed to be involved in the regulation of glucose metabolism via at least two mechanisms. First, central nervous system serotonin influences appetite (7) and hence indirectly adiposity level, which is an important determinant of insulin resistance and glucose level (8). Second, central nervous system serotonin plays a role in regulating the release of counterregulatory hormones such as epinephrine and cortisol (9), which are well known to influence glucose metabolism (10, 11). There is also evidence that individual variation in central nervous system serotonin function, as indexed by the prolactin response to drugs that enhance serotonin neurotransmission, is associated with glucose metabolism. Specifically, studies conducted in predominantly white samples have shown fasting glucose to vary inversely with the prolactin response to both fenfluramine and citalapram (12). Central nervous system serotonin has also been implicated in a wide range of behavioral traits including ones related to hostility (13, 14). Much of the research on hostility has focused on the association of central nervous system serotonin to aggressive behavior and impulsivity and suggests that lower levels of central nervous system serotonin function are associated with a greater propensity to engage in those behaviors (14-17). There is also evidence that suggests serotonin is related to the cognitive aspects of hostility, like cynicism and mistrust, especially in women. One study found the prolactin response to fenfluramine was related inversely to a paper and pencil measure of suspiciousness in a sample of post-menopausal women (14) but not in men or in pre-menopausal women.

The foregoing indicates that central nervous system serotonin may play an important role in both glucose metabolism and the personality trait hostility, suggesting that the association of hostility with fasting glucose in African American women could reflect individual

differences in central nervous system serotonin function. As no previous study has evaluated the role of central nervous system serotonin on hostility and glucose metabolism in African American women, we set out to test this hypothesis in the current study by examining the associations between hostility and fasting glucose and insulin and indices of central nervous system serotonin activity in a sample of African American females and males and white females and males. Central nervous system serotonin activity was indexed by cerebrospinal fluid levels of tryptophan (the amino acid precursor to serotonin), 5-hydroxytryptophan (5-HTP) (the immediate precursor to serotonin) and 5-hydroxyindoleacetic acid (5-HIAA) (the major metabolite of serotonin) (18).

METHODS

Participants

The originally study sample was recruited to take part in a study designed to examine the moderating effects of genetic, behavioral, and environmental mechanisms on health disparities (19), and consisted of 163 participants (42 African American females, 32 white females, 39 white males, and 50 African American males). As the metabolomics analysis was not part of the original study design, there was insufficient cerebrospinal fluid available to perform metabolomics profiling in all participants. Complete metabolomics and fasting glucose and insulin data were available for 37 African American women, 27 white women, 35 African American men, and 21 white men. One African American woman with an extremely high level of 5-HTP, distribution ($>3SDs$) was excluded from further analysis resulting in an analysis sample of 36 African American females, leaving a final sample of 119 African American and white men and women with complete data. Participants were recruited via advertisements in the local media, flyers posted in supermarkets and other public locations, and outreach at public events. For details on recruitment procedures, see our previous publication (20). This study was conducted at Duke University Medical Center, and all subjects gave informed consent prior to their participation in the study using a form approved by the Duke University Medical Center Institutional Review Board. Those enrolled in the study received \$500 for their participation. Participants underwent a comprehensive psychological examination, as well as medical history, physical exam, electrocardiogram, chest radiograph, hemoglobin, hematocrit, white cell count, and blood chemistries to rule out current medical and psychiatric disorders. Use of prescription drugs as well as use of illegal drugs (as detected by a urine screen prior to entry into study) was grounds for exclusion.

Procedure

Participants were admitted to the General Clinical Research Unit at Duke University Medical Center during the early afternoon. After completing the admission procedures and without a period of bed rest, lumbar puncture was performed by a board-certified anesthesiologist. We obtained a 4-5 ml cerebrospinal fluid sample, which was mixed (to abolish the expected gradient across successive samples during the collection) and separated into 2-ml aliquots and frozen for later assay of monoamine metabolites.

For more details, see our previous publication (20). Sociodemographic and personality data were gathered after the lumbar puncture. Blood samples for the assessment of glucose and insulin were collected the next morning after an overnight fast.

Sample preparation and metabolomic analysis

Cerebrospinal fluid levels of tryptophan, 5-HTP, and 5-HIAA were quantitated by a high pressure liquid chromatography coupled with electrochemical coulometric array detection (LCECA) (21). Cerebrospinal fluid samples were thawed to 4°C in the dark under mild vortexing. Duplicate aliquots of 80uL were pipetted into auto sampler vials, 50uL of each sample was taken for a pool and 80uL aliquots pipetted into autosampler vials. All autosampler vials were then re archived at -80°C until assay. The LCECA method used has been previously described (22). Briefly, it utilizes a 110 minute gradient from an A mobile phase of 1% w/v sodium pentane sulfonic acid with 0.5% v/v acetic acid to a B mobile phase of Methanol/acetonitrile/isopropanol 80/10/10 % with 0.05 M lithium acetate at pH3.8. The sulfonic acid solubilizes any protein material in the sample and the high organics in the B mobile phase remove any lipids allowing continuous repetitive runs without column degradation. Allowable time on the autosampler at 0°C was determined as 18 hours from repetitive pool assay. Samples were thawed and loaded every 12 hours. Aliquots of 50uL were injected into the LCECA. The samples were run in randomized order in a sequence of authentic reference mixed standard of 80 compounds, 5 samples, pool, 5 samples, duplicate. Duplicates were spaced from 1 to 100 runs apart. Pools which represent the maximum expected complexity of the sample set were used for time normalization of all data and for assessment of precision of the data base. Secondary assessment of precision was made from duplicate pairs for analytes with a high degree of biological variability. All values reported were less than $\pm 15\%$ relative standard deviation. The sensitivity of the assay is 0.5 ng/sample, and values are reported as ng/ml.

Hostility measurement

Hostility was measured by an abbreviated 27 item version of the Cook-Medley Hostility Scale which primarily assesses the cognitive aspects of hostility, cynicism and mistrust (23). The 27-item version of the Cook-Medley scale comprised of the 3 item subsets 'Cynicism', 'Hostile Affect' and 'Aggressive Responding' has been found to be a better predictor of survival compared to the original 50 item scale (24). Higher scores on the Cook Medley Hostility scale indicate higher levels of hostility.

Assessment of other psychological constructs

Depressive symptoms were measured using the 21-item Beck Depression Inventory (Psychological Corporation, Orlando, Florida) (25) and trait anxiety was measured by the anxiety facet of the NEO-Personality Inventory (26). The measures were included to ascertain whether any associations between hostility and glucose metabolism could be accounted for by the disposition to experience negative affect. Measures of depression and anxiety have shown to be more strongly associated with glucose metabolism in African American women compared to white women (27, 28).

Smoking, exercise and alcohol habits

Smoking was assessed as 'currently smoking' (yes/no). Activity level was assessed as a 3 level variable: Sedentary, Moderate and High. Alcohol was assessed by combining frequency of drinking with amount per occasion, resulting in a measure of amount of servings/week. Those were grouped into the following categories: 'None', '1-4 drinks/week' and '>4 drinks/week'.

Socioeconomic Position

Socioeconomic position was indexed by educational attainment, measured in years, and yearly household income measured as dollars per year rounded to the nearest thousand.

Glucose, Insulin and Homeostatic Model Assessment (HOMA-IR)

Plasma glucose was measured by the Beckman Glucose Analyzer (Beckman Instruments, Chicago IL), a device that has been used as a reference method for the analysis of glucose concentrations employing the glucose oxidase method in heparinized plasma (29). Plasma insulin concentration was determined by radioimmunoassay (Millipore, USA). HOMA-IR was used to estimate insulin resistance and calculated with the formula: fasting glucose (mg/dl) * fasting insulin (μ U/ml) /405.

Body mass index

Body mass index was calculated as weight in kilograms (kg) divided by the square of height in meters (m^2).

Statistical Analysis

All variables were tested for skewness insulin, HOMA-IR and 5-HIAA were determined to be positively skewed and subjected to natural log (ln) transformations to achieve appropriate distributional properties for correlation and factor analysis. Pre- and post- transformations skewness statistics were 5.0 vs .52 for insulin, 6.4 vs. 54 for HOMA-IR and 1.2 vs -.75 for 5HIAA. To ensure that findings are not affected by height differences, analyses evaluating effects of the cerebrospinal fluid metabolites used height adjusted metabolite values. Even though we have shown previously that hostility was associated with fasting glucose (4) and associated with the minimal model outcomes (5) specifically in the African American women only, we initially evaluated associations between hostility and glucose metabolism indices separately in the four race/sex groups using Pearson partial correlations adjusting for age. We also used Pearson partial correlations adjusting for age to examine the associations between the height adjusted central nervous system serotonin metabolites and hostility, glucose, insulin and HOMA-IR separately in the four race/sex groups. We then fitted regression models to test whether any of the observed associations among the variables differed between the African American women and the other groups. In these models we compared the African American women to the combination of the other groups (i.e. African American men and white women and men). This was done based on our earlier results (4, 5) showing that hostility was only associated with glucose in the African American women and because of the low power in the present study for testing three way interactions (e.g. Race $\times$ Sex $\times$ Hostility) in relation to our variables of interest (i.e. glucose, insulin, HOMA-IR and

cerebral spinal fluid metabolites). The initial set of regression models (Model 1) contained four variables: Age, Group (African American women versus 'Others'), Hostility, and a Group $\times$ Hostility product term. Subsequent regression models included additional control for body mass index (Model 2) as well as a fully adjusted model (Model 3) that included the addition of the Beck Depression Inventory score, the NEO-Personality Inventory Anxiety Facet score, household income, education, smoking, exercise and alcohol intake. Statistical analyses were performed using SAS (version 9.1) and SPSS (version 17.0).

RESULTS

Table 1 presents descriptive statistics (means $\pm$ std) of all study variables by the four sex and race groups. P-values are shown for the main effects of Race and Sex and the Race $\times$ Sex interaction effect. There was a main effect of Sex on fasting glucose ($p = .05$), with men having significantly higher fasting glucose compared to the women. This has been shown previously in large scale studies of non-diabetic subjects (30). There were also significant main effects of Sex ($p = .05$) and Race ($p < .001$) for hostility scores, with higher levels of hostility in men compared to women and African Americans compared to whites. Both effects have been previously reported in the literature (31). There was a main effect of Sex on Anxiety scores ($p = .01$), with women having higher anxiety scores than men in the present study. This is consistent with studies showing women having significantly higher risk for anxiety disorders (32) as well as higher state and trait anxiety levels (33). There was a significant main effect of Sex on exercise ($p = .05$), with men reporting conducting more intense exercise more than women. Finally, there was a significant effect of Sex on 5HIAA levels, with women having higher levels compared to men ($p = .01$).

Pearson partial correlations examining the association between hostility and the glucose metabolism variables in the race/sex groups revealed significant positive correlations for glucose (see Figure 1a), insulin, and HOMA-IR only for African American women (See Table 2). Analysis of the serotonin metabolites in relation to hostility and glucose, insulin and HOMA-IR are presented in Table 3. There were no significant associations between tryptophan levels and hostility, glucose, insulin and HOMA-IR within each race/sex group (See Table 3). 5HTP and 5HIAA were significantly associated with hostility and glucose, but only in African American women; 5HTP was also significantly associated with insulin and HOMA-IR only in African American women (See Table 3).

Regression analysis testing the Hostility by Group (African American women vs 'Other') interaction in relation to the glucose metabolism and the cerebrospinal fluid serotonin variables are presented in Table 4. Results revealed significant Hostility $\times$ Group interactions for glucose, insulin, HOMA-IR, 5HTP, and 5HIAA in age adjusted analysis. These effects were only slightly attenuated after additional adjustment for body mass index (Model 2), and Beck Depression Inventory score, anxiety score, household income, education, smoking, exercise habits and alcohol intake (Model 3). Only the effect for insulin was not significant in the fully adjusted model ($p = .07$). Finally, regression analyses of the association of hostility to glucose, insulin, HOMA-IR and serotonin metabolites within the African American women are presented in Table 5. They revealed significant effects for glucose, insulin, HOMA-IR, 5HTP, and 5HIAA in age adjusted analysis that continued to be

significant after further adjustment for body mass index (Model 2) and Beck Depression Inventory score, anxiety score, household income, education, smoking, exercise and alcohol intake (Model 3). As shown above, among African American women both 5HIAA and 5HTP correlated significantly with hostility and glucose, whereas tryptophan was not significantly associated with either variable (see Table 3). Examination of the inter-correlations of these metabolites in the African American women revealed a significant correlation between 5HTP and both 5HIAA ($r = .39, p < .02$) and tryptophan ($r = .36, p = .03$), and a non-significant correlation between tryptophan and 5HIAA ($r = .05, p = .78$). Given that 5HTP and 5HIAA share significant variance and were both correlated with glucose and hostility we used them to create a composite score using principal components analysis. The purpose of creating the composite score was twofold. First, we wanted to see if the covariation of these two metabolites was also associated with hostility, glucose, insulin, and HOMA-IR in African American women. Second, using a single composite score representing central nervous system serotonin function would simplify the analysis examining its role in the hostility-glucose association.

A principal components analysis using age and height adjusted 5-HTP and 5-HIAA values yielded a single factor (Eigenvalue = 1.45 in which both variables loaded above .55. The central nervous system 5HT factor was positively associated with fasting glucose ($r = .45, p < .01$) (see Figure 1b) and hostility ($r = .55, p < .01$) (Figure 1c) as well as insulin ($r = .47, p < .01$) and HOMA-IR ($r = .49, p < .01$). Controlling for the factor score resulted in substantial reductions in the associations of hostility to glucose, insulin, and HOMA-IR. The corresponding correlations were $r = .36, p = .04$ for the hostility to glucose association, $r = .20$ (NS) for the hostility to insulin, and $r = .24$ (NS) for the hostility to HOMA-IR associations. Though the hostility to glucose correlation was still significant after adjustment for the factor score, the proportion of variance accounted for was nearly halved, to 13.4% as compared to 27% in the age-adjusted only analysis. For insulin and HOMA-IR, the proportion of variance accounted for was reduced from 16.8% to 4% and 20.3% to 5.8%, respectively.

DISCUSSION

There is accumulating evidence suggesting that there is a stronger association between hostility and other indicators of negative affect and glucose dysregulation among African American women than in African American men and white men and women (4, 27, 28). Previous research by our group has shown that the association of hostility with fasting glucose is more pronounced among African American women (4). Our group has also found hostility to be linked with early signs of glucose dysregulation during an intravenous glucose tolerance test (5) in African American women. This larger effect of hostility on glucose metabolism in African American women has important clinical implications, given their almost two-fold increased risk of type 2 diabetes as compared to their white counterparts (34).

In the current study we used a targeted electrochemistry platform to quantify various metabolites of the serotonin pathway in order to identify metabolic pathways that might influence both hostility and glucose metabolism in African American women. We found

significant associations between hostility and indices of glucose metabolism (i.e. glucose, insulin, and HOMA-IR) and indices of central nervous system serotonin function (5-HTP and 5-HIAA) in African American women. Those associations survived adjustment by a host of lifestyle variables (i.e. smoking, exercise and alcohol intake), measures of negative affect (BDI scores and NEO-PI anxiety scores), and indices of socio-economic position (i.e. education and household income). Further, 5-HTP and 5-HIAA were positively correlated with hostility, glucose, insulin and HOMA-IR only in African American women. We also found that a composite score representing the shared variance of 5-HTP and 5-HIAA accounted for a substantial proportion of the variance of the associations of hostility to glucose metabolism. These findings suggest that the previously reported association between high hostility and high fasting glucose in African American women may result from both being driven by elevated central nervous system serotonin function.

Previous results from our group and others suggest that hostility may impact glucose kinetics in African American women via multiple behavioral and endocrine pathways, with a key component being the release of non-esterified fatty acids mediated by adrenomedullary effects on excess fat stores (35). Central nervous system serotonin stimulates the release of counterregulatory hormones, such as epinephrine and cortisol (8), suggesting that the physiological cascade resulting in altered glucose metabolism could be initiated by increased central nervous system serotonin activity. More specific evidence for the role of central nervous system serotonin in glucose metabolism comes from studies suggesting that enhanced central nervous system serotonergic activity at particular receptors might contribute to alterations in glucose metabolism. For example, stimulation of central 5-HT_{1A} receptors in rats causes hyperglycemia that is mediated by release of epinephrine (36). Recent work from our laboratory demonstrated that enhancing central nervous system serotonin levels via intravenous infusion of tryptophan resulted in a significant increase in epinephrine, an effect that was believed to be mediated by activation of central nervous system 5-HT_{1A} receptors (37). Stimulation of 5-HT_{2C} receptors in the paraventricular nucleus of the hypothalamus has been shown to cause release of corticotrophin releasing hormone that results in activation of the hypothalamic-adrenocortical axis (38) and we have reported that a functional 5-HT_{2C} polymorphism is associated with a marked increase in cortisol levels during stress (39). These findings suggest that higher central nervous system serotonin could account for higher levels of fasting glucose in African American women via effects to increase both sympathetic nervous system and hypothalamic-adrenocortical axis activation.

Hostility has previously been linked both to increased caloric intake and waist circumference (40) as well as body mass index (3), suggesting that elevated adiposity could have been responsible for the association between hostility and glucose metabolism among African American women. However, both the present study and other recent studies by our group (4, 5) show that the association between hostility and fasting glucose remained significant even after adjusting for body mass index. Thus, the present findings cannot be explained by differences in adiposity levels alone. However, adiposity may still play a significant role in explaining the apparent stronger effect of hostility on fasting glucose in the African American women. Epinephrine increases hepatic glucose production, the major determinant of fasting glucose and it is likely that beta-adrenergic receptors mediate this

response. Previous studies have shown a higher beta receptor density in the omental adipose tissue of African American women (41) potentially making African American women more sensitive to the effects of epinephrine, even at similar levels of adiposity. Our group has shown that impaired fasting glucose is predicted by the interaction of epinephrine and central adiposity and that obese African American women show a very strong association between plasma epinephrine levels and fasting glucose (42).

The present study found, in African American women only, that hostility was associated with higher levels of 5-HTP, the immediate precursor to serotonin, and 5-HIAA, the major metabolite of serotonin, suggesting that in this group hostility is associated with higher levels of both central nervous system serotonin synthesis and breakdown. However, the positive associations of hostility to 5-HTP and 5-HIAA seen in this study do not appear to be due to having higher levels of the precursor tryptophan. One possible explanation is that in African American females, higher levels of hostility are associated with elevated levels of tryptophan hydroxylase-2, the rate limiting enzyme that converts tryptophan to 5-HTP (43). Further documenting differences in serotonin metabolism in African American women compared to other race/sex groups, we have found that the serotonin transporter promoter polymorphism (5HTTLPR) short/short genotype is associated with 5-HIAA levels in cerebrospinal fluid that are 50-100% higher among African American women than those in other race/sex groups (20).

A stronger association between hostility and glucose in African American women has been reported in several studies from our laboratory (4, 5) and similar differences between African American women and their white counterparts in the association of fasting glucose with traits such as depression and anxiety have been reported by other labs (27, 28). Effects of central nervous system are plausible mechanisms that could be responsible for the observed stronger association between hostility and glucose metabolism in African American women. However, these findings should not be interpreted as suggesting that central nervous system serotonin has no effect on hostility and glucose metabolism in African American males and white men and women. One limitation of the current study is the small sample size, which may have resulted in low power to detect significant associations in the other groups. However, despite the relatively small sample size, we were able to show robust correlations among hostility, glucose, and cerebrospinal fluid serotonin metabolites in the African American women. This study has provided a unique opportunity to explore the role of central nervous system serotonin function in the hostility and fasting glucose association we have repeatedly found in African American women.

Finally, we have discussed the findings of the serotonin metabolites measured in the cerebrospinal fluid as reflecting some effect of central nervous system serotonin on glucose metabolism in the African American women. However, we cannot rule out an effect of peripheral serotonin. There is recent evidence suggesting that gut-derived serotonin has important effects on fasting glucose metabolism. Animal studies have shown that gut-derived serotonin has a strong influence on fasting glucose metabolism by favoring lipolysis and liver gluconeogenesis and preventing glucose uptake by hepatocytes (44). Although central nervous system serotonin and gut-derived serotonin are in separate compartments, it

has been shown that serotonin levels measured in cerebrospinal fluid correlates well with peripheral levels of serotonin measured in platelets, as well as in plasma (45).

In summary, we used an electrochemistry based platform to identify metabolic pathways in the central nervous system that might account for the relationship between hostility and glucose metabolism that is seen in African American women (4), a group that is at elevated risk of developing type 2 diabetes (34). We found that central nervous system serotonin metabolites 5-HTP and 5-HIAA account for a substantial proportion of variance in hostility's association with glucose metabolism in African American women but not other race/sex groups, suggesting that elevated central nervous system serotonin function may influence hostility and glucose metabolism differently in this group. Thus, the present research is novel in that it extends previous work by identifying a serotonergic metabolic pathway in the central nervous system that might account for the association of hostility to important health outcomes in this population at high risk for type 2 diabetes. If confirmed in further research, these findings imply that interventions that alter central nervous system serotonin function could be effective in preventing and reducing both hostility and dysregulated glucose metabolism in African American women.

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Figure 1.

(A) Association of Cook Medley Hostility score to fasting glucose in African American women (age adjusted); **(B)** Association of central nervous system serotonin to fasting glucose in African American women (age and height adjusted); **(C)** Association of Cook Medley Hostility score to central nervous system serotonin in African American women (age and height adjusted).

Table 1

Descriptive statistics (means $\pm$ SD) of study variables by race and gender groups

	African American Females	African American Males	White Females	White Males	P Main effect Race	P Main effect Sex	P Interaction Race $\times$ Sex
Age (years)	33.2 $\pm$ 8.7	32.8 $\pm$ 8.8	35.5 $\pm$ 7.6	36.8 $\pm$ 8.5	.06	.85	.61
Hostility	10.5 $\pm$ 4.5	11.6 $\pm$ 5.1	7.4 $\pm$ 4.7	10.10 $\pm$ 4.42	<.001	.05	.37
Depression score	4.8 $\pm$ 4.5	4.5 $\pm$ 4.6	5.0 $\pm$ 4.7	4.5 $\pm$ 4.6	.79	.15	.32
Anxiety score	49.2 $\pm$ 6.2	47.1 $\pm$ 8.7	50.7 $\pm$ 8.5		.99	.01	.19
Education (years)	13.9 $\pm$ 2.2	13.8 $\pm$ 2.4	15.8 $\pm$ 2.6	15.3 $\pm$ 2.6	<.001	.70	.82
Household income (k\$)	31.7 $\pm$ 20.8	28.6 $\pm$ 20.1	39.4 $\pm$ 25.6	31.2 $\pm$ 17.9	.15	.20	.39
Currently smoking (%)	19	29	22	33	.83	.39	.79
Exercise							
- Sedentary (%)	11	5	17	0			
- Moderate	83	75	79	88			
- High	6	19	4	12	.38	.05	.82
Alcohol intake/week							
- None	14	21	15	4			
- 1- 4 drinks/week	75	50	55	48			
- >4 drinks/week	11	29	30	48	.17	.11	.32
Body mass index(kg/m ²)	27.8 $\pm$ 6.8	26.3 $\pm$ 5.1	25.4 $\pm$ 5.5	26.3 $\pm$ 3.8	.21	.57	.25
Glucose (mg/dl)	81.3 $\pm$ 9.3	81.9 $\pm$ 6.2	80.2 $\pm$ 5.6	85.7 $\pm$ 9.2	.31	.05	.08
Insulin	11.4 $\pm$ 11.6	8.3 $\pm$ 4.4	8.7 $\pm$ 7.4	8.9 $\pm$ 4.5	.45	.38	.30
HOMA-IR	44.5 $\pm$ 58.8	30.4 $\pm$ 16.5	32.8 $\pm$ 29.7	34.9 $\pm$ 20.0	.53	.46	.27
Tryptophan	103.9 $\pm$ 21.1	106.4 $\pm$ 19.5	108.3 $\pm$ 23.2	111.4 $\pm$ 23.9	.24	.50	.94
5-HTP	93.3 $\pm$ 38.4	84.1 $\pm$ 29.2	96.9 $\pm$ 35.5	94.1 $\pm$ 26.5	.32	.39	.68
5-HIAA	121.2 $\pm$ 64.5	85.3 $\pm$ 47.3	95.6 $\pm$ 39.7	79.7 $\pm$ 64.9	.13	.01	.32

Table 2

Partial correlations^a examining associations of hostility with fasting glucose, insulin and HOMA-IR in African American women (AAW), African American men (AAM), white women (WW) and white men (WM).

	AAW	AAM	WW	WM
Glucose (mg/dl)	.52**	-.05	.03	.27
lnInsulin	.41*	-.17	.41*	.26
lnHOMA-IR	.45**	-.17	.36	.30

^a Analysis of glucose, insulin, and HOMA-IR are age adjusted.

* P<0.05

** P<0.01

Table 3

Associations among serotonin metabolites, hostility and fasting glucose, insulin and HOMA-IR in African American women (AAW) and African American men (AAM) and white women (WW) and white men (WM) (the cerebrospinal fluid variables are adjusted for age and height).

	Hostility				Glucose				lnInsulin				lnHOMA-IR			
	AAW	AAM	WW	WM	AAW	AAM	WW	WM	AAW	AAM	WW	WM	AAW	AAM	WW	WM
Metabolite	AAW	AAM	WW	WM	AAW	AAM	WW	WM	AAW	AAM	WW	WM	AAW	AAM	WW	WM
Tryptophan	-.03	.06	.16	.30	-.01	.05	-.34	.23	.18	.14	-.02	.36	.16	.15	-.03	.37
5-HTP	.43*	.11	.18	.00	.41**	.00	-.20	.03	.55**	.15	.18	-.12	.56***	-.14	.17	-.10
ln5-HIAA	.51**	-.14	.12	.09	.36*	.20	.20	.29	.26	.11	.07	.17	.28	.14	.08	.22

* P<0.05

** P<0.01

Table 4

Interaction analysis on the effect of hostility by Group (African American women vs 'Other', i.e. African American men, white women and white men combined) on indices of glucose metabolism and serotonin metabolites.

	Model 1 ^a			Model 2 ^b			Model 3 ^c		
	B	SE	P-value	B	SE	P-value	B	SE	P-value
Glucose (mg/dl)	.84	.32	<.01	.76	.31	.01	.78	.31	.01
lnInsulin	.06	.02	.02	.04	.02	.04	.05	.02	.02
lnHOMA-IR	.07	.02	.01	.06	.02	.02	.06	.02	.01
ln5-HIAA	.06	.03	.03	.05	.03	.05	.05	.03	.07
5-HTP	3.2	1.4	.02	3.2	1.4	.03	3.3	1.4	.02
Tryptophan	-.26	.92	.77	-.33	.92	.72	-.19	.93	.84
5-HT Factor	.12	.04	<.01	.11	.04	<.01	.11	.04	<.01

^aModel 1: Adjusted for age (and height for serotonin metabolites)

^bModel 2: Adjusted for age and body mass index (and height for serotonin metabolites)

^cModel 3: Adjusted for age, body mass index, depression score, anxiety score, household income, education, smoking, exercise and alcohol intake (and height for serotonin metabolites)

Table 5

Associations of hostility to serotonin metabolites and fasting glucose, insulin and HOMA-IR in African American women.

African American women (N=36)									
	Model 1 ^a			Model 2 ^b			Model 3 ^c		
	B	SE	P-value	B	SE	P-value	B	SE	P-value
Glucose (mg/dl)	1.0	.29	<.001	.99	.30	.002	1.14	.38	.007
lnInsulin	.06	.02	.01	.06	.03	.02	.08	.03	.02
lnHOMA-IR	.08	.03	.007	.07	.03	.01	.09	.04	.02
ln5-HIAA	.06	.02	.002	.05	.02	.004	.04	.02	.05
5-HTP	3.7	1.35	.01	3.6	1.4	.01	4.51	1.74	.02
Tryptophan	-.13	.80	.87	-.22	.82	.79	.07	1.04	.95
5-HT Factor	.14	.04	<.001	.12	.04	.002	.13	.05	.008

^aModel 1: Adjusted for age (and height for serotonin metabolites)^bModel 2: Adjusted for age and body mass index (and height for serotonin metabolites)^cModel 3: Adjusted for age, body mass index, depression score, anxiety score, household income, education, smoking, exercise and alcohol intake (and height for serotonin metabolites)