Title

Reactivity of salivary uric acid in response to social evaluative stress in African Americans.

Authors

Lucas, Todd

Riis, Jenna

Buchalski, Zachary

et al.

Publication Date

2020-05-01

DOI

10.1016/j.biopsycho.2020.107882

Peer reviewed

HHS Public Access

Author manuscript

Biol Psychol. Author manuscript; available in PMC 2021 May 01.

Published in final edited form as:

Biol Psychol. 2020 May ; 153: 107882. doi:10.1016/j.biopsycho.2020.107882.

Reactivity of Salivary Uric Acid in Response To Social Evaluative Stress in African Americans

Todd Lucas[a,b,c], **Jenna L. Riis**[c,d], **Zachary Buchalski**[a], **Caroline E. Drolet**[a], **Anurag Dawadi**[a], **Douglas A. Granger**[c,e]

[a]Division of Public Health, College of Human Medicine, Michigan State University, 200 East 1st Street, Flint, MI 48502

[b]Department of Epidemiology and Biostatistics, College of Human Medicine, Michigan State University, 909 Wilson Road, B636, East Lansing, MI 48824

[c]Institute for Interdisciplinary Salivary Bioscience Research, University of California Irvine, 4201 SBSG., Irvine, CA, 92697-7085

[d]Department of Psychological Science, School of Social Ecology, University of California Irvine, 4201 SBSG., Irvine, CA 92697-7085

[e]Department of Acute and Chronic Care, Johns Hopkins University School of Nursing; Department of Population, Family, and Reproductive Health, Johns Hopkins University Bloomberg School of Public Health; Department of Pediatrics, Johns Hopkins University School of Medicine 615 North Wolfe St., Baltimore, MD 21205; Salivary Bioscience Laboratory and Department of Psychology, University of Nebraska-Lincoln, Lincoln NE 68588-0156

Abstract

High uric acid (UA) is associated with hypertension and cardiovascular disease (CVD), both of which occur disproportionately among African Americans. High UA also predicts greater blood pressure reactivity responses to acute social stress. However, whether UA itself shows reactivity in response to stress is unknown. We evaluated salivary uric acid (sUA) and blood pressure reactivity in response to acute social stress. Healthy African Americans (N=103; 32% male; M age=31.36 years), completed the Trier Social Stress Test. sUA and blood pressure measurements were taken before, during and after the stressor task. sUA showed significant reactivity and recovery, especially among older African Americans. Total sUA activation was also associated with systolic and diastolic blood pressure total activation. Findings illuminate that acute stress may be a way in

Correspondence concerning this article may be addressed to Todd Lucas, Division of Public Health, College of Human Medicine, Michigan State University, 200 East 1st Street, Flint, MI 48502 (lucastod@msu.edu).

Disclosure

In the interest of full disclosure, DAG is founder and chief scientific and strategy advisor at Salimetrics LLC and Salivabio LLC and these relationships are managed by the policies of the committees on conflict of interest at the Johns Hopkins University School of Medicine and University of California at Irvine.

which UA is implicated in hypertension and CVD, suggesting a critical need to explore UA reactivity as a novel parameter of the acute stress response.

Keywords

Uric Acid; Trier Social Stress Test; Cardiovascular Disease; Blood Pressure; Health Disparities; Stress Reactivity

Introduction

African Americans are disproportionately burdened by cardiovascular disease (CVD; (Carnethon et al., 2017), and by hypertension (Flack, Ferdinand, & Nasser, 2003) – an influential and modifiable CVD precursor (Mouton, Hayden, & Southerland, 2017). Although access to medical care and low socioeconomic status contribute to racial disparities in both CVD and hypertension, they do not fully explain them. Rather, psychosocial stress is viewed as a parallel contributor (Dimsdale, 2008). In turn, dysregulation of acute stress responses, including both reactivity to and recovery from psychosocial stress, is prospectively associated with stress-related illness, including through links to CVD (Chida & Steptoe, 2010; Obrist, 2012; Panaite, Salomon, Jin, & Rottenberg, 2015; Phillips & Hughes, 2011). One critical aspect of CVD prevention is thus to better understand and promote adaptive stress reactivity (Lovallo, 2011), particularly among at-risk individuals.

In the present study, we consider the potential of uric acid (UA) to portray reactivity in response to acute social stress. In doing so, we consider whether this largely overlooked biosocial pathway might furnish a route through which UA affects hypertension and CVD disparities among African Americans (Kawai et al., 2012). Emerging research highlights that a priori measures of UA predict blood pressure reactivity responses to acute social stress (Mrug et al., 2017; Woerner, Lucas, Pierce, Riis, & Granger, 2019). However, whether UA itself shows reactivity in response to acute stress is unknown. Our goal was thus to consider whether UA responds to social evaluative stress, much like other psychobiological stress systems. With an eye towards extant CVD and disparity, including connections to hypertension, we also considered whether UA reactivity would predict blood pressure (BP) reactivity responses to acute social stress.

UA occurs naturally and is mainly produced in the liver during purine nucleotide breakdown (El Ridi & Tallima, 2017). UA is perhaps best known for the condition of hyperuricemia – systemic elevation in UA stemming from dietary behaviors (Dornas, de Lima, Pedrosa & Silva 2015; Kanbay et al., 2016), or from conditions such as impaired renal function (Kushiyama, Tanaka, Hara & Kawazu 2014; Sah & Qing, 2015). Hyperuricemia is implicated in the pathophysiology of several diseases, including gout, chronic kidney disease, metabolic syndrome, insulin-resistance, obesity, and Type-2 diabetes (Feig, 2014; Feig, Kang, & Johnson, 2008). Of relevance to CVD, hyperuricemia is also implicated in hypertension through the capacity of UA to activate the renin-angiotensin system – high UA concentrations signal growth factors, hormones, and cytokines that activate signal transduction pathways (El Ridi & Tallima, 2017), which in turn express inflammation and

increase arterial pressure that can eventuate in atherosclerosis, and in long-term sodium-sensitive hypertension (Feig, 2014). Corroborating evidence suggests that UA may indeed play a causal role in hypertension and CVD disparities (Johnson, Titte, Cade, Rideout, & Oliver, 2005). However, these consequences of hyperuricemia must also be balanced against the potential of UA to serve protective physiologic functions. Crucially, UA is both a powerful antioxidant and a mediator and amplifier of the type 2 inflammatory response. High levels of UA have also been linked to lower risk of age-related cognitive diseases, such as Parkinson's disease (de Lau, Koudstaal, Hofman, & Breteler, 2005; Latourte, Bardin, & Richette, 2018). The seemingly double-edged implications of UA for long term health underscore a critical need to better understand how UA is connected to stress, including through acute stress response.

Potentially relevant, UA has been connected to a handful of stress-related mood disorders that are likewise associated with CVD, including depression and anxiety (Cheffer et al., 2018). UA has also been implicated in neurological regulation of the psychobiological stress response (Goodman et al., 2016), and to personality traits that are linked to stress and coping (Armon, 2016). Moreover, brain structures implicated in a range of mood disorders, including bipolar disorder, contain numerous purinergic system receptors (for review, Ortiz, Ulrich, Zarate, & Machadi-Vieira, 2015). However, to the best of our knowledge, the reactivity of UA in response to social stress has not yet been directly considered (though see, Manowitz, Amorosa, Goldstein & Carlton, 1993).

Available literature points to several potential functions that could be served by an acute UA reactivity response. Perhaps most apparent is the potential of UA to play a role in regulating co-occurring acute phase inflammatory stress responses. Elevated concentrations of UA either precede or occur in parallel to several antibody immune responses (for review, El Ridi & Tallima, 2017). For example, UA can both initiate and amplify allergic inflammation in humans (Kool et al., 2011). In parallel, numerous studies have shown that acute stress can induce changes in a range of inflammatory factors, most notably including C-reactive protein (CRP), tumor necrosis factor alpha (TNF-α), and interleukin-6 (IL-6; for review, Slavish, Graham-Engeland, Smyth, & Engeland, 2014). It follows that an acute UA response, if present, could play a role in regulating these inflammatory stress responses. Lending some support, UA and TNF-α concentrations appear to be positively associated within the context of diagnosed CVD (Olexa et al., 2002). Moreover, epidemiological evidence suggests that UA is positively associated with CRP, TNF-α, and IL-6, including after adjustment for sociodemographic characteristics and pre-existing health (Ruggiero et al., 2006). However, associations between UA and inflammatory markers in the context of acute stress response remain largely unclear.

An interconnected possibility concerns the potential of UA reactivity to contribute to regulation of oxidative stress that can occur in response to acute stress. UA is a strong reactive oxygen species (ROS; Ames, Cathcart, Schwiers, & Hochstein, 1981), and in humans, UA comprises over half of the antioxidant capacity of blood plasma (for review, El Ridi & Tallima, 2017). Although oxidative stress responses have been less well attended to in the psychosocial stress literature than other biological stress systems, some available research suggests that acute psychological stress can suppress phagocytic production of ROS

(Atanackovic, Schulze, Kröger, Brunner-Weinzierl, & Deter, 2003). In turn, an increase of UA in response acute stress could indicate a biological attempt to balance production of ROS that is suppressed by stress exposure. Further buoying this potential, there is some evidence that acute psychosocial stress bolsters production of peripheral lymphocytes, while simultaneously lowering ROS production (Atanackovic et al., 2002).

Beyond potentially guiding concomitant inflammatory stress responses, UA reactivity could also play a role in directing stress appraisal. Goodman and colleagues (2016) showed that hippocampal and surrounding cortex activity increased as a function of higher UA concentration. Psychosocial stress has been shown to decrease hippocampal activity, leading to greater expression (i.e., disinhibition) of emotional response to stress. It follows that UA could play a role in efforts to control or regulate affective stress responses, or that UA may act as a stress alarm through activating limbic system structures (see also, Fleshner, 2013; Maslanik et al., 2013). Connections to hippocampal activity further suggest that UA responses could be linked to hypothalamic-pituitary-adrenocorti1cal (HPA) axis and autonomic nervous system (ANS) stress responses, which are similarly controlled by the limbic system (for review, Ulrich-Lai & Herman, 2009). Thus, Goodman and colleagues (2016) highlight that UA reactivity could be implicated in regulating cognitive and affective stress responses, while also suggesting links to multisystem stress responses (Laurent, Lucas, Pierce, Goetz & Granger, 2016; Lucas, Wegner, Pierce, Lumley, Laurent & Granger, 2017).

Mechanistically, available literature points to several signaling pathways that could be implicated in an acute UA reactivity response (for overviews, Abbracchio, Burnstock, Verkhratsky, & Zimmermann, 2009; Di Virgilio, Ceruti, Bramanti, & Abbracchio, 2009; Ortiz, et al., 2015). Perhaps most notable, purine receptors for adenosine (P1) and adenosine triphosphate (P2) are present in numerous brain structures that are implicated in stress responses, especially including limbic system structures (Burnstock, 2008). Activation of these receptors indicates increased purinergic transformation and results in elevated downstream uric acid levels, which further accelerates purinergic transformation. Through these signaling channels, uric acid could play a crucial role in stress appraisal processes that are governed in part by the limbic system.

In the present study, we undertake a vital first step in better connecting uric acid to stress-related health by examining whether sUA itself is reactive to acute social stress. In addition, we extend recent research by evaluating whether BP reactivity responses are associated with sUA reactivity. Although a handful of studies have considered whether a priori measurement of UA predicts stress reactivity (Mrug et al, 2017; Woerner et al., 2019), little research to date has attempted to consider the reactivity of UA in and of itself, and whether such reactivity would be associated with concomitant BP responses to stress. Aligned with recent research in this area, we again focus on BP given known connections to UA, hypertension, and related CVD and disparity. A community sample of healthy African Americans completed the Trier Social Stress Test (Kirschbaum, Pirke, & Hellhammer, 1993) to induce social-evaluative stress. Systolic and diastolic blood pressure readings were recorded before, during, and after the task to assess reactive change in BP. Salivary samples were taken contiguously to BP measurements, and were subsequently assayed to evaluate sUA

reactivity. Recent studies confirm a modest-to-strong positive association between circulating and salivary levels of UA (Cheng, Xia, Peng, & Zhou, 2013; Nunes, Brenzikofer, & Macedo, 2011), and that sUA can indicate trait-like individual differences (Riis et al., 2018), which in turn are linked to cardiovascular risk measures (Soukup et al., 2012). Moreover, the ease with which repeated oral fluid collections can be taken suggest that salivary measurement offers a practical modality for evaluating reactivity of UA in response to acute stress, highlighting a critical need to evaluate this potential application. To the extent that sUA reactivity has not been evaluated in prior research, our focus was largely exploratory. Nonetheless, our working hypothesis was that sUA reactivity responses would be associated with more reactive BP responses to the stressor task (Mrug et al., 2017; Woerner et al., 2019; see also Gerin, Goyal, Mostofsky, & Shimbo, 2008; Kannel, 2000). Given much prior research that has shown sex and age differences in both levels and health implications of UA (Fang & Alderman, 2000; Martinez, Ruelas, & Granger, 2017; Tuttle, Short, & Johnson, 2001; Woerner et al., 2019), we also examined main and moderator effects of these demographic variables on sUA reactivity.

Method

This study was performed in adjunct to alternate considerations of this data (Lucas et al., 2016; Woerner et al., 2019), after conducting additional assays to obtain the subsequently described reactivity measurements of sUA. Our participant sample, as well as procedures for recruiting participants and implementing the stressor task are therefore largely identical to previous descriptions, excepting small changes in sample size due to requiring a complete panel of sUA measurements from each participant to consider reactivity.

Participants

Participants were recruited from the Detroit metropolitan community via advertisements and completed a brief online prescreen survey to determine eligibility. Eligibility criteria included being 18 years of age or older and African American, and not taking an interfering medication or having a pre-existing medical or psychiatric condition that would preclude undertaking a minor stress induction. A sample of 118 participants enrolled and completed all study procedures approved by the Institutional Review Board, of which 106 had complete data for sUA. Data were excluded for 3 participants whose sUA levels were below the acceptable threshold. Thus, the present sample was limited to the 103 participants (33 male, 70 female). Participant ages ranged from 18 to 60 years (M = 31.41, SD = 13.84). Table 1 provides additional demographic information. All participants provided informed consent, received modest financial compensation for participating in a single 3-hour laboratory session, and were fully debriefed following study completion.

Procedures

Task procedure.

The Trier Social Stress Test (TSST) was used to induce mild psychosocial stress and associated physiological responses (Kirschbaum, Pirke, & Hellhammer, 1993). All sessions were scheduled for late morning or early afternoon. Participants were first given 10 minutes

to acclimate, and the remaining TSST protocol was then presented, which included a task description phase, a 10-minute speech preparation period, and a 10-minute performance (5-minute speech and 5-minute arithmetic task) given in front of a 2-person panel, consisting of one male and one female. Participants were given a 1-hour recovery period following task performance. Participants completed paper and pencil questionnaires immediately following the fourth salivary collection. To gauge a true recovery response, participants were instructed to do nothing following the fifth and sixth salivary collections.

Measures

Saliva collection and preparation.

Saliva samples were collected in accordance with guidelines set forth by previous research (Granger, Hibel, Fortunato, & Kapelewski, 2009; Granger et al., 2012; Riis et al., 2018). Six saliva samples were collected from each participant. An initial sample was collected following the 10-minute acclimation period. The second and third samples were collected immediately before and after the TSST performance. Samples 4 through 6 were collected during the recovery period 15, 30, and 60 minutes after task completion. Participants drank 2.5ml of water upon arrival to the laboratory, as well as after each salivary collection. Participants provided at least 2 ml whole saliva by passive drool at each collection. Two minutes were allotted to saliva collection, and time was added if participants failed to produce 2 ml. Collection time and volume were recorded. After collection, samples were stored at −80°C until shipped frozen overnight for laboratory analysis. Participants were asked to refrain from consuming food, caffeine, citric drinks and dairy, and to avoid exercise or brushing teeth in the 30 minutes prior to saliva collection, and to report adherence to these guidelines. Participants also self-reported oral health by answering four yes-no questions that asked ‘Did you brush your teeth today?’ (Yes = 61, No=42), ‘did your gums bleed today? (Yes=11, No=92), ‘Do you have any mouth bruises?’ (Yes = 4, No = 99), and ‘have you had any recent dental work?’ (Yes = 1, No = 102). Oral health variables were previously probed for potential associations with sUA (Woerner et al., 2019).

Salivary uric acid.

Saliva samples were assayed in duplicate for sUA using a commercially available enzymatic reaction kit specifically designed for use with saliva (Catalog #1–3802, Salimetrics, Carlsbad, CA). The sUA test kit enables detection of UA in saliva through production of a red chromogen after brief incubation, which is measured at a wavelength of 515 nm. The amount of UA present in saliva is directly proportional to the increase in wavelength absorbence. The test volume was 10 μl and the lower limit of detection (LLD) was 0.07 mg/dL. Uric acid determinations for three participants were undetectable (< LLD), who were thus excluded from further consideration (see Participants). The average of duplicate tests was used in subsequently described statistical analyses. Coefficients of variations for sUA measurements across all six timepoints ranged from 2.89% (time 4) to 5.11% (time 1). Bivariate correlations of sUA across the six timepoints ranged from $r = .77$, $p < .001$ (time 1 and time 5) to $r = .89$, $p < .001$ (time 4 and time 6).

Blood pressure measurement.

Blood pressure reactivity was measured using a Dinamap 8100 (Critikon, Tampa, FL). The Dinamap 8100 is a fully portable, non-invasive blood pressure device that measures systolic and diastolic pressure, as well as pulse rate and mean arterial pressure, using the oscillometric technique. This instrument has been used and evaluated in numerous studies and has achieved acceptable or better standards in a vast majority according to accuracy criteria established by the British Hypertensive Society (BHS) and the Association for the Advancement of Medical Instrumentation (Jin, Donaghue, Fairchild, Chan, & Silink, 2001). Blood pressure readings were taken following the protocol established by the BHS (Gerin, Goyal, Mostofsky, & Shimbo, 2008). The blood pressure cuff was applied to participants' non-dominant arm, and the lower edge of the cuff was placed 2 cm above the elbow crease, with the marked arrow placed over the brachial artery. An appropriate cuff size was selected using measurement of the mid-upper arm circumference, and the cuff was wrapped sufficiently tight to allow two fingers to be inserted at the top and bottom.

Blood pressure readings were collected from each participant at six time points that corresponded to salivary collection timepoints. Readings were collected in triplicate at one minute intervals for all six time points. Prior to taking measurements at all occasions, participants were comfortably seated, with their feet flat to the floor, and the arm was raised to heart level and supported. Participants were also instructed to relax and not to speak during blood pressure measurements. An average systolic and diastolic reading was calculated at each timepoint using all three readings. Coefficients of variation for systolic blood pressure across all six timepoints ranged from 3.50% (time 2) to 4.75% (time 4). Bivariate correlations of systolic blood pressure across the six timepoints ranged from $r = .85$, $p < .001$ (time 3 and time 6) to $r = .92$, $p < .001$ (time 5 and time 6). Coefficients of variation for diastolic blood pressure across all six timepoints ranged from 5.55% (time 6) to 6.22% (time 5). Bivariate correlations of diastolic blood pressure across the six timepoints ranged from $r = .78$, $p < .001$ (time 2 and time 6) to $r = .92$, $p < .001$ (time 4 and time 5). Across all six timepoints, correlations between systolic and diastolic blood pressure ranged from $r = .68$, $p < .001$(time 2) to $r = .78$, $p < .001$(time 6).

Statistical analysis

To begin, we assessed the isolated reactivity and recovery profiles of sUA and BP measures across the six timepoints using one-way repeated measures ANOVAs and a series of repeated measures t-tests. We then computed summative measures of sUA reactivity and recovery. Based on available TSST literature, we anticipated heterogeneity in sUA peak timing. Reactivity was therefore calculated following Miller and colleagues (2018) recommended approach (see also Wadsworth et al., 2019). Specifically, we used each participant's highest post-TSST sUA level [time 3 (35%), time 4 (15.5%), time 5 (7.8%), time 6 (19.4%)] to index peak sUA. Reactivity scores were then calculated by subtracting each participant's lowest pre-TSST sUA level [time 1 (62.1%), time 2 (37.9%)] values from their peak value. Recovery scores were calculated by subtracting each participant's peak value from their lowest subsequent recovery point [time 4 (35.0%), time 5 (33.0%), time 6 (32.0%)] value. Specifically, we subtracted the lowest time 4 through time 6 value for

participants who peaked at time 3, whereas we subtracted the lowest time 5 through time 6 for participants who peaked at time 4. We subtracted time 6 from time 5 for participants who peaked at time 5, with negative values indicating no recovery for nine participants (i.e., linear increase across the recovery timepoints). We ran subsequently reported analyses with and without non-recovering participants included and found no differences in statistically significant results. Thus, these participants were retained. We also computed total activation of sUA using a well-established area under the curve (AUCg) method of integration, and mathematical formulas developed specifically for use in biological reactivity paradigms (Pruessner, Kirschbaum, Meinlschmid, & Hellhammer, 2003). Identical sets of reactivity, recovery, and total activation measures were calculated for systolic and diastolic BP.

Using summative measures, and after assessing multiple regression statistical assumptions, we considered potential age and sex differences in sUA responses by conducting hierarchical multiple regressions, with sex and age serving as predictor variables and sUA reactivity, recovery and total activation responses serving as criterion variables. Sex was contrast coded (−1 = male, 1 = female) and age was mean centered. Main effects of sex and age were then simultaneously entered at the first step. A sex x age interaction term was computed and entered at the second step. At both steps, significance was assessed using R^2 change and individual regression weights of predictors newly entered at each step. Following recommendations, we controlled for Time 1sUA when assessing total activation (Miller et al., 2018).

Lastly, we considered associations between sUA and BP stress responses by once again conducting hierarchical multiple regressions, with sex, age, and sUA responses serving as predictor variables, and systolic and diastolic BP responses serving as criterion variables. sUA reactivity, recovery, and total activation responses were also mean centered. Sex and age and sUA main effects were entered and evaluated on the first step of all regressions. Two-way interactions of age, sex, and sUA reactivity measures were computed and entered as on the second step of each multiple regression. At both steps, significance was again assessed using R^2 change and individual regression weights of predictors newly entered at each step. Significant interactions that included sUA x sex interactions were probed separately for males and females, whereas significant sUA x age interaction were probed separately for older versus younger (±1 SD) participants (Aiken, West & Reno, 1991). Although reactivity responses precede recovery responses, we included multiple regressions in which sUA recovery predicted BP reactivity, given the potential for recovery stress responses to indicate trait-like individual differences (Roy, Kirschbaum & Steptoe, 2001; Williams, Smith, Gunn & Uchino, 2011).

For all hierarchical multiple regression that included either total activation or recovery measures, we controlled for two minor variations to the traditional TSST protocol. One variation led participants to believe that their individual performance during the TSST was judged to be either satisfactory or unsatisfactory by a speech expert. A second variation called for a laboratory assistant to treat participants either politely or slightly impolitely just prior to the post-task recovery portion of the session. These variations were fully crossed and implemented ten minutes prior to the fourth salivary collection timepoint. Substantive consideration of these manipulations is provided elsewhere (Lucas et al., 2016; Lucas,

Pierce, et al., 2017). Presently, we entered a dummy coded variable for each variation on the first regression step, as well as a cross product variable to covary for their potential interaction.

Prior to conducting multiple regressions, we also assessed for potential differences in sUA reactivity, recovery, and total activation based on TSST panel composition. Specifically, we probed for differences in sUA responses across each of 4 male TSST judges, which included 1 African American judge (n = 16), 2 Caucasian Americans judges (n's = 27, 40), and 1 Asian American judge (n = 20). We also probed for differences across four Caucasian American female TSST judges [judge 1 (n = 18), judge 2, (n = 40), judge 3 (n = 13), judge 4 (n = 32)]. One way ANOVASs revealed that there were no differences in sUA responses across male judges for sUA reactivity ($F(3, 99) = 1.581$, $p = .199$), sUA recovery ($F(3, 99) = 1.180$, $p = .321$), or sUA total activation ($F(3, 99) = 0.705$, $p = .551$). Likewise, there were no differences in sUA responses across female judges for sUA reactivity ($F(3, 99) = 1.173$, $p = .324$), sUA recovery ($F(3, 99) = 0.070$, $p = .976$), or sUA total activation ($F(3, 99) = 1.380$, $p = .253$). Thus, TSST panel composition was not subsequently considered.

Results

Isolated sUA reactivity and recovery responses

An isolated consideration of sUA acute responses across the six measurements is portrayed in Figure 1. Consistent with anticipated TSST reactivity, the highest concentration occurred at the third timepoint, just after stressor task completion. A Greenhouse-Geisser corrected repeated measures one-way ANOVA was significant ($F(5, 102) = 7.118$, $p < .001$, $\eta_p^2 = .065$), indicating overall differences in sUA concentration across the six timepoints. To assess the reactivity phase response, we probed these differences using paired t-tests between time 1 and time 3. Time 1 concentration did not significantly differ from time 2 ($t(102) = -1.808$, $p = .074$). However, time 3 sUA was significantly higher than time 1 ($t(102) = 5.597$, $p < .001$) and time 2 ($t(102) = 4.154$, $p < .001$). In addition, there was a significant linear trend from time 1 to time 3, ($F(2, 102) = 31.321$, $p < .001$, $\eta_p^2 = .235$). Thus, there was strong evidence of sUA reactivity in response to the TSST over the preparation and performance phases.

To assess the recovery phase, we computed paired t-tests between the third and sixth timepoints. Time 3 concentration was significantly higher than time 4 ($t(102) = 2.042$, $p = .044$), time 5 ($t(102) = 3.343$, $p < .001$), and time 6 ($t(102) = 2.300$, $p = .023$). However, time 4 concentration was not significantly different than time 5 concentration, ($t(102) = 1.033$, $p = .304$), nor time 6 concentration ($t(102) = -0.222$, $p = .825$). Time 5 concentration also did not significantly differ from time 6 concentration ($t(102) = -1.458$, $p = .148$). As with reactivity, there was a significant negative linear trend from time 3 to time 6, ($F(1, 102) = 6.824$, $p = .010$, $\eta_p^2 = .063$), though this trend was more robust when time 6 was excluded ($F(1, 102) = 11.176$, $p < .001$, $\eta_p^2 = .099$). Thus, there was also evidence for sUA recovery.

Isolated blood pressure reactivity and recovery responses

Isolated consideration of systolic and diastolic BP reactivity and recovery across the six measurements are also portrayed in Figure 1. Similar to sUA, systolic and diastolic BP were both highest at the third timepoint. A Greenhouse-Geisser corrected repeated measures one-way ANOVA was significant for both systolic BP ($F(5, 102) = 53.191$, $p < .001$, $\eta_p^2 = .343$) and diastolic BP ($F(5, 102) = 29.800$, $p < .001$, $\eta_p^2 = .226$) indicating overall differences in both BP measures across the six timepoints. To assess the reactivity phase responses, we again probed differences using paired t-tests between time 1 and time 3. Time 1 systolic BP was lower than time 2 ($t(102) = -10.204$, $p < .001$) and time 3 ($t(102) = -11.692$, $p < .001$), although time 2 systolic was not significantly lower than time 3 ($t(102) = -1.523$, $p = .131$). In addition, there was a significant linear trend from time 1 to time 3 for systolic BP, ($F(1, 102) = 33.939$, $p < .001$, $\eta_p^2 = .250$). Results for diastolic BP reactivity were nearly identical. Namely, time 1 diastolic BP was lower than time 2 ($t(102) = -10.124$, $p < .001$) and time 3 ($t(102) = -11.086$, $p < .001$), although time 2 was additionally lower than time 3 ($t(102) = -2.405$, $p = .018$). There was also a significant linear trend from time 1 to time 3 for diastolic BP, ($F(1, 102) = 122.904$, $p < .001$, $\eta_p^2 = .546$). Overall, there was strong evidence of both systolic and diastolic BP reactivity in response to the TSST.

To assess BP recovery, we again computed paired t-tests between the third and sixth timepoints. Time 3 systolic BP was higher than time 4 ($t(102) = 9.694$, $p < .001$), time 5 ($t(102) = 10.746$, $p < .001$), and time 6 ($t(102) = 9.326$, $p < .001$). However, time 4 systolic BP did not significantly differ from time 5 ($t(102) = 0.503$, $p = .616$), nor time 6 ($t(102) = -0.096$, $p = .924$), and time 5 systolic BP did not differ from time 6 ($t(102) = -0.671$, $p = .504$). As with reactivity, there was a significant negative linear trend from time 3 to time 6, ($F(1, 102) = 78.883$, $p < .001$, $\eta_p^2 = .436$). Diastolic BP recovery results were identical. Namely, time 3 diastolic BP was higher than time 4 ($t(102) = 5.645$, $p < .001$), time 5 ($t(102) = 6.713$, $p < .001$), and time 6 ($t(102) = 5.611$, $p < .001$). Likewise, time 4 diastolic BP did not significantly differ from time 5 ($t(102) = 1.417$, $p = .160$), nor time 6 ($t(102) = 1.346$, $p = .181$), and time 5 diastolic BP did not differ from time 6 ($t(102) = 0.418$, $p = .677$). There was also a significant negative linear trend for diastolic BP from time 3 to time 6, ($F(1, 102) = 30.694$, $p < .001$, $\eta_p^2 = .231$). Thus, there was also evidence of a recovery response for systolic and diastolic BP measures, in addition to BP reactivity.

Age and sex differences in sUA reactivity and recovery

Also seen in Figure 1, the overall sUA reactivity profile was more pronounced among older and male participants, and this included both the reactivity and recovery phases. Formal evaluation of age and sex differences via two-step hierarchical multiple regression revealed significant main effects on the first step for each of sUA reactivity ($\Delta r^2 = .070$, $p = .028$), and total activation ($\Delta r^2 = .805$, $p < .001$), though sUA recovery was not statistically significant ($\Delta r^2 = .054$, $p = .064$). Age was associated with greater sUA reactivity ($\beta = .201$, $p = .042$), and greater sUA total activation ($\beta = .256$, $p = .008$), though not less sUA recovery ($\beta = .186$, $p = .064$). Sex differences were not significant for sUA reactivity ($\beta = -.152$, $p = .122$), recovery ($\beta = -.121$, $p = .220$), or total activation ($\beta = -.060$, $p = .191$). On the second step, age x sex interactions were not significant for sUA reactivity ($\Delta r^2 = .001$, $\beta = -.037$, $p = .750$), recovery ($\Delta r^2 = .003$, $\beta = .056$, $p = .573$), or total activation ($\Delta r^2 = .001$,

β = .029, p = .532), indicating that associations between age and sUA reactivity, recovery, and total activation were not qualified by sex.

sUA predicting blood pressure reactivity

Hierarchical multiple regressions predicting systolic BP responses from sUA reactivity, recovery, and total activation are presented in Table 2, Evaluation of main effects on the first step revealed that sUA reactivity predicted greater total activation of systolic BP (β = 0.20, p = .037) and diastolic BP (β = 0.20, p < .029). sUA recovery responses also predicted greater total activation of systolic BP (β = 0.28, p = .006) and diastolic BP (β = 0.21, p = .031), in addition to predicting greater reactivity of systolic BP (β = 0.21, p = .044). Lastly, total activation of sUA predicted greater total activation of systolic BP (β = 0.44, p < .001) and diastolic BP (β = 0.40, p < .001).

A significant sUA total activation x age interaction emerged for total activation of systolic BP (ΔR^2 = .02, p = .02, β = 0.13, p = .02). As seen in Figure 2, sUA total activation was more strongly associated with total activation of systolic BP among older African Americans (β = 0.63, p < .001) than among younger African Americans (β = 0.41, p = .003). A significant sUA total activation x sex interaction emerged for total activation of diastolic BP (ΔR^2 = .01, p = .05, β = 0.10, p = .03). As seen in Figure 2, sUA total activation was more strongly associated with higher diastolic BP total activation among females (β = 0.59, p < .001) than among males (β = 0.38, p = .001).

Discussion

To our knowledge, this study is the first to both consider and establish reactivity of UA in response to acute social stress. Among healthy African Americans, sUA concentration significantly increased across the preparation and performance phases of the TSST, indicating an acute sUA stress reactivity response. In addition, sUA concentration significantly decreased after the performance phase, indicating an observable recovery response. Although sUA reactivity and recovery were observed generally, these responses were strongest among older African Americans. Finally, we observed that sUA reactivity was associated with greater systolic and diastolic BP activation in response to the TSST. Several implications and vital future directions can be extracted from these results.

Foremost, current findings provide the foundation for considering a new direction in stress reactivity research. Paradigms such as the TSST have been extensively used to explore cognitive, emotional, biological, and behavioral responses to social-evaluative threat, and in turn, numerous markers of ANS, HPA-axis, and inflammatory stress response systems have been evaluated. To our knowledge, the current study is the first to explore UA as a possible marker of the purinergic system response to acute social stress induced either by the TSST, or by other stress reactivity paradigms. In turn, results highlight that UA may respond to acute stress, much like other biological stress systems and markers. A highly critical future direction is thus to explore the function, health implications, and concomitants of this hitherto overlooked acute stress response. For example, and much like ongoing debates surrounding other acute stress responses, the extent to which UA reactivity comprises a healthy versus harmful biological response to stress must be further considered. This

direction may prove uniquely challenging to the extent that UA has been shown to promote both harmful and healthy effects, and given multiple potential functions that UA could serve. Related, prospective research linking UA reactivity to long term health outcomes may be especially revelatory. This perhaps most readily includes evaluating links between developing hyperuricemia and UA reactivity, although links to long term CVD outcomes will also be especially valuable.

The potential function and resulting health implications of UA reactivity must also be further considered by also evaluating links to concomitant acute stress responses. This encompasses ANS and HPA-axis responses, and especially inflammatory stress responses that are directly implicated in UA production. Related, the physiological processes underlying UA reactivity should be further considered in future research. For example, although purinergic receptors exist in a number of limbic system structures, the extent to which these receptors are activated by acute social stress, and thus play a role in response to acute sUA production, is not yet known. Better understanding these and other physiological processes can better explain the role of UA in stress appraisal processes. Also related, the secretory delay of uric acid into saliva should receive attention in future research, as this delay may lend to interpretation of acute stress response processes and function, although there is initial evidence that serum and salivary UA increase similarly after acute stress exposure (González-Hernández et al., 2019).

In showing that UA is itself reactive to social evaluate stress, the current findings also broaden the realm of potential connections between UA, stress, and CVD and disparity. High UA is well linked to greater hypertension and CVD risk (Feig et al., 2008; Loeffler, Navas-Acien, Brady, Miller, & Fadrowski, 2012; Viazzi et al., 2013). Related, Woerner and colleagues (2019) have recently shown that baseline sUA may be positively associated with acute BP responses to social evaluative stress (see also, Mrug et al., 2017), illuminating that hyperuricemina may eventuate in hypertension and CVD and disparity in part through links to stress reactivity responses (Panaite et al., 2015). The current findings extend and enrich this literature by highlighting a potentially unique role of sUA reactivity among these relationships.

This study also found that UA activation may be especially pronounced among older and male African Americans. The implications of these potential differences are unclear at present. For example, some research has suggested that links between UA and CVD are more pronounced among women than men (Fang & Alderman, 2000; Tuttle et al., 2001). Furthermore, the extent to which sex or age differences might be impacted by antecedent sources of UA also remains unknown. For example, some evidence suggests that hyperuricemia may be more strongly linked to diet in men than women (Gao et al., 2007). Adding complexity, we also found sex and age moderator effects in the links between sUA and BP reactivity. With respect to age, sUA total activation was more strongly associated with systolic BP total activation among older participants. With respect to sex, we found that sUA total activation was more strongly associated with greater diastolic total activation among female participants. This sex difference is curious to the extent that males showed more overall sUA reactivity than females. Future research should not only attend to whether UA reactivity differs by age and sex, but also the origins and implications of these

differences for accompanying stress responses and associated health outcomes. These future studies are especially needed given the relatively modest number of males in the current study.

Several limitations suggest both a cautious interpretation and other future directions. These limitations are largely shared with prior consideration of this data (Woerner et al., 2019). Foremost, our interpretations are limited in important ways by only evaluating African Americans. Focusing only on African Americans is prudent to the extent that CVD and other illnesses stemming from dysregulated UA very often disproportionately burden African Americans. Nonetheless, we are unable to decipher whether the UA reactivity responses observed presently extend more generally to non-African Americans. Future research should therefore include racial comparisons and cultural explorations of the role that UA plays in stress reactivity, which may further clarify contributions to stress-related health disparities, including CVD. The current research is also limited by our relatively modest sample size, by the largely correlational nature of the data, by the large number of multiple regression analyses, and by only evaluating BP reactivity as an outcome. Related, several potential UA covariates were not presently evaluated, notably including body mass index – a known correlate of UA. Taken together, these limitations also suggest a critical need for replication of the current findings in future explorations.

We note three additional limitations specific to evaluating stress reactivity. First, this research did not include a resting control, which would provide additional fidelity to support the presently observed reactivity responses. Second, this study used the TSST to induce acute stress responses due to social evaluative threat. Although this paradigm is widely used, and social evaluative stress is known to carry strong implications for health, it is not known whether acute stress responses derived from other oft-used paradigms (e.g., cold suppression) would produce similar UA reactivity responses. Future research therefore should deploy additional stress reactivity protocols, which could better illuminate UA reactivity structure and function. Third, this research does not link UA reactivity responses to indices of long term health. Although several reactivity responses have been prospectively linked to CVD, such links are unknown with respect to UA. Future studies should therefore consider if and how UA reactivity predicts longer term health and disease states. Such research may also carry implications for one day considering UA-oriented interventions, including dietary and pharmacological interventions, although the potential of such intervention approaches should be thoroughly evaluated, given some potential for antioxidant or health-enhancing effects of UA (de Lau, Koudstaal, Hofman, & Breteler, 2005; Latourte, Bardin, & Richette, 2018).

Acknowledging limitations, this study provides a novel contribution in showing that UA is reactive to acute social stress, and in turn is associated with BP reactivity. Additional research is needed to further understand the function and concomitants of this hitherto overlooked acute stress response. Future studies should also seek to establish if UA reactivity responses carry implications for long term hypertension and CVD, including CVD disparities among African Americans.

Acknowledgments

This research was supported by Award Number R21HL097191 from the National Heart, Lung, and Blood Institute awarded to the first author. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Heart, Lung, And Blood Institute or the National Institutes of Health. We thank Mercedes Hendrickson, Nathan Weidner, Lenwood Hayman, Edyta Debowska, Kaitlyn Simmonds, Kevin Wynne, Stefan Goetz, Rhiana Wegner, and the Clinical Research Center at Wayne State University for assistance with data collection and preparation. Finally, we appreciate biotechnical support with salivary assays provided by Carla Slike, Becky Zavacky, and Jessica Acevedo.

References

Abbracchio MP, Burnstock G, Verkhratsky A, & Zimmermann H (2009). Purinergic signalling in the nervous system: an overview. Trends in neurosciences, 32, 19–29. [PubMed: 19008000]

Aiken LS, West SG, & Reno RR (1991). Multiple regression: Testing and interpreting interactions. Sage.

Ames BN, Cathcart R, Schwiers E, & Hochstein P (1981). Uric acid provides an antioxidant defense in humans against oxidant-and radical-caused aging and cancer: a hypothesis. Proceedings of the National Academy of Sciences, 78, 6858–6862.

Armon G (2016). Serum uric acid and the Five Factor Model of personality: Implications for psychopathological and medical conditions. Personality and Individual Differences, 97, 277–281.

Atanackovic D, Atanackovic D, Brunner-Weinzierl MC, Kröger H, Serke S, & Deter HC (2002). Acute psychological stress simultaneously alters hormone levels, recruitment of lymphocyte subsets, and production of reactive oxygen species. Immunological Investigations, 31, 73–91. [PubMed: 12148950]

Atanackovic D, Schulze J, Kröger H, Brunner-Weinzierl MC, & Deter HC (2003). Acute psychological stress induces a prolonged suppression of the production of reactive oxygen species by phagocytes. Journal of Neuroimmunology, 142, 159–165. [PubMed: 14512175]

Burnstock G (2008). Purinergic signalling and disorders of the central nervous system. Nature reviews Drug discovery, 7, 575. [PubMed: 18591979]

Carnethon MR, Pu J, Howard G, Albert MA, Anderson CA, Bertoni AG, … & Yancy CW (2017). Cardiovascular health in African Americans: a scientific statement from the American Heart Association. Circulation, 136(21), e393–e423. [PubMed: 29061565]

Cheffer A, Castillo A, Corrêa-Velloso J, Gonçalves M, Naaldijk Y, Nascimento I, … Ulrich H (2018). Purinergic system in psychiatric diseases. Molecular psychiatry, 23, 94. [PubMed: 28948971]

Cheng P, Xia Y, Peng C, & Zhou Z (2013). Evaluation of dialysis in patients with end-stage renal disease by salivary urea, creatinine and uric acid. Zhong nan da xue xue bao. Yi xue ban= Journal of Central South University. Medical sciences, 38, 1260–1263. [PubMed: 24384951]

Chida Y, & Steptoe A (2010). Greater cardiovascular responses to laboratory mental stress are associated with poor subsequent cardiovascular risk status. Hypertension, 55, 1026–1032. [PubMed: 20194301]

de Lau LM, Koudstaal PJ, Hofman A, & Breteler MM (2005). Serum uric acid levels and the risk of Parkinson disease. Annals of Neurology: Official Journal of the American Neurological Association and the Child Neurology Society, 58, 797–800.

Dimsdale JE (2008). Psychological stress and cardiovascular disease. Journal of the American College of Cardiology, 51, 1237–1246. [PubMed: 18371552]

Dornas WC, de Lima WG, Pedrosa ML, & Silva ME (2015). Health implications of high-fructose intake and current research. Advances in Nutrition, 6, 729–737. [PubMed: 26567197]

El Ridi R, & Tallima H (2017). Physiological functions and pathogenic potential of uric acid: A review. Journal of advanced research, 8, 487–493. [PubMed: 28748115]

Fang J, & Alderman MH (2000). Serum uric acid and cardiovascular mortality: the NHANES I epidemiologic follow-up study, 1971–1992. Jama, 283, 2404–2410. [PubMed: 10815083]

Feig DI (2014). Serum uric acid and the risk of hypertension and chronic kidney disease. Current opinion in rheumatology, 26, 176–185. [PubMed: 24419747]

Feig DI, Kang D-H, & Johnson RJ (2008). Uric acid and cardiovascular risk. New England Journal of Medicine, 359, 1811–1821. [PubMed: 18946066]

Flack JM, Ferdinand KC, & Nasser SA (2003). Epidemiology of hypertension and cardiovascular disease in African Americans. The Journal of Clinical Hypertension, 5, 5–11.

Fleshner M (2013). Stress-evoked sterile inflammation, danger associated molecular patterns (DAMPs), microbial associated molecular patterns (MAMPs) and the inflammasome. Brain, Behavior, and Immunity, 27, 1–7.

Gao X, Qi L, Qiao N, Choi HK, Curhan G, Tucker KL, & Ascherio A (2007). Intake of added sugar and sugar-sweetened drink and serum uric acid concentration in US men and women. Hypertension, 50, 306–312. [PubMed: 17592072]

Gerin W, Goyal TM, Mostofsky E, & Shimbo D (2008). The measurement of blood pressure in cardiovascular research Handbook of physiological research methods in health psychology, 115–131.

Goodman AM, Wheelock MD, Harnett NG, Mrug S, Granger DA, & Knight DC (2016). The hippocampal response to psychosocial stress varies with salivary uric acid level. Neuroscience, 339, 396–401. [PubMed: 27725214]

González-Hernández JM, Franco L, Colomer-Poveda D, Martinez-Subiela S, Cugat R, Cerón JJ, … & Tvarijonaviciute A (2019). Influence of Sampling Conditions, Salivary Flow, and Total Protein Content in Uric Acid Measurements in Saliva. Antioxidants, 8, 389.

Granger DA, Fortunato CK, Beltzer EK, Virag M, Bright MA, & Out D (2012). Focus on methodology: Salivary bioscience and research on adolescence: An integrated perspective. Journal of Adolescence, 35, 1081–1095. [PubMed: 22401843]

Granger DA, Hibel LC, Fortunato CK, & Kapelewski CH (2009). Medication effects on salivary cortisol: Tactics and strategy to minimize impact in behavioral and developmental science. Psychoneuroendocrinology, 34, 1437–1448. [PubMed: 19632788]

Jin R, Donaghue K, Fairchild J, Chan A, & Silink M (2001). Comparison of Dinamap 8100 with sphygmomanometer blood pressure measurement in a prepubertal diabetes cohort. Journal of paediatrics and child health, 37, 545–549. [PubMed: 11903832]

Johnson RJ, Titte S, Cade JR, Rideout BA, & Oliver WJ (2005). Uric acid, evolution and primitive cultures. Paper presented at the Seminars in nephrology.

Kanbay M, Jensen T, Solak Y, Le M, Roncal-Jimenez C, Rivard C, … & Johnson RJ (2016). Uric acid in metabolic syndrome: from an innocent bystander to a central player. European Journal of Internal Medicine, 29, 3–8. [PubMed: 26703429]

Kannel WB (2000). Elevated systolic blood pressure as a cardiovascular risk factor. The American Journal of Cargiology, 85, 251–255.

Kawai T, Ohishi M, Takeya Y, Onishi M, Ito N, Yamamoto K, … Rakugi H (2012). Serum uric acid is an independent risk factor for cardiovascular disease and mortality in hypertensive patients. Hypertension Research, 35), 1087. [PubMed: 22739421]

Kirschbaum C, Pirke K-M, & Hellhammer DH (1993). The 'Trier Social Stress Test'–a tool for investigating psychobiological stress responses in a laboratory setting. Neuropsychobiology, 28, 76–81. [PubMed: 8255414]

Kool M, Willart MA, van Nimwegen M, Bergen I, Pouliot P, Virchow JC, … & Lambrecht BN (2011). An unexpected role for uric acid as an inducer of T helper 2 cell immunity to inhaled antigens and inflammatory mediator of allergic asthma. Immunity, 34, 527–540. [PubMed: 21474346]

Kushiyama A, Tanaka K, Hara S, & Kawazu S (2014). Linking uric acid metabolism to diabetic complications. World Journal of Diabetes, 5, 787. [PubMed: 25512781]

Latourte A, Bardin T, & Richette P (2018). Uric acid and cognitive decline: a double-edge sword? Current opinion in rheumatology, 30, 183–187. [PubMed: 29389776]

Laurent HK, Lucas T, Pierce J, Goetz S, & Granger DA (2016). Coordination of cortisol response to social evaluative threat with autonomic and inflammatory responses is moderated by stress appraisals and affect. Biological psychology, 118, 17–24. [PubMed: 27155141]

Loeffler LF, Navas-Acien A, Brady TM, Miller ER, & Fadrowski JJ (2012). Uric acid level and elevated blood pressure in US adolescents. Hypertension, 59, 811–817. [PubMed: 22353609]

Lovallo WR (2011). Do low levels of stress reactivity signal poor states of health? Biological psychology, 86, 121–128. [PubMed: 20079397]

Lucas T, Lumley MA, Flack JM, Wegner R, Pierce J, & Goetz S (2016). A preliminary experimental examination of worldview verification, perceived racism, and stress reactivity in African Americans. Health Psychology, 35, 366–375. [PubMed: 27018728]

Lucas T, Pierce J, Lumley MA, Granger DA, Lin J, & Epel ES (2017). Telomere length and procedural justice predict stress reactivity responses to unfair outcomes in African Americans. Psychoneuroendocrinology, 86, 104–109. [PubMed: 28938175]

Lucas T, Wegner R, Pierce J, Lumley MA, Laurent HK, & Granger DA (2017). Perceived discrimination, racial identity, and multisystem stress response to social evaluative threat among African American men and women. Psychosomatic Medicine, 79, 293. [PubMed: 27806018]

Manowitz P, Amorosa LF, Goldstein HS, & Carlton PL (1993). Uric acid level increases in humans engaged in gambling: A preliminary report. Biological Psychology, 36, 223–229. [PubMed: 8260567]

Martinez AD, Ruelas L, & Granger DA (2017). Association between body mass index and salivary uric acid among Mexican- origin infants, youth and adults: Gender and developmental differences. Developmental Psychobiology, 59, 225–234. [PubMed: 27888639]

Maslanik T, Mahaffey L, Tannura K, Beninson L, Greenwood BN, & Fleshner M (2013). The inflammasome and danger associated molecular patterns (DAMPs) are implicated in cytokine and chemokine responses following stressor exposure. Brain, Behavior, and Immunity, 28, 54–62.

Miller R, Wojtyniak JG, Weckesser LJ, Alexander NC, Engert V, & Lehr T (2018). How to disentangle psychobiological stress reactivity and recovery: A comparison of model-based and non-compartmental analyses of cortisol concentrations. Psychoneuroendocrinology, 90, 194–210. [PubMed: 29370954]

Mouton CP, Hayden M, & Southerland JH (2017). Cardiovascular health disparities in underserved populations. Primary Care: Clinics in Office Practice, 44, e37–e71. [PubMed: 28164826]

Mrug S, Mrug M, Morris AM, Reynolds N, Patel A, Hill DC, & Feig DI (2017). Uric Acid Excretion Predicts Increased Blood Pressure Among American Adolescents of African Descent. The American journal of the medical sciences, 353, 336–341. [PubMed: 28317621]

Nunes LAS, Brenzikofer R, & Macedo DV (2011). Reference intervals for saliva analytes collected by a standardized method in a physically active population. Clinical biochemistry, 44, 1440–1444. [PubMed: 21986592]

Obrist PA (2012). Cardiovascular psychophysiology: A perspective: Springer Science & Business Media.

Olexa P, Olexová M, Gonsorcík J, Tkác I, Kisel'ová J, & Olejníková M (2002). Uric acid- -a marker for systemic inflammatory response in patients with congestive heart failure?. Wiener Klinische Wochenschrift, 114, 211–215. [PubMed: 12238311]

Ortiz R, Ulrich H, Zarate CA Jr, & Machado-Vieira R (2015). Purinergic system dysfunction in mood disorders: a key target for developing improved therapeutics. Progress in Neuro-Psychopharmacology and Biological Psychiatry, 57, 117–131. [PubMed: 25445063]

Panaite V, Salomon K, Jin A, & Rottenberg J (2015). Cardiovascular recovery from psychological and physiological challenge and risk for adverse cardiovascular outcomes and all-cause mortality. Psychosomatic Medicine, 77, 215–226. [PubMed: 25829236]

Phillips AC, & Hughes BM (2011). Introductory paper: Cardiovascular reactivity at a crossroads: where are we now? Biological psychology, 86, 95–97. [PubMed: 20226227]

Pruessner JC, Kirschbaum C, Meinlschmid G, & Hellhammer DH (2003). Two formulas for computation of the area under the curve represent measures of total hormone concentration versus time-dependent change. Psychoneuroendocrinology, 28, 916–931. [PubMed: 12892658]

Riis JL, Bryce CI, Matin MJ, Stebbins JL, Kornienko O, Huisstede L. v., & Granger DA (2018). The validity, stability, and utility of measuring uric acid in saliva. Biomarkers in medicine, 12, 583–596. [PubMed: 29873515]

Roy MP, Kirschbaum C, & Steptoe A (2001). Psychological, cardiovascular, and metabolic correlates of individual differences in cortisol stress recovery in young men. Psychoneuroendocrinology, 26, 375–391. [PubMed: 11259858]

Ruggiero C, Cherubini A, Ble A, Bos AJ, Maggio M, Dixit VD, … & Ferrucci L (2006). Uric acid and inflammatory markers. European heart journal, 27, 1174–1181. [PubMed: 16611671]

Sah OSP, & Qing YX (2015). Associations between hyperuricemia and chronic kidney disease: a review. Nephro-Urology Monthly, 7.

Slavish DC, Graham-Engeland JE, Smyth JM, & Engeland CG (2015). Salivary markers of inflammation in response to acute stress. Brain, Behavior, and Immunity, 44, 253–269.

Soukup M, Biesiada I, Henderson A, Idowu B, Rodeback D, Ridpath L, … Bridges KG (2012). Salivary uric acid as a noninvasive biomarker of metabolic syndrome. Diabetology & metabolic syndrome, 4, 14. [PubMed: 22515434]

Tuttle KR, Short RA, & Johnson RJ (2001). Sex differences in uric acid and risk factors for coronary artery disease. The American journal of cardiology, 87, 1411–1414. [PubMed: 11397367]

Ulrich-Lai YM, & Herman JP (2009). Neural regulation of endocrine and autonomic stress responses. Nature reviews neuroscience, 10, 397. [PubMed: 19469025]

Di Virgilio F, Ceruti S, Bramanti P, & Abbracchio MP (2009). Purinergic signalling in inflammation of the central nervous system. Trends in neurosciences, 32, 79–87. [PubMed: 19135728]

Viazzi F, Antolini L, Giussani M, Brambilla P, Galbiati S, Mastriani S, … Genovesi S (2013). Serum uric acid and blood pressure in children at cardiovascular risk. Pediatrics, 132, e93–9. [PubMed: 23776119]

Wadsworth ME, Broderick AV, Loughlin- Presnal JE, Bendezu JJ, Joos CM, Ahlkvist JA, … & McDonald A (2019). Co- activation of SAM and HPA responses to acute stress: A review of the literature and test of differential associations with preadolescents' internalizing and externalizing. Developmental psychobiology.

Wang Y, & Wang QJ (2004). The prevalence of prehypertension and hypertension among US adults according to the new joint national committee guidelines: new challenges of the old problem. Archives of Internal Medicine, 164, 2126–2134. [PubMed: 15505126]

Williams PG, Smith TW, Gunn HE, & Uchino BN (2011). Personality and stress: Individual differences in exposure, reactivity, recovery, and restoration The handbook of stress science: Biology, psychology, and health, 231–245.

Woerner J, Lucas T, Pierce J, Riis JL, & Granger DA (2019). Salivary uric acid: Associations with resting and reactive blood pressure response to social evaluative stress in healthy African Americans. Psychoneuroendocrinology, 101, 19–26. [PubMed: 30399459]

Highlights

- Salivary uric acid shows reactivity in response to acute social stress.
- Salivary uric acid predicts blood pressure reactivity to acute social stress.
- Uric acid reactivity may be critical to understanding hypertension.

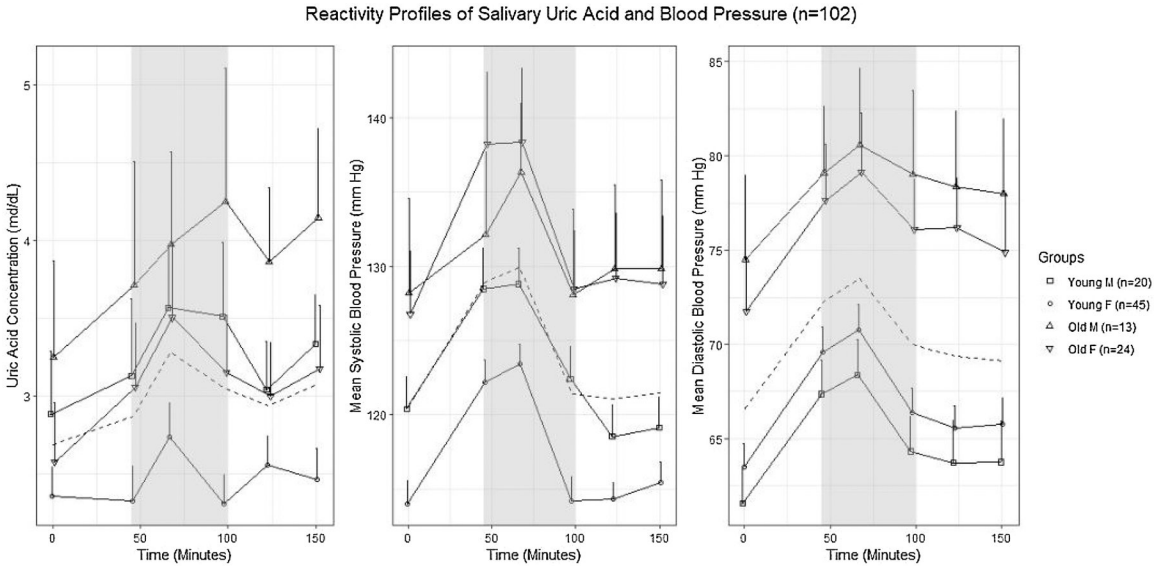

Figure 1.

Reactivity of salivary uric acid and blood pressure in response to Trier Social Stress Test by age and sex. Shaded area indicates performance phase of the task. Error bars are standard error of the mean. Dashed line represents overall mean at each time point.

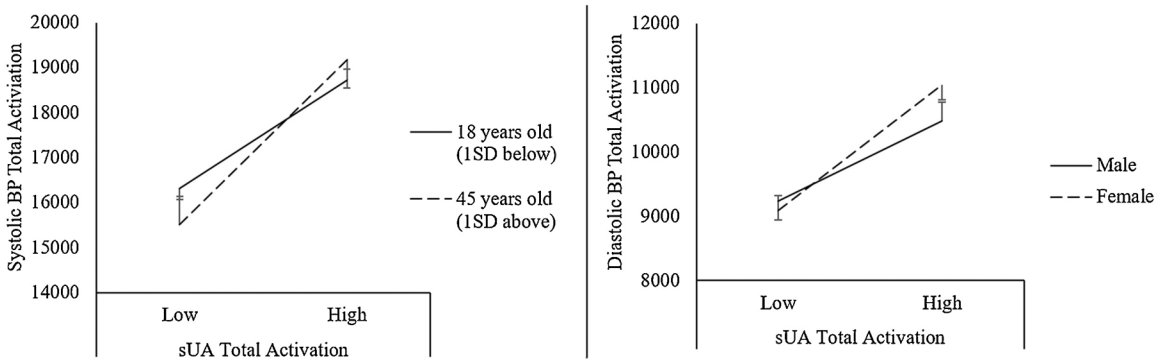

Figure 2.

Predicted total activation of systolic and diastolic blood pressure responses: Age and sex moderator effects on salivary uric acid. For age, 1 SD below = 18 years (n = 9), 1 SD above = > 45 years (n = 26). For sex male n = 33, female n = 70. Error bars represent one standard error of the mean.

Table 1.

Sample Characteristics ($N = 103$).

Demographic Characteristics	***n* (%)**
Sex	
Male	33 (32.0%)
Female	70 (68.0%)
Age	
18–20	26 (25.2%)
21–40	50 (48.5%)
41–60	26 (25.2%)
Missing	1 (1.0%)
Income	
Less than $25,000	57 (55.3%)
$25,000–$49,999	22 (21.4%)
$50,000–$99,999	21 (20.4%)
$100,000 and above	3 (2.9%)
Education	
High School/GED or Less	52 (50.5%)
Some College or Trade School	27 (26.2%)
College Graduate	16 (15.5%)
Professional/Advanced Degree	8 (7.8%)

Biol Psychol. Author manuscript; available in PMC 2021 May 01.

Table 2

Salivary Uric Acid Acute Responses Predicting Systolic and Diastolic Blood Pressure Acute Responses.

	BP Reactivity		**BP Recovery**		**BP Total Activation**	
sUA Reactivity	Systolic	Diastolic	Systolic	Diastolic	Systolic	Diastolic
Step1 Model Δr^2	**.09**	**.07**	**.06**	**.04**	**.70*****	**.75*****
Time 1 Systolic BP	--	--	--	--	.81***	--
Time 1 Diastolic BP	--	--	--	--	--	.80***
sUA Reactivity	.15	−.01	−.16	−.12	.10	.08
Age	.18^{+}	.03	.13	.02	.05	.08
Sex	.14	.02	.04	−.02	.04	.02
Step 2Model Δ r^2	**.04**	**.04**	**.04**	**.03**	**.01**	**.01**
sUA Reactivity x Age	.19	.08	.00	−.13	.00	.01
sUA Reactivity x Sex	.00	.21*	−.05	.00	.01	.07
Age x Sex	.14	.05	.19^{+}	.10	.10	.07
sUA Recovery						
Step1 Model Δr^2	**.11**$^{+}$	**.09**	**.04**	**.03**	**.72*****	**.77*****
Time 1 Systolic BP	--	--	--	--	.81***	--
Time 1 Diastolic BP	--	--	--	--	--	.81***
sUA Recovery	.20^{+}	.14	.06	.03	.18**	.17**
Age	.17	.00	.08	−.01	.03	.06
Sex	.14	.04	.07	.00	.05	.03
Step 2Model Δ r^2	**.01**	**.03**	**.05**	**.02**	**.02**$^{+}$	**.02**
sUA Recovery x Age	.09	−.18	.14	.00	.12^{+}	.05
sUA Recovery x Sex	.04	−.01	.07	.09	.06	.02
Age x Sex	.08	.05	.20^{+}	.12	.10^{+}	.07

	BP Reactivity		BP Recovery		BP Total Activation	
sUA Total Activation						
Step1 Model Δr^2	**.08**	**.09**	**.08**	**.06**	**.79*****	**.83*****
Time 1 Systolic BP	--	--	--	--	.73***	--
Time 1 Diastolic BP	--	--	--	--	--	.75***
Time 1 sUA	--	.19	--	.23	−.35**	−.27***
sUA Total Activation	.12	−.04	.12	−.04	60***	.53***
Age	.18^{+}	.02	−.02	−.02	−.01	.02
Sex	.14	.04	.10	.02	.08	.07
Step 2Model Δ r^2	**.02**	**.01**	**.03**	**.02**	**.02***	**.01***
sUA Total Activation x Age	.12	−.05	−.02	.02	.13*	.07
sUA Total Activation x Sex	−.01	.02	.03	.05	.08	.10*
Age x Sex	.11	.06	.15	.12	.10^{+}	.04

Notes. Coefficients are standardized regression weights.

*** p<.001,

** p<.01,

* p<.05,

$^{+}$ p=.10.

For sex: −1 = male, 1 = female. sUA = Salivary Uric Acid. BP = Blood Pressure.

Time 1 systolic and diastolic BP included as covariates for BP total activation. Time 1 sUA included as a covariate for sUA total activation.

Experimental fairness manipulation covariates included for 2 main effects and two-way interaction in all models.