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Differences in pituitary-adrenal reactivity in Black and White men with and without alcohol use disorder

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ABSTRACT

Background: Treatment-seeking men with alcohol use disorder (AUD) classically exhibit a blunted hypothalamic-pituitary-adrenal (HPA) axis response to pharmacologic and behavioral provocations during the early phases of abstinence from alcohol. Independent of alcohol, a significant muting of HPA axis reactivity is also observed among racial minority (e.g. Black) individuals. The effect of AUD upon the altered HPA axis response of racial minority individuals has not been explored. The current work represents a secondary analysis of race and AUD status among a sample of men.

Methods: Healthy male controls (17 White, 7 Black) and four-to six-week abstinent men with AUD (49 White, 13 Black) were administered a psychosocial stressor and two pharmacologic probes [ovine corticotropin releasing hormone (oCRH) and cosyntropin] to assess HPA axis reactivity. Plasma cortisol and adrenocorticotropin hormone (ACTH) were assessed at 10–20 min intervals prior to and following behavioral and pharmacological stimulation. Basal and net-integrated responses following provocations were analyzed to identify potential group differences. A measure of childhood adversity was also obtained to consider the implications of prior stressors upon HPA axis function.

Results: A three-fold increase in oCRH-induced ACTH was seen in Black men relative to White men regardless of AUD status. Adversity exerted a dampening effect on this pituitary sensitivity within Black controls only. Adjusted for adversity, a significant blunting effect of AUD status on ACTH reactivity was identified within White participants following oCRH. No group differences were present following cosyntropin administration. In response to the psychosocial stressor, White, but not Black, men with AUD experienced the expected blunting of cortisol reactivity relative to White controls. Rather, Black men with AUD exhibited greater cortisol reactivity relative to White men with AUD.

Conclusions: Differences in HPA axis reactivity associated with race were present in men with and without AUD. Explanatory biological mechanisms of the relationship between alcohol use and/or stress, in both healthy and unhealthy populations, may require a reassessment in different racial populations.

1. Introduction

Individuals with alcohol use disorder (AUD) display a wide array of neurophysiological disturbances, including dysregulation of the hypothalamic-pituitary-adrenal (HPA) axis. However, other contributing factors have been shown to influence this dysregulation including sex (Adinoff et al., 2010; Kudielka and Kirschbaum, 2005) and psychopathology (Brady et al., 2006). Racial minority status, although implicated in altered HPA axis function (Chong et al., 2008; Skinner et al., 2011), has never been evaluated as a potential factor in AUD-related HPA axis dysregulation.

The physiologic response to stress is regulated by the glucocorticoid cascade of the HPA axis. Central activation of the hypothalamic corticotropin-releasing-hormone (CRH) triggers adrenocorticotropin hormone (ACTH) release from the anterior pituitary. ACTH in turn stimulates cortisol secretion from the adrenal cortex, which then acts as

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an inhibitory feedback signal, deactivating the system at both the hypothalamic and pituitary levels. Repeated activation of the HPA axis from exposure to chronic stressors can lead to long-lasting alterations of the system, commonly identified by blunted ACTH and cortisol reactivity to stress (Herman et al., 2003; McEwen, 1998; Stephens and Wand, 2012).

During acute and chronic alcohol intoxication and withdrawal, heightened HPA axis reactivity in response to pharmacologic stimulation and acute-stress is observed in men with AUD (Adinoff et al., 2003; Heinz et al., 1995). Following approximately one week of abstinence from alcohol, blunted ACTH and cortisol reactivity are present and continue through protracted abstinence (Adinoff et al., 2005a; Blaine and Sinha, 2017; Lovallo et al., 2000). These noted alterations to the stress response system have been shown to predict increased craving, decreased length of abstinence, and greater relapse severity (Adinoff et al., 2017; Breese et al., 2005; Junghanns et al., 2003). However, only a handful of studies reported a non-White sample. The maximum racial minority participation rate was < 30% (Adinoff et al., 2003: 20% Black participants;Brady et al., 2006: 13% Black participants;Sinha et al., 2011: 25% Black participants; Sinha et al., 2011: 18% Non-White participants) and none of these studies examined the potential influence of race on HPA axis functioning.

Independent of alcohol use, the literature on racial differences in HPA axis function has notably expanded in the last decade. Relative to healthy White controls, healthy Black controls display flatter diurnal cortisol slopes (Hajat et al., 2010; Skinner et al., 2011) and decreased ACTH and cortisol provocation following a psychosocial stressor (Chong et al., 2008). The racial differences in HPA axis function are highly associated with measures of stress and emerge around late adolescence (Skinner et al., 2011; Krieger, 2005). For this reason, minority stress, rather than genetic differences, has been proposed as the underlying cause of the alterations in HPA axis reactivity seen in racial minorities. The chronic effects of minority stressors on mental and physical health outcomes have been characterized in Black Americans, carry significant public health implications (Clark et al., 1999; Jackson et al., 2016), and play an apparent role in the development of AUD (Keyes et al., 2011).

This post-hoc analysis stemmed from a study originally designed to assess the interaction between HPA axis reactivity, chronic stress, and drinking in treatment-seeking men and controls (Adinoff et al., 2017; Meng et al., 2011). Due to the inclusion of a considerable number of minority participants, we took this opportunity to explore race as a possible contributing factor in the dysregulation associated with AUD.

ACTH and cortisol were assessed in Black and White men with and without AUD following a psychosocial stress task (to assess an ecologically valid stimulation of the HPA axis) and the administration of oCRH (to assess a more specified activation at the pituitary level) and cosyntropin (to assess activation at the adrenal level). For this study, we examined basal levels and reactivity of endocrine response (i.e. ACTH and cortisol) for pharmacologic and acute-stress HPA activations. Due to previous work suggesting women with AUD do not display blunted HPA axis reactivity to provocation (Adinoff et al., 2010), their inclusion was not supported in the current work's parent study on HPA alterations and post-treatment drinking. For this reason, the current analyses are limited to men.

We anticipated a main effect of race to identify blunted HPA axis reactivity in Black men relative to White men. We further expected a main effect of AUD to show blunting in treatment-seeking men relative to controls. Of primary interest, we expected an interaction between race and AUD status in which Black men with AUD would show a multiplicative effect, exhibiting the greatest magnitude of hypoactivation of HPA axis reactivity. Moreover, factors associated with lifetime stress and adversity are related to HPA axis activity independent of race (Hajat et al., 2010; Lovallo et al., 2012) but may also speak to the differential impact of stressors on Black and White individuals' allostatic mechanisms (Krieger, 2005; Williams and Mohammed, 2009). We therefore included an exploratory analysis investigating the explanatory power of a measure of childhood adversity on the hypothesized relationship between race, AUD, and HPA axis reactivity.The assessment of childhood adversity provides a measure of external stressors that preceded the development of race-based differences in HPA axis function as well as the development of AUD in the clinical sample.

2. Methods and materials

2.1. General criteria

Selection criteria and methods have been reported previously (Adinoff et al., 2017). Participants were men between the ages of 21 and 59. Exclusionary criteria included a current diagnosis of a DSM-IV Axis I disorder [with the exception of substance use disorders for AUD participants and post-traumatic stress disorder (PTSD) for either group], use of medications known to affect the HPA axis or central nervous system (e.g. psychotropics, calcium channel blockers, hypoglycemics), and any medical condition that might affect HPA axis function (e.g. diabetes).

2.2. Participants with AUD

Sixty-two (49 White, 13 Black) non-Hispanic male participants with AUD were recruited from inpatient residential treatment programs at the VA North Texas Health Care System and Homeward Bound, Inc. (a public sector treatment program). Recruiting participants from the residential units allowed for monitoring of abstinence as participants remained on the unit prior to participation. AUD participants must have endorsed alcohol as their drug of choice, self-reported daily alcohol use of > 80 gm a day (e.g., six-pack of beer or half of a pint of 100-proof liquor) for at least two weeks prior to admission. Criteria for alcohol dependence was met per the Diagnostic and Statistical Manual on Mental Disorders [DSM-IV (First et al., 2002)].

2.3. Healthy control participants

Twenty-four healthy non-Hispanic male controls (17 White, 7 Black) without a lifetime history of Axis I substance dependence (with the exception of nicotine) or current Axis I non-substance dependence were recruited from the community.

2.4. Clinical assessment

The study was approved by the Institutional Review Boards at both the University of Texas Southwestern Medical Center and the VA North Texas Health Care System. Informed consent was obtained from all participants. All participants were assessed for Axis I disorders using the Structured Clinical Interview for DSM–IV Axis I Disorders—Lifetime Version [SCID (First et al., 2002)]. Participants with current Axis I Disorders were not included. Comorbid substance use disorders are listed in Table 1. Additional assessments included the Beck Depression Inventory [BDI (Beck et al., 1979)], State Trait Anxiety Inventory [STAI-S (Speilberger, 1971)] and Drinking Inventory of Consequences [DrInC (Miller et al., 1995)]. The Time Line Follow Back [TLFB (Sobell and Sobell, 1992)] estimated the number of drinking days and number of standardized drinks over the participants' lifetime and the daily drinking over the 90 days prior to recent abstinence. Participants were compensated for their participation.

2.5. Childhood adversity inventory

Participants completed the Childhood Adversity Inventory [CAI (Dienes et al., 2006)], a semi-structured interview focusing on seven areas of adversity occurring before the age of 13: separation or loss of