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Family History of Alcoholism Does Not Influence Adrenocortical Hyporesponsiveness in Abstinent Alcohol-Dependent Men

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Abstract

Background—Early abstinence in alcohol-dependent subjects is marked by adrenocortical hyporesponsivity. However, it is uncertain whether the blunted response is primarily attributable to a genetic vulnerability or to the chronic abuse of alcohol. In the present study, the authors investigated the influence of a family history (FH) of alcoholism upon suppressed glucocorticoid reactivity.

Methods—Twenty-two abstinent alcohol-dependent and 14 control men were studied. The cortisol response was assessed in 11 patients following oCRH infusion (.4 ug/kg) and in a separate group of 11 patients following cosyntropin infusion (.01 ug/kg) preceded by high-dose intravenous dexamethasone (8 mg). FH, as determined by self-report, was assessed using two different methods: history of parental alcoholism and number of alcohol-dependent first- and second-degree relatives.

Results—Neither a parental history or familial loading of alcoholism had a significant effect upon glucocorticoid responsivity in abstinent alcohol-dependent men.

Conclusions—Adrenocortical responsiveness in recently abstinent alcohol-dependent men does not appear to reflect a preexisting biologic vulnerability to alcoholism.

Keywords

Alcoholism; pituitary-adrenal system; cosyntropin; Corticotropin-Releasing Hormone; dexamethasone

INTRODUCTION

Adrenocortical hyposensitivity in early abstinence is one of the most consistent biological findings in alcohol dependence. A muted glucocorticoid response has been observed for up to 12-weeks of abstinence following pharmacological (i.e., alcohol [1], insulin [2], nicotine [3], ovine corticotropin releasing hormone (oCRH) [4, 5], cosyntropin [6, 7]), physical (i.e.,

operative trauma [8], exercise [9], hyperthermia [10], cold pressor [11]) and psychosocial (i.e., public speaking [12]) challenges in alcohol-dependent subjects. It is presumed that the suppressed adrenocortical response is a result of the persistent hypercortisolemia that accompanies repeated episodes of alcohol intoxication (13–15) and withdrawal (16–19). The allostatic glucocorticoid load then induces an adaptive downregulation of the cortisol response to both exogenous and endogenous stressors. Given recent evidence that suppressed adrenocortical responsiveness may heighten the risk of relapse (20, 21), it is important to identify the contributions to this physiological disruption.

However, the suppressed adrenocortical response may be, at least in part, a preexisting biologic disruption that is present prior to the onset of alcohol use. In fact, hypothalamic-pituitary-adrenal (HPA) disruption may serve as a vulnerability factor in the development of alcohol dependence. Schuckit et al. (22), for example, has observed that young men with alcohol-dependent fathers are more likely to exhibit a blunted cortisol response to an alcohol challenge relative to men without a family history (FH) of alcohol dependence. Sorocco et al. (23) has similarly observed an attenuated cortisol response to a public speaking task in young adults with a FH of alcoholism. These findings would suggest that a muted glucocorticoid response may predate the onset on alcohol dependence. In contrast, several other studies suggest that subjects with a family history demonstrate an increased—not decreased—HPA axis stress response. For example, Zimmerman et al. (24) reported that young men with a family history of alcohol dependence exhibit an exaggerated cortisol response to a public speaking task. Several investigators have also reported that FH positive subjects demonstrate a heightened cortisol response to opioid antagonists (e.g., naloxone or naltrexone) (25–27). Others have found no difference between the adrenocortical response in family history positive and negative subjects following oCRH (28), cosyntropin (29), or an alcohol challenge (30). Thus, these studies offer a mixed assessment of the potential contribution of premorbid HPA dysregulation upon adrenocortical hyposensitivity in alcohol-dependent subjects.

In a previously published study, we reported that abstinent alcohol-dependent men exhibit an attenuated cortisol response following both an oCRH challenge (5) and a cosyntropin challenge following high-dose dexamethasone (7). In order to determine the potential contribution of pre-existing pathology upon the observed disruption in glucocorticoid reactivity, we assessed the impact of family history of alcoholism upon the cortisol response to these two challenges.

METHODS

Alcohol Dependent Patients

Two separate groups of four- to six-week abstinent alcohol-dependent men were recruited for each infusion paradigm (e.g., oCRH and cosyntropin following dexamethasone). These groups have been previously described in detail (5, 7) and will only be briefly described here. Alcohol-dependent subjects were recruited from patients requesting treatment for alcohol dependence at the Dallas V.A. Medical Center. These patients were detoxified from alcohol and then housed on a residential treatment until the studies were initiated. Patients reported an alcohol intake of at least 80 g of absolute alcohol on a daily basis for at least 2

weeks before the cessation of drinking and had at least a 10-year history of problematic drinking. Patients with a lifetime history of other *DSM-IV* Axis I psychiatric disorders not associated with alcohol use, other substance use disorders (or weekly drug use) within the previous 12 months (excluding caffeine or nicotine use disorders), active medical disorders, or a history of major head trauma were excluded from the study. Exclusion criteria also included use of any medications that may interfere with HPA axis functioning within 2 weeks of the study, Beck Depression Inventory (31) scores above 15 at the time of assessment, or an alanine aminotransferase (ALT) or aspartate aminotransferase (AST) 3.0 times greater than the clinical laboratory's upper limit of normal. Controls reported no lifetime history of any *DSM-IV* Axis I disorder (except caffeine or nicotine use disorders), reported no medical disorders, and were taking no medications. Controls with a single first-degree relative or two second-degree relatives with an axis I disorder were excluded. All participants underwent a history and physical examination, routine clinical laboratory testing, electrocardiography, and urine drug screening. Psychiatric and substance use disorders were assessed using the Structured Clinical Interview for *DSM-IV*-Lifetime. Separate informed consents from both the University of Texas Southwestern Medical Center and the Dallas V.A. Medical Center were obtained after the study was fully explained, and participants were financially compensated for their participation.

Eleven patients (aged 43.5 ± 4.8 years; range, 36–49 years; mean $\pm$ SD) participated in the oCRH challenge, and 11 patients (aged 42.8 ± 4.0 years; range, 38–49 years) participated in the cosyntropin challenge following dexamethasone. Fourteen healthy men (38.0 ± 5.72 years, range 30–47 years) were individually age-matched within a 5-year period with alcohol-dependent patients. Four of these subjects participated in both challenge paradigms, separated by at least six weeks.

Family History

Subjects were first asked to describe their biologic family tree and then queried as to whether family members had a problem with alcohol. First, alcohol-dependent subjects were designated as parental FH positive if either their mother or father had a problem with alcohol. Second, familial loading was determined by totaling the number of first- and second-degree family members with alcohol problems. Additional relatives were not included due to decreasing accuracy with more distant relatives as well as the decreased weight ascribed to more distant relatives. First-degree relatives (i.e., mother, father, brother, sister) with alcohol problems were weighted as 1 and second-degree relatives (i.e., aunt, uncle, grandparent, half-siblings) were weighted at 1/2. Since a complete family pedigree was missing on some subjects, a common denominator (the total number of relatives for each subject) was not always available. An upper limit FH loading score was therefore set at 4 to avoid skewing of the data (only two subjects had a score above 4).

Infusion Procedures

All neuroendocrine studies were performed at the General Clinical Research Center (GCRC) at the University of Texas Southwestern Medical Center. Nicotine-dependent patients were given a nicotine patch appropriate to their level of cigarette use.

oCRH Stimulation Test

Participants arrived at the GCRC the day prior to the oCRH challenge. After the placement of intravenous lines into both arms, blood sampling was obtained every 10 minutes from 0800 hr for 12 hours for basal measures. oCRH .4 ug/kg was administered at 2000 hr. Blood sampling was increased immediately after oCRH administration to every 5 min through 2100 hr and then decreased to every 10 min through 2200 hr.

Cosyntropin Following Dexamethasone Suppression

Participants arrived at the GCRC at 2000 hr and intravenous lines were placed into both arms at 2100 hr. Dexamethasone, 8 mg, in 50 ml of dextrose 5% water (D5W) was administered intravenously from 2300 to 2330 hr. Cosyntropin .01 ug/kg was administered the following morning at 0800 hr. Blood sampling was obtained every 10 minutes between 0500 and 0800 hr to assess basal concentrations, and then increased immediately after cosyntropin administration to every 5 min through 0900 and then decreased to every 10 min through 1000 hr.

Assays

Serum concentrations of cortisol were measured by radioimmunoassay (RIA) using reagents from DiaSorin. This assay has a low-end sensitivity of .21 µg/dl, with an intra-assay coefficient of variation of 6.6–7.7% in the concentration range 2.9–47.1 µg/dl. The interassay coefficient of variation is 8.8–9.8% in the concentration range 3.7–36.9 µg/dl.

Statistics

oCRH and Cosyntropin Infusion Tests—Cortisol secretion after each challenge (oCRH and cosyntropin) was quantified using the area-under-the-curve method, or net integrated response. The net integrated response was calculated by taking the average hormone concentration between consecutive measurement points, multiplying by the time interval between the points, summing across time, and netting out basal hormone levels multiplied by the total time interval over which measurement occurred (i.e., 120 min). Basal hormone values were based on mean levels for the 30 min prior to the infusion. Missing values (five total) were estimated based on the mean of hormone measures taken directly before and after the missing values.

Family History

Due to the small number of subjects, the data from both studies was combined. Since two different infusion paradigms were utilized, all cortisol responses were converted to Z scores with 0 being the mean cortisol response in the control group following oCRH and following cosyntropin. Student's t-test analysis was used to compare parental FH+ (PFH+) vs. parental FH– (PFH–) Z scores as well as cortisol response following each infusion. The relationship between familial loading and cortisol response was determined using Pearson's correlation.

RESULTS

As previously described (5, 7), the mean integrated cortisol response was significantly less in alcohol-dependent subjects relative to controls following each infusion of oCRH: controls -1027 ± 235 ug/dl·2 hr, patients -715 ± 216 ug/dl·2 hr [$t = 2.86$, $df = 19$, $p < .01$]; cosyntropin: controls -1107 ± 249 ug/dl·2 hr, patients -804 ± 363 ug/dl·2 hr [$t = 2.21$, $df = 19$, $p < .04$]. As observed in Figure 1, 8 of the 11 alcohol-dependent subjects in each study showed a cortisol response almost 1 SD or more below the control response. Following Z score conversion and combining the two samples (oCRH and cosyntropin infusion), alcohol-dependent subjects continued to exhibit a significantly blunted response relative to controls (controls: $.00 \pm .97$, patients: -1.27 ± 1.26 ; $t = 3.62$, $df = 40$, $p = .0008$).

Eight of the 22 alcohol-dependent subjects endorsed a parental FH of alcoholism (see Figure 1). The cortisol response in PFH+ subjects did not significantly differ from PFH- subjects (PFH: -1.15 ± 1.06 ; PFH-: -1.34 ± 1.40 ; $t = .33$, $df = 20$, $p = .74$). Post-hoc analysis following each infusion also did not differ between groups (oCRH: $t = 1.30$, $df = 9$, $p = .22$; cosyntropin: $t = .48$, $df = 9$, $p = .64$).

Thirteen patients endorsed a family history of alcoholism in first- and/or second-degree relatives (see Figure 1). There was not a significant correlation between familial loading and integrated cortisol response ($r = 0.09$, $df = 21$, $p = 0.70$) (Figure 2). Post-hoc analyses of each infusion group analyzed separately also did not reveal a significant relationship between familial loading and cortisol response (oCRH: $r = 0.07$, $df = 10$, $p = 0.84$; cosyntropin: $r = .13$, $df = 10$, $p = 0.70$).

DISCUSSION

These findings suggest that the blunted glucocorticoid response observed in recently abstinent alcohol-dependent subjects is not significantly influenced by a genetic vulnerability to alcohol-dependence. The absence of a relationship between a FH of alcoholism and glucocorticoid hyporeactivity is consistent with a number of studies demonstrating adrenocortical responses either increased or no different in FH+ relative to FH- subjects (24, 28–30). Junghanns et al. (20) has also reported that an attenuated cortisol response to a public speaking stressor in alcohol-dependent subjects was not associated with a family history of alcoholism.

The resolution of HPA axis dysregulation with abstinence (9, 32) further supports the causal relationship between heavy drinking and adrenocortical suppression rather than premorbid influences. In a recent study, for example, Coiro et al. (9) assessed the cortisol response to exercise in alcohol-dependent patients at 4, 6, and 8 weeks abstinence. A markedly suppressed adrenocortical response at 4 weeks abstinence gradually normalized to control responses by 8 weeks abstinence.

Methodological weaknesses in the present study include a relatively small sample size, the combining of two different neuroendocrine challenges, and the inclusion of only male veterans in the sample population. Also, only the proband's self-report to a single question regarding a family member's alcohol problems was obtained, thus limiting our ability to

detect a history of alcoholism in any given family member. However, this methodology is similar to that used in the National Epidemiologic Survey on Alcohol and Related Conditions (NESARC) and 60% of our patient sample endorsed alcohol problems in a first- or second-degree relative. In addition, errors of omission would be expected to be relatively stable across the sample rather than only in subjects with a higher or lower glucocorticoid response.

In conclusion, our findings suggest that the blunted glucocorticoid response observed during early abstinence is not directly influenced by a family history of alcoholism. In addition to chronic alcohol use and repeated withdrawal, other experiences or disorders (i.e., trauma, stress, anxiety, depression)—either premorbid to the onset of alcohol-dependence or concurrent with chronic drinking—may also influence HPA axis activity. In addition, heightened reactivity of the HPA axis in at-risk men and women (possibly as a result of the aforementioned experiences or disorders) may culminate into blunted responsivity following alcohol- and withdrawal-induced hypercortisolemia. More sophisticated measures of genetic contributions, including genotyping, will confirm the relevance of genetic vulnerability to HPA disruption in alcoholism.

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Figure 1.

Net integrated cortisol response to oCRH or cosyntropin following high-dose dexamethasone. Columns on the left of each group reflect integrated cortisol response to oCRH infusion; columns on the right of each group reflect cortisol response to cosyntropin. For alcohol-dependent subjects: Open circles—parental FH of alcoholism. Gray circles—1st or 2nd degree FH of alcoholism, no parental FH. Black circles—no FH of alcoholism.

Figure 2. Association between net integrated cortisol response following oCRH or cosyntropin and familial loading of alcoholism. $r = .09$, $df = 21$, $p = .70$.