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Suppression of the HPA Axis Stress-Response: Implications for Relapse

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Abstract

This article presents the proceedings of a symposium held at the meeting of the International Society for Biomedical Research on Alcoholism (ISBRA) in Mannheim, Germany, in October 2004. This symposium explored the potential role of hypothalamic-pituitary-adrenal (HPA) axis dysregulation upon relapse. HPA axis stimulation induces the release of the glucocorticoid cortisol, a compound with profound effects upon behavior and emotion. Altered stress-responses of the HPA axis in abstinent alcohol-dependent subjects, therefore, may influence their affective and behavioral regulation, thus impacting their potential for relapse. Bryon Adinoff began the symposium with a review of HPA axis dysfunction in alcohol-dependent subjects, including recent studies from his lab demonstrating an attenuated glucocorticoid response to both endogenous and exogenous stimulation in one-month abstinent men. Klaus Junghanns presented his work demonstrating that a blunted ACTH or cortisol response to subjective stressors (social stressor or alcohol exposure) is predictive of a return to early drinking. The final two presenters examined the interaction between naltrexone and HPA responsiveness in alcohol-dependent or at-risk subjects, as naltrexone induces an increase in ACTH and cortisol. Falk Kiefer discussed the relationship between basal HPA axis responsivity and clinical outcome following treatment with naltrexone or acamprosate. Plasma ACTH significantly decreased over the course of the study in the medication groups, but not the placebo group. Lower basal concentrations of ACTH and cortisol were associated with quicker relapse in the placebo group only. Suchitra Krishnan-Sarin described her preliminary work, in which family-history positive (FH+) and family history negative (FH-) subjects were administered naltrexone, followed by an assessment of alcohol-induced craving. The cortisol response to alcohol was significantly and inversely related to craving in the FH+, but not the FH-, subjects. Alterations in HPA axis responsivity may therefore have a negative impact upon clinical outcome in alcohol-dependent subjects, and disinhibition of the axis with medication may have therapeutic potential.

Keywords

Adrenal Cortex; Alcoholism; Pituitary-Adrenal System; Naltrexone

Hypothalamic-pituitary-adrenal (HPA AXIS) activation is a key component of the physiological response to stress, particularly stress accompanied by anxiety or fear. Stress initiates a cascade of events, beginning with central nervous system stimulation of

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hypothalamic corticotropin releasing hormone (CRH), which, in turn, increases secretion of pituitary adrenocorticotropin (ACTH) and finally glucocorticoid (cortisol, in humans) production from the adrenal glands. Acute and chronic alcohol intoxication (Adinoff et al., 2003; Mendelson and Stein, 1966) as well as alcohol withdrawal (Adinoff et al., 1991; Keedwell et al., 2001; Mendelson et al., 1971) all produce a robust increase in cortisol. Resolution of the withdrawal syndrome, however, is quickly followed by normalized or low basal levels of cortisol. More notable, however, is the suppression of pituitary-adrenal responsiveness evident in recently abstinent alcohol-dependent subjects. Hyporesponsiveness of the axis is observed in reaction to psychological stressors as well as pharmacologic and neuroendocrine provocation (see next section).

The end-product of HPA axis stimulation, cortisol, has a profound influence upon behavior and emotion. The altered HPA response to stress in abstinent alcohol-dependent subjects, therefore, may have a significant influence upon their affective and behavioral regulation, thus potentially impacting their vulnerability for relapse. Persistent changes in cortisol release may also alter central nervous system feedforward and feedback setpoints, altering emotional responsivity even in the absence of stress, and the subjective response to alcohol reward may be effected by cortisol's modulation of mesolimbic dopaminergic transmission (Barrot et al., 2000).

This symposium brought together investigators from the United States and the host-country, Germany, who are exploring the relationship between pituitary-adrenal reactivity and alcohol relapse. It was hoped that this symposium would highlight the clinical importance of HPA axis disruption during abstinence, encouraging the inclusion of HPA axis responsivity in future studies of relapse vulnerability and suggesting a promising target for medication development. The first presentation by Bryon Adinoff reviews HPA axis dysfunction in abstinent alcohol-dependent subjects, including recent studies from his lab. This review is followed by three studies exploring the association of HPA axis functioning with clinical measures of relapse and craving. Klaus Junghanns presents his work assessing both ACTH and cortisol responsivity to subjective stressors (social stressor or alcohol exposure) as a predictor of return to early drinking. The final two presenters explore the relationship between alterations in HPA axis responsiveness and the clinical response to the opioid antagonist naltrexone. This interaction is of particular interest as naltrexone, a medication used to prevent alcohol relapse, induces an increase in ACTH and cortisol. Falk Kiefer will discuss the relationship between basal HPA axis responsivity and clinical outcome following treatment with naltrexone or acamprosate, and Suchitra Krishnan-Sarin presents her work examining the interaction of alcohol-induced cortisol release, family history, alcohol craving, and naltrexone treatment.

BLUNTED ADRENOCORTICAL RESPONSIVENESS IN ABSTINENT ALCOHOL-DEPENDENT MEN

Bryon Adinoff

An array of pharmacological and endocrine challenges, including alcohol (Merry and Marks, 1972), nicotine (Coiro and Vescovi, 1999), insulin (Chalmers et al., 1978; Costa et al., 1996), m-chlorophenylpiperazine (mCPP) (Krystal et al., 1996), naloxone (Inder et al., 1995), ovine or human CRH (oCRH or hCRH, respectively) (Adinoff et al., 1990; Bardeleben and Holsboer, 1988; Costa et al., 1996; Ehrenreich et al., 1997; Inder et al., 1995; Wand and Dobs, 1991), and cosyntropin (exogenous ACTH) (Knudsen et al., 1987; Margraf et al., 1967; Wand and Dobs, 1991), induce an attenuated response of plasma ACTH and/or cortisol in alcohol-dependent subjects relative to controls. A similarly muted response is observed in response to psychological and physical stressors, such as operative trauma (Margraf et al., 1967), cold pressor (Errico et al., 1993), public speaking (Lovallo et al., 2000), and hyperthermia (Vescovi

et al., 1997). The consistency of this work is confounded, however, by uncertainties over the specific level of axis disruption (hypothalamus, pituitary, adrenals, or feedback receptors), ceiling effects of adrenal response, the temporal persistence of axis disruption, and complicating issues of other psychiatric and substance abuse diagnosis.

In a series of studies designed to define the specific level(s) of organizational disruption in HPA axis responsiveness (Adinoff et al., 2005a; 2005b), two groups of one-month abstinent alcohol-only male subjects ($n = 10$ or 11 per group) were assessed with various neuroendocrine stimuli and compared to age-similar controls (30 to 50 y/o). Alcohol-dependent subjects were on no medications known to interact with the endocrine or central nervous systems, had no lifetime history of other Axis I disorders, and no other substance use disorder (other than nicotine) in the previous twelve months. In one group, basal concentrations of ACTH and cortisol were obtained every ten minutes from 8 AM to 8 PM to assess for pulsatility and axis sensitivity was assessed following the intravenous injection of oCRH (0.4 μg/kg) and naloxone (0.125 mg/kg) at 8 PM (separated by 48 hr). In the other group, basal ACTH and cortisol concentrations were obtained from 8 PM to 8 AM and plasma cortisol was assessed following the intravenous administration of cosyntropin (0.01 μg/kg) at 8 AM. Adrenocortical sensitivity was also assessed in the relative absence of endogenous ACTH by suppressing pituitary secretion with high-dose dexamethasone (8 mg IV) at 11 PM prior to cosyntropin administration.

Abstinent alcohol-dependent subjects demonstrated significantly lower cortisol ($p = 0.05$), but not ACTH, concentrations in the early morning and cortisol pulse amplitude was decreased between 8 PM and 8 AM ($p < 0.05$). In response to oCRH, the net integrated cortisol response was lower in abstinent subjects compared to controls ($p < 0.01$), although the ACTH response did significantly differ between groups (Adinoff et al., 2005b). The net integrated cortisol response to cosyntropin was suppressed in alcohol-dependent subjects following endogenous ACTH suppression by high-dose dexamethasone ($p < 0.04$), but not without dexamethasone pretreatment. Mean ACTH ($p < 0.004$) and cortisol ($p < 0.05$) concentrations in response to dexamethasone were decreased in the patients compared to controls (Adinoff et al., 2005a). Surprisingly, the ACTH and cortisol response to naloxone did not significantly differ between groups. In general, these findings further confirm HPA axis hyporeactivity in alcohol-dependent subjects, and suggest that the defect in the HPA axis following four weeks of abstinence is isolated at the level of the adrenal axis. Furthermore, a nonhomeostatic accentuation of pituitary glucocorticoid inhibition may further exaggerate adrenocortical hyposensitivity.

BLUNTED HPA AXIS RESPONSE IS ASSOCIATED WITH AN INCREASED RISK OF EARLY RELAPSE

Klaus Junghanns

The risk of relapse in alcohol-dependent patients and HPA axis responsiveness was explored in two separate studies. In the first study, a standardized psychosocial stressor of public speaking, the Trier Social Stress Test (TSST) (Kirschbaum et al., 1992), was applied to 36 alcohol dependent male inpatients and 15 age-matched controls. Half of the alcohol-dependent subjects also had a comorbid anxiety disorder. HPA responsivity was assessed by serum ACTH and cortisol at several time points before and after the TSST. While there was no difference between the two groups of alcohol-dependent subjects (with and without an anxiety disorder), both the ACTH and cortisol stress response was lower among both of these groups compared to the control group (area under curve, ANOVA with Bonferroni post hoc test: $p < 0.05$) (Junghanns et al., 2003). Thirty-one of the alcohol dependent patients were reassessed for relapse six weeks after discharge from hospital. Thirteen patients, or 42%, had relapsed at the

six-week follow-up. Relapsers demonstrated a significantly lower cortisol response to the TSST than the controls (ANOVA with Bonferroni post hoc test: $p < 0.05$) and a significantly lower ACTH-response when compared to abstainers (ANOVA with Bonferroni post hoc test: $p < 0.05$).

To further explore the relationship between cortisol reactivity and relapse, the cortisol response to an alcohol cue-exposure (CE) and subsequent relapse was assessed in 32 alcohol-dependent men and women (Junghanns et al., 2005). Six CE experiments were performed over a three-week period. In the first (week one) and fifth session (week three), subjects were assessed for their salivary cortisol response after explanation of the CE procedure (basal) and after the CE session itself. Furthermore, a resting measure of salivary cortisol was obtained in week one and week three. Six weeks after discharge from inpatient treatment, patients were assessed for relapse by personal interview and laboratory assessment. Fifty-three percent of the subjects were considered relapsers, including ten reassessed patients and seven patients who did not show for follow-up. ANOVA with repeated measurements yielded a significant Time and Time × Group effect for the two investigated sessions combined (Time effect: $F = 10.04$, $p < 0.001$; Time × Group effect: $F = 3.44$, $p < 0.05$). The basal salivary cortisol was higher than cortisol at the end of the sessions, probably due to expectancy effects stimulating cortisol secretion more than CE itself. Relapsed subjects showed a significantly lower basal salivary cortisol concentration in week three (post hoc t-test, $T = 2.79$, $p < 0.01$). While subjective experiences were not correlated with relapse, expectancy of an enhancement of social contacts through alcohol (i.e., factor 1 of the Brief Alcohol Expectancy Questionnaire, B-AEQ) (Demmel and Hagen, 2003) correlated negatively with the decline found in salivary cortisol in week three (Spearman's rho = 0.44, $p = 0.019$).

In both studies, an attenuation of cortisol response during early abstinence was associated with an increased risk of relapse within the follow up period. These findings support the hypothesis that a derangement of HPA reactivity during early abstinence from alcohol may play a role in the (dis)ability of patients to stay sober.

HPA-AXIS ACTIVATION AS A KEY MECHANISM OF PHARMACOLOGICAL ANTI-CRAVING TREATMENT?

Falk Kiefer

Naltrexone, a medication efficacious in the treatment of alcohol dependence, stimulates CRH release via disinhibition of CRH containing neurones in the paraventricular nucleus. It has therefore been suggested that the efficacy of naltrexone in relapse prevention may, in part, reflect its ability to heighten hypothalamic tone (Adinoff et al., 1998). In a recent study of naltrexone in nontreatment seeking alcohol-dependent subjects, increased plasma cortisol following naltrexone was associated with a lower intensity of craving for alcohol (O'Malley et al., 2002). As our study comparing the efficacy of naltrexone, acamprosate, combined naltrexone/acamprosate, and placebo in 160 recently detoxified alcohol-dependent patients revealed an apparent superiority of naltrexone over acamprosate in promoting abstinence over 12 weeks (Kiefer et al., 2003), we hypothesized that the heightened efficacy of naltrexone may have been due to its effect upon the HPA axis.

To explore this hypothesis, four PM plasma concentrations of ACTH and cortisol were obtained from unrelapsed patients during initial assessment and at study week four, eight, and 12. Patients relapsing to alcohol were terminated from the study. Changes in ACTH and cortisol over time were assessed, as well as the relationship between plasma ACTH and cortisol with abstinence duration.

Plasma ACTH decreased significantly from baseline to week 12 in the placebo group, but not during active treatment with naltrexone, acamprosate, or both compounds combined (Kiefer et al., 2002). After 12 weeks of treatment, ACTH was significantly higher in the naltrexone group and in the combined treatment group compared to placebo. Also, in the acamprosate group a trend emerged toward increased plasma ACTH after 12 weeks compared to placebo. Similar changes were observed with cortisol. In the placebo group, cortisol decreased significantly from baseline until week 12. In contrast, during treatment with naltrexone or combined medication no decrease was detectable, and cortisol was significantly elevated relative to placebo at week 12. Again, a trend toward increased cortisol was also detected in the acamprosate group.

Thus, both ACTH and cortisol were shown to be higher in those treatment groups that were associated with a lowered probability of relapse (i.e., naltrexone alone and combined with medication). Moreover, a direct relation with abstinence duration was also observed. The subanalysis of the placebo-treated patients revealed basal concentrations of serum cortisol and ACTH that were significantly lower in those patients that subsequently relapsed than in those that remained abstinent (*t*-test; $p < 0.05$; Kiefer et al., 2002). Moreover, no such association was detectable in groups that received the active treatments. Since the risk of early relapse associated with low basal cortisol occurred only in the placebo group, one might surmise that efficacy of anticraving treatment was directly associated with its ability to heighten HPA-activity in alcohol-dependent patients. The additional observation that basal plasma cortisol positively correlated with shortened abstinence duration supports this hypothesis.

HPA AXIS RESPONSIVITY AND ALCOHOL DRINKING: INTERACTIVE EFFECTS OF FAMILY HISTORY OF ALCOHOLISM AND NALTREXONE TREATMENT

Suchitra Krishnan-Sarin

Alcohol drinking behavior is influenced by both genetic factors (i.e., family history of alcoholism) and environmental factors (i.e., stress exposure). There is a great deal of interest in determining the interactive effects of these factors in mediating continued drinking behavior as well as relapse to drinking. Importantly, when compared those subjects having a negative family history of alcoholism (FH-), individuals with a positive family history of alcoholism (FH +) have lower HPA axis responses both to alcohol and stress (Dai et al., 2002; Schuckit, 1988) and to challenges with an opioid antagonist (Wand et al., 1999),

Previous research conducted by our group showed that pretreatment with 50 mg naltrexone/day for six days resulted in an augmentation of basal (un-stimulated) and alcohol-induced cortisol levels in a small sample of alcohol dependent, heavy drinking individuals participating in an alcohol self-administration paradigm (O'Malley et al., 2002). Moreover, cortisol levels were also inversely related to craving for alcohol, as measured using the Alcohol Urge Questionnaire (AUQ) (Bohn et al., 1995). In the current project, we have replicated and extended these findings to examine changes in cortisol levels produced by different doses of naltrexone in FH+ and FH- individuals. 72 alcohol-dependent, nontreatment seeking participants (23 FH+, 49 FH-; 16 females, 56 males) consuming between 20 and 50 drinks/week at baseline (20–45 for females, 25–50 for males) received one of three doses of naltrexone (0, 50 and 100 mg/day) for a six-day period. On the sixth day subjects participated in an alcohol-drinking paradigm which was conducted at the General Clinical Research Center (GCRC) of Yale-New Haven Hospital. During these sessions participants were given a priming drink of alcohol (0.03 g/dl) at 4 PM, following which they were exposed to two consecutive, one-hour choice periods at 4:50 PM and 6 PM. During each choice period, participants were offered the choice of consuming four drinks (0.015 g/dl each) or receiving $3 in exchange for each drink.

Alcohol Craving was measured using the AUQ every 10 min during the priming dose period and then every half hour during the self-administration period. Blood samples to determine cortisol levels were obtained at baseline prior to alcohol consumption, every ten minutes for forty minutes following the priming drink, and every half-hour thereafter during the two one-hour choice drinking periods. Cortisol samples were analyzed using the "Direct 125-I RIA kit" (Diagnostic Products Corporation, Los Angeles, CA) at the GCRC Core Laboratory.

Preliminary analyses suggest that family history of alcoholism is an important predictor of response to naltrexone. Significantly, greater reductions in total number of drinks consumed were observed during the choice period in FH+ when compared with FH- participants ($p < 0.05$). Preliminary analyses with total AUQ scores (summarized using Area Under the Curve or AUC values) during the priming dose period indicates a trend toward a FH treatment interaction ($p = 0.096$), with FH+ individuals experiencing dose-dependent decreases in craving, an effect that was not seen in FH- individuals. We did not observe any significant naltrexone-induced changes in baseline or alcohol-stimulated cortisol levels. However, during the priming dose period, total cortisol release (as summarized by AUC values) was significantly and inversely related to AUC AUQ scores in FH+ subjects ($r = -0.66$, $p < 0.05$); in FH- individuals, this relationship, while in the same direction ($r = -0.22$, NS), was attenuated and not significant. These intriguing and very preliminary results suggest a potential role for cortisol in altering craving for alcohol, especially in alcohol dependent individuals with a positive family history of alcoholism. However, these results should be interpreted with caution considering the small sample size of FH+ individuals and need to be replicated in a larger sample. Moreover, future experiments should be designed to examine whether cortisol has a causal or proximal influence on alcohol craving.

SUMMARY

These findings offer preliminary confirmation that the well-documented impairment in HPA axis responsivity in recently abstinent alcohol-dependent subjects has a significant negative impact upon subsequent clinical outcome. Although these associations suggest a relationship between neuroendocrine changes and alcohol-related behaviors, they do not yet demonstrate causality. It is also uncertain whether it is basal cortisol, stimulated cortisol, feedback responses, or a combination that is the critical association, whether attenuation of the axis is a consequence of drinking or is a marker for vulnerability, or how long these alterations persist upon abstinence. The affective and biological route from subdued pituitary-adrenal release to increased drinking is also unanswered, as these changes may affect mood and anxiety symptoms, dopaminergic release in the nucleus accumbens, and/or hippocampal and amygdalar activation. Finally, the relationship between cortisol and relapse may be an epiphenomenon, related to the coproduction of GABAergic neurosteroids, which alter drinking behavior in preclinical studies (Morrow et al., 2001). These hypotheses offer several potential avenues of investigation for understanding the biological and affective underpinnings of relapse as well as targets for medication development.

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References

Adinoff B, Iranmanesh A, Veldhuis JD, Fisher L. Disturbances of the stress response: The role of the HPA axis during alcohol withdrawal and abstinence. Alcohol Health Res World 1998;22(I):67–72. [PubMed: 15706736]

Adinoff B, Krebaum SR, Chandler PA, Ye W, Brown MB, Williams MJ. Dissection of the hypothalamic-pituitary-adrenal axis pathology in one-month abstinent alcohol-dependent men: 1. Adrenocortical and pituitary glucocorticoid responsiveness. Alcohol Clin Exp Res. 2005ain press

Adinoff B, Krebaum SR, Chandler PA, Ye W, Brown MB, Williams MJ. Dissection of the hypothalamic-pituitary-adrenal axis pathology in one-month abstinent alcohol-dependent men: 2. Response to oCRH and naloxone. Alcohol Clin Exp Res. 2005bin press

Adinoff B, Martin PR, Bone GHA, Eckardt MJ, Roehrich L, George DT, Moss HB, Eskay R, Linnoila M, Gold PW. Hypothalamic-pituitary-adrenal axis functioning and cerebrospinal fluid corticotropin releasing hormone and corticotropin levels in alcoholics after recent and long-term abstinence. Arch Gen Psychiatry 1990;47:325–330. [PubMed: 2157379]

Adinoff B, Risher-Flowers D, De Jong J, Ravitz B, Bone GHA, Nutt DJ, Roehrich L, Martin PR, Linnoila M. Disturbances of hypothalamic-pituitary-adrenal axis functioning during ethanol withdrawal in six men. Am J Psychiatry 1991;148:1023–1025. [PubMed: 1853950]

Adinoff B, Ruether K, Krebaum S, Iranmanesh A, Williams MJ. Increased salivary cortisol concentrations during chronic alcohol intoxication in a naturalistic clinical sample of men. Alcohol Clin Exp Res 2003;27(9):1420–1427. [PubMed: 14506402]

Bardeleben UV, Holsboer F. Human corticotropin releasing hormone: Clinical studies in patients with affective disorders, alcoholism, panic disorder and in normal controls. Prog Neuropsychopharmacol Biol Psychiatry 1988;12:S165–S187. [PubMed: 2854897]

Barrot M, Marinelli M, Abrous DN, Rouge-Pont F, Le Moal M, Piazza PV. The dopaminergic hyper-responsiveness of the shell of the nucleus accumbens is hormone-dependent. Eur J Neurosci 2000;12 (3):973–979. [PubMed: 10762327]

Bohn MJ, Krahn DD, Staehler BA. Development and initial validation of a measure of drinking urges in abstinent alcoholics. Alcohol Clin Exp Res 1995;19(3):600–606. [PubMed: 7573780]

Chalmers RJ, Bennie EH, Johnson RH, Masterton G. Growth hormone, prolactin, and corticosteroid responses to insulin hypoglycaemia in alcoholics. BMJ 1978;1(6115):745–748. [PubMed: 630327]

Coiro V, Vescovi PP. Effect of cigarette smoking on ACTH/cortisol secretion in alcoholic after short- and medium-term abstinence. Alcohol Clin Exp Res 1999;23(9):1515–1518. [PubMed: 10512318]

Costa A, Bono G, Martignoni E, Merlo P, Sances G, Nappi G. An assessment of hypothalamo-pituitary-adrenal axis functioning in non-depressed, early abstinent alcoholics. Psychoneuroendocrinology 1996;21:263–275. [PubMed: 8817725]

Dai X, Thavundayil J, Gianoulakis C. Response of the hypothalamic-pituitary-adrenal axis to stress in the absence and presence of ethanol in subjects at high and low risk of alcoholism. Neuropsychopharmacology 2002;27(3):442–452. [PubMed: 12225701]

Demmel, R.; Hagen, J. Eine gekürzte deutschsprachige Version des Alcohol Expectancy Questionnaire (Brief AEQ-G) [An abbreviated German version of the Alcohol Expectancy Questionnaire (Brief AEQ-G)]. In: Glockner-Rist, A.; Rist, F.; Kufner, H., editors. Elektronisches Handbuch zu Erhebungsinstrumenten im Suchtbereich (EHES) [Electronic handbook of assessment instruments in addiction], Version 3.00. Zentrum fuer Umfragen, Methoden und Analysen; Mannhiem: 2003.

Ehrenreich H, Schuck J, Stender N, Pilz J, Gefeller O, Schilling L, Poser W, Kaw S. Endocrine and hemodynamic effects of stress versus systemic CRF in alcoholics during early and medium term abstinence. Alcohol Clin Exp Res 1997;21(7):1285–1293. [PubMed: 9347091]

Errico AL, Parson OA, King AC, Lovallo WR. Attenuated cortisol response to biobehavioral stressors in sober alcoholics. J Stud Alcohol 1993;54:393–398. [PubMed: 8341041]

Inder WJ, Joyce PR, Ellis MJ, Evans MJ, Livesey JH, Donald RA. The effects of alcoholism on the hypothalamic-pituitary-adrenal axis: interaction with endogenous opioid peptides. Clin Endocrinol (Oxf) 1995;43(3):283–290. [PubMed: 7586596]

Junghanns K, Backhaus J, Tietz U, Lange W, Bernzen J, Wetterling T, Rink L, Driessen M. Impaired serum cortisol stress response is a predictor of early relapse. Alcohol Alcohol 2003;38(2):189–193. [PubMed: 12634269]

Junghanns K, Tietz U, Dibbelt L, Kuether M, Jurth R, Ehrenthal D, Blank S, Backhaus J. Attenuated salivary cortisol secretion under cue exposure is associated with early relapse. Alcohol Alcohol 2005;40(1):80–85. [PubMed: 15550447]

Keedwell PA, Poon L, Papadopoulos AS, Marshall EJ, Checkley SA. Salivary cortisol measurements during a medically assisted alcohol withdrawal. Addict Biol 2001;6(3):247–256. [PubMed: 11900603]

Kiefer F, Jahn H, Schick M, Wiedemann K. Alcohol self-administration, craving and HPA-axis activity: an intriguing relationship. Psychopharmacology 2002;164(2):239–240. [PubMed: 12404089]

Kiefer F, Jahn H, Tarnaske T, Helwig H, Briken P, Holzbach R, Kampf P, Stracke R, Baehr M, Naber D, Wiedemann K. Comparing and combining naltrexone and acamprosate in relapse prevention of alcoholism: a double-blind, placebo-controlled study. Arch Gen Psychiatry 2003;60(1):92–99. [PubMed: 12511176]

Kirschbaum C, Wust S, Hellhammer D. Consistent sex differences in cortisol responses to psychological stress. Psychosom Med 1992;54(6):648–657. [PubMed: 1454958]

Knudsen GM, Christensen H, Benld D, Melgaard B, Kirkegaard C, Has-selbalch H. Discordance between the cortisol response to insulin-hypoglycemia and 30-minute ACTH stimulation test in chronic alcoholic men. Alcohol Clin Exp Res 1987;11:323–325. [PubMed: 2820261]

Krystal JH, Webb E, Cooney NL, Kranzler HR, Southwick SW, Heninger GR, Charney DS. Serotonergic and noradrenergic dysregulation in alcoholism: m-chlorophenylpiperazine and yohimbine effects in recently detoxified alcoholics and healthy comparison subjects. Am J Psychiatry 1996;153(1):83–92. [PubMed: 8540598]

Lovallo WR, Dickensheets SL, Myers DA, Thomas TL, Nixon SJ. Blunted stress cortisol response in abstinent alcoholic and polysubstance-abusing men. Alcohol Clin Exp Res 2000;24(5):651–658. [PubMed: 10832906]

Margraf HW, Moyer CA, Ashford LE, Lavalle LW. Adrenocortical function in alcoholics. J Surg Res 1967;7(2):55–62. [PubMed: 4289157]

Mendelson JH, Ogata M, Mello NK. Adrenal function and alcoholism I. serum cortisol. Psychosom Medicine 1971;33:145–157.

Mendelson JH, Stein S. Serum cortisol levels in alcoholic and nonalcoholic subjects during experimentally induced ethanol intoxication. Psychosom Med 1966;XXVIII:616–626.

Merry J, Marks V. The effect of alcohol, barbiturate, and diazepam on hypothalamic, pituitary/adrenal function in chronic alcoholics. The Lancet 1972;2:990–992.

Morrow AL, VanDoren MJ, Penland SN, Matthews DB. The role of GABAergic neuroactive steroids in ethanol action, tolerance and dependence. Brain Res Brain Res Rev 2001;37(1–3):98–109. [PubMed: 11744078]

O'Malley SS, Krishnan-Sarin S, Farren C, Sinha R, Kreek J. Naltrexone decreases craving and alcohol self-administration in alcohol-dependent subjects and activates the hypothalamo-pituitary-adrenocortical axis. Psychopharmacology (Berl) 2002;160(1):19–29. [PubMed: 11862370]

Schuckit MA. Reactions to alcohol in sons of alcoholics and controls. Alcohol Clin Exp Res 1988;12(4):465–470. [PubMed: 3056066]

Vescovi PP, DiGennaro C, Coiro V. Hormonal (ACTH, cortisol, beta-endorphin, and met-enkephalin) and cardiovascular responses to hyperthermic stress in chronic alcoholics. Alcohol Clin Exp Res 1997;21(7):1195–1198. [PubMed: 9347078]

Wand GS, Dobs AS. Alterations in the hypothalamic-pituitary-adrenal axis in actively drinking alcoholics. J Clin Endocrinol Metab 1991;72(6):1290–1295. [PubMed: 2026749]

Wand GS, Mangold D, Ali M. Adrenocorticotropin responses to naloxone in sons of alcohol-dependent men. J Clin Endocrinol Metab 1999;84(1):64–68. [PubMed: 9920063]