Is withdrawal-induced anxiety in alcoholism based on beta-endorphin deficiency?

Falk Kiefer · Mirko Horntrich · Holger Jahn · Klaus Wiedemann

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Abstract Rationale: Associations between several psychopathological alterations and lowered beta-endorphin (betaE) plasma levels have already been stated in former studies. However, whereas single measures during static conditions generally failed in linking betaE levels with psychopathology, dynamic changes of betaE in particular have been shown to be associated with spells of anxiety and depression. During alcohol withdrawal, a decreased secretion of betaE with a delayed normalization has been reported, but up to now only few data became available regarding the interaction of plasma betaE and psychopathological parameters. Objectives: The aim of our study was to test the hypothesis whether betaE during acute alcohol withdrawal is associated with anxiety, depression, and craving. Methods: We observed self-rated anxiety, depression, and craving during alcohol withdrawal and assessed betaE levels (RIA) in a consecutive sample of 60 alcoholics on day 1 and day 14 after onset of withdrawal, and in 30 healthy volunteers. To control for mutual interactions of betaE and the pituitary–adrenocortical hormone secretion, plasma corticotropin (ACTH) and corticosterol were also determined. Results: In accordance with prior studies, betaE was significantly lowered on day 1 and day 14 of alcohol withdrawal relative to controls. Plasma levels of ACTH correlated significantly with betaE in alcoholics at both time points and in controls, without differing significantly between the groups. Self-rated anxiety, depression, and alcohol craving decreased significantly between day 1 and day 14. Levels of betaE were inversely correlated with anxiety day 1 (r=−0.58) and day 14 (r=−0.71). Partial correlation coefficients controlling for ACTH plasma levels revealed that this correlation was largely independent from ACTH. In addition, a significant inverse relationship was found between betaE and craving on day 14 (r=−0.28). No association appeared between betaE and depression. Conclusions: Our results give first evidence that lowered betaE during alcohol withdrawal may contribute to anxiety as a common disturbance during this state.

Keywords beta-Endorphin · Anxiety · Alcoholism · Withdrawal · HPA · Opioid

Introduction

Whereas early expectations of the impact of the opioid system for psychiatric disorders have declined in recent years, some work in this area continued successfully, especially with regard to affective disorders and addiction (Naber 1988). Associations between anxiety, depression, and beta-endorphin (betaE) plasma levels have been reported repeatedly (Leboyer 1986; Darko et al. 1992). Especially in contrast to single measures during static conditions, associations of psychopathology with dynamic changes of betaE concentrations have been shown to be relevant, e.g., during the premenstrual syndrome (Giannini et al. 1994) and in depression after dexamethasone challenges (Meador-Woodruff et al. 1987).

Also, in chronic alcoholism, an altered secretion of betaE has been described. Alcohol stimulates the release of endogenous opioids, such as betaE or enkephalins and, thus, stimulates opioid receptors indirectly (Patel and Pohorecky 1989; de Waele and Gianoulakis 1993). During the period of increasing betaE levels after alcohol consumption, subjects usually have feelings of euphoria, relaxation, and general well being (Lukas and Mendelson 1988). However, when blood alcohol exceeds these concentrations or declines, a majority of subjects experiences depression and anxiety due to decreasing betaE levels (McGuire et al. 1966). Additionally, alcohol and the use of opioid substances were suggested to be a form of self-medication to reduce anxiety, since anxiety disorders are also related to a deficiency in the endogenous opioid system (Sher 1998). However, after habituation to ethanol, the results are inconsistent. In rodents, alcohol exposure has been reported to increase (Cheng and Tseng 1982), decrease (Schulz et al. 1980) or leave...
unchanged (Seizinger et al. 1983) the brain and pituitary content of βE. Whereas chronic alcohol exposure has shown a rather blurred picture also in man, during alcohol withdrawal alcoholics consistently showed βE levels lower than normal (Aguirre et al. 1990; Vescovi et al. 1992; Inder et al. 1998; Esele et al. 2001). Moreover, Borg et al. (1982) presented evidence that βE in the cerebrospinal fluid (CSF) and depression were associated during late alcohol withdrawal. Up to now, only one small-sample study (n=22) has been conducted to study the effects of changing βE plasma levels on anxiety during alcohol withdrawal, however, without measuring craving for alcohol (Esele et al. 2001). Hence, the determination of βE plasma levels during alcohol withdrawal might be important to correlate the effects of decreased βE with psychopathology using standardized measures. The aim of our study was to prove whether βE during acute alcohol withdrawal is associated with distinct alterations regarding anxiety, depression, and craving.

### Materials and methods

#### Subjects

A sample of 60 alcoholic inpatients (44 male, 16 female, age 44.1±8.7 years) admitted consecutively to the psychiatric department for detoxification purposes was included in the study. Subjects had no psychiatric co-morbidity or substance abuse other than alcohol or nicotine. Patients fulfilled at least six of nine diagnostic criteria for dependence according to the Diagnostic and Statistical Manual of Mental Disorders, 4th edn (DSM-IV; American Psychiatric Association 1995).

Subjects suffering from delirium tremens were excluded from the study. All patients were off medication prior to the study, including neuroleptics, antidepressants, benzodiazepines, glucocorticoids, antihypertensives and hypoglycemic drugs for at least 3 months. The following data were gathered for the present investigation: years since first alcohol-related problems and first physical withdrawal symptoms occurred, number of inpatient detoxifications, amount of alcohol consumed daily, tobacco consumption, family history of alcoholism, routine laboratory parameters were drawn at 0900 hours on the 1st and 14th days following admission to the detoxification unit. Basic data were obtained with a structured interview. Anxiety was measured using a 100-mm visual analogue scale (VAS; mean intensity of anxiety or fear during the last 3 days). For the assessment of depressive symptoms, the self-rating depression scale (SDS) (Zung 1974) was used. Craving was assessed on day 1 and day 14 with the German version of the obsessive-compulsive drinking scale (OCDS; Anton et al. 1995; Mann and Ackermann 2000).

#### Hormonal measures

Blood samples were cooled and anticoagulated with ethylene diamine tetraacetic acid (EDTA). After centrifugation and separation, plasma was stored at −80°C until analysis. βE was measured in the plasma using a radioimmunometric assay (Nichols Institute, San Juan Capistrano, Calif.) adapted to our requirements. The detection limit was 15 pg/ml plasma; intra- and interassay coefficients of variation were below 10% at 250 pg/ml.

Plasma ACTH concentrations were analyzed using a radioimmunometric assay without extraction (Nichols Institute). The detection limit was 4 pg/ml plasma; intra- and interassay coefficients of variation at 20 pg/ml were below 8%.

Plasma cortisol concentrations were analyzed using a commercially available radioimmunoassay using a coated tube technique (ICN Biomedicals, Carson, Calif.). The detection limit was 0.3 ng/ml plasma; intra- and interassay coefficients of variation at 20 ng/ml and 40 ng/ml levels were below 7%.

#### Data analysis

All data were expressed as mean±SD. For the statistical analysis of group effects (inpatients day 1, day 14, and volunteers) regarding hormone levels, analysis of variance followed by post-hoc Bonferroni’s correction was applied. Whenever a significant F ratio was detected, means were compared using t-tests. To compare the patients’ psychometric data of day 1 and day 14, paired t-tests were used. Normal distribution of data was tested using the Kolmogorov-Smirnov test. Correlations were analyzed using Pearson’s correlation coefficients. Statistical significance was accepted if a P value less than 0.05 was obtained.

### Results

#### Hormonal measures

**βE**

Plasma levels of βE remained unchanged in alcoholics between day 1 (65±30 pg/ml) and day 14 (66±21 pg/ml),