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# TNF-α and IL-6 serum levels: Neurobiological markers of alcohol consumption in alcohol-dependent patients?

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A B S T R A C T

We investigated the serum levels of IL-6 and TNF-α in 30 male alcohol-dependent patients during withdrawal (day 1, 7, and 14) and compared them with the levels obtained from 18 healthy male controls. IL-6 (day 1: $T = 2{,}593$, $p = 0.013$; day 7: $T = 2{,}315$, $p = 0.037$; day 14: $T = 1{,}650$, $p = 0.112$) serum levels were significantly increased at the beginning of alcohol withdrawal. TNF-α ($T = 3{,}202$, $p = 0.03$) serum levels were significantly elevated in the patients' group during the whole period of withdrawal. IL-6 serum levels decreased significantly during withdrawal ($F = 16.507$, $p < 0.001$), whereas TNF-α levels did not change significantly (day 1–14). IL-6 serum levels were directly associated with alcohol consumption ($r = 0.392$, $p = 0.047$) on day 1. Moreover, the IL-6 serum levels were associated with alcohol craving (PACS total score day 1: $r = -0.417$, $p = 0.022$, the score of the obsessive subscale of the OCDS on day 14 [$r = -0.549$, $p = 0.022$]), depression ($r = -0.507$, $p = 0.005$), and trait anxiety ($r = -0.674$, $p < 0.001$) on day 1. We found an association with the duration of active drinking following the last period of abstinence and the TNF-α serum levels (day 1:$r = 0.354$, $p = 0.009$; day 7: $r = 0.323$, $p = 0.022$; day 14: $r = 0.303$, $p = 0.034$) as well as an association with the severity of alcohol dependence measured by the SESA scale ($r = 0.454$, $p = 0.015$). Moreover, we found a significant association between the BDNF serum levels and the TNF-α serum levels ($r = -0.426$, $p = 0.021$). Our results support an association between alterations in TNF-α and IL-6 serum levels and alcohol consumption.

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## Introduction

Recent preclinical study results suggest a central induction of proinflammatory cytokines during alcohol withdrawal (Freeman et al., 2012) within brain regions that regulate emotions.

Consistent with such observations, alterations in the expression of the proinflammatory cytokines interleukin-6 (IL-6) and tumor necrosis factor-α (TNF-α) were found to be associated with affective symptoms in clinical studies (Dantzer, O'Connor, Freund, Johnson, & Kelley, 2008; Zunszain, Hepgul, & Pariante, 2013). For example, Fumaz and colleagues (Fumaz et al., 2012) found a positive correlation between self-reported anxiety, psychological stress, and peripheral blood levels of IL-6 and TNF-α in HIV-infected patients. Moreover, Kiecolt-Glaser and colleagues (Kiecolt-Glaser et al., 2012) reported that treatment with omega-3 polyunsaturated fatty acids decreased the level of self-reported anxiety and lipopolysaccharide (LPS) induced IL-6 release, suggesting a potential link between anxiety and IL-6 release in healthy persons. A possible explanation for the link between affective symptoms and cytokine release is offered by pre-clinical study results, which show that cytokine release may impact the reactivity of the hypothalamic-pituitary-adrenal (HPA) axis: Salome and colleagues showed in an animal model a reciprocal association between low basal IL-6 levels, IL-6 release following an LPS challenge, and consecutive activation of the HPA (Salome et al., 2008). In their study, the total change in IL-6 release was related to the strength of the consecutive HPA activation. These results suggest that low basal IL-6 levels may be inversely associated with the intensity of negative emotions in stress situations reasoned by its relation to HPA activity.

Consistent with a possible association of cytokine release and stress regulation, IL-6 blood levels were reported to decrease during alcohol abstinence (Zgierska et al., 2008), and IL-6 and TNF-α levels were linked to affective symptoms in alcohol-dependent patients. In particular, the peripheral blood levels of TNF-α and IL-6 were found to be positively correlated with depressive symptoms and craving (Leclercq et al., 2012) during alcohol withdrawal. Moreover, TNF-α release was linked to the duration of abstinence in alcohol-

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dependent patients (Kiefer, Jahn, Schick, & Wiedemann, 2002). Although the mechanisms by which cytokine release may impact alcohol consumption are rather unclear, preclinical study results offer a putative explanation by reporting a linkage between the release of TNF-α and IL-6 and the expression of neurotrophic growth factors such as brain-derived neurotrophic growth factor (BDNF) (Huang et al., 2014). Neurotrophic growth factors have previously been associated with the symptomatology of various addictive diseases. In particular, we found a direct association between BDNF serum levels and craving in a sample of opiate-dependent patients (Heberlein et al., 2011), whereas we could confirm (Heberlein, Muschler, Wilhelm, et al., 2010) results reported by other study groups regarding a linkage of BDNF serum levels and withdrawal intensity (Huang et al., 2008) in alcohol-dependent patients. Even more important, clinical study results point toward a possible role of high BDNF serum levels protecting against relapse in abstinent alcohol-dependent patients (Costa, Girard, Dalmay, & Malauzat, 2011), implicating a possible cross-talk between cytokines, i.e., TNF-α release, and BDNF expression regarding alcohol consumption.

With respect to these study results, we hypothesized a possible interaction between the proinflammatory cytokines and BDNF serum expression, as well as a possible association of these cytokines with the symptomatology of alcohol withdrawal.

Regarding the study results reviewed above we hypothesized 1) alterations in the expression of TNF-α and IL-6 during alcohol withdrawal, 2) associations between the 2 cytokines and affective symptoms of alcohol withdrawal, and 3) a possible link to the expression of the neurotrophic growth factor BDNF. Therefore we aimed to investigate 1) alterations of IL-6 and TNF-α blood levels in alcohol-dependent patients compared with healthy controls, 2) the course of IL-6 and TNF-α during alcohol withdrawal, 3) a possible association with serum levels of the neurotrophic growth factor BDNF, and 4) possible associations with psychometric dimensions of alcohol dependence and withdrawal, e.g., anxiety, depression, and alcohol craving.

## Materials and methods

The present study was part of a large prospective research project (Studies in Neuroendocrinology and Neurogenetics in Alcoholism [NENA]) (Heberlein, Muschler, Lenz, et al., 2010) that was approved by the local Ethics Committee of the Friedrich-Alexander-University of Erlangen-Nuremberg. The investigation was conducted in accordance with the Declaration of Helsinki. Each participant gave written informed consent. In total, we investigated the IL-6 and TNF-α serum levels of 30 male patients who suffered from alcohol dependence according to ICD 10 and DSM IV. All patients were admitted for detoxification treatment (Klinik für Psychiatrie, Psychotherapie und Psychosomatik, Bezirksklinikum Obermain, Kutzenberg, Germany). All patients who participated in this study were active smokers. All patients were treated with carbamazepine and clomethiazole during alcohol withdrawal. Table 1 shows the mean and standard deviation (SD) of the carbamazepine and clomethiazole dosages. Patients with concomitant psychiatric illnesses, substance abuse apart from alcohol or nicotine, existence of severe somatic illnesses (in particular patients suffering from any type of cancer), known autoimmune diseases, or known HPA axis deregulations were not enrolled in the study. Also, patients with a positive history of cerebral damage (e.g., ischemia or cerebral hemorrhage) were excluded. All patients underwent a detailed physical examination, routine laboratory testing, and urine drug screening.

Breath alcohol concentration (BAC) was measured on admission and during alcohol withdrawal using the alcohol breath analyzer (Draeger, Dietikon, CH). Additional data such as age, body mass index (BMI), years of drinking (YD), and daily intake of alcohol in grams (DI) were obtained by interview. Data regarding affective symptoms were collected by the Beck's Depression Inventory (BDI) (Beck, Ward, Mendelson, Mock, & Erbaugh, 1961) and the State and Trait Anxiety Inventory (STAI I and STAI II) (Spielberger, Gorusch, & Lushene, 1970). Intensity of alcohol craving was measured by the Obsessive and Compulsive Drinking Scale (OCDS) (Anton, Moak, & Latham, 1995). Severity of alcohol withdrawal was measured by the Clinical Institute Withdrawal Assessment for Alcohol (CIWA Ar) (Sullivan, Sykora, Schneiderman, Naranjo, & Sellers, 1989). Severity of alcohol dependence was assessed by the SESA questionnaire and its subscales (John, Hapke, & Rumpf, 2003). The subscales of the SESA questionnaire measure narrowing of the drinking repertoire (SESA XE), somatic withdrawal symptoms (SESA XK), alcohol consumption to avoid withdrawal symptoms (SESA XV), psychological withdrawal symptoms (craving) (SESA XP), increase of tolerance (SESA XT), extreme increase of tolerance (SESA XTE), and decrease of tolerance (SESA XTU).

Psychometric measurements of affective symptoms of alcohol withdrawal were taken once a day on day 1, day 7, and day 14.

As a control group, we enrolled randomly selected healthy men ($n = 18$) who did not suffer from any current somatic disease. Controls were screened for alcohol dependence and abuse using the CAGE questionnaire (Mayfield, McLeod, & Hall, 1974) and the alcohol use disorder identification test – alcohol consumption questions (AUDIT C) (Saunders, Aasland, Babor, de la Fuente, & Grant, 1993). A score of 0 points in the CAGE questionnaire and a

**Table 1**
Demographic data of the patients' and the control group, means, and standard deviation (SD) of the test results.

| | Patients' group | Control group | *p* value |
|---|---|---|---|
| Age | 42,98 ± 6,91 | 43,48 ± 10,47 | n.s. |
| BMI | 24,04 ± 3,22 | 25,13 ± 2,91 | n.s. |
| Years of drinking (y) | 9,37 ± 6,92 | n.a. | n.a. |
| Daily intake (g) | 199,30 ± 91,61 | n.a. | n.a. |
| Carbamazepine dosage (mg) | Day 1: 772,34 ± 223,31<br>Day 7: 652,17 ± 270,59<br>Day 14: 160.71 ± 242,07 | n.a. | n.a. |
| Clomethiazole (capsules) | Day 1: 8,47 ± 4.11<br>Day 7: 0.13 ± 0.65<br>Day 14: 0 ± 0 | n.a. | n.a. |
| BDNF (pg/mL) | Day 1: 667,07 ± 533,17<br>Day 7: 494,92 ± 372,19<br>Day 14: 613,42 ± 515,021 | 590,96 ± 332,29 | n.s. |
| IL-6 (ng/mL) | Day 1: 10,046 ± 11,42<br>Day 7: 6,06 ± 12,69<br>Day 14: 5,64 ± 8,69 | 3,89 ± 1,37 | Day 1: 0.013<br>Day 7: 0.037<br>Day 14: n.s. |
| TNF-α (ng/mL) | Day 1: 8,56 ± 2,03<br>Day 7: 8,06 ± 1,75<br>Day 14: 8,26 ± 1,71 | 7,23 ± 1,36 | Day 1: 0.03<br>Day 7: 0.022<br>Day 14: 0.05 |
| OCDS total score | Day 1: 19,38 ± 7,36<br>Day 7: 10,72 ± 7,02<br>Day 14: 10, 28 ± 6,98 | n.a. | n.a. |
| PACS score | Day 1: 15,65 ± 8198<br>Day 7: 7,04 ± 6,17<br>Day 14: 5,33 ± 6,49 | n.a. | n.a. |
| CIWA | Day 1: 15,74 ± 3,64<br>Day 7: 13,30 ± 2,76<br>Day 14: 12,57 ± 2,55 | n.a. | n.a. |
| BDI | Day 1: 17,22 ± 8,75<br>Day 7: 9,07 ± 8,12<br>Day 14: 6,44 ± 7,72 | 2,89 ± 3,08 | <0.001 |
| STAI-I | Day 1: 48,51 ± 12,443<br>Day 7: 37,63 ± 12,448<br>Day 14: 37,39 ± 12,76 | 31,77 ± 7,05 | <0.001 |
| STAI-II | Day 1: 48,15 ± 11,45 | 31,44 ± 7,6 | <0.001 |
| SESA | Day 1: 50,49 ± 17,82 | n.a. | n.a. |

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