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Association of testosterone and BDNF serum levels with craving during alcohol withdrawal

Annemarie Heberlein [a,e,*], Bernd Lenz [b], Birgitt Opfermann [d], Michael Gröschl [c], Eva Janke [a], Katrin Stange [a], Adrian Groh [a], Johannes Kornhuber [b], Helge Frieling [a], Stefan Bleich [a], Thomas Hillemacher [a]

[a] Center for Addiction Research (CARe), Department of Psychiatry, Social Psychiatry and Psychotherapy, Medical School Hanover, Germany
[b] Department of Psychiatry and Psychotherapy, Friedrich-Alexander University Erlangen-Nürnberg, Germany
[c] Bioanalytical Laboratory, Celerion Switzerland AG, Allmendstr. 32, 8320 Fehraltorf, Switzerland
[d] Medizinischer Dienst der Krankenversicherungen Niedersachsen, Hildesheimer Str. 265-267, 30519 Hannover, Germany
[e] Fachklinikum Uchtspringe, Emil-Kraepelin-Str. 6, 39576 Stendal, Germany

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ABSTRACT

Preclinical and clinical studies show associations between testosterone and brain-derived neurotrophic growth factor (BDNF) serum levels. BDNF and testosterone have been independently reported to influence alcohol consumption. Therefore, we aimed to investigate a possible interplay of testosterone and BDNF contributing to alcohol dependence. Regarding possible interplay of testosterone and BDNF and the activity of the hypothalamic pituitary axis (HPA), we included cortisol serum levels in our research. We investigated testosterone and BDNF serum levels in a sample of 99 male alcohol-dependent patients during alcohol withdrawal (day 1, 7, and 14) and compared them to a healthy male control group ($n = 17$). The testosterone serum levels were significantly ($p < 0.001$) higher in the patients' group than in the control group and decreased significantly during alcohol withdrawal ($p < 0.001$). The decrease of testosterone serum levels during alcohol withdrawal (days 1–7) was significantly associated with the BDNF serum levels (day 1: $p = 0.008$). In a subgroup of patients showing high cortisol serum levels (putatively mirroring high HPA activity), we found a significant association of BDNF and testosterone as well as with alcohol craving measured by the Obsessive and Compulsive Drinking Scale (OCDS). Our data suggest a possible association of BDNF and testosterone serum levels, which may be relevant for the symptomatology of alcohol dependence. Further studies are needed to clarify our results.

Introduction

Alterations in testosterone and brain-derived neurotrophic factor (BDNF) serum levels have been associated with alcohol consumption. For example, Etelälahti and colleagues reported a positive association between testosterone release and alcohol consumption in alcohol-preferring rats (Etelälahti, Saarikoski, & Eriksson, 2011). Preclinical data also show higher basal testosterone levels in alcohol-preferring rats compared to non-preferring rat lines (Apter & Eriksson, 2003), and link testosterone administration with alcohol intake (Lakoza & Barkov, 1980): in clinical studies a decrease of circulating testosterone levels related to duration of drinking has been observed, as well as a direct association between the amount of alcohol consumed per day and the amount of free testosterone serum levels (Shiels et al., 2009). Consistently, high estradiol and testosterone levels were found to be associated with alcohol consumption in boys (de Water, Braams, Crone, & Peper, 2013). Moreover, in adolescents, testosterone serum levels were reported to predict the amount of alcohol consumed in adulthood (Braams, Peper, van der Heide, Peters, & Crone, 2016). Concretely, high testosterone levels in younger males predicted high alcohol consumption in adult males, an association that the authors suggest to be attributable to neural reward response. While testosterone seems to affect alcohol drinking behavior, conversely, alcohol consumption is known to affect testosterone secretion (Ruusa & Bergman, 1996) in a dose-dependent fashion: in males, intake of lower ethanol doses (0.5 g/kg) was reported to increase testosterone levels 2 h after ingestion (Sarkola & Eriksson, 2003), whereas intake of higher

* Corresponding author. Center for Addiction Research (CARe), Department of Psychiatry, Social Psychiatry and Psychotherapy, Medical School Hanover, Carl-Neuberg-Straße 1, D-30625, Germany. Fax: +49 393 257 0208.
E-mail address: a.heberlein@salus-lsa.de (A. Heberlein).

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ethanol dosages (1.5 g/kg) was reported to reduce testosterone release 10 h after ingestion (Välimäki et al., 1990).

BDNF serum levels were frequently reported to be decreased in alcohol-dependent patients compared to healthy controls (Huang et al., 2011; Zanardini et al., 2011). Moreover, high BDNF serum levels have been associated with withdrawal intensity during early alcohol withdrawal (Heberlein, Muschler, Wilhelm, et al., 2010; Huang et al., 2008). Further results suggest that BDNF serum levels may even be a possible marker of alcohol relapse probability. For example, Costa and colleagues presented data that indicate that high BDNF serum levels reduce the risk of relapse in alcohol-dependent patients (Costa, Girard, Dalmay, & Malauzat, 2011). Consistent with these results, we found an association between drinking history and promoter methylation of the BDNF gene in our own data: we found a negative association of BDNF IV-promoter methylation and duration of abstinence before relapse, which supports a possible protective effect of high BDNF expression regarding alcohol relapse (Heberlein et al., 2015). Further support for a possible association comes from animal data, which demonstrate that prolonged alcohol consumption results in a decrease of central BDNF expression (McGough et al., 2004; Raivio, Miettinen, & Kiianmaa, 2014), suggesting that the decrease of central BDNF expression resulting from alcohol consumption may promote further alcohol consumption.

Considering these study results, the question arises of a relevant interplay of testosterone and BDNF regarding alcohol intake. Indeed, there is research that supports a possible association between the neurotrophic growth factor BDNF and testosterone. For example, testosterone-dependent increase of hippocampal neuronal growth and testosterone-induced increase of synaptic plasticity were associated with concomitant BDNF expression (Atwi, McMahon, Scharfman, & MacLusky, 2016). Moreover, testosterone administration was shown to decrease cerebral ischemic infarct volume in rats by increasing BDNF expression in the affected area (Fanaei et al., 2014). Nevertheless, the concrete mechanisms of this possible interplay have not yet been elucidated. However, study results point toward an interaction between cytokine release, sex hormones, and neurotrophic growth factors. For example, Xu and colleagues reported that increased survival of bulbocavernosus motoneurons by testosterone was blocked by tropomycin receptor kinase B (TrkB), which is the high-affinity receptor for BDNF antagonists (Xu, Gingras, Bengston, Di Marco, & Forger, 2001). Conversely, there are study results which demonstrate interplay between cytokine release and the TrkB receptor, suggesting that neurotransmission via the TrkB may link inflammation, sex hormones, and neurotrophic growth factors (Zhang, Yao, & Hashimoto, 2016). Consistent with these reports are study results which suggest that the activity of the hypothalamic pituitary axis (HPA) (Moonat & Pandey, 2012) may be a relevant factor, which supports a possible association of BDNF and testosterone. Indeed, there are preclinical study results that demonstrate the influence of HPA activity on BDNF as well as on testosterone release. For example, basal HPA activity was negatively associated with cerebral BDNF expression. Moreover, a negative association between *de novo* synthesis of BDNF and the adaption of the stress response was reported (Maghsoudi et al., 2014; Naert, Maurice, Tapia-Arancibia, & Givalois, 2007). Regarding a possible influence of HPA activity on testosterone levels, Toufexis and colleagues reported that physiological doses of dihydrotestosterone decreased basal levels of serum cortisol in male and female macaques and also decreased corticotrophin-releasing factor- (CRF) induced activation in male macaques (Toufexis & Wilson, 2012).

Study results also suggest a link between testosterone-related behavioral impulsivity (Cooper, Goings, Kim, & Wood, 2014) and HPA activity (Mehta, Welker, Zilioli, & Carré, 2015). Mehta et al. (2015) reported that risk taking and testosterone serum levels were positively associated in male and female probands when HPA activity was low, suggesting a link between impulsivity, testosterone release, and HPA activity. Partly closing the gap between alterations of testosterone levels, HPA activity, and alcohol consumption, prenatal exposure to ethanol was reported to reduce testosterone's effect on the HPA (Lan, Hellemans, Ellis, Viau, & Weinberg, 2009). Moreover, corticosterone replacement therapy was reported to result in increased alcohol consumption in adrenalectomized alcohol-preferring male rats, implicating a direct corticosterone effect on alcohol consumption in vulnerable populations (Fahlke & Eriksson, 2000).

These results suggest an association of high testosterone release, decreased HPA activity, increased BDNF expression, and behavioral traits, which may influence impulsive behavior such as alcohol consumption. Strengthening the hypothesis of a multilateral association of sex hormones, HPA activity, and BDNF, Franklin and colleagues reported that stress increased or decreased BDNF release, depending on the availability of sex hormones (Franklin & Perrot-Sinal, 2006).

The aim of our study was to investigate alterations of testosterone serum levels due to intoxication and during withdrawal in alcohol-dependent patients. Moreover, we focused on possible associations between the symptomatology of alcohol withdrawal, testosterone, and BDNF. Regarding the possible relevance of the activity of the HPA axis, we also investigated a possible association between testosterone and BDNF serum levels in subgroups of patients displaying high versus low cortisol levels.

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 Erlangen-Nürnberg. In this sample we had already investigated alterations of BDNF serum levels during alcohol withdrawal (Heberlein, Muschler, Wilhelm, et al., 2010). The investigation was conducted in accordance with the Declaration of Helsinki. Each participant gave written informed consent.

In total, we investigated the testosterone and BDNF serum levels of 99 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). The patients' group consisted of smokers and non-smokers (10 non-smokers, 81 smokers, 6 former smokers, 2 unknown). Table 1 shows the demographic data of the patients' group. 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. In addition, 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. Patients received carbamazepine and/or clomethiazole in order to treat alcohol-withdrawal symptomatology. Dosages were adjusted to the individual severity of alcohol withdrawal. Blood samples were taken before the patients took their morning medication.

Breath alcohol concentration 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, and daily intake of alcohol in grams