Prolactin Serum Levels and Alcohol Craving – An Analysis Using Lesch's Typology

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Key Words

Alcohol craving · Prolactin · Lesch's typology · Anxiety

Abstract

Background: Prolactin secretion is closely connected to dopaminergic transmission that is known to play a crucial role in mediating reinforcement and craving in alcoholism. **Objectives:** The study was performed to analyze the association between prolactin serum levels and alcohol craving during withdrawal differentiating alcohol-dependent patients using Lesch's typology. **Methods:** We assessed 115 male patients with the Obsessive Compulsive Drinking Scale at early alcohol withdrawal. In addition, serum was obtained to measure prolactin concentration and the patients were classified according to Lesch's typology into one of four subgroups. **Results:** Correlation analysis showed a significant association between prolactin serum levels and the extent of craving in Lesch's type 2 patients ($r = 0.32$, $p = 0.015$; $n = 57$); however, no association was found for any other subgroup. The results were confirmed comparing patients with low and high craving (Mann-Whitney U test: $Z = -2.805$, $p = 0.005$). **Conclusions:** In patients of Lesch's type 2, who are characterized to suffer from anxiety and to use alcohol because of its anxiolytic effects, prolactin is associated with craving during early alcohol withdrawal.

Introduction

Research on neurobiological mechanisms in alcohol dependency has shown that the dopaminergic reward system plays a crucial role in reinforcement and craving [1–3]. Recent studies have proposed that downregulated central dopaminergic receptors normalize during detoxification [4]. Apart from the important role of dopamine in central neurotransmission, it is known to act as prolactin inhibiting factor [5], which leads to a possible association between dopaminergic function (mediated mainly via dopamine D_2 receptors), prolactin levels and psychological changes during alcohol dependence such as craving. In a recent study, we described an association between individual changes of prolactin serum levels during detoxification and craving in female patients, while we found no association in male patients [6].

The aim of this study was to analyze a possible association between prolactin serum levels and craving using a well-established classification of alcohol dependence. Numerous studies in alcohol research point towards the importance of classifying patients into subgroups, while different classifications have been proposed in the past. The Lesch typology has been used in various investigations [7–10] and takes social, mental and somatic factors into account [11, 12]. The typology distinguishes four different subtypes: type 1 patients (model of 'allergy') are characterized to suffer from heavy alcohol withdrawals

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Table 1. Demographic characteristics of the study population (mean $\pm$ SD)

	Lesch's type 1 (n = 27)	Lesch's type 2 (n = 57)	Lesch's type 3 (n = 19)	Lesch's type 4 (n = 12)
OCDS total ¹	17.3 $\pm$ 7.3	21.2 $\pm$ 7.4	21.4 $\pm$ 8.0	24.8 $\pm$ 7.1
Prolactin ¹ , ng/ml	18.6 $\pm$ 12.8	13.6 $\pm$ 9.0	13.1 $\pm$ 7.8	10.1 $\pm$ 3.5
Age, years	44.3 $\pm$ 8.9	44.4 $\pm$ 9.1	43.7 $\pm$ 8.4	39.7 $\pm$ 8.5
Years of drinking	19.5 $\pm$ 10.2	19.9 $\pm$ 10.1	21.7 $\pm$ 10.1	19.7 $\pm$ 10.1
Daily intake, g	214.7 $\pm$ 137.6	259.3 $\pm$ 182.8	283.4 $\pm$ 213.2	263.2 $\pm$ 127.2
Lifetime drinking, kg	1,476 $\pm$ 1,094	1,908 $\pm$ 2,173	2,620 $\pm$ 3,374	1,850 $\pm$ 1,483

¹ Significant differences between the different types of Lesch's typology, tested with the Kruskal-Wallis test for independent samples ($p < 0.05$).

and tend to use alcohol to weaken withdrawal symptoms. Patients of type 2 (model of anxiety or conflict) use alcohol as self-medication because of anxiolytic effects. The main characteristic of type 3 patients (alcohol as an anti-depressant) is an underlying affective disorder as the origin of alcohol abuse. Type 4 patients (alcohol as adaptation) show premorbid cerebral defects, behavioral disorders and a high social burden.

Materials and Methods

The present study was part of a larger prospective investigation (Franconian Alcoholism Research Studies) [13–15] and was approved by the Ethics Committee of the Medical Faculty, University of Erlangen-Nuremberg, Germany. Written, informed consent was obtained from all patients who all met criteria for alcohol dependency according to ICD-10 and DSM-IV. One hundred and nineteen men and 26 women participated in the study. The female patients were not included in the present analysis due to the small number for subgroup analysis (Lesch's typology). In 4 male patients, data were not recorded completely enough to classify the patients referring to Lesch's typology, which reduced the number of patients for analysis to 115. All patients underwent withdrawal treatment after admission using clomethiazole and carbamazepine. Patients with concomitant psychiatric diseases and other substance abuse apart from alcohol or nicotine dependence, known dysfunction of the hypothalamic-pituitary-adrenal axis or thyroid diseases were not included in the study. Abstinence during hospitalization was monitored by carbohydrate-deficient transferrin, continuous urine and breath analysis. We obtained serum for prolactin analysis at the same time (8:00 a.m.) on day 0 or day 1. Blood samples were centrifuged directly after blood withdrawal and stored continuously at -80°C until assaying Prolactin concentrations were measured using the Abbott AxSYM (cat. No. 7A62-22, Abbott Park, Ill., USA) based on microparticle enzyme immunoassay technology. Additionally, blood alcohol concentration was measured at admission.

The extent of craving during withdrawal treatment was assessed with the Obsessive Compulsive Drinking Scale (OCDS) [16, 17] on the day of hospitalization. The OCDS is a well-validated instrument that assesses craving more constantly and more stably than

for example a visual analogue scale. Patients were classified according to Lesch's typology into one of four subgroups. Furthermore, sociodemographic data [educational status, known somatic illnesses, preceding withdrawals, daily intake of alcohol (in grams), the period of drinking (in years) and lifetime drinking (daily intake in kilograms $\times$ 365 days $\times$ years of drinking)] were taken in a semi-structured interview by a trained observer (K.B.).

Descriptive results are given as mean (SD) and median. To compare patients with low and high craving, we applied a previously described median split division of the OCDS [18]. For all statistical tests, we assessed a significance level of $\alpha < 0.05$. The statistical analysis was performed using SPSSTM for Windows version 11.5 (SPSS Inc., Chicago, Ill., USA).

Results

The sociodemographic characteristics of the four groups of Lesch's typology (differences between the groups were tested with the Kruskal-Wallis test) are shown in table 1. Prolactin serum levels were highest in patients of Lesch's type 1 while Lesch's type 4 patients showed the most elevated craving scores. Spearman correlation analysis revealed a significant association between prolactin serum levels and the OCDS for patients of Lesch's type 2 ($r = 0.32$, $p = 0.015$; $n = 57$). None of the other subgroups of Lesch's typology (type 1: $r = 0.18$, $p = 0.359$, $n = 27$; type 3: $r = 0.04$, $p = 0.883$, $n = 19$; type 4: $r = -0.02$, $p = 0.939$, $n = 12$) nor the whole study population ($r = 0.13$, $p = 0.174$, $n = 115$) showed significant results with the OCDS in the correlation analysis.

Comparing patients with low and high craving (using the above-mentioned median split division of the OCDS), we found a significant difference regarding prolactin serum levels in the group of patients with Lesch's type 2 (Mann-Whitney U test: $Z = -2.805$, $p = 0.005$, $n = 57$; fig. 1); however, no difference was found for any of the other subtypes.

Receiver operating characteristic curves also showed significant predictive qualities for craving in Lesch's type 2 patients (area under the curve = 0.717, 95% confidence interval = 0.577–0.857, $p = 0.005$; fig. 2).

Discussion

To our knowledge, this is the first study investigating prolactin levels in alcoholic patients classified according to Lesch's typology. As a main result, we observed a significant association between the extent of alcohol craving and prolactin levels in patients with alcohol dependency according to Lesch's type 2. These patients tend to suffer from anxiety disorders and use alcohol consumption especially for its anxiolytic effect. Prolactin has been suggested to be associated with anxiety and panic attacks in previous studies [19, 20]. Also, elevated baseline prolactin has been reported in patients with panic disorders [21].

Long-term alcohol consumption is known to lead to a chronic stimulation of dopaminergic receptors [22, 23]. We suggest that the association between elevated prolactin levels and craving during alcohol withdrawal may be the result of a reduction of mesolimbic dopaminergic activity that has been associated with dysphoric emotional states and craving during alcohol withdrawal [24, 25]. The present results link two different dopaminergic pathways, the tuberoinfundibular and the mesocorticolimbic dopamine system. The tuberoinfundibular system has not been discussed to be relevant to alcohol craving up to now. However, recent research has shown evidence that both the tuberoinfundibular and the mesocorticolimbic system may be regulated by D_2 receptors, which have been associated with cognitive and affective functions of the mesocorticolimbic system [26], prolactin secretion, and activity of the tuberoinfundibular dopamine neurons [27]. Hence, our results suggest an association of both dopaminergic pathways in the pathophysiology of alcohol craving.

Furthermore, glutamatergic neurotransmission, which is also supposed to play an important role in withdrawal craving [28, 29], has been linked with prolactin secretion [30–32]. The present study suffers from the following limitations: because of the small number of patients in the groups 1, 3 and 4 of Lesch's typology, we cannot generally rule out an association between craving and prolactin in these patients. On the other hand, the whole male population showed no association between both variables and also the correlation coefficient was low in type 1, 3

Fig. 1. Box plot comparing patients of Lesch's type 2 with high and low craving in early withdrawal after using a median split division of the OCDS. Statistical significance was tested with Mann-Whitney U test: $Z = -2.805$, $p = 0.005$, $n = 57$.

Fig. 2. Receiver operating characteristic curve for Lesch's type 2 patients in early withdrawal; area under the curve = 0.717, 95% confidence interval = 0.577–0.857, $p = 0.005$.

and 4 patients, which makes a relevant association in these groups improbable. Another important limitation is the lack of measuring thyrotropin-releasing hormone, which is known to influence the release of prolactin [33].

In conclusion, we found first evidence for an association between prolactin secretion and craving in a specific subgroup of patients. Further research is necessary to elucidate the pathophysiological mechanisms linking prolactin and craving in alcoholism and to investigate clinical implications for a subgroup-specific therapy.

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