Progress in Neuro-Psychopharmacology & Biological Psychiatry 35 (2011) 568–572

Contents lists available at ScienceDirect

Progress in Neuro-Psychopharmacology & Biological Psychiatry

journal homepage: www.elsevier.com/locate/pnp

Decreased galanin serum levels are associated with alcohol-craving during withdrawal

Annemarie Heberlein [a,b,*], Marc Muschler [a], Helge Frieling [a,b], Bernd Lenz [b], Julia Wilhelm [a,b], Michael Gröschl [c], Johannes Kornhuber [b], Stefan Bleich [a,b], Thomas Hillemacher [a,b]

[a] Center for Addiction Research, Department of Psychiatry, Social Psychiatry and Psychotherapy, Hannover Medical School, Germany
[b] Department of Psychiatry and Psychotherapy, University Hospital Erlangen, Germany
[c] Department of Pediatrics, University Hospital Erlangen, Germany

ARTICLE INFO

Article history:
Received 21 November 2010
Received in revised form 18 December 2010
Accepted 22 December 2010
Available online 31 December 2010

Keywords:
Alcohol craving
Alcohol dependence
Alcohol withdrawal
Galanin
Neurotrophic growth factors

ABSTRACT

Background: The hypothalamic galanin expression has been associated with increased intake of carbohydrates and fats in preclinical studies. The appetite stimulating effect of galanin is thought to underlie the positive association between alcohol consumption and hypothalamic galanin expression observed in preclinical studies.
Methods: In this pilot study we investigated alterations in galanin serum levels (33 male patients) in alcohol-dependent patients during alcohol withdrawal (days 1, 7 and 14) in comparison to healthy controls (19 male controls). In order to assess the putative association between appetite regulation, galanin serum levels and alcohol consumption we additionally investigated the serum levels of insulin, glucose and triglycerides.
Results: The galanin serum levels on day 1 of alcohol withdrawal were significantly reduced in the alcohol-dependent patients ($T = -3.302$, $p = 0.002$) and increased significantly from day 1 to day 14 of alcohol withdrawal ($F = 6.437$, $p = 0.002$). We found a significant negative association between the galanin serum levels and alcohol craving measured by the Obsessive Compulsive Drinking Scale (OCDS) ($r = -0.449$, $p = 0.009$) and the obsessive subscale of the OCDS ($r = -0.521$, $p = 0.002$) on day 1 of alcohol withdrawal. There was no association between the galanin serum levels and the parameters of energy homeostasis (triglycerides, cholesterol, insulin, and glucose) investigated.
Conclusions: Acute alcohol withdrawal was associated with decreased galanin serum levels in this pilot study. There was no association between the galanin serum levels and the parameters of energy homeostasis. Further research of galanin serum levels in active drinkers will be necessary to clarify the putative association between galanin serum levels, appetite regulation and alcohol consumption.

1. Introduction

Galanin is a regulatory neuropeptide that is known to be widely distributed within the nervous system and in the gut. Centrally, galanin has been described to interact with dopaminergic, serotonergic and noradrenergic neurotransmission (Leibowitz et al., 2003; Sevcik et al., 1993).

Modulation of dopaminergic neurotransmission by galanin is thought to underlie reduced behavioural responses following treatment with several non-caloric addictive substances like morphine or amphetamines as demonstrated in animal studies investigating either galanin overexpression or intracerebral galanin treatment (Pierce and Kumaresan, 2006; Tsuda et al., 1998). Contrasting to the anti-addictive effects of galanin regarding these non-caloric addictive substances a positive association between the central galanin expression and alcohol consumption has been reported in preclinical studies. In particular, central microinjection of galanin (Lewis et al., 2004; Rada et al., 2004) was observed to increase voluntary alcohol self-administration. Moreover, alcohol consumption has been associated with an increase of galanin mRNA expression (Leibowitz et al., 2003) indicating a stimulatory feedback loop between alcohol intake and the central galanin expression. This positive association between the central galanin expression and alcohol consumption is thought to

Abbreviations: AAT, aspartate aminotransferase; ALAT, alanine aminotransferase; AUDIT-C, Alcohol Use Disorder Identification Test — Alcohol Consumption Questions; BAC, Breath Alcohol Concentration; BDI, Beck's Depression Inventory; BMI, body mass index; CIWA-Ar, Clinical Institute Withdrawal Assessment for Alcohol; DI, daily intake of alcohol in grams; DSM-IV, Diagnostic and Statistical Manual of Mental Disorders; GGT, gamma glutamyl transferase; ICD-10, International Classification of Diseases; LC, leukocyte count; N.A., not available; OCDS, Obsessive and Compulsive Drinking Scale; SD, standard deviation; SESA, Severity Scale of Alcohol Dependence; STAI-I, State Anxiety, State and Trait Anxiety Inventory; STAI-II, Trait Anxiety, State and Trait Anxiety Inventory; TC, thrombocyte count; YD, years of drinking.

* Corresponding author. Center for Addiction Research, Department of Psychiatry, Social Psychiatry and Psychotherapy, Hannover Medical School, Carl-Neuberg-Straße 1, D-30625 Hanover, Germany. Tel.: +49 176 1 532 8235.
E-mail address: heberlein.annemarie@mh-hannover.de (A. Heberlein).

0278-5846/$ – see front matter © 2010 Elsevier Inc. All rights reserved.
doi:10.1016/j.pnpbp.2010.12.021

be based on the appetite stimulating function of galanin. Preclinical evidence shows that galanin increases food intake, in particular the intake of carbohydrates and fats, via the activation of hypothalamic neuronal circuits (Kyrkouli et al., 1990). Consistently, clinical studies report an association between circulating galanin levels, obesity (Poritsanos et al., 2009) and circulating triglycerides (Plaisier et al., 2009). In particular, it has been suggested that there is a positive feedback-loop between the hypothalamic galanin expression and alcohol consumption, which is stimulated by alcohol induced increase of peripheral triglyceride levels (Leibowitz, 2007). Consistent with the impact of galanin in energy homeostasis the hypothalamic galanin expression was found to be inhibited by insulin in diabetic as well as in nondiabetic rats (Tang et al., 1997; Wang and Leibowitz, 1997).

Although in humans a putative association between the galanin serum levels and the symptomatology of alcohol dependence and alcohol withdrawal has not been investigated yet, there are study results that show associations between polymorphisms of the galanin gene and alcohol dependence (Belfer et al., 2006, 2007).

In respect with these study results we investigated galanin serum levels in alcohol-dependent patients undergoing alcohol withdrawal and compared them with galanin serum levels obtained from healthy controls. Moreover, we aimed to assess a putative association between the appetite regulatory function of galanin and alcohol craving in the alcohol dependent patients. Therefore we investigated associations between peripheral blood levels of galanin in the alcohol-dependent patients, insulin, triglyceride levels and alcohol craving measured by the Obsessive Compulsive Drinking Scale (OCDS).

2. Materials and methods

The present pilot study was part of a large prospective research project (Studies in Neuroendocrinology and Neurogenetics in Alcoholism (NENA), Heberlein et al., 2010) that was approved by the local Ethics Committee of the University of Erlangen-Nuremberg. The investigation was conducted in accordance with the Declaration of Helsinki of 1975 (revised in 2008). Each participant gave written informed consent. Because animal studies suggest gender differences regarding the regulation of galanin (Leibowitz et al., 2007) we included only male patients in the study. In total we investigated galanin serum levels of 33 male patients suffering from alcohol dependence according to ICD-10 and DSM-IV after admission for detoxification treatment (Clinic for Psychiatry, Psychotherapy and Psychosomatics, Obermain, Kutzenberg, Germany).

Patients suffering from axis-one diagnoses other than alcohol and nicotine dependence were excluded from the study. Smokers (28 smokers) and non-smokers (5 non-smokers) were included in the group of patients. Further exclusion criteria were substance abuse apart from alcohol or nicotine (controlled for by drug urine screening), overweight (defined by age related body mass index), diabetes mellitus, diseases of the gastrointestinal tract, severe neurological diseases like cerebral ischemia, cerebral haemorrhage and epilepsy, and cardiovascular and renal diseases.

All patients included in this study were treated with clomethiazole and oxcarbazepine (Martinotti et al., 2007) in order to prevent alcohol withdrawal symptoms. The dosage increase or decrease was adjusted in response to the severity of individual withdrawal symptoms. There was no further psychopharmacological treatment. All patients underwent a detailed physical examination, routine laboratory testing (including liver enzyme levels, blood count, glucose, and triglyceride levels) and additional measurements of serum insulin and serum cortisol.

As a control group we enrolled randomly selected healthy male persons that did not suffer from any current somatic disease (19 male controls). Smokers (4 controls) and non-smokers (15 controls) were included in the control group. Controls were screened for mental diseases by a structured clinical interview. Controls were screened for alcohol dependence and abuse using the CAGE questionnaire (Mayfield et al., 1974) and the Alcohol Use Disorder Identification Test — Alcohol Consumption Questions (AUDIT-C) (Saunders et al., 1993). Controls received no psychopharmacological treatment. Controls were negative for alcohol abuse, alcohol dependence and any other mental disease according to ICD-10 or DSM-IV. There was no significant difference regarding sociodemographic characteristics in both groups (see Table 1 for details).

Patients and controls were instructed to fast overnight. Fasting blood samples were taken directly on admission between 8 and 10 a.m. All blood samples were centrifuged and stored at −80 °C immediately after collection. The galanin serum levels, serum insulin levels and serum glucose were investigated on day 1, day 7 and day 14 of alcohol withdrawal and were compared to the serum levels of the healthy control group. Galanin serum levels were assessed using the enzyme-linked immunosorbent assay (ELISA) (E1084Hu, USCN Life Science & Technology Co., Wuhan, China). Insulin serum levels were assessed by enzyme immuno assay (DSL 10-1600, Beckman Coulter Inc., Krefeld, Germany).

The sample concentrations in each plate were calculated according to standard curves and dilution factors.

Bodily symptoms of alcohol withdrawal like alterations in pulse frequency, blood pressure and body temperature were assessed directly before blood was taken on day 1, day 7 and day 14. In addition, cortisol serum levels were assessed by ELISA (DRG EI-1887, DRG Instruments GmbH, Marburg, Germany).

Additional data like age, body mass index (BMI), years of drinking (YD) and daily intake of alcohol in grams (DI) were obtained in a structured interview.

Table 1
Characteristics of the alcohol dependent patients in comparison with the healthy controls.

	Alcohol dependent patients (n = 33) Mean +/− SD			Healthy control group (n = 19) Mean +/− SD
Age (years)	42.91 +/− 7.34			41.11 +/− 19.58
BMI	22.97 +/− 2.49			23.74 +/− 3.16
Years of drinking	9.09 +/− 7.19			N.A.
Daily alcohol consumption (in g)	202.50 +/− 98.23			N.A.
SESA	55.63 +/− 18.77			N.A.
BAC	1.00 +/− 1.04			N.A.
	Day 1	Day 7	Day 14	
Galanin serum levels (pg/mL)	12.94 +/− 9.03	33.25 +/− 57.08	29.74 +/− 17.71	81.11 +/− 137.92
OCDS	19.42 +/− 7.39	10.59 +/− 6.99	9.34 +/− 6.73	N.A.
BDI	17.03 +/− 9.53	9.35 +/− 9.27	5.86 +/− 7.89	3.89 +/− 4.67
STAI-I	48.33 +/− 12.54	37.55 +/− 13.12	36.64 +/− 11.62	33.89 +/− 7.10
STAI-II	48.70 +/− 11.30			33.32 +/− 9.38

Legend: BMI: body mass index, SESA: Severity Scale of Alcohol Dependence, BAC: Breath Alcohol Concentration, OCDS: Obsessive and Compulsive Drinking Scale, STAI: State–Trait Anxiety Inventory, BDI: Beck's Depression Inventory, and N.A.: not available.