Behavioural Brain Research 316 (2017) 131–135

Contents lists available at ScienceDirect

Behavioural Brain Research

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

Short communication

Altered neural oscillations and elevated dopamine levels in the reward pathway during alcohol relapse

Ravit Hadar[a], Mareike Voget[a,b], Valentina Vengeliene[c], Jens K. Haumesser[d], Christoph van Riesen[d], Yosef Avchalumov[a], Rainer Spanagel[c], Christine Winter[a,*]

[a] Department of Psychiatry and Psychotherapy, Medical Faculty Carl Gustav Carus, Technische Universität Dresden, Germany
[b] International Graduate Program Medical Neurosciences, Charité – Universitätsmedizin Berlin, Germany
[c] Institute of Psychopharmacology, Central Institute of Mental Health, Medical Faculty Mannheim, Heidelberg University, Mannheim, Germany
[d] Department of Neurology, Charité – Universitätsmedizin Berlin, Germany

HIGHLIGHTS

- Altered reward network activity was studied in a DSM-based rat model of AUD.
- Relapse presented with increased dopamine availability in the nucleus accumbens.
- Enhanced dopamine levels went along with reduced synchronous oscillatory activity.
- Altered oscillatory activity presumably relates to dopaminoceptive MSN.
- Reduced β band oscillations may be indicative of a vulnerable state for relapse.

ARTICLE INFO

Article history:
Received 8 July 2016
Received in revised form 19 August 2016
Accepted 24 August 2016
Available online 25 August 2016

Keywords:
Alcohol use disorder
Relapse
Alcohol deprivation effect
Medial prefrontal cortex
Nucleus accumbens
Dopamine
Local field potentials
Beta band oscillations

ABSTRACT

Alcohol use disorder (AUD) is a severe chronic condition characterized by compulsive alcohol use, cravings and high relapse rates even after long periods of abstinence. It is suggested that alterations in neuronal network activity, especially in the reward pathway accompany or even mediate relapse behavior. Here we used a DSM-based rat model to map in a first set of experiments neurochemical alterations in the reward pathway during alcohol relapse. Compared to the abstinence condition, we found specific elevation of dopamine levels in the nucleus accumbens shell and the medial prefrontal cortex. We then conducted local field potential (LFP) recordings in these brain sites and observed decreased low-beta oscillatory activity in the nucleus accumbens shell and increased high beta activity in the medial prefrontal cortex. In conclusion, as in comparison with abstinence from alcohol, alcohol relapse is associated with enhanced dopamine levels in the mesolimbic system and an inverse correlation between β oscillatory activity and dopamine availability in the nucleus accumbens shell. These findings suggest that during a relapse situation reduced synchronous oscillatory activity of the local neural population in the nucleus accumbens shell occurs. This local neural population presumably relates to dopaminoceptive medium spiny neurons that show reduced synchronicity during a relapse situation.

1. Introduction

Alcohol consumption is known to adversely affect societies worldwide, resulting in an enormous health, social and economic burden. Alcohol use disorder (AUD) (5th ed.; DSM-5; American Psychiatric Association, 2013) is characterized by compulsive alcohol use, craving and relapses. As relapses are often observed even years after abstinence, this component of the disorder constitutes the most challenging aspect in the attempts to treat AUD. As for today, three lines of approved pharmacotherapies exist, entailing different mechanisms of action; interference with alcohol's metabolism (disulfiram), targeting neuronal reward pathways (naltrexone and nalmefene) and interference with the hyper-glutamatergic system (acamprosate) [1]. However, high relapse rates and overall moderate effect size have been reported. These suboptimal therapeutic outcomes, observed despite a diverse and differentiated pharmacological profile, suggest that our neurobiological under-

* Corresponding author at: Department of Psychiatry and Psychotherapy, University Hospital Carl Gustav Carus, Technische Universität Dresden, Germany.
E-mail address: christine.winter@uniklinikum-dresden.de (C. Winter).

http://dx.doi.org/10.1016/j.bbr.2016.08.045
0166-4328/

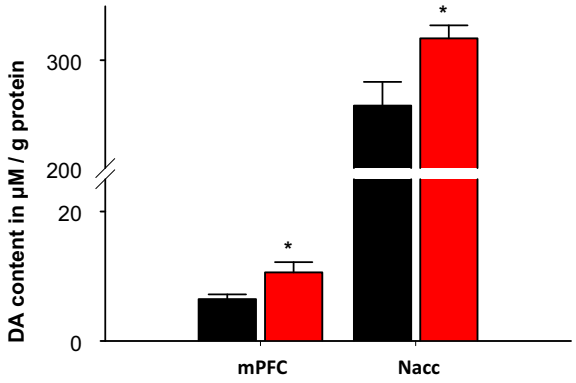

Fig. 1. Contents of dopamine (DA) in the medial prefrontal cortex (mPFC) and nucleus accumbens (NAcc) shell of long-term alcohol drinking rats under alcohol deprivation (black) and alcohol relapsing (red) conditions. Data are presented as means ± S.E.M. * indicates a statistically significant difference of $p < 0.05$. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

standing of alcohol relapse behavior is still very limited. Altered neural network activity is seen in many brain pathologies and one hypothesis is that altered neural network activity at different scales may accompany or even mediate alcohol relapse behavior [2]. To test this hypothesis we used a DSM-based rat model. In this model rats are subjected to long-term voluntary alcohol consumption which is repeatedly interrupted with abstinence periods [3]. These rats eventually develop a relapse-like drinking behavior characterized by a temporal increase in alcohol intake over baseline drinking upon the re-presentation of alcohol. Previous studies have demonstrated that such long-term exposure to alcohol drinking with repeated deprivation phases resulted in a compulsive drinking behavior during a relapse situation together with alcohol tolerance and physical as well anxiety-related withdrawal symptoms [4,5]. The alcohol deprivation effect (ADE) model has been widely used to screen for and identify new treatment agents with good predictive validity and entails a great translational value. For most, the ADE offers a unique insight into the relapse phenomenon, which we sought to study here.

The aim of the present study was to investigate the neurochemical events and neuronal network oscillations during alcohol relapse. In a first step we screened for altered neurotransmitter levels in different brain sites of the reward pathway [6]. The findings of this initial screen guided us for the recordings of multi-unit local field potentials (LFP) to identify aberrant network activities in rats undergoing alcohol relapse.

2. Methods

Male Wistar rats from a breeding colony of the Central Institute of Mental Health ((CIMH), Mannheim, Germany) were housed individually in a temperature- and humidity-controlled vivarium with a 12 h light/dark cycle, with lights on at 7:00 a.m. Food and water were available ad libitum. Experimental procedures were approved by Local Ethics Committees (Regierungspräsidia Dresden und Karlsruhe), and carried out in accordance with European Union guidelines on the care and use of laboratory animals. All efforts were made to reduce animal suffering and the number of animals used. Long-term alcohol consumption with repeated deprivation phases was induced as described previously [7]. Briefly, 2-month old rats were given ad libitum access to tap water as well as to 5%, 10%, and 20% ethanol solutions in their home-cages. After 8–12 weeks of stable voluntary alcohol consumption rats were deprived from alcohol for 2 weeks. Thereafter, rats were again given access to alcohol followed by further deprivation periods lasting from 2 to 5 weeks each. The intermittent long-term voluntary alcohol drinking procedure lasted for a total of 1 year. Rats had access to alcohol for an average of 55 weeks with 9 deprivation periods in between. Rats exhibited a stable baseline drinking (approximately 2.6 g/kg/day) with a 2–3 fold increase upon alcohol representation.

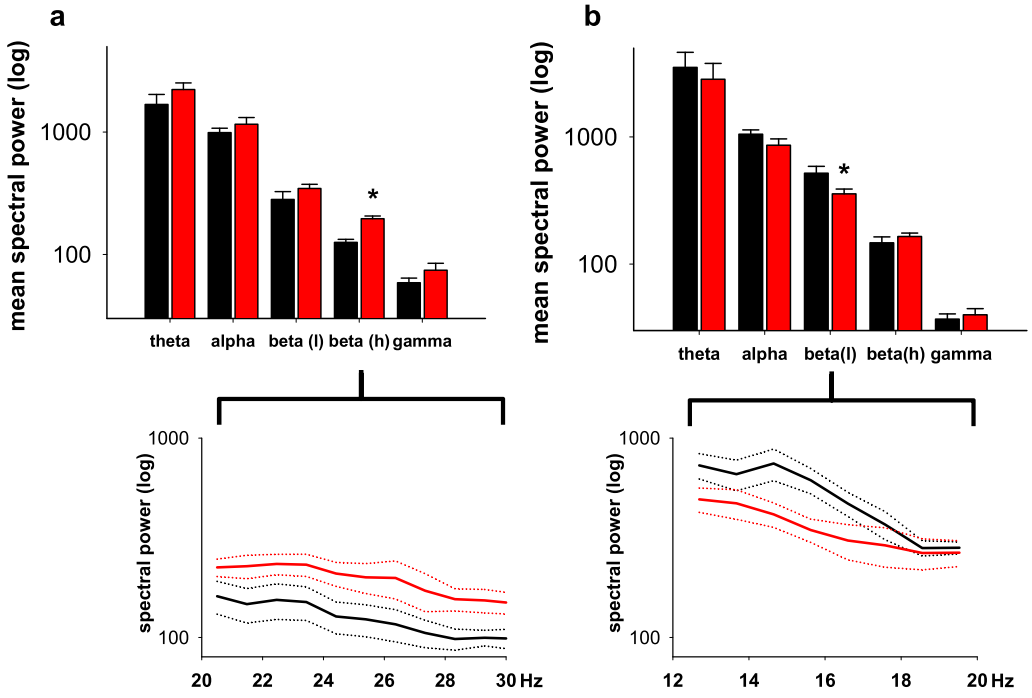

Fig. 2. Oscillatory activity of the medial prefrontal cortex (mPFC) (a) and the nucleus accumbens (NAcc) shell (b) under baseline alcohol deprived (black) and alcohol exposure conditions (red). Data are presented as means ± S.E.M. * indicates a statistically significant difference of $p < 0.05$. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)