Drug and Alcohol Dependence 190 (2018) 29–36

Contents lists available at ScienceDirect

Drug and Alcohol Dependence

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

Full length article

Adverse effects of GHB-induced coma on long-term memory and related brain function

Filipa Raposo Pereira[a,b,c,*], Minni T.B. McMaster[a,b,c], Nikki Polderman[a], Yvon D.A.T. de Vries[a], Wim van den Brink[a,b,c], Guido A. van Wingen[a,b,c]

[a] Department of Psychiatry, Academic Medical Center, The University of Amsterdam, AMC (PA.3-220), Meibergdreef 9, 1105 AZ, Amsterdam, The Netherlands
[b] Amsterdam Neuroscience, De Boelelaan 1085, 1081 HV, Amsterdam, The Netherlands
[c] Amsterdam Brain and Cognition, The University of Amsterdam, P.O. Box 19268, 1000 GG, Amsterdam, The Netherlands

ARTICLE INFO

Keywords:
Functional magnetic resonance imaging (fMRI)
Functional connectivity
Drug addiction
Gamma-hydroxybutyric acid (GHB)
GHB-induced coma
Long-term memory

ABSTRACT

Background: Gamma-Hydroxybutyric acid (GHB) is a drug of abuse associated with increasing numbers of GHB-dependent patients and emergency attendances often related to GHB-induced coma. Animal studies suggest that GHB induces oxidative stress in the hippocampus, resulting in memory impairments. However, the consequences of chronic GHB use and GHB-induced coma on human brain function and cognition are unknown.

Methods: We recruited 27 GHB users with ≥4 GHB-induced comas (GHB-Coma), 27 GHB users without a coma (GHB-NoComa), and 27 polydrug users who never used GHB (No-GHB). Participants completed verbal and spatial memory tests and an associative memory encoding task during functional magnetic resonance imaging (fMRI) to probe hippocampus functioning.

Results: The GHB-Coma group showed a lower premorbid IQ ($p = 0.006$) and performed worse on the verbal memory test ($p = 0.017$) compared to the GHB-NoComa group, despite exhibiting similar levels of education. Compared with the other two groups, the GHB-Coma group showed lower left hippocampus ($p_{SVC} = 0.044$) and left lingual gyrus ($p_{FWE} = 0.017$) activity, and a trend for lower hippocampal functional connectivity with the left superior temporal cortex during performance of the associative memory encoding task ($p_{FWE} = 0.063$). No significant differences were observed between the GHB-NoComa group and the No-GHB group.

Conclusions: These results suggest that multiple GHB-induced comas, but not the use of GHB per se, are associated with alterations of memory performance and memory-related brain, although no causal link can be inferred from this cross-sectional study. The results highlight the need for public awareness to minimize the negative health consequences of recreational GHB use, in particular when related with GHB-induced comas.

1. Introduction

Gamma-Hydroxybutyric acid (GHB) is a drug of abuse that has been popular as party drug over the last few decades (EMCDDA, 2016; Miró et al., 2017; Public Health England, 2015; United Nations Office on Drugs and Crime, 2017). Its recreational use produces positive effects such as euphoria, loss of inhibition and sexual arousal (Bosch et al., 2018, 2017b; Korf et al., 2014; Liakoni et al., 2016). However, GHB is also associated with severe side effects and has a serious abuse potential. Despite the relatively low prevalence of recreational GHB use in the population, there is a steady increase in the number of individuals seeking treatment for GHB dependence and in the number of emergency attendances related to GHB-induced coma (European Monitoring Centre for Drugs and Drug Addiction (EMCDDA, 2016; Public Health England, 2015). Consequently, these trends led the World Health Organization (WHO) to consider GHB to be a substantial risk for public health (World Health Organization, 2015).

GHB is a central nervous system depressant that poses a high risk of intoxication due to its narrow dose response window between the amount required for the desirable recreational effects, and overdose (Carter et al., 2009a; Van Amsterdam et al., 2012). Accordingly, a disproportional number of severe adverse effects such as GHB-induced coma is observed amongst regular users (Korf et al., 2014; Liechti et al., 2016; Miró et al., 2017; Van Amsterdam et al., 2012).

Temporary GHB-induced coma generally lasts between 1 and 4 h and often reaches the most severe classification on the Glasgow coma scale (Korf et al., 2014; Liechti et al., 2006; Miró et al., 2017). Remarkably, no side effects are apparent after sudden awakening from this coma, and despite regular GHB users may experience GHB-induced coma repeatedly, they still consider its use to be safe (Korf et al., 2014;

* Corresponding author at: Department of Psychiatry, The University of Amsterdam, AMC (PA.3-220), Meibergdreef 9, 1105 AZ, Amsterdam, The Netherlands.
E-mail address: f.raposopereira@amc.uva.nl (F. Raposo Pereira).

https://doi.org/10.1016/j.drugalcdep.2018.05.019
Received 1 March 2018; Received in revised form 3 May 2018; Accepted 21 May 2018
Available online 26 June 2018

Liechti et al., 2006; Miró et al., 2017; Van Amsterdam et al., 2012). However, research suggests that coma can produce oxygen deprivation (hypoxia) in brain areas that are highly sensitive to oxidative stress (Nayak et al., 2006; Perouansky and Hemmings, 2009). One of those areas is the hippocampus, which coincidently is a region with high concentration of GHB binding sites (Castelli et al., 2000).

The hippocampus is a key region of a larger long-term memory network and has a prominent role on episodic memory (Eustache et al., 2016). Although previous research suggesting that GHB might has the potential to prevent memory deficits in Alzheimer's disease, most animal studies have shown that regular GHB administration has a neurotoxic effect on the hippocampus, being frequently accompanied by memory impairments (Klein et al., 2015; Pedraza et al., 2009; Van Nieuwenhuijzen et al., 2010). Similarly, human studies assessing regular use of GHB suggest a link between regular GHB use and memory complaints (Barker et al., 2007; Durgahee et al., 2014)

Recent studies have started to investigate the acute effects of GHB on neural activity and connectivity (Bosch et al., 2018, 2017a,b). However, apart from a few animal studies assessing the influence of GHB on memory, no neuroimaging studies have yet assessed the influence of GHB and aspects of use on human memory. (Carter et al., 2009b; Pedraza et al., 2009; Perouansky and Hemmings, 2009). Here we investigated the effect of GHB-induced comas on long-term memory performance and memory-related brain function. In addition, we investigated whether repeated GHB use itself, i.e. without the induction of coma, would have an impact on these measures. We used verbal and spatial tests to assess memory performance, and an implicit associative memory encoding task during functional magnetic resonance imaging (fMRI) scanning, known to probe hippocampal activity and functional connectivity (de Quervain and Papassotiropoulos, 2006). In order to distinguish between the effects of GHB-induced comas and GHB-use per se, three different groups of participants were recruited: (1) GHB users who experienced ≥4 GHB-induced comas, (2) GHB users who never experienced GHB-induced coma, and (3) polydrug users who never used GHB. We tested the following hypotheses: (a) GHB users who had multiple comas show more severe impairments in memory performance, hippocampal activity, and hippocampal connectivity compared to GHB users who never had a GHB-induced coma and polydrug users who never used GHB; and (b) GHB users who never had a GHB-induced coma perform worse on the memory tests, have reduced hippocampal activity, and aberrant hippocampal connectivity, compared to polydrug user controls who never used GHB.

2. Material and methods

2.1. Participants

A total of 81 participants were included in this cross-sectional neuroimaging study. Three groups of participants were recruited, matched for age and education level: (1) 27 GHB users who had ≥4 GHB-induced comas (GHB-Coma); (2) 27 GHB users who never had GHB-induced coma (GHB-NoComa); (3) 27 polydrug-users who never used GHB (No-GHB). The GHB-Coma group could be further sub-divided between 9 GHB-coma participants currently under therapy for GHB-addiction and 15 GHB-Coma participants not in therapy for GHB-addiction. We used an arbitrary threshold of 4 coma episodes for the GHB-Coma group, to increase potential differences with the GHB-NoComa group. GHB users were required to have used GHB ≥ 25 times in the 2 years preceding the assessment (De Jong and Dijkstra, 2013). Polydrug use considered the co-use of recreational drugs such as the use of alcohol, nicotine, cannabis, cocaine, stimulants (amphetamines, khat, methylphenidate), ecstasy, ketamine, and sedatives (barbiturates, benzodiazepines). All groups were matched for age and education level. To be included in this study every participant had to be between 18–40 years old, a native Dutch speaker and male, since the majority of GHB users are men (Miró et al., 2017). For all groups exclusion criteria were the following: a history of epilepsy; underwent general anesthesia for a medical intervention within the last 2 years; contra-indications for MRI scanning (e.g. metal objects in the body or head injury); experiencing a coma episode for any other reason than GHB intoxication; diagnoses of narcolepsy with cataplexy and if currently under treatment with Xyrem® (brand name for GHB). Recruitment was performed through addiction centers in the Netherlands and through flyers, internet advertisement and snowball sampling directed at the general population. Data from all 81 included participants were used for behavioral analysis. MRI data from 3 GHB-Coma participants, 2 GHB-NoComa participants and 1 No-GHB participant were not available or had to be discarded due to insufficient data quality. After explanation of the study, written informed consent was obtained from all participants prior to study initiation. This study was in accordance with the Helsinki Declaration principles (7th revision, 2013), the Medical Research Involving Human Subjects Act (WMO, 1998), and approved by the Medical Ethics Review Committee of the Amsterdam Academic Medical Center (Büller et al., 2010; World Medical Association, 2013). The data presented in this manuscript are part of a larger study assessing the effect of GHB use on the brain and cognition. Here, we present the data related to long-term memory, and results from other experiments will be presented elsewhere.

2.2. Neuropsychological assessment

The primary cognitive outcome measures included two memory tests from the Cambridge neuropsychological test battery (CANTAB®; www.cantab.com) that were used to assess spatial and verbal memory performance. The spatial-recognition memory (SRM) test, measures the ability to memorize and retrieve spatial locations. During the presentation phase a white square was shown at 5 different locations in sequence. During the recognition phase, pairs of squares were presented. One of the squares was located at one of the 5 locations used during the presentation phase, and one was not. Participants were asked to choose the square previously seen in the presentation sequence. An adapted version of the verbal-recognition memory (VRM) test was used to measure the ability to retrieve newly encoded verbal information. During the encoding phase 18 words were presented sequentially. During the recognition phase, the participants were requested to select the words initially presented amongst 18 novel ones. The Dutch version of the National Adult Reading test, was used to assess premorbid verbal intellectual functioning (Schmand et al., 1991).

2.3. Statistical analysis

Demographic and behavioral data were analyzed using SPSS 24 (IBM Software Analytics, New York, USA). Normally distributed data were analyzed using analysis of variance (ANOVA). Not-normally distributed data were transformed to obtain a normal distribution or analyzed using non-parametric tests (see Tables 1 and 2). Co-use of other recreational drugs was assessed by asking participants about the number of days they used specific drugs in preceding 30 days, typically daily dose and the number of years of weekly use for each drug. We defined drug exposure as years of weekly use × daily dose for all recreational drugs (Table 2; MATE2.1) (Schippers et al., 2011). In addition, group differences in GHB daily dose (ml/day), years since first use, prevalence of days using GHB on the previous month, months of daily use, and total exposure as defined by years of use × daily dose were tested. The performance of memory tests was corrected for differences in IQ by introducing it as a covariate of no interest. An exploratory post-hoc analysis was performed to test whether differences in memory performance and brain function were related to the amount of GHB exposure or the number of experienced comas. As these measures were highly positively skewed, the GHB-Coma group was sub-divided into high and low GHB exposure groups and high and low number of comas experienced groups using a median split. Two-sample t-tests on the