Neural underpinnings of prosexual effects induced by gamma-hydroxybutyrate in healthy male humans

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Abstract
Gamma-hydroxybutyrate (GHB) is a GHB-/GABA2-receptor agonist currently used as treatment for narcolepsy but also as a drug of abuse. Non-medical GHB users have repeatedly reported prosexual effects including libido-enhancement and lowering of attractiveness standards for partner selection. Here, we examined the putative prosexual effects of oral GHB in healthy males in two experiments both employing randomized, placebo-controlled, double-blind, balanced, and cross-over study designs. In experiment I, subjective effects of 20 and 35 mg/kg GHB vs. placebo were tested in 32 participants using the Sexual Arousal and Desire Inventory. In experiment II, brain reactivity towards erotic vs. neutral pictures was investigated in 15 participants using functional magnetic resonance imaging after 35 mg/kg GHB vs. placebo. In experiment I, prosexual effects of GHB were shown by increased SADI ratings regarding physiological, evaluative, and motivational aspects of sexual arousal. In experiment II, erotic visual stimuli activated the bilateral insula, nucleus accumbens (NAcc), fusiform gyrus, thalamus, and left occipital pole under placebo. After GHB administration, even sexually neutral pictures of persons induced subjective sexual arousal and increased activation of the

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bilateral NAcc and right anterior cingulate cortex, which significantly correlated (left NAcc by trend). Moreover, a psychophysiological interaction analysis showed that GHB increased connectivity between NAcc and ventromedial prefrontal cortex during processing of visual erotic cues, i.e., in the condition in which subjective sexual arousal was highest. Our data show that GHB stimulates hedonic sexual functioning and lowers the threshold for erotic perception, which is related to increased susceptibility of mesolimbic reward pathways. © 2017 Elsevier B.V. and ECNP. All rights reserved.

1. Introduction

Gamma-hydroxybutyrate (GHB) is an endogenous fatty acid and a metabolite of gamma-aminobutyric acid (GABA) (Bessman and Fishbein, 1963). Due to the presence of specific G-protein-coupled high and low affinity binding sites and the specificity of the GHB antagonist NCS-382, GHB was postulated to be a neurotransmitter (Benavides et al., 1982; Snead, 2000). Although the physiological role of endogenous GHB is still unclear, some evidence points to neuroprotective, anti-apoptotic activity (Wendt et al., 2014). The compound binds to specific GHB- (Benavides et al., 1982) and GABA_A receptors (Engberg and Nissbrandt, 1993b). However, physiological concentrations of GHB seem to be insufficient to stimulate GABA_A receptors but this mechanism is discussed to be responsible for its psychotropic effects when administered orally in humans (Carter et al., 2009; Engberg and Nissbrandt, 1993a). Furthermore, GHB has neuromodulatory properties on glutamate, dopamine, serotonin, norepinephrine, and acetylcholine neurotransmission (Andresen et al., 2011). Clinically, GHB is internationally approved for the treatment of narcolepsy and in some countries also for the treatment of alcohol withdrawal (Bosch et al., 2012).

The drug exerts a broad spectrum of subjective effects, including sedation, stimulation, euphoria, disinhibition, and enhanced vitality (Bosch et al., 2015), for which the drug is instrumentalized by illicit users (Bosch and Seifritz, 2016). Moreover, non-medical users have repeatedly reported prossexual effects of the drug, including increased sexual desire and decreased sexual inhibition (Kapitany-Foveny et al., 2015; Lee and Levounis, 2008; Teltzrow and Bosch, 2012). Consequently, poor decision-making under GHB in erotic situations has been described as “lowering of sexual standards” for partner selection (Palamar et al., 2014).

Neural underpinnings of sexual arousal are commonly studied using functional magnetic resonance imaging (fMRI) and visual erotic stimulation. Processing of visual erotic stimuli without pharmacological challenges was studied in depth, and identified a canonical network consisting of cognitive (anterior cingulate cortex [ACC], fusiform gyrus, parietal cortex, thalamus, insula), emotional (amygdala, insula), motivational (precentral gyrus, ACC, hypothalamus, orbitofrontal cortex [OFC], ventral striatum/nucleus accum-bens [NAcc]), and autonomic (ACC, hypothalamus, thalamus, insula) components (Kuhn and Gallatin, 2011; Stoleru et al., 2012). In contrast, putative prossexual drug effects in humans are not sufficiently studied so far. The indirect dopamine/noradrenaline receptor agonist methylphenidate has been shown to elicit prossexual effects in laboratory settings (Schmid et al., 2015; Volkow et al., 2007), while the exact neural correlates of these effects remain unknown. Moreover, the dopamine D2 receptor agonist apomorphine activates occipitotemporal areas, ACC, and NAcc (Montorsi et al., 2003), as well as the prefrontal cortex (PFC) (Hagemann et al., 2003) during visual erotic stimulation; however, in all of these studies subjective sexual arousal was not assessed.

In order to characterize putative prossexual effects of GHB and associated neuronal underpinnings, we performed two experiments in healthy male volunteers. In the experiment I, subjective effects of GHB were assessed, using the Sexual Arousal and Desire Inventory (SADI) (Toledano and Pfaus, 2006), after oral administration of 20 and 35 mg/kg GHB vs. placebo in a total sample of 32 participants. In experiment II, neural correlates of GHB-induced (35 mg/kg GHB vs. placebo) alterations of the perception of erotic vs. neutral visual stimuli were studied using fMRI in 15 participants. We hypothesized that GHB increases sexual arousal, and that an increased activation of the above mentioned functional network will occur during visual erotic stimulation.

2. Experimental procedures

2.1. Design and participants

For both experiments, a randomized, double-blind, placebo-controlled, balanced, crossed within-subject design was used. Participants were heterosexual, non-smoking, healthy males. Thirty-two participants with a mean age of 24.5 years (±3.6 years; range 19-36), a mean verbal intelligence quotient (IQ) of 108.9 (±14.7, 86-145), and a mean weight of 74.9 kg (±8.3, 59-96) took part in experiment one. In experiment two, fifteen participants with a mean age of 23.5 years (±3.6, 20-36), a mean verbal IQ of 113.4 (±18.4, 88-145), and a mean weight of 72.2 kg (±7.4, 59-85) participated. Volunteers were recruited via online advertising and underwent a medical and psychiatric examination applying the Structured Clinical Interview for DSM-IV Axis-I Disorders (First et al., 2002). Exclusion criteria were any DSM-IV psychiatric disorder, neurological disorder, severe medical disease, left-handedness, and regular illegal drug use (lifetime use > 5 occasions, with exception of occasional cannabis use), latter assessed using the Interview for Psychotropic Drug Consumption (Quednow et al., 2004). Moreover, participants were requested to perform the Mehrfachwahl-Wortschatz-Intelligenztest (Lehri, 2005) to estimate their verbal IQ. Volunteers in experiment 2 were a subsample from experiment 1. They had to abstain from drinking alcohol 24 h before the experiments and from drinking caffeinated beverages on the morning before and during the measurements. Abstinence from illegal drugs was ensured by semi-quantitative drug urine tests (Dimension RKL Max, Siemens, Erlangen, Germany). The study was approved by the Cantonal Ethics Committee of Zurich and by Swissmedic, and was registered at ClinicalTrials.gov (NCT02342366).
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