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Gamma-hydroxybutyrate enhances mood and prosocial behavior without affecting plasma oxytocin and testosterone

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ABSTRACT

Gamma-hydroxybutyrate (GHB) is a GHB-/$GABA_B$-receptor agonist. Reports from GHB abusers indicate euphoric, prosocial, and empathogenic effects of the drug. We measured the effects of GHB on mood, prosocial behavior, social and non-social cognition and assessed potential underlying neuroendocrine mechanisms. GHB (20 mg/kg) was tested in 16 healthy males, using a randomized, placebo-controlled, cross-over design. Subjective effects on mood were assessed by visual-analogue-scales and the GHB-Specific-Questionnaire. Prosocial behavior was examined by the Charity Donation Task, the Social Value Orientation test, and the Reciprocity Task. Reaction time, memory, empathy, and theory-of-mind were also tested. Blood plasma levels of GHB, oxytocin, testosterone, progesterone, dehydroepiandrosterone (DHEA), cortisol, aldosterone, and adrenocorticotropic-hormone (ACTH) were determined. GHB showed stimulating and sedating effects, and elicited euphoria, disinhibition, and enhanced vitality. In participants with low prosociality, the drug increased donations and prosocial money distributions. In contrast, social cognitive abilities such as emotion recognition, empathy, and theory-of-mind, and basal cognitive functions were not affected. GHB increased plasma progesterone, while oxytocin and testosterone, cortisol, aldosterone, DHEA, and ACTH levels remained unaffected. GHB has mood-enhancing and prosocial effects without affecting social hormones such as oxytocin and testosterone. These data suggest a potential involvement of GHB-/$GABA_B$-receptors and progesterone in mood and prosocial behavior.

1. Introduction

Gamma-hydroxybutyrate (GHB) is an endogenous short-chain fatty acid neuromodulator which is biosynthetically derived from the major inhibitory neurotransmitter gamma-aminobutyrate (GABA) (Bessman and Fishbein, 1963). It appears to bind to specific GHB- and $GABA_B$-receptors (Snead, 2000). A potent interaction of GHB with extrasynaptic $\alpha4\beta\delta$ $GABA_A$ receptors suggested previously has recently been challenged (Connelly et al., 2013). While physiological concentrations of GHB seem to be insufficient to stimulate $GABA_B$ receptors, this mechanism is discussed to be responsible for its psychotropic effects when administered orally (Andresen et al., 2011). Although the physiological role of endogenous GHB is still unclear, some evidence points to an anti-apoptotic activity (Wendt et al., 2014). Apart from its direct effects on GHB- and $GABA_B$-receptors, GHB has neuromodulatory properties on glutamate, dopamine, serotonin, norepinephrine, and cholinergic transmission (Andresen et al., 2011). Clinically, GHB is internationally registered for the treatment of narcolepsy, and in some European countries for the treatment of alcohol withdrawal and craving (Keating, 2014). Moreover, it was recently proposed as an experimental therapeutic in depression (Bosch et al., 2012).

GHB abusers report enhancing effects on sociability and mood (Sumnall et al., 2008), whereby the drug has gained some notoriety as a "club drug" used by a small but growing part of the population (Carter et al., 2009). In some aspects, the acute effects of GHB

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resemble the entactogenic effects (i.e., feelings of closeness, desire for physical contact) of 3,4-methylenedioxymethamphetamine (MDMA, ecstasy), which has stimulated its most widespread street name "liquid ecstasy" (Uys and Niesink, 2005). MDMA is known to enhance emotional empathy and prosocial behavior (Bedi et al., 2010; Hysek et al., 2014), which was paralleled by increased oxytocin plasma levels (Schmid et al., 2014). Additionally to the MDMA-like entactogenic effects, GHB was reported to enhance sexually connoted affiliative behavior (Lee and Levounis, 2008), indicating an involvement of more neuroendocrine mechanisms than the oxytoninergic pathway. GHB is known to affect levels of several steroidal hormones such as neurosteroids and cortisol in animals and humans (Bosch et al., 2012), and $GABA_B$ receptors are discussed in the regulation of testosterone secretion (Amikishieva, 2007). Testosterone is a sex steroid hormone which is known to play an important role in human social interaction (Eisenegger et al., 2010; Bos et al., 2012). Taking these evidences together, the androgen system with the primary hormone testosterone and its precursor dehydroepiandrosterone (DHEA) seems another plausible candidate neuroendocrine mechanism of the prosocial effects of GHB.

Anxiolytic and stress reducing effects are attributed to neurosteroids such as progesterone, tetrahydroprogesterone (3α, 5α-THP), and tetrahydrodeoxycorticosterone (THDOC), whose syntheses are promoted by GHB in animals (Barbaccia et al., 2002). Moreover, animal and human data show that progesterone release mirrors an individual's level of social-affiliative motivation (Maner et al., 2010). Also, hypothalamic-pituitary-adrenal (HPA-) axis activity was bidirectionally altered by the drug (Van Cauter et al., 1997; Nava et al., 2007), and it was shown that stress influences social interactions (Tomova et al., 2014). Consequently GHB might elicit its social effects either directly via GHB/GABA receptors or indirectly by increasing plasma levels of hormones such as oxytocin and testosterone, by altering neurosteroidogenesis or through the modulation of the HPA-axis.

In order to characterize the acute effects of GHB on prosocial behavior, social cognition, and mood, we assessed a social decision-making and social cognition test battery, as well as subjective mood ratings in a randomized, placebo-controlled, balanced, cross-over design in 16 healthy males. We decided to focus on male individuals to reduce variance due to steroid hormone fluctuations during menstrual cycle. Potential neuroendocrine parameters mediating GHB effects were investigated by determination of plasma time-courses of oxytocin, testosterone, DHEA, progesterone, and stress hormones such as cortisol, aldosterone, and adrenocorticotropic hormone (ACTH). We hypothesized that GHB enhances mood, emotional empathy, and prosocial behavior, while increasing plasma levels of oxytocin, testosterone, and progesterone and altering HPA axis activity.

2. Methods and materials

2.1. Participants

Sixteen healthy, male, and non-smoking participants with mean age of 23.9 years (±2.9 SD, range 19–29), a mean verbal intelligence quotient (IQ) of 104.2 (±14.6 SD, range 86–145), and a mean weight of 74.4 kg (±8.2 SD, range 60.4–87.0) participated in the study. Exclusion criteria were any Axis-I DSM-IV psychiatric disorder, any form of addiction or regular illegal drug use (lifetime use ≥5 occasions) with exception of occasional cannabis use, a lifetime history of GHB use, a neurological disorder or head injury, clinically relevant medical diseases, a family history of schizophrenia or bipolar disorder, and any use of prescription drugs. All participants had to abstain from caffeine on the study days and from alcohol for at least 24 h before the experiments. In order to ensure drug abstinence on the test days, a urine screening was done using a Dimension RXL Max (Siemens, Erlangen, Germany) immunoassay. The study was approved by the Cantonal Ethics Committee of Zurich and by Swissmedic and registered at ClinicalTrials.gov (NCT02342366). All participants gave written informed consent according to the Declaration of Helsinki and were compensated for their participation.

2.2. Procedure

The study design consisted of four sessions: screening session, experimental day I, experimental day II, and follow-up session, all separated by an interval of seven days. We used a randomized, double-blind, placebo-controlled, and balanced cross-over design. A trained psychiatrist carried out a Structured Clinical Interview for DSM-IV Axis-I Disorders during the screening session. We assessed drug use with the Interview for Psychotropic Drug Consumption (Quednow et al., 2004). Subjects also performed the Mehrfachwahl-Wortschatz-Intelligenztest (Lehrl, 2005), a standardized German vocabulary test, in order to estimate potential premorbid verbal IQ. Finally, in the screening session subjects performed a brief neuropsychological test battery to assure normal cognitive functions (data not shown). On the experimental days a peripheral venous catheter for blood sampling was placed at 8:30am, and GHB (Xyrem® solution; 20 mg/kg in juice) or placebo (salted juice) was given orally at 9:00am. Each experimental session lasted for 225 min (Supplementary Fig. 1). Subjects had to be fasting during the morning of the experiments. At the follow-up session, the neuropsychological test battery of the screening session was repeated (data will be published elsewhere).

2.3. Measures

2.3.1. Subjective effects

For the measurement of acute subjective drug effects we used four Visual Analogue Scales (VAS) assessing the general drug effect, sedation, stimulation, and dizziness at the time points *t*-15, +40, +60, +100, +120, and +180 min, as well as a GHB Specific Questionnaire (GSQ) (Kim et al., 2008) at *t*-17, +38, +66, +104, +138, +198 min. The GSQ consists of 15 sensory-motor and cognitive items measuring involuntary muscle jerking, silliness, happiness, loss of memory or amnesia, acoustic hallucinations, increased sexuality, visual hallucinations, tendency to talk, disinhibition, heightened sense of touch, increased sensitivity to sound, stimulation, euphoria, and vitality. Subjects rate the occurrence/intensity of each item via five scales, ranging from 0 to 4 ("not present" to "strong").

2.3.2. Charity donation task

Subjects performed a computer-based Charity Donation Task (CDT, adapted from Hare et al. (2010) at *t* + 70 min. Subjects were asked to read a description of 10 charities (Supplementary Table 1), and were then informed that they could donate 0–40 Swiss Francs (CHF) from their study compensation to one of the listed charities. Finally, subjects were asked to rate on a 7-point rating scale ("not at all" to "very much"), how much the charity deserved the donation, and how much pleasure the subject felt about having donated.

2.3.3. Social value orientation

The Social Value Orientation (SVO) test was implemented at *t* + 90 min. It is a paper-based, resource allocation test to assess social behavior (Murphy et al., 2011). The subjects were instructed to choose their favorite joint distribution between themselves and another person, from six primary and nine secondary SVO slider items with a resource allocation choice over a defined continuum of