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# Gamma-hydroxybutyrate (GHB) reduces operant behavior without impairing working memory in rats responding under fixed-consecutive-number schedules

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**Abstract**

The use of gamma-hydroxybutyrate (GHB), a therapeutic agent and recreational drug, has increased since the late 1990s. Researchers have primarily studied GHB's neurochemical, discriminative, and reinforcing effects, but little is known about the drug's effects on learning, memory, or other complex behavioral processes. This study examined the acute and chronic effects of GHB in rats responding under fixed-consecutive-number (FCN) schedules, which assess working memory. Additionally, we examined stimulus control and response effort as modulators of GHB's effects. GHB dose-dependently reduced operant activity and response rates, but tolerance developed to these effects. GHB had no effect on accuracy or efficiency (i.e., working memory). Stimulus control and response effort did not modulate GHB's effects. These results suggest that GHB produced non-selective behavioral disruption but not working memory impairment.


*Keywords:* Gamma-hydroxybutyrate; GHB; Xyrem®; Fixed-consecutive-number schedules; Working memory; Conditional discriminations; Stimulus control; Response effort; Tolerance; Rats

Gamma-hydroxybutyrate (GHB), a metabolite of gamma-aminobutyric acid (GABA), is a drug of abuse, a putative neurotransmitter, and a therapeutic agent (Nicholson and Balster, 2001). GHB produces its effects in the mammalian nervous system, in part, by binding with GHB and $GABA_B$ receptors, although the drug may also interact with other receptors (Carter et al., 2004). GHB receptors occur in diverse areas of the CNS, with high concentrations located in structures relevant to neurobehavioral processes, including the hippocampus, hypothalamus, and basal ganglia (Nicholson and Balster, 2001; Wong et al., 2004). In humans, GHB shares some effects, notably sedation and euphoria, with other GABA-ergic drugs, such as ethanol, pentobarbital, and triazolam (Carter et al., 2006; Freese et al., 2002; O'Connell et al., 2000). Reported adverse effects of acute GHB administration include motor impairment, nausea and vomiting, agitation, confusion, amnesia, lack of balance, dizziness, drowsiness, sleep, loss of consciousness, anesthesia, coma, and death (Bialer, 2002; Ferrara et al., 1999; Xyrem®, 2005). Chronic use can result in tolerance to at least some of these effects and physical dependence (Galloway et al., 1997; Miotto et al., 2001).

GHB gained public attention due to its use to facilitate sexual assault and as a recreational drug of abuse (DEA, 2001; Galloway et al., 2000; Nicholson and Balster, 2001). Public concern regarding the safety and increased use of GHB led the USA to pass the Hillary J. Farias and Samatha Reed Date-Rape Drug Prohibition Act of 1999 (Pub. L. 106–172) and to assign GHB as a Schedule I drug of the Controlled Substance Act in 2000. Furthermore, that same year, the National Institute on Drug Abuse (NIDA) discussed GHB and its two precursors, gamma-butyractone (GBL) and 1,4-butanediol (BDL), both of which are found in commercially available solvents, as the first "Internet drugs" because of the online availability of recipes for these substances. In 2005, the Drug Abuse Warning Network (DAWN) estimated number of emergency room visits for GHB abuse or misuse was 1861, this was down slightly from 2004, in which 2340 visits occurred (SAMHSA, 2005).

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Although GHB originally gained widespread public attention due to its illegal uses, the drug also has therapeutic uses for some medical conditions, and research into new indications continues. For example, recently the use of GHB was approved by the Food and Drug Administration (FDA) in 2002 (at Schedule III status) as an orphan drug under the name *Xyrem®* for the treatment of cataplexy in narcoleptic patients (Fuller and Hornfeldt, 2003; Fuller et al., 2004; Xyrem®, 2005). In Europe, clinical trials have successfully used GHB to treat alcohol-and heroin-dependence (e.g., Gallimberti et al., 1993, 1994, 2000; Nimmerrichter et al., 2002). Additionally, GHB has been examined as treatment for sleep apnea and schizophrenia and as an anesthetic (Galloway, 2000; Lane et al., 1991). Increasing recognition of GHB's therapeutic uses will likely result in more people taking the drug, perhaps for relatively long periods of time. Therefore, it is important to assess the behavioral effects of GHB.

In attempting to characterize GHB's behavioral effects, most studies have examined the drug's effects on motor activity, as a discriminative stimulus, or as a reinforcer (e.g., Baker et al., 2004; Beardsley et al., 1996; Benton et al., 1974; Carter et al., 2003, 2006; Colombo et al., 1995a,c; Cook et al., 2002, 2006; Lobina et al., 1999; Metcalf, 2001; Winter, 1981; Woolverton et al., 1999). Some studies have examined GHB's effects on schedule-controlled operant behavior, typically lever-press responding under fixed-ratio (FR) schedules of appetitive reinforcement (e.g., Carter et al., 2004; Cook et al., 2002; Lamb et al., 2003). In these studies, GHB produced dose-dependent reductions in response rates, with effective doses near 200 mg/kg and above.

Despite the recent increase in research on the behavioral effects of GHB, only a few studies have examined the drug's effects in nonhuman assays relevant to learning, memory, or other complex behavioral processes (Sircar and Basak, 2004). These studies have reported conflicting results, with some studies reporting that GHB had no effect on memory (Ferrara et al., 1999; Nakamura et al., 1987) and others reporting significant memory impairments following GHB administration (Davila et al., 2004; Luna et al., 2002; Sircar and Basak, 2004). There are many possible reasons for these discrepant findings (e.g., the use of different assays and species). Nevertheless, given these equivocal findings, GHB's neurobiological effects, and reports of GHB-induced confusion and memory impairment in humans (e.g., Carter et al., 2006; Grove-White and Kelman, 1971; Wong et al., 2004; Xyrem®, 2005) further investigation of GHB's effects on memory appears warranted. Therefore, we sought to characterize the acute and chronic effects of GHB on working memory in rats responding under fixed-consecutive-number (FCN) schedules of reinforcement (Mechner, 1958a,b).

FCN schedules require subjects (e.g., rats) to respond a fixed number of times on a *work lever* and then respond once on a separate, *reinforcement lever*. Sequences of responses on the work lever preceding a response on the reinforcement lever are termed *response runs*, and the nominal *run length* defines the work requirement for reinforcer delivery. The percent of runs that meet the work requirement, resulting in reinforcer delivery, quantifies the accuracy of the conditional discriminations (i.e., the functioning of subjects' working memory). FCN schedules have proven utility in the study of the effects of sedative and other drugs on working memory (e.g., Doty et al., 1992; Evenden, 1998; Evenden and Ko, 2005; Picker et al., 1986a,b; Snodgrass et al., 1997; Willmore et al., 2001a,b). In addition, FCN schedules allow for the examination of various environmental determinants of drug action, such as external stimulus changes and response effort, which may influence drug effects on memory under these schedules (e.g., Clark and Poling, 1990; Laties, 1972; Picker, 1988; Szostak and Tombaugh, 1981). The identification of variables that modulate GHB's effects may help predict situations in which the drug would likely produce more severe disruption in human users' behavior. Currently, scant information exists on the variables that modulate GHB's effects on memory.

Although examination of GHB's acute effects is important, it is also of interest to determine the extent to which tolerance develops to GHB's effects on memory, given that researchers have reported tolerance to some of the effects of GHB in humans (Dyer et al., 2001; Galloway et al., 1997) and nonhumans (Bania et al., 2003; Colombo et al., 1995b; Van Sassenbroeck et al., 2003). Therefore, we investigated the development of tolerance to GHB's effects. To summarize, this study sought to characterize the effects of GHB on working memory, the influence of two environmental variables (external stimulus changes and response effort) on these effects, and the development of tolerance to these effects.

## 1. Method

### 1.1. Subjects

Eleven experimentally naïve male Sprague–Dawley rats (Charles River, Portage, MI), approximately 50 days old at the start of the study, served as subjects. Rats were randomly assigned to one of two groups (FCN 8 or FCN 16) of six rats each. (A twelfth rat, in the FCN 8 group, became ill and did not complete testing; its data are not reported.). Rats were housed individually in plastic home cages (24 cm wide × 31.5 cm long × 21 cm high) located in a colony room maintained on a 12-hr light/12-hr dark schedule and kept at a relatively constant temperature (20–22 °C). Rats were maintained at 80% ad libitum weights. Throughout the study, rats had free access to water in their home cages. This study was conducted in accordance with the *Guide for the Care and Use of Laboratory Animals* promulgated by the National Research Council (National Academy of Sciences, 1996) and was approved by a university Institutional Animal Care and Use Committee.

### 1.2. Apparatus

All experimental sessions were conducted in six operant conditioning chambers, each 31.5 cm long × 25.5 cm wide × 25 cm high (Med Associates, Georgia, VT). Each chamber contained two retractable response levers located 6 cm above the floor on the right and left sides of the front