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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

response panel. The left and right levers were designated as the work and reinforcement levers, respectively. Each lever had a white 28-v stimulus light located above it. An aperture located 2 cm above the floor in the middle of the response panel allowed access to a food cup. A food-delivery mechanism provided 45-mg food pellets (BioServ, Frenchtown, NJ). An overhead 28-v light signaled which component of the multiple schedule was in effect (off for the FCN-S^D component and on for the FCN). Each chamber was housed in a sound-and light-attenuating shell equipped with an exhaust fan that provided masking noise and ventilation. Experimental events were controlled and recorded by MED-PC® software (v. IV for Windows) operating on an IBM-compatible personal computer interfaced with the operant chambers using MED Associates equipment.

1.3. Drug

GHB (National Institute on Drug Abuse, Rockville, MD) was dissolved in sterile water prepared at an injection volume of 1 ml/kg in sterile vials and was injected i.p. with a sterile syringe 10 min prior to behavioral testing. Following injections, rats were immediately placed in the operant conditioning chambers, which remained darkened until the start of the session. The pre-session injection interval was based on pilot data from our laboratory.

1.4. Behavioral procedures

Before experimental procedures began, all rats received, on two consecutive days, 30-min sessions of exposure to a variable-time (VT) 30-s schedule of pellet delivery, in which food pellet deliveries occurred on average every 30 s regardless of the rats' behavior. Levers were retracted during VT sessions. All rats approached the food cup and ate the pellets immediately after each pellet delivery, and no food pellets remained following these sessions.

Following VT sessions, rats were trained to press the work lever on an FR 1 schedule of pellet delivery. When rats made at least 100 responses in two consecutive 1-hr sessions, the schedule changed to a FCN 1-S^D (with S^D indicating the addition of an external discriminative stimulus upon completion of the work requirement). This schedule required one response on the work lever followed by one response on the reinforcement lever for pellet delivery. When the percent of reinforced response runs reached 80% in two consecutive sessions, the work requirement increased until the terminal FCN value was reached for each group (i.e., FCN 8 and FCN 16). At that time, one group started training under a multiple FCN 8-S^D FCN 8 and the other group started training under a multiple FCN 16-S^D FCN 16 schedule. As indicated above, groups were formed via random assignment before training started.

Under the multiple schedules, the FCN-S^D component started each session and the components alternated, with each occurring three times per session. At the start of the FCN-S^D component, the house light remained off and the left light switched on. The left light remained on until rats met the work requirement, at which point the left light switched off and the right light switched on. Following pellet delivery, the lights returned to their starting values (i.e., left on, right off). At the start of the FCN component, the house light switched on and remained on until the component ended. No other stimuli changed during the FCN component. Under both components, runs shorter than the nominal required run length (i.e.,<8 or <16) reset the counter. Components switched when rats earned 10 pellets or 5 min had elapsed, whichever came first. Thus, experimental sessions ended after rats earned 60 pellets (30 in the two schedules) or 30 min had elapsed. For both groups, most baseline and vehicle sessions ended when rats earned 60 pellets before 30 min had elapsed. Sessions were conducted at approximately the same time each day.

1.5. Pharmacological procedures

During the acute phase, doses of GHB were administered according to a BBCD design, in which B represents baseline (no-injection sessions), C represents vehicle control sessions, and D represents drug sessions. Vehicle was administered only if behavior did not differ substantially across the two previous baseline sessions, and drug was administered only if behavior on vehicle control days did not differ substantially from the previous two baseline days. Doses started at 100 mg/kg and increased by 100 mg/kg in an ascending order until a given rat reached a terminal dose that suppressed responding such that it earned 20% or fewer of available pellets in either component (i.e., 6 pellets or fewer). Each dose was administered once.

Following the terminal acute dose, rats were returned to baseline conditions for at least 10 sessions, after which the chronic phase began. During this phase, rats received a single daily injection for at least 20 consecutive days. The initial dose for the chronic phase was 100 mg/kg lower than the terminal dose that suppressed responding during the acute phase. The chronic dose for 6 of the 11 rats (3 in the FCN 8 group, 3 in the FCN 16 group) was 200 mg/kg; it was 300 mg/kg for the remaining five. Performance did not differ as a function of the chronic dose administered, so data for rats that received 200 and 300 mg/kg chronic doses were combined for analysis.

When a given rat's performance under chronic administration achieved stability (i.e., accuracy showed no visually evident trend) for five consecutive sessions (following at least 15 days of daily injections), that rat started its ascending series of substitution doses, beginning at 0 mg/kg and increasing by 100 mg/kg. Substitution doses occurred about every other day until a dose was reached that suppressed responding such that a rat earned 20% or less of the available pellets in either component (i.e., 6 or fewer pellets). Each substitution dose was administered once. Following sessions in which substitution doses were lower than the chronic dose, each rat received a make-up dose that brought its daily dose equal to its nominal chronic dose.

1.6. Response measures and data analysis

Four response measures were recorded for each experimental condition: operant activity, accuracy, running rate, and efficiency.

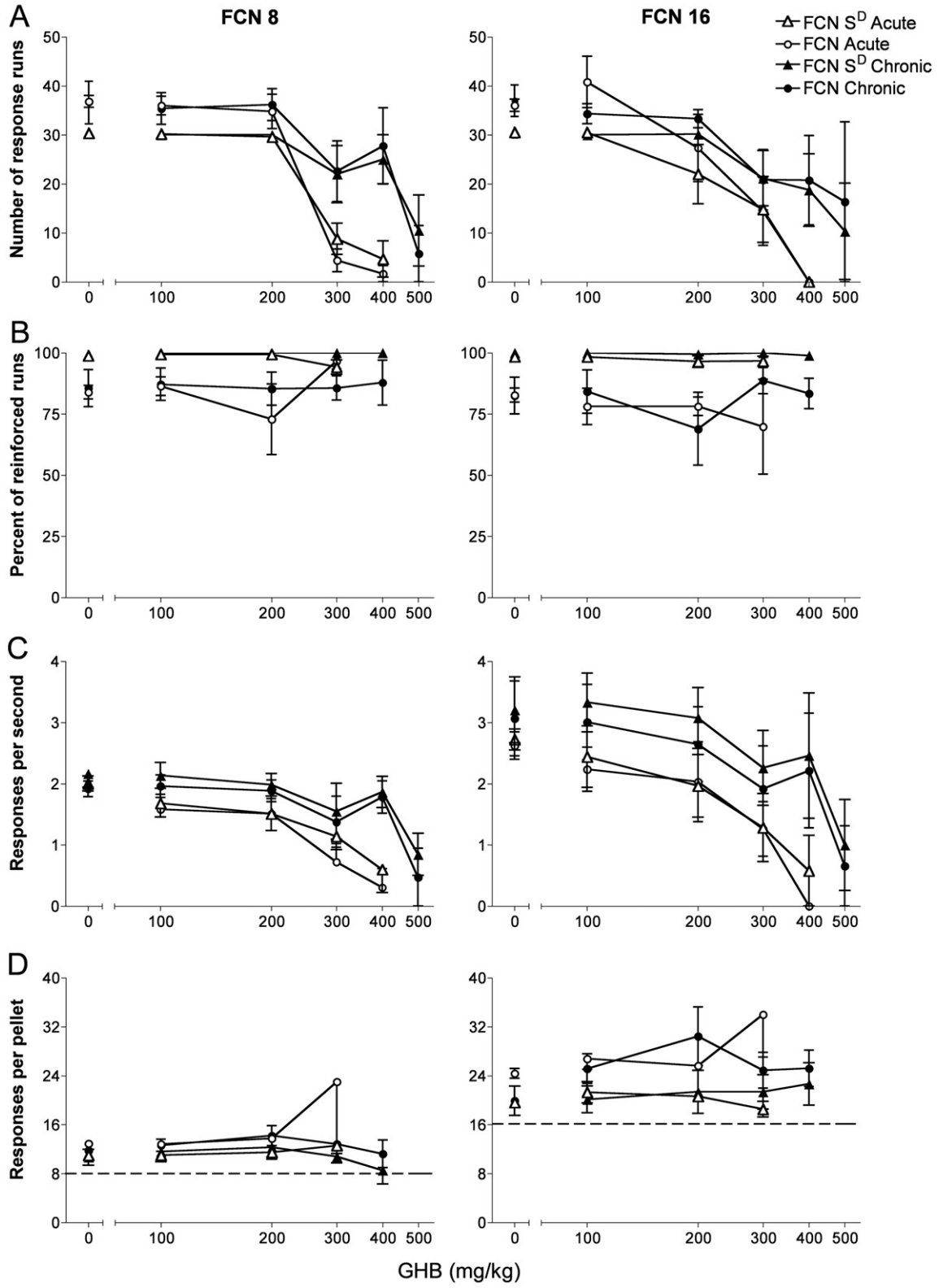

Fig. 1. Effects of GHB under all experimental conditions. The left-hand graphs depict data for the FCN 8 group ($n=5$ rats) and the right-hand graphs depict data for the FCN 16 group ($n=6$ rats). Each data point represents the mean (±1 SE) for all rats in each condition. Open points represent data from the acute phase and solid points represent data from the chronic phase. Triangles represent data for the FCN-S^D component and circles represent data from the FCN component. Panel A depicts the number of response runs (operant activity). Panel B depicts the percent of reinforced runs (accuracy). Panel C depicts responses per second during response runs (running rates). Panel D depicts the number of work-lever responses per pellet earned (efficiency); the dashed line indicates perfectly efficient performance for each group. Accuracy and efficiency graphs do not include data for severely impaired performances, so these graphs show fewer data points than the graphs for operant activity and running rates. Note that GHB dose is plotted on a logarithmic scale.

Operant activity, defined as the number of response runs completed under each condition, reflects the extent to which rats engaged in the operant task as opposed to some other behavior (e.g., grooming, sleeping). Accuracy, defined as the percent of reinforced runs [(number of reinforced runs/total number of runs)×100], quantifies the ability of rats to recall the number of work-lever presses they just emitted. Running rate, defined as the response rate within each run (total work-lever responses in each run/seconds within each run), indicates the mean speed with which rats completed each response run. Efficiency, defined as the mean number of work-lever responses per pellet (total number of work-lever responses/number of pellets earned), provides a measure of the approximate length of the typical response run, with most efficient responding equal to the nominal work requirement for a given rat's group.

Following the rationale described by Willmore et al. (2001a, b), the accuracy and efficiency measures exclude data for rats that made fewer than 180 total lever presses in a given session. Briefly, this exclusion minimizes the confounding of changes in working memory with non-specific changes produced by severe drug-induced impairment. Because the operant activity and rate measures do not reflect working memory they do include these data. To avoid making inferences based on data from a single rat, calculation of all measures only include data for those conditions in which $n>1$. To quantify the effects of the independent variables, ED_{50} values and 95% confidence intervals (95% CIs) were computed using the method described by Tallarida (2000, pp. 26–31). All doses were transformed to $\log_{10}$ (dose) for these analyses. Dose–response curves for the FCN-S^D and FCN schedules greatly overlapped, so their data were combined to assess the effects of the other experimental manipulations. The ED_{50} values for $\log_{10}$ (dose) were obtained by fitting regression lines to at least three points on the descending limb of each dose–response curve, except in cases where this portion of the curve consisted of one dose that had little effect on responding (>75% of control) and a second dose that substantially reduced responding (<25% of control). When this occurred, the ED_{50} values were calculated using these two doses and interpolation (cf. Carter et al., 2004; Doty et al., 1992). ED_{50} values were considered statistically different when their respective 95% CIs did not overlap. Analyses were conducted using Excel® for Mac OS X (Microsoft, Corp., Redmond, WA) and GraphPad Prism® for Mac OS X (v. 3.0; GraphPad Software, Inc., San Diego, CA).

2. Results

2.1. Operant activity

Fig. 1 (Panel A) depicts, for the acute and chronic phases, the effects of GHB on operant activity for the FCN 8-S^D and FCN 8 components (left graph) and the FCN 16-S^D and FCN 16 components (right graph). For the FCN 8 group, acute and chronic administration of lower doses (100–200 mg/kg) generally had small effects on rats' performance of the operant response compared to vehicle, whereas higher doses (300 mg/kg and above) greatly suppressed operant activity. Although higher doses of GHB suppressed responding in both phases, these doses produced greater reductions in the number of response runs in the acute phase versus the chronic phase. For example, in the acute phase 300 mg/kg reduced the number of runs to 19.83% of control but only reduced this measure to 66.77% of control in the chronic phase. Similarly, 400 mg/kg reduced the number of runs to 9.51% of control in the acute phase compared to 78.97% of control in the chronic phase. Finally, 500 mg/kg given in the chronic phase had smaller effects (24.33% of control) than did either 300 or 400 mg/kg given in the acute phase. The FCN 8 group's ED_{50} values (95% CI) for the acute and chronic phases equaled 255.22 (243.69–267.29) and 450.23 (415.28–488.16), respectively. For the FCN 16 group, the pattern of results was generally similar, except that the descending limbs of the dose–response curves for the acute and chronic phases were less steep than those limbs in the FCN 8 group and the FCN 16 group showed more variability. Nevertheless, tolerance developed to the response-suppressing effect of higher doses of GHB in the FCN 16 group, with this group's ED_{50} values (95% CI) for the acute and chronic phases equaling 249.34 (205.65–302.32) and 420.70 (305.66–579.03), respectively. In sum, these data demonstrate that GHB suppressed operant responding to a similar extent in both groups and that tolerance developed to this effect.

2.2. Accuracy

Mean accuracy after vehicle administration did not differ between the FCN 8 S^D and FCN 16 S^D components or between the FCN 8 and FCN 16 components. Regardless of phase and run length, mean accuracy following vehicle administration averaged 14.93% higher (95% CI=9.611–20.24%) in the presence of an external discriminative stimulus than in its absence. Visual inspection of Fig. 1 (Panel B) indicates that doses of GHB did not systematically change accuracy, relative to vehicle, under any experimental condition. Nevertheless, higher doses of GHB appeared to have greater effects under the FCN component, especially in the FCN 16 group. The lack of curvature in the dose–response plot made calculation of ED_{50} values impossible.

2.3. Response rate

Fig. 1 (Panel C) depicts running rates (responses per second) for each experimental condition. The FCN 16 group generally had higher rates and showed more variability than did the FCN 8 group. The dose–response curves for the two groups show similar patterns to those seen in the operant-activity measure. In the acute phase, 100–200 mg/kg produced relatively small decreases in rates compared to vehicle, whereas 300–400 mg/kg produced larger reductions in this measure. Moreover, rates in the acute phase showed larger decreases than did those in the chronic phase. Again, the two groups demonstrated comparable ED_{50} values. The FCN 8 group's ED_{50} values (95% CI) for the acute and chronic phases equaled 284.74 (271.53–298.60) and 465.71 (433.49–500.34), respectively. The FCN 16 group's ED_{50} values (95% CI) for the acute and chronic phases equaled

272.49 (225.92–328.66) and 448.12 (391.06–513.50), respectively. Regardless of stimulus conditions or FCN value, higher doses of GHB reduced response rates, but did so to a lesser extent in the chronic phase compared to the acute phase. That is, tolerance developed to this effect, as indicated by an increase in the ED_{50} values from the acute phase to the chronic phase.

2.4. Efficiency

Fig. 1 (Panel D) depicts the mean number of work-lever responses per pellet earned. Under vehicle conditions, rats in both groups made more than the required number of responses per pellet. For most rats in the FCN 8 group, the range of doses of GHB had little effect on efficiency, but one rat showed a large increase in this measure at the 300 mg/kg dose. For the FCN 16 group, the results were generally similar, but there was more separation in the dose–response curves for the FCN-S^D and the FCN components, with the FCN-S^D component showing slightly better efficiency. In addition, the FCN 16 group was much less efficient than the FCN 8 group, as indicated by the distance of the former group's data from the optimum value for this measure (i.e., 16 responses per pellet). As with the FCN 8 group, one rat in the FCN 16 group showed a large increase in the efficiency measure at 300 mg/kg. Visual inspection of Fig. 1 (Panel D) indicates that doses of GHB did not systematically change efficiency, relative to vehicle, under any experimental condition. The lack of curvature in the dose–response plot made calculation of ED_{50} values impossible.

3. Discussion

This study sought to: (a) characterize the effects of acute and chronic administration of several doses of GHB on rats' responding under FCN schedules of food reinforcement, and (b) examine the effects of two procedural manipulations (i.e., external stimulus changes and response effort) that previously have been shown to influence the effects of sedative drugs (e.g., Evenden, 1998; Picker et al., 1986a,b; Picker, 1988; Snodgrass et al., 1997). Acute administrations of GHB produced dose-dependent reductions in operant activity and response rates. The decreases in these two measures suggests that higher doses of GHB suppressed responding by non-selectively interfering with the rats' ability to engage in the operant response. Other studies of GHB have reported similar suppression of operant responding within a dose range comparable to that used in this study (e.g., Carter et al., 2004; Cook et al., 2002; Redgrave et al., 1982). The behavioral suppression observed in this study likely resulted from the drug's depressant effects on locomotor activity. Several studies have reported GHB-induced reductions in locomotor behavior (Benton et al., 1974; Colombo et al., 1995b; Cook et al., 2006). The doses used in these studies are similar to those used in the present study, so it seems likely that GHB produced its disruptions in operant behavior via motor impairment.

During the chronic phase, GHB also reduced operant behavior, but it did so at higher doses compared to the acute phase. The increases in ED_{50} values from the acute phase to the chronic phase for both operant activity and running rates demonstrate that tolerance developed to the behavioral disruption produced by higher doses of GHB. Despite procedural differences, these findings are consistent with those of previous studies that found tolerance to GHB-induced behavioral disruption (Bania et al., 2003; Colombo et al., 1995a,b,c). Moreover, the demonstration of tolerance to the behavioral effects of GHB is consistent with reports of tolerance in human users (Nicholson and Balster, 2001).

After controlling for severely intoxicated performances (cf. Willmore et al., 2001a,b), GHB did not systematically affect accuracy or efficiency of responding. In other words, doses of GHB did not impair working memory as measured under our procedures. The lack of GHB-induced memory impairment observed in our study is consistent with the findings of some studies (Ferrara et al., 1999; Nakamura et al., 1987) but not others (Luna et al., 2002; Davila et al., 2004; Sircar and Basak, 2004). Given the drug's reported ability to produce confusion and amnesia in human users (e.g., Xyrem®, 2005), it is not clear why these cognitive effects do not consistently appear in assays with nonhumans.

A possible reason why we did not observe memory impairment in this study is that both the FCN-S^D and FCN schedules established strong, stable baseline levels of behavior that were relatively resistant to the disruptive effects of GHB until rats received doses that eliminated responding. Rats underwent several weeks of training before drug testing, and their behavior appeared to be under strong schedule control, regardless of the addition of the external stimulus change in the FCN-S^D schedule. The substantial overlap seen in the FCN-S^D and FCN dose–response curves provides evidence that both schedules engendered similar levels of schedule-controlled behavior. Arranging multiple FCN-S^D FCN schedules has been found to establish FCN responding that is more resistant to drug effects than responding maintained under simple FCN schedules (Snodgrass et al., 1997). Examining behavior that is weakly controlled by the prevailing schedule of reinforcement and stimulus conditions (e.g., behavior in transition) may allow for more sensitive detection of GHB's effects on memory.

The addition of an external discriminative stimulus and manipulating response effort did not systematically influence GHB's effects, in contrast to other studies that found that these variables often modulate the effects of drugs under FCN schedules (e.g., Clark and Poling, 1990; Evenden, 1998; Laties, 1972; Picker, 1988; Picker et al., 1987; Snodgrass et al., 1997). Interestingly, Sircar and Basak (2004) found that GHB disrupted spatial memory in the Morris Water Maze only when the platform was hidden from rats' sight, but adding an external stimulus (a flag) to the platform attenuated GHB's effects on memory. The lack of interaction between GHB and stimulus conditions in our study could have resulted from a relatively high level of stimulus control engendered by the multiple schedules. Under baseline conditions, accuracy was relatively high (above 75%) regardless of whether or not an external discriminative stimulus was programmed. It is not too surprising, then, that similar drug effects were observed under

both stimulus conditions. Although clear differences in the effects of GHB doses between the FCN 8 and FCN 16 groups were not apparent, the FCN 16 group generally showed more variability in responding, especially as the dose of GHB increased. The failure of response effort to modulate GHB's effects may be due to relatively small difference in work requirements, and it is possible that a larger difference would have resulted in more clear modulation of GHB's effects.

Although we did not observe clear GHB-induced changes in working memory, we did find that GHB produced steep dose–response curves for measures of behavioral output, with small differences between doses that produced little effect and doses that produced severe behavioral disruption. This finding is consistent with other reports of GHB's effects (e.g., NIDA, 2000; Goodwin et al., 2005). The possibility of GHB producing general or specific behavioral impairment (e.g., sedation or disruption of working memory) should be examined carefully in the post-marketing surveillance of GHB as a therapeutic agent. That significant impairment will occur is not, however, foregone. The present findings suggest that GHB disrupted behavior only at relatively high doses, for which pronounced sedative actions are obvious. Human patients are unlikely to receive comparable doses. Moreover, the present findings demonstrate some degree of tolerance to the behavioral disruption produced by GHB. Such tolerance might well mitigate behavioral disruption as a side effect, because the treatment of cataplexy involves chronic exposure to GHB (Xyrem®, 2005). Be that as it may, the present findings and those of prior investigations provide clear evidence that high doses of GHB – which sometimes are self-administered or administered to unsuspecting others by GHB abusers – produce general and marked behavioral disruption. Such disruption is one of several risks the drug poses for users, and to society at large.

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