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Self-administration of gamma-hydroxybutyric acid (GHB) precursors gamma-butyrolactone (GBL) and 1,4-butanediol (1,4-BD) in baboons

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Abstract

Rationale—Gamma-butyrolactone (GBL) and 1,4-butanediol (1,4-BD) are gamma-hydroxybutyrate (GHB) pro-drugs and drugs of abuse.

Objective—Given the reports of abuse, and the ease at which GBL and 1,4-BD may be obtained, we investigated the reinforcing of GBL (n=5) and 1,4-BD (n=4) in baboons using IV self-administration procedures.

Methods—Sessions ran 24 h/day. Each injection was contingent upon completion of a fixed number (120 or 160) of lever responses. A 3-h timeout period followed each injection, limiting the total number of injections to 8/day. Self-administration was first established with cocaine (0.32 mg/kg/injection). GBL (10–130.0 mg/kg/injection), 1,4-BD (10–100 mg/kg/injection) or vehicle were substituted for cocaine at least 15 days. Food pellets were available ad libitum 24 h/day and were contingent upon completion of 10 lever responses.

Results—GBL (32–100 mg/kg/injection) maintained significantly greater numbers of injections when compared to vehicle in 4 of 5 baboons and mean rates of injection were high (>6 per day) in 3 baboons and moderate in the fourth baboon (4–6 per day). 1,4-BD (78–130 mg/kg/injection) maintained significantly greater numbers of injections when compared to vehicle in only 2 out of 4 baboons and rates were moderate to high in both baboons. Self-injection of these doses of GBL and 1,4-BD generally inhibited food-maintained responding.

Conclusions—GBL and 1,4-BD have abuse liability. Given that GBL and 1,4-BD are self-administered, are easier to obtain than GHB, and are detected in seized samples, additional legal control measures of these GHB pro-drugs may be needed.

Keywords

gamma-hydroxybutyrate; Self-Administration; Abuse Liability; Zolpidem; Cocaine; Reinforcement; Operant Behavior; Drug Abuse

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Conflict of Interest

The authors have no conflict of interest.

Introduction

Gamma-hydroxybutyrate (GHB) is currently used therapeutically to treat narcolepsy. Following escalating reports of its recreational abuse, GHB received a dual classification under the Controlled Substances Act in 2000. A specific formulation containing GHB (sodium oxybate, Xyrem®) is a Schedule III substance approved for medical use, but all other forms of GHB are DEA Schedule I substances (DEA 2000). Gamma-butyrolactone (GBL) and 1,4-butanediol (1,4-BD) are GHB pro-drugs used commercially as industrial solvents and for the manufacturing of paints, plastics, textiles and other chemicals. Illicit use of GBL and 1,4-BD increased following legal restrictions on the production and sale of GHB (Carter et al. 2009; Palmer 2004; Wojtowicz et al. 2008; Wood et al. 2011). The widespread and legitimate commercial use of GBL and 1,4-BD makes the control of these compounds difficult.

The abuse potential of a drug is influenced by a number of variables including drug availability, the form in which the drug is available, bioavailability, and other pharmacokinetic parameters such as onset and duration of drug effects. Both GBL and 1,4-BD are rapidly metabolized into GHB after ingestion. GBL is metabolized into GHB via serum lactonase while 1,4-BD is metabolized in a two-step conversion via alcohol dehydrogenase into gamma-hydroxybutyraldehyde and then into GHB (Andresen et al. 2011; Roth and Giarman 1965; Snead et al. 1989). An additional risk is that both GBL and 1,4-BD can be converted to GHB prior to ingestion using instructions easily found on the Internet (Andresen et al. 2011), which has emerged as a popular marketplace for purchasing psychoactive substances including GHB pro-drugs (Hillebrand et al. 2010; Jones 2010; Karila and Reynaud 2010).

Recreational users of GHB, GBL, and 1,4-BD typically ingest the compounds orally and report feelings of euphoria, relaxation, drowsiness, and disinhibition. However, the range between doses used recreationally and overdose is very narrow. Adverse effects, such as nausea, vomiting, anxiety, dizziness, agitation, respiratory depression leading to coma, and sometimes death have been reported (Galloway et al. 2000; Karila and Reynaud 2010; Miotto et al. 2001; Teter and Guthrie 2001). The behavioral effects of GBL and 1,4-BD are most likely associated with their conversion to GHB (Andresen et al. 2011; Duer et al. 2001; Shannon and Quang 2000). Indeed, we previously examined the pharmacokinetics and acute behavioral effects of GHB, GBL and 1,4-BD administered via an intragastric (IG) catheter and found that the onset and duration of behavioral effects of GBL and 1,4-BD drug correlated with plasma levels of GHB (Goodwin et al. 2009; Goodwin et al. 2005). Compared to acute administration of GHB, however, GBL and 1,4-BD administration resulted in a faster onset of behavioral effects which were associated with higher maximum concentrations of GHB in plasma and shorter times to maximum concentrations (Goodwin et al. 2009). Given that these GHB pro-drug are less regulated and more readily available than GHB, and appear to be more potent with a faster onset of action, they may have greater abuse liability than GHB. Only one other study has examined the reinforcing effects of GBL and 1,4-BD under short-term limited access condition, and results were negative (McMahon et al. 2003).

The current study examined the IV reinforcing effects of a wider range of doses of both GBL and 1,4-BD than examined previously (McMahon et al. 2003), using a 24-hr procedure and long-term drug access. Individuals who abuse GHB and its pro-drugs report around-the-clock patterns of intake with dosing every 2–3 hours (Andresen et al. 2011; Galloway et al. 1997; McDonough et al. 2004; Palmer 2004; Stein et al. 2011). In our procedure, each dose of GBL and 1,4-BD was substituted for cocaine for at least 15 days during sessions that ran continuously (24 h/day). Drug access was limited to a maximum of 8 injections per day by a

3-h timeout between each injection. We previously reported that GHB maintained IV self-administration and functioned as a reinforcer in the majority of baboons using these same procedures (Goodwin et al. 2011). Comparison of self-injection of drug and vehicle under conditions of 24-h access, with long timeouts between injections (hours) and long periods of availability (weeks), has historically provided an accurate assessment of the reinforcing properties of drugs with sedative properties as well as quantitative data for assessment of abuse liability (Ator 2000; Griffiths et al. 1981; Griffiths and Weerts 1997; Weerts et al. 1999). Given the evidence of GBL and 1,4-BD abuse reported via ER visits, drug seizures and case reports (Couper et al. 2004; Ingels et al. 2000; McDonough et al. 2004; Wojtowicz et al. 2008; Wood et al. 2011; Wood et al. 2008; Zvosec et al. 2001), an additional abuse liability evaluation of GBL and 1,4-BD was warranted. The information obtained from these drug self-administration studies can inform considerations regarding possible increased legal control of these compounds, such discussion was a recent topic by the World Health Organization (ECDD 2012).

Methods and Materials

Subjects

Five adult male baboons (*Papio anubis*, Primate Imports, New York, NY) were surgically prepared with chronically indwelling silastic catheters implanted in either femoral or jugular veins (using procedures described in Lukas et al., 1982). The catheters were protected by a vest and tether system described previously (Lukas et al. 1982) and subjects were permitted to adapt to this system for at least 2 weeks prior to surgery. Average body weights for each baboon during the experiment were as follows: DS (34.8 kg), GR (28.0 kg), JN (40.5 kg), KR (22.7 kg), and RG (23.6 kg). Baboons DS, JN, and KR had previous experience self-injecting GHB. Baboons DS, JN, KR, and RG had a history of drug self-injection with various classes of compounds (e.g. stimulants and sedative-anxiolytics). Baboon GR had a history of acute exposure to IG administered GHB, GBL, and 1,4-BD but had no previous self-administration experience.

Tap water from a drinking spout located on the front of the cage was continuously available and water intake was recorded daily. Baboons had ad libitum access to food pellets (as described below) and were given two pieces of fresh produce and a multivitamin at approximately 11:00h each day. As in our previous studies (Goodwin et al. 2009; Goodwin et al. 2005; Goodwin et al. 2006; Weerts et al. 2005), baboons received supplementation with monkey biscuits when pellets per day decreased below 125 g and continued until pellet intake returned to normal levels. Food was supplemented to maintain general health when drug suppression of food-intake was prolonged (3 days or more). In our experience, baboons will return to working for the preferred banana-flavored pellets and leave biscuits as they become tolerant to suppression of food-maintained behavior produced by the drug. Baboons were anesthetized every 2–3 weeks with ketamine hydrochloride (preceded by atropine sulfate) to permit cage washing, weighing, and physical examinations. The facilities were maintained in accordance with USDA and AALAC standards.

Apparatus

Baboons were housed in standard stainless steel primate cages that also served as experimental chambers and have been described in detail previously (Goodwin et al. 2011). Briefly, cages were equipped with an aluminum intelligence panel that was mounted on the rear wall and contained a pull-and-release lever (Med-Associates model ENV-122) for drug self-injection and a vertically-operated lever (Med-Associates model ENV-121). Pellets (1g banana pellets, Bio-Serv, Inc., Frenchtown, NJ) were delivered into a recessed food hopper located in the center of the panel using a pellet feeder. The room ceiling lights were brightly

illuminated for 13 h/day (6:00–19:00h) and were dimly illuminated for the remaining 11 h/day.

The catheters were attached to a custom infusion system that allows fluid delivery from three separate peristaltic pumps (Model 1201 or Model 66 Harvard Apparatus, Natick, MA). Drug was injected into the catheter with the first pump and then flushed into the vein with saline from the second pump. To maintain catheter patency, a third pump continuously infused heparinized saline (5–10 units/ml) for a total of 200–250 ml/24h. The peristaltic pumps, infusion systems, drug solutions, pellet feeder and drinking water bottles were located on a metal grating that ran above the cage.

Experimental control and data collection were accomplished using personal computers with MED Associates Inc. (East Fairfield, VT) software and instrumentation.

Drugs

Cocaine hydrochloride (0.32 mg/kg, Research Triangle Institute, Research Triangle, NC) and zolpidem tartrate (0.32–1.0 mg/kg, Research Biochemicals International, Natick, MA) were dissolved in physiological saline at a volume of 5 ml per injection. Cocaine and zolpidem doses were calculated based on the salt. Stock solutions of pure GBL (1.12 g/ml) and 1,4-BD (1.17 g/ml) were obtained from Sigma-Aldrich (St. Louise, MO, USA). Doses of GBL (10.0–130.0 mg/kg) and 1,4-BD (10.0–100.0 mg/kg) were obtained by dilution of stocks with physiological saline to a volume of 10–15 mls per injection. Initial doses selected for testing were based on prior studies in the baboon (Goodwin et al. 2009; Goodwin et al. 2005) and included doses reportedly abused by humans (Bell and Collins 2011; CDC 1999; Ingels et al. 2000; Schneir et al. 2001; Wojtowicz et al. 2008; Zvosec et al. 2001). The large volume of injection was used to match our earlier GHB self-administration study, which required high volume injections for GHB solubility. All drug solutions were sterilized by filtration (25 mm Swinnex, Minipore Corp., Bedford, MA).

Experimental Procedures

Drug Self-injection procedure

The drug self-injection procedure has been described previous (see Goodwin et. al. 2011). Briefly, experimental sessions were continuous (i.e., 24 h/day) and all drug changes and data collection were conducted between 8:00 and 8:30 am. Each injection was available according to a fixed-ratio (FR) 160 reinforcement schedule (FR 120 for GR) on the pull-and-release lever (i.e., completion of the 160 responses produced a drug infusion). Upon completion of the FR response requirement, the drug injection was initiated and then followed by a 5-ml saline flush delivered over approximately 3 min. This was followed by a 3-h time-out period, limiting the total number of injections that could be obtained per day to 8. Responses on the drug lever during the time-out period had no consequence. There was no time limit for completion of the response requirement. At the same time, food pellets (1 g banana-flavored) were continuously available according to an FR 30 response requirement on the vertically-operated lever.

Research technicians observed baboons immediately following the first injection, which generally occurred between 8 and 10am, and throughout the day for each dose of each drug and recorded in the daily records if overt drug-related behaviors were observed (e.g., ataxia, limb tremors, jerks, and vomit/retch). These behaviors have been defined previously (Weerts et al. 2005).

Cocaine substitution procedure

Baboons were first trained to respond for cocaine (0.32 mg/kg/injection) using procedures described previously (Goodwin et al. 2011). Once self-injection responding was established and stabilized (criterion performance was defined as 6–8 self-injections per day for at least 3 consecutive days), a dose of each test drug (GBL and 1,4-BD) or vehicle was substituted for cocaine; the opportunity to self-inject the test dose or vehicle was provided for a minimum of 15 days. The cocaine self-injection baseline was re-established, and criterion performance met, before each dose evaluation. The procedure of replacing the baseline dose of cocaine with a test dose or vehicle was repeated throughout the study. The rationale for using cocaine as a baseline drug was to utilize a short acting drug, which engenders maximum levels of responding using the 24-hr procedure. The reinstatement of the cocaine baseline prior to dose substitution provides evidence that maximal performance was demonstrated for each baboon prior to availability of the test dose, and ensures subjects will sample the test compounds and encounter drug effects. The rationale for the extended access period (15 days) is to allow sufficient time for tolerance to develop to the sedative effects, which may initially suppress responding and stabilization of behavior. Immediately after the substitution of each test dose there is typically a period of transition, followed by stabilization of responding by days 11–15. The period of substitution was occasionally extended beyond 15 days when equipment problems occurred or to further characterize self-injection of doses that were judged to be reinforcing.

After initial assessments of GBL and 1,4-BD, we tested selected doses of zolpidem (0.32 and 1.0 mg/kg) as a comparison drug in some subjects (GR, JN, and RG). Zolpidem is an imidazopyridine sedative/hypnotic that acts as a positive GABA modulator via the benzodiazepine receptor site. Zolpidem was tested as an additional ‘positive control’ as it reliably maintains self-administration in baboons (Griffiths et al. 1992; Weerts and Griffiths 1998). These doses were based on our previous studies as those that maintained the highest rates of zolpidem self-administration (Griffiths et al. 1992; Weerts and Griffiths 1998). Test doses for each baboon included both inactive doses and those that produced overt behavioral effects (sedation/immobility, ataxia, vomiting and food suppression). Due to the steep dose effect curves for these compounds, dose increases were carefully selected based on tolerability of prior doses tested and decisions were aided by results from other baboons tested. KR was tested with GBL, 1,4-BD, and then a second exposure to 1,4-BD. JN and GR were first tested on GBL, followed by 1,4-BD and then a second exposure to 1,4-BD, and then finally zolpidem. RG was first exposed to 1,4-BD, followed by zolpidem, then a second exposure to 1,4-BD, and finally GBL. DS was tested only with GBL; further testing was not possible due to catheter failure.

Data analysis

A single-subject design was used in which each baboon served as his own experimental control. Cocaine was typically maintained for 3–5 days to obtain criterion performance (i.e., 6–8 injections per day for 3 consecutive days). Data reported for cocaine are the grand mean from the last 3 days of the cocaine baseline periods that preceded each test dose throughout the study. The mean number of injections/24 hours over the last 5 days of a test condition was used to represent level of self-injection of each dose and vehicle. The criterion for concluding reinforcement by a dose is defined as a mean rate of self-administration being greater than two standard deviations of the mean (SD) for vehicle (analogous to a one-tailed test). Using classifications defined by our previous studies, rate of self-injection was characterized as high when the mean was greater than 6 to 8 injections per day, moderate when mean self-injection was 4 to 6 injections per day, and low if the mean was below 4 injections per day. Using the same procedures and classifications across studies allows cross drug comparisons of levels of self-administration.

The number of pellets earned each day under the concurrent food reinforcement schedule was analyzed to determine effects of self-injection on food-maintained behavior. Pellets per day were concluded to have changed significantly if the mean number of pellets delivered during the last 5 days of the self-injection period was at least one pellet higher or lower than one SD of the mean intake during the last 5 days of vehicle availability (i.e., analogous to a two-tailed test, because it was predicted that pellets/day could either be increased or decreased).

Results

Figure 1 shows rate of self-injection for individual baboons during periods in which GBL, 1,4-BD (1st exposure and 2nd exposure), zolpidem, and vehicle were substituted for 0.32 mg/kg/injection cocaine and data for the group (excluding GR). For each individual graph, the vehicle data for each drug was pooled to yield a grand mean of all vehicle data for each subject. The mean number of injections over the last 5 days of multiple vehicle substitution periods was less than 3 for all baboons.

GBL doses of 32–100 mg/kg maintained self-administration at levels significantly higher than vehicle in four out of five subjects tested. As shown in figure 1, the mean number of injections/day would be characterized as high in 3 baboons (DS, JN and KR) and moderate in 1 baboon (RG). Baboon GR never took more than 1 injection/day during the last five days of any GBL dose. As shown in Figure 1 (bottom right panel), the mean number of injections for the 4 subjects (DS, JN, KR, RG) in which reinforcement was demonstrated was increased in a dose-dependent manner.

Figure 2 shows the number of injections across consecutive days of self-injection for peak reinforcing doses of (a) GBL and (b) 1,4-BD in comparison to a representative vehicle for individual baboons in which reinforcement was demonstrated. As shown in figure 2a, the pattern of day-to-day self-injection of GBL at these doses was relatively stable across days, with some evidence of an increasing trend in some subjects. Over the last 5 days of GBL availability injections ranged from 3 to 7 injections/day in one subject (RG) and 7–8 injections/day for the remaining three subjects (DS, JN, and KR).

1,4-BD doses of 78 mg/kg and 100 mg/kg maintained self-administration at levels significantly higher than vehicle in two (KR and JN) of the four subjects tested and mean numbers of self-injections would be characterized as moderate (figure 1). Baboon GR never self-administered more than 2 injections of any 1,4-BD dose. During the first exposure to 1,4-BD, baboon RG never took more than 2 injections/day of any 1,4-BD dose (32–78 mg/kg). During the second exposure to 1,4-BD (and following self-administration of zolpidem), the number of injections increased across doses, but the highest mean rate of self-injection at 32 mg/kg (3.8 injections/day) did not exceed the critical value (mean+2SD) of 3.9 injections/day for vehicle for baboon RG. When data for both exposures to 1,4-BD for 3 subjects (JN, KR, RG) were combined (excluded GR), a dose-dependent increase in the mean number of 1,4-BD injections is evident (figure 1).

As shown in Figure 2b, the pattern of 1,4-BD self-injection was relatively stable across days, with an increasing trend over consecutive days of drug availability in the two baboons in which reinforcement was demonstrated. Over the last 5 days of 1,4-BD availability, injections ranged from 5 to 8 for both subjects.

Zolpidem doses of 0.32 and 1.0 mg/kg were tested in the two subjects that did not reliably self-administer 1,4-BD (RG and GR) and in one of the baboons in which both GBL and 1,4-BD maintained self-administration (JN). Both doses of zolpidem maintained self-injection above vehicle in two subjects (RG and JN; figure 1) and the rate of self-injection in these

two subjects was high (6–7 injections/day during the last five days of exposure). Baboon GR did not self-administer either dose of zolpidem tested.

The mean number of food pellets delivered daily across the last five days of vehicle, GBL, and 1,4-BD conditions, along with the mean total dose of each compound that was self-administered during the same periods of time and the cumulative drug intake across 15 days of each drug dose, are described in table 1. Three (DS, JN, and RG) of the four subjects that self-administered GBL at rates higher than vehicle exhibited suppression of food-maintained behavior during self-administration of these doses. In subjects that self-administered GBL significantly above vehicle, the mean total dose (g) across each of the last 5 days of the peak reinforcing dose (DS and JN = 56 mg/kg; KR = 78 mg/kg; RG = 100 mg/kg) ranged from 9.2–16.8 g, with the cumulative intake across 15 days of access ranging from 101.2–217.2 g (table 1). Food-maintained behavior was suppressed in both subjects (JN and KR) that self-administered 1,4-BD (78–100 mg/kg), though results differed between the first and second exposure (table 1). The mean total dose (g) of 1,4-BD self-administered across each of the last 5 days of the peak reinforcing dose (JN and KR = 100 mg/kg) ranged from 15.7–22.8 g, with the cumulative intake across 15 days ranging from 210.2–295.4 g (table 1). The mean total doses of GBL and 1,4-BD over the last five days of access, as well as the cumulative drug intake over the 15 day exposure periods, that were associated with the suppression of food-maintained behavior were variable. In addition, self-injection of 1,4-BD, which was not significantly higher than rates of vehicle self-administration, sometimes resulted in suppression of food-maintained behavior (e.g., baboon RG 78–100 mg/kg).

IV administration of GBL and 1,4-BD produced ataxia, limb tremors, jerks, and vomiting/retching in the three hours following injections. During self-administration of 78 mg/kg GBL (n=5), ataxia, limb tremors, jerks, and vomiting/retching were each observed in three subjects. Ataxia and jerks were noted in both subjects exposed to the 100 mg/kg dose of GBL. During self-administration of 78 mg/kg 1,4-BD (n=4), ataxia was observed in one subject and jerks were observed in two. Administration of 100 mg/kg 1,4-BD (n=4) produced ataxia in three subjects, limb tremors in one subject, jerks in one subject, and vomiting/retching in one subject.

Discussion

The primary finding of the current study was that GBL and 1,4-BD maintained self-administration at one or more doses in most subjects, indicating both compounds functioned as reinforcers using our procedures. One subject (GR) failed to self-administer GBL and 1,4-BD, as well as the positive control drug, zolpidem.

In general, self-administration of GBL and 1,4-BD increased in a dose-related manner in baboons. While higher doses of GBL and 1,4-BD would likely have produced the typical inverted-U dose-response function, the drugs dose response curve is very steep for both GBL and 1,4-BD. Higher doses could not be safely tested due to emergence of overt behavioral effects. In one previous study in rhesus monkeys, lower dose of GBL (0.1–3.2 mg/kg/injection) and 1,4-BD (0.1–3.2 mg/kg/injection) did not reliably maintained self-injection (McMahon et al. 2003). The maximal dose of GBL and 1,4-BD examined in that study was 3.2 mg/kg (i.e., 38.4 mg per injection in a 12 kg monkey). In the current study, only doses of 32 mg/kg (i.e., 960 mg per injection in a 30 kg baboon) or higher maintained self-injection. Additionally, we employed a 3-h timeout following injections, allowing sufficient time both for onset of drug effects and for recovery from the sedative effects prior to availability of the next injection. McMahon and colleagues used a limited drug access period (130 min) with short timeouts between injections (10 sec) which may have limited self-injection responding. GBL and 1,4-BD are CNS depressants with behavioral effects that

can last for hours (Goodwin et al. 2009) and under limited access conditions with short timeouts, drug-induced behavioral suppression interferes with self-injection responding. Similar differences in results from limited access vs. 24 access procedures with GHB self-administration have also been identified (Beardsley et al. 1996; Goodwin et al. 2011; Woolverton et al. 1999). Thus, the lack of GBL and 1,4-BD self-administration in the earlier study is likely due to differences the doses and period of drug access examined and/or species tested. As with other illicit substances, it is difficult to determine the exact doses of GBL and 1,4-BD abused in humans, especially given that both compounds are metabolized into GHB once ingested and that users typically describe the amount ingested as a number of 'liquid capfuls' (EMCDDA 2008; Palmer 2004). Still, in case studies of GBL and 1,4-BD abuse, patients self-reported taking doses every 2–3 hour of 2–8 g of GBL (25–100 mg/kg orally in an 80 kg human) and 1–14 g of 1,4-BD (12.5–175 mg/kg orally in an 80 kg human) (Bell and Collins 2011; CDC 1999; Ingels et al. 2000; Schneir et al. 2001; Wojtowicz et al. 2008; Zvosec et al. 2001). The dose ranges of GBL (56–100 mg/kg IV; 1.7–2.3 g in a 30 kg baboon) and 1,4-BD (78–100 mg/kg IV; 2.3–3 g in a 30 kg baboon) that maintained self-administration in the current study were those that produced overt behavioral effects (e.g. ataxia). In addition, the pattern of intake and doses of GBL and 1,4-BD self-administered were comparable to those reported by human abusers.

Previously, we have shown that the acute behavioral effects of GHB, GBL, and 1,4-BD following IG administration were very similar in baboons. All three compounds impaired food-maintained responding, and produced gastrointestinal symptoms and tremors/jerks in baboons when high doses (100 mg/kg or more) were administered as an acute bolus infusion IG (Goodwin et al. 2009; Goodwin et al. 2005). Similar behavioral effects were also observed after IV self-administration of GHB in our previous study (Goodwin et al. 2011) and following IV self-administration of GBL and 1,4-BD in the present study.

Although GHB, GHB and GBL shared similar behavioral profiles when administered IG, there were differences in pharmacokinetic parameters of the three drugs as well as the latency to on-set of behavioral effects, and the time required to fully recover from those effects (Goodwin et al. 2009; Goodwin et al. 2005). GBL and 1,4-BD are converted to GHB via different metabolic pathways, differences in the latency to on-set of effects and time course of effects of these compounds are likely related to differences in the formation, elimination, and distribution of the compounds in tissue (Arena and Fung 1980; Irwin 1996). In our previous study (Goodwin et al. 2009), we found the order of onset of motor impairment was GBL > 1,4-BD > GHB. There were also differences in potency and duration of action of GHB, GBL and 1,4-BD. Lower doses of 1,4-BD (180–240 mg/kg IG) and GBL (100–180 mg/kg IG) produced the same behavioral effects observed after higher doses of GHB (320–420 mg/kg IG), and levels of GHB in plasma were higher following GBL and 1,4-BD administration when compared to GHB administration. The longest-acting of the three drugs was 1,4-BD. Differences in potency of these drugs are thought to be related to polarity, bioavailability, and/or first pass metabolism (Andresen et al. 2011; Schep et al. 2012; Vree et al. 1978). In addition, drugs with a faster onset of action are generally more readily established as reinforcers and have greater abuse liability than those with a slow onset of effects.

Previously, we demonstrated that GHB maintained self-administration in the majority of subjects tested (six of nine subjects; 67%). In the present study, peak rates of IV self-injection were observed at similar doses of GBL (56–100 mg/kg) and 1,4-BD (100 mg/kg) when compared to GHB (56–130 mg/kg) (Goodwin et al. 2011), but there were differences in the number of subjects that self-administered GBL (four of five subjects; 80%) verses those that self-administered 1,4-BD (two of four subjects; 50%). These data are consistent with drug trafficking reports showing that GBL is found more often than 1,4-BD in seized

samples and 1,4-BD is not often self-reported in patients seeking assistance for drug-related issues in emergency rooms (EMCDDA 2008; Palmer 2004; Wood et al. 2011; Wood et al. 2008).

Some of the baboons in the current study had prior experience with GHB self-administration, and this experience may have contributed to the demonstration of GBL and 1,4-BD reinforcement in the current study. Subjects in the present study that previously self-administered GHB at high rates (DS, JN, KR) also self-administered GBL and 1,4-BD at moderate to high rates. One of the subjects that lacked GHB self-administration experience (RG) self-administered GBL at a moderate rate but did not self-administer 1,4-BD. The second subject lacking GHB self-administration experience (GR) did not self-administer GBL or 1,4-BD but also failed to self-administer zolpidem. This is surprising given zolpidem has been shown to function as an intravenous reinforcer in nonhuman primates (Ator 2002; Griffiths et al. 1992; Rowlett and Lelas 2007; Weerts et al. 1998). In a previous baboon study using the same procedure, zolpidem doses of 0.32–1.0 maintained self-administration in 100% of baboons (8 of 8) (Griffiths et al. 1992). This suggests that GR was an outlier. It is possible the unique experimental history of GR, which included exposure to acute and chronic effects of experimenter administered GBL and 1,4-BD via an IG catheter (Goodwin et al. 2009; Goodwin et al. 2006), may have influenced GR's behavior in the present study. Thus, we cannot rule out that different experience with GHB exposure and reinforcement may be a factor in the reinforcing effects of GBL and 1,4-BD.

In conclusion, the present results indicate that GBL and 1,4-BD can function as reinforcers, which is consistent with a potential for abuse. GBL was self-administered at higher rates and in a higher percentage of subjects when compared to 1,4-BD in the present study. We previously reported that GBL is more potent with a faster onset of action when compared to 1,4-BD and GHB (Goodwin et al. 2009). Like GHB, chronic administration of GBL produces physical dependence as evidenced by a withdrawal syndrome upon discontinuation (Goodwin et al., 2006). GBL is easier to obtain than the more strictly controlled GHB, and GBL is detected in seized samples sold as GHB more often than GHB is found (EMCDDA 2008; Wood et al. 2008). The fact that both pro-drugs can be used to synthesize GHB for illicit use further adds to their abuse liability. Thus, GBL and 1,4-BD abuse remains a significant public health concern. The current demonstration of GBL and 1,4-BD reinforcement, taken together with reported abuse, suggest these GHB pro-drugs may warrant increased legal control.

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Fig. 1.

Mean number of injections of GBL, 1,4-BD, and zolpidem for individual subjects (designated DS, GR, JN, KR and RG) and the group. For individual graphs, data points shown are mean ($\pm$ SD) of the last 5 days of each dose substitution or vehicle ("V") availability. Data shown for cocaine ("C") are the grand means from the last 3 days of the cocaine baseline periods that preceded each test dose. "N/A" indicates condition was not applicable; Baboon DS was not exposed to 1,4-BD or zolpidem and KR was not exposed to zolpidem. *Indicates the mean number of self-injections across days 11–15 of the dose condition exceeded two standard deviations of the mean across days 11–15 of vehicle. Data shown for the Group are the mean ($\pm$ SEM) of subjects in which GBL (n=4) and 1,4-BD (n=3) reinforcement was demonstrated and includes the average of both exposures to 1,4-BD. One baboon that failed to self-administer all test compounds (GR) was excluded from the group panel.

Fig. 2. Number of injections per day across consecutive days of a) GBL and b) 1,4-BD availability in individual baboons (DS, KR, JN, RG) in which reinforcement was demonstrated. Data shown are the peak reinforcing doses of GBL and 1,4-BD. The vehicle condition that occurred closest in time to the peak reinforcing dose for each baboon is shown for comparison.

Table 1

Mean number of food pellets delivered across each of the last 5 days of GBL and 1,4-BD self-administration, mean total dose (g) self-administered across each of the last five days for each drug dose condition, and total drug intake across 15 days of each drug dose condition.

Subject	VEH (±SD)	10 mg/kg	32 mg/kg	56 mg/kg	78 mg/kg	100 mg/kg	130 mg/kg
GBL							
DS							
food pellets	307.6(75.0)	268.6	305.6	202.8 ^a	4.2 ^a	n/a	n/a
mean total dose	n/a	0.7	4.6	15.4	18.1	n/a	n/a
total drug intake	n/a	14.0	69.3	198.8	240.8	n/a	n/a
GR							
food pellets	263.8(78.5)	n/a	153.2 ^a	208.0	274.2	152.0 ^a	204.8
mean total dose	n/a	n/a	0.0	0.0	1.3	0.0	0.0
total drug intake	n/a	n/a	8.4	9.4	26.0	22.4	7.3
JN							
food pellets	384.9(64.1)	378.6	331.0	344.8	205.0 ^a	n/a	n/a
mean total dose	n/a	1.0	5.4	16.8	16.5	n/a	n/a
total drug intake	n/a	20.2	83.2	217.2	197.3	n/a	n/a
KR							
food pellets	252.8(66.7)	280.8	270.0	239.6	284.0	n/a	n/a
mean total dose	n/a	0.7	3.4	4.7	13.6	n/a	n/a
total drug intake	n/a	11.9	51.1	81.2	186.1	n/a	n/a
RG							
food pellets	291.3(54.7)	108.0 ^a	307.2	151.2 ^a	29.2 ^a	232.0 ^a	n/a
mean total dose	n/a	0.5	3.0	4.0	4.4	9.2	n/a
total drug intake	n/a	8.8	39.1	57.1	58.7	101.2	n/a
1,4-BD 1st Exposure							
GR							
food pellets	263.8(78.5)	n/a	326.0	363.4	382.4	379.2	n/a
mean total dose	n/a	n/a	0.0	0.6	2.8	0.6	n/a
total drug intake	n/a	n/a	12.1	24.2	25.6	17.9	n/a
JN							
food pellets	384.9(64.1)	n/a	378.2	352.4	n/a	337.2	n/a
mean total dose	n/a	n/a	4.2	7.8	n/a	21.2	n/a
total drug intake	n/a	n/a	67.9	155.4	n/a	291.9	n/a
KR							
food pellets	252.8(66.7)	293.4	163.8 ^a	284.8	141.2 ^a	168.2 ^a	n/a
mean total dose	n/a	0.6	2.0	3.5	12.5	15.7	n/a
total drug intake	n/a	8.9	38.8	63.4	155.4	210.2	n/a

Subject	VEH (±SD)	10 mg/kg	32 mg/kg	56 mg/kg	78 mg/kg	100 mg/kg	130 mg/kg
RG	food pellets	291.3(54.7)	n/a	214.3 ^a	262.6	213.2 ^a	n/a
	mean total dose	n/a	n/a	0.0	0.5	0.4	n/a
	total drug intake	n/a	n/a	5.0	11.3	7.1	n/a
1,4-BD 2nd Exposure							
GR	food pellets	263.8(78.5)	339.0	n/a	n/a	n/a	n/a
	mean total dose	n/a	0.1	n/a	n/a	n/a	n/a
	total drug intake	n/a	2.7	n/a	n/a	n/a	n/a
JN	food pellets	384.9(64.1)	n/a	355.8	327.8	180.8 ^a	n/a
	mean total dose	n/a	n/a	4.4	6.8	18.2	n/a
	total drug intake	n/a	n/a	64.4	102.5	249.4	n/a
KR	food pellets	252.8(66.7)	n/a	n/a	179.0 ^a	294.4	n/a
	mean total dose	n/a	n/a	n/a	4.2	11.8	n/a
	total drug intake	n/a	n/a	n/a	75.5	149.9	n/a
RG	food pellets	291.3(54.7)	n/a	203.0 ^a	171.2 ^a	56.4 ^a	n/a
	mean total dose	n/a	n/a	3.04	3.9	3.4	n/a
	total drug intake	n/a	n/a	51.2	51.4	56.9	n/a

^a mean number of pellets delivered during the last 5 days of the self-injection period was below one SD of the mean intake during the last 5 days of vehicle availability; analogous to a two-tailed test