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Cardiovascular responses elicited by intragastric administration of BDL and GHB

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Abstract

Gamma-hydroxybutyrate (GHB) and its metabolic precursor, 1,4-butanediol (BDL) are widely used recreational drugs. Although most commonly described as CNS depressants, GHB and BDL elicit significant sympathomimetic cardiovascular responses (increases in mean arterial pressure (MAP) and heart rate) when administered parenterally. Given that humans most commonly ingest both drugs orally, we examined the dose-response relationships for intragastrically administered GHB and BDL on MAP and heart rate in conscious rats using radiotelemetry. The intragastric administration of GHB increased MAP. BDL increased both MAP and heart rate, and was approximately 10-fold more potent as a cardiovascular stimulant than GHB when administered intragastrically. Pretreatment with ethanol prevented the lethality of BDL. These data indicate that 1) both GHB and BDL produce cardiovascular responses when administered intragastrically, and 2) BDL is more potent and potentially more dangerous than GHB when administered via this route.

Keywords

Gamma-hydroxybutyrate; 1,4-butanediol; rat; radio telemetry; alcohol

INTRODUCTION

As a recreationally used club drug and dietary supplement, the use of γ -hydroxybutyrate (GHB) has increased during recent years (1). An endogenous compound metabolically linked to gamma aminobutyric acid, GHB is considered a CNS depressant; however, GHB also has significant sympathomimetic cardiovascular properties when administered parenterally (2–4). Accompanying the increased recreational use of GHB has been an increase in drug-related toxicity. As a result, the availability of GHB is strictly regulated leading to an increase in the use of a readily available industrial solvent, 1,4-butanediol (BDL) (5). BDL is degraded to GHB in vivo by the same enzymes responsible for the metabolism of ethanol, alcohol and aldehyde dehydrogenase (6–8). In fact, the behavioral and cardiovascular actions of parenterally administered BDL occur after its metabolism to GHB (8,9). Like GHB, BDL produces paradoxical responses in the CNS (i.e., sedation, decreases in response rates) and cardiovascular system (i.e., increases in mean arterial pressure (MAP) and heart rate) (9). Considering that both GHB and BDL are most

commonly ingested orally by humans, we sought to characterize the MAP and heart rate responses elicited by the intragastric administration of each drug in conscious rats.

METHODS

Subjects

All procedures were in accordance with the National Institutes of Health guidelines for the care and use of experimental animals and were approved by the Institutional Animal Care and Use Committee at Louisiana State University Health Sciences Center. Male Sprague-Dawley rats (195–303 g, Harlan, IN, n=20) were instrumented with radiotelemetry probes (Data Sciences International, St. Paul, MN) to continuously record MAP and heart rate after drug administration (10). Briefly, the pressure catheter of a battery-operated radiotelemetry probe (TL11M2-C50-PXT, Data Sciences International) was inserted into the descending abdominal aorta of an anesthetized rat rostral to the femoral bifurcation. The probe was then secured to the abdominal musculature. Rats were also instrumented with an intragastric polyethylene cannula (PE50) bubbled 1 cm from the tip to allow for drug delivery. For implantation of the intragastric cannulae, the stomach was visualized and retracted. A small incision was made in a minimally vascularized portion of the muscle along the greater curvature of the stomach between the fundus and body. The saline-filled cannula was inserted past the bubble into the incision and secured to the stomach wall. The free end of the cannula was then tunneled through the abdominal musculature and subcutaneously to the dorsal body side and exteriorized through an incision at the nape of the neck. The incision sites were then irrigated with sterile saline and closed using 4-0 nonabsorbable silk suture. Animals were allowed to recover for 7–10 d before beginning any protocol. Placement of the intragastric cannulae was confirmed post mortem by visualization of methylene blue dye in the stomach.

Experimental Design

Baseline MAP and heart rate were recorded daily for 30–60 min in conscious, unrestrained rats. To minimize differences in gastric absorption, rats were denied access to food for 4 hrs prior to drug administration. Rats were randomly divided into four groups of five. The first group received a single daily intragastric dose of saline (0.9%) or GHB (0.56, 1.0, 1.8, 5.6 or 10.0 g/kg) in mixed order. The second group received a single daily intragastric dose of saline (0.9%) or BDL (0.18, 0.32, 0.56 or 1.0 g/kg) in mixed order. The third group received a single intragastric dose of BDL (1.8 g/kg). The fourth group received a single intraperitoneal injection of ethanol (2.0 g/kg) 10 min prior to intragastric administration of BDL (1.8 g/kg).

Data Analysis

The output from the telemetry probes was recorded (250 Hz) using receivers placed underneath the rats' home cages. Data acquisition was controlled using Data Sciences Acquisition software. Data were collected in 2-s bins and analyzed using Data Sciences Analysis software. The magnitude of the peak changes in MAP and heart rate were calculated off-line as the difference between baseline and the peak drug response. The times to peak response were calculated off-line as the interval between drug administration and the peak drug response.

Drugs Used

GHB (1.0 g/ml) and BDL (1.0 g/ml) were obtained from Sigma-Aldrich (St. Louis, MO). Ethanol was diluted with saline to obtain a 20% (v/v) solution that was administered intraperitoneally. Rats were anesthetized with a combination of ketamine (90 mg/ml;

Phoenix Scientific, Inc., St. Joseph, MO) and xylazine (10 mg/ml; Vedco, Inc., St. Joseph, MO).

RESULTS

Figure 1 shows a typical experimental recording of the MAP (bottom panel) and heart rate (top panel) responses elicited by the intragastric administration of BDL (0.56 g/kg) in a conscious rat. In this rat, BDL elicited pronounced and prolonged increases in MAP and heart rate that peaked approximately 60 min and 90 min, respectively after drug administration (Fig. 1). Figure 2 summarizes the MAP and heart rate responses elicited by both BDL (n=5) and GHB (n=5) in two groups of rats. BDL elicited increases in MAP and heart rate which peaked 33 ± 11 to 90 ± 29 min and 26 ± 13 to 139 ± 37 min, respectively. At doses approximately 10 times greater than those used for BDL, GHB also elicited increases in MAP which peaked 165 ± 14 to 246 ± 36 min after drug administration (Fig. 2); however, the heart rate responses elicited by GHB were more variable. Unlike BDL, the intragastric administration of GHB tended to elicit an initial bradycardia (-63 ± 11 to -75 ± 4 bpm) that reached a nadir 117 ± 27 to 173 ± 31 min after drug administration. Subsequently, heart rate returned towards baseline levels coinciding with the peak of the GHB-mediated increase in MAP (Fig. 2). The administration of 1.8 g/kg of BDL (the minimal intragastric dose of GHB needed to increase MAP) killed four of five rats. Pretreatment with ethanol protected against BDL lethality (1.8 g/kg, i.g.) in 5 rats.

DISCUSSION

These data provide the first direct demonstration that the intragastric administration of BDL and GHB elicits significant sympathomimetic cardiovascular responses in conscious, unrestrained rats. There is great variability in the dose of GHB used by humans and little information describing the doses of BDL ingested by humans. Therapeutic doses of GHB used to treat narcolepsy are approximately 64 mg/kg which is below the lowest cardiovascular effective dose of BDL used in our rats (180 mg/kg); however, the doses used by individuals who abuse GHB are more difficult to document. There are reports of individuals ingesting as much as 570 mg/kg of GHB per day (11). When used as an anesthetic in humans, intravenous doses of GHB ranged from 69 to 210 mg/kg (12). The dose-response relationships for the cardiovascular effects elicited by the intragastric administration of BDL in rats are in good agreement with the doses used to define the drug's behavioral and cardiovascular effects when administered intravenously or intraperitoneally. The large doses of GHB administered intragastrically in the current set of studies were needed to define the difference in potency between BDL and GHB when administered enterally as smaller doses produced no cardiovascular responses. Although the intragastric administration of GHB increased MAP, the bioavailability of GHB appeared to be reduced when administered enterally. In fact, the effective doses for intragastrically administered GHB were 10-fold greater than the range of effective doses (1.0 to 10 g/kg, i.g. versus 0.18 to 1.0 g/kg) reported to increase both MAP and heart rate following intravenous and intraperitoneal administration of GHB (2–4). The decreased bioavailability of GHB following enteral administration is not surprising given the drug is most likely susceptible to first pass metabolism in the liver (13). The MAP increasing effect of parenterally administered GHB has been shown to be mediated via the activation of central GABA_B receptors; however, the ability of parenterally administered GHB to elicit increases in heart rate have been attributed to the its' ability to selectively inhibit baroreceptor reflex control of heart rate via the activation of specific GHB receptors (2). Given that the intragastric administration of GHB did not elicit dose-dependent, parallel increases in heart rate at doses which increased MAP, it is possible that the enteral absorption of GHB alters the affinity of the compound for the GHB receptor without altering GHB's affinity for GABA_B receptors.

As such, the intragastric administration of GHB does not result in the activation of GHB receptors preventing any increase in heart rate.

BDL is metabolized to GHB in both humans and rats by the same enzymes responsible for the degradation of ethanol (14,15). Recent publications have demonstrated that the cardiovascular and behavioral responses elicited by BDL require its metabolism to GHB via alcohol and aldehyde dehydrogenase (9,16). Like GHB, the dose-response relationships for BDL and MAP and heart rate are nearly identical following parenteral administration of BDL (0.18 to 1.0 g/kg, i.p. and i.v.) (9). The intragastric administration of BDL (0.18 to 1.0 g/kg) elicited increases in MAP and heart rate that were similar to those reported following intraperitoneal and intravenous administration (9). In fact, the sympathomimetic cardiovascular responses elicited by the intragastric administration of BDL are consistent with its conversion to GHB by alcohol and aldehyde dehydrogenase in the liver and the subsequent activation of central GABA_b and GHB receptors (9). Unlike GHB, the current data indicate that the bioavailability of BDL is not affected by the route of administration. In fact, BDL is approximately 10-fold more potent than GHB in terms of the drugs' respective abilities to elicit sympathomimetic cardiovascular responses when administered enterally.

The intragastric dose of GHB (1.8 mg/kg) that produced only a minimal increase in arterial pressure corresponded to a lethal dose of BDL via this route of administration. Furthermore, the ability of ethanol to prevent the lethality of BDL demonstrates that the toxic effects of the drug, like its cardiovascular and behavioral responses, are dependent on its metabolism to GHB. The fact that BDL and ethanol are both substrates for alcohol dehydrogenase raises the possibility that the order of ingestion may play an important role in determining the lethality of BDL when coingested with ethanol. Although the mechanism(s) underlying the toxic effects of BDL have not been directly defined, clinical descriptions of GHB overdose in humans describe loss of consciousness, respiratory and cardiovascular depression (5). Conversely, there does not appear to be an interaction between ethanol and GHB as ethanol pretreatment did not alter the cardiovascular responses elicited by GHB (data not shown). Taken together, these data show the increased potential for orally administered BDL to elicit clinically significant cardiovascular responses when substituted for GHB.

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Figure 1.

Typical experimental recording of the mean arterial pressure (MAP, bottom panel) and heart rate (HR, top panel) responses elicited by the intragastric administration of 1,4-butanediol (BDL, 0.56 g/kg) in a conscious, telemetered rat. Arrow denotes injection of BDL.

Figure 2.

Dose-response relationships for the mean arterial pressure (MAP) and heart rate (HR) responses elicited by the intragastric administration of γ -hydroxybutyrate (GHB) (n=5) and 1,4-butanediol (BDL) (n=5) in conscious rats.