ELSEVIER

Pharmacology, Biochemistry and Behavior 68 (2001) 291–299

PHARMACOLOGY BIOCHEMISTRY AND BEHAVIOR

www.elsevier.com/locate/pharmbiochembeh

The effect of gamma-vinyl-GABA on the consumption of concurrently available oral cocaine and ethanol in the rat

Michael F. Stromberg[a,c,*], Scott A. Mackler[a,b,c], Joseph R. Volpicelli[a,c], Charles P. O'Brien[a,c], Stephen L. Dewey[d]

[a]*Center For Studies of Addiction, Department of Psychiatry, University of Pennsylvania, 3900 Chestnut Street, Philadelphia, PA 19104, USA*
[b]*Departments of Medicine and Pharmacology, University of Pennsylvania, Philadelphia, PA, USA*
[c]*Philadelphia VAMC, Philadelphia, PA, USA*
[d]*Brookhaven National Laboratory, Upton, NY, USA*

Received 5 July 2000; received in revised form 2 October 2000; accepted 10 October 2000

Abstract

It has frequently been reported that a high percentage of individuals, identified as either alcohol- or cocaine-dependent, concurrently abuse both drugs. The experiments reported here represent a continuing effort to develop an animal model to predict the effects of a potential pharmacotherapeutic agent on concurrently available oral ethanol and cocaine. These experiments utilized drinkometer circuitry to assess the effects of gamma-vinyl-GABA (GVG), a γ-aminobutyric acid (GABA) transaminase inhibitor, on the consumption and temporal pattern of responses for orally self-administered ethanol and cocaine. The results of these experiments showed that GVG, at doses of 100, 200 and 300 mg/kg, reduced both ethanol and cocaine consumption in a dose-related manner. When compared to vehicle, GVG at all doses significantly reduced ethanol consumption while consumption of cocaine was significantly reduced only at 300 mg/kg. This is consistent with data showing that GVG reduces consumption of these drugs when administered alone and data showing that GVG is more potent in reducing ethanol-induced compared to cocaine-induced extracellular dopamine in the nucleus accumbens. Analysis of the temporal pattern of drinking across the session suggests that GVG's effects are due to a disruption of the reinforcing properties of ethanol and cocaine rather than a more general reduction in motor behavior. These data suggest that GVG has potential for clinical use in populations that abuse either alcohol or cocaine alone or in combination.

Keywords: GABA; Gamma-vinyl-GABA; Ethanol; Cocaine

A significant proportion of those individuals seeking treatment for either alcohol or cocaine abuse concurrently use both of these drugs. For example, in alcohol-dependent patients 20% to 30% were also found to qualify as cocaine-dependent (Miller and Giannini, 1991), while in a cocaine-dependent population, comorbid alcohol dependence has been estimated to have a lifetime prevalence of 62% (Rounsaville et al., 1991). Thus, development of effective treatment for both addictions with a single drug would be advantageous.

The CNS neurotransmitter γ-aminobutyric acid (GABA) helps regulate addictive behaviors. Recently, a novel approach to targeting the GABA system has been developed. Gamma-vinyl-GABA (GVG, Vigabratin) is an irreversible inhibitor of GABA-transaminase. Because GABA transminase is responsible for the breakdown of GABA, inhibition by GVG produces a dose-dependent long-lasting elevation of GABA and acts as an indirect GABA agonist (Mattson et al., 1995). GVG has been shown to be effective in reducing responding by rats for each of many drugs with abuse potential including oral alcohol self-administration (Wegelius et al., 1993), intravenous (iv) cocaine self-administration (Kushner et al., 1999), and oral morphine self-administration (Buckett, 1981). In addition, GVG has been shown to inhibit the ethanol-, methamphetamine-, heroin- (Gerasimov et al., 1999) and cocaine-induced (Ashby et al.,

* Corresponding author. Center For Studies of Addiction, Department of Psychiatry, University of Pennsylvania, 3900 Chestnut Street, Philadelphia, PA 19104, USA. Tel.: +1-215-823-4325; fax: +1-215-823-5171.

E-mail address: stromberg@research.trc.upenn.edu (M.F. Stromberg).

0091-3057/01/$ – see front matter
PII: S0091-3057(00)00456-1

1999; Dewey et al., 1997) increase in extracellular DA in the nucleus accumbens (Nacc).

Animal models are typically designed to evaluate those factors maintaining drug-seeking behavior, but little effort has been directed at developing animal models of polydrug use. One potential reason constraining the development of models of concurrent alcohol–cocaine use is related to the differences in route of administration employed for each of these drugs. Alcohol is orally self-administered, while cocaine is most often self-administered intravenously. Animal models have avoided oral self-administration of cocaine for a number of reasons. Apart from the issue of delay of reinforcement, it was believed that most of the orally consumed cocaine would be hydrolyzed by exposure to the gastrointestinal environment (Ritchie and Cohen, 1975). However, it has since been demonstrated in humans that oral cocaine produces both comparable bioavailability and a greater subjective "high" compared to intranasal cocaine (VanDyke et al., 1978). Similarly, Ma et al. (1999) using rats have recently reported that oral cocaine was more potent than intravenous cocaine, despite its lower bioavailability when comparing their effects on both response rates and reinforcement rates in a DRL schedule. This difference in potency was hypothesized as attributable to differences in the presence of active metabolites of cocaine and the rate of development of acute tolerance dependent on route of administration. The ability to develop animal models that employ comparable routes of delivery across multiple drugs with abuse potential is important because these models, in turn, can be used for preclinical evaluation of potential pharmacotherapeutic agents. In the experiments reported here, we employed an animal model of concurrently available oral ethanol and cocaine to further evaluate the efficacy of GVG.

1. Methods

1.1. Subjects

Eight male Wistar rats were purchased from Ace Animals, Boyertown, PA and arrived at the laboratory weighing between 250 and 300 g. The rats were housed in individual acrylic cages in a temperature-controlled (22°C) animal colony on a 12 h/12 h reverse light/dark cycle with lights out from 0700 to 1900 h. Animals were provided with ad lib food and 18 h of fluid deprivation for the entire experiment. All research was approved by the Institutional Animal Care and Use Committee of the Philadelphia VAMC and conducted according to The Guide for the Care and Use of Laboratory Animals as adopted and promulgated by the National Institutes of Health.

1.2. Apparatus

All experiments were conducted in Coulbourn Operant Chambers placed inside of sound attenuating chambers. Two Med Associates photobeam drinkometers were mounted in the sidewall equidistant from the front and back walls and 3.2 cm from the grid floor. A water bottle was mounted on the sidewall equidistant between the drinkometer spouts, but was not connected to drinkometer circuitry. Drinkometers were connected to a PC using Med Associates interface equipment and data were collected by a computer program written in Medstate notation language.

1.3. Procedures

All experimental procedures were conducted during the dark cycle between 1100 and 1700 h. Rats were initially habituated to the drinkometer chambers for 2 days. On the following 2 days they were fluid deprived for 18 h and allowed to drink water from the two drinkometer bottles. The next day, in one bottle, the rats were presented with an ascending series of alcohol concentrations as follows: 2% for 4 days, 4% for 4 days, and 6% (v/v) for the next 30 days of the experiment or, in a second bottle, cocaine 0.01% for 4 days and 0.02% for the next 30 days. Water was available in a third bottle placed equidistant between the drinkometers but was not monitored by a drinkometer circuit. After one month of exposure to these concentrations, the alcohol solution was increased to 8% (v/v) and cocaine increased to 0.04% (w/v). All bottles were weighed to the nearest 0.1 g at both the beginning and end of each session and the drug bottles were rotated on a random basis to prevent the development of a side preference. Once consumption was stable at asymptote, saline was injected intraperitoneally (ip) 30 min prior to being placed in the drinkometer chambers. On the following day, rats were injected ip with GVG, 300 mg/kg. Rats were returned to baseline consumption for a period of 60 days and the procedure repeated with GVG, 100 mg/kg. Following another 60-day baseline period, the procedure was again repeated with GVG, 200 mg/kg.

2. Results

GVG, at all three doses tested, reduced both oral alcohol and cocaine self-administration in a dose-related manner. Table 1 shows the percent reduction in the consumption of ethanol and cocaine across each dose of GVG compared to predrug saline baseline for ethanol and cocaine. Fig. 1 shows ethanol consumption following either saline or GVG at all three doses. A repeated measures ANOVA of

Table 1
Difference in ethanol and cocaine consumption for each dose of GVG tested expressed as percent change from consumption following pre-GVG saline injections

GVG dose (mg/kg)	Ethanol	Cocaine
100	− 30	− 20
200	− 46	− 32
300	− 69	− 54

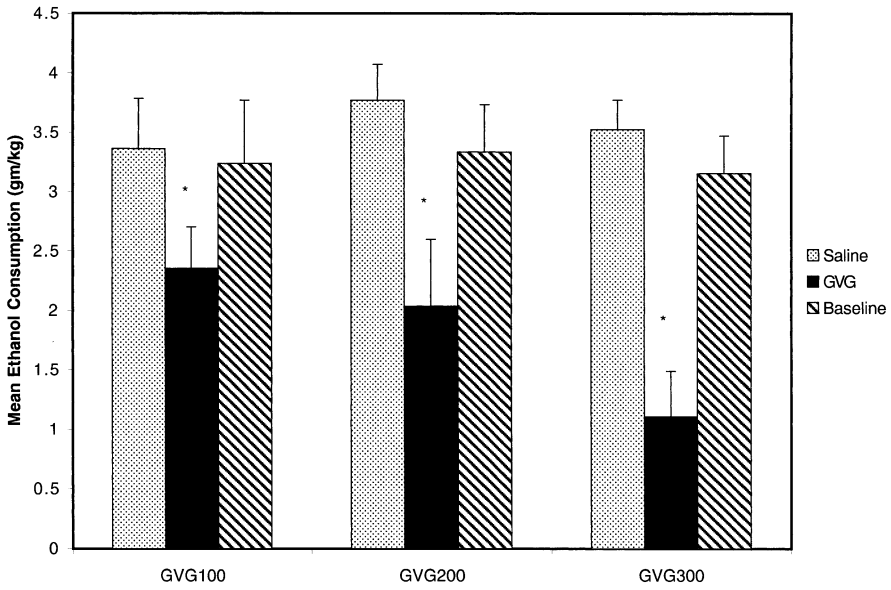

Fig. 1. Ethanol consumption (gm/kg) following pre-GVG saline control injections, GVG at doses of 100, 200 or 300 mg/kg, or post-GVG baseline for the day immediately following drug injection (±S.E.M.). * Significant at $\alpha = .05$.

the three doses across saline- or drug-treatment days yielded a significant effect for days [$F(1,21) = 71.310$, $P < .001$] and a significant days by dose interaction [$F(2,21) = 3.717$, $P = .04$]. Subsequent t tests for ethanol consumption following saline or drug treatment at each dose revealed that GVG, at each dose, significantly reduced ethanol consumption compared to predrug saline control injections in the same animals. Fig. 2 shows cocaine consumption following either saline or GVG at all three doses. A repeated measures ANOVA of the three doses across saline or drug treatment days yielded a significant effect for days [$F(1,20) = 9.246$, $P = .006$]. Subsequent simple effects test for cocaine consumption following saline or drug treatment at each dose revealed that only GVG, 300 mg/kg, significantly reduced cocaine consumption.

Fig. 3 shows water consumption across saline- and drug-treatment days at all three doses. A repeated measures ANOVA of water consumption by the three levels of GVG across the saline or drug treatment days was nonsignificant.

2.1. Microanalysis of temporal responding

A microanalysis of the temporal distribution of the ethanol and cocaine drinking data, evaluating both the

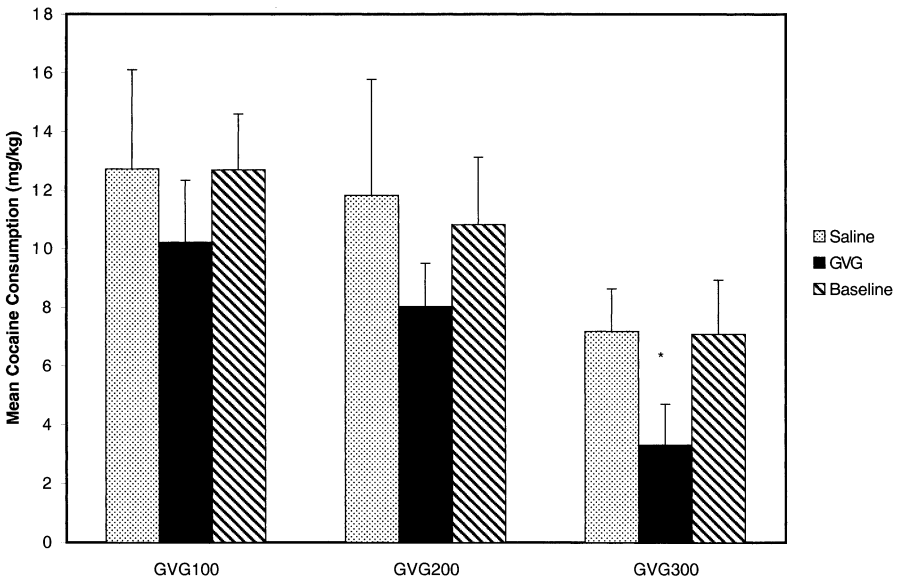

Fig. 2. Cocaine consumption (mg/kg) following pre-GVG saline control injections, GVG at doses of 100, 200 or 300 mg/kg, or post-GVG baseline for the day immediately following drug injection (±S.E.M.). (* significant at $\alpha = .05$)

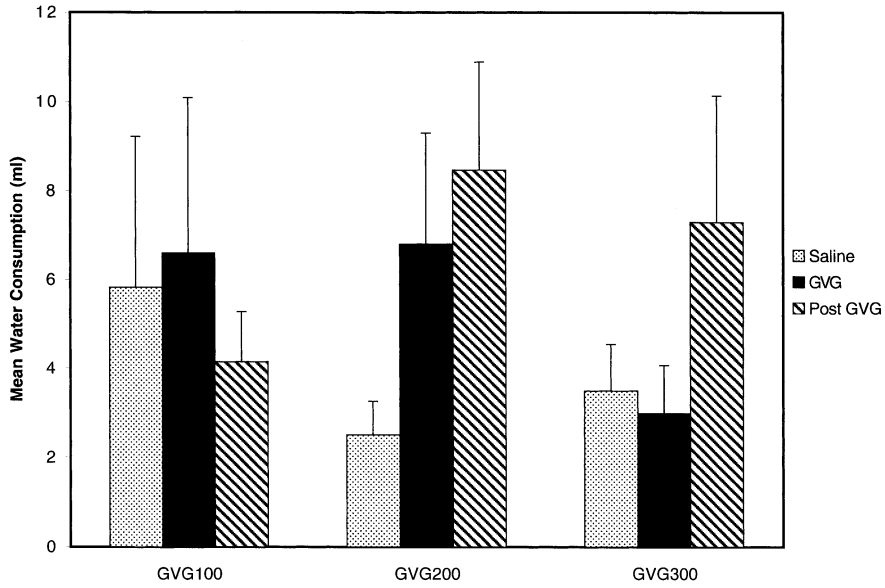

Fig. 3. Water consumption (ml) following pre-GVG saline control injections, GVG at doses of 100, 200 or 300 mg/kg, or post-GVG baseline for the day immediately following drug injection (±S.E.M.).

number and size of drinking bouts across the 6-h session, showed that the effect of GVG emerged from its effect on the size of individual drinking bouts rather than the number of bouts. The drinkometer data was recorded by computer as individual licks and accumulated in 5-min bins across the 6-h session. Drinking bouts were defined as the presence of responses in any given bin and continued until a 5-min bin occurred with no recorded responses. Drinking bout size was determined by converting the number of responses in a 5-min bin to a percentage of total responses. This was then converted to drug by converting percent of total responses into percent of total drug (Percent of total responses × Total drug consumed). Because of a problem with the computer collection of temporal data on saline and drug day for the GVG 200 mg/kg dose, these data are not included in the analysis. Fig. 4 shows the effect of saline and both GVG 100 and 300 mg/kg on the number and size of ethanol drinking bouts. A repeated measures ANOVA for ethanol bout size

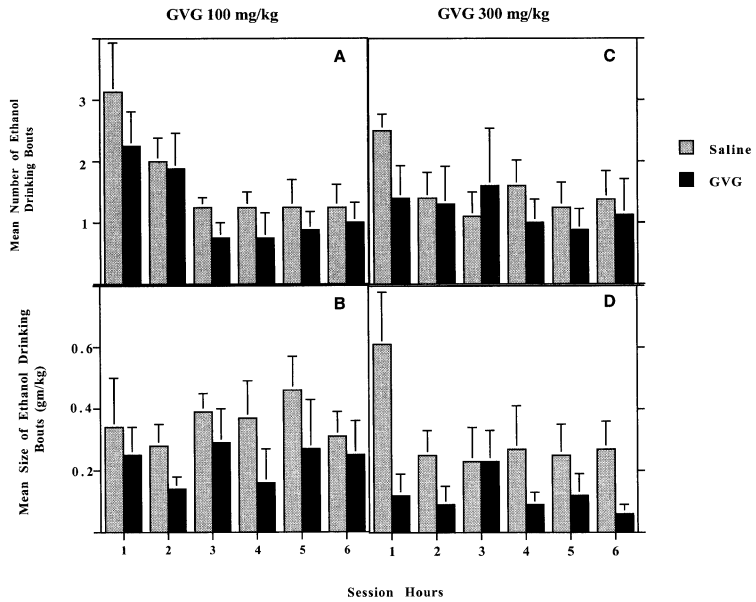

Fig. 4. The effect of GVG on ethanol drinking bout size and number. Panel A: the effect of GVG 100 mg/kg and Panel C: the effect of GVG 300 mg/kg on number of ethanol drinking bouts per session hour. Panel B: the effect of GVG 100 mg/kg and Panel D: the effect of GVG 300 mg/kg on size of ethanol drinking bouts. (±S.E.M.)

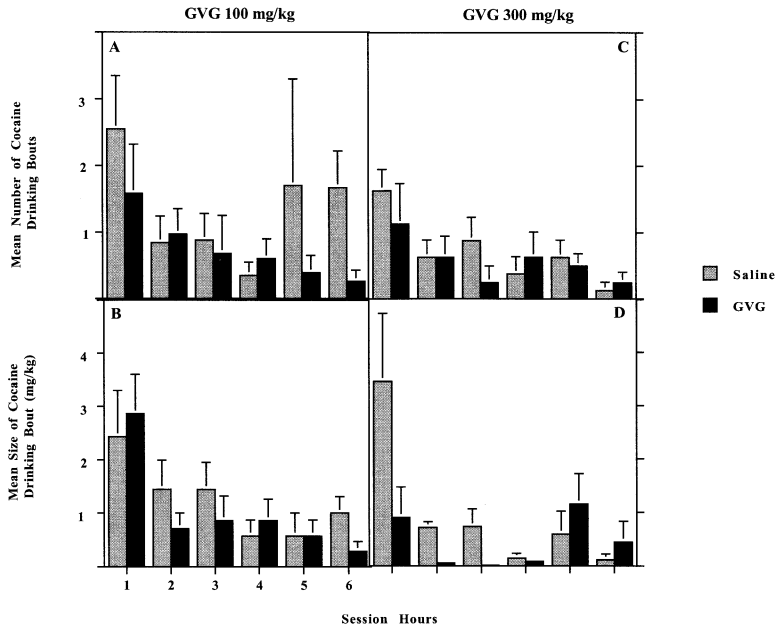

Fig. 5. The effect of GVG on cocaine drinking bout size and number. Panel A: the effect of GVG 100 mg/kg and Panel C: the effect of GVG 300 mg/kg on number of cocaine drinking bouts per session hour. Panel B: the effect of GVG 100 mg/kg and Panel D: the effect of GVG 300 mg/kg on size of cocaine drinking bouts. (±S.E.M.)

across the two levels of both dose and treatment, repeated across the six session hours, yielded a significant effect for treatment [$F(1,28) = 11.267$, $P = .002$]. Simple effects tests on each of the doses revealed a nonsignificant effect for GVG 100 mg/kg and a significant effect for GVG 300 mg/kg [$F(1,14) = 13.209$, $P = .003$]. A similar analysis for number of ethanol drinking bouts across the six session hours for both doses was nonsignificant. Fig. 5 shows the effect of saline and both GVG 100 and 300 mg/kg on the number and size of cocaine-drinking bouts. A repeated measures ANOVA for cocaine bout size across the two levels of both dose and treatment, repeated across the six session hours, yielded a significant effect for treatment [$F(1,26) = 6.893$, $P = .014$]. Simple effects tests on each of the doses revealed significant effects for both GVG 100 and 300 mg/kg. A similar analysis for number of cocaine-drinking bouts across the six session hours for both doses was nonsignificant.

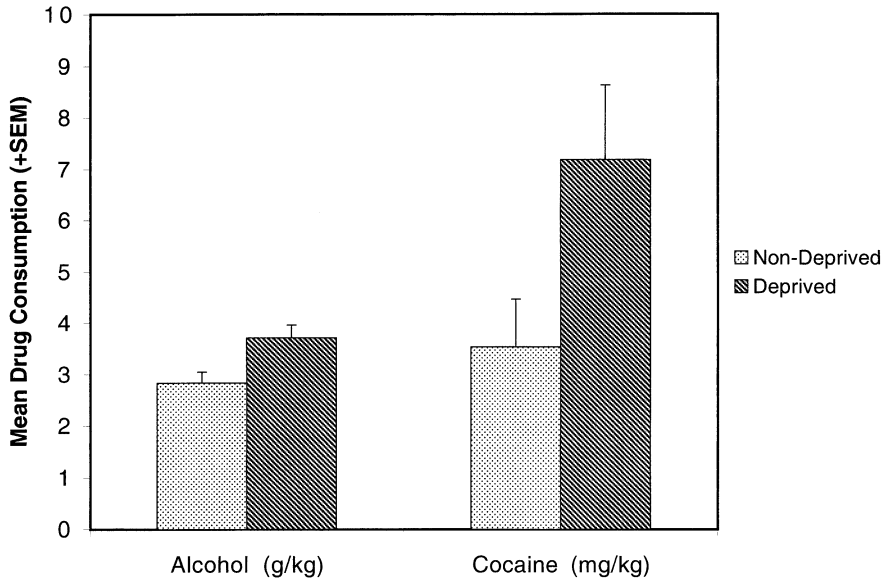

Fig. 6. The effect of fluid deprivation or ad lib water on consumption of alcohol and cocaine.

2.2. Analysis of deprivation effects

Approximately 2 weeks before evaluation of GVG 300 mg/kg rats were given ad lib access to water between consecutive 6-h experimental sessions in order to assess for the effect of deprivation on fluid choice. Fig. 6 shows the consumption of both ethanol and cocaine solutions under both deprived and nondeprived conditions. Consumption during the session following ad lib water was compared to consumption following predrug saline using *t* tests. Ethanol and cocaine consumption following ad lib water did not differ significantly from consumption following predrug saline under deprived conditions.

2.3. Analysis of blood levels of benzoylecognine and ethanol

A separate group of three rats was utilized to determine an indirect measure of blood cocaine level. These rats were trained to drink a 0.04% cocaine solution in their home cages. After a 23-h fluid deprivation period, these rats were presented with the 0.04% cocaine solution as their sole choice. After a 1-h drinking session these rats were immediately removed from their home cages and anesthetized with ketamine and a small amount of blood was removed from their tail veins and placed in a heparinized eppendorf. This blood was then analyzed using an Abbott Axsym System for the cocaine metabolite benzoylecognine. Table 2 shows cocaine consumption and blood levels of benzoylecognine. The Axsym System is used at Penn/VA Center For Studies of Addiction to screen urine samples of clinical populations for drug use. A reading >300 mg/dl is considered positive for cocaine use. These data demonstrate a dose–effect relationship between consumed cocaine and blood levels of the principal metabolite.

Similarly, four rats were used to determine blood ethanol levels. These rats were treated identically as the cocaine rats and were given a 0.08% (v/v) ethanol solution as their sole fluid choice. After a 1-h drinking session these rats were immediately removed from their home cages and anesthetized with ketamine and a small amount of blood was removed from their tail veins and placed in a heparinized eppendorf. This blood was then analyzed using an Abbott Axsym System for blood ethanol level using Abbott's REA Ethanol assay. Table 3 shows ethanol consumption and corresponding blood alcohol levels and demonstrate that rats in this type of experiment drink ethanol levels that are pharmacologically meaningful.

Table 2
Blood level of cocaine metabolite benzoylecognine compared to cocaine consumption

Rat no.	Cocaine consumption (mg/kg)	Benzoylecognine (mg/dl)
501-2	12.60	364.27
501-1	19.72	435.42
501-6	21.17	555.65

Table 3
Blood ethanol level compared to ethanol consumption

Rat no.	Ethanol consumption (gm/kg)	Blood ethanol level (mg/dl)
501-3	0.98	47.86
501-8	1.07	45.10
501-4	1.15	70.62
501-5	1.18	57.38

3. Discussion

The present findings demonstrate that GVG produced a dose-related decrease in both ethanol and cocaine when these drugs were concurrently available for oral self-administration. This is the first report that we are aware of that uses an animal model of concurrent oral ethanol and cocaine self-administration to evaluate the efficacy of a potential pharmacotherapeutic agent. These results are consistent with the effects of GVG reported for oral ethanol consumption (Wegelius et al., 1993) and for intravenously self-administered cocaine (Kushner et al., 1999) when these drugs were self-administered alone.

This effect of GVG on both cocaine and ethanol drinking supports the view that a common mechanism mediates the consumption of both drugs. The mesolimbic dopamine (DA) system has been identified as crucial for the expression of the reinforcing properties of most drugs with abuse potential (Koob, 1992). However, in the present model of polydrug drug use GVG appears to be more potent in suppressing ethanol consumption than cocaine consumption. Rather than having a direct effect on the dopaminergic pathways underlying the consumption of cocaine and ethanol, GVG's effect is on the GABA system.

There is substantial evidence indicating that GABA is crucial for the regulation of the mesolimbic DA pathways. Three distinct GABAergic sources that innervate the ventral tegmental area (VTA), the site of the dopamine cell bodies that project to terminal fields in the nucleus accumbens, have been identified (Churchill et al., 1992; Kalivas et al., 1990). At the behavioral level, several studies have shown that manipulation of GABA by agonists and antagonists alter ethanol (Boyle et al., 1999; Nowak et al., 1998; Petry, 1997; Roberts and Andrews, 1997; Soderpalm and Hansen, 1998) and cocaine consumption (Brebner et al., 1999; Campbell et al., 1999; Rounsaville et al., 1991). Experimental evidence has demonstrated that GVG inhibits the release of extracellular DA in the nucleus accumbens during administration of ethanol (Gerasimov et al., 1999) and cocaine (Ashby et al., 1999; Dewey et al., 1997; Gerasimov et al., 1999). These data suggest the reason for GVG's greater potency in reducing ethanol versus cocaine consumption. For example, GVG, at a lower dose, comple-

tely suppressed the release of DA in the Nacc following acute ethanol administration (Gerasimov et al., 1999) while GVG at a higher dose suppressed the cocaine-induced DA release in the Nacc by 25% (Ashby et al., 1999).

An interesting question about GVG's effect arises, however, because the involvement of GABAergic mechanisms in separate ethanol or cocaine self-administration appears to differ. For example, the effect of GVG on cocaine consumption appears to be related to its effect at $GABA_B$ receptors. This has been demonstrated by the elimination of GVG's inhibition of cocaine-induced increases in extracellular DA in the Nacc by preadministration of the $GABA_B$ receptor antagonist SCH 50911 (Ashby et al., 1999; Morgan and Dewey, 1998). This is consistent with other experimental data demonstrating that the $GABA_B$ receptor agonist baclofen (Brebner et al., 1999; Campbell et al., 1999; Shoaib et al., 1998) and CGP44532 (Brebner et al., 1999) attenuate cocaine self-administration dependent on factors such as unit dose. Conversely, the $GABA_A$ agonist, tetrahydrisoxazolo [5,4-c]pyridin-3-ol hydrochloride (THIP) failed to reduce cocaine self-administration (Shoaib et al., 1998). To the extent that activity in GABAergic pathways is critical for the ultimate expression of the positive reinforcing properties that maintain cocaine consumption, these data suggest that the $GABA_B$ receptor subtype is critical.

On the other hand, the relationship between the GABA system and ethanol consumption appears more complex. In contrast to cocaine, baclofen has been demonstrated to both increase (Petry, 1997; Smith et al., 1999) and decrease (Daoust et al., 1987) ethanol consumption. The $GABA_A$ agonist, muscimol has been shown to decrease (Petry, 1997; Roberts et al., 1996), increase (Tomkins et al., 1994) or have no effect on ethanol consumption (Nowak et al., 1998), while the $GABA_A$ antagonists picrotoxin (Nowak et al., 1998; Petry, 1997) and SR 95531 (Hyytia and Koob, 1995) have been shown to decrease ethanol consumption.

Unlike these selective agonists/antagonists GVG is an indirect GABA agonist nonselective for receptor subtype and can therefore be assumed to affect each receptor subtype in equal measure. The reported differences in the effects of the selective $GABA_B$ agonist baclofen on cocaine and ethanol consumption would seem to suggest a possibility for different GABAergic mechanisms mediating cocaine and ethanol consumption. One possibility is that GVG's effects on alcohol consumption are mediated by $GABA_A$ receptor subtypes, but this has yet to be tested and the data derived from experiments examining selective $GABA_A$ agonists is mixed. The evidence demonstrating that GVG blocks both ethanol- and cocaine-induced increases in extracellular DA in the Nacc in a dose-related manner suggests a common GABAergic mechanism modulating the reinforcing properties underlying the consumption of these two drugs. Another potential explanation for the apparent differences in effect of GVG and baclofen may be related to the fact that the experiments reported here employed concurrent consumption of both alcohol and cocaine while the other reports examined each drug alone. However, GVG has been shown to effectively reduce both oral ethanol self-administration (Wegelius et al., 1993) and iv cocaine self-administration (Kushner et al., 1999) when these drugs were presented alone. The fact that GVG is an indirect agonist with global effects on all GABA systems, when compared to selective agonists, may underlie the differences in action. For example, given the three known sources of GABAergic enervation to the VTA in addition to GABA receptors on presynaptic terminals in the nucleus accumbens and in other areas related to reinforcement such as the prefrontal cortex and amygdala, it is possible for differences to emerge related to site of action.

Another possibility is that GVG acts more generally to suppress the reward value of all appetitive behavior. While GVG produced no significant change in water consumption in the experiments reported here, it has been reported to reduce responding for food on both a fixed ratio (FR) and progressive ratio (PR) schedule at higher dose levels (Kushner et al., 1999). Microanalysis of drinking bouts across the session provide a better view of the effect of potential pharmacotherapeutic agents like GVG on drug consumption. In these experiments, GVG had no significant effect on the number of drinking bouts across the 6-h session. Instead, its effect was apparent in the significant reduction in the size or duration of individual drinking bouts. Unpublished preclinical data from our laboratory have shown that naltrexone exhibits a similar pattern of effects on alcohol consumption, while clinical data show that those subjects on naltrexone, and who sample alcohol, are much less likely to meet relapse criteria and subjectively report a decrease in liking for alcohol (Volpicelli et al., 1992; 1997). Because the rats in the experiments reported here continue to seek alcohol at a constant rate represented by bout number, the effect of GVG in these experiments can't be attributed to a general suppression of motor behavior. Instead, these data, when compared to the naltrexone data, suggest that GVG's effect emerges from a disruption of those factors mediating ethanol's reinforcing properties.

The use of oral cocaine in this model raises some questions. The traditional approach for studying cocaine self-administration with animal models has used iv self-administration, however, oral self-administration has been frequently employed in rats (Carlson and Perez, 1997; Dixon et al., 1989; George and Goldberg, 1988; Jentsch et al., 1998; Ma et al., 1999; Mosner et al., 1997; Tang and Falk, 1987; Taylor et al., 1990), mice (Alexander et al., 1993; George et al., 1991) and nonhuman primates (Meisch and Stewart, 1995; Meisch et al., 1990, 1993). While the bioavailability of cocaine is substantially lower following oral administration as compared to iv administration, the work by Ma et al. (1999) has shown that bioavailability may not be highly correlated with potency. The apparent higher potency of oral cocaine in their studies was suggested as due to the presence of the active metabolite, norcocaine, following oral cocaine or differences in the development of acute tolerance dependent on route of administration. This is consistent with an

earlier report in a clinical population reporting a greater subjective "high" with comparable bioavailability following oral as compared to intranasal cocaine (VanDyke et al., 1978). Additionally, studies on the effect of coadministration of alcohol with cocaine demonstrate a significant increase in the area under the cocaine time–concentration curve in rats with an alcohol history compared to alcohol-naive rats (Pan and Hedaya, 1999). These authors hypothesized that this greater cocaine bioavailability is due to increased absorption and decreased elimination of cocaine due to its interaction with alcohol. This cocaine–alcohol interaction is suggested also to reduce the percentage of cocaine reduced to benzoylecognine while increasing the presence of the active metabolites norcocaine and cocoaethylene. An increased presence of these active metabolites, which have reinforcing properties of their own, as also suggested by Ma et al. (1999), can increase the potency beyond that suggested by pharmacokinetics alone. The primary advantage of utilizing oral cocaine self-administration is that it allows a direct comparison with ethanol self-administration employing the same response system. This avoids any potential confounds that may arise when examining the potential efficacy of potential pharmacotherapeutic agents across multiple response systems. The benzoylecognine data reported above suggest that the oral route of consumption is sensitive to the actual dose of cocaine consumed and is consistent with a psychoactive dose as reported in a clinical population.

In summary, these data show that GVG attenuates both oral ethanol and cocaine consumption in a dose-related manner when those drugs are available for concurrent self-administration. This is consistent with those data showing that GVG reduces oral self-administration of ethanol (Wegelius et al., 1993) and iv self-administration of cocaine (Kushner et al., 1999). In addition, the greater potency of GVG in reducing ethanol consumption compared to cocaine is consistent with its effect on extracellular DA in the Nacc induced by administration of these drugs. Analysis of drinking bout data indicates that GVG has its effect by reducing the reinforcing properties of ethanol and cocaine rather than through a more general reduction in motor behavior. These results suggest that GVG may have potential for use in clinical populations who abuse ethanol or cocaine alone or in combination.

Acknowledgments

This work was supported in part by National Institute on Alcohol Abuse and Alcoholism Grant AA00228 to M.F. Stromberg. The authors thank Till Sengpiel and Robert Zell for their technical support of this research.

References

Alexander RC, Duda J, Garth D, Vogel WH, Berrettini WH. Morphine and cocaine preference in inbred mice. Psychiatr Genet 1993;3:33–8.

Ashby CR, Rohatgi R, Ngsouwan J, Borda T, Gerasimov MR, Morgan AE, Kushner S, Brodie J, Dewey SL. Implication of the $GABA_B$ receptor in gamma-vinyl GABA's inhibition of cocaine-induced increases in nucleus accumbens dopamine. Synapse 1999;31:151–3.

Boyle AE, Segal R, Smith BR, Amit Z. Bidirectional effects of GABAergic agonists and antagonists on maintenance of voluntary ethanol intake in rats. Pharmacol Biochem Behav 1999;46:179–82.

Brebner K, Froesti W, Andrews M, Phelan R, Roberts DC. The GABA(B) agonist CGP 44532 decreases cocaine self-administration in rats: demonstration using a progressive ratio and discrete trial procedure. Neuropharmacology 1999;38:1797–804.

Buckett WR. The influence of a GABA transaminase inhibitor, γ-vinyl-GABA, on voluntary morphine consumption in the rat. Psychopharmacology 1981;75:214–6.

Campbell UC, Lac ST, Carroll ME. Effects of baclofen on maintenance and reinstatement of intravenous cocaine self-administration in rats. Psychopharmacology 1999;143:209–14.

Carlson KR, Perez L. Ethanol and cocaine intake by rats selectively bred for oral opioid acceptance. Pharmacol Biochem Behav 1997;57:309–13.

Churchill L, Dilts RP, Kalivas PW. Autoradiographic localization of gamma-aminobutyric acid A receptors within the ventral tegmental area. Neurochem Res 1992;17:101–6.

Daoust M, Saligaut C, Lhuintre JP, Moore N, Filipo JL, Boismare F. GABA transmission, but not benzodiazepine receptor stimulation, modulates ethanol intake by rats. Alcohol 1987;4:469–72.

Dewey SL, Chaurasia CS, Chen CE, Volkow ND, Clarkson FA, Porter SP, Straughter-Moore RM, Alexov DL, Tedeshi D, Russo NB, Fowler JS, Brodie JD. GABAergic attenuation of cocaine-induced dopamine release and locomotor activity. Synapse 1997;25:393–8.

Dixon WR, Chang AP, Machado J, Lau B, Thompson A, Gallagher S, Sanders W. Effect of intravenous infusion and oral self-administration of cocaine on plasma and adrenal catecholamine levels and cardiovascular parameters in the conscious rat. NIDA Res Monogr 1989;95:335–6.

George FR, Goldberg SR. Genetic differences in response to cocaine. NIDA Res Monogr 1988;88:239–49.

George FR, Elmer GI, Meisch RA, Goldberg SR. Orally delivered cocaine functions as a positive reinforcer in C57BC/6J mice. Pharmacol Biochem Behav 1991;38:897–903.

Gerasimov MR, Ashby CR, Gardner EL, Mills MJ, Brodie JD, Dewey SL. Gamma-vinyl GABA inhibits methamphetamine, heroin, or ethanol-induced increases in nucleus accumbens dopamine. Synapse 1999; 34:11–9.

Hyytia P, Koob GF. $GABA_A$ receptor antagonism in the extended amygdala decreases ethanol self-administration in rats. Eur J Pharmacol 1995;283: 151–9.

Jentsch JD, Henry PJ, Mason PA, Merritt JH, Ziriax JM. Establishing orally self-administered cocaine as a reinforcer in rats using home-cage pre-exposure. Prog Neuro-Psychopharmacol Biol Psychiatry 1998;22:229–39.

Kalivas PW, Duffy P, Eberhardt H. Modulation of A10 dopamine neurons by γ-aminobutyric acid agonists. J Pharmacol Exp Ther 1990;253: 858–66.

Koob GF. Neural mechanisms of drug reinforcement. In: Kalivas PW, Samson HH, editors. The neurobiology of drug and alcohol addiction. New York: New York Academy of Science, 1992. p. 171.

Kushner SA, Dewey SL, Kornetsky C. The irreversible γ-aminobutyric acid (GABA) transaminase inhibitor γ-vinyl-GABA blocks cocaine self-administration in rats. J Pharmacol Exp Ther 1999;29:797–802.

Ma F, Falk JL, Lau CE. Cocaine pharmacodynamics after intravenous and oral administration in rats: relation to pharmacokinetics. Psychopharmacology 1999;144:323–32.

Mattson RH, Petroff OA, Rothman D, Behar K. Vigabratin: effect on brain GABA levels measure by nuclear magnetic resonance spectroscopy. Acta Neurol Scand, Suppl 1995;162:27–30.

Meisch RA, Stewart RB. Relative reinforcing effects of different doses of orally delivered cocaine. Drug Alcohol Depend 1995;37:141–7.

Meisch R, George FR, Lemarie GA. Orally delivered cocaine as a reinforcer for rhesus monkeys. Pharmacol Biochem Behav 1990;35:245–9.

Meisch RA, Bell SM, Lemarie GA. Orally self-administered cocaine in rhesus monkeys: transition from negative or neutral behavioral effects to positive reinforcing effects. Drug Alcohol Depend 1993;32:143–58.

Miller NS, Giannini AJ. Drug misuse in alcoholics. Int J Addict 1991; 26:851–7.

Morgan AE, Dewey SL. Effects of pharmacologic increase in brain GABA levels on cocaine-induced changes in extracellular dopamine. Synapse 1998;28:60–5.

Mosner A, Kuhlman G, Roehm C, Vogel WH. Serotonergic receptors modify the voluntary intake of alcohol and morphine but not of cocaine and nicotine by rats. Pharmacology 1997;54:186–92.

Nowak KL, McBride WJ, Lumeng L, Li T-K, Murphy JM. Blocking GABA (A) receptors in the anterior ventral tegmental area attenuates ethanol intake of the alcohol-preferring P rat. Psychopharmacology 1998;139:108–16.

Pan WJ, Hedaya MA. Cocaine and alcohol interactions in the rat: effect of cocaine and alcohol pretreatments on cocaine pharmacokinetics and pharmacodynamics. J Pharm Sci 1999;88:1266–74.

Petry NM. Benzodiazepine-GABA modulation of concurrent ethanol and sucrose reinforcement in the rat. Exp Clin Psychopharmacol 1997;5: 183–94.

Ritchie JM, Cohen PJ. Cocaine, prococaine and other synthetic anesthetics. In: Goodman AG, Gillman LS, editors. The pharmacological basis of therapeutics. New York: MacMillan, 1975. pp. 349–403.

Roberts DC, Andrews MN. Baclofen suppression of cocaine self-administration: demonstration using a discrete trials procedure. Psychopharmacology 1997;131:271–7.

Roberts AJ, Cole M, Koob GF. Intra-amygdala muscimol decreases operant ethanol self-administration in dependent rats. Alcohol: Clin Exp Res 1996;20:1289–98.

Rounsaville BJ, Anton SF, Carroll K, Budde D, Prusoff BA, Gawin F. Psychiatric diagnoses of treatment-seeking cocaine abusers. Arch Gen Psychiatry 1991;48:43–51.

Shoaib M, Swanner LS, Beyer CE, Goldberg SR, Schindler CW. The $GABA_B$ agonist baclofen modifies cocaine self-administration in rats. Behav Pharmacol 1998;9:195–206.

Smith BR, Boyle AEL, Amit Z. The effects of the $GABA_B$ agonist baclofen on the temporal and structural characteristics of ethanol intake. Alcohol 1999;17:231–40.

Soderpalm AH, Hansen S. Benzodiazepines enhance the consumption of and palatability of alcohol in the rat. Psychopharmacology 1998;137: 215–22.

Tang M, Falk JL. Oral self-administration of cocaine: chronic excessive intake by schedule induction. Pharmacol Biochem Behav 1987;28: 517–9.

Taylor J, Harris N, Vogel WH. Voluntary alcohol and cocaine consumption in ''low'' and ''high'' stress plasma catecholamine responding rats. Pharmacol Biochem Behav 1990;37:359–63.

Tomkins DM, Sellers EM, Fletcher PJ. Effect of dorsal raphe injections of the GABAA agonist, muscimol, on ethanol intake and measures of intoxication in the Wistar rat. Alcohol Alcohol 1994;Suppl 2:551–8.

VanDyke C, Jatlow P, Ungerer J, Barash PG, Byck R. Oral cocaine: plasma concentrations and central effects. Science 1978;200:211–3.

Volpicelli JR, Alterman AI, Hayashida M, O'Brien CP. Naltrexone in the treatment of alcohol dependence. Arch Gen Psychiatry 1992;49: 876–80.

Volpicelli JR, Rhines KC, Rhines JS, Volpicelli LA, Alterman AI, O'Brien CP. Naltrexone and alcohol dependence. Role of subject compliance. Arch Gen Psychiatry 1997;54:737–42.

Wegelius K, Honkanen A, Korpi ER. Gamma-vinyl GABA decreases voluntary alcohol consumption in alcohol-preferring AA rat. Pharmacol Toxicol 1993;73:150–2.