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A Novel Strategy for the Treatment of Cocaine Addiction

STEPHEN L. DEWEY,[1,6,*] ALEXANDER E. MORGAN,[1] CHARLES R. ASHBY, JR.,[2] BRYAN HORAN,[2] STEPHANIE A. KUSHNER,[3] JEAN LOGAN,[1] NORA D. VOLKOW,[4] JOANNA S. FOWLER,[1] ELIOT L. GARDNER,[5] AND JONATHAN D. BRODIE[6]

[1]*Chemistry Department, Brookhaven National Laboratory, Upton, NY 11973*
[2]*Department of Pharmaceutical Health Sciences, St. John's University, Jamaica, NY 11439*
[3]*Department of Pharmacology, Boston University School of Medicine, Boston, MA 02118*
[4]*Medical Department, Brookhaven National Laboratory, Upton , NY, 11973*
[5]*Departments of Psychiatry and Neuroscience, Albert Einstein College of Medicine, Bronx, NY*
[6]*Department of Psychiatry, New York University School of Medicine, New York, NY 10016*

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ABSTRACT Cocaine's addictive liability has been linked to its pharmacologic actions on mesotelencephalic dopamine (DA) reinforcement/reward pathways in the central nervous system (CNS). Dopaminergic transmission within these pathways is modulated by gamma-aminobutyric acid (GABA). With this knowledge, we examined the utility of gamma vinylGABA (GVG), a selective and irreversible inhibitor of GABA-transaminase (GABA-T) known to potentiate GABAergic inhibition, to alter cocaine's biochemical effects as well as its effects on behaviors associated with these biochemical changes. GVG significantly attenuated cocaine-induced increases in neostriatal synaptic DA in the non-human primate (baboon) brain as assessed by positron emission tomography (PET) and abolished both the expression and acquisition of cocaine-induced conditioned place preference (CPP). It had no effect on CPP for a food reward, the delivery of cocaine to the brain or locomotor activity. These findings suggest the possible therapeutic utility in cocaine addiction of a pharmacologic strategy targeted at the GABAergic neurotransmitter system, a system distinct from but functionally linked to the DA mesotelencephalic reward/reinforcement system. However, rather than targeting the GABA receptor complex with a direct GABA agonist, this novel approach with GVG takes advantage of the prolonged effects of an irreversible enzyme inhibitor that raises endogenous GABA levels without the addictive liability associated with GABA agonists acting directly at the receptor itself. Human trials with GVG are currently being developed to directly examine the utility of this novel strategy for the treatment of cocaine addiction. **Synapse 30:119–129, 1998.**

INTRODUCTION

Addicting drugs have in common the direct, indirect, and in some cases, trans-synaptic enhancement of dopamine (DA) within the mesotelencephalic reward/reinforcement circuitry of the forebrain (Gardner, 1997), presumably producing the enhanced brain reward that constitutes the drug user's "high". Alterations in the function of these DA systems have also been implicated in drug craving and in relapse to the drug-taking habit in recovering addicts (Gardner, 1997; Nestler, 1993). Cocaine acts on these systems by binding to the dopamine transporter (DAT) and preventing DA reuptake into the presynaptic terminal. There is considerable evidence that cocaine's addictive liability is linked to reuptake blockade in central nervous system (CNS) reward/reinforcement pathways. For example, cocaine-induced increases in extracellular DA have been linked to its rewarding and craving effects in rodents (Fontana, et al., 1993). In humans, the pharmacokinetic binding profile of [^{11}C]-cocaine indicates that the uptake of labeled cocaine is directly correlated with the

*Correspondence to: Stephen L. Dewey, Ph.D., Chemistry Department Brookhaven National Laboratory, Upton, New York 11973. E-mail: Sld@bnl.gov

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self-reported "high" (Volkow, et al., 1997). In addition, human cocaine addicts exposed to cocaine-associated environmental cues experienced increased cocaine craving which is antagonized by the DA receptor antagonist haloperidol (Berger, 1996). Based upon the presumptive link between cocaine's addictive liability and the DA reward/reinforcement circuitry of the forebrain, many pharmacologic strategies for treating cocaine addiction have been proposed (O'Brien, 1997).

One strategy is to directly target the DAT with a high-affinity cocaine analog, thereby blocking cocaine's action (Morgan, et al., 1997). Another strategy is to modulate synaptic DA directly by the use of DA agonists and antagonists. Yet another is to modulate synaptic DA, indirectly or trans-synaptically, by specifically targeting a functionally-linked but biochemically different neurotransmitter system. Numerous reports demonstrate that GABAergic neurons in the nucleus accumbens (NACC) and ventral pallidum inhibit DA in the NACC and, to a lesser extent, the corpus striatum. In light of this functional inhibition, we investigated the ability of gamma vinyl-GABA (GVG, Vigabatrin®), the systemic administration of which causes a dose-dependent and prolonged elevation of extracellular endogenous brain GABA levels (Jung, et al., 1977), to attenuate the biochemical and behavioral effects of cocaine in the primate and rodent CNS. GVG does not bind to any receptor or reuptake complex, but increases endogenous intracellular GABA levels by selectively and irreversibly inhibiting GABA-transaminase (GABA-T), the enzyme that normally catabolizes GABA (Jung, et al., 1977). GVG is not an addictive drug (animals will not self-administer), and it does not appear to produce tolerance or withdrawal (Takada and Yanagita, 1997). Finally, it is used clinically for the treatment of partial complex seizures in pediatric and adult patients.

We have shown that acute or chronic administration of GVG will attenuate cocaine-induced increases in extracellular DA dose-dependently (Morgan and Dewey, 1998; Dewey, et al., 1997). This effect occurs in both the NACC and corpus striatum of naïve and chronically cocaine-exposed freely moving rats. In addition, we demonstrated that GVG dose-dependently decreases cocaine self-administration on a fixed ratio 5 reinforcement schedule (Kushner, et al., 1997a) as well as on a progressive ratio schedule (unpublished data) and attenuates cocaine's ability to lower brain stimulation reward thresholds in rodents (Kushner, et al., 1997b). Now, for the first time, we report the use of positron emission tomography (PET) and [^{11}C]-raclopride (Volkow, et al., 1994) for non-invasive measurement of the effects of GVG on cocaine-induced increases in extracellular neostriatal DA in the non-human primate (baboon) brain. In addition, using the conditioned place preference (CPP) paradigm, we extend these PET findings to include an independent assessment of the behavioral consequences associated with GVG on cocaine-induced behaviors in rodents.

The CPP paradigm is widely used to evaluate the incentive motivational effects of drugs in laboratory animals (Van Der Kooy, 1995). Animals are tested, in a drug-free state, to determine whether they prefer an environment in which they previously received cocaine as compared to an environment in which they previously received saline. If the animal, in a drug-free state, consistently chooses the environment previously associated with cocaine, the inference is drawn that the appetitive value of cocaine was encoded in the brain and is accessible in the drug-free state.

MATERIALS AND METHODS

Non-human primate (baboon) PET studies

Adult female baboons (n=20) (*Papio anubis*, 13–18 kg) were used for all studies and carbon-11 labeled raclopride, previously shown to be sensitive to changes in synaptic DA was synthesized as previously described (Volkow, et al., 1994). Arterial blood samples were obtained throughout the study and selected plasma samples were analyzed for the presence of unchanged radiotracer. Animals were not removed from the gantry between isotope injections. Regions of interest (ROI's) were drawn directly on the PET images. Briefly, the corpus striatum was bilaterally outlined on every transaxial slice upon which it appeared. The cerebellar ROI was drawn across the midline at the level of the cerebellar vermis. ROI's from the first study were then copied directly onto the corresponding slice from the second. By examining placement of the ROI's on the second scan, changes could be made, if necessary, in ROI position only. This multiplanar method of analysis reduces differences that may arise due to movement of the animal within the gantry during the scanning interval. A graphical method for determining the distribution volume (DV) had been developed previously for the kinetic analysis of our [^{11}C]-raclopride data. The most reproducible measure of raclopride uptake was found to be the DV ratio — the ratio of the DV from a receptor-rich region (corpus striatum) to the DV of a non-receptor region (cerebellum). The free receptor concentration is directly proportional to the DV ratio – 1. Animal preparation was conducted as detailed previously (Dewey, et al., 1992). The statistical analysis was designed to test the hypothesis that, 1) the cocaine challenge differed from the test/retest variability of this radiotracer (performed in the same animals under identical experimental conditions) and, 2) the challenge conditions differed from each other. The fact that significant results were obtained for the striatum and striatum to cerebellum ratio, but not for the cerebellum, indicates that the effects of the intervention were limited to the specific, but not the non-specific binding component. GVG altered neither the regional distribution nor the rate of metabolism of the radiotracer.

Cocaine-induced conditioned place preference

In all rodent studies, male Sprague-Dawley rats were used (200–225g, Taconic farms, Germantown, NY). Animals were allowed to acclimate to the animal housing facility for at least 5 days prior to beginning the experiments. We used CPP chambers as previously described (Lepore et al., 1995), except instead of one chamber being entirely white and the other black, one chamber was entirely light blue with a stainless steel floor and the second chamber was light blue with horizontal black stripes (2.5 cm wide) spaced 3.8 cm apart with a smooth plexiglass floor. In all CPP studies with GVG, the saline volume was (1 ml/kg), and the cocaine doses were 20 mg/kg. The saline, cocaine and GVG were all injected intraperitonealy (i.p.). The conditioning procedure for the acquisition phase consisted of 12 sessions carried out consecutively over 12 days. The CPP pairings were: 1) saline/saline; 2) saline/cocaine; 3) GVG/saline, and 4) saline/cocaine + GVG. The animals in each group were randomly assigned to a 2 × 2 factorial design with one factor being the pairing chamber and the other factor being the order of conditioning. The animals that received either saline or cocaine were injected and confined to the appropriate compartment for 30 minutes. The GVG injections were given 3 hours before saline or cocaine injection and subsequent placement of the animals in the appropriate chamber. This was done as it has been shown that GABA levels reach maximal values 3 to 4 hours following GVG administration. On the test day (day 12), neither drugs nor saline were administered and the animal was allowed to move freely between both chambers for fifteen minutes. The amount of time spent in each chamber was recorded using an automated infrared beam electronically coupled to a timer. For the expression phase of CPP to cocaine, the animals were habituated and conditioned to cocaine as described in the acquisition studies, but no animals in the expression studies were given GVG on conditioning days. On the test day (day 12), the animals being tested in the expression phase, unlike the animals in the acquisition phase, received either saline or GVG 2.5 hours before they were placed in the apparatus and allowed free access both chambers for 15 minutes.

Food-induced conditioned place preference

For food conditioning, four groups of rats were allowed access to food ad libitum during the entire 12 session CPP procedure. The 12 session CPP procedure was exactly the same as the procedure used in the cocaine induced CPP studies except the appetitive substance was food rather than cocaine. Group one was given saline, group two was given 150 mg/kg i.p. of GVG, group 3 was given saline and group 4 was given 300 mg/kg i.p. of GVG prior to food exposure and pairing to a side of the CPP box. The animals in all four groups were habituated to Froot Loops, a fruit-flavored breakfast cereal that is very appealing to laboratory rats, in the appropriate chamber in the test room during four habituating sessions. Twenty-four hours after the last pairing, the animals were placed in the chamber and neither drug nor saline (nor food) were administered (or available) Animals were allowed to move freely within the CPP apparatus for 15 minutes. The amount of time spent in the paired and unpaired chambers was recorded using an automated device.

Locomotor activity

Animals were prehandled for 5 minutes each day for one week prior to the experiment to reduce handling stress. On the day of the study, GVG (150 mg/kg or 300 mg/kg) or saline (1 ml/kg or 0.5 ml/kg) was administered i.p. 2.5 hours prior to the experiment. The animals were transported to the testing area one hour before each experiment. 2.5 hours after GVG or saline administration, animals were placed in the behavior cages and the locomotor activity was recorded in 10 minute intervals for 90 minutes onto a PC-AT computer using the hardware for the Photobeam Activity System. The locomotor cages themselves are 41.3 × 41.3 × 30.5 cm clear acrylic cages. The electronic system (Photobeam Activity system, San Diego Instruments, San Diego, Calif.) used to monitor locomotor activity consists of 16 infrared beams projecting across the cages from left to right and 16 beams from front to back. All the infrared beams are approximately 0.39 cm from the floor.

Catalepsy studies

The degree of catalepsy following the administration of 150 mg/kg i.p. GVG, 300 mg/kg i.p. GVG or saline (1 ml/kg, i.p. 0.9% saline) was determined using the bar test (Ferre, et al., 1990). Briefly, male Sprague-Dawley rats were handled and transported to the test room three days prior to the experiments to allow for acclimation. On the test day, the animals (n = 10 per treatment group) received either saline or GVG, and the degree of catalepsy was measured 60, 120 and 240 minutes following injection. The experimenter was blind to the treatment received by each animal. The bar was composed of wood and had a diameter of 1.2 cm and the height from the floor to the top of the bar was 10 cm. For each determination, the forepaws of the animals were gently placed over the bar and the time it took the animal to move both forepaws to the floor was measured.

[^{11}C]-Cocaine studies in rodents and primates

Animals (n=10) were placed into two groups. In group 1, saline (1 ml/kg) was administered via intraperitoneal (i.p.) injection 3 hours prior to i.p. [^{11}C]-cocaine administration. In group 2, GVG (300 mg/kg) was

TABLE I. Groups and experimental conditions

Group	Pharmacologic condition
1	Control (test/retest)
2	Cocaine treated
3	GVG/Cocaine treated

administered via i.p. injection 3 hours prior to i.p. [^{11}C]-cocaine administration. Animals were sacrificed 10 minutes following [^{11}C]-cocaine injection. Brains were removed and counted for radioactivity. In two additional primate PET studies, GVG was administered (300 mg/kg) immediately following a baseline scan with labeled cocaine. Approximately 3 hours later, labeled cocaine was again administered and animals were scanned for 60 minutes.

RESULTS

Each non-human primate (n=20) received two [^{11}C]-raclopride injections. The first served as a baseline and the second followed cocaine or placebo. Test/retest primates (n=7, Group 1, Table I) received placebo (0.9% saline, 1 ml/kg) prior to the second radiotracer injection in order to determine the test/retest variability of this imaging method. All remaining primates (n=13) received a systemic injection of cocaine hydrochloride (0.5, 1.0 or 2.0 mg/kg) either 5 or 30 minutes prior to the second [^{11}C]-raclopride injection. Of these 13 animals, five received GVG (300 mg/kg, iv) 3 hours prior to cocaine administration. The different cocaine doses and cocaine pretreatment time intervals produced no significant changes in cocaine's effects on the distribution volume (DV), in line with expectations (Gatley, et al., 1997; Fowler, et al., 1989; Hurd, et al., 1988). Thus, we report here the average % change in the DV ratio for animals treated with cocaine alone (n=8) versus GVG/cocaine (n=5) as Groups 2 and 3, respectively (Figure 1).

As a competitive antagonist, [^{11}C]-raclopride's binding is dependent upon the concentration of DA in the synaptic cleft (Seeman, et al., 1989). That is, as synaptic DA concentrations decrease, [^{11}C]-raclopride binding increases. Conversely, as synaptic DA concentrations increase, [^{11}C]-raclopride binding decreases. As seen in Figure 1, the test/retest variability of this imaging method was less than 7% (group 1). The variability of these PET measurements is consistent with previous values obtained with [^{11}C]-raclopride in non-human primates. In group 2, cocaine produced a greater than 30% reduction in the mean DV ratio ($p<0.0002$, Student's two-tailed t-test, Fig 1). These data are consistent with simultaneous PET and microdialysis studies in which an amphetamine challenge increased extracellular DA and decreased [^{11}C]-raclopride binding in the primate brain (Breier, et al., 1997). In addition, these findings are similar to a recent report which examined the effects of a cocaine challenge on labeled raclopride binding in the human brian (Schlaeper, et al., 1997). Finally, these data are consistent with our own microdialysis studies (Morgan and Dewey, 1998) as well as our primate and human PET studies with amphetamine, GBR 12909, tetrabenazine, methylphenidate, and [^{11}C]-raclopride (Dewey et al., 1993; Volkow, et al., 1994). GVG pretreatment, however, significantly blocked this cocaine-induced decrease (group 2) in the DV ratio (group 2, $p<0.002$, Student's two-tailed t-test, Figure 1). These differences are readily apparent in the parametric DV ratio images (Fig. 2). Values for groups 1 and 3 were not statistically different ($p>0.1$, Student's two-tailed t-test).

Cocaine-induced conditioned place preference studies

Cocaine produced a dose-dependent CPP response, with the most reliable and robust response occurring at 20 mg/kg (Table II). Therefore we chose a 20 mg/kg cocaine dose with which to examine the effect of GVG administration on the acquisition and expression phases of cocaine-induced CPP. The results clearly indicate that 112, 150 and 300 mg/kg, but not 75 mg/kg, of GVG blocked the acquisition and expression of cocaine-induced CPP (Tables III–X). By itself, GVG produced neither a CPP nor a conditioned aversive response (Tables III–X).

Food-induced conditioned place preference studies

In agreement with other CPP studies in rats (Spyraki, et al., 1982; Swerdlow, et al., 1989; Carr, et al., 1988; Lepore et al., 1995), our results indicate that food elicited an incentive or rewarding effect (Table XI). The administration of 150 or 300 mg/kg of GVG did not alter the CPP response to food (Table XI) despite attenuating the incentive motivational effects of cocaine in the above noted CPP experiments

Locomotor activity and catalepsy studies

Although it is widely accepted that the CPP paradigm differentiates incentive motivational effects from motoric effects (Van Der Kooy, 1995; Carr, et al., 1988), we nevertheless assessed GVG's effects on locomotion and catalepsy (Ferre, et al., 1990) in rats. We found that pretreatment with GVG at doses of 150 mg/kg or 300 mg/kg did not alter locomotor activity compared to saline pretreated controls (Figs. 3a, 3b). In addition, pretreatment with GVG at doses of 150 mg/kg or 300 mg/kg did not induce catalepsy in rats. Catalepsy duration after 300 mg/kg GVG was 1.1 ± 0.4 seconds (n=10), which was not significantly different from 0.7 ± 0.3 seconds (n=10) in saline-treated rats.

[^{11}C]-Cocaine levels in rodents and primates

In order to assess the possibility that GVG might attenuate cocaine's actions by altering its penetration

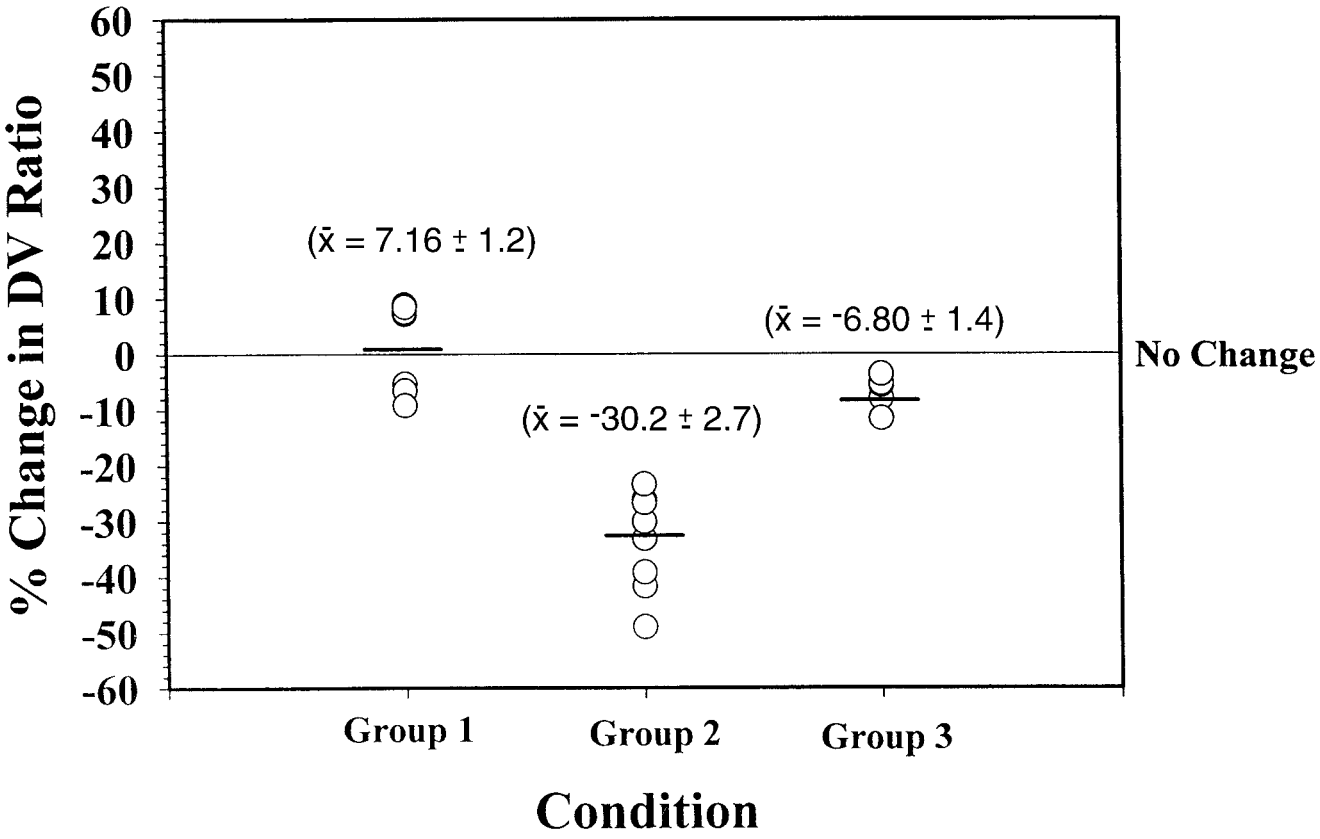

Fig. 1. Comparison of cocain's effects on the DV ratio in froup 1,2,and 3, animals. Each data point is derived from the calculation:

$$\frac{(\text{DVSTscan1})}{(\text{DVCBscan2})} \Big/ \frac{(\text{DVSTscan2})}{(\text{DVCBscan2})}$$

Individual points are shown for each study (n = 20).

into the brain, we examined the effect of saline and GVG on [^{11}C]-cocaine levels in the whole rat and primate brain. In rodents, the levels of [^{11}C]-cocaine in the brain following intraperitoneal administration of saline and 300 mg/kg GVG were 0.110 ± 0.03 and 0.091 ± 0.02, respectively, which did not statistically differ. In primates, the pharmacokinetic profile of labeled cocaine binding in the neostriatum was not significantly different from the baseline scan both in terms of absolute uptake as well as clearance.

DISCUSSION

In previous PET studies, we showed that GVG alone reduces extracellular DA concentrations resulting in an increase in [^{11}C]-raclopride binding in the non-human primate brain (Dewey, et al., 1992). In the PET studies presented here, GVG-induced decreases in extracellular DA levels prior to cocaine administration clearly underlie the attenuation of cocaine's effects observed in group 3. However, the seemingly identical values found for groups 1 and 3, combined with our previous findings using GVG alone (Dewey, et al., 1992), indicate that cocaine increased extracellular DA levels in the present study despite GVG administration, *but only to baseline values.*

However, based on the CPP data presented here, this cocaine-induced return to baseline was apparently insufficient to produce incentive motivational effects. As previously reported (Carr et al., 1989), our results indicate that cocaine produces a CPP response. In contrast, vehicle pairings did not produce a CPP response, indicating that the animals did not display a chamber preference, i.e., the apparatus is unbiased. In addition, the CPP response to cocaine was dose-dependent, with the most reliable and robust response occurring at the 20 mg/kg dose.

Administration of 112, 150, 300 mg/kg but not 75 mg/kg of GVG blocked the acquisition and expression of the CPP response elicited by cocaine. In contrast, GVG, when paired with saline, did not produce a CPP or

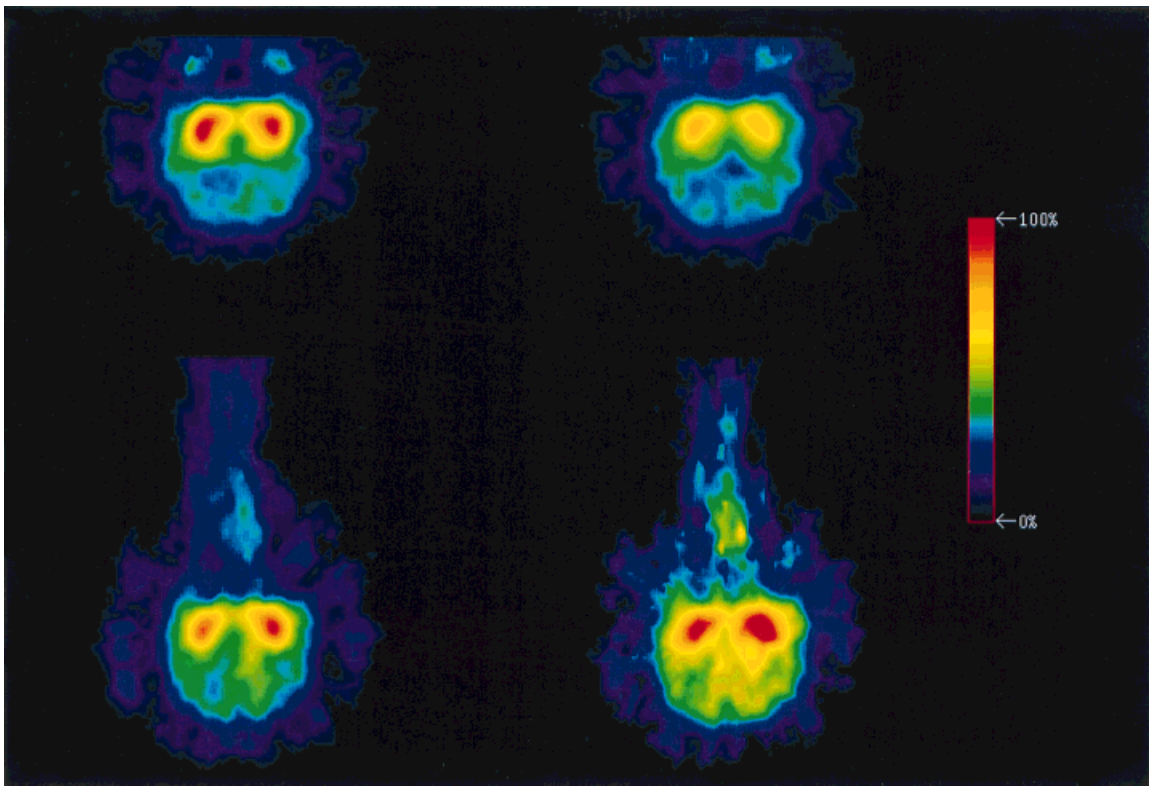

Fig. 2. Transaxial parametric DV ratio images of the non-numan primate brain at the level of the corpus striatum. The color scale indicates intensity of receptor availability (red indicates higher availibility vs. magenta indicating a lower receptor availability). Cocaine decreases receptor availability **(top right)** compared to baseline values **(top left)**. When pretreated with GVG, however, cocaine did not alter receptor availability **(lower right)** compared to baseline values **(lower left)**.

TABLE II. Conditioned place preference to cocaine

	Time spent in chambers (mins)	
Cocaine (mg/kg)	Paired	Unpaired
0	7.4 ± 0.3	7.6 ± 0.3
5.0	8.2 ± 0.4	6.8 ± 0.5
10.0	9.6 ± 0.5*	5.4 ± 0.5
20.0	11.8 ± 0.4**	3.2 ± 0.4***

*Significantly greater than the 0 and 5 mg/kg doses of cocaine, $p < 0.05$, ANOVA and Student-Newman-Keuls test.
**Significantly greater than the 0, 5 and 10 mg/kg doses of cocaine, $p < 0.05$, ANOVA and Student-Newman-Keuls test.
***Significantly less than the 0, 5 and 10 mg/kg doses of cocaine, $p < 0.01$, ANOVA and Student-Newman-Keuls test.

TABLE III. Effect of GVG and saline on the acquisition of cocaine-induced conditioned place preference

	Time spent in chambers (min)	
Treatment pairings[1]	Paired	Unpaired
Saline/Saline	7.3 ± 0.5	7.7 ± 0.6
Saline/Cocaine	11.1 ± 0.3*	3.9 ± 0.4
75 mg/kg GVG[2]/Saline	7.3 ± 0.5	7.7 ± 0.6
75 mg/kg GVG[2]/Cocaine	9.1 ± 1.1	5.9 ± 1.2

[1]Each value represents the mean number of minutes spent in each chamber ± S.E.M. (n = 8–10).
[2]Animals received GVG or Saline 2.5 hours prior to receiving saline or cocaine (20 mg/kg).
*Significantly greater than all treatment groups, $p < 0.05$, ANOVA and Newman-Keuls Test.
**Significantly less than all treatment groups, $p < 0.01$, ANOVA and Newman-Keuls test.

aversive response. This indicates that the blockade of the CPP to cocaine by GVG was not related to its eliciting an aversive or appetitive response by itself.

In agreement with other CPP studies in rats (Lepore et al., 1995; Spyraki et al., 1982; Swerdlow et al., 1983), our results indicated that food elicits an incentive or rewarding effect. The administration of 150 or 300 mg/kg of GVG did not alter the CPP response to food, despite attenuating the incentive effects of cocaine. This finding suggests that GVG specifically attenuates the rewarding/incentive effects of cocaine.

Our results are consistent with previous studies suggesting that the augmentation of GABAergic function can attenuate the rewarding/reinforcing actions of cocaine and other drugs of abuse. For example, it has been shown that, using the progressive ratio paradigm, the selective $GABA_B$ agonist baclofen produces a dose-dependent decrease in the break points for i.v. administration of cocaine in male Wistar rats, although it did not affect the rate of drug intake (Roberts et al., 1996). These results suggest that baclofen attenuates the reinforcing effects of cocaine, as a decrease in the break point represents a decrease in the motivation to self-administer cocaine. It has also been hypothesized that

TABLE IV.

Treatment pairings[1]	Time spent in chambers (min) Paired	Unpaired
Saline/Saline	7.2 ± 0.5	7.8 ± 0.4
Saline/Cocaine	11.8 ± 0.5*	3.2 ± 0.5
112 mg/kg GVG[2]/Saline	7.6 ± 0.6	7.4 ± 0.6
112 mg/kg GVG[2]/Cocaine	8.2 ± 0.5	6.8 ± 0.5

[1]Each value represents the mean number of minutes spent in each chamber ± S.E.M. (n = 8–10).
[2]Animals received GVG or Saline 2.5 hours prior to receiving saline or cocaine (20 mg/kg).
*Significantly greater than all treatment groups, $p < 0.05$, ANOVA and Newman-Keuls Test.
**Significantly less than all treatment groups, $p < 0.01$, ANOVA and Newman-Keuls test.

TABLE V.

Treatment pairings[1]	Time spent in chambers (min) Paired	Unpaired
Saline/Saline	7.4 ± 0.3	7.6 ± 0.4
Saline/Cocaine	11.6 ± 0.5*	3.4 ± 0.4**
150 mg/kg GVG[2]/Saline	7.8 ± 0.5	7.2 ± 0.5
150 mg/kg GVG[2]/Cocaine	7.9 ± 0.8	7.1 ± 0.8

[1]Each value represents the mean number of minutes spent in each chamber ± S.E.M. (n = 8–10).
[2]Animals received GVG or Saline 2.5 hours prior to receiving saline or cocaine (20 mg/kg).
*Significantly greater than all treatment groups, $p < 0.05$, ANOVA and Newman-Keuls Test.
**Significantly less than all treatment groups, $p < 0.01$, ANOVA and Newman-Keuls test.

TABLE VI.

Treatment pairings[1]	Time spent in chambers (min) Paired	Unpaired
Saline/Saline	7.7 ± 0.3	7.3 ± 0.3
Saline/Cocaine	11.2 ± 0.6*	3.8 ± 0.5**
300 mg/kg GVG[2]/Saline	7.2 ± 0.4	7.8 ± 0.4
300 mg/kg GVG[2]/Cocaine	7.8 ± 0.7	7.2 ± 0.7

[1]Each value represents the mean number of minutes spent in each chamber ± S.E.M. (n = 8–10).
[2]Animals received GVG or Saline 2.5 hours prior to receiving saline or cocaine (20 mg/kg).
*Significantly greater than all treatment groups, $p < 0.05$, ANOVA and Newman-Keuls Test.
**Significantly less than all treatment groups, $p < 0.01$, ANOVA and Newman-Keuls test.

TABLE VII. Effect of GVG and saline on the expression of cocaine-induced conditioned place preference

Treatment pairings[1]	Drug given on test day	Time spent in chambers (min) Paired	Unpaired
Saline/Saline	Saline	7.5 ± 0.4[1]	7.5 ± 0.4
Saline/Saline	GVG, 75 mg/kg	7.5 ± 0.3	7.5 ± 0.3
Saline/Cocaine	Saline	11.8 ± 0.5*	3.2 ± 0.5
Saline/Cocaine	GVG, 75 mg/kg	10.6 ± 0.6*	4.4 ± 0.9

TABLE VIII.

Treatment pairings[1]	Drug given on test day	Time spent in chambers (min) Paired	Unpaired
Saline/Saline	Saline	7.1 ± 0.5	7.9 ± 0.5
Saline/Saline	GVG, 112 mg/kg	7.2 ± 0.3	7.8 ± 0.3
Saline/Cocaine	Saline	12.2 ± 0.6*	2.8 ± 0.5
Saline/Cocaine	GVG, 112 mg/kg	8.1 ± 0.7	6.9 ± 0.6

TABLE IX.

Treatment pairings[1]	Drug given on test day	Time spent in chambers (min) Paired	Unpaired
Saline/Saline	Saline	7.2 ± 0.2[1]	7.8 ± 0.2
Saline/Saline	GVG, 150 mg/kg	7.7 ± 0.2	7.3 ± 1.1
Saline/Cocaine	Saline	11.1 ± 0.5*	3.9 ± 0.4**
Saline/Cocaine	GVG, 150 mg/kg	7.9 ± 0.3	7.1 ± 0.3

TABLE X.

Treatment pairings[1]	Drug given on test day	Time spent in chambers (min) Paired	Unpaired
Saline/Saline	Saline	7.8 ± 0.5[1]	7.2 ± 0.6
Saline/Saline	GVG, 300 mg/kg	7.3 ± 0.4	7.7 ± 0.3
Saline/Cocaine	Saline	12.5 ± 0.8***	2.5 ± 0.6****
Saline/Cocaine	GVG, 300 mg/kg	7.9 ± 0.5	7.1 ± 0.6

[1]Each value represents the mean number of minutes spent in each chamber ± S.E.M. (n = 10).
*Significantly greater than all other treatment pairings, $p < 0.01$, ANOVA and Student Newman-Keuls test.
**Significantly less than all other treatment pairings, $p < 0.01$, ANOVA and Student Newman-Keuls test.
***Significantly greater than all other treatment pairings, $p < 0.05$, ANOVA and Student Newman-Keuls test.
****Significantly less than all other treatment pairings, $p < 0.05$, ANOVA and Student Newman-Keuls test.

TABLE XI. Effect of GVG (150, 300 mg/kg, ip) on conditioned place preference to food

Treatment group	Time spent in chambers (mins) Paired	Unpaired
Saline/Saline	7.3 ± 0.6	7.7 ± 0.6
GVG/Saline	7.5 ± 0.7	7.5 ± 0.7
Saline/Food	9.3 ± 0.7	5.7 ± 0.7
GVG (150 mg/kg)/Food	9.4 ± 0.4	5.6 ± 0.5
GVG (300 mg/kg)/Food	9.0 ± 0.5	6.0 ± 0.5

augmentation of $GABA_A$ receptor function may attenuate cocaine self-administration, as chlordiazepoxide and alprazolam, positive allosteric modulators of the $GABA_A$ receptor complex, decrease the rate of cocaine self-administration (Goeders et al., 1989, 1993). However, this effect is probably related to an increase in the reinforcing value of each unit dose of cocaine, as chlordiazepoxide will increase the break point for cocaine self-administration on a progressive ratio schedule (Roberts et al., 1996). The findings with baclofen are reinforced by a recent study from the same laboratory indicating that acute pretreatment of rats with baclofen (1.25 - 5 mg/kg i.p.) will suppress self-administration of cocaine in a discrete trials paradigm for at least four hours without significantly altering responding for food reinforcement (Roberts and Andrews, 1997). Microinjection of baclofen into the ventral tegmental area ipsilateral to a stimulating electrode in the lateral hypothalamus of rats produces a rightward shift of the rate-current intensity curve, indicating that baclofen attenuates the rewarding value of the electrical stimulation (Willick and Kokkinidis, 1995). However, baclofen

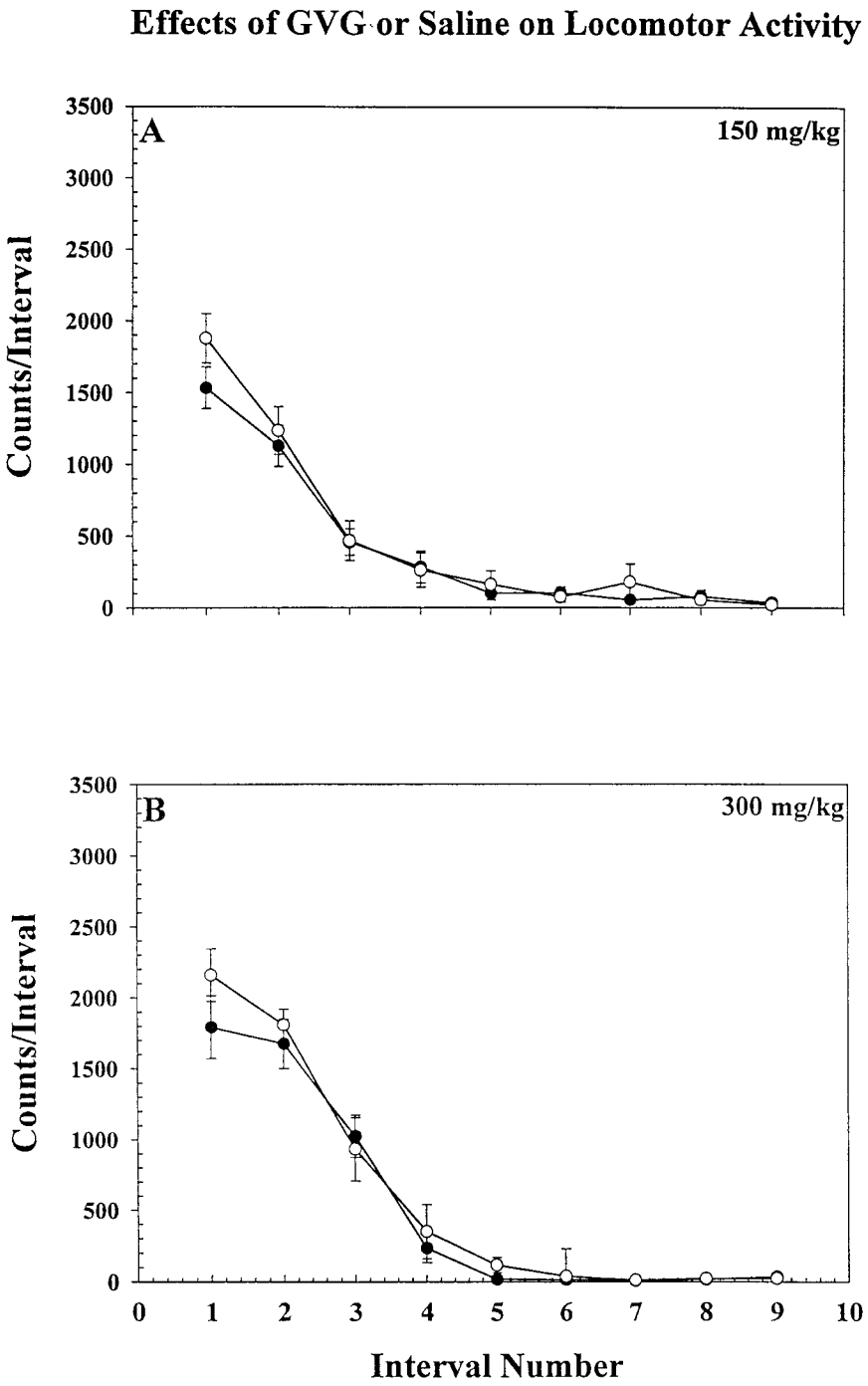

Fig. 3. **A.** Effects of GVG (150 mg/kg)on locomotor behavior compared with saline controls (open circles are GVG pretreated animals, closed circles are saline controls). **B.** Effects of GVG (300 mg/kg) on locomotor behavior compared with saline controls (open circles are GVG pretreated animals, closed circles are saline controls).

did not affect the maximal responding rate for electrical brain stimulation reward or non-reinforced performance levels, suggesting that baclofen's action was not related to alterations in motor performance/dexterity. A recent study has shown that GVG (100 - 400 mg/kg i.p.) produces a dose-dependent increase in brain stimulation reward thresholds in male F344 rats (Kushner et al., 1997b), without significant effects on motor performance. The decrease in brain stimulation reward thresholds produced by 2.5 and 5 mg/kg i.p. of cocaine was significantly antagonized by a 400 mg/kg dose of GVG. Finally, the CPP response elicited by morphine (8

mg/kg) was significantly attenuated by microinjection of baclofen (0.1–1 nmol) into the ventral tegmental area and this effect was antagonized by the $GABA_B$ antagonist 2-hydroxysaclofen (Tsuji et al., 1995). Thus, despite using different paradigms to assess reward/reinforcement, these studies suggest that activation of $GABA_B$ receptors attenuates the appetitive value of cocaine, morphine and electrical brain stimulation reward. However, because GVG elevates GABA levels, leading to the stimulation of both $GABA_A$ and $GABA_B$ receptors, the specificity of GVG's action remains uncertain.

Previously, it was reported that pretreatment with the GABA-mimetic compound progabide (which augments GABA levels in the brain via its metabolism to GABA), which alone does not produce place preference or aversion, did not alter the CPP response to 1.5 mg/kg i.p. of amphetamine (Di Scala et al., 1985). However, it is difficult to compare this finding to the present as there were differences in rat strains, GABAergic compounds and drugs used to elicit CPP. It should also be noted that progabide was only present for 35 minutes. Since it has been shown that the maximal increase in GABA levels in the brain following systemic progabide occurs four – six hours after injection (Worms et al., 1982), GABA levels were not at their maximum during the determination of amphetamine-induced CPP.

Given the evidence suggesting that augmentation of dopaminergic function in the mesolimbic system plays a role in mediating the rewarding/reinforcing effects of cocaine, the abolition of the CPP response to cocaine by GVG may be related to an alteration of dopaminergic activity/function. This hypothesis is supported by our in vivo microdialysis study indicating that acute (300 and 500 mg/kg i.p.) or repeated administration (100, 300, and 500 mg/kg i.p.) of GVG produced a significant dose-dependent decrease in the elevation of extracellular DA levels in the NACC and striatum produced by 20 mg/kg i.p. of cocaine (Dewey, et al., 1996; Morgan and Dewey, 1998). At the same time, it is unlikely that an alteration in the sensitivity of DA receptors following GVG administration is responsible for its attenuation of cocaine's action, as the repeated administration of GVG does not alter D_1 or D_2 receptor sensitivity in the rat striatum (Gardner et al., 1983). However, no evidence exists regarding GVG's effects on other DA receptors (D_3, D_4 and D_5). Alternatively, it is possible that cocaine could alter $GABA_B$ receptor function, thereby potentially altering the release of neurotransmitters such as DA and this could be antagonized by GVG via elevation of GABA levels and consequent stimulation of $GABA_B$ receptors. It has been shown that the repeated administration of cocaine diminishes the effectiveness of presynaptic $GABA_B$ auto and heteroreceptors on lateral septal nucleus neurons in rat brain slices (Shoji et al., 1997). This may lead to a disinhibtory action and enhanced neurotransmitter release. It is also possible that baclofen could attenuate the action of DA and this would attenuate cocaine's actions. This is indirectly supported by the findings of Lacey et al. (1988), showing that in intracellular recordings from rat substantia nigra zona compacta neurons, the outward currents elicited by DA were occluded by maximal currents produced by baclofen. Although these studies were not conducted with GVG or done in behaving animals, they may provide some additional hypotheses as to why GVG might attenuate cocaine's appetitive action in the CPP paradigm. It might prove useful to perform CPP studies and determine DA in various brain areas on the test day using in vivo microdialysis in animals paired with saline-cocaine and cocaine-GVG.

There are potential caveats to interpretation of the present results. First, it is possible that GVG could increase the metabolism of cocaine, thereby decreasing the amount which reaches the brain and subsequently diminishing its neurochemical effects and ultimately its behavioral actions. However, this is unlikely as brain levels of [^{11}C]-cocaine were not significantly altered in rats or primates pretreated with GVG (300 mg/kg). Furthermore, cocaine is primarily metabolized by plasma cholinesterases (Catterall and Mackie, 1996) whereas GVG is excreted primarily unchanged in the urine, making a pharmacokinetic interaction unlikely. Second, it has been reported that drugs which augment GABAergic function can produce sedation and ataxia (McNamara, 1996). Consequently, it is reasonable to postulate that GVG, by producing such adverse behavioral effects, may non-specifically antagonize cocaine's action. However, the results in the present study indicate that GVG does not produce catalepsy or significantly alter locomotor activity, making this hypothesis less tenable. Furthermore, the present study shows that GVG does not produce conditioned place aversion, indicating that its antagonism of cocaine's action is not the result of a counterbalancing aversive action. In addition, GVG does not elicit CPP alone, indicating that it is not shifting the preference of animals from the cocaine-paired to the GVG-paired environment.

It has been shown that GVG administration can alter food consumption in rats (Palfreyman et al., 1979). Based on this, it is possible that GVG may decrease or attenuate the hedonic value of natural rewards, as well as that elicited by cocaine. However, the present study shows that neither 150 nor 300 mg/kg of GVG alters CPP to food.

Finally, there is evidence indicating that behavior in the place preference paradigm depends upon both the affective and memory-improving properties of the reinforcers under test (White and Carr, 1985). Therefore, one might argue that GVG's blockade of the expression and acquisition of cocaine-induced CPP is the result of GVG interfering with the association of cocaine-induced positive incentive value with the appropriate stimuli by interfering with memory. Indeed, it is known

that certain drugs which augment GABAergic function can impair memory (Hindmarch and Ott, 1988; McNamara, 1996). However, GVG does not affect place conditioning for food, suggesting that this hypothesis cannot explain GVG's antagonism of cocaine's action in the CPP paradigm.

In conclusion, our results indicate that the 112, 150 and 300 mg/kg doses of GVG antagonize the acquisition and expression of cocaine-induced CPP. In contrast, GVG did not elicit a CPP or conditioned place aversion response, indicating that GVG does not antagonize cocaine's action by producing a CPP response alone or by attenuating CPP by producing an aversive effect. Furthermore, GVG does not elicit catalepsy and does not alter the incentive value of food. There is evidence that cocaine-related stimuli or cues will reinstate drug-seeking behavior and craving in detoxified cocaine addicts, thereby leading to relapse (Childress et al., 1986a,b, 1988; O'Brien, 1997). The expression of the CPP to cocaine, determined in the absence of cocaine, is antagonized by GVG. These results suggest that the craving experienced by cocaine addicts may be attenuated by GVG.

Dopaminergic transmission in the NACC has been specifically implicated in the reinforcing properties of cocaine. In our PET studies, measurements were made in the corpus striatum rather than the NACC. Although DA neurotransmission in the corpus striatum has not been implicated in cocaine reward and reinforcement, the effects of cocaine on extracellular DA levels are qualitatively similar in both areas (Izenwasser, et al., 1990). In addition, our in vivo microdialysis studies demonstrated the ability of GVG to attenuate cocaine-induced increases in extracellular DA levels to a similar extent in both areas (Dewey, et al., 1997; Morgan and Dewey, 1998).

In the present study, we used two different species for the imaging and behavioral experiments. However, the mesocorticolimbic DA system is neuroanatomically and neurophysiologically homologous in both species. In addition, the biochemical effects of cocaine on extracellular DA, measured by in vivo microdialysis techniques, are similar in both species, and both rodents and non-human primates readily self-administer cocaine (Morgan, et al., 1998; Iyer, et al., 1995; Bergman, et al., 1989; Kosten, et al., 1992).

Together, we hypothesize that the blockade of the behaviors in the CPP paradigm was due to an attenuation of cocaine's effects on brain DA secondary to the GVG-induced increases in GABAergic inhibition of the mesocorticolimbic DA system.

GVG offers the conceptual advantage of blocking cocaine's incentive motivational and biochemical effects on brain DA by irreversiby inhibiting GABA-T, making the relatively slow de novo synthesis of this enzyme the rate determining step in reversing the inhibition of cocaine's effects. Finally, a recent case report of a cocaine abuser suggests that gabapentin, an anticonvulsant that also potentiates GABAergic transmission via unknown mechanisms, attenuated cocaine withdrawal and craving (Markowitz, et al., 1997). Taken together, these data indicate that drugs selectively targeted at the GABAergic system may be beneficial for the treatment of cocaine addiction. More specifically, GVG-induced GABA-T inhibition, which produces an increase in extracellular brain GABA levels, represents a potentially effective drug and novel strategy for the treatment of cocaine addiction. Future studies will include clinical trials with GVG as well as further characterization of the biochemical and pharmacologic mechanisms (i.e., receptor subtypes) associated with the measured effects.

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