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Gamma-Hydroxybutyric Acid Decreases Intravenous Cocaine Self-Administration in Rats

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MARTELLOTTA, M. C., C. BALDUCCI, L. FATTORE, G. COSSU, G. L. GESSA, L. PULVIRENTI AND W. FRATTA. *Gamma-hydroxybutyric acid decreases intravenous cocaine self-administration in rats.* PHARMACOL BIOCHEM BEHAV **59**(3) 697–702, 1998.—Gamma-hydroxybutyric acid (GHB) is an endogenous compound present in mammalian brain suggested as a putative neurotransmitter, which has been shown to affect several aspects of dependence from various classes of drugs of abuse. In the present study, two sets of experiments were performed to investigate the effects of acute pretreatment with GHB on intravenous cocaine self-administration in rats. In the first experiment GHB was administered intragastrically at the doses of 175, 350, and 700 mg/kg to Long–Evans rats trained to self-administer cocaine using nose-poke as operandum. In the second experiment, GHB was administered intraperitoneally at the doses of 100, 200, and 400 mg/kg to Wistar rats trained to self-administer cocaine intravenously using lever-pressing as operandum. In both experiments acute pretreatment with GHB significantly and dose dependently reduced cocaine self-administration. The effectiveness of GHB was similar in both experiments, indicating that the effect of GHB on cocaine self-administration is independent of animal strain, route of administration, and type of operant response required. These results indicate that GHB reduces cocaine-seeking behavior in rats, modulating the acute reinforcing effect of cocaine. The clinical effectiveness of GHB in dependence from various classes of abused drugs warrants further studies to evaluate the possibility that GHB might represent a useful therapeutic agent for cocaine addiction in humans. © 1998 Elsevier Science Inc.

Gamma-hydroxybutyric acid Cocaine Intravenous self-administration Rats Dependence

GAMMA-HYDROXYBUTYRIC ACID (GHB) is an endogenous compound present in mammalian brain (38,43) and nonneuronal tissues (35). Studies aiming to define GHB biosynthesis indicate this compound to be formed from gamma-aminobutyric acid (GABA) via succinic semialdehyde reductase in both rat (39) and human brain (6). Both the existence of specific high affinity binding sites for GHB in synaptosomal fractions (28) and the mechanisms of GHB release, which is calcium dependent and blocked by tetrodotoxin (29), suggest the hypothesis that GHB might represent a putative neurotransmitter or neuromodulator (44).

Although little is known about its possible physiological role, several pharmacological effects have been observed after GHB administration in both animals and humans. GHB was originally presented by Laborit (26) as an useful agent in anaesthesia and in the treatment of narcolepsy (4). More recently, a role for GHB in drug dependence has been hypothesized on the basis of the efficacy shown by GHB, in nonhypnotic doses, in decreasing alcohol craving (17) and suppressing the withdrawal syndrome in both alcohol (16) and heroin addicts (18). Further support for an action of GHB on the neural systems mediating drug reinforcement comes from warnings from the United States Food and Drug Administration and the National Institute on Drug Abuse suggesting the potential abuse liability of GHB, which is described as an unapproved drug easily available on the black market, and often

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taken with alcohol or other drugs to produce a "high" (14,15,19).

Preclinical evidence further supports this possibility. Studies in laboratory animals have shown that GHB reduces alcohol intake in genetically selected alcohol-preferring rats (10), alleviates the severity of the withdrawal syndrome in ethanol-dependent rats (11), and substitutes for ethanol in the drug-discrimination paradigm (7). In addition, GHB is orally self-administered by rats (9), intravenoulsy self-administered by drug-naive mice (31) and induces conditioned place preference in rats (32). All these data strongly support the hypothesis that GHB could interact with the rewarding processes in the mammalian brain.

Intravenous cocaine self-administration in rodents has been regarded as a useful animal analog to study cocaine dependence in humans (24). Pharmacological treatments have been shown to affect the acute reinforcing properties of cocaine both reducing cocaine-seeking behavior in animals (23, 37) and achieving effective therapies in humans (46).

These observations prompted us to conduct a study aimed at the investigation of the effects of systemically administered GHB in rats self-administering cocaine intravenously to establish whether pretreatment with GHB could modify the acute reinforcing properties of cocaine. For this purpose, the effects of pretreatment with GHB through two different routes of administration (intragastric and intraperitoneal) were studied in two strains of rats (Long–Evans and Wistar) trained to self-administer cocaine using two different operant paradigms (nose poking and lever pressing).

METHOD

Experiment 1

Animals. Male Long–Evans rats (Harlan–Nossan), weighing 300–350 g at the start of the experiments, were individually housed with ad lib access to food and water, and maintained on a 12-h reversed light–dark cycle (dark on 0900 to 2100 h). Temperature (22 ± 1°C) and humidity (60%) were constant.

Drugs. Cocaine hydrochloride (Sigma) was dissolved in sterile saline solution in a volume of 0.5 ml/kg/inj. Doses were adjusted by injection volume before each self-administration session, according to the animal's body weight. GHB, in the form of sodium salt (Sigma) was dissolved in tap water and administered by intragastric route (IG) in a volume of 5 ml/kg 30 min before the start of the cocaine self-administration session. GHB administration pretreatment time was chosen to ensure that the peak drug plasma concentration coincided with the session interval on the basis of previous results (27). All doses are expressed as the salt.

Procedure. The animals were anesthetized with chloral hydrate (400 mg/kg IP) and implanted with silastic catheters inserted into the right external jugular vein, as previously described (33). The catheter was passed under the skin and exited in the midscapular region. Free passage of liquid through the catheters was checked before the start of each self-administration session with a solution of heparinized saline (100 UI/ml).

The self-administration apparatus consisted of eight Plexiglas cages 30 × 30 × 30 cm. Two holes, provided with fotobeam detectors, were made 2 cm above the floor, distant each other 15 cm. Nose poking in one of the holes (defined as active) switched on the infusion pump, injecting the cocaine solution into the animal's venous system. Nose poking in the other hole (defined as passive) had no effect on the pump. The assessment of self-administration schedules and the collection of data were programmed through a PC software (Ecos, Italy).

Starting 5 days after surgery, each rat was allowed access to cocaine at the dose of 0.5 mg/kg/inj under a continuous reinforcement (FR-1) schedule with the time out corresponding to the infusion time (∼5 s), during 3-h daily sessions. Only rats that developed a stable pattern of cocaine intake with a range of less than 10% over three consecutive baseline sessions were selected for the study. Each dose was tested, once for each animal, in a random order and a minimum of 3 no-pretreatment days separated each test day.

Because not all animals completed the entire set of experiments (due to catheter blockages), data were computed as for independent rather than correlated samples. Each treatment, however, included a minimum of six subjects.

The number of injections earned during the 180-min session was recorded and statistical analysis of the data was computed using a one-way factorial analysis of variance (ANOVA). Individuals means comparisons were made using the Newman–Keuls post-hoc test. Nose-poking activity in the passive hole was virtually absent once a stable baseline of drug intake was reached and throughout the experiment, so this factor was not computed in the analysis of data.

Experiment 2

Animals. Male Wistar rats (Charles River), weighing 200–225 g at the start of the experiment, were housed three to a cage and provided with ad lib access to food and water and maintained on a 12-h light-dark cycle (lights on at 0700–1900 h).

Drugs. Cocaine hydrochloride (Sigma) was dissolved in sterile saline solution in a volume of 0.75 ml/kg/inj. GHB sodium salt (Sigma) was dissolved in distilled water and administered intraperitoneally (IP) at the doses of 0, 100, 200, and 400 mg/kg in a volume of 1 ml/kg immediately before the beginning of the experiment. All doses are expressed as the salt.

Procedure. All animals were surgically implanted with a cronic silastic jugular vein catheter under halothane anesthesia, as previously described (5). The catheter passed subcutaneously to a piece of marlex mesh secured SC on the animal's back. At the time of the self-administration session, the catheter was connected to a swivel system through a metal spring, which was in turn, connected to an infusion pump.

Four days following surgery the animals were allowed 2-h access every day to a metal lever mounted on the side wall of a standard operant-conditioning cage. The cages themselves were housed inside sound-attenuating chambers. A lever press resulted in an intravenous injection of 0.1 ml of cocaine hydrochloride (0.25 mg/injection) dissolved in 0.9% physiological saline and delivered over a period of 4 s. A swivel system allowed free movement of the animal in the cage. Coincident with the onset of the injection, a stimulus light was turned on for 20 s, during which time the lever became inactive. Lever presses during the period when the signal light was not lit were reinforced on a FR-1. Once the animals demonstrated stable drug intake for 3 days (a range of less than 15% of the daily intake over 3 days), this was taken as baseline and the study was begun. On a test day, the animals were pretreated immediately before the beginning of the session with GHB. There were four different doses of GHB (0, 100, 200, and 400 mg/kg): each dose was tested only once for each animal using a Latin-square design. The drug was prepared in a vehicle solution of 0.9% physiological saline and injected in a volume of 1.0 ml/kg of body weight. At least 2 days of baseline

self-administration separated testing days. The number of reinforcers earned during the 120-min session was recorded and statistical analysis of the data was computed using a one-way factorial analysis of variance with repeated measures (ANOVA). Individuals means comparisons were made using the Newman–Keuls post-hoc test.

RESULTS

Experiment 1

The effect of acute administration of GHB in rats responding for cocaine self-administration in a continuous reinforcement schedule is shown in Fig. 1. GHB produced a dose-dependent decrease in responding for cocaine or a dose-dependent increase in the interinjection interval, $F(3, 20) = 120.3$ $p < 0.01$. Individual mean comparisons with saline revealed that the effect of GHB reached statistical significance at the doses of 350 and 700 mg/kg (Newman–Keuls test), while the lowest dose was ineffective.

Figure 2 shows the pattern of cocaine self-administration and time course of the effect of GHB throughout the 3-h session in one representative rat. In this figure, each mark represents an infusion of the drug. Injections were delivered at equal time intervals and, as the dose of GHB was increased the regular pattern of responding was maintained, though with longer inter-reinforcement intervals. The onset of the effect of GHB was rapid and the dose of 350 mg/kg seemed to produce its effect mainly in the first part of the self-administration session, while the inter-reinforcement interval was increased regularly throughout the entire session when the rat was pretreated with GHB at the dose of 700 mg/kg. No episodes of sedation or sleep were observed in GHB pretreated rats during or after the self-administration sessions.

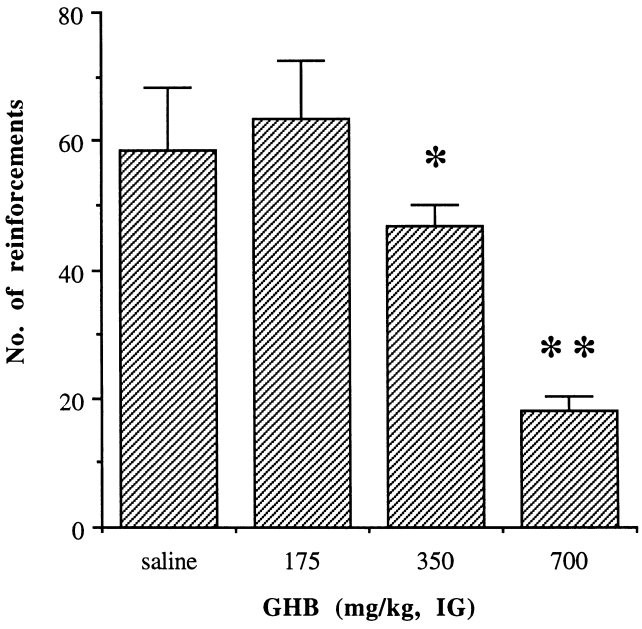

FIG. 1. Effect of intragastric GHB pretreatment on cocaine self-administration (0.5 mg/kg/inj) in rats allowed to nose poking as operant paradigm. Each bar represents mean ± SEM of the cumulative number of reinforcements of six animals. $*p < 0.05$ and $*p < 0.01$ Newman–Keuls test.

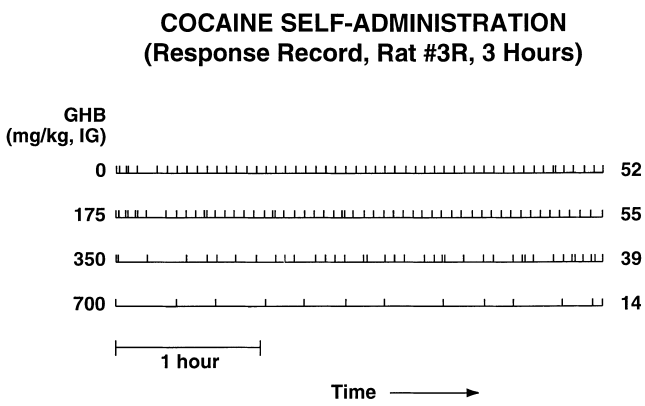

FIG. 2. Cocaine self-administration event record for a representative rat following intragastric acute pretreatment with GHB (nose poking). Each record represents a separate session and each mark represents an intravenous infusion of cocaine (0.5 mg/kg/inj). Injections were delivered at equal time intervals and, as the dose of GHB was increased the regular pattern of responding was maintained, though with longer inter-reinforcement intervals.

It has been shown that animals self-administering drugs at stable levels tend to adjust the dose during the session by modifyng the response frequency (25). In animals self-administering cocaine, a decrease of the rate of responding usually occurs when the unit dose of the reinforcer is increased and vice versa. Therefore, the effect of GHB on cocaine self-administration pattern is similar to an increase of the unit dose of cocaine dispensed per reinforcement.

Experiment 2

Figure 3 shows the effects of acute pretreatment with GHB on lever pressing for cocaine self-administration. ANOVA revealed that GHB significantly reduced cocaine self-administration, $F(3, 27) = 7.817$, $p < 0.001$. Individual mean comparisons with saline revealed that statistical significance was reached at the dose of GHB of 200 and 400 mg/kg (Newman–Keuls post-hoc test).

Figure 4 shows the event record of lever pressing for cocaine self-administration for a representative rat following acute pretreatment with various doses of GHB. Each record represents a separate session and each mark represents an IV infusion of cocaine. GHB dose dependently increased the inter-reinforcement intervals, particularly during the first half of the session, while the regular pattern of responding was generally maintained during the remaining of the session. The onset of the action of GHB was rapid and, occasionally, a temporary suspension of lever pressing was observed in a few individual rats after adimistration of the highest dose, but this occurred in the absence of any episode of sedation or sleep either during or after the self-administration sessions.

DISCUSSION

The aim of the present study was to investigate whether acute pretreatment with GHB affected IV cocaine self-administration in rats. The present results show that pretreatment with GHB dose-dependently decrased cocaine self-administration in two strains of rats trained under two different operant conditions (nose poking and lever pressing) after both intragastric and intraperitoneal administration.

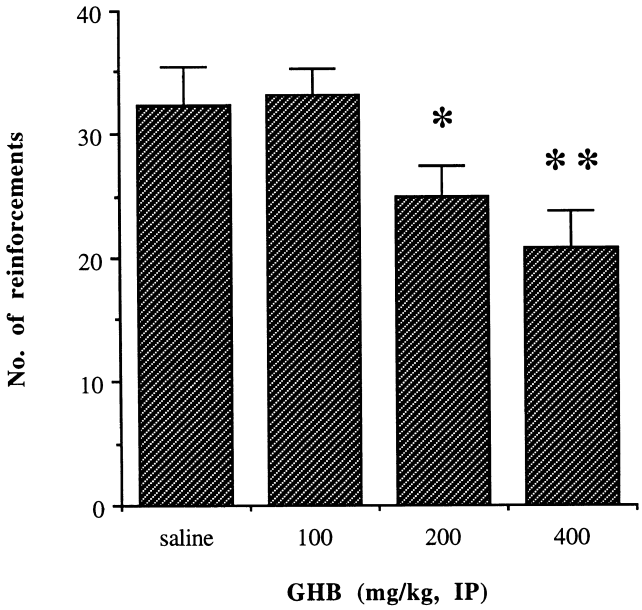

FIG. 3. Effect of intraperitoneal GHB pretreatment on cocaine self-administration (0.25 mg/kg/inj) in rats allowed to lever pressing as operant paradigm. Each bar represents mean ± SEM of the cumulative number of reinforcements of seven animals. *$p < 0.05$ and *$p < 0.01$ Newman–Keuls test.

In the first experiment, GHB pretreatment significantly reduced the intake of cocaine in rats self-administering the unit dose of 0.5 mg/kg/injection. By causing a decrease of cocaine intake, GHB pretreatment seems to mimic the effect of changes in the unit dose of the reinforcer: a decreased rate of responding usually follows an increase of the unit dose of cocaine and vice versa. This suggests a synergistic action of GHB on reinforcing properties of cocaine or a decreased desire to self-administer cocaine.

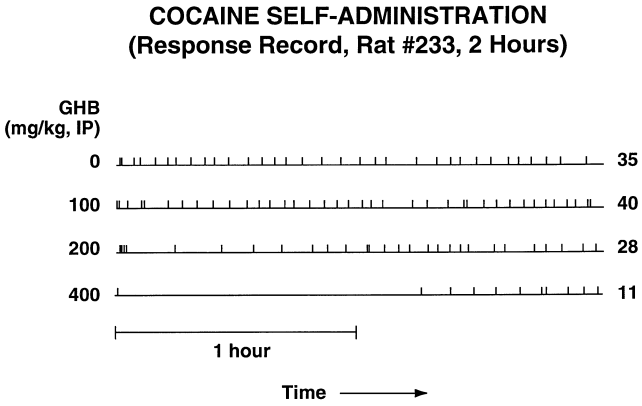

FIG. 4. Cocaine self-administration event record for a representative rat following intraperitoneal acute pretreatment with GHB (lever pressing). Each record represents a separate session and each mark represents an intravenous infusion of cocaine (0.25 mg/kg/inj). Injections were delivered at equal time intervals and, as the dose of GHB was increased the regular pattern of responding was maintained, though with longer inter-reinforcement intervals, particularly during the first half of the session. Occasionally a temporary suspension of lever pressing was observed in individual rats after administration of the highest dose, but this occurred in the absence of any episode of sedation or sleep either during or after the self-administration sessions.

The marked decrease in cocaine intake in rats pretreated with GHB, however, might raise some doubts about a possible sedative effect of this compound. It is important to note that no sedation or hypnotic episodes were observed in the present study in rats pretreated with GHB during or after the self-administration sessions. Also, GHB has been reported to be devoid of any hypnotic effect when administered orally in doses up to 1.5 mg/kg, twice as high as the highest dose used in the present experiments (27). In addition, spontaneous motor activity in rats pretreated with GHB at doses up to 700 mg/kg IP has been measured and no sign of sedation was found even at the highest dose (32).

In the second experiment, under different conditions, GHB produced similar effects. Pretreatment with GHB at the doses of 200 and 400 mg/kg IP significantly decreased cocaine self-administration, further confirming the effects of GHB on the maintenance of cocaine self-administration. The inter-reinforcement interval was increased by pretreatment with GHB and, unlike after intragastric treatment, this was more evident during the first half of the session, especially at the highest dose tested. This is probably due to the different pharmacodynamics of GHB after intraperitoneal and intragastric administration. The stability of the effects over time observed after intragastric administration in rats together with the rapid onset of the effects (15 min) persisting for 2–3 h observed in humans after oral administration of GHB (18) suggest that the oral route of administration might be desirable.

These results are in agreement with a number of observations suggesting that GHB may interfere with the brain systems responsible for the expression of the acute reinforcing properties of drugs of abuse and for the expression of the neuroadaptative changes of the dependence process. Previous findings have shown that GHB reduces ethanol intake in alcohol-preferring rats (10), alleviates the withdrawal syndrome in ethanol-dependent rats (11), induces conditioned place preference (32) and is self-administered by rodents (9,31). In addition, GHB has been reported to ameliorate symptoms of the alcohol withdrawal syndrome (16) as well as the opiate abstinence in humans (18). The present results showing that GHB reduces cocaine self-administration indicate that GHB may also interfere with the neurochemical events involved in the rewarding effects produced by psychostimulant drugs. It is important to observe that GHB use in combination with psychostimulants, such as methamphetamine has been reported (15) and GHB-stimulants interactions has been detected, even with controversial results, by Beardsley et al. (1). This may lead to speculate that the effects of GHB may be mediated by a complex neurochemical substrate, also affected by alcohol, opiates, and cocaine.

The intimate mechanism through which GHB affects dependence from various classes of abused drugs is still unknown, and although the present results do not allow a precise mechanistic relationship to be established, various neurochemical mechanisms may play a role on the basis of previous evidence.

Specifically, the brain dopamine system has been suggested as a critical neurochemical component of the neural circuitry mediating the reinforcing properties of several classes of drug of abuse (24). Interaction between GHB and dopamine has indeed been described (13) and GHB has been shown to participate in the regulation of dopamine synthesis

(34) and release (20,22,30) and to interact with dopamine receptors (2). Therefore, a modulation of brain dopamine system, possibly within areas of the limbic forebrain, could represents a candidate mechanism to explain the effect of GHB on cocaine reinforcement. However, more specific study aimed at the understanding of the effects of GHB on dopamine function (i.e., "in vivo" dopamine release) in conditions in which GHB exerts its effects on drug reinforcement are needed because this might provide more direct indication on the role of dopamine neurotransmission in mediating the effects of GHB.

GHB also interferes with other neurotransmitter systems, including GABA, opioids, serotonin, and acetylcholine [see (30), for a review] and the possibility that the interaction of GHB with these neural systems is at least partly responsible for the effects of GHB observed in the present study cannot be ruled out. Several effects of GHB, such as cross-tolerance against ethanol (8), self-administration by rats (9), decrease of alcohol withdrawal symptoms (16) and abuse in humans (14,15,19), are similar to those induced by barbiturates and benzodiazepines, which primarily interact with the $GABA_A$ receptor complex, [see (35) for a critical discussion]. However the possibility that the effects of GHB on alcohol intake could be due to an interaction at $GABA_A$ level has been ruled out (3). Moreover, there is growing evidence suggesting a relationship between GHB and $GABA_B$-mediated mechanisms (12), although at present this interaction seems limited to an involvement in the pathogenesis of experimental absence seizures (41). On the other hand, there is evidence that GHB and $GABA_B$ binding sites are completely different in their regional distribution, apart from layers I–III of the rat's cerebral cortex (40).

The accumulation of Met-enkephalin in the striatum induced by GHB has been reported (21), possibly through a nigrostriatal dopamine-mediated mechanism. Whether such potentiation of the endogenous opioid system might explain some of the effect of GHB on drug dependence merits further investigation.

Finally, GHB increases the serotonin turnover in striatum and mesolimbic areas (45), possibly through an increase in the availability of tryptophan within the brain. Also, GHB might influence excitatory amino acid neurotransmission, in particular though a modulation of NMDA receptors via accumulation of tryptophan catabolites (42).

In conclusion, the present results indicate that GHB interferes with tha maintenance of cocaine self-administration, providing preclinical evidence for the possibile use of GHB in cocaine dependence. A possibility worth of testing is that GHB might represent a cocaine substitute and, consequently, a useful pharmacological agent to be employed in the treatment of cocaine addicts as it is currently used in alcoholics. Further studies on the effects of GHB during the various phases of the natural history of psychostimulant dependence both in animals and in humans are, therefore, warranted.

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