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Effects of Carbamazepine on Self-Administration of Intravenously Delivered Cocaine in Rats

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CARROLL, M. E., S. T. LAC, M. ASENCIO, J. A. HALIKAS AND R. KRAGH. *Effects of carbamazepine on self-administration of intravenously delivered cocaine in rats.* PHARMACOL BIOCHEM BEHAV **37**(3) 551–556, 1990.—Carbamazepine (Tegretol) is widely used therapeutically as an anticonvulsant. Based on an hypothesis that links electrical kindling in the limbic system (leading to seizures) to reverse tolerance or sensitivity to cocaine's effects, carbamazpine is being tested as a treatment for human cocaine users. The purpose of this experiment was to examine the effects of carbamazepine on intravenous cocaine self-administration in rats. Rats self-administered intravenously delivered cocaine (0.2 mg/kg) under a fixed-ratio 4 schedule. When cocaine injections reached stable levels, carbamazepine was mixed with the rats' food for 8 days. Three doses of carbamazepine were tested (80, 120, and 160 mg/kg) in different groups of 5 rats each. The rats were later separated into groups with a high (>750 infusions) and a low (500–750 infusions) cocaine baseline. Two control groups of 5 rats each received carbamazepine treatments (120 or 160 mg/kg) and self-administered an orally delivered solution of glucose and saccharin (G+S). At the highest carbamazepine dose in the high cocaine baseline group, carbamazepine reduced cocaine infusions by at least 50 percent and food intake by approximately 25 percent during the 8 days of treatment. Cocaine infusions returned to baseline within 24 hr after the regular diet was restored. Carbamazepine had a minimal effect in groups of rats with lower cocaine baselines. Responding reinforced by the G+S solution was reduced by both the 120 and 160 mg/kg carbamazepine doses. Water intake was not systematically affected by the addition of carbamazepine to the food; however, activity measures were significantly lower in some groups at the higher carbamazepine doses. The results of this experiment indicate that the combination of a high dose of carbamazepine combined with a high rate of cocaine self-administration not only reduced cocaine intake, but it resulted in convulsions and death in some animals. These data suggest that carbamazepine is not likely to be the drug of choice for cocaine abuse treatment.

Carbamazepine Cocaine Glucose and saccharin Intravenous Rats Self-administration Taste aversion Tegretol

HIGH relapse rates among cocaine users suggest that treatment for cocaine abuse has been largely ineffective. Sixty to 100 percent of cocaine-dependent patients relapse within the first 12 months posttreatment regardless of their initial motivation (1). This high relapse rate has been attributed to an overwhelming craving for the drug (14). Successful medical treatment of dependence on cocaine and other stimulants awaits an understanding of underlying neural mechanisms associated with craving episodes. Several behavioral [e.g., (32)] and pharmacological approaches are currently being tested in the clinical setting (17).

Various pharmacologic agents that have been used in attempts to treat cocaine dependence. Treatment drugs include dopamine agonists such as bromocriptine (13, 20, 21), bromocriptine-desipramine combination (20), amantadine (30,48), or antidepressants such as imipramine (in combination with L-tyrosine and L-tryptophan) (43) and desipramine (16, 18, 19, 30, 47). A number of drugs that have been suggested for reducing cocaine use and relapse in humans (31) have been tested with animal models of IV stimulant self-administration. For instance, IV amphetamine self-administration in rats is reduced by fluoxetine (a serotonin uptake blocker) (26), L-tryptophan (a serotonin precursor) (27), and quipazine (a serotonin agonist) (26). Similarly, IV cocaine self-administration is reduced by fluoxetine injections (9) and an L-tryptophan-supplemented diet (10).

Recently, an open trial with carbamazepine showed that in 6 of 21 patients self-reported cocaine use decreased from 78.5 days out of 100 pretreatment to 0.55 per 100 during treatment (22). There was partial success (73.4/100 days pretreatment vs. 28.4/100 days during treatment) in 7 subjects, and 8 patients refused to take the drug for more than 3 days. These findings await confirmation with a placebo-controlled, double-blind design. The rationale for using carbamazepine to treat cocaine abuse was based on a kindling hypothesis (36) that suggests that increased sensitivity to cocaine may be related to the electrical kindling that has been demonstrated in animals. In these studies repeated subthreshold electrical stimulation of the limbic system eventually produces major motor seizures [e.g., (50)]. Pharmacological kindling or reverse tolerance has been investigated using subconvulsive doses of cocaine and lidocaine [cf. (37)].

The testing of these drugs, including carbamazepine, has been supported by the National Institute of Drug Abuse drug development program (31). Carbamazepine (Tegretol) is a chemical com-

pound that has proven highly effective for over 20 years in the treatment of different types of seizure disorders (35), and, more recently, affective disorders (7,38) and temporal lobe syndromes (35). In generalized seizures thought to arise from the limbic system and the temporal lobe, carbamazepine has been an especially effective treatment (5,36). Carbamazepine has been shown to have a variety of effects on a number of neurotransmitter systems including dopamine [e.g., (15, 23–25)], serotonin [e.g., (40,42)], acetylcholine (12,39), and norepinephrine [e.g., (4, 34, 41)]. It is not yet known whether carbamazepine's reported effect on cocaine intake is specifically related to its anticonvulsant properties or to its effects on dopamine, serotonin, acetylcholine and/or norepinephrine transmission, or to a combination of effects.

The purpose of the present experiment was to test the effect of carbamazepine on cocaine-reinforced behavior in rats. Although there are initial clinical reports that carbamazepine reduces cocaine craving in humans (22), an animal study will provide an indication of dose effects and an examination of the generality of possible suppressant effects of the drug by testing behavior that is rewarded by nondrug substance. In the present experiment several doses of carbamazepine were tested on responding maintained by a moderate unit dose (0.2 mg/kg) of cocaine (7,33). Control groups were trained to self-administer an orally delivered solution of glucose and saccharin (G + S) that functions as a reinforcer and competes with cocaine self-administration (11). At specific concentrations (3% glucose and 0.125% saccharin, wt./vol.) large amounts of this substance are consumed by rats (49). The G + S solution is low in calories compared to the standard laboratory diet, and others have shown that its high rate of consumption is based on taste rather than caloric content (44,45). These groups were also fed the carbamazepine-supplemented diet to determine whether the effects of this drug were specific to cocaine reinforced behavior or to behavior maintained by a nondrug reinforcer as well.

METHOD

Subjects

Seven groups of rats containing 5 rats each completed this experiment. Approximately 12 rats did not complete the experiment due to cocaine overdose, infections or catheter blockage. New rats were added to the experiment until each of the 7 groups contained 5 rats that completed the experiment. The rats were experimentally naive males from the Wistar strain (Harlan-Sprague Dawley, Madison, WI) with mean body weights (± S.E.) at the start of the experiment of 439.7 (± 6.8). A chronic jugular catheter was surgically implanted in each rat according to methods described previously (7,51), and the rats recovered from surgery in their experimental chambers with free food and water for 24–48 hr before the experiment began. Ground food (Purina Laboratory Chow) was available from a recessed jar, and water was available from both a water bottle and an automatic drinking device. This protocol was approved by the IACUC at the University of Minnesota (No. 8910037).

Apparatus

Details of the experimental chambers and infusion system have been previously described (6). The 22 stainless steel and Plexiglas chambers used in this experiment were octagonal in shape with alternating stainless steel and Plexiglas walls. Each chamber contained 2 response levers (Coulbourn Instruments, Inc., Lehigh Valley, PA), a tongue-operated solenoid-driven drinking device (3) and a receptacle for ground food. Each of these devices was located on a separate stainless steel wall of the chamber. A stimulus light was mounted above each lever, and the light was illuminated for the duration of an infusion after the response requirements were completed. A light above the drinking device indicated the availability of a liquid. Above the automatic drinking device, a standard water bottle was mounted, with a drinking tube protruding into the chamber. The chamber was constantly illuminated by a house light. Infusion pumps (Fluid Metering Inc., Oyster Bay, NY, Model rhsyockc) were located outside the wooden enclosures that contained the experimental chambers. The wooden enclosures provided sound attenuation. Experimental events and data recording were controlled by microcomputers (8) located in an adjacent room.

Cocaine HCl was provided by the National Institute on Drug Abuse (Research Triangle Institute, Research Triangle Park, NC). Infusion solutions were mixed in sterile saline and contained in 500 ml reservoirs beside the experimental chambers. Dose was controlled by infusion duration which was 1 sec/100 g body weight or approximately 4.4 sec depending upon the rat's weight. The volume per infusion was approximately 0.125 ml. Carbamazepine was purchased from Sigma Chemical Co. (St. Louis, MO) and mixed with ground Purina Laboratory Chow. Drug doses are expressed in terms of the salt. Reagent grade glucose and saccharin were also purchased from Sigma Chemical Co. The G + S solution consisted of 3% (wt./vol.) glucose and 0.125% (wt./vol.) saccharin which was mixed daily and presented to the rats at room temperature.

Procedure

After recovery from surgery the rats were allowed unlimited access to cocaine, ground food (Purina Laboratory Chow) and water during successive 24-hr sessions beginning at 10:00 a.m. each. At 9:30 a.m. cages were cleaned, intake measurements were made and food and liquids were replenished. There was no time out in the experimental contingencies from 9:30–10:00 a.m. Sessions were conducted 7 days per week. Cocaine deliveries (0.2 mg/kg) were contingent upon a response on the left lever. After cocaine infusions had stabilized for at least 3 days the fixed ratio (FR) value for each infusion was increased from 1 to 2 and then 4. Each response on the right lever was counted but had no programmed consequences. Responses on the right lever served as a measure of nonspecific lever pressing that may have been attributed solely to the stimulant effects (e.g., stereotypy) of cocaine, to carbamazepine or to the combination. Each lick on the automatic drinking device initially resulted in delivery of 0.015 ml water. When behavior had again stabilized for at least 5 days, 2 groups of 5 rats were given a G + S solution instead of water in the automatic drinking device, and at the same time, saline replaced cocaine in the infusion reservoir. Stability was defined as no steadily increasing or decreasing trend over a 5-day period. These rats then served as controls for the cocaine-injecting rats to determine whether the effects of carbamazepine were specific to cocaine-reinforced behavior or behavior maintained by a nondrug reinforcer (G + S) and/or saline infusions.

Food was limited to 20–25 g per day in all groups. Previous work had shown that rats self-injecting cocaine under similar conditions consume approximately 20 g of ground food per day, while those self-injecting saline and drinking G + S consume 25–30 g per day (11). Thus, food availability was held constant at the lower amount (20 g) for all groups, to minimize differences due to feeding conditions or body weight. After cocaine and G + S had been available for at least 30 sessions, and behavior maintained by both substances had stabilized for at least 5 days, carbamazepine was given in the standard laboratory food for 8 consecutive days. Generally, the carbamazepine was mixed uni-

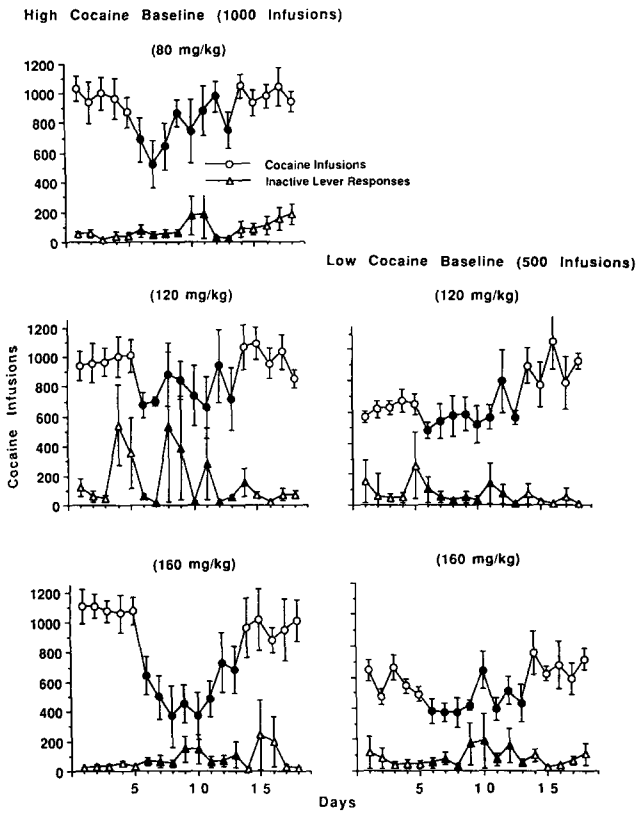

FIG. 1. Mean (±S.E.) cocaine infusions (0.2 mg/kg) and responses on an inactive lever are presented for 18 consecutive 24-hr sessions. Each cocaine infusion was contingent upon 4 lever press responses (FR 4). Responding on an inactive lever was monitored as an indicator drug effects on nonspecific lever pressing, but the behavior had no programmed consequences. The left frames represent 3 groups of rats that had a "high" baseline of cocaine infusions (defined more than 750 per 24-hr session). The two groups on the right were designated as "low" cocaine baseline groups. Their total infusions ranged between 500–750 per 24-hr period. The drug was mixed with 20–25 g of ground laboratory rat chow and presented at 9:30 a.m. each day for 8 days. *Circles* refer to the cocaine infusions, and *triangles* indicate the number of responses on the inactive lever. *Filled* symbols refers to the 8 days of carbamazepine treatment. Each point represents a mean for 5 rats.

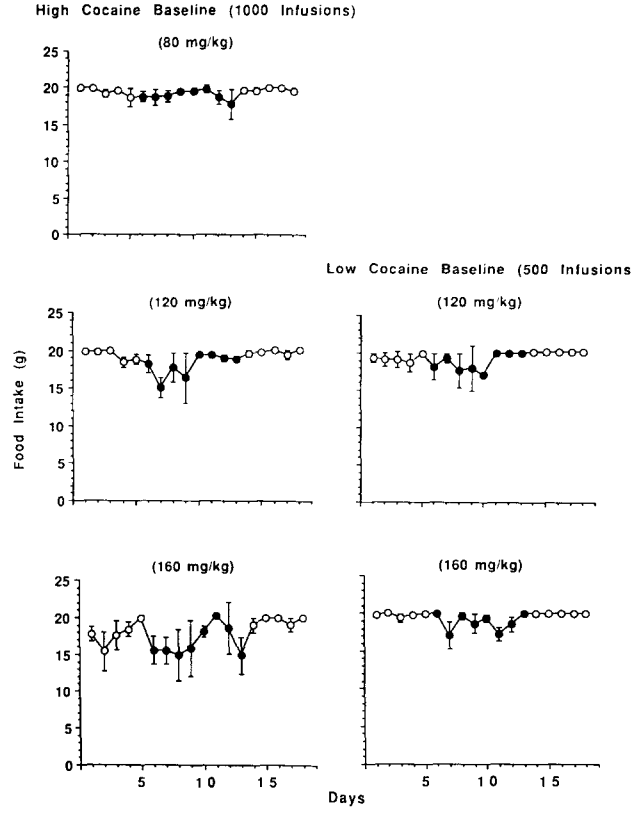

FIG. 2. Mean (±S.E.) food intake is presented for 18 consecutive 24-hr sessions. Ground Purina Laboratory Chow (20–25 g) was placed in a recessed jar and measured once daily at 9:30 a.m., the end of a session. As described in Fig. 1, the groups shown on the left had a high cocaine baseline (more than 750 infusions), and those on the right had a baseline of 500–750 infusions. Filled circles represent the 8 days of carbamazepine treatment. Each point represents a mean for 5 rats. These data are for the same groups of rats shown in Fig. 1.

formly throughout the 20–25 g of food; however, if it was noted that a rat did not consume the entire amount, the carbamazepine was added to the top portion of the jar containing ground food to ensure that most of the drug was ingested.

RESULTS

Initial findings indicated that carbamazepine effects differed according to the baseline levels of cocaine intake. Thus, the rats were subdivided further into groups with baselines of 500–750 infusions per day and more than 750 infusions per day. Mean number of infusions in these low and high baseline groups was approximately 500 and 1000, respectively. The 500–750 infusion baseline groups were tested with 120 and 160 mg/kg carbamazepine, and the >750 infusion baseline groups were tested with doses of 80, 120 and 160 mg/kg. There were 2 control groups that received the G+S drinking solution instead of cocaine infusions; one was given 120 mg/kg carbamazepine and the other was given 160 mg/kg. In all 7 groups after 8 days of carbamazepine treatment, the standard diet was restored and behavior was allowed to stabilize for at least 5 sessions. Statistical comparisons were made between the last 5 baseline days, the first 5 days of carbamazepine and the first 5 days after carbamazepine was removed for each group using paired *t*-tests. Behavioral observations were made nonsystematically after carbamazepine ingestion.

Figure 1 shows the effect of the 3 carbamazepine doses on cocaine infusions and inactive lever responses in groups with high and low cocaine self-administration baselines. In the high baseline groups receiving the 80 and 120 mg/kg doses, carbamazepine significantly, $t(4)s = 4.13$ and 5.76, respectively, $ps < 0.05$, reduced cocaine infusions by 28% and 21%, when the last 5 baseline days were compared to the first 5 days of carbamazepine treatment. Cocaine-reinforced behavior was markedly reduced on the first 2 or 3 days of carbamazepine at the 80 and 120 mg doses. At the 160 mg/kg dose carbamazepine produced decreases of 57% of baseline during the first 5 days of testing, $t(4) = 14.2$, $p < 0.05$. The lower baseline groups showed no significant changes in cocaine self-administration due to carbamazepine treatment ($p > 0.05$). Responding on the inactive lever was generally low for most rats; the high rates that appeared in Fig. 1 were due to one rat in each group.

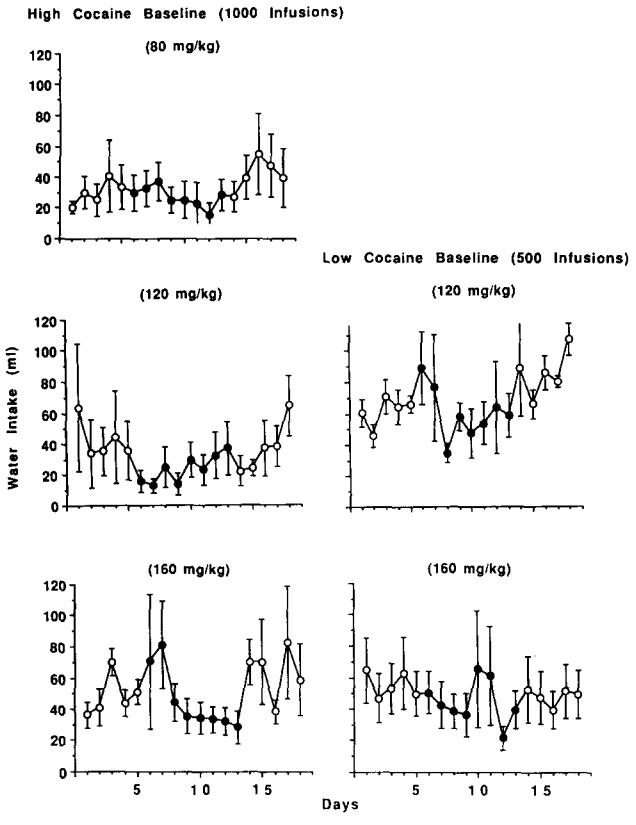

FIG. 3. Mean (±S.E.) water intake is presented for 18 consecutive 24-hr sessions. Water was available from an automatic drinking device that delivered 0.015 ml for each tongue contact response; thus, the total number of responses on the drinking device was approximately 67 times the intake as shown in ml. Intake was measured once daily at 9:30 a.m., the end of a session; however, number of licks was continuously monitored and printed hourly by the computers. As described in Fig. 1 the groups shown on the left had a high cocaine baseline (more than 750 infusions), and those on the right had a baseline of 500–750 infusions. *Filled circles* represent the 8 days of carbamazepine treatment. Each point represents a mean for 5 rats. These data are for the same groups of rats shown in Figs. 1 and 2.

Figure 2 shows that food intake was substantially reduced in some rats during the 160 mg carbamazepine treatment; however, the overall effect was not statistically significant ($p>0.05$) in any of the groups. The lowered food intake was more severe in the high cocaine baseline group, and it increased with carbamazepine dose. The high rates shown for each group were due to one or two rats in the group.

Figure 3 shows that water intake was not substantially altered by any dose of carbamazepine under either the high or low cocaine baseline conditions. There were no observable behavioral changes (other than those noted in Fig. 1) at the two lower carbamazepine doses. At the highest carbamazepine dose some of the rats occasionally showed tremors and/or convulsions on the first day of carbamazepine administration. Approximately 10 percent of the rats tested died of apparant drug overdose on the first or second day following treatment with the 160 mg/kg dose and the high cocaine intake. These rats were replaced to maintain 5 in each group.

Figure 4 shows that carbamazepine also reduced behavior reinforced by the G+S solution at the 120 and 160 mg doses, $t(4)$s = 4.58, and 8.79, respectively, ps<0.05. This suppression generally persisted throughout 8 days of the carbamazepine treatment, and in the higher dose group (160 mg/kg) responding did not return to baseline after carbamazepine treatment was stopped, $t(4) = 6.42$, $p<0.05$. A comparison of G+S to water intake from the automatic drinking spouts indicated that G+S intake exceeded water intake by at least a factor of 7 and that the substance was functioning as a reinforcer. Responses on the inactive lever and saline infusions in the G+S-drinking groups were very low with the exception of 1 or 2 rats. Throughout the 8 days responding on the inactive lever was significantly decreased by carbamazepine in the 160 carbamazepine group receiving G+S, $t(4) = 2.90$, $p = <0.05$. Saline infusions were also significantly decreased in the 160 mg/kg carbamazepine group, $t(4) = 3.32$, $p<0.05$. Food intake was not altered by carbamazepine in either of the G+S self-administering groups, and it was comparable to the cocaine self-injecting groups receiving 80 and 120 mg carbamazepine. Water intake from the bottle with a standard drinking tube is not presented for any of the groups as it was almost negligible, and it did not vary as a function of carbamazepine dose or experimental condition (cocaine or G+S groups).

DISCUSSION

Cocaine was clearly functioning as a reinforcer at the dose (0.2 mg/kg) used in the present experiment as responding maintained by the drug greatly exceeded that maintained by the vehicle, saline. The present results show that carbamazepine markedly reduced cocaine-reinforced behavior at the highest dose tested (160 mg/kg) in a group of rats that had a high baseline of cocaine-reinforced behavior (approximately 1000 infusions or 200 mg/kg cocaine was self-administered per day by this group). A group that self-administered approximately half that amount in 24 hr showed no significant decrement in responding during carbamazepine treatment. These results suggest that decreases in self-administration behavior are a result of the interaction of high doses of carbamazepine and cocaine. Previous studies have shown that drugs that reduce cocaine self-administration (e.g., L-tryptophan and fluoxetine) are less effective as cocaine dose increases (9,10). These high doses combined to produce toxic effects (seizures, death) in some rats and decrements in food and water intake were found in a few rats in these groups. Carbamazepine (120 and 160 mg/kg) also produced significant and persistent decreases in G+S intake, suggesting a general suppressant effect on behavior maintained by a highly reinforcing substance.

The present results may be subject to a number of possible interpretations. One hypothesis is that carbamazepine alters the reinforcing effects of drugs such as cocaine and nondrug substances. One form of alteration may be to increase the reinforcing effect of these substances. If this were the case, the lower response rates as shown in the present experiment would be expected, as less cocaine or G+S would be needed to achieve a result comparable to baseline. A second mechanism by which carbamazepine may have altered the reinforcing effects of cocaine is to block the reinforcing effects. The expected result would be an initial increase or "extinction burst" in responding on both active and inactive levers, followed by a decline. This has been reported with other treatments (e.g., fluoxetine, L-tryptophan) and cocaine self-administration (9,10) as well as amphetamine self-administration, but it was not found with carbamazepine. A third mechanism would be that carbamazepine could have had reinforcing effects of its own that partially substituted for the reinforcing effects of cocaine. The present experiment was not designed to examine the reinforcing effects of carbamazepine, but there are no published data to indicate that this drug functions as a reinforcer for animals. Furthermore, there are no clinical reports of carbamazepine abuse in humans, although it has been in used for

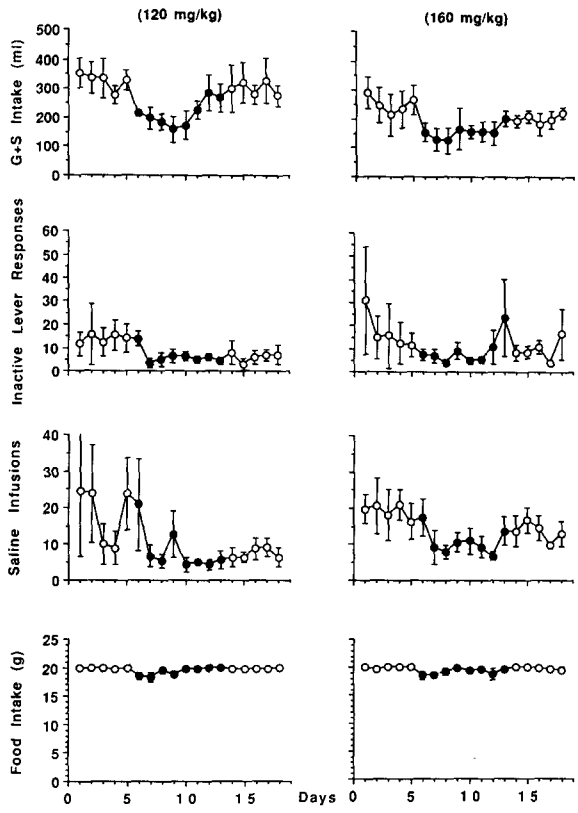

FIG. 4. Mean (±S.E.) GA+S intake, inactive lever responses, saline infusions and food intake are presented for 2 groups of rats that received G+S instead of water in the automatic drinking spout. Although they were initially trained to self-administer IV cocaine, saline replaced cocaine in the infusion pumps. *Filled circles* refer to the 8 days of carbamazepine treatment. Each point represents a mean of 5 rats.

seizure control for more than twenty years and is the largest selling anticonvulsant in the United States.

A second hypothesis regarding the carbamazepine-related decreases in cocaine- and G+S-maintained responding is that carbamazepine produced a nonspecific decrease in motor activity. This was not reflected in eating and drinking behavior in the low cocaine baseline groups. Furthermore, responding on the inactive lever did not differ from baseline when carbamazepine was ingested.

A third hypothesis is that carbamazepine produced aversive or punishing effects via illness, or malaise. In addition, the specific combination of cocaine and carbamazepine could have increased the negative effects of carbamazepine or unmasked aversive effects of cocaine. It has been demonstrated earlier with other experimental designs that cocaine (46) and amphetamine (52) have both rewarding and aversive effects depending on the testing situation. In the present study the punishment hypothesis is further implied by the slow return to baseline levels of cocaine and G+S intake when the carbamazepine was discontinued. Previous studies have also shown a delay of recovery to baseline levels of cocaine intake of one or two days after either dietary L-tryptophan supplements (10), L-tryptophan injections (27) or fluoxetine treatment in rats (9).

In conclusion, it appears that the suppression in cocaine and G+S self-administration may have been mediated by potentially aversive effects of carbamazepine, and the combination of high doses of cocaine and carbamazepine further increase the behavioral toxicity of this combination. Therefore, the value of this drug for potential treatment of cocaine abuse should be determined by careful monitoring of possible negative interactions if it is used in clinical studies.

ACKNOWLEDGEMENTS

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