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Self administration of cocaine in monkeys receiving LAAM acutely or chronically

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Abstract

Polydrug abuse remains a common problem among opioid abusers as well as patients in opioid maintenance programs. Although cocaine abuse has been reported in patients receiving methadone, the incidence of cocaine use in patients receiving l-alpha-acetylmethadol (LAAM) has not been well established. The goal of this study was to determine whether acute or chronic administration of LAAM modified the reinforcing effects of cocaine using a self administration procedure in rhesus monkeys. Four monkeys responded under a fixed ratio (FR) 30 schedule to receive i.v. infusions of cocaine (0.0032–0.32 mg/kg/infusion) in the absence of other treatment, after acute LAAM administration (0.1–1.0 mg/kg, s.c.), and during daily administration of 1.0 mg/kg of LAAM. Cocaine maintained self administration responding that exceeded responding maintained by saline; acutely administered LAAM had small and variable effects on self administration of cocaine. Daily LAAM administration increased the number of infusions received of at least one dose of cocaine. These studies indicated that LAAM administration did not attenuate the reinforcing effects of cocaine, suggesting that LAAM would not likely alter cocaine abuse in patients undergoing treatment for opioid abuse.

Keywords

LAAM; cocaine; self administration; rhesus monkeys

Opioid abuse remains a public health issue that is associated with significant morbidity and mortality; several important treatment goals appear to be achieved by opioid maintenance programs, including retention in treatment and reduced opioid-related mortality [1–3]. Methadone was recognized in the 1960s for its potential in treating opioid abuse and has become the most common form of treatment [1]. Despite its relative success, a number of issues remain and the search for improved therapies continues. In order to address some of the deficiencies of methadone, other drugs have been developed for maintenance treatment, including the methadone derivative l-alpha-acetylmethadol (LAAM). Like methadone, LAAM

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is a μ-opioid agonist; however, its conversion to active metabolites results in a long duration of action and its primary advantage is that daily administration is not required in maintenance treatment [2]. In fact, 67% of patients who preferred LAAM over methadone report the reason for this preference is that less frequent trips to the treatment clinic are needed [4]. Thus, differences in pharmacokinetics largely account for differences between methadone and LAAM, and while some problems associated with methadone maintenance therapy, such as the inconvenience of daily dosing, might be resolved by using a drug with a longer duration of action, treatment of opioid abuse could still be improved.

One important goal of opioid maintenance treatment is to reduce drug abuse, and one benefit of achieving this goal is that cessation of opioid abuse appears to predict prolonged retention in treatment [5]. Unfortunately, both methadone [5–8] and LAAM [4] eliminate drug abuse in only some patients. Moreover, the effectiveness of LAAM in decreasing opioid abuse varies among studies with the percentage of urine samples that are positive for other opioids during LAAM treatment ranging from 15–50% [9–12]. In addition to continued opioid abuse during treatment, abuse of drugs other than opioids has also been observed. For example, cocaine is abused by patients receiving methadone, with the incidence of cocaine use ranging from 12–44% [5,8,11]; the effects of LAAM treatment on abuse of other drugs, such as cocaine, have not been well characterized. Thus, LAAM treatment may alter abuse of other drugs, although such effects of LAAM have not been systematically investigated in the laboratory.

One procedure that has been used extensively to study drug-taking behavior in the laboratory is the i.v. self-administration procedure. Generally, drugs that are self administered by animals [13] are also abused by humans [14], and self administration of cocaine has been demonstrated in many studies in rhesus monkeys (e.g., [15]). In contrast, the effects of LAAM on self administration of other drugs have not been studied extensively. One study has shown that, when administered chronically, LAAM reduces morphine self administration [16]; however, the effects of chronic LAAM treatment on cocaine self-administration have not been characterized. Although chronic methadone treatment does not decrease cocaine self administration in humans or monkeys [17,18], another drug used for opioid maintenance therapy, buprenorphine, reduces cocaine self administration in humans [17] and rhesus monkeys [19–21]. Given that effects on cocaine self administration during chronic methadone treatment do not necessarily predict effects obtained during chronic treatment with other opioids, the goal of the current studies was to examine the effectiveness of acute or chronic administration of LAAM to decrease responding for i.v. infusions of cocaine in rhesus monkeys.

Material and Methods

Subjects

Four rhesus monkeys (*Macaca mulatta*), 1 male (OS) and 3 females (MA, SH, TO), weighed between 6 and 10 kg and were housed individually in stainless-steel cages with free access to water. Monkeys were maintained under a 14/10 hr light/dark cycle with lights on at 0600 hr. Prior to these studies, each monkey received other drugs acutely under a variety of conditions (e.g., [22–24]). In addition, the efficiency of these experiments was maximized by conducting other studies in these monkeys during the same course of treatment. Monkeys were maintained at 90% of their free-feeding weight by post-session feeding with monkey chow (Harlan Teklad High Protein Monkey Diet, Madison, WI), fresh fruit and peanuts. Animals used in these studies were maintained in accordance with the Institutional Animal Care and Use Committee, The University of Texas Health Science Center at San Antonio, and guidelines of the Committee on Care and Use of Laboratory Animal Resources, National Research Council [Department of Health, Education and Welfare, publication No. (NIH) 85-23, revised 1996].

Surgery

Monkeys were anesthetized with a dose of 10 mg/kg of ketamine (*s.c.*, Fort Dodge Laboratories, Fort Dodge, IA) prior to intubation, after which anesthesia was maintained by halothane (Butler Animal Health Supply, Grand Prairie, TX) and ventilation was sustained by the delivery of oxygen at a flow rate of 2 l/min. A polyurethane catheter (SIMS Deltec Inc., St. Paul, MN) was implanted in the jugular or femoral vein and exteriorized through the skin (OS and SH) or connected to s.c. vascular access ports (Access Technologies, Skokie, IL; MA and TO) according to methods described elsewhere [25]. OS and SH wore jackets (Lomir Biomedical Inc., Malone, NY) in which the exteriorized catheters were stored.

Apparatus

Monkeys were seated in chairs (Primate Products, Redwood City, CA) that were placed in sound attenuating, ventilated chambers. Response panels located in each chamber contained response levers, pellet dispensers, food cups and stimulus lights that could be illuminated red or green. Food (300 mg banana-flavored pellets) could be delivered to cups through a plastic tube that was located behind the panel. Drugs were delivered i.v. by connecting exteriorized catheters to a 60-cm extension set (*Abbott Laboratories*, Stone Mountain, GA) with 18-g needles or by accessing vascular ports with 20-g huber-point needles (Access Technologies, Skokie, IL). The opposing end of the extension set was connected to a 30-ml syringe that was mounted in a syringe driver (Razel Scientific Instruments, Inc., Stamford, CT) located outside the chambers. An interface (*Med Associates, Inc*., East Fairfield, VT) connected panels to a computer which controlled experimental events and recorded data.

Behavioral Procedure

Initially, monkeys responded for food in 1-hr sessions during which red lights were illuminated above the right lever and monkeys received a pellet after each response on the right lever. Responding on the left lever had no programmed consequence. Daily sessions ended after 1 hr or delivery of 50 pellets, whichever occurred first. The response requirement was increased to FR 2 after 3 consecutive sessions during which 50 pellets were delivered. Subsequently, the response requirement was increased by 2 or 3 after 2 consecutive sessions during which the maximum number of pellets was delivered. Beginning in the first session at the terminal fixed ratio value (FR30), delivery of each pellet was followed by a 10-sec timeout, during which chambers were dark and lever presses had no programmed consequence. On each subsequent session, the duration of the timeout was increased by 10 sec until the final timeout duration of 60 sec was reached.

Drug self-administration studies began once responding was reliable under the FR30 schedule of food presentation. *When the green light located above the right lever was illuminated*, 30 responses on the right lever resulted in the illumination of red lights for 2 sec and infusion of 0.032 mg/kg of cocaine, which was followed by a 60-sec timeout period. Sessions ended after 90 min. Cocaine was available daily for i.v. self administration until the number of infusions did not vary by more than ± 20% from the average number of infusions over the last three sessions. Saline was then substituted for cocaine until no more than 5 infusions were received per session.

The acute effects of LAAM on self administration of cocaine were evaluated in 3 of the 4 monkeys by determining dose-effect curves for cocaine alone or in combination with LAAM. A single dose of cocaine (0.0032, 0.032 and 0.32 mg/kg/infusion) was available in each daily session, and this dose remained the same until it was studied in combination with all doses of LAAM; these doses of cocaine have been shown to maintain responding under similar conditions in monkeys [21]. Studies with a particular dose of cocaine began with at least 3 consecutive sessions during which that dose of drug was available in the absence of other

treatment. When the number of infusions received per session did not exceed ± 20% of the average number of infusions received for the last three sessions, monkeys received a single dose of LAAM (0.1, 0.32 or 1 mg/kg) 90 min before the next daily session. In *a drug discrimination procedure in* rhesus monkeys, the maximum effect of LAAM occurred 90 min after administration [26]. During subsequent sessions, the same dose of cocaine was available in the absence of other treatment, and the criterion had to be satisfied again before administration of another dose of LAAM. Consequently, LAAM injections were separated by at least 3 sessions, although the number of intervening sessions varied. Once each dose of LAAM had been studied with a particular dose of cocaine, saline was available in daily sessions until the number of infusions received in one session was not more than 5. Subsequently, a different dose of cocaine was available for self administration, and this new dose was available in each session until it had been studied in combination with all doses of LAAM. The order in which monkeys were tested with the three different doses of LAAM was mixed. Finally, the same doses of LAAM that were studied in combination with cocaine were also studied when only saline was available. *After the criterion for saline infusions was satisfied, a* single dose of LAAM (0.1, 0.32 or 1 mg/kg) was administered 90 min before the next daily session. During subsequent sessions, saline was available in the absence of other treatment, and the criterion had to be satisfied again before administration of another dose of LAAM. LAAM injections were separated by at least 3 sessions, although the number of intervening sessions varied.

Once acute interactions had been assessed, the method for determining dose-effect curves for cocaine was changed so that an entire dose-effect curve could be determined in a shorter period of time. Three doses of cocaine (0.0032, 0.032 and 0.32 mg/kg/infusion) were available for i.v. self administration with each dose studied for just one day (i.e., 0.0032 mg/kg/infusion on day 1, 0.032 on day 2). Doses were always available in ascending order. Beginning on the fourth session, saline was substituted for drug until the number of infusions received in one session was not more than 8.

In order to determine whether chronic treatment with LAAM modified the reinforcing effects of cocaine, 1.0 mg/kg/day of LAAM was administered 2 hr after daily self-administration sessions; *LAAM was given after sessions to avoid the development of nonselective (e.g., behavioral) tolerance.* Monkeys could self administer 0.032 mg/kg/infusion of cocaine (c) or saline (s) according to the following order of presentation across days: c, c, s, c, c, c, s. At the beginning of the second and fourth weeks of LAAM treatment, cocaine (0.0032, 0.032 and 0.32 mg/kg/infusion) dose-effect curves were determined with a single dose of drug available in each daily session and the dose sequence ascending across days.

Data analyses

The number of infusions received per session was plotted as a function of time or unit dose of drug. For acute studies, control dose-effect curves were obtained by averaging the number of infusions from the 3 sessions that immediately preceded administration of each of the 3 doses of LAAM for a total of 9 determinations per unit dose (95% CL). The number of infusions received when saline was available for self administration was obtained by averaging data from the 10 sessions during which saline was available prior to chronic LAAM treatment (95% CL). Each dose of LAAM was studied in combination with each dose of cocaine on one occasion; thus, data points for cocaine determined in the presence of LAAM represent single determinations in three monkeys. Dose-effect curves for cocaine determined before and during chronic LAAM treatment were obtained over three consecutive days with increasing doses of drug available during each session; consequently, data points represent single determinations in each of four monkeys. *For acute studies, the number of infusions obtained when cocaine was available in the absence of other treatment was considered different from the number of infusions obtained when saline was available if their 95% confidence limits did not overlap.*

When the number of cocaine infusions determined in the presence of acutely administered LAAM was outside of the 95% confidence limits of the number of cocaine infusions determined in the absence of LAAM, those points were considered different. For chronic studies, the number of cocaine infusions was considered different from the number of saline infusions if the number of drug infusions was outside of the 95% confidence limits of the number of saline infusions.

Drugs

The compounds studied were *l*-alpha acetylmethadol (LAAM) hydrochloride and cocaine hydrochloride (National Institute on Drug Abuse, Research Technology Branch, Rockville, MD). Both compounds were dissolved in saline. Cocaine was administered i.v.; infusion duration varied from 10 to 15 sec, corresponding to infusion volumes of 0.4 to 0.7 ml. LAAM was administered s.c. in a volume of 0.4–1.05 ml.

Results

Cocaine maintained self-administration responding that was greater than responding maintained by saline, as indicated by differences in the number of infusions received in the 90-min session (closed symbols, all panels, Figure 1). The average number (95% CL) of infusions received in 10 sessions during which saline was available was 4.6 (1.6, 7.6) for monkey SH, 8.9 (6.2, 11.6) for monkey OS, 7.7 (5.4, 10.0) for monkey MA and 8.4 (5.5, 11.3) for monkey TO. *Although monkeys occasionally emitted a small number of responses on the inactive lever during sessions, the percentage of total sessions during which they emitted ≥30 responses (i.e., 1 FR) on the inactive lever was <4%*. In the absence of other treatment, a unit dose of 0.032 mg/kg/infusion of cocaine occasioned the largest number of infusions, resulting in between 18.8 and 37.0 infusions in the session. Drug intake increased monotonically for all monkeys over the doses of cocaine examined in this study (data not shown) with maximal intakes varying from 2.03 to 3.63 mg/kg/session for cocaine.

Self administration of cocaine was not markedly altered by acute injections of LAAM, although LAAM modified the number of cocaine infusions received in some monkeys (Figure 1). For example, the largest dose of LAAM (1.0 mg/kg) increased the number of infusions of the smallest (0.0032 mg/kg/infusion) unit dose of cocaine and either decreased (TO) or had no effect (OS and MA) on self administration of larger unit doses of cocaine. Acute administration of the same doses of LAAM did not systematically alter the number of infusions of saline (open symbols above S, Figure 1). Overall, acute administration of LAAM did not alter intake of cocaine (data not shown) with the exception of decreased intake in monkey TO. For example, when the dose of cocaine available for self administration was 0.32 mg/kg/infusion, intake was 3.48 mg/kg/session in the absence of LAAM and 1.92 mg/kg/session when 0.1 mg/kg of LAAM was administered 90 minutes before sessions in monkey TO.

In order to determine dose-effect curves more efficiently during chronic treatment, the procedure was changed so that the unit dose of cocaine was increased each session for three consecutive sessions. Dose-effect curves for cocaine that were determined using the two methods were similar (compare solid symbols; Figures 1 and 3) with one exception. In monkey TO, the number of infusions of 0.032 mg/kg of cocaine that were self administered under the procedure used for chronic studies was more than double the number of infusions of the same unit dose of cocaine that were self administered under the procedure used for acute studies.

During the first and third weeks of daily treatment with 1.0 mg/kg of LAAM, monkeys could self administer 0.032 mg/kg/infusion of cocaine; within each of these periods, there were single intervening sessions during which saline was available. For three monkeys, the number of infusions of 0.032 mg/kg/infusion of cocaine that were self administered tended to increase

during the third week of LAAM treatment; for the fourth monkey the number of infusions tended to decrease during the third week of LAAM treatment, as compared to the number of infusions that were self administered during the first week (Figure 2). Dose-effect curves for cocaine were evaluated twice during the period of LAAM treatment. Although the number of infusions received was increased for one or more doses of cocaine in all four monkeys, as compared to number of infusions received prior to chronic treatment, the overall pattern of self administration was generally retained (Figure 3). When the largest unit dose of cocaine (0.32 mg/kg/infusion) was available for self administration, the number of infusions for SH, OS, MA and TO was 11, 12, 14 and 13 prior to LAAM treatment and 15, 20, 11 and 22 during the fourth week of LAAM treatment; this increase in number of infusions resulted in less than a 2-fold increase in cocaine intake.

Discussion

Drug self-administration procedures in non-humans are used routinely to evaluate the abuse liability of unknown substances and also to evaluate the potential value of pharmacotherapeutics for modifying the reinforcing effects of abused drugs. Maintenance treatment with long-acting, highly efficacious, μ-opioid receptor agonists has proven effective in reducing drug taking in some opioid abusers. Several different μ opioids have been used in the treatment of opioid abuse, although the pharmacologic features of these drugs that are most important for and predictive of clinical effectiveness are largely unknown. By examining the effects of repeated LAAM administration on self administration of a pharmacologically unrelated drug, cocaine, the current study can begin to determine the effectiveness of LAAM specifically in altering the reinforcing effects of cocaine in a controlled laboratory setting.

Consistent with many previous studies that were conducted in a variety of species, i.v. cocaine served as a positive reinforcer in this study. Monkeys received significantly more infusions of cocaine than of saline, both under control conditions and after acute or repeated daily injections of LAAM. Moreover, the relationship describing the number of infusions received as a function of dose generally yielded an inverted U-shaped curve, and the relationship describing total drug intake as a function of dose yielded a monotonically increasing function. Thus, the baseline performance of monkeys in this study was not qualitatively different from many others studies using similar procedures in non-human primates (e.g., [21]). Changing the procedure in order to generate dose-effect curves in shorter periods of time did not markedly alter cocaine dose-effect curves. Consequently, dose-effect curves obtained during chronic LAAM treatment were determined using the rapid procedure with the entire curve generated in 3 days, thereby minimizing the impact of changes in treatment conditions resulting from accumulation of LAAM and its active metabolites.

In the current study, although LAAM had small and variable effects on cocaine self administration, sensitivity to cocaine did not markedly change when LAAM was administered acutely. One possible explanation for the modest interaction between LAAM and cocaine is that the dose of LAAM was too small; however, when administered 2 hr before sessions *in a drug discrimination procedure*, a dose of 1 mg/kg of LAAM produced an 18-fold shift to the left in the morphine dose-effect curve [27]. Furthermore, the 90-min interval between acute LAAM administration and the beginning of experimental sessions was selected because peak blood concentrations of LAAM and its metabolite norLAAM have been shown to occur 60 min after LAAM administration in rhesus monkeys [26] and because maximum *discriminative stimulus* effects of a dose of 1 mg/kg of LAAM occurred between 60 and 90 min after administration [27]. In the current study, mydriasis was observed 90 min after administration of the largest dose of LAAM, further suggesting that LAAM was pharmacologically active under the conditions used in this study. Doses of LAAM larger than 1 mg/kg were not administered because of the risk of toxicity [26,28,29]. Finally, LAAM increased self

administration of the smallest dose of cocaine, which might indicate an additive effect between pharmacologically unrelated drugs. Collectively, these data suggest that acutely administered LAAM was pharmacologically active *under the conditions used in these studies*.

The interaction between LAAM and cocaine observed during chronic LAAM treatment clearly occurs only under a limited set of conditions. In fact, the effects of a dose of 0.032 mg/kg/infusion of cocaine, which produced the largest increase in number of infusions in the absence of other treatment, were similar during the first and third weeks of LAAM treatment. In the current study, LAAM was administered daily 2 hr after sessions and physical dependence developed during chronic treatment. Although not quantified, laboratory personnel who are experienced in observing monkeys reported signs that are characteristic of opioid withdrawal, including holding abdomen, rigid abdomen, yawning, wet dog shakes and diarrhea; *these signs were evident 48–72 hr after termination of LAAM treatment*. One possibility is that withdrawal was beginning to emerge 22 hr after the last dose of LAAM and monkeys might have increased self administration of small doses of cocaine in order to reduce withdrawal signs. Indeed, some patients continue to take heroin during methadone treatment in order to relieve withdrawal signs [30]. Moreover, when monkeys can choose between responding for cocaine or food, termination of chronic methadone treatment dramatically increases cocaine choice in some monkeys [18]. Taken together, these results suggest that opioid withdrawal might lead to increased cocaine abuse at least under some conditions.

The effects of other opioids on cocaine self administration have also been studied. When administered acutely, large doses of heroin or buprenorphine markedly decrease response rates, regardless of the unit dose of cocaine that is available [21]; however, smaller doses have different effects on small unit doses of cocaine with heroin having no effect and buprenorphine decreasing responding for small units doses of cocaine [21]. Effects obtained when opioids are administered chronically are similar to those obtained when they are administered acutely. Neither chronic morphine treatment, which decreases self administration of opioids, nor termination of treatment alters cocaine self administration [31]. Chronic buprenorphine treatment decreases responding for small unit doses of cocaine [19]. Thus, the effects of chronic administration of opioids on cocaine self administration may be predicted by their acute effects. More importantly, drugs used in opioid maintenance therapy have markedly different effects on cocaine self administration; results from the current study would suggest a therapeutic disadvantage for LAAM, as compared to buprenorphine.

In conclusion, the results of these studies indicate that *chronic LAAM administration failed* to decrease and, in some cases, increased the self-administration of cocaine. These results are consistent with clinical data indicating that some patients continue to abuse drugs during opioid maintenance treatment and further suggest that some long-acting opioids do not attenuate the reinforcing effects of other drugs. *In 2001, concerns about adverse effects of LAAM caused regulatory agencies in both the United States and the European Union to withdraw LAAM from the market. Although more recent reports have indicated that very large doses of methadone also produce these adverse effects, specifically prolongation of the QTc interval [32], results of the current studies do not support a reconsideration of the clinical use of LAAM.*

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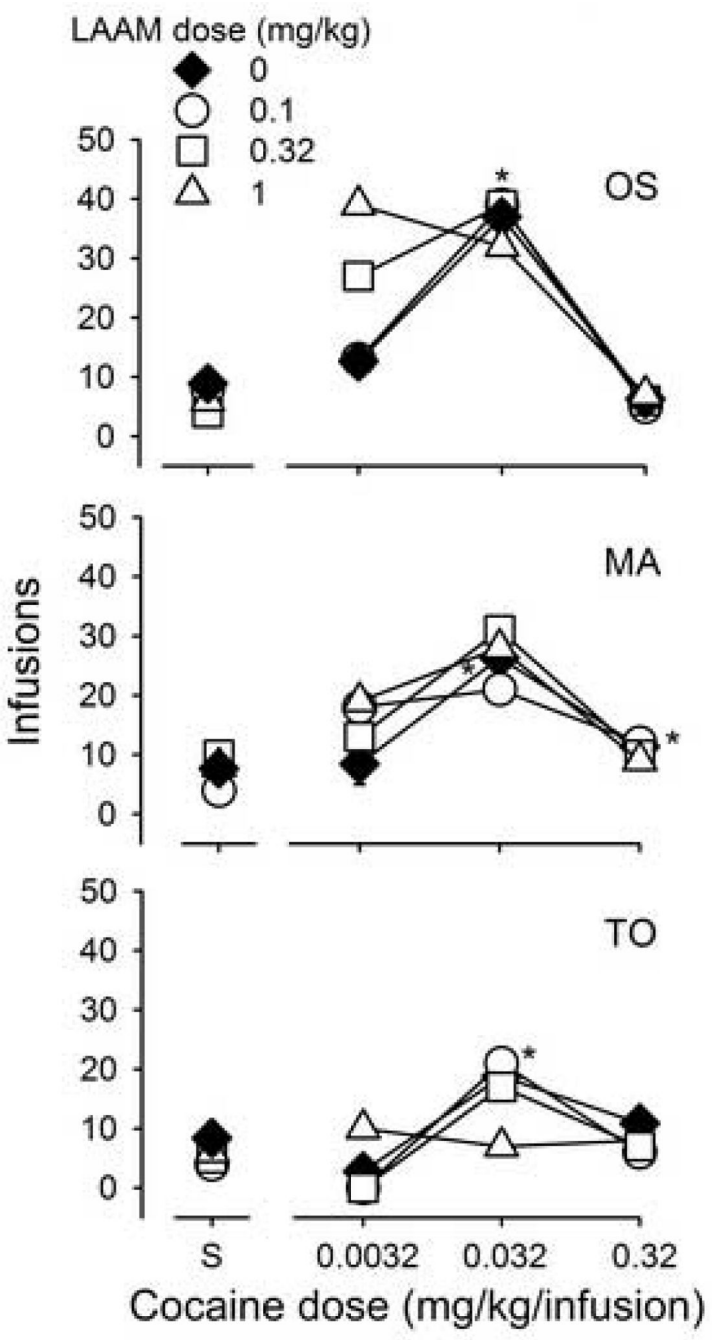

Figure 1.

Self administration of cocaine (n=3) in the absence and presence of LAAM administered acutely 90 min before sessions (0.1, 0.32 or 1.0 mg/kg administered s.c.). The number of infusions received in the 90-min session (ordinate) is plotted as function of unit dose of drug (abscissae) expressed in mg/kg/infusion. Closed symbols represent the average of 10 (saline) or 9 (cocaine) determinations for each dose in each monkey (95% CL); data points without *error bars* indicate an instance in which the 95% CL is encompassed by the symbol. Open symbols represent data from a single session that was preceded by administration of LAAM. *Each panel represents effects obtained in individual monkeys.* S=saline. *=*the 95% CL of*

number of cocaine infusions does not overlap with the 95% CL of the number of saline infusions in otherwise untreated monkeys.

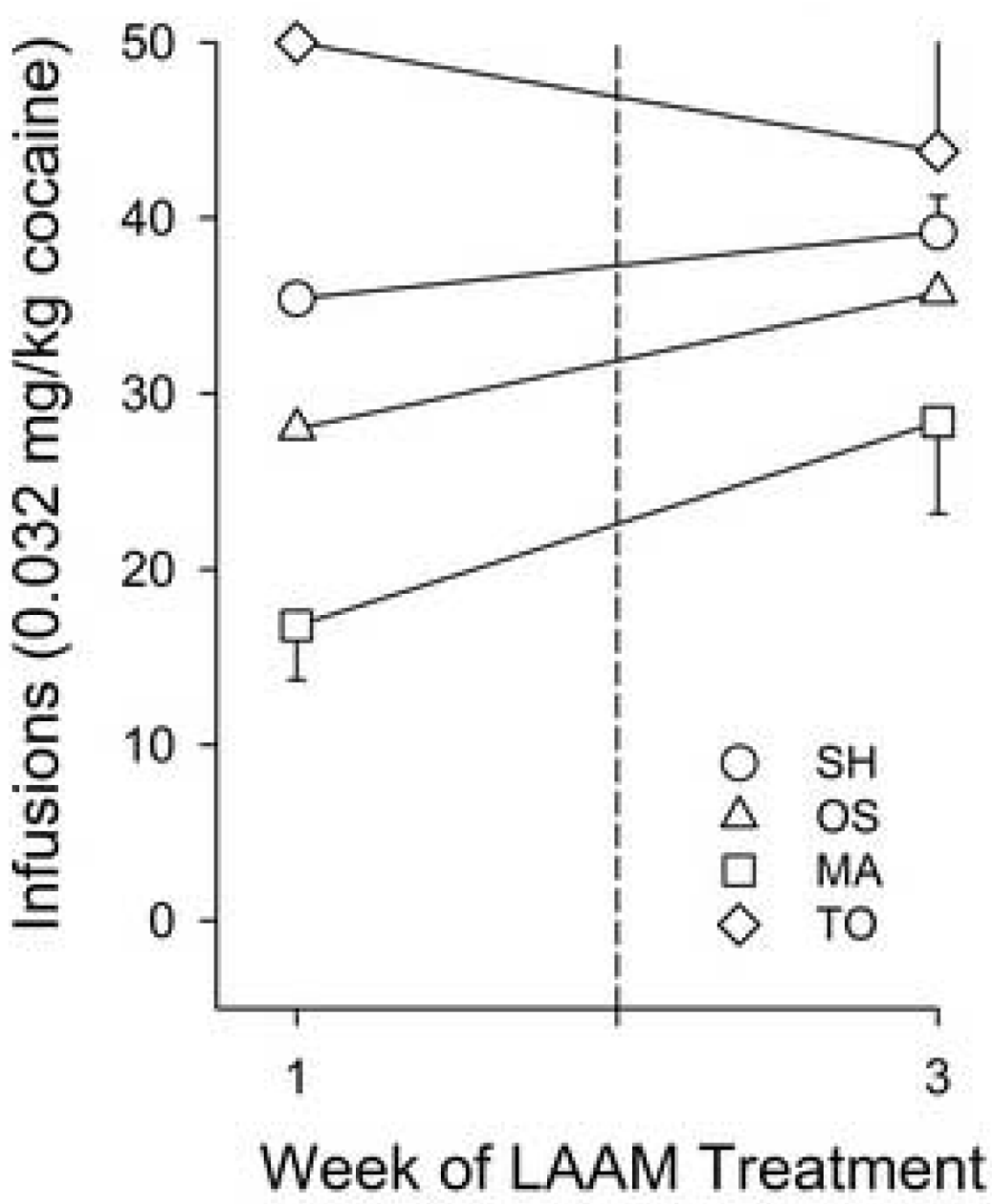

Figure 2.
Number of infusions of 0.032 mg/kg of cocaine received during the first and third weeks of daily treatment with 1.0 mg/kg of LAAM. *Each symbol represents effects obtained in individual monkeys; data from 5 sessions were averaged to obtain each point. Error bars indicate 95% CL.* Abscissa: week of LAAM treatment. See Figure 1 for other details.

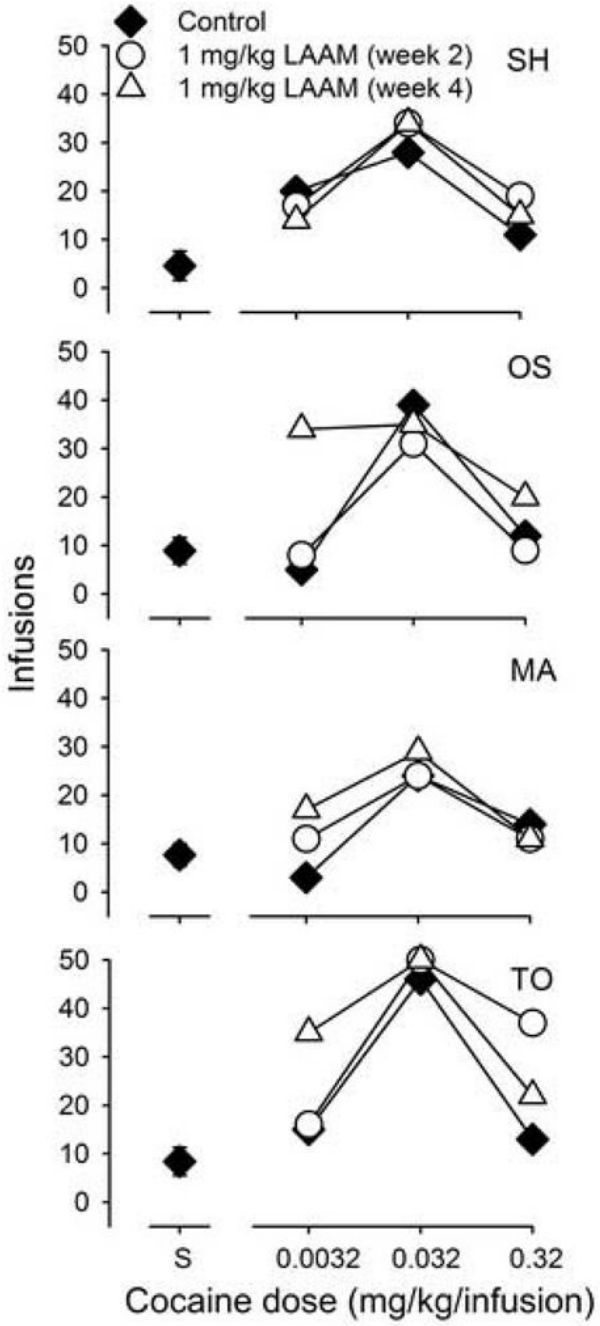

Figure 3.
Self administration of cocaine (n=4) determined before and during the second and fourth weeks of daily treatment with 1 mg/kg/day of LAAM administered 2 hr after sessions. See Figure 1 for other details.