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Kinetics and Rat Locomotor Activity Following Cocaine and Lidocaine Administration

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Key words:

Cocaine abuse is a widespread problem in the USA. Illicit cocaine is usually never found in pure form but is adulterated with other agents, among which are the local anesthetics such as lidocaine. Adulteration of cocaine with another active agent allows the potential for various drug–drug interactions to occur. The presence of an additional active agent in illicit cocaine samples can complicate the pharmacological and toxicological responses elicited and possibly the mode of emergency medical care thereafter. When studying drug interactions, both the kinetic and dynamic aspects of each agent must be considered. This study investigated the plasma time course and tissue distribution of cocaine and lidocaine alone and in combination following a 5 mg kg^{-1} intravenous injection in rats. The plasma time course of cocaine and lidocaine in combination did not differ from that seen when each drug was alone. Tissue contents were without change when administered alone or in combination at 5, 10 and 15 min following treatment. However, rats treated with cocaine and lidocaine in combination had significantly greater locomotor activity initially than animals treated with cocaine alone. The results suggest that cocaine and lidocaine interact on a pharmacodynamic basis without a change in the drug level of each agent.

INTRODUCTION

Cocaine abuse is an extensive problem in the USA. In 1990, it was estimated that upwards of 6 million individuals have used cocaine at some time.[1] As of 1992, 3.4 million Americans were believed to be regular users.[2] The actual number of cocaine abusers is probably even greater because people more likely to participate in it, such as the homeless, prisoners and inner city dwellers, are not easily surveyed and therefore not accurately represented.[3] A report in 1989 showed that people between the ages of 20 and 39 years accounted for over 83% of emergency room visits associated with cocaine abuse.[4]

Cocaine abusers utilize different routes of administration to ingest the drug. Nasal insufflation (snorting) appears to be most common, followed by free-base smoking and intravenous injection.[5] Intravenous injection and free-base cocaine smoking produce similar effects because smoking free-base cocaine permits large amounts of the drug to reach the pulmonary vasculature, making it readily available to enter the bloodstream.[6] Euphoria has been reported to occur within 10 s after smoking free-base and last for a mere 5–10 min.[7]

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Illicit cocaine is rarely obtained in pure form and is usually found adulterated with other substances, thereby varying in purity.[8,9] Local anesthetics such as lidocaine are often employed as adulterants in illicit cocaine because they also produce a numbing sensation when tasted and are not readily identified by the purchaser.[9] A study that investigated 634 cocaine samples obtained on the street revealed that 211 of them had lidocaine and other local anesthetics in varying amounts.[8] In fact, lidocaine appears to be the predominant local anesthetic used for cocaine adulteration.[10] The presence of adulterants can complicate the toxicity of cocaine and conceivably the mode of medical treatment required in an emergency.[9] Toxicity due to cocaine is manifested in anxiety, hyperthermia, seizures and convulsions, cardiac arrhythmia, hypertension and respiratory failure.[11]

When more than one drug is present simultaneously, the potential for drug–drug interactions exists. Previous research has shown that lidocaine potentiates cocaine-induced toxicity.[12] These findings have shown that the frequency of seizures and lethality is significantly increased when cocaine and lidocaine are both present. Other substances also have been shown to interact with cocaine. The use of beta-adrenergic antagonists, such as propranolol, in the treatment of the cardiovascular effects of cocaine have been shown to result in potentiated coronary vasoconstriction.[13] Calcium channel blockers have been shown to increase the incidence of cocaine-induced seizures.[14]

Drug–drug interactions can be kinetic, dynamic or both in nature. The pharmacokinetics of cocaine have

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been investigated before.[15,16] The objective of this study was to investigate the kinetics of cocaine and lidocaine in combination in order to assess the role that the kinetic component may play in the interaction of these agents. Preliminary work in this laboratory found that rats receiving cocaine and lidocaine in combination demonstrated more activity than those receiving cocaine alone. Locomotor activity was investigated in order to study the psychomotor effects of this interaction.

METHODS

Animals

Male Sprague-Dawley rats (225–250 g) were obtained from Taconic Farms, Germantown, NY. The rats were housed three per cage in a room with controlled temperature (25°C) and humidity and access to Purina Lab Chow and water *ad libitum*. All animals were maintained in accordance with the National Institutes of Health (NIH) guidelines for the care and use of laboratory animals. The use of animals in these experiments was approved by the Institutional Animal Care and Use Committee of the University of Medicine and Dentistry of New Jersey, Newark.

Drugs

Cocaine hydrochloride and its metabolites (purity $>$ 99.5%) were obtained from the National Institute of Drug Abuse (NIDA), Bethesda, MD. Lidocaine hydrochloride (purity $>$ 99.5%) was obtained from Astra Pharmaceuticals, Westborough, MA.

Analytical methodology

Detection and quantification of cocaine, its metabolites and lidocaine in plasma and tissues were performed by reversed-phase high-performance liquid chromatography (Waters, Milford, MA) utilizing a method developed and validated in this laboratory with minimum detectable concentrations of 1 ng ml^{-1} for cocaine and 5 ng ml^{-1} for lidocaine.[17]

Individual animal horizontal locomotor activity was monitored by an Opto-Varimex (Columbus Instruments, Columbus, OH) animal activity monitor consisting of a plexiglass cage surrounded by a series of infra-red emitters and detectors connected to a counter. Animals were monitored individually in the laboratory without disturbance. Data were reported as the number of beam crossings (counts) for each time period of observation.

Plasma time-course study

Three groups of male Sprague-Dawley rats ($n = 6$–8 per group) were treated intravenously with a single injection of cocaine, lidocaine or both drugs in combination (5 mg kg^{-1} each). The dose of 5 mg kg^{-1} of each agent was determined to be the maximally tolerated dose of each drug when administered in combination. Doses beyond this were fatal and resulted in violent convulsions, respiratory failure and death within seconds. During drug administration, rats treated with cocaine and lidocaine would often develop seizures. Occasionally, a slight delay in the duration of drug administration would occur in order to prevent lethality. The drugs were administered slowly (3–5 min) in a 200-μl volume into the lateral tail vein under restraint. Blood samples (200 μl) were obtained via cardiac puncture with heparinized syringes under light ether anesthesia at 1, 5, 15, 30 and 45 min as well as 1, 1.5, 2, 3, 4, 5 and 6 h post-injection. Plasma was obtained by centrifuging the blood at 1000 *g* for 15 min at 4°C and stored at −70°C until analysis.

Tissue distribution study

Rats were treated with cocaine, lidocaine or both drugs in combination as described above. Five animals per group at 5, 10 and 15 min post-injection were sacrificed for immediate excision of brain, heart and liver. One gram of each tissue was homogenized on ice in 2.5 ml of cold saline using a Tek-Mar (Tek-Mar Co., Cincinnati, OH) homogenizer. Homogenates were stored at −70°C until analysis.

Locomotor activity study

Three groups of male Sprague-Dawley rats ($n = 5$ per group) were treated intravenously as described above. The control group was treated with saline. Saline was the vehicle in all treatment groups and was also included as a mechanical control in order to account for any effects other than those of the drug. The animals were acclimated to the environment in the activity monitor for 15 min before treatment. Mean horizontal counts per minute were taken at 5, 15, 30, 45, 60 and 90 min post-injection.

Statistics

Multiple comparisons were performed by ANOVA and followed up with the Tukey–Kramer Honestly Significant Difference (HSD) test. Statistical analysis between two groups was performed by Student's independent *t*-test. In all analyses, the level of significance was set to $P < 0.05$. Statistical analysis was performed with the JMP 2.0 statistical package (SAS Institute, Inc. Cary, NC) and an Apple Macintosh computer (Apple Computer, Inc., Cupertino, CA).

RESULTS

Plasma time-course study

Cocaine administered intravenously to rats followed a two-compartment model of elimination with a rapid distribution phase. The plasma time courses of cocaine alone (Fig. 1) and in combination with lidocaine (Fig. 2) are depicted. Cocaine half-lives of distribution and elimination were 8.03 and 89.9 min when given alone and 8.02 and 91.4 min when administered in combination with lidocaine. Because the route of administration was intravenous, the peak plasma concentration was reached immediately with the com-

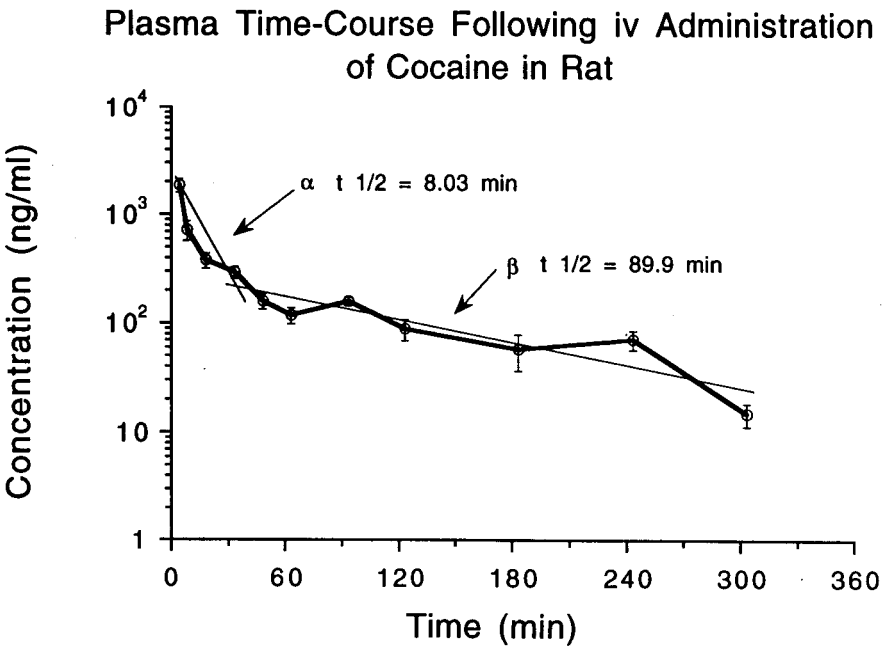

Figure 1. Plasma time course following intravenous administration of cocaine in rats. Values represent the mean plasma concentration ± SEM of 6–8 animals per group following intravenous administration of cocaine alone (5 mg kg^{-1}).

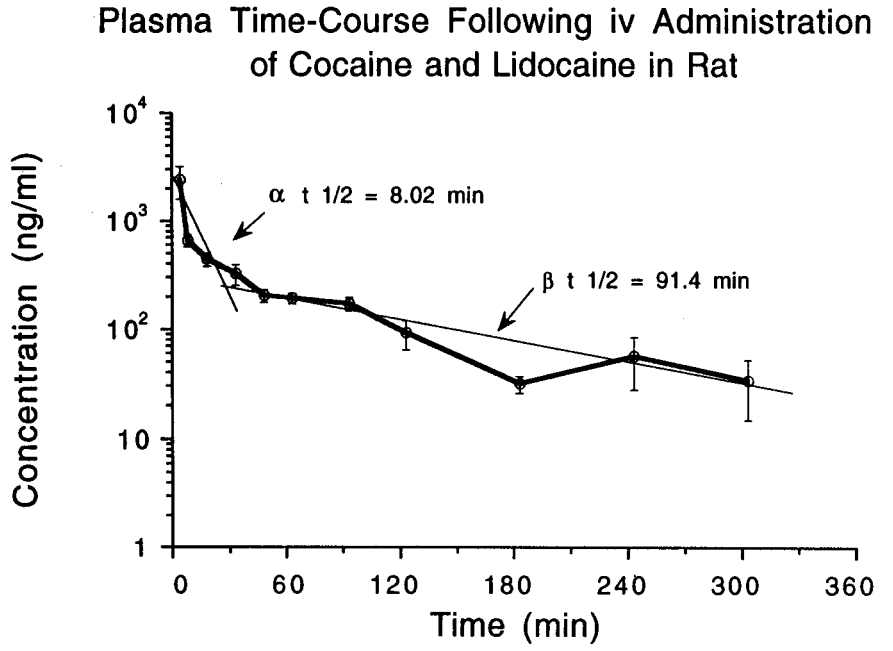

Figure 2. Plasma time course following intravenous administration of cocaine and lidocaine in rats. Values represent the mean plasma concentration ± SEM of 6–8 animals per group following intravenous administration of cocaine and lidocaine (5 mg kg^{-1} each).

pletion of the injection. In both treatment groups cocaine had a short distributional phase accompanied by a drop in plasma concentration, resulting in a rapid rate of change of plasma drug concentration per unit time. This is consistent with the short duration of the presence of cocaine in plasma. The elimination phase of cocaine was approximately 11-fold greater than the distribution phase. Cocaine was not detected 360 min post-injection.

The plasma time courses of lidocaine alone and in combination with cocaine are depicted in Fig. 3. Lidocaine followed a one-compartment model of elimination, with a half-life of 13.7 min when administered alone and in combination with cocaine. The short plasma half-life and rapid disappearance of lidocaine from plasma following intravenous administration is consistent with previous reports in the literature.[17] The simultaneous presence of cocaine did not change the values or the half-life of lidocaine.

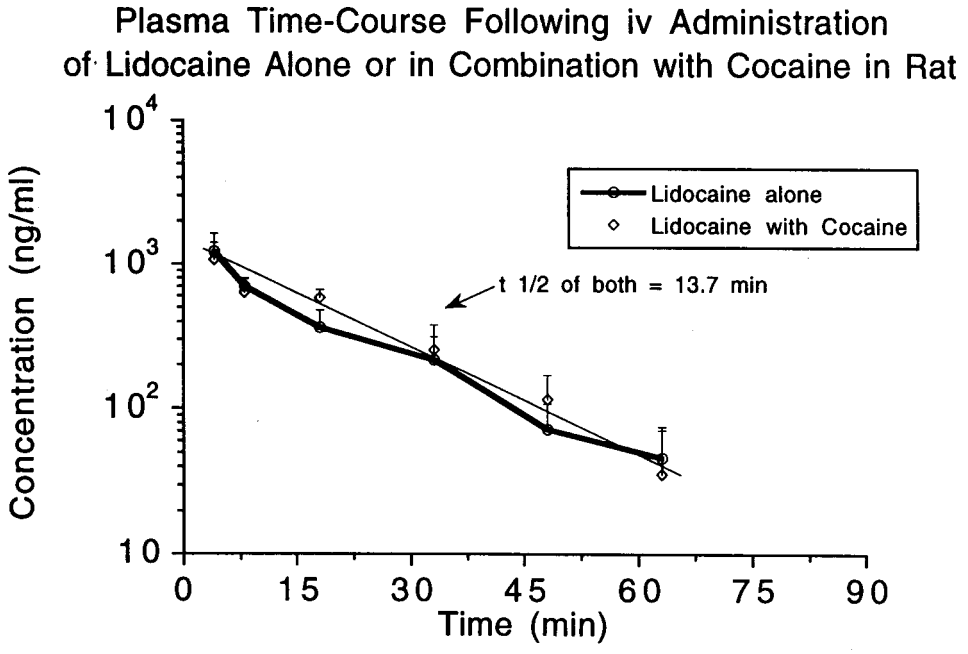

Figure 3. Plasma time course following intravenous administration of lidocaine alone or in combination with cocaine in rats. Values represent the mean plasma concentration ± SEM of 6–8 animals per group following intravenous administration of lidocaine alone or with cocaine (5 mg kg^{-1} each).

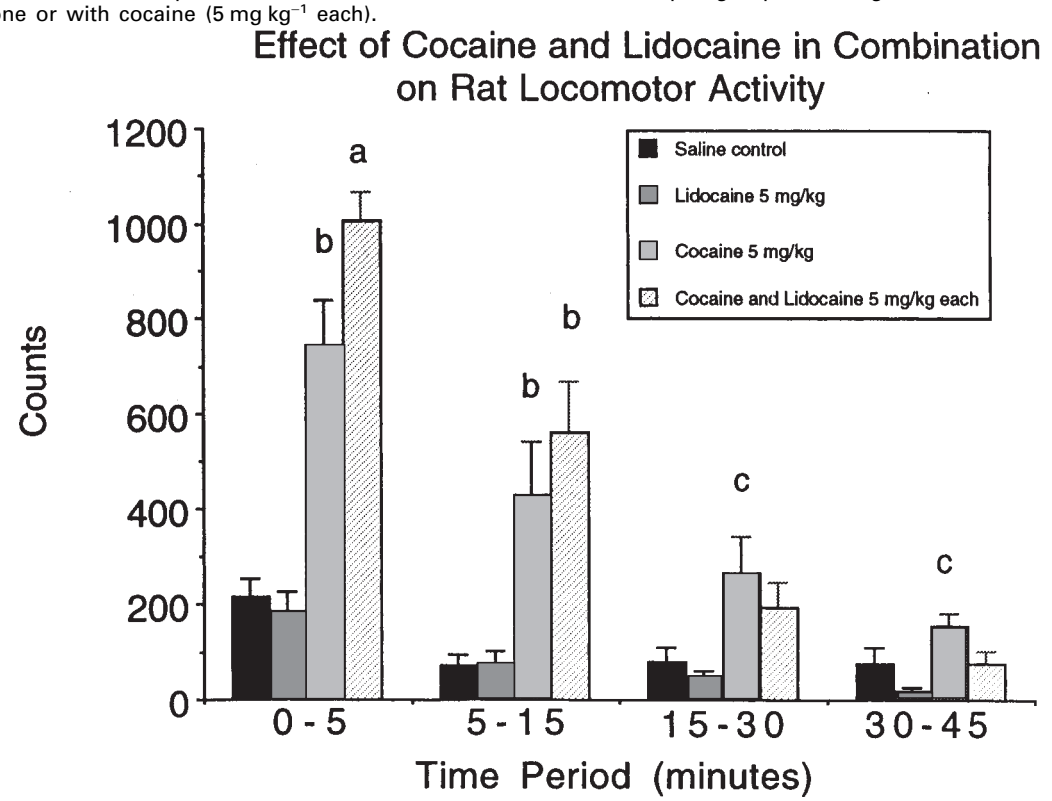

Figure 4. Effect of cocaine and licocaine in combination on rat locomotor activity. Values represent the mean counts ± SEM of five animals per group ($P < 0.05$): (a) significantly different from saline-, cocaine- or lidocaine-treated rats; (b) significantly different from saline- or lidocaine-treated rats; (c) significantly different from lidocaine-treated rats.

Tissue distribution

Tables 1 and 2 depict the amounts of cocaine and lidocaine, respectively, at 5, 10 and 15 min post-injection in different tissues. Brain drug content was of particular interest because of the resultant neurological complications that often occur with cocaine abuse. Furthermore, drug abusers intentionally ingest cocaine and other drugs of abuse because of the psychoactive effects that are elicited. Therefore, the central nervous system was the primary target organ of interest. In addition to the brain, the heart and liver contents were also studied because both organs are susceptible to cocaine-induced damage and have been the subject of other investigations studying the toxicity of cocaine.

Of the tissues studied, cocaine was found in the highest amount in the brain, especially at 5 and 10 min post-injection (Table 1). This is indicative of rapid

Table 1. Cocaine distribution following intravenous administration of lidocaine in rats[a]

	5 min		10 min		15 min	
Tissue	Alone	With lidocaine	Alone	With lidocaine	Alone	With lidocaine
Brain	8.9 ± 1.2	5.8 ± 1.0	4.3 ± 0.9	4.5 ± 0.5	3.1 ± 0.7	2.7 ± 0.4
Liver	0.7 ± 0.04	0.6 ± 0.1	0.6 ± 0.1	0.6 ± 0.1	1.5 ± 0.2	1.0 ± 0.06
Heart	5.3 ± 1.9	3.1 ± 0.3	2.1 ± 0.2	1.6 ± 0.3	3.1 ± 0.5	3.1 ± 0.7

[a]Values represent the mean ± SEM ($\mu g\ g^{-1}$ wet tissue) from five rats per group after treatment with cocaine alone or in combination with lidocaine (5 mg kg^{-1} each).

Table 2. Lidocaine distribution following intravenous administration of cocaine in rats[a]

	5 min		10 min		15 min	
Tissue	Alone	With cocaine	Alone	With cocaine	Alone	With cocaine
Brain	1.0 ± 0.07	0.7 ± 0.1	0.4 ± 0.06	0.3 ± 0.1	0.3 ± 0.07	0.4 ± 0.05
Liver	1.3 ± 0.08	0.9 ± 0.02	0.8 ± 0.2	0.9 ± 0.4	1.9 ± 0.4	2.1 ± 1.0
Heart	5.3 ± 1.2	4.1 ± 0.3	1.8 ± 0.3	1.7 ± 0.3	2.0 ± 0.6	3.4 ± 1.3

[a]Values represent the mean ± SEM ($\mu g\ g^{-1}$ wet tissue) from five rats per group after treatment with lidocaine alone or in combination with cocaine (5 mg kg^{-1} each).

distribution into it and is consistent with the psychoactive effects that are seen during and immediately after drug treatment. At 5 min, the amount of cocaine when given with lidocaine appeared to be lower than when given alone. This most likely reflects differences in the duration of drug administration. At 10 and 15 min post-injection, brain cocaine content decreased with time. Liver and heart cocaine levels increased by 15 min, suggesting redistribution into these tissues. Lidocaine was found in the highest amount at 5 min post-injection in the heart (Table 2). Lidocaine did not significantly change the content of cocaine in brain, liver and heart. Overall, the amount of the drugs in brain and other tissues was not significantly different for either agent when administered alone or in combination.

Locomotor activity study

A graphical representation of the results of the locomotor activity study is shown in Fig. 4. The psychomotor stimulant activity of cocaine is seen in rats receiving it alone or in combination with lidocaine. Rats treated with cocaine and lidocaine in combination had significantly greater locomotor activity than those treated with cocaine or lidocaine individually at 5 min post-injection. Rats treated with lidocaine alone did not differ significantly from saline-treated controls. However, when in combination with cocaine, the degree of cocaine-induced locomotor activity was significantly increased in comparison to rats treated with cocaine or lidocaine alone. At 15 min post-injection, rats treated with cocaine and lidocaine demonstrated greater locomotor activity than rats treated with cocaine alone, but the effect was not significant. At 30 and 45 min post-injection, cocaine-treated animals had the greatest degree of locomotor activity among all the treatment groups.

DISCUSSION

Illicit cocaine is adulterated with various substances, but usually local anesthetics, predominantly lidocaine.[9,10] Other drugs interact with cocaine through different mechanisms, such as the calcium channel blockers and propranolol.[13,14] When investigating possible drug–drug interactions, both kinetic and dynamic aspects must be considered. Previous research has shown that lidocaine can potentiate cocaine-induced toxicity manifested in an increase in the frequency of seizures and convulsions.[12] To date, there have not been any reports describing the pharmacokinetics of cocaine in the presence of lidocaine and the assessment of the role, if any, this may play in the observed toxicity of this drug combination.

In this study, the intravenous route of administration was employed because it is a reasonable paradigm to those modes employed during illicit substance abuse. The plasma kinetic study revealed that cocaine behaves in a similar fashion whether alone or in combination with lidocaine. The half-lives of distribution and elimination of cocaine were not affected by the simultaneous presence of lidocaine. Furthermore, cocaine did not affect the elimination half-life of lidocaine. No significant change in the tissue contents or patterns of distribution of either agent was found. Cocaine was found in the highest amount in the brain following injection. The brain content of cocaine appeared to be lower when given in combination with lidocaine than when given alone at 5 min. This is most likely to be

due to the presence of the seizures that occasionally result during treatment, which in turn prolong the duration of the injection in order to avoid lethality. By 10 min post-injection, the brain levels were nearly equal.

Although kinetic parameters were not affected by the simultaneous presence of the two drugs, there was an increase in animal activity. This was reflected in the locomotor activity study. The measurement of animal activity has been employed in pharmacological studies for some time. In particular, locomotor activity has been used as a response variable for measuring animal excitability following drug treatment in various investigations involving cocaine.[18–20] Rats treated with cocaine and lidocaine had significantly greater locomotor activity initially, which lasted up to 5 min post-injection, in comparison to rats treated with saline or cocaine and lidocaine individually. This time frame is consistent with the duration of effects that are reported to occur in humans.[7] Lidocaine-treated rats did not differ significantly from saline-treated controls. Rats treated with cocaine or cocaine + lidocaine demonstrated an initial increase in locomotor activity, manifested in brisk perimeter walking. By 90 min post-injection, rats would usually be asleep regardless of drug treatment.

The activity of the animals decreased with time, as did the drug concentration in plasma. However, the additional degree of locomotor activity seen with cocaine + lidocaine in comparison to cocaine alone was not due to a difference in the concentration of the drugs in plasma or in the content of the brain, as evidenced in the plasma time-course and tissue distribution studies. Furthermore, the actions and toxicity observed occurred immediately after drug administration. These results suggest that the nature of this drug interaction involves the pharmacodynamic actions of each drug at the cellular level. Further studies to elucidate the nature of this interaction are under way in this laboratory.

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