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Influence of Infused Catecholamines on the Pharmacokinetics of Cocaine and Benzoylecgonine Formation after Bolus Dose or Continuous Cocaine Administration in the Rat

BEREND METS, SUBHASH JAMDAR AND JAIME DIAZ

Department of Anesthesiology, College of Physicians and Surgeons of Columbia University, New York, NY 10032, USA

Abstract

The purpose of this study was to determine whether a catecholamine infusion administered to simulate a stress state could alter the pharmacokinetics of administered cocaine and effect the formation of benzoylecgonine, its major metabolite, in the rat. In a previous investigation we determined that catecholamine infusion enhanced the toxicity of continuous cocaine infusion by reducing the time before the onset of convulsions and respiratory arrest. We postulated that this enhanced toxicity was an effect of catecholamines on the pharmacokinetics of cocaine.

To test this hypothesis we studied plasma cocaine and benzoylecgonine disposition after intravenous bolus administration of cocaine ($5\,mg\,kg^{-1}$) to 19 male Sprague-Dawley rats and to 10 rats which received an initial loading-dose cocaine infusion of $1\,mg\,kg^{-1}\,min^{-1}$ (for 5 min) followed by continuous infusion of $100\,\mu g\,kg^{-1}\,min^{-1}$. Rats in both studies randomly received either continuous catecholamine infusion comprising adrenaline ($7{\cdot}25\,\mu g\,mL^{-1}$), noradrenaline ($4{\cdot}4\,\mu g\ mL^{-1}$) and dopamine ($8{\cdot}0\,\mu g\,mL^{-1}$) or saline, administered at a similar rate. Bolus dose cocaine administration, simultaneously with catecholamine infusion, resulted in significantly higher C_{max} levels for cocaine (3·8 compared with $2{\cdot}5\,\mu g\,mL^{-1}$) and lower distribution half-lives (3·3 compared with 5·9 min) and central compartment volumes of distribution (1·5 compared with $2{\cdot}1\,L\,kg^{-1}$) compared with saline infusion. Benzoyl-
ecgonine formation was significantly reduced in rats receiving catecholamines whereas the elimination half-lives (26·3 compared with 25·0 min) and systemic clearances (146 compared with $146\,mL\,kg^{-1}\,min^{-1}$) were not different. Continuous cocaine infusion (after an initial loading infusion) resulted in the doubling of plasma cocaine levels in rats receiving catecholamines compared with the control group.

These data indicate that elevated plasma catecholamines have significant effects on cocaine pharmacokinetics. This might serve to explain the enhanced toxicity from concomitant cocaine and catecholamine infusion demonstrated in previous experiments.

Sudden death from low concentrations of cocaine is usually preceded by a state of agitated delirium (Prahlow & Davis 1994) or restraint and incarceration (Wetli & Fishbain 1985), circumstances associated with exaggerated stress responses either as a result of central nervous over-stimulation (Harruff et al 1991) or of "stress from restraint" (Wetli & Fishbain 1985). Because these clinical data suggest that the massive release of catecholamines associated with stress might enhance cocaine toxicity, to model this stress state in previously conducted experiments, we infused a mixture of catecholamines to achieve plasma levels consistent with extreme stress in rats (Mets et al 1996). In these circumstances we demonstrated enhanced toxicity from cocaine infusion in the presence of elevated plasma catecholamine levels. When compared with saline controls catecholamine infusion dose-dependently elicited earlier convulsions and respiratory arrest in conscious rats and circulatory arrest in anaesthetized and ventilated rats from continuous cocaine infusion. However, despite lower cocaine cumulative dose administration, rats receiving catecholamines had similar plasma cocaine concentrations at the onset of

Correspondence: B. Mets, Department of Anesthesiology, College of Physicians and Surgeons of Columbia University, 630 West 168 St, New York, NY 10032, USA.

convulsions and respiratory arrest compared with those with cocaine infusion alone (Mets et al 1996). The data thus suggested that catecholamines enhance the convulsive, respiratory and circulatory toxicity of cocaine as a result of a pharmacokinetic interaction. We designed the present experiments to assess whether catecholamine infusion could affect the pharmacokinetics of cocaine administered either as a bolus dose or as a continuous infusion at concentrations unlikely to cause systemic toxicity.

Materials and Methods

Animals

Adult male Sprague-Dawley outbred rats, 380 g (approx.), 13–14 weeks, n = 29, conforming to the International Genetic Standard Colony (K92; Charles River Laboratories, Kingston, NY) were housed in groups and had free access to both standard rat chow (Purina, Rodent Chow, 5001; W. Fischer, NJ) and water. The animals were maintained for at least one week before the study, according to NIH guidelines in our institutional animal facility, at 21 ± 2°C, 55% relative humidity, and a 12-h light–dark cycle with lights on at 0700 h. The protocol for the use of the rats in this research was approved by the Institutional Animal Care and Use Committee of Columbia University.

Surgical preparation

Rats were anaesthetized by intraperitoneal injection of ketamine hydrochloride (80 mg kg^{-1}) and xylazine (8 mg kg^{-1}) 24 h before the study day. They were shaved over the left inguinal area and nape and a 1-cm incision was made over the femoral artery and vein for catheterization of these vessels with 60-cm lengths of PE-50 Intramedic polyethylene tubing (Clay Adams, Parsippany, NJ). Catheters were flushed with heparin (8 units mL^{-1}; 0·5 mL), sealed and tunnelled under the skin to the nape, exteriorized, and coiled under a plastic cover sutured to the skin. All incisions were sutured closed but no antibiotics were administered. The rats were then left to recover on a warming blanket, and again allowed free access to rat chow and water when returned to the vivarium over night. The next day, before the pharmacokinetic study, the knotted catheters were severed 7 cm from the tip and patency confirmed in both by observing the back-flow of blood.

Bolus-dose study

Nineteen rats prepared as indicated above were randomly divided into two groups, weighed, and placed in a cage. The group "cocaine–catecholamines" (n = 9) received a catecholamine mixture comprising adrenaline (7·25 μg mL^{-1}), noradrenaline (4·4 μg mL^{-1}) and dopamine (8·0 μg mL^{-1}) by infusion at 6 mL h^{-1} by means of a previously calibrated infusion pump, (model AS 20GH-2; Baxter, NJ). The group "cocaine–saline" (n = 10) received a saline infusion at the same rate. After exactly 10 min an arterial blood sample (0·5 mL) was taken from both groups for plasma catecholamine determination. All blood samples taken were meticulously replaced with an equivalent volume of saline. Cocaine hydrochloride (5 mg kg^{-1}; 2·5 mg mL^{-1}) was then administered intravenously over 2 min (time 0 when complete); the catecholamine or saline infusion, started earlier, was continued until the end of the study. Samples for plasma cocaine and benzoylecgonine determination were taken 5, 10, 15, 30, 45, 60, 90 and 120 min after cocaine administration. Additional plasma samples were taken from three animals in the cocaine–catecholamines group and from four animals in the cocaine–saline group 0·5, 1 and 2 min after completion of the bolus cocaine dose.

Continuous infusion study

Ten rats were randomly selected to receive the catecholamine (cocaine–catecholamines group) or saline (cocaine–saline group) infusion and were prepared and studied as indicated above. However, instead of a single cocaine bolus, a two stage cocaine hydrochloride infusion (1·5 mg mL^{-1}), was started at an initial "loading" infusion rate of 1000 μg kg^{-1} min^{-1} for 5 min which was then reduced to a "maintenance" infusion rate of 100 μg kg^{-1} min^{-1} for the rest of the study. Samples for plasma cocaine and benzoylecgonine determination were taken at 5-min intervals from 30 to 55 min after start of the initial infusion.

Cocaine and catecholamine analysis

Cocaine hydrochloride and benzoylecgonine were gratefully received from the National Institute of Drug Abuse (Research Triangle Park, NC). Cocaine hydrochloride was used to prepare solutions (2·5 mg mL^{-1}) in sterile water immediately before administration to the rat. Plasma samples for cocaine analysis were collected into precooled Eppendorf tubes (1·5 mL) pretreated with saturated NaF (20 μL) and heparin (1000 units mL^{-1}, 20 μL) and samples for catecholamine analysis were collected into similar precooled tubes pretreated with EDTA only. Plasma cocaine and benzoylecgonine concentrations were determined by high-performance liquid chromatography (HPLC), by use of a further modification of our original method, using bupivacaine as an internal standard (Virag et al 1995).

Chemicals and reagents
Standard solutions of cocaine and benzoylecgonine were prepared freshly from stock solutions ($1\,mg\,mL^{-1}$) in methanol and stored at $-15°C$. All organic solvents (acetonitrile, chloroform, methanol, dichloromethane and 2-propanol) were of HPLC-grade and purchased from sources reported elsewhere (Virag et al 1995). All reagents were certified-grade including anhydrous sodium carbonate, monosodium phosphate, ammonium hydroxide; 0·1 and 1 M hydrochloric acid, and were obtained from Fisher Scientific (Fair Lawn, NJ). Drug-free plasma from male Sprague-Dawley rats was purchased from Rockland, (Gilbertville, PA).

Sample extraction and chromatography
Solid-phase extraction of cocaine and benzoylecgonine was performed by use of Bond Elute Certify columns (300 mg) from Varian Analytical (Harbor City, CA) and a Vac-Elut manifold. The extraction columns were conditioned by successive washing with methanol (6 mL), water (3 mL) and phosphate buffer (0·01 M, pH 2·0; 5 mL) without drying the columns. To study 200-μL plasma samples internal standard (20 μL containing 2 μg bupivacaine) and phosphate buffer (3 mL) were added. After brief mixing the samples were applied to the preconditioned extraction columns and drawn slowly through. The columns were dried under full vacuum for 1–2 min and then sequentially eluted with water (3 mL) and HCl (0·1 M, 3 mL). Columns were again dried under full vacuum, washed rapidly with methanol (6 mL) and dried again for 5 min under vacuum. Elution of cocaine benzoylecgonine was performed with dichloromethane-2-propranol (4 : 1, v/v; 6 mL) containing 2% ammonium hydroxide, without application of vacuum. The eluents were evaporated at 50°C under a gentle stream of nitrogen and reconstituted in dichloromethane (2 mL). The resultant solution was dried under nitrogen. The dry residue was reconstituted in mobile phase (300 μL) and quantitative analysis of cocaine and benzoylecgonine was performed by HPLC.

HPLC was performed with a Waters 590 isocratic pump, a Rheodyne model 7125 NS injector with 100-μL sample loop, and a 3200 variable-wavelength detector connected to the Hewlett-Packard (San Fernando, CA) integrator. Separation of cocaine, benzoylecgonine and internal standard were achieved on a cyano column (4·6 mm i.d. × 250 mm, 5 μm particles; J. T. Baker, Phillipsburg, NJ) connected in series to a C8-spheric column (4·6 mm i.d. × 150 mm, 5 μm particles; Varian). The mobile phase (degassed for 10 min under helium) was a mixture of HPLC-grade water (1000 mL), HPLC-grade acetonitrile (400 mL) and trifluoroacetic acid (1 mL; Sigma, St Louis, MO); the flow rate was $1{\cdot}2\,mL\,min^{-1}$. Samples (100 μL) were injected manually and the elution of the analytes was monitored at 235 nm for 20 min with the detector range set at 0·01–0·02 AUFS (absorbance units full scale). Plasma calibration standards (25–1000 ng) were prepared in drug-free plasma. Each calibration point was acquired in triplicate and the peak-height ratio of each analyte to the internal standard was plotted against analyte concentration by linear regression. Linear regression analysis (correlation coefficient $> 0{\cdot}99$) enabled interpolation of unknown values. Assay sensitivity was $25\,ng\,mL^{-1}$ for both cocaine and benzoyl-ecgonine. The extraction efficiency for cocaine and benzoylecgonine varied from 80 to 86%; it was 90% for the internal standard. The coefficients of variation were 8, 6·7 and 2·9% for benzoyl-ecgonine, cocaine and the internal standard, respectively.

Catecholamines were analysed by HPLC by use of an adapted method (Davis & Kissinger 1981). Catecholamines and the internal standard, 3,4-dihydroxybenzylamine, were extracted from plasma. Catecholamines were detected by use of a Coulochem II electrochemical detector. Calibration curves were linear over the range $1–20\,ng\,mL^{-1}$; the correlation coefficient was $> 0{\cdot}99$. The limit of detection was $35\,pg\,mL^{-1}$ and the extraction efficiency 82% for the three catecholamines. Within-day CV was 5% for noradrenaline and adrenaline and 15–20% for dopamine; between-day CV was 6–13% for noradrenaline and adrenaline and 20% for dopamine. Multiple dilutions of the plasma samples were performed to measure concentrations within the linear range of the calibration curves.

Pharmacokinetic analysis
Pharmacokinetic analysis of plasma concentrations after cocaine bolus dose injection in the two groups was performed by use of WinNonlin (SCI software, NC) in the Gaus-Newton (Levenberg and Hartley) mode. Plotting of data points suggested that data would be appropriately fitted to a bi-exponential equation. However, to establish whether the pharmacokinetic disposition of cocaine could be better described by a three-compartment model rather than a two-compartment model, mean data points for the different sampling times were fitted to bi and tri-exponential equations by use of WinNonlin (Hull 1991a). In each instance the models were subjected to the criteria of Boxenbaum (Boxenbaum et al 1974), Akaike (Akaike 1974) and Schwarz (Schwarz 1978). A three-compartment model was only considered an improvement if the Akaike and Schwarz criteria were lower and if there was a significant improvement in the weigh-

ted sum of squared residuals as indicated by use of the F test at the $P < 0.05$ level after Boxenbaum (Boxenbaum et al 1974). The criteria which justify the use of the more complex three-compartment model were not fulfilled. The data from two rats in the cocaine–catecholamines group and one in the cocaine–saline group were rejected because the data sets were either incomplete or resulted in poor conditioning on pharmacokinetic analysis. For all other analyses conditioning was acceptable and thus individual pharmacokinetic parameters were determined for each animal and the means of these were subjected to statistical analysis.

Statistics

Between-group comparisons were performed by use of the unpaired two-tailed Students t-test. Data are presented as means ± s.e.m. $P < 0.05$ was taken as indicative of significance.

Results and Discussion

Rats were similar in weight in the four groups studied (379 ± 5·1 g) (one-way analysis of variance). Plasma catecholamine concentrations measured just before bolus dose cocaine administration were 14·7 ± 6·9, 23·1 ± 10·5 and 10·8 ± 6·3 ng mL^{-1}, respectively, for noradrenaline, adrenaline and dopamine; the levels were 26·0 ± 10·7, 22·3 ± 4·2 and 11·9 ± 3·5 ng mL^{-1}, respectively, just before the start of the initial constant infusion. These catecholamine levels are of the same order as those found in decapitated rats (Popper et al 1977; Kvetnansky et al 1978). This contrasted with the mean values for these three catecholamines in the saline controls of between 0·4 to 0·8 ng mL^{-1}.

The pharmacokinetic disposition of cocaine after a bolus dose in the presence of raised or normal levels of circulating catecholamines is depicted in Figure 1A. These decay data were best described by a two-compartment open model when the data points were fitted using WinNonlin. Benzoylecgonine formation was significantly less in animals to which catecholamine had been administered than in the saline controls, as measured by the values for area under the concentration–time curves (AUC) which were 36·79 compared with 76·01 μmol min^{-1}, respectively ($P = 0.0184$). This was so despite similar AUC values for the parent compound, cocaine (Table 1) implying similar clearance. Further, the volume of distribution of the central compartment (Vd) and the distribution half-life ($t_{\frac{1}{2}\alpha}$) were lower in the cocaine–catecholamines group, whereas C_{max} was higher; elimination half-life ($t_{\frac{1}{2}\beta}$) values were similar in both groups (Table 1).

The two-stage cocaine infusion regime resulted in significantly higher cocaine concentrations in rats administered catecholamines than in those administered saline (Figure 1B, continuous infusion) whereas benzoylecgonine concentrations were not different (measured using AUC or two-way analysis of variance, although at the 30, 35 and 40 min time points there was a trend ($P = 0.09$) indicating a difference). This early trend showing lower concentrations of benzoylecgonine in rats receiving catecholamines could be expected to be a result of factors operative after a bolus dose of cocaine.

Taking these data together, this study suggests that elevated catecholamine levels reduce the volume of distribution of the central compartment (Vd) (probably by vasoconstriction). This would

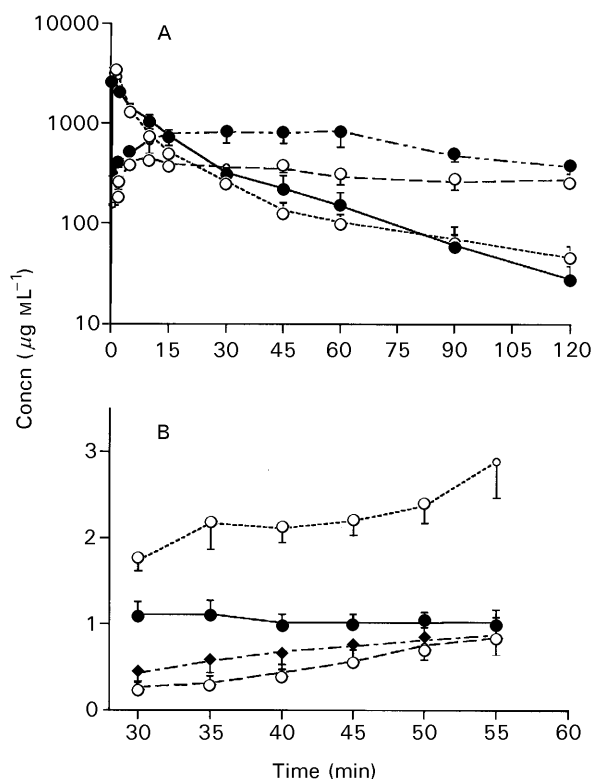

Figure 1. Plasma cocaine and benzoylecgonine concentrations (mean ± s.e.m.) in rats after a bolus dose of cocaine hydrochloride (5 mg kg^{-1}) (A) and during a continuous infusion of 1000 μg kg^{-1} min^{-1} for 5 min and then 100 μg kg^{-1} min^{-1} (B). A. ---○--- Cocaine, —○— benzoylecgonine after a bolus dose of cocaine in seven rats administered a catecholamine infusion, —●—cocaine, --● benzoylecgonine after a bolus dose of cocaine in nine rats which received a saline infusion. B. ---○-- Cocaine, --○– benzoylecgonine in five rats administered a continuous cocaine infusion plus a catecholamine infusion, —●–cocaine, ---●--- benzoylecgonine in five rats which received a continuous cocaine infusion plus a saline infusion.

Table 1. Pharmacokinetic parameters for rats administered a bolus dose of cocaine with a catecholamine (cocaine–catecholamine group) or a saline (cocaine–saline group) infusion.

Parameter	Group		P
	Cocaine–catecholamine	Cocaine–saline	
Vd (L kg^{-1})	1·47 ± 0·21	2·13 ± 0·23	0·024
$t_{\frac{1}{2}\alpha}$ (min)	3·3 ± 0·4	5·9 ± 0·9	0·014
$t_{\frac{1}{2}\beta}$ (min)	26·3 ± 4·1	25·0 ± 3·1	0·78
C_{max} (μg mL^{-1})	3816 ± 417	2463 ± 182	0·003
CL (mL kg^{-1} min^{-1})	146 ± 17	146 ± 16	0·98
Vd_{SS} (L kg^{-1})	3·38 ± 0·43	3·22 ± 0·21	0·71
AUC (ng min^{-1})	36690 ± 3547	38940 ± 5587	0·71

Data are means ± s.e.m. n = 7 for the cocaine–catecholamine group and n = 9 for cocaine-saline group. Vd is the volume of distribution of the central compartment; $t_{\frac{1}{2}\alpha}$ and $t_{\frac{1}{2}\beta}$ are the distribution and elimination half-lives, respectively; CL is the clearance = AUC/dose; Vd_{SS} is the volume of distribution at steady state; AUC is the area under the concentration–time curve.

explain the higher levels of cocaine measured after administration of a bolus dose of 5 mg kg^{-1} compared with the saline group. It would also explain the higher constant concentration over the period 35–50 min (defined as no variation of plasma concentration with time) of 2 μg mL^{-1} (approx.) compared with 1 μg mL^{-1} achieved from an initial loading dose infusion of the same dose (5 mg kg^{-1}) over 5 min followed by a continuous infusion of 100 μg kg^{-1} min^{-1}. This assertion is made on the basis of the observation that after a bolus dose the clearance (dose/AUC) was not different in the presence or absence of elevated catecholamines. Hence, in the absence of the effects of elimination, the smaller the volume of distribution of the central compartment for a given drug, the higher the concentration from a bolus dose or infusion (Hull 1991b).

Elevation of plasma lidocaine concentrations from a continuous lidocaine infusion (100 μg kg^{-1} min^{-1}) upon administration of a continuous infusion of noradrenaline has been demonstrated in monkeys (Benowitz et al 1974). The investigators speculated that this was because of alterations in the volume of distribution and the clearance of lidocaine associated with adrenaline infusion.

In the rat, cocaine (benzoylecgonine methyl ester) is metabolized to norcocaine (Stewart et al 1978) by liver cytochrome P-450IIB1 enzymes (Boelsterli et al 1992), and to benzoylecgonine by specific liver carboxylesterases (Dean et al 1995) and non-enzymatic degradation in plasma (Stewart et al 1979). Ecgonine methyl ester formation occurs as a result of a non-specific liver decarboxylase (Dean et al 1995). Although plasma pseudocholinesterase is responsible for ecgonine methyl ester formation from cocaine in man (Stewart et al 1977), this might not be so in the rat (Stewart et al 1978). Benzoylecgonine seems to be the major cocaine metabolite in the rat, accounting for approximately 60% of the cocaine concentration after prolonged cocaine infusion (Mets & Virag 1995).

In the current study elevated plasma catecholamines were associated with less benzoylecgonine formation after bolus dose cocaine administration and with an initial tendency toward lower concentrations during two-stage continuous cocaine infusion. This occurred in the absence of a difference in cocaine disposition or clearance after a bolus of cocaine. It is not readily apparent why benzoylecgonine metabolism should have been impaired, but it could be because this metabolism occurs in the liver (Dean et al 1995). Catecholamines have been shown to inhibit the rate of hexobarbitone metabolism in an isolated perfused rat-liver model (Boobis & Powis 1974) because of redistribution of perfusate away from the periphery, probably resulting in hepatic hypoxia, a factor known to impair hexobarbitone metabolism. A similar mechanism might explain the impaired formation of benzoylecgonine from cocaine in the current study, because we have demonstrated impaired monoethylglycinexylidide formation, the major metabolite of another local anaesthetic, lidocaine, in the presence of hepatic hypoxia (Mets et al 1993).

However, because the clearance of cocaine was not affected by catecholamine administration (Table 1) despite a decrease in metabolite formation, it is likely that instead of benzoylecgonine formation, the formation of another metabolite was enhanced (Kambam et al 1992). We did not measure other cocaine metabolites in this study and so are unable to confirm this.

Although there are several reports of intravenous cocaine administration in rats (Nayak et al 1976; Wiggins et al 1989; Robinson et al 1994), surprisingly few report data from pharmacokinetic analysis of cocaine disposition which enable comparison with the current study. Booze et al (1997) administered intravenous cocaine in doses of 0·5, 1·0 or 3·0 mg kg^{-1} and established values for $t_{\frac{1}{2}\alpha}$ (< 1 min) and $t_{\frac{1}{2}\beta}$ (approx. 13 min). Levine & Tebbet (1994) administered cocaine at 2 mg kg^{-1} and found $t_{\frac{1}{2}\alpha}$ and $t_{\frac{1}{2}\beta}$ to be 1–2 min and 20 min (approx.), respectively. In the current study we found distribution and elimination half-lives to be 6 and 25 min, respectively, in the saline–control animals. These different half-lives, compared with the quoted studies, and the lower total clearance in

the current study of 146 compared with $200\,\text{mL}\,\text{kg}^{-1}\,\text{min}^{-1}$ (approx.) found in the study of Booze et al (1997) might be attributed to the different durations of bolus dose administration employed and the different plasma cocaine sampling regimens used—Booze et al administrated cocaine bolus doses over 30 s and sampled for only 30 min. In contrast, for fear of toxicity demonstrated in preliminary experiments, we administered bolus doses of cocaine over 2 min and took plasma samples over a period of 120 min.

Conclusions

This study has shown that in a rat model catecholamines infused at levels consistent with extreme stress had significant effects on the pharmacokinetics of administered cocaine. Initial cocaine plasma levels after a bolus dose and during continuous infusion were higher than in saline controls. In addition, the volume of distribution of the central compartment for cocaine was found to be less in these circumstances, explaining the altered plasma cocaine concentrations. Cocaine metabolism to benzoylecgonine, its major metabolite in the rat, was impaired by catecholamine administration, a phenomenon that requires further investigation. These data serve to provide an explanation of the enhanced toxicity of cocaine demonstrated in previous experiments with the rat.

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