

Effects of Cocaine on Rat Embryo Development *in Vivo* and in Cultures

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ABSTRACT. Intraperitoneal injections of 6.25, 12.5, 25, 50, and 100 $\mu\text{mol/kg}$ cocaine into pregnant Sprague-Dawley rats once a day from d 0 to 19 of gestation caused a dose-dependent increase in fetal soft tissue malformations, primarily of the genitourinary tract. At 100 $\mu\text{mol/kg}$, all implants were lost and three of the five animals died after six to seven injections. At 50 and 100 $\mu\text{mol/kg}$ but not at lower doses, cocaine caused a small but significant decrease in body weight and food intake. Cocaine did not affect mean fetal and placental weights, although it increased the number of runts and edematous fetuses, and did not cause skeletal malformations. After intraperitoneal injection of 50 $\mu\text{mol/kg}$, the plasma $t_{1/2}$ of cocaine was 21 ± 5 min and peak plasma concentration (1682 ± 260 pmol/mL, measured by HPLC) was achieved in 5–10 min; a lower peak plasma concentration (486 ± 103 pmol/mL) was achieved in 20–60 min after s.c. injection. Concentrations of dopamine, epinephrine, and norepinephrine in brains of fetuses or newborn pups (<12 h old) of cocaine (50 $\mu\text{mol/kg}$)-treated rats were not significantly elevated. Cocaine injections did not affect gestational duration nor the growth pattern and the locomotor activity of offspring. However, three pups born to one cocaine-treated animal died 20 d after birth. Cocaine inhibited the growth of 10.5-d-old embryos in culture in a concentration-dependent manner and was more toxic than procaine. Approximately 80% of cocaine was metabolized during a 48-h period in embryo culture medium. It is concluded that cocaine possesses teratogenic potential that may be partly independent of maternal toxicity. (*Pediatr Res* 29: 187–190, 1991)

fetuses and newborn pups and locomotor activity of offsprings at 5–7 wk of age were also measured.

MATERIALS AND METHODS

Animals. Sprague-Dawley virgin female rats (Charles River, St. Constant, Quebec, Canada) weighing 200–225 g were maintained on a 12-h light-dark schedule and fed *ad libitum* rat food pellets and tap water. For all *in vivo* studies, females were housed with males during the night. The following morning, sperm-positive rats (d 0 of pregnancy) were placed individually in suspended steel cages and randomly selected to receive once a day between 0900 and 1000 h either an intraperitoneal injection of saline (controls) or cocaine hydrochloride (6.25, 12.5, 25, 50, or 100 $\mu\text{mol/kg}$) from d 0 to 19 of gestation and their body weights and food consumption were recorded. Intraperitoneal route of cocaine administration was selected as a convenient and less stressful alternative to chronic i.v. injections primarily because both these routes yield comparable peak plasma cocaine concentrations (25–28). In the absence of obvious signs of pregnancy, corpora lutea were counted to ascertain pregnancy loss. Rats were anesthetized with ether on the morning of d 20 of gestation; live and dead fetuses, number of runts or edematous fetuses, resorption sites, and fetal and placental weights were recorded (30). However, a number of rats treated with saline or 50 $\mu\text{mol/kg}$ cocaine (d 0–20 of gestation) were allowed to deliver spontaneously and the body weights of offspring were recorded up to 3 wk.

Cocaine pharmacokinetics. Pharmacokinetics of cocaine was determined in 13- to 15-d pregnant rats after intraperitoneal ($n = 6$) and s.c. injection ($n = 5$). For this purpose, a polyethylene cannula (PE30) was placed inside the femoral artery and exteriorized at the back through a s.c. tunnel under ether anesthesia. Approximately 6 h after surgery and recovery from anesthesia, 50 $\mu\text{mol/kg}$ cocaine was injected intraperitoneally or s.c.; blood samples (0.25 mL) were collected at 5, 10, 20, 30, 45, 60, 90, and 120 min after the injection by heparinized syringes into conical tubes containing 1 mg EDTA and 2 mg NaF. Plasma was immediately separated by centrifugation and stored at -80°C .

For the extraction of plasma and assay of cocaine and benzoylecgonine (25), 300 μL acetonitrile was added to 100 μL plasma in a conical 1.5-mL polyethylene tube. The tube was vortexed and centrifuged and the supernatant was transferred to another conical tube to which was added 700 μL chloroform:ethanol (4:1) followed by 70 μL of 0.1 M NaHCO_3 . The tube was vortexed for 30 s and centrifuged. The upper aqueous phase was aspirated off and the remaining organic phase was dried under a stream of nitrogen. To the dry extract was added 30 μL of the mobile phase (0.25 M KH_2PO_4 , 25% acetonitrile, pH 2.7) and the tube was vortexed for 15 s. Standards of cocaine and benzoylecgonine were added to blank rat plasma and subjected to the identical procedure of extraction. Standards and samples were injected into Waters HPLC system (Waters, Mississauga, Ontario). The injection loop was 20 μL . The mobile phase was delivered to a

Cocaine use by pregnant women has been reported to cause a decrease in fetal body weight (1–9), premature delivery (2), genitourinary abnormalities (10, 11), cerebral hemorrhage (12), abruptio placentae (1, 2, 13, 14), behavioral abnormalities (14, 15), ocular complications (16), and so on. In general, animal studies (17–23) have provided support for the clinical data. However, in most animal studies cocaine was administered s.c. or orally (17, 18, 20–24), which would result in a lower peak plasma concentration of a longer duration than would occur after equivalent intraperitoneal (25–27) or i.v. (28) doses. We therefore studied the effects of chronic intraperitoneal injections of cocaine on fetal development. Effects of cocaine on the growth of embryos in culture were studied to find out if cocaine's maternal and fetal toxicity could be dissociated. In view of the reported neurochemical effects of cocaine, especially on the dopaminergic system (29), catecholamine levels in brains of

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μ Bondapak C18 reversed-phase column (300 \times 3.9 mm, 10 μ m, Waters) by Waters pump (model 510) at a flow rate of 2 mL/min. Absorbance was monitored at 235 nm (Waters UV/VIS detector, model 481) and recorded by Waters data module (model 740). Cocaine and benzoylecgonine were quantitated on the basis of peak areas. The retention time for benzoylecgonine and cocaine were 2.64 and 4.83 min, respectively; the sensitivity limit was 0.5 ng (1.5 pmol) for cocaine and 2 ng (\sim 7 pmol) for benzoylecgonine. The efficiency of extraction was 50 \pm 4%.

Examination of fetal soft tissues and skeleton. Day 20 fetuses were either fixed in Bouin's fluid for internal organ examination by free-hand serial razor sectioning or in ethanol for skeletal examination after staining by Alzarin red (30).

Brain catecholamines. For the assay of catecholamines (31), brains from a number of 20-d fetuses or newborn pups (<12 h old) were removed and cerebella discarded. Brains were homogenized with 2 mL Tris buffer (pH 8.6) and centrifuged at 2000 \times g. Catecholamines and the internal standard (4.5 fmol), 3,4-dihydroxybenzylamine, added to the supernatant were adsorbed to activated alumina and the catecholamines from the alumina were eluted with 150 μ L of 0.1 M phosphoric acid; an aliquot of this was used for the assay of catecholamines by HPLC (Waters, pump model 510) using WISP (M712, Waters) injector, a BioRad silica-based weak cation-exchange column (195-6002; BioRad Laboratories, Richmond, CA) with a guard column (195-6003) using a 0.07 M citric acid-acetonitrile (88:12) solvent at a flow rate of 1.3 mL/min. Catecholamines were detected by Waters electrochemical detector (model 460) and quantitated on the basis of the ratio of the peak height generated by authentic amines to that by the internal standard.

Locomotor activity. At 5–7 wk of age, offspring of saline- and cocaine (50 μ mol/kg)-treated rats were tested for their locomotor activity. Animals were placed singly in transparent plastic cages between 0900 and 1200 h in a sound-proof room and the frequency of rearing, cage-crossing, and grooming recorded for 20-s periods with a gap of 10 s between two recordings for a total duration of 15 min; scores were computed for the 1st, 2nd, and 3rd 5-min periods.

Embryo cultures. For these experiments, rats were mated during a 2-h period between 0700 and 0900 h. Embryos (10–12 somite stage) harvested from 10.5-d pregnant rats were cultured for 48 h as described previously (32). Saline or increasing concentrations (1 μ M–1 mM) of cocaine or procaine dissolved in saline were added at the start of the culture. At the end of the incubation, embryo size, mortality (absence of heart beat), and protein content (33) were determined.

Statistics. Two means were compared by *t* test and multiple means by one-way analysis of variance followed by the Bonferroni test for significance. Incidence of fetal mortality or abnormality was compared by χ^2 test.

Chemicals. Cocaine hydrochloride was purchased from BDH, Toronto, Canada. Cocaine base and benzoylecgonine were obtained from the Bureau of Drug Abuse, Health and Welfare, Ottawa, Canada. Dopamine, epinephrine, norepinephrine and 3,4-dihydroxybenzylamine were purchased from Sigma Chemical Co., St. Louis, MO. Only high purity grade chemicals were used for the HPLC.

RESULTS

General effects of cocaine. At 50 to 100 μ mol/kg but not at lower doses (6.25–25 μ mol/kg), cocaine caused a significant decrease in food intake and body weight gain. After 5 to 6 d of treatment, animals appeared excited for 15 to 30 min after receiving cocaine (6.25 to 50 μ mol/kg) injections. After 4 to 5 injections of 100 μ mol/kg cocaine, animals exhibited a sudden loss in body weight, appeared lethargic, and three of the five animals died within 15–30 min after the 6th or 7th injection. When an animal died, the death occurred within 15 to 30 min after injection and was preceded by convulsions. In view of the

obvious toxicity, injections of 100 μ mol/kg cocaine were discontinued and preimplantation loss was recorded in all five animals. No obvious behavioral differences were noted in d-20 fetuses from cocaine-treated or saline-treated rats. There was no difference in the time for spontaneous delivery (\sim 21.5 d) of saline- and cocaine (50 μ mol/kg)-treated rats ($n = 4$, each group).

Pharmacokinetics of cocaine. The peak plasma concentration of cocaine after intraperitoneal injection was 1682 \pm 260 pmol/mL and significantly ($p < 0.001$) greater than that (486 \pm 103 pmol/mL) after s.c. injection. The peak plasma concentration was observed 5 (in five of six rats) to 10 min (in one of six rats) after intraperitoneal injections. On the other hand, peak plasma concentration of cocaine was achieved 20–60 min after s.c. injections (20 min in two, 40 min in two, and 60 min in one of five rats). The plasma $t_{1/2}$ of cocaine after intraperitoneal injection was 21 \pm 5 min. The elimination phase of cocaine after s.c. injection was not discernible and plasma $t_{1/2}$ could not be derived. Although benzoylecgonine peaks were observed in most sample runs, their concentrations were too low to permit quantitation.

Maternal and fetal effects of cocaine. These effects are described in Tables 1 and 2. No skeletal abnormalities were recorded in fetuses of cocaine-treated animals and data are not shown. The body weight of d-20 fetuses ($n = 170$) of saline-treated rats was 3.6 \pm 0.1 g. Fetuses ($n = 160$) of rats treated with 50 μ mol/kg cocaine could be subdivided as overweight (>4 g, $n = 32$), underweight (<3.2 g, $n = 23$), and normal weight (3.2–4 g, $n = 95$). However, there was no significant difference in the mean body weight of all fetuses of saline- and cocaine-treated animals.

Brain catecholamines. Although the dopamine, epinephrine, and norepinephrine concentrations in brains (whole brain minus the cerebellum) of 20-d gestational age fetuses and newborn pups of cocaine-treated rats were higher than the corresponding values for the saline-treated group, the differences were not significant (Table 3).

Offspring growth pattern and locomotor activity. Body weights of offspring born to saline- and cocaine (50 μ mol/kg)-treated rats were, respectively, 6.3 \pm 0.1 and 5.9 \pm 0.3 g on d 1, 16.4 \pm 0.3 and 14.9 \pm 0.5 g on d 7, 30.7 \pm 0.8 and 29.2 \pm 0.5 g on d 14, and 49.2 \pm 0.6 and 49.2 \pm 0.5 g on d 21 after birth. There was no significant difference in the body weights and locomotor activity (Table 4) of the offspring of rats treated during pregnancy with saline or 50 μ mol/kg cocaine.

Effect of cocaine on embryos in culture. Cocaine caused concentration-dependent inhibition of embryo development in culture and was lethal (as judged by the absence of heart beat) to all embryos at a concentration of 300 μ M (Fig. 1). Cocaine was approximately 10-fold more toxic than procaine. The concentration of cocaine at the end of the 48-h culture period was 18 \pm 2% of the initial concentration.

DISCUSSION

Most workers studying cocaine teratogenicity administered the drug s.c. (17, 21–23) or orally (18, 20), which would result in a slower absorption and, in turn, a relatively low peak plasma concentration. Results of this study and a comparison of pharmacokinetic data from other studies (25–28, 34) indicate that this is in fact the case. This may explain why the highest dose of 100 μ mol/kg/d used in our study was far more toxic than 120 to 270 μ mol/kg administered s.c. by other workers (17, 21–23) and why several investigators found little or no effect of s.c. injections of 60 to 120 μ mol/kg cocaine (17, 21–23), whereas we observed significant maternal and fetal toxicity at 25- to 50- μ mol/kg dose levels. It would appear that high concentrations of cocaine for shorter durations are more relevant from a toxicologic point of view (and perhaps better mimic abuse by humans) than lower sustained concentrations.

Our study shows that prenatal exposure to cocaine causes dose-dependent maternal and fetal toxicity. Fetal abnormalities such as urogenital malformation and cerebral hemorrhage are in

Table 1. Maternal and fetal effects of cocaine in rats*

Variables	Cocaine ($\mu\text{mol/kg}$)					
	0	6.25	12.5	25	50	100
<i>n</i>	13	6	6	6	17	5
Day 0 body wt (g)	231 \pm 4	227 \pm 5	235 \pm 4	224 \pm 6	234 \pm 4	227 \pm 4
Day 20 body wt (g)	375 \pm 6	368 \pm 8	374 \pm 8	357 \pm 10	357 \pm 6†	
Food intake (g/d)	23.2 \pm 0.2	23.7 \pm 0.4	22.6 \pm 0.4	22.1 \pm 0.5	20.5 \pm 0.4†	16 \pm 0.4†
Maternal death (<i>n</i>)	0	0	0	0	2†	3†
Litter size (<i>n</i>)	13.1 \pm 0.8	13.1 \pm 0.8	14.8 \pm 0.8	13.0 \pm 0.9	13.3 \pm 0.5	0†
Fetal body wt (g)	3.6 \pm 0.1	3.4 \pm 0.1	3.4 \pm 0.1	3.6 \pm 0.1	3.6 \pm 0.1	
Placental wt (mg)	465 \pm 14	440 \pm 21	431 \pm 17	476 \pm 13	438 \pm 7	
Edematous fetuses (<i>n</i>)	0/170	0/79	0/80	5/63	15/160	
Runs (<i>n</i>)	0/170	2/79	3/89†	2/63	12/160†	
Resorptions (<i>n</i>)	6	9†	1	5	12†	

* Cocaine was injected intraperitoneally once a day from d 0 to 19 of gestation inclusive and animals were killed on d 20; 0 dose refers to saline injections.

† Significantly ($p < 0.05$) different from the corresponding value for the saline-treated animals; data are either means \pm SEM or total numbers.

Table 2. Fetal abnormalities after daily intraperitoneal injections of cocaine in rats from d 0 to 19 of gestation

Variables*	Cocaine ($\mu\text{mol/kg}$)				
	0	6.25	12.5	25	50
Litters examined (<i>n</i>)	13	6	6	5	12
Fetuses examined (<i>n</i>)	37	19	21	18	34
Enlarged bladder	0	3†	6†	5†	9†
Hydronephrosis	2	7†	8†	8†	16†
Cerebral hemorrhage	0	0	0	1	4
Total abnormal fetuses (<i>n</i>)	2	8†	8†	9†	20†

* Refer to fetuses on d 20 of gestation.

† Significantly ($p < 0.05$) different from corresponding values for saline-treated (0 dose of cocaine) animals.

Table 3. Effect of prenatal exposure to cocaine on brain catecholamines of fetuses and newborn pups of rats.

Group*	Dopamine	Epinephrine	Norepinephrine
Fetus—saline	184 \pm 42.2†	5.0 \pm 1.4	147 \pm 37.9
Fetus—cocaine	218 \pm 32.7	20.5 \pm 8.5	163 \pm 20.9
Newborn—saline	196 \pm 24.2	28.6 \pm 7.9	311 \pm 28.4
Newborn—cocaine	242 \pm 18.9	38.0 \pm 11.3	352 \pm 14.8

* Day 20 fetuses or newborn pups (<12 h old) from rats injected with saline or 50 $\mu\text{mol/kg}$ cocaine from d 0 to 19 of gestation; the treatment is indicated in the first column after the hyphen.

† Values are fmol/mg brain protein, mean \pm SEM; $n = 5-8$.

Table 4. Locomotor activity of offspring of rats treated with saline or cocaine (50 $\mu\text{mol/kg}$) intraperitoneally from d 0 to 20 of gestation*

Offspring of rats treated with	Activity	1st 5 min	2nd 5 min	3rd 5 min
Saline	Cage crossing	6.4 \pm 0.5	2.6 \pm 0.3	1.1 \pm 0.3
Cocaine	Cage crossing	7.3 \pm 0.9	3.3 \pm 0.5	1.5 \pm 0.4
Saline	Rearing	24.3 \pm 0.4	13.3 \pm 1.4	6.3 \pm 1.1
Cocaine	Rearing	21.4 \pm 1.8	16.1 \pm 1.7	10.1 \pm 1.5
Saline	Grooming	1.3 \pm 0.5	2.2 \pm 0.5	1.9 \pm 0.6
Cocaine	Grooming	0.9 \pm 0.3	2.5 \pm 0.6	1.9 \pm 0.5

* Activity was recorded at 5-7 wk of age and is shown as the mean \pm SEM of 10 20-s observation periods during the 1st, 2nd, and 3rd 5 min. Data are derived from 17-18 offspring in each group from four separate litters.

agreement with clinical data (10-12). On the other hand, certain effects of prenatal exposure to cocaine in humans such as premature delivery and a decrease in fetal weight (1-9) were not observed in this study; in this sense, rat may not be a perfect

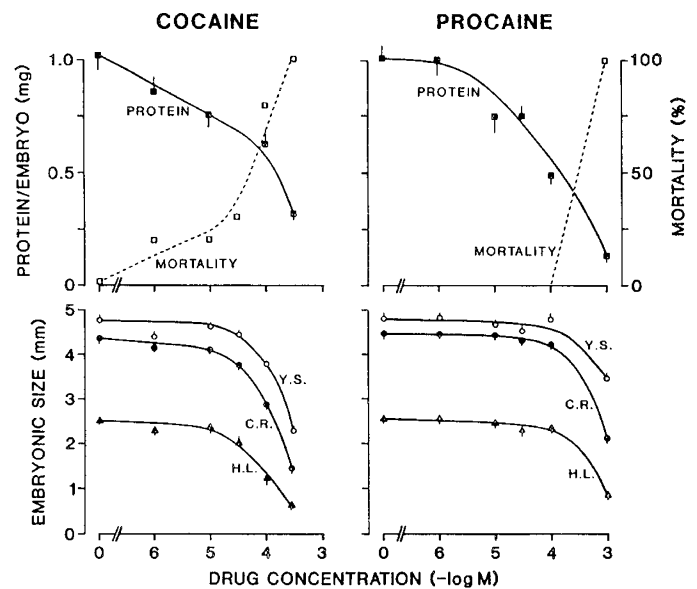


Fig. 1. Effects of cocaine and procaine on the development of rat embryos in culture. Each data point represents mean \pm SEM of five to 10 embryos. *Y.S.*, yolk sac diameter; *C.R.*, crown rump; and *H.L.*, head length; absence of heart beats denoted mortality. Significant ($p < 0.05$) differences (not shown in the figure to avoid overcrowding): effects of cocaine on protein content and mortality were significant at all concentrations; procaine significantly inhibited protein content at $>10^{-5}$ M and was lethal to embryos only at 10^{-3} M; embryonic sizes at $>10^{-5}$ cocaine and $>10^{-4}$ procaine are significantly different from the corresponding values at 0 drug (saline) concentration.

model for the study of cocaine teratogenicity. The lack of difference in body weights of fetuses from saline- and cocaine-treated rats (Table 1) is similar to data of other workers using a rodent model (17, 20-23); however, this may not represent the true picture because some litters of cocaine-treated rats were underweight and some overweight and edematous. Determinants of these variable effects of cocaine on fetal weight are not apparent from our studies.

The lack of a significant effect of prenatal exposure to cocaine on fetal and newborn brain catecholamines (Table 3) and on the locomotor activity of offspring (Table 4) is in conformity with other data (24). Also, chronic cocaine abuse in humans was found to be without effects on circulating catecholamines and lymphocyte adrenoceptors (35). On the other hand, an increase in motor activity of rat offspring exposed to cocaine *in utero* was found by others (22, 23) for a temporary period during suckling but not after weaning.

Our data showing that prenatal exposure to cocaine did not affect the growth pattern of pups is in accordance with other reports using a rodent model (20, 21). On the other hand, death of three pups in one litter from a cocaine-treated mother may be of relevance; we did not encounter any deaths during weaning in a small number of control animals in this series nor in more than 100 litters over the last few years.

It has been argued that the teratogenic effects of cocaine may be due to its ability to decrease placental blood flow and fetal oxygenation (21, 36, 37). Although this is possible, our studies with embryo cultures *in vitro* suggest that cocaine can exert direct fetal toxicity, albeit at concentrations much higher than could have been achieved *in vivo* at the highest dose of 50 $\mu\text{mol/kg}$ used in our studies. Because procaine was also embryotoxic although less so than cocaine, it may be a common property of local anesthetics and the underlying mechanism may be independent of interactions with catecholamines.

In conclusion, this study demonstrates teratogenic potential of prenatal exposure to cocaine and shows that fetal toxicity of cocaine may involve a maternal and a direct fetal component.

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