

© 2002, Acta Pharmacologica Sinica  
ISSN 1671-4083  
Shanghai Institute of Materia Medica  
Chinese Academy of Sciences  
<http://www.ChinaPhar.com>

## Developmental toxicity of cocaine exposure in mid-pregnancy mice<sup>1</sup>

SONG Jun, GUAN Xiao-Wei, REN Jia-Qian<sup>2</sup>, HE Wei<sup>3</sup>

*Department of Histology and Embryology, <sup>2</sup>Institute of Brain Research, China Medical University, Shenyang 110001, China*

**KEY WORDS** pregnancy; cocaine; fetal development; nervous system

### ABSTRACT

**AIM:** To investigate the toxic effects of mid-pregnancy cocaine exposure on embryo-fetus. **METHODS:** A trans-placental murine model of cocaine exposure on embryo-fetus mice was established, in which pregnant dams of comparable weight were assigned into three groups: cocaine with food *ad lib* (COC), saline and pair-fed with COC (SPF), and saline with food *ad lib* (SAL). From embryonic d 8 (E8) to E17, physiological variables of dams and offspring were recorded and concentrations of dopamine and serotonin in fetal striatum were examined. **RESULTS:** Compared with SAL dams, COC and SPF dams showed lower weight gain. But only COC fetuses demonstrated low brain weight and low striatum weight on E17, as well as small biparietal diameter (BPD) on postnatal d1 (P1). Surprisingly, low brain/body weight ratio was seen in COC offspring, which might reflect disproportionate growth delay in these fetuses. Neurotransmitter and histological analysis revealed high level of dopamine and serotonin in COC fetal striatum, as well as morphological alterations of liver. **CONCLUSION:** Mid-pregnancy cocaine exposure induces fetal growth delay in utero, especially disproportionate brain developmental retardation. Maternal undernutrition does not play a key role in fetal developmental retardation when exposed to cocaine in utero.

### INTRODUCTION

Within the last decade, although many investigators have focused on the physical, neurodevelopmental, and neuropsychological effects of prenatal cocaine exposure on infants and young children, many crucial issues are still inconclusive<sup>[1]</sup>. Clinical data suggest that the gestational timing of cocaine exposure relates critically to outcomes, as first trimester exposure to cocaine may result in impaired neonatal behavior<sup>[2]</sup>,

whereas transplacental exposure to cocaine during the later gestational periods may have a higher likelihood of resulting in intrauterine growth retardation, postnatal growth retardation, and cognitive impairments in exposed children through 2-3 a of age<sup>[3,4]</sup>. However, studies on the effects of mid-pregnancy cocaine exposure were very few, because compared with early- and late-pregnancy, mid-pregnancy was a relatively safe period. In current research, we established a transplacental model that permitted control over the timing and frequency of exposure, as well as nutritional factor to investigate the developmental toxicity of mid-pregnant cocaine exposure.

There are a number of candidate mechanisms that can be used to account for toxicity of cocaine exposure on adults. But the mechanism of developmental effects of cocaine on brain is still inconclusive. This

<sup>1</sup> Project supported by the National Natural Science Foundation of China, No. 39970772.

<sup>3</sup> Correspondence to Prof HE Wei.

Phn 86-24-2326-1454. Fax 86-24-2325-4417.

E-mail carolsj1017@sina.com

Received 2001-11-20

Accepted 2002-07-10

study focused on the monoamine system, one to the primary sites of actions of cocaine in the adult. In the developing organism, monoamines play critical trophic roles through all phases of central nervous system (CNS) ontogeny: cell proliferation, neural migration, growth, maturation, and synaptogenesis. Because of their trophic roles in CNS ontogeny, cocaine's effects on developing nervous system may be mediated in part through effects on monoamine system ontogeny<sup>[1]</sup>. Striatum is a major postsynaptic target of dopaminergic projections<sup>[5]</sup>. So striatum dopamine (DA) and serotonin (5-HT) concentrations were measured in fetal mice of all groups by high-performance liquid chromatography (HPLC) on E17. Histological analysis was carried out to value the effects of prenatal cocaine exposure on the whole bodies. The aim of this study was to make the mechanism of mid-pregnancy cocaine exposure on fetuses clearly and provide scientific basis to guide abusive mothers to cut down cocaine dosage during pregnancy and reduce the birth rate of "cocaine babies."

## MATERIALS AND METHODS

**Materials** Cocaine HCl from Qinghai Pharmaceutical Company; octyl sulfate salt, standard dopamine, standard serotonin, and dihydroxybenzylamine (DHBA) from Sigma; HPLC-grade methanol, analysis-grade edetic acid, sodium citric acid, sodium acetic acid, dibutylamine, NaHSO<sub>3</sub>, HCl, and perchloric acid from Tianjin Siyou Company. HPLC system included Waters HPLC 6000A pump, Waters 3.9 mm×15 cm Nova-pak C<sub>18</sub> column (4 μm spheres) and a Waters 464 electrochemical detector.

**Animal preparation** Female KM Mice at 49 d of age were obtained from Animal Laboratories of Shenyang Pharmaceutical University (Grade II, Certificate No 01-012). They were housed at (21±2) °C and on a 12-h light: dark cycle (lights on at 07:00). Females were placed with males at 17:00. The presence of a vaginal sperm plug the following morning defined the beginning of pregnancy (E0). Mice with sperm plug were weighed and caged individually. Pregnant dams of comparable weight were divided into three groups: cocaine HCl (COC) group, saline (SAL) group, and saline and pair-fed with cocaine group (SPF). From E1 to E7, all dams were treated identically, with food and water *ad lib*. COC and SAL groups were allowed free access to the diet from E8 to term, but each dam in the SPF group was only allowed to the same amount of food consumed on the same day of paired animals in

COC group<sup>[6]</sup>.

**Protocol** Dams in the COC group (sc in the region of the nape of the neck back) treated with cocaine HCl 20 mg/kg twice daily, at 07:00 and 19:00 from E8 to E12 inclusive. SPF and SAL mice received injections of 0.9 % physiological saline solution 20 mL·kg<sup>-1</sup>·d<sup>-1</sup> following the same schedule. On E17, all dams of three groups were sacrificed. Cocaine 2 g/L was dissolved in physiological saline and the cocaine dose was initially determined according to prior study in rodent<sup>[7]</sup>.

On E17, dams were anesthetized and fetuses were rapidly removed and weighed. After decapitated on ice, fetal brains were obtained and weighed, and striatum were separated and weighed. Striatum samples were frozen and stored at -70 °C till analysis. Some fetal brain tissues were collected for histological procedures.

All dams were weighed daily from E8 to E17. Diet consumption was recorded daily for the COC and SAL groups. Gestational length and abortion rate were recorded for each dam. On E17 the number of whole fetus and live fetus was recorded and the number of whole pups and live pups, pup weight, and biparietal diameter (BPD), measured with a micrometer placed in front of the external auditory meati, were recorded on P1 (postnatal d 1).

**Histological analysis** After observation for gross pathology, placenta, and fetal livers were dissected and fixed in 4 % buffered paraformaldehyde. Following dehydration, the tissues were embedded in paraffin, sectioned at 5 μm, mounted, and stained with hematoxylin and eosin. The histologies were read blind to route of cocaine administration.

**HPLC analysis** To determine the effects of pregnancy cocaine exposure on fetal neurotransmitters *in vivo*, levels of striatal DA, and 5-HT were analyzed by HPLC with electrochemical detector. Prior to homogenization, 100 μL ice-cold homogenate buffer was added to the vial containing 100 mg striatal tissue samples. Homogenate buffer included perchloric acid 0.16 mol/L containing 0.02 % edetic acid and dihydroxybenzylamine (DHBA) as the internal standard<sup>[8]</sup>. Homogenates were centrifuged at 15 000×g for 30 min at 4 °C. The supernatant was transferred to a new vial and used for HPLC assay. Mobile phase was prepared by adding methanol and HPLC-grade water (1:8) containing edetic acid 0.283, sodium citric acid 20, sodium acetic acid 50, and dibutylamine 3.5 mmol/L, adjusted pH to 3.7 with HCl. Mobile phase was pumped at am-

bient temperature at a rate of 0.7 mL/min and recycled during use but made fresh each week. Peak areas were measured and referenced to the peak areas of various concentrations of the standards, which were chromatographed randomly during the assay of the tissue samples. DA and 5-HT were expressed as nanograms per gram of tissue wet weight for fetal brain.

**Statistical analysis** ANOVA, Student's *t*-test, and  $\chi^2$ -test were used to determine statistical significance.  $P < 0.05$  was considered significant. All data were expressed as mean  $\pm$  SD.

## RESULTS

**Effects of mid-pregnancy cocaine exposure on the mothers** ANOVA test indicated that there was a significant effect of prenatal treatment on gestational weight gain from E8 to E12 in COC group ( $P < 0.01$ ), but not from E13 to E17. SAL dams gained significantly more weight than SPF and COC dams; SPF dams gained a little more weight than COC dams through E8-12. *t*-test revealed that cocaine given twice daily for 5 d (E8-12) reduced food intake: COC (24  $\pm$  6) g, SAL (39  $\pm$  5) g,  $P < 0.01$ . Significant differences across groups in gestational lengths were not observed ( $P > 0.05$ ). Compared with SAL and SPF dams, COC dams had absolutely higher abortion rate than SAL and SPF: four COC dams aborted during pregnancy after cocaine injection (Tab 1).

**Tab 1. Effect of pregnancy cocaine treatment on mothers. Mean  $\pm$  SD. <sup>a</sup> $P > 0.05$ , <sup>c</sup> $P < 0.01$  vs SAL (SNK and *t*-test). <sup>a</sup> $P > 0.05$ , <sup>f</sup> $P < 0.01$  vs SPF (SNK and  $\chi^2$ ).**

Group	<i>n</i>	WG/g E8-12	WG/g E13-17	FI/g E8-12	FI/g E13-17	GL/d	Pa/ %
SAL	18	6.4 $\pm$ 1.3	16 $\pm$ 3	39 $\pm$ 5	39 $\pm$ 6	19.0 $\pm$ 0.4	6
SPF	19	2.6 $\pm$ 0.3 <sup>c</sup>	17.0 $\pm$ 1.4			18.8 $\pm$ 0.5	5 <sup>a</sup>
COC	16	2.5 $\pm$ 0.4 <sup>cd</sup>	17.1 $\pm$ 2.4	24 $\pm$ 6 <sup>c</sup>	41 $\pm$ 5	18.6 $\pm$ 0.3	25 <sup>cf</sup>

WG: weight gain; FI: food intake; GL: gestational length; Pa: percentage abortion.

**Effects of mid-pregnancy cocaine exposure on embryo-fetus body and brain growth** On E17, litter size through three groups was similar, but the ratio of dead and dysplastic fetuses in COC group was much higher than controls ( $P < 0.01$ ). In spite of low brain

weight and striatum weight, COC offspring had nearly normal body weight compared with SAL and SPF offspring. And there was no significant difference in brain and striatum weight between SAL and SPF fetuses,  $P > 0.01$ . Examination revealed no significant difference on the ratio of striatum and brain weight among SAL, SPF, and COC offspring. As for the ratio of brain and body weight, it was 1:19 in COC group, which was a bit lower than that of others ( $P < 0.05$ , Tab 2).

**Tab 2. Effect of prenatal treatment on fetal body weight, brain weight, and striatum weight on E17. *n* = 7 litters. Mean  $\pm$  SD. <sup>a</sup> $P > 0.05$ , <sup>b</sup> $P < 0.05$ , <sup>c</sup> $P < 0.01$  vs SAL ( $\chi^2$  and SNK); <sup>e</sup> $P < 0.05$ , <sup>f</sup> $P < 0.01$  vs SPF ( $\chi^2$  and SNK).**

Group	LS	Rdd	BoW/g	BrW/mg	SW/mg	b/b	s/b
SAL	11 $\pm$ 3	1:19	1.27 $\pm$ 0.11	74 $\pm$ 5	10.5 $\pm$ 1.9	1:17	1:7.4
SPF	10.1 $\pm$ 1.4	1:36 <sup>a</sup>	1.29 $\pm$ 0.08	73 $\pm$ 2 <sup>a</sup>	10.1 $\pm$ 1.4 <sup>a</sup>	1:17 <sup>a</sup>	1:7.4
COC	11.2 $\pm$ 1.5	1:6 <sup>cf</sup>	1.21 $\pm$ 0.14	64 $\pm$ 5 <sup>cf</sup>	8.1 $\pm$ 0.7 <sup>cf</sup>	1:19 <sup>bc</sup>	1:7.8

LS: litter size; Rdd: ratio of dead and dysplastic fetuses; BoW: body weight; BrW: brain weight; SW: striatum weight; b/b: brain/body weight; s/b: striatum/body weight.

On P1, litter size was unaltered by prenatal cocaine exposure (COC: 11  $\pm$  3; SPF: 11.2  $\pm$  2.1; SAL: 10.7  $\pm$  1.7). Moreover, body weight of all pups was examined and no difference was found among these groups ( $P > 0.05$ ). Separate one-way ANOVA indicated significantly main effects of treatment on biparietal diameter. SAL and SPF pups had wider biparietal diameters than COC pups on P1 ( $P < 0.01$ , Tab 3).

**HPLC analysis data** DA concentrations in the striatum of fetuses were increased by cocaine expo-

**Tab 3. Effect of prenatal treatment on offspring body weight and BPD on P1. Mean  $\pm$  SD. <sup>a</sup> $P > 0.05$ , <sup>c</sup> $P < 0.01$  vs SAL ( $\chi^2$  and SNK). <sup>f</sup> $P < 0.01$  vs SPF ( $\chi^2$  and SNK).**

Group	<i>n</i>	LS	Rdd	BoW/g	BPD/mm
SAL	10	10.7 $\pm$ 1.7	1:50	2.14 $\pm$ 0.07	10.2 $\pm$ 0.7
SPF	11	11.2 $\pm$ 2.1	1:41 <sup>a</sup>	2.11 $\pm$ 0.05	10.1 $\pm$ 0.6 <sup>a</sup>
COC	5	11 $\pm$ 3	1:9 <sup>cf</sup>	2.13 $\pm$ 0.06	9.1 $\pm$ 0.3 <sup>cf</sup>

LS: litter size; Rdd: ratio of dead and dysplastic fetuses; BoW: body weight; BPD: biparietal diameter.

sure (SAL: 61 ng/g $\pm$ 6 ng/g; SPA: 58 ng/g $\pm$ 9 ng/g; COC: 85 ng/g $\pm$ 10 ng/g); COC group fetuses also had higher concentration of 5-HT than SPF and SAL groups ( $P<0.01$ ). And there was no significant difference between SPF and SAL groups ( $P>0.05$ , Tab 4).

**Tab 4. Prenatal treatment on the concentrations of DA and 5-HT in fetal striatum.  $n=7$  litters. Mean $\pm$ SD. <sup>a</sup> $P>0.05$ , <sup>c</sup> $P<0.01$  vs SAL (SNK); <sup>f</sup> $P<0.01$  vs SPF (SNK).**

Group	DA/ng·g <sup>-1</sup>	5-HT/ng·g <sup>-1</sup>
SAL	61 $\pm$ 6	192 $\pm$ 22
SPF	58 $\pm$ 9 <sup>a</sup>	170 $\pm$ 21 <sup>a</sup>
COC	85 $\pm$ 10 <sup>cf</sup>	284 $\pm$ 30 <sup>cf</sup>

**Histological examination analysis** Examination revealed no overt gross pathology of any organ for mice exposed to cocaine. Histopathological examinations, however, distinguished COC fetuses from saline-injected mice. The most common hepatocellular pathology associated with cocaine included less number of normal hepatocytes, and the deterioration of the architecture of the hepatic lobules and cords. No pathological changes of placenta in COC offspring was observed.

## DISCUSSION

Considerable attention has been given to the impact on the developing fetuses and newborn when women abuse cocaine during pregnancy. But it is unclear that whether mid-pregnancy cocaine exposure has the same severe effects on fetal development as early- and late-pregnancy exposure. Knowing this information will facilitate the clearness of cocaine exposure on fetuses developmentally. In current research, we selected brain, liver, and placenta as target organs to investigate the effects of mid-pregnancy cocaine exposure on the fetuses in order to provide academic basis to guide abusive mother to cut down cocaine exposure during pregnancy and to reduce the birth rate of “cocaine babies.”

Our result of impaired maternal food ingestion and weight gain in COC group, and low weight gain in SPF dams from E8 to E12 was consistent with our previous findings. When stopped injecting with cocaine from E13 to E17, compared with SAL dams, COC dams showed normal food consumption and weight gain,

suggesting cocaine could inhibit maternal appetite and decrease food intake. The repetitive dosing of cocaine in our model led to decreased food intake, which was the most likely explanation for comprise in gestational weight gain in COC dams.

Prior experiments in mice had validated that the safety of the sc route of cocaine administration was up to 60 mg·kg<sup>-1</sup>·d<sup>-1</sup> [9]. Our mouse model followed the same regimen of cocaine 40 mg·kg<sup>-1</sup>·d<sup>-1</sup> sc as others, and revealed higher abortion percentage and ratio of dead and dysplastic offspring in COC group than controls, suggesting mid-pregnancy cocaine exposure could increase fetal wastage by some unclear mechanisms. Whether it was the result of cocaine-induced vasoconstriction or the toxicological effects of cocaine remained to be determined.

It has been difficult to rule out the contribution of maternal undernutrition to the observed reduction in birth weights of cocaine-exposed babies. However, we used the pair-fed group (SPF) to make it easy to clarify the effect of nutritional factor. In our study, reductions of fetal brain and striatum weight were not observed for the fetuses of SPF dams which exhibited attenuated weight gains during pregnancy similar to that of cocaine-injected dams. A number of reports have indicated that offspring development, particularly the brain, is frequently maintained at the expense of dam under conditions of substantial undernutrition<sup>[10]</sup>. Based on these results we concluded the toxicological effects of cocaine might play an important role in the reductions of fetal brain and striatum weight, but not maternal undernutrition.

In our model, COC offspring demonstrated significantly lower brain weight, striatum weight (E17), as well as smaller BPD (P1) than SAL and SPF offspring. Additionally, low E17 brain/body weight ratio was only observed in COC fetuses, suggesting that when exposed to cocaine in mid-pregnancy, the impairment of nervous system was more severe than the other systems, and brain growth delay was a marker of gestational cocaine exposure. It was likely that cocaine-induced reductions in brain weight and BPD were the result of decreased striatal volume, because the striatum represented the largest contributor to this measure.

There were a number of candidate mechanisms that could be used to account for toxicity of cocaine exposure on adult brain, and dopaminergic system in striatum had been demonstrated important in the rein-

forcing effects of cocaine. However, the mechanism of developmental effects of cocaine on brain was still inconclusive. Our purpose of assessing concentrations of DA and 5-HT in the fetal striatum was to determine if cocaine affected fetal brain by impairment of monoaminergic system. Neurotransmitter analysis indicated high concentrations of dopamine and serotonin in COC offspring compared with SAL and SPF offspring. However, cocaine-induced increasing of serotonin was higher than that of dopamine, suggesting serotonin system was much more sensitive than dopamine system when exposed to cocaine in utero. Because serotonin plays an important role in the normal development of the CNS, including neuronal differentiation<sup>[11-13]</sup>, neural cell migration, synaptogenesis<sup>[14,15]</sup>, and release of glial-derived growth factor S100 $\beta$ , we speculated prenatal cocaine exposure impaired brain development through some unclear mechanisms mediated by monoaminergic system, especially by serotonin.

Histological analysis revealed morphological alterations in liver of COC fetuses, including less number of normal hepatocytes and the deterioration of the architecture of the hepatic lobules and cords, but no pathological alterations were seen in placenta. This result was inconsistent with our prior studies, in which cocaine exposure was from E8 to E17 at the dose of 20 mg·kg<sup>-1</sup>·d<sup>-1</sup> and morphological changes in both liver and placenta were observed. It might be different cocaine injection timing that led to this effect. We inferred mid-pregnancy cocaine exposure could cause hepatic damage, and morphological changes of placenta were "transient," but impairments of liver were relatively "persistent." One explanation to hepatic damage being "persistent" was that cocaine had been metabolized and resorted in liver for some time.

In general, though mid-pregnancy is a relatively safe period compared with early and later gestational periods, cocaine mid-pregnancy exposure still leads to fetal growth retardation. This developmental delay is not a paralleled process, because brain impairment is more severe than the whole body impairment, and serotonin system is more sensitive than dopamine system. Maternal undernutrition is not a critical factor in impacts of cocaine exposure on fetuses in utero.

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妊娠中期可卡因对小鼠的发育毒性<sup>1</sup>

宋 君, 关晓伟, 任嘉谦<sup>2</sup>, 何 威<sup>3</sup>

(中国医科大学组胚教研室,<sup>2</sup> 脑研究所, 沈阳 110001, 中国)

**关键词** 妊娠; 可卡因; 胎儿的发育; 神经系统

**目的:** 探讨可卡因对小鼠妊娠中期的发育毒性, 尤其是对脑发育的影响. **方法:** 建立妊娠中期给药的小鼠动物模型, 体重相近的妊娠母鼠被分为三组: (1) 可卡因注射自由饮食组(COC); (2) 盐水注射伴有饮食对照组(SPF), 饮食参考体重相近、妊娠时间相同的COC组母鼠; (3) 盐水注射自由饮食组(SAL). 从妊娠第8天(E8)至第12天(E12)给药, 记录母鼠、胎鼠和仔鼠的各项生理指标, 并用HPLC分析各组胎鼠纹状体中多巴胺、5-HT含量的变化. **结果:** 尽管COC和SPF组母鼠与SAL组母鼠相比摄食量少, 体重增加量少, 但E17天取材时, 仅COC组胎鼠表现为脑

和纹状体重量低; COC组仔鼠生后第1天(P1)双顶径(BPD)也小于其它两组仔鼠. 此外, COC组胎鼠表现出脑/体重比的降低, 说明宫内暴露可卡因引起的胎鼠的发育迟缓是一个不平衡过程, 脑组织的受累比其它组织严重. 神经递质分析和组织学分析表明COC组胎鼠脑内多巴胺和5-羟色胺的水平增高, 肝脏呈现出形态学改变. **结论:** 妊娠中期暴露可卡因可引起胎鼠宫内发育迟缓, 尤其是脑发育迟缓. 单纯母体营养不良在宫内暴露可卡因引起的后代发育迟缓过程中不能起决定性作用, 而可能是药物直接作用的结果.

(责任编辑 韩向晖)

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## Chinese Journal of New Drugs and Clinical Remedies

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