British Journal of Pharmacology (2005) 144, 887–888
www.nature.com/bjp

CLINICAL COMMENTARY

Postnatal consequences of prenatal cocaine exposure and myocardial apoptosis: does cocaine *in utero* imperil the adult heart?

*,[1]Qingping Feng

[1]Departments of Medicine, Physiology and Pharmacology, Lawson Health Research Institute, London Health Sciences Centre, University of Western Ontario, London, Ontario, Canada

Cocaine use is common among pregnant women with a history of substance abuse, and has been shown to cause abnormalities in the heart during fetal and postnatal development. However, mechanisms underlying the detrimental effects of cocaine on the developing heart are not fully understood. In this issue, Bae and Zhang show that prenatal cocaine exposure increases the susceptibility of the postnatal heart to ischemia and reperfusion injury. Their results suggest that myocardial apoptosis induced by cocaine during fetal development may represent one of the mechanisms by which prenatal cocaine exposure exerts its long-term, deleterious consequences on postnatal cardiac function.
British Journal of Pharmacology (2005) **144,** 887–888. doi:10.1038/sj.bjp.0706130
Published online 31 January 2005

Keywords: Cocaine; apoptosis; heart development; myocardial ischemia and reperfusion

Substance abuse is a very common problem in the developed countries. According to the 2002 National Survey on Drug Use and Health conducted by Substance Abuse and Mental Health Services Administration (SAMHSA) in the United States, approximately 2 million Americans aged 12 and older are regular cocaine users. More than 3% of women are reported using an illicit drug—including cocaine—during pregnancy. This represents tens of thousands of cocaine-exposed babies born every year. Most common problems with these babies include low birth weight, abnormalities in the liver, lungs, genitals and neurological system. Cardiac malformations include atrial and ventricular septal defects, hypoplastic right or left side of the heart, and absent ventricle (Plessinger & Woods, 1998). In addition, prenatal cocaine exposure is associated with coarctation of the aorta, peripheral pulmonary stenosis, patent ductus arteriosus, aortic valve prolapse, and arrhythmias (Lipshultz *et al*., 1991; Plessinger & Woods, 1998). In some children, these cardiovascular abnormalities are associated with congestive heart failure, cardiorespiratory arrest and death (Gintautiene *et al*., 1990).

Cocaine is a monoamine reuptake blocker, which interferes with catecholamine and serotonin uptake in catecholaminergic and serotonergic neurons (Knuepfer, 2003). It has been well-documented that inhibition of catecholamine reuptake is responsible for many of the cardiovascular effects of cocaine while inhibition of serotonin reuptake is believed to be important in its euphoric effects. Acute administration of cocaine increases peripheral vascular resistance, coronary vasoconstriction and arterial pressure. Cocaine also increases cardiac contractility and myocardial oxygen demand with an increase or no change in heart rate. Owing to the low molecular weight (MW = 303.4), cocaine can readily cross the placenta into the fetal circulation. Thus, when a pregnant woman uses cocaine, the placenta and fetus are affected with detrimental consequences. Numerous reports have documented an increased risk for placental abruption with cocaine use (Plessinger & Woods, 1998). Decreased blood flow in the placenta may reduce oxygen and nutrients to the fetus, which may be responsible for fetal growth retardation and congenital malformations following prenatal exposure of cocaine. However, the cellular and molecular mechanisms responsible for cocaine-induced fetal abnormalities are not fully clear. Recent studies from Zhang's laboratory showing that cocaine induces apoptosis in the fetal rat heart provide insights into the understanding of cocaine's cardiac effects *in utero* (Xiao *et al*., 2001; Li *et al*., 2004).

Apoptosis, a form of programmed cell death or cell 'suicide', is believed to be responsible for the deletion of unwanted cells during organ and tissue development. Apoptosis is an energy-requiring molecular suicide program characterized by cytoplasmic shrinkage, nuclear condensation, and DNA fragmentation of multiples of ~200 bp (Jacobson *et al*., 1997). A key phenomenon of apoptotic cell death is the activation of a unique class of cysteine proteases named caspases that specifically cleave a number of cellular substrates (Cohen, 1997; Haunstetter & Izumo, 1998). Caspase activation is a prerequisite step in the sequence of events leading to DNase activation that cleaves DNA. Death receptor related signal transduction and cytochrome *c* release from the mitochondria represent two major pathways by which caspase-8 and -9 are activated, respectively (Cohen, 1997; Haunstetter & Izumo, 1998). In this regard, cocaine has recently been shown to downregulate Bcl-2 and increase caspase-9 but not caspase-8 activity in cardiomyocytes, suggesting that cocaine induces cardiomyocyte apoptosis through mitochondrial pathway (Li *et al*., 2004).

Morphogenesis and developmental remodeling of cardiovascular tissues involve coordinated regulation of cell proliferation and apoptosis (Fisher *et al*., 2000). During early embryonic and postnatal development, low or physiological levels of apoptosis contribute to normal heart development.

*Author for correspondence; E-mail: qfeng@uwo.ca
Published online 31 January 2005

This is a highly regulated process as excessive apoptosis may result in congenital heart defects and postnatal heart failure (Pexieder, 1975; Feng *et al*., 2002). More recently, Wencker *et al*. (2003) have provided definitive evidence for a causal relationship between ongoing low levels of cardiomyocyte apoptosis and development of heart failure. Using a transgenic mouse model that expresses a conditionally active caspase exclusively in the myocardium, they demonstrated that ongoing low levels of myocyte apoptosis (23 myocytes per 10^5 nuclei) are sufficient to cause a lethal, dilated cardiomyopathy (Wencker *et al*., 2003). Thus, excessive myocardial apoptosis may cause cardiac abnormalities at both fetal and postnatal stages.

In this issue of the *British Journal of Pharmacology*, Bae & Zhang (2005) demonstrated that prenatal cocaine exposure significantly increases the susceptibility of the postnatal heart at day 30 to ischemia and reperfusion injury by increasing myocardial infarct size and decreasing postischemic recovery of left ventricular function. This novel finding suggests that prenatal cocaine exposure impairs the ability of the heart to fight against an ischemic insult at postnatal life, which may have detrimental consequences. Notably, this effect occurs at the doses of cocaine that do not cause any major structural or functional changes in the heart at basal conditions. If this result can be extrapolated to humans, it will have profound clinical implications. It means that, in babies with prenatal cocaine exposure, even if they are born with normal cardiac structure and function, they may be more susceptible to ischemic injuries in their adult life.

Mechanisms underlying the increased susceptibility to ischemic and reperfusion insult in the postnatal hearts with prenatal cocaine exposure are not clear, and are likely to be multiplex as these investigators suggested (Bae & Zhang, 2005). Previous work from Zhang laboratory showed that cocaine induces myocardial apoptosis in fetal rat hearts (Xiao *et al*., 2001). The present study extends this observation to the postnatal rat hearts. They showed that prenatal cocaine exposure increased myocardial apoptosis in postnatal hearts at day 30, suggesting prenatal cocaine exposure has long-term consequences in cardiomyocyte survival. It is possible that cocaine exposure during fetal development may cause *in utero* programming of apoptotic pathways, leading to persistent myocardial apoptosis in postnatal hearts. Cocaine-induced myocardial apoptosis may represent one of the mechanisms responsible for the increased susceptibility of the heart to ischemia and reperfusion injury in postnatal life. Therefore, this study showed for the first time an interesting association (but not a cause–effect relationship) between myocardial apoptosis and increased susceptibility of the heart to ischemia and reperfusion injury in the postnatal hearts with prenatal cocaine exposure. Since persistent myocardial apoptosis leads to the development of heart failure as demonstrated by recent studies (Wencker *et al*., 2003), the increased myocardial apoptosis caused by prenatal cocaine exposure may have deleterious long-term consequences on cardiac function.

Despite this interesting work by Bae & Zhang (2005), many questions remain unanswered. For example, is the total number of cardiomyocytes in the heart decreased as a result of myocyte apoptosis? Does cocaine affect myocyte proliferation in the fetal heart? Can the increased susceptibility of the heart to ischemia and reperfusion injury in postnatal life be restored by inhibition of myocardial apoptosis? Experiments that address this question may establish a causal relationship between apoptosis and cocaine-induced cardiac consequence. Furthermore, does prenatal cocaine exposure increase myocardial necrosis? If it does, what is the relative contribution to the increased susceptibility to ischemia and reperfusion injury in these animals? Prenatal cocaine exposure also induced myocyte hypertrophy, which increases the vulnerability of the heart to the ischemic insults. It is not clear the relative contribution of myocyte hypertrophy vs apoptosis to the cocaine-induced effects in the heart. Answers to these questions may further increase our understanding on the cardiac consequences of prenatal cocaine exposure.

References

BAE, S. & ZHANG, L. (2005). Prenatal cocaine exposure increases apoptosis of neonatal rat heart and heart susceptibility to ischemia/reperfusion injury in one-month-old rat. *Br. J. Pharmacol*., **144,** 900–907 (this issue).

COHEN, G.M. (1997). Caspases: the executioners of apoptosis. *Biochem. J.,* **326,** 1–16.

FENG, Q., SONG, W., LU, X., HAMILTON, J.A., LEI, M., PENG, T. & YEE, S.P. (2002). Development of heart failure and congenital septal defects in mice lacking endothelial nitric oxide synthase. *Circulation,* **106,** 873–879.

FISHER, S.A., LANGILLE, B.L. & SRIVASTAVA, D. (2000). Apoptosis during cardiovascular development. *Circ. Res.,* **87,** 856–864.

GINTAUTIENE, K., LONGMORE, W., ABADIR, A.R., GOY, G.R., BERMAN, S., LEVENDOGLU, H. & GINTAUTAS, J. (1990). Cocaine-induced deaths in pediatric population. *Proc. West Pharmacol. Soc.,* **33,** 247–248.

HAUNSTETTER, A. & IZUMO, S. (1998). Apoptosis: basic mechanisms and implications for cardiovascular disease. *Circ. Res.,* **82,** 1111–1129.

JACOBSON, M.D., WEIL, M. & RAFF, M.C. (1997). Programmed cell death in animal development. *Cell,* **88,** 347–354.

KNUEPFER, M.M. (2003). Cardiovascular disorders associated with cocaine use: myths and truths. *Pharmacol. Ther.,* **97,** 181–222.

LI, G., XIAO, Y. & ZHANG, L. (2004). Cocaine induces apoptosis in fetal rat myocardial cells through the p38 MAPK and mitochondrial/cytochrome *c* pathways. *J. Pharmacol. Exp. Ther*., [E-pub ahead of print] doi:10.1124/jpet.104.073494.

LIPSHULTZ, S.E., FRASSICA, J.J. & ORAV, E.J. (1991). Cardiovascular abnormalities in infants prenatally exposed to cocaine. *J. Pediatr.,* **118,** 44–51.

PEXIEDER, T. (1975). Cell death in the morphogenesis and teratogenesis of the heart. *Adv. Anat. Cell Biol.,* **51,** 1–99.

PLESSINGER, M.A. & WOODS Jr, J.R. (1998). Cocaine in pregnancy. Recent data on maternal and fetal risks. *Obstet. Gynecol. Clin. N. Am.,* **25,** 99–118.

WENCKER, D., CHANDRA, M., NGUYEN, K., MIAO, W., GARANTZIOTIS, S., FACTOR, S.M., SHIRANI, J., ARMSTRONG, R.C. & KITSIS, R.N. (2003). A mechanistic role for cardiac myocyte apoptosis in heart failure. *J. Clin. Invest.,* **111,** 1497–1504.

XIAO, Y., XIAO, D., HE, J. & ZHANG, L. (2001). Maternal cocaine administration during pregnancy induces apoptosis in fetal rat heart. *J. Cardiovasc. Pharmacol.,* **37,** 639–648.

(Received November 12, 2004
Revised November 23, 2004
Accepted December 1, 2004)