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Short- and long-term adverse effects of cocaine abuse during pregnancy on the heart development

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Abstract

The effect of cocaine on the developing fetus is a topic of considerable interest and debate. One of the potential effects of fetal cocaine exposure is damage to the developing heart. This review provides an overview of the current understanding of the short- and long-term effects of fetal cocaine exposure on the heart in both humans and animal models. Human studies are still preliminary but have suggested that fetal cocaine exposure impacts on the developing heart. Studies in animal models provide strong evidence for a programming effect resulting in detrimental long-term changes to the heart induced by fetal cocaine exposure. In the rat model, fetal cocaine results in apoptosis in the term heart, left ventricular remodeling and myocyte hypertrophy, as well as increased sensitivity to ischemia/reperfusion injury in the adult male offspring. The rat model has also shown evidence of epigenetic modifications in response to intrauterine cocaine. Increased DNA methylation of promoter regions leads to a long-term decrease in the expression of the cardioprotective gene, PKCε. The current data shows fetal cocaine exposure has significant immediate and long-term cardiac consequences in animal models and while human studies are still incomplete they suggest this phenomenon may also be significant in humans exposed to cocaine during development.

Keywords

fetal; programming; cocaine

Introduction

Despite massive government spending to combat illicit drug use (‘the war on drugs’), cocaine abuse remains widespread and its use among women of childbearing age is prevalent in the United States. Currently it is estimated that prevalence of cocaine abuse in the United States is 2.8% in the general population [United Nations Office on Drugs and Crime, 2006]. Although there have been numerous studies of the effects of cocaine on the adult heart, studies of cocaine on the fetal heart and its potential pathophysiologic consequences of cardiac function in offspring are limited. In addition to neurobehavioral effects, offspring born to mothers with a history of cocaine abuse have a high incidence of congenital cardiovascular malformations, including abnormalities of ventricular structure and function, arrhythmias, and intracardiac conduction abnormalities, which persist beyond the period of exposure to cocaine [Mone *et*

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al. 2004; Frassica *et al.* 1994; Mehta *et al.* 1993; Norris and Hill, 1992; Lipshultz *et al.* 1991; Shaw *et al.* 1991; Wiggins, 1992; Van de Bor *et al.* 1990]. Cocaine crosses the placenta and the maternal use of cocaine results in a rapid distribution of the drug to fetal tissues with several times higher concentrations in organs than in blood [Schenker *et al.* 1993; Wiggins, 1992; Klein *et al.* 1992; DeVane *et al.* 1989; Poklis *et al.* 1985]. Thus, it is very likely that cocaine has direct toxic effects on the fetal heart. While human studies are limited, recent animal studies have shown that maternal cocaine administration during gestation increases apoptosis in the term fetal heart, causes cardiac remodeling with myocyte hypertrophy in the left ventricle during postnatal development, and increases heart susceptibility to ischemia and reperfusion injury in adult male offspring in a gender-dependent manner [Bae and Zhang, 2005].

Human studies

Determining the extent of damage caused to a developing fetus when it is exposed to cocaine during gestation is a topic of interest and some controversy. Many assumptions about the effects of cocaine on fetal development leading to the label ‘crack babies’ have been found to be vastly overstated or largely due to other prenatal and postnatal environmental factors [Frank *et al.* 2001]. Despite these findings, fetal cocaine exposure is not without consequence. Evaluating the wide range of studies on all the possible consequences of prenatal cocaine exposure is beyond the scope of this article but other articles provide insight [Schiller and Allen, 2005]. Of natural interest to the field of cardiology is both the short-term and long-term effects of cocaine on the developing heart.

Growing epidemiological evidence shows that a person can be predisposed to heart disease in adult life as a result of an adverse intrauterine environment [Barker, 2000, 1997; Forsen *et al.* 1999; Leon *et al.* 1998; Stein *et al.* 1996; Barker *et al.* 1993, 1989]. A variety of insults can result in an adverse intrauterine environment that either animal studies or human studies have shown leads to an increased risk of adult heart disease. These insults include: maternal under nutrition, exposure to glucocorticoids, hypoxia, and drug abuse including cocaine abuse [Meyer and Zhang, 2007]. Currently there are not any human data that show a direct connection between maternal cocaine use and heart disease in adult offspring. This lack of research is due to the difficulty in performing such a study. Cocaine abuse has not been a widespread social problem long enough to determine the effects on middleaged or elderly offspring exposed prenatally. Furthermore, many of the early studies on the effect of fetal cocaine exposure have not followed the subjects into adult life. Additionally, the challenge of correctly identifying cocaine users and the multidrug use commonly found among cocaine users make it difficult to assess the effect of fetal cocaine exposure in human studies and make a retrospective study over the time period in question implausible. There are two main lines of evidence supporting the hypothesis that fetal cocaine exposure has long-term cardiac consequences: animal studies and studies demonstrating cardiac effects of cocaine exposure in neonates and children subsequent to intrauterine cocaine exposure.

Due to the aforementioned reasons, investigation into the effect of fetal cocaine exposure on the heart in human studies is mostly limited to the first decade of life. Furthermore, some of the results are conflicting. This may be due to a difficulty in quantifying the degree and timing of maternal cocaine use. It is probable that the effects that cocaine has on development depend both on the dose and at what point in gestation the fetus is exposed. Many studies rely on either self-reporting or a urine screen. Not only can these methods misidentify users as nonusers but they do not adequately differentiate between heavy and light users or provide significant insight into the window of exposure. Despite these limitations human studies have found some significant cardiovascular effects that cocaine appears to induce in humans.

Prenatal cocaine exposure has been found to have significant clinical effects including increasing the rate of arrhythmias in the neonate [Frassica *et al.* 1994; Lipshultz *et al.* 1991], decreasing cardiac output [Van de Bor *et al.* 1990], increasing the risk of heterotaxy heart disease [Kueh and Loffredo, 2002], and an increased risk of transient ST segment elevation, which was consistent with transient myocardial ischemia [Mehta *et al.* 1993]. However, in a blinded cross-sectional study to determine whether chronic cocaine exposure *in utero* produces abnormalities in left ventricular function showed no significant differences in left ventricular shortening fraction, heart rate, rhythm, and conduction in term neonates with or without prenatal cocaine exposure [Tuboku-Metzger *et al.* 1996]. Additionally, Mehta *et al.* [2002c] have reported that prenatal cocaine exposure results in changes in diastolic filling in neonates (under 48 hours old) with the degree of change observed being correlated to degree of fetal cocaine exposure. While most of these changes appear to be transient, some changes persisted to the age of 26 months particularly in the infants exposed to high levels of intrauterine cocaine [Mehta *et al.* 2002b].

As cocaine inhibits the reuptake of dopamine, serotonin and norepinephrine, the majority of research into the effect of cocaine on human development has been on the effect on the nervous system – both the central nervous system (CNS) and the autonomic nervous system (ANS). Naturally, the effects of fetal cocaine on the CNS and cognition may be significant but are not related to the cardiac effects of cocaine. Of possible consequence to the heart are the alterations that have been documented to the ANS in response to fetal cocaine exposure. There is a strong indication that there are changes in the monoaminergic receptor pathways after fetal cocaine exposure [Meyer and Dupont, 1993; Akbari and Azmitia, 1992; Henderson *et al.* 1991] and such changes have been suggested to be a mechanism of altered cardiovascular function [Meyer and Dupont, 1993]. Alterations to the ANS can manifest in multiple ways both cardiovascular and noncardiovascular. Infants exposed to cocaine *in utero* have been reported to be more difficult to calm and have increased physiological arousal [Bard *et al.* 2000; Bendersky and Lewis, 1998; Mayes *et al.* 1996] which suggests the ANS may have been altered. A study involving over 8000 neonates (717 exposed to cocaine) demonstrated fetal cocaine exposure was associated with ANS changes such as hyperalertness and autonomic instability [Bauer *et al.* 2005].

Changes to the ANS are also manifest as alterations in cardiovascular parameters and can affect cardiovascular function. If persistent, changes to the ability to regulate the cardiovascular system may increase the risk for heart disease later in adult life. Heart rate (HR) and heart rate variability (HRV) are the most commonly studied parameters in human studies examining the effect of cocaine on the ANS as they can be monitored noninvasively. Respiratory sinus arrhythmia (RSA), or the increase in heart rate during inspiration and decrease during exhalation, has been shown to be an indicator of the ability to self-regulate [Porges, 1991] the parasympathetic response to stressors [Grossman and Svebak, 1987].

Studies on the effects of fetal cocaine on resting HR and HRV have found conflicting results. Some studies have not observed alteration in resting HR or HRV [Garde et al. 2001; Dipietro *et al.* 1995], others have observed an increase in neonatal HR and decreased HRV [Mehta *et al.* 2002a, 2001; Oriol *et al.* 1993] or increased HR and HRV [Regalado *et al.* 1996]. While the conflicting results can be explained in part by differences in populations and methodology, it is difficult to draw a strong conclusion. However, Schuetze and Eiden [2006] reported that fetal cocaine has a dose dependent effect on HR increase at 4–8 weeks of age. This study differed from many previous investigations in a couple of important ways. The study's timeframe was 4–8 weeks after birth instead of a few days after birth and the mother's level of cocaine abuse was taken into account. This suggests that fetal cocaine exposure does increase HR but further studies are needed to draw a definite conclusion.

Studies have found that the stress response in terms of HR, HRV and RSA is altered in infants that suffered fetal cocaine exposure compared with controls. John *et al.* [2007] demonstrated an interaction between prenatal cocaine exposure and response to orthostatic stress in the form of a head tilt. All neonates responded to the head tilt with increased HRV and HR. However, the duration of the response was altered by prenatal cocaine exposure; the control neonates have an immediate but short-lived response to the head tilt, while neonates with prenatal cocaine exposure have a slower onset and longer duration of response indicating an alteration in the functioning of the ANS. A separate investigation found that 7-month-old infants exposed to cocaine did not have an increase in RSA when a negative affect test was administered while the control group did have a significant increase in RSA under the same conditions [Schuetze *et al.* 2007]. Analysis of ECG taken of sleeping neonates revealed alterations in HRV and RSA suggesting that fetal cocaine results in an increase in both sympathetic and vagal stimulation of the heart [Regalado *et al.* 2001, 1996]. A recent study demonstrated that exposure to high levels of cocaine resulted in a decrease in resting RSA in infants (4–8 weeks) [Schuetze and Eiden, 2006]. These findings strongly suggest that human neonates exposed to cocaine have alterations in the ANS some of which last as long as 2–7 months [Schuetze *et al.* 2007; Mehta *et al.* 2002a]. It has not been determined if these changes persist longer and what the long-term consequences of these changes are.

It is unknown precisely how many pregnant women use cocaine as there are several difficulties in obtaining an accurate estimate of the prevalence of cocaine abuse in this (or any) patient population. Many women do not give accurate histories due to fear of the consequences of admitting to illicit substance abuse or from a fear of criticism by the physician. One study found that based on urine screening 24% of pregnant women who were using cocaine denied use. However, urine screening can only detect recent use. In fact, in the same study 51% of self-reported users had a negative urine screen [Frank *et al.* 1988]. Screening the meconium or maternal hair provides a higher sensitivity and can detect exposure earlier in gestation than a urine test at the time of delivery [Savitz *et al.* 2002; Lester *et al.* 2001]. These difficulties highlight the importance of controlled animal studies.

Overall, human studies suggest that maternal cocaine use is associated with increased rates of arrhythmias and filling abnormalities. Additionally, alterations to the ANS as manifested by behavioral changes have been associated with fetal cocaine exposure. The effect of cocaine on neonatal heart rate and HRV is not entirely clear due to conflicting reports but the majority of literature and a longer-term study suggest that infant heart rate is increased by fetal cocaine exposure. Fetal cocaine has also been associated with a reduction in RSA and an altered stress response. Taken together these studies suggest that fetal cocaine has at least a short-term impact on the heart in humans.

Animal studies

It is unknown if the cardiovascular changes documented in infants prenatally exposed to cocaine will persist into adulthood and what, if any, implications these changes have for future cardiovascular health. It is possible that the changes observed are temporary and the long-term impact is minimal, but it is likely that these changes or other long-term consequences of fetal cocaine exposure result in an increased risk of cardiovascular disease later in adult life. While human studies are still preliminary and do not demonstrate long-term cardiovascular consequences of prenatal cocaine exposure, animal studies have provided additional insights that suggest that fetal cocaine exposure has long-term cardiovascular consequences.

Animal studies have demonstrated many effects of prenatal cocaine exposure both in the neonate and in the adult animal. As in human studies, alterations to the ANS as a result of prenatal cocaine exposure have been reported. Fetal cocaine exposure also reduces the function

but not the expression of norepinephrine transporters in the myocardium of neonatal rats [Zhao and Sun, 2004] resulting in a decrease in norepinephrine uptake. HRV in rats subject to prenatal cocaine exposure is altered in a way that suggests a decrease in parasympathetic activity and an alteration in sympathetic activity [Hseu *et al.* 1998]. Interestingly, the effect of cocaine on resting HR varied depending on the frequency of dosing. Pups of dams exposed to cocaine once a day had an increased resting HR while those injected two times per day had no significant change [Hseu *et al.* 1998]. The reason for this difference is not clear. However, the finding that the effect of fetal cocaine on resting HR is variable depending on the frequency of dosing may provide some insight into the conflicted human studies. As mentioned in the prior section studies have been conflicted regarding changes in resting HR and HRV in response to fetal cocaine exposure in humans. Different patient populations may have had different patterns of use. If the outcome in humans is also dependent on frequency of exposure it is reasonable to expect different outcomes in different populations.

Fetal cocaine has a clear effect on β-adrenergic signaling in animal models. In a rabbit model fetal cocaine exposure results in a decrease in K^+-induced norepinephrine release and an increase in ionomycin-induced norepinephrine release in the cardiac adrenergic nerve terminals [Snyder *et al.* 1995]. However, the alterations in norepinephrine seen in the rabbit model did not persist and were no longer observed at 50 days after birth. Changes to adrenergic signaling are also seen in a neonatal rat model. In the first day of life rat pups exposed to cocaine had an increase in myocardial β receptors but no increase in isoproterenol-induced adenylyl cyclase activity [Sun, 2000]. By day 7 of life the density of the β receptors had normalized but the level of isoproterenol-induced adenylyl cyclase activity was significantly decreased in the cocaine group. Cocaine exposure inhibits myocardial β-adrenergic signaling by increasing G_i protein expression and a subsequent reduction in GTP-induced adenylyl cyclase activity [Sun, 2000]. An apparent functional consequence of this reduction is that rats subject to prenatal cocaine exposure have a similar resting contractile function compared with saline controls but have a reduced response to β-agonist stimulation [Sun *et al.* 2003].

Prenatal cocaine also alters myocardial gene expression in the rat model. As mentioned above a transient alteration in β-adrenergic receptor expression has been reported [Sun, 2000]. Additionally, perinatal cocaine exposure (animals were administered cocaine while pregnant and nursing) increases the expression of the transcription factor cAMP response binding protein (CREB) [Sun and Quamina, 2003]. While the CREB's effect in the heart has not been fully characterized, it has been demonstrated that transgenic mice expressing a dominate-negative form of CREB develop dilated cardiomyopathy [Fentzke *et al.* 1998]. CREB expression is related to β-adrenergic signaling; cAMP response elements are found in the β_1 and β_2 receptors' promoter regions [Tseng *et al.* 1998; Collins *et al.* 1990] and CREB expression is decreased after chronic β-adrenergic stimulation [Muller *et al.* 1995].

In addition to studies demonstrating effects of fetal cocaine exposure on neonates, long-term effects of fetal cocaine exposure have been found in animal models. One area where long-term changes have been observed is the renin–angiotensin system. The angiotensin system plays a role in cardiac contractility [Bader *et al.* 2001] and angiotensin II can activate adenylyl cyclase in the myocardium [Ostrom *et al.* 2003]. In aged (19–24.5-month-old) rats treated with cocaine prenatally angiotensin II treatment caused a higher peak tension development in the left atria compared with saline-treated controls. Additionally, insulin-like growth factor 1 attenuated the inotropic increase from angiotensin II in the control animals and those exposed to a low dose of cocaine but the offspring of dams given a high dose of cocaine during pregnancy lacked this protection [Haddad *et al.* 2005]. Thus offspring exposed to cocaine may be more vulnerable to the angiotensin-II induced oxidative damage to the myocardium associated with aging [De Cavanagh *et al.* 2004].

Church *et al.* [2004] demonstrated that fetal cocaine exposure reduced the lifespan of the offspring. Male rats exposed to cocaine had 7–10% reduction in life span compared to control and females had a 10–12% reduction in lifespan [Church *et al.* 2004]. While the cocaine exposed animals did not exhibit a significant increase in gross cardiac pathology, there were some indications that cardiovascular problems may play a role in the reduced lifespan. The female offspring exposed to higher doses of cocaine had a reduced heart-to-body weight ratio at time of death while the some of the cocaine exposed males had symptoms suggestive of congestive heart failure shortly before dying [Church *et al.* 2004]. These findings suggest that in the rat model fetal cocaine may have a long-term impact on the heart that reduces life expectancy.

Recent studies in a rat model have demonstrated that maternal cocaine exposure during gestation increases apoptosis in the fetal heart both *in vivo* and in cultured cardiomyocytes [Li *et al.* 2005; Xiao *et al.* 2000, 2001; Zhang *et al.* 1999]. In addition, prenatal cocaine exposure caused an increase in apoptosis in neonatal hearts during the first two weeks of postnatal life and cardiac remodeling with myocyte hypertrophy in the left ventricle [Bae and Zhang, 2005]. During the early developmental period, either excessive and/or persistent cardiomyocyte loss through apoptosis has been suggested to lead to a variety of cardiac disease [Gill *et al.* 2002; Fernandez *et al.* 2001; Haunstetter and Izumo, 1998; James, 1998]. The developing heart may show remarkable plasticity in compensating for the loss of cardiomyocytes by an increase in myocyte size for the remaining cells [Li *et al.* 2004; Bae *et al.* 2003]. Although myocyte hypertrophy may compensate for the loss of myocytes and maintain cardiac function at the resting level, there appeared to be a cost of this compensation; that is, an increase in ischemic vulnerability of the heart. Indeed, recent studies have demonstrated that prenatal cocaine exposure results in left ventricular myocyte hypertrophy and an increase in heart susceptibility to ischemia and reperfusion injury in juvenile and adult offspring rats [Bae and Zhang, 2005; Bae *et al.* 2005]. Similarly, studies in humans and rodent models of prenatal cocaine exposure have shown plasticity of the developing nervous system in compensating for some cocaine-induced perturbations in the fetus, with a cost of an increased vulnerability to environmental and cognitive demands and stressors in postnatal life [Spear *et al.* 2002, 1998; Mayes *et al.* 1998].

While the mechanisms whereby prenatal cocaine exposure causes an increase in the vulnerability of ischemic injury in the heart of adult offspring has not been fully elucidated, the downregulation of PKCε gene expression in the heart appears to have an important role. During ischemic disease, the heart can benefit from protective measures from an endogenous source. Among other mechanisms, PKCε plays a pivotal role of cardioprotection during cardiac ischemia and reperfusion injury [Murriel and Mochly-Rosen, 2003; Chen *et al.* 2001; Ping *et al.* 2001]. Studies in a PKCε knockout mouse model have demonstrated that PKCε expression is not required for cardiac function under normal physiological conditions, but PKCε activation is necessary and sufficient for acute cardioprotection during cardiac ischemia and reperfusion [Gray *et al.* 2004]. Prenatal cocaine exposure caused a significant decrease in PKCε protein levels in the left ventricle of adult male offspring [Bae *et al.* 2005], suggesting an in-utero epigenetic modification and programming of PKCε gene repression in the heart. Epigenetic mechanisms are essential for development and differentiation, and allow an organism to respond to the environment through changes in gene expression. DNA methylation is a chief mechanism for epigenetic modification of gene expression pattern and occurs at cytosines of the dinucleotide sequence of CpG [Jones and Takai, 2001]. Methylation in gene promoter regions is generally associated with repression of transcription, leading to long-term shutdown of the associated gene. It has been demonstrated in a rat model that prenatal cocaine exposure causes a significant increase in methylation status of CpG dinucleotides at the proximal promoter region of the PKCε gene resulting in decreased binding of transcription factors to the promoter and PKCε gene repression in the heart of adult offspring [Zhang *et al.* 2007; Zhang

et al. 2008]. The pathophysiological significance of the decreased PKCε levels in the heart was demonstrated by the findings that prenatal cocaine exposure abolished ischemic preconditioning-mediated protection in the adult heart, in which PKCε played a key role [Meyer *et al.* 2008].

A point of interest is that the detrimental effect of prenatal cocaine exposure on cardiac function in offspring appears to show a gender dimorphism with males being more susceptible than females [Meyer *et al.* 2008; Bae *et al.* 2005]. Consistent with the finding in the heart, this gender dichotomy has been demonstrated in offspring on a diversity of measures to the effects of prenatal cocaine exposure in the rat [Spear *et al.* 2002, 1998; Wood and Spear, 1998; Goodwin *et al.* 1995; Heyser *et al.* 1995; Molina *et al.* 1994; Grimm and Frieder, 1985]. Gender dimorphism has also been demonstrated in animal models of intrauterine undernutrition when measuring the severity of hypertension in adult offspring [do Carmo Pinho Franco *et al.* 2003]. It is not clear at present whether the gender-specific effects of prenatal cocaine exposure on the heart of offspring are primarily mediated by the differences in sex steroid hormones developed postnatally or by the differences exist between genetically male (XY) and female (XX) cells in determining a ‘programming-sensitive’ phenotype.

Concluding remarks

The evidence indicates that in animal models, fetal cocaine exposure results in changes on the cellular and genetic level that do not manifest as gross cardiac problems but result in an increased risk of heart disease. The finding that fetal cocaine results in epigenetic changes provides an explanation for long-term consequences of prenatal cocaine exposure despite minimal or absent gross cardiac changes in offspring. As there have been no long-term studies into the effect of prenatal cocaine in humans, evidence for cocaine-induced cardiac programming is lacking in humans. Despite the lack of direct evidence of long-term human programming, studies in human neonates clearly show that prenatal cocaine exposure results in alterations to the heart and the autonomic nervous system. The findings in human neonates and long-term effects seen in animal models strongly suggest that fetal cocaine exposure is capable of inducing cardiac programming and is likely a significant risk factor for morbidity and mortality secondary to myocardial ischemia in adulthood. These findings are consistent with recent epidemiological studies in humans, as well as studies in animals, showing an association of adverse intrauterine environment and an increased risk of health problems; for example, ischemic heart disease, in later adult life [Meyer and Zhang, 2007; Zhang, 2005; Barker *et al.* 1989]. It is possible and perhaps common for an organ to be programmed and then vulnerable for life without evidence until a late-life stressor challenges its adaptive capabilities. This possibility could influence our understanding of the origin of heart diseases and have a significant impact on public health given the high rates of cocaine abuse in urban areas and that cardiovascular disease is the leading cause of death in the United States.

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