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Review Article

Fetal Nicotine Exposure Increases the Risk of Cardiovascular Disease in Late Life. A Review of the Literature

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Abstract

Maternal cigarette smoking is one of the major worldwide health concerns and is associated with numerous adverse pregnancy outcomes. Epidemiological studies have shown that maternal smoking is associated with increased risk of cardiovascular disease in offspring later in life. As one of the major active components in cigarette smoking, nicotine is likely to contribute to the developmental programming of cardiovascular system dysfunction. Indeed, nicotine readily crosses the placenta and produces higher nicotine concentrations in the fetal circulation than that experienced by the mother. Studies in different animal models show that nicotine use during pregnancy can cause cardiovascular disorders and hypertension of offspring. It is well documented that maternal smoking or nicotine use during pregnancy not only decreases fetal body weight but also impairs fetal development. First, the present review will examine the recent findings regarding intrauterine nicotine exposure and fetal programming of cardiovascular dysfunction in adulthood. Then, the review will present novel epigenetic mechanisms underlying nicotine-induced development of cardiovascular dysfunctional phenotype in offspring. Understanding these mechanisms is of pivotal important for the development of potentially strategies for prevention and treatment of nicotine/tobacco-related fetal original cardiovascular diseases.

Keywords: Maternal smoking; Nicotine; Cardiovascular disease; Epigenetic regulation

Introduction

Although cigarette smoking during pregnancy is associated with numerous adverse fetal and developmental outcomes, as well as an increased risk of adverse health consequences in the adult offspring [1-4], 15-20% of all women smoke during pregnancy [5,6]. In addition, many pregnant women, who are highly dependent and unable to quit smoking, have used Nicotine Replacement Therapy (NRT) for smoking cessation. Although NRT use during pregnancy may be relatively safe for the mother, recent studies have raised the concerns about NRT use during pregnancy, based on evidence of fetotoxicity and neuroteratogenicity associated with maternal nicotine exposure [3,6]. Epidemiologic studies have indicated that maternal smoking is associated with an increased risk of elevated Blood Pressure (BP) and cardiovascular diseases in the postnatal life [7,8]. As one of the major components in cigarette smoking, nicotine is likely to contribute to the developmental programming of cardiovascular disorders. Indeed, nicotine readily crosses the placenta and produces higher nicotine concentrations in fetal circulation than that in the mother [9,10], resulting in fetal growth restriction and permanent alteration of fetal cardiovascular system [3,11,12]. The present review will mainly focus on the effect of fetal nicotine exposure on the subsequent development of cardiovascular dysfunction in postnatal life. However, it should bear in mind that although nicotine is a predominant factor in maternal cigarette smoking-mediated cardiovascular dysfunction in offspring, other components of smoke may also be contributed to the detrimental effects of cigarette smoking on fetal programming of cardiovascular disease in late life.

Relationship between the body weight and cardiovascular disease in response to fetal nicotine exposure

In the "fetal origins of disease" hypothesis, Barker have proposed that low birth weight in response to adverse environmental exposure in pregnancy is one of important predictors for development of cardiovascular disease in late life [13-15]. Recently, growing evidences from epidemiological and experimental studies have supported Barker's hypothesis [16,17]. In addition, previous reports have also shown a strong association between maternal cigarette smoking and low birth weight, which is the major predictor of infant mortality and adverse development outcome [4,18-20]. Among other factors, nicotine is likely the key factor to contribute to the low birth weight among smokers. Studies in different pregnant animal model have confirmed and supported that nicotine is the key factor for fetal growth restriction [5,21-25]. Maternal nicotine use produces at least two major different families of potential effects on fetal growth: indirect actions on the maternal unit and direct actions on the fetal system. First, the nicotine's effect on body weight may involve an increase in energy expenditure and a decrease in maternal food intake which then indirectly leads to fetal growth retardation [26,27]. However, our recent studies in a maternal food restricted animal model have indicated that paired-food restriction does not affect fetal and neonatal body weight, which suggests that nicotine-induce fetal

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and neonatal growth retardation may be independent of maternal food intake [22]. The nicotine-induced fetal growth retardation may involve the indirect regulation of utero-placental circulation by nicotine. Nicotine can activate nicotinic acetylcholine receptors and increase neurotransmitters release, leading to uterine and placental vasoconstriction. The increased vasoconstriction results in placental insufficiency or fetal hypoxia leading to attenuation of oxygen delivery to the fetus consequence to fetal growth retardation [9,10,28]. In our previous studies have demonstrated that chronic nicotine-treatment increases α_1-adrenoceptor-mediated contractions in ovine pregnant uterine arteries and decreases nitric oxide-mediated relaxations of the uterine arteries [28]. The inhibition of endothelium-dependent relaxation and enhanced uterine vasoconstriction could be a major reason for the reduced uterine blood flow observed with smoking/nicotine exposure during pregnancy [9,10]. Secondly, recent studies suggest that decreased birth weight from maternal nicotine exposure may result from direct effects of nicotine rather than indirect effects due to placental insufficiency [11]. This is because that nicotine has many direct detrimental effects on fetal metabolism and development. Nicotine readily crosses the placenta with fetal blood levels 15% greater than those of the mother [9]. Therefore, nicotine could potentially exert direct effects on fetal development and growth.

Fetal nicotine exposure increase the risk of hypertension in late life

Epidemiologic studies have demonstrated that maternal cigarette smoking has a substantial effect in increase blood pressure not only in newborns [7,29], and children [8,30,31], but also adults [1,6]. These investigations show that maternal smoking in pregnancy is associated with lower birth-weight and higher blood pressure later in life. Nicotine is a ganglionic agonist and is likely to contribute to the developmental programming of cardiovascular disorders. Indeed, fetal nicotine exposure results in increased the risk of high blood pressure during adulthood in different animal models [12,32-34]. However, the effect of nicotine on fetal programming of high blood pressure is complex. The animal species, individual variability in genetic background, gender difference, the window of nicotine exposure time and the dose used are likely to modify the response of the fetus to nicotine exposure. Pausova et al. reported that Spontaneously Hypertensive Rat (SHR) and normotensive Brown Norway (BN) rat differed in their response to intrauterine exposure to nicotine [12]. Fetal nicotine exposure enhances blood pressure in SHR but not in BN offspring [12]. However, fetal nicotine exposure results in increased blood pressure during adulthood in the normotensive Wistar-Kyoto rat strain [32]. Our recent studies in Sprague-Dawley rat model have demonstrated that perinatal nicotine exposure increases in blood pressure response in adult male but not female offspring [25]. In a similar pregnant rat model, perinatal nicotine exposure has no significant effect on basal blood pressure at the age 5 month-old rat offspring [25] but significantly increases it at the age of 22 month-old rat offspring [34]. These studies suggest that the effect of nicotine exposure on blood pressure may depend on the genetic background, age and gender, and support the notion that the intrauterine environment interacts with genes in determining an individual's health later in life.

There are multiple mechanisms that are likely to contribute to the fetal nicotine exposure-induced elevation of blood pressure in adulthood. One of the mechanisms is the changes in renal structure or function. Recent studies have reported that prenatal exposure to nicotine decreases kidney size and glomerular mass in offspring [12,35,36]. These studies have demonstrated that prenatal nicotine exposure alters expression of multiple genes involved in the renal nervous system function. The renal nervous system involves in the control of blood pressure by regulating renal blood flow, glomerular filtration rate, and hormonal release. In addition, prenatal nicotine exposure also significantly enhances Angiotensin II Receptor Type 1 (AT_1R) gene expression and the ratio of AT_1R/AT_2R gene expression in the kidney [35,36], which mediates most of the presser effects of the renin-angiotensin system, a key regulator of blood pressure. Thus, the nicotine-induced morphological and molecular changes in the kidneys likely contribute to fetal programming of hypertension.

In addition to alterations in kidney function, previous studies have demonstrated changes in vascular function in response to fetal nicotine exposure [24,25,32,37-41]. Impaired vascular function includes changes in arterial stiffness and the ability of the vasculature to respond properly to vaso-stimuli, or factors that can dilate or constrict the blood vessel. Studies in a maternal nicotine-treated monkey model have demonstrated that total wall and tunica adventitia thickness of pulmonary vessels in fetal monkeys increase significantly in response to nicotine treatment [40]. Furthermore, nicotine exposure significantly enhances collagen I and III gene expression but decreases the levels of elastin protein in tunica adventitia in the vessels of fetal monkeys. These observations suggest that nicotine may directly interacts with nicotine acetylcholine receptors in pulmonary vessels to alter connective tissue expression and therefore cause vascular structural alterations, which results in increased the risk of persistent pulmonary hypertension. Results from Gao et al reports [32,38] suggest that perinatal nicotine exposure in rats causes elevated blood pressure postnatally because of changes in perivascular adipose tissue surrounding arterial walls. These studies have shown that perinatal nicotine exposure-induced elevated blood pressure in offspring is associated with changes the composition and amount of perivascular adipose tissue and the ability of the perivascular adipose tissue to regulate the contractile response of blood vessels. Investigator have shown that nicotine has toxic effects on endothelium, and thus nicotine may play a key role in impaired nitric oxide syntheses dependent arteriolar dilatation observed in users of tobacco [42]. Recent studies from our laboratory [24,43] have demonstrated that acetylcholine-induced relaxations are significantly decreased in nicotine exposed offspring, suggesting a reduction of Nitric Oxide (NO)-mediated signaling in response to fetal nicotine exposure. We further demonstrated that the perinatal nicotine treatment does not alter endothelium NO Synthase (eNOS) protein expression in arteries of offspring, suggesting that NO bioavailability but not NO synthesis is altered by the nicotine exposure [24]. Indeed, it has been demonstrated that cigarette smoking causes dysfunctional eNOS due to the reduced bioactivity of tetra hydrobiopterin [44,45], which leads to uncoupling of eNOS and an increased production of superoxide. The excess superoxide reacts with NO and disrupts its physiological signaling by generating peroxynitrite ($ONOO^-$) [46,47]. Results from our recent studies have shown that perinatal nicotine exposure enhances Reactive Oxygen Species (ROS)-related protein expressions and ROS production in vasculatures in adult offspring

[43]. The result that treatment with ROS inhibitors restores perinatal nicotine-enhanced NO-dependent relaxation in nicotine-treated offspring provides direct evidence that increased ROS contributes to the scavenging of NO and the reduction of relaxation induced by acetylcholine. It further suggests that programming of ROS-related enzymes or proteins and heightened ROS may be one of the key mechanisms leading to impair NO-dependent relaxation and an increased risk of hypertension in response to fetal nicotine exposure.

In addition to changes in endothelium-dependent vasodilation, previous studies suggests that vascular smooth muscle function and vascular contractile response to agonists are also programmed in response to perinatal nicotine exposure [24,25,37,40,41,43]. Previous studies have provided direct evidence to show abundant expression of nicotinic Acetylcholine Receptors (nAChR) in blood vessels and have also reported that prenatal nicotine exposure strikingly up regulated nAChR expression in vessels [48,49], which suggest that nicotine may directly interact with nAChR in vasculature and regulate vascular reactivity. Interestingly, results from previous studies have shown an increase in KCl-induced vaso-contraction in male offspring of nicotine-treated rat [24]. Given the fact that nicotine increases membrane depolarization and enhances Ca2+ influx through L-type Ca2+ channels resulting in increased contractions of rat tail arteries [50], it is speculated that perinatal nicotine exposure may up-regulate L-type Ca2+ channels leading to increased KCl-induced contraction. In addition to regulation of KCl-mediated contractions, perinatal nicotine exposure also increases norepinephrine-induced vaso-contractions in offspring [24]. However, the enhanced norepinephrine-induced contractions in offspring of nicotine-treated animals are primary due to the loss of the eNOS-mediated relaxation component, rather than increased norepinephrine-induced contractions per se, in adult vessels [24]. The perinatal nicotine exposure-mediated exaggerated vascular response to Angiotensin II (Ang II) stimulation is also seen in the similar animal model [25,43]. The authors have reported that perinatal nicotine exposure enhances Ang II-induced vascular contractions and elevates arterial blood pressure associated with increased Angiotensin II Receptor Type I (AT_1R) but decreased Type 2 (AT_2R) protein levels [25]. The authors also provide new evidence of an important role of fetal programming of vascular oxidative stress in nicotine-mediated Ang II-induced vascular contraction [43]. Remarkably, nicotine treatment in pregnant rats throughout gestation results in augmented Ang II-induced vasoconstriction, which can be abrogated by acute treatment of the vessels with the NADPH oxidase inhibitor, apocynin, or the superoxide dismutase mimetic, tempol. Furthermore, these functional changes were associated with increased NOX2 protein expression and ROS production in the vascular wall. These results suggest that fetal epigenetic changes of ROS- and/or Ang II-mediated signaling following maternal nicotine exposure are, at least, one of the important mechanisms in fetal programming of adult hypertension and other vascular disease.

Fetal nicotine exposure increases the risk of cardiac dysfunction

Epidemiological studies have shown that maternal cigarette smoking significantly increases the risk for Sudden Infant Death Syndrome (SIDS) associated with abnormal cardiac conduction and malignant arrhythmia [51-54]. Nicotine has been proposed to be the link between maternal smoking and SIDS [3-5,55]. Previous reports indicate that fetal nicotine exposure exaggerates the responses and changes the types of nicotine receptors involved in exciting premotor cardiac vagal neurons [56]. Fetal nicotine exposure significantly increases the endogenous activation of nicotine receptors response for an inward current and augmentation of miniature Excitatory Postsynaptic Current (mEPSC) frequency and amplitude in cardiac vagal neurons. In addition, nicotine evokes both an exaggeration and change in nicotine receptors responsible for the nicotine-evoked responses that consist of an inward current and increases in mEPSC frequency and amplitude. These alterations could contribute to the pronounced bradycardia that occurs during apnea in SIDS victims. Although an exaggeration of parasympathetic responses to hypoxia may be involved in SIDS, increased parasympathetic activity with nicotine receptor activation may be cardio protective in adults [56].

Results from previous studies in pregnant sheep have provided direct evidence that exposure to maternal nicotine at near-term could induce cardiac cycle irregularity, single dropped cardiac cycle and multiple dropped cardiac cycles in the fetus in utero. Remarkably, exposure to nicotine during pregnancy increases tachycardia and ventricular arrhythmia in the adult offspring under the stress stimulation [57]. Similarly, Slotkin et al have demonstrated that prenatal nicotine exposure increases the risk of cardiac dysfunction during postnatal hypoxia [4]. The authors reported that saline control rat offspring responded to hypoxic stimulation with initial tachycardia and a subsequent slow decline in heart rate; whereas prenatal nicotine treated offspring show no tachycardia but a rapid decline in heart rats [4]. During hypoxia, respiratory frequency and heart rate transiently increase and subsequently decrease. These biphasic cardio respiratory responses normally serve to prolong survival during hypoxia by reducing the metabolic demands of cardiac and respiratory muscle. However, exaggerated responses to hypoxia may be life threatening and have been implicated in SIDS. Indeed, during hypoxia, rats exposed to nicotine prenatally become apneic more rapidly that unexposed animals [33]. In addition, previous studies have established a likely neurochemical mechanism for the heart rate response to hypoxia, provided a link between prenatal nicotine exposure and an exaggerated bradycardia during hypoxia that may contribute to SIDS [2].

Perinatal nicotine exposure also leads to stress-induced cardiac defects and development of heart ischemia sensitive phenotype in the offspring [22,58]. Our previous studies have demonstrated that perinatal nicotine exposure alters cardiac function in adult offspring and increases heart susceptibility to ischemia/reperfusion injury in rats [22,58]. Our results shows that perinatal nicotine exposure significantly attenuates Left Ventricle (LV) developed pressure, heart rate, and coronary flow rate in female but not male hearts at baseline. However, nicotine increases LV infarct size and attenuates post ischemic recover of LV function in both male and female offspring. Furthermore, the changes in cardiac function are associated with a significant decrease in protein levels of Protein Kinase (PK) Cε in the hearts [22,58]. Given the facts that PKCε plays a pivotal role of cardio protection in heart ischemia and reperfusion [59-61], the results suggest that perinatal nicotine exposure-induced fetal programming of the PKCε gene expression pattern in the developing heart may be the key molecular link between perinatal nicotine exposure and the

increased heart susceptibility to ischemia/reperfusion injury in adult offspring.

Epigenetic mechanisms underlying nicotine-induced fetal programming of adult cardiovascular dysfunction

The molecular mechanisms underlying nicotine-induced fetal programming of long-term cardiovascular dysfunction are not fully understood. Growing evidence from animal experimental studies and the observation in humans suggests a key role of epigenetic regulation of specific gene expression patterns in the fetal programming of adult disease [62,63]. Epigenetic regulation refers to the heritable changes in gene expression without alteration of the DNA sequence [64]. Unlike genetic regulation, which is extremely stable, epigenetic regulation is sensitive to environmental stimuli, resulting in modified gene expression patterns and phenotypes later in life. The major epigenetic mechanisms in regulation of gene expression are including DNA methylation, Histone modification, and some non-coding RNAs which can target mRNA to interfere with transcription or translation [65-67]. Maternal smoking/nicotine use during pregnancy-induced fetal programming of adult cardiovascular disease has been found to be associated with alteration of DNA methylation or miRNA profile in offspring [58,68-70]. It has been shown that maternal cigarette smoking alters global and gene-specific DNA methylation in offspring [71]. It is known that prenatal exposure to nicotine is associated with the increased risk of hypertension and cardiac disease. Recent studies showed that epigenetic mechanisms, at least, mediate some of the consequences of fetal nicotine exposure through methylation of DNA in genes important for cardiovascular development and function [58,70]. In recent studies, Xiao et al. [25,70] investigated in the rat model, whether perinatal exposure to nicotine can alter vascular function and its-related gene expression. The results showed that perinatal nicotine exposure enhances vascular contractile and blood pressure response to Angiotensin II stimulation associated with an increased AT_1R but decreased AT_2R gene expression. Furthermore, the increased AT_1R gene expression is associated with a decreased DNA methylation at specific CpG units of the proximal promoter of this gene. Xiao et al has identified several CpG islands located in the transcription factor binding sites in rat $AT_{1a}R$ promoter. Of these CpG sites, nicotine selectively decreased the methylation levels at -484 and -96 CpG locus, suggesting that hypomethylation of the selective CpG locus may be an important epigenetic mechanism in up-regulation of AT_1R gene expression of vasculatures in response to perinatal nicotine exposure. Since the nicotine-altered CpG sites have been identified respectively as ERα,β and Sp1 transcription factor binding sites in rat $AT_{1a}R$ promoter, it speculates that nicotine-mediated decrease in sequence-specific CpG methylation at ERα,β or Sp1 binding site may be a novel mechanism of increasing those transcription factors binding affinity to $AT_{1a}R$ promoter and enhancing $AT_{1a}R$ promoter activity and gene expression. In contrast to the hypomethylation at specific CpG islands in $AT_{1a}R$ promoter, nicotine treatment selectively increased the methylation levels at -444 and +11 CpG locus in AT_2R promoter in vasculatures, which suggests that the effect of perinatal nicotine exposure on DNA methylation is gene-specific. In a similar animal model, previous studies have demonstrated that perinatal nicotine exposure decreases DNA methylation at AT_2R promoter and AT_2R protein repression of neonatal brain in male offspring but not in female offspring, which, in turn, lead to modifications in both development and plasticity of the brain exposed in utero to nicotine [35,72,73]. Studies in spontaneously hypertensive rats have shown that prenatal nicotine exposure decreases kidney glomerular mass and increases blood pressure associated with increased renal expression of the AT_1R gene in offspring. However, the programmed AT_1R gene is not mediated through changes in DNA methylation of the proximal promoter of this gene [12,36]. These observations suggest that the DNA methylation is one of the key epigenetic mechanisms underlying nicotine-mediated programming of gene expression, but it may be gene-specific and tissue-, specie-, and gender-dependent.

Previous studies in rat model have demonstrated that perinatal nicotine exposure causes protein kinase C epsilon (PKC_ε) gene repression in the developing heart via an increase in methylation of the Egr-1 binding site at the PKC_ε promoter, linking fetal nicotine exposure to development of heart ischemia-sensitive phenotype in adulthood [22,58]. Lawrence et al [58] reported that nicotine stimulates the release of sympathetic neurotransmitter norepinephrine in the fetal heart, resulting in inhibition of PKC_ε gene expression through DNA methylation mechanism. Interestingly, maternal hypoxia also increases sympathetic activity [74] and recent studies have shown that maternal hypoxia causes an increase in methylation at the Egr-1 binding sites of PKCε promoter in the fetal heart [75]. It can be speculated that the increased Egr-1 methylation at the PKC_ε promoter in fetal hearts is due to an increase in sympathetic neurotransmitter norepinephrine release in the heart in response to hypoxic stress. Although these studies demonstrate the different patterns of promoter methylation between maternal hypoxia and nicotine exposure, they provide a possible common mechanism of norepinephrine-mediated increase in methylation of the Egr-1 binding site at the PKC_ε promoter in the developing heart. Such mechanism could, in turn, lead to development of heart ischemia-sensitive phenotype in late life.

As one of the pivotal epigenetic mechanisms, miRNAs are sensitive to various perinatal stressful insults, resulting in aberrant regulation of target gene expression in developing fetus and contributing to the development of cardiovascular disease in offspring [76]. The role of miRNA signaling in maternal smoking and nicotine-mediated path-physiological function has been reported in human and animal models [69,77,78]. Maternal smoking during pregnancy significantly down-regulates miRNA-16, miRNA-21 and miRNA-146a in the placenta [69]. Taki et al has demonstrated that chronic nicotine exposure systemically alters miRNA expression profiles during post-embryonic stages and proposed a model where nicotine addiction is mediated by miRNAs' regulation of fos-1 and is maintained by epigenetic factors. However, up-to now, to our knowledge there is lack of direct evidence whether miRNAs link maternal smoking/nicotine exposure during pregnancy to development of cardiovascular disease in offspring.

Conclusion

Fetal nicotine exposure, either from maternal cigarette smoking or nicotine use during pregnancy, not only cause fetus growth restriction, but also increase the risk of cardiovascular disease and cause adverse health consequence in later life. A fully understanding of the epigenetic mechanisms underlying fetal nicotine exposure-induced cardiovascular dysfunction in adulthood could help

professional to identify early epigenetic biomarker and provide new leads in the development of preventive diagnosis and therapeutic strategies of fetal programming of cardiovascular disease.

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References

1. de Jonge LL, Harris HR, Rich-Edwards JW, Willett WC, Forman MR, Jaddoe VW, et al. Parental smoking in pregnancy and the risks of adult-onset hypertension. Hypertension. 2013; 61: 494-500.
2. Neff RA, Simmens SJ, Evans C, Mendelowitz D. Prenatal nicotine exposure alters central cardiorespiratory responses to hypoxia in rats: implications for sudden infant death syndrome. J Neurosci. 2004; 24: 9261-9268.
3. Slotkin TA. Fetal nicotine or cocaine exposure: which one is worse? J Pharmacol Exp Ther. 1998; 285: 931-945.
4. Slotkin TA, Saleh JL, McCook EC, Seidler FJ. Impaired cardiac function during postnatal hypoxia in rats exposed to nicotine prenatally: implications for perinatal morbidity and mortality, and for sudden infant death syndrome. Teratology. 1997; 55: 177-184.
5. Bamford OS, Carroll JL. Dynamic ventilatory responses in rats: normal development and effects of prenatal nicotine exposure. Respir Physiol. 1999; 117: 29-40.
6. Cupul-Uicab LA, Skjaerven R, Haug K, Melve KK, Engel SM, Longnecker MP. In utero exposure to maternal tobacco smoke and subsequent obesity, hypertension, and gestational diabetes among women in the MoBa cohort. Environ Health Perspect. 2012; 120: 355-360.
7. Beratis NG, Panagoulias D, Varvarigou A. Increased blood pressure in neonates and infants whose mothers smoked during pregnancy. J Pediatr. 1996; 128: 806-812.
8. Blake KV, Gurrin LC, Evans SF, Beilin LJ, Landau LI, Stanley FJ, et al. Maternal cigarette smoking during pregnancy, low birth weight and subsequent blood pressure in early childhood. Early Hum Dev. 2000; 57: 137-147.
9. Lambers DS, Clark KE. The maternal and fetal physiologic effects of nicotine. Semin Perinatol. 1996; 20: 115-126.
10. Lindblad A, Marsál K, Andersson KE. Effect of nicotine on human fetal blood flow. Obstet Gynecol. 1988; 72: 371-382.
11. Huang LZ, Hsiao SH, Trzeciakowski J, Frye GD, Winzer-Serhan UH. Chronic nicotine induces growth retardation in neonatal rat pups. Life Sci. 2006; 78: 1483-1493.
12. Pausova Z, Paus T, Sedova L, Berube J. Prenatal exposure to nicotine modifies kidney weight and blood pressure in genetically susceptible rats: a case of gene-environment interaction. Kidney Int. 2003; 64:829-835.
13. Barker DJ. In utero programming of chronic disease. Clin Sci (Lond). 1998; 95: 115-128.
14. Barker DJ, Osmond C, Law CM. The intrauterine and early postnatal origins of cardiovascular disease and chronic bronchitis. J Epidemiol Community Health. 1989; 43: 237-240.
15. Barker DJ, Winter PD, Osmond C, Margetts B, Simmonds SJ. Weight in infancy and death from ischaemic heart disease. Lancet. 1989; 2: 577-580.
16. Ong KK, Dunger DB. Perinatal growth failure: the road to obesity, insulin resistance and cardiovascular disease in adults. Best Pract Res Clin Endocrinol Metab. 2002; 16: 191-207.
17. Ozanne SE, Fernandez-Twinn D, Hales CN. Fetal growth and adult diseases. Semin Perinatol. 2004; 28: 81-87.
18. Ellard GA, Johnstone FD, Prescott RJ, Ji-Xian W, Jian-Hua M. Smoking during pregnancy: the dose dependence of birthweight deficits. Br J Obstet Gynaecol. 1996; 103: 806-813.
19. Horta BL, Victora CG, Menezes AM, Halpern R, Barros FC. Low birthweight, preterm births and intrauterine growth retardation in relation to maternal smoking. Paediatr Perinat Epidemiol. 1997; 11: 140-151.
20. Vik T, Jacobsen G, Vatten L, Bakketeig LS. Pre- and post-natal growth in children of women who smoked in pregnancy. Early Hum Dev. 1996; 45: 245-255.
21. Gauda EB, Cooper R, Akins PK, Wu G. Prenatal nicotine affects catecholamine gene expression in newborn rat carotid body and petrosal ganglion. J Appl Physiol (1985). 2001; 91: 2157-2165.
22. Lawrence J, Xiao D, Xue Q, Rejali M, Yang S, Zhang L. Prenatal nicotine exposure increases heart susceptibility to ischemia/reperfusion injury in adult offspring. J Pharmacol Exp Ther. 2008; 324: 331-341.
23. Simakajornboon N, Vlasic V, Li H, Sawnani H. Effect of prenatal nicotine exposure on biphasic hypoxic ventilatory response and protein kinase C expression in caudal brain stem of developing rats. J Appl Physiol (1985). 2004; 96: 2213-2219.
24. Xiao D, Huang X, Lawrence J, Yang S, Zhang L. Fetal and neonatal nicotine exposure differentially regulates vascular contractility in adult male and female offspring. J Pharmacol Exp Ther. 2007; 320: 654-661.
25. Xiao D, Xu Z, Huang X, Longo LD, Yang S, Zhang L. Prenatal gender-related nicotine exposure increases blood pressure response to angiotensin II in adult offspring. Hypertension. 2008; 51: 1239-1247.
26. Collins LC, Walker J, Stamford BA. Smoking multiple high- versus low-nicotine cigarettes: impact on resting energy expenditure. Metabolism. 1996; 45: 923-926.
27. Grunberg NE. Nicotine as a psychoactive drug: appetite regulation. Psychopharmacol Bull. 1986; 22: 875-881.
28. Xiao D, Huang X, Yang S, Zhang L. Direct effects of nicotine on contractility of the uterine artery in pregnancy. J Pharmacol Exp Ther. 2007; 322: 180-185.
29. Geerts CC, Grobbee DE, van der Ent CK, de Jong BM, van der Zalm MM, van Putte-Katier N, et al. Tobacco smoke exposure of pregnant mothers and blood pressure in their newborns: results from the wheezing illnesses study Leidsche Rijn birth cohort. Hypertension. 2007; 50: 572-578.
30. Lawlor DA, Najman JM, Sterne J, Williams GM, Ebrahim S, Davey Smith G. Associations of parental, birth, and early life characteristics with systolic blood pressure at 5 years of age: findings from the Mater-University study of pregnancy and its outcomes. Circulation. 2004; 110: 2417-2423.
31. Williams S, Poulton R. Twins and maternal smoking: ordeals for the fetal origins hypothesis? A cohort study. BMJ. 1999; 318: 897-900.
32. Gao YJ, Holloway AC, Su LY, Takemori K, Lu C, Lee RM. Effects of fetal and neonatal exposure to nicotine on blood pressure and perivascular adipose tissue function in adult life. Eur J Pharmacol. 2008; 590: 264-268.
33. Fewell JE, Smith FG, Ng VK. Prenatal exposure to nicotine impairs protective responses of rat pups to hypoxia in an age-dependent manner. Respir Physiol. 2001; 127: 61-73.
34. Tao H, Rui C, Zheng J, Tang J, Wu L, Shi A, et al. Angiotensin II-mediated vascular changes in aged offspring rats exposed to perinatal nicotine. Peptides. 2013; 44: 111-119.
35. Mao C, Wu J, Xiao D, Lv J, Ding Y, Xu Z, et al. The effect of fetal and neonatal nicotine exposure on renal development of AT(1) and AT(2) receptors. Reprod Toxicol. 2009; 27: 149-154.
36. Toledo-Rodriguez M, Loyse N, Bourdon C, Arab S, Pausova Z. Effect of prenatal exposure to nicotine on kidney glomerular mass and AT1R expression in genetically diverse strains of rats. Toxicol Lett. 2012; 213: 228-234.
37. Fox KA, Longo M, Tamayo E, Gamble P, Makhlouf M, Mateus JF, et al. Sex-specific effects of nicotine exposure on developmental programming of blood pressure and vascular reactivity in the C57Bl/6J mouse. Am J Obstet Gynecol. 2012; 207: 208.

38. Gao YJ, Holloway AC, Zeng ZH, Lim GE, Petrik JJ, Foster WG, et al. Prenatal exposure to nicotine causes postnatal obesity and altered perivascular adipose tissue function. Obes Res. 2005; 13: 687-692.

39. Jiang JS, Chou HC, Yeh TF, Chen CM. Maternal nicotine effects on vascular endothelial growth factor expression and morphometry in rat lungs. Early Hum Dev. 2012; 88: 525-529.

40. Sekhon HS, Proskocil BJ, Clark JA, Spindel ER. Prenatal nicotine exposure increases connective tissue expression in foetal monkey pulmonary vessels. Eur Respir J. 2004; 23: 906-915.

41. Xiao D, Huang X, Yang S, Zhang L. Estrogen normalizes perinatal nicotine-induced hypertensive responses in adult female rat offspring. Hypertension. 2013; 61: 1246-1254.

42. Mayhan WG, Patel KP. Effect of nicotine on endothelium-dependent arteriolar dilatation in vivo. Am J Physiol. 1997; 272: 2337-2342.

43. Xiao D, Huang X, Yang S, Zhang L. Antenatal nicotine induces heightened oxidative stress and vascular dysfunction in rat offspring. Br J Pharmacol. 2011; 164: 1400-1409.

44. Heitzer T, Brockhoff C, Mayer B, Warnholtz A, Mollnau H, Henne S, et al. Tetrahydrobiopterin improves endothelium-dependent vasodilation in chronic smokers: evidence for a dysfunctional nitric oxide synthase. Circ Res. 2000; 86: 36-41.

45. Ueda S, Matsuoka H, Miyazaki H, Usui M, Okuda S, Imaizumi T. Tetrahydrobiopterin restores endothelial function in long-term smokers. J Am Coll Cardiol. 2000; 35: 71-75.

46. Grunfeld S, Hamilton CA, Mesaros S, McClain SW, Dominiczak AF, Bohr DF, et al. Role of superoxide in the depressed nitric oxide production by the endothelium of genetically hypertensive rats. Hypertension. 1995; 26: 854-857.

47. Myatt L. Review: Reactive oxygen and nitrogen species and functional adaptation of the placenta. Placenta. 2010; 31: 66-69.

48. Sekhon HS, Keller JA, Proskocil BJ, Martin EL, Spindel ER. Maternal nicotine exposure up regulates collagen gene expression in foetal monkey lung. Association with alpha7 nicotinic acetylcholine receptors. Am J Respir Cell Mol Biol. 2002; 26: 31-41.

49. Sekhon HS, Jia Y, Raab R, Kuryatov A, Pankow JF, Whitsett JA, et al. Prenatal nicotine increases pulmonary alpha7 nicotinic receptor expression and alters fetal lung development in monkeys. J Clin Invest. 1999; 103: 637-647.

50. Wang R, Wang Z. Three different vasoactive responses of rat tail artery to nicotine. Can J Physiol Pharmacol. 2000; 78: 20-28.

51. Hoffman HJ, Damus K, Hillman L, Krongrad E. Risk factors for SIDS. Results of the National Institute of Child Health and Human Development SIDS Cooperative Epidemiological Study. Ann N Y Acad Sci. 1988; 533: 13-30.

52. Malloy MH, Kleinman JC, Land GH, Schramm WF. The association of maternal smoking with age and cause of infant death. Am J Epidemiol. 1988; 128: 46-55.

53. Matturri L, Ottaviani G, Ramos SG, Rossi L. Sudden Infant Death Syndrome (SIDS): a study of cardiac conduction system. Cardiovasc Pathol. 2000; 9: 137-145.

54. Mitchell EA, Milerad J. Smoking and the sudden infant death syndrome. Rev Environ Health. 2006; 21: 81-103.

55. Nachmanoff DB, Panigrahy A, Filiano JJ, Mandell F, Sleeper LA, Valdes-Dapena M, et al. Brainstem 3H-nicotine receptor binding in the sudden infant death syndrome. J Neuropathol Exp Neurol. 1998; 57: 1018-1025.

56. Huang ZG, Wang X, Evans C, Gold A, Bouairi E, Mendelowitz D. Prenatal nicotine exposure alters the types of nicotine receptors that facilitate excitatory inputs to cardiac vagal neurons. J Neurophysiology. 2004; 92: 2548-2554.

57. Feng Y, Caiping M, Li C, Can R, Feichao X, Li Z, et al. Fetal and offspring arrhythmia following exposure to nicotine during pregnancy. J Appl Toxicol. 2010; 30: 53-58.

58. Lawrence J, Chen M, Xiong F, Xiao D, Zhang H, Buchholz JN, et al. Foetal nicotine exposure causes PKCÎμ gene repression by promoter methylation in rat hearts. Cardiovasc Res. 2011; 89: 89-97.

59. Chen L, Hahn H, Wu G, Chen CH, Liron T, Schechtman D, et al. Opposing cardioprotective actions and parallel hypertrophic effects of delta PKC and epsilon PKC. Proc Natl Acad Sci U S A. 2001; 98: 11114-11119.

60. Ping P, Zhang J, Pierce WM, Bolli R. Functional proteomic analysis of protein kinase C epsilon signaling complexes in the normal heart and during cardioprotection. Circ Res. 2001; 88: 59-62.

61. Murriel CL, Mochly-Rosen D. Opposing roles of delta and epsilonPKC in cardiac ischemia and reperfusion: targeting the apoptotic machinery. Arch Biochem Biophys. 2003; 420: 246-254.

62. Gicquel C, El-Osta A, Le Bouc Y. Epigenetic regulation and fetal programming. Best Pract Res Clin Endocrinol Metab. 2008; 22: 1-16.

63. Hochberg Z, Feil R, Constancia M, Fraga M, Junien C, Carel JC, et al. Child health, developmental plasticity, and epigenetic programming. Endocr Rev. 2011; 32: 159-224.

64. Egger G, Liang G, Aparicio A, Jones PA. Epigenetics in human disease and prospects for epigenetic therapy. Nature. 2004; 429: 457-463.

65. Auclair G, Weber M. Mechanisms of DNA methylation and demethylation in mammals. Biochimie. 2012; 94: 2202-2211.

66. Verdone L, Agricola E, Caserta M, Di Mauro E. Histone acetylation in gene regulation. Brief Funct Genomic Proteomic. 2006; 5: 209-221.

67. Portnoy V, Huang V, Place RF, Li LC. Small RNA and transcriptional upregulation. Wiley Interdiscip Rev RNA. 2011; 2: 748-760.

68. Suter M, Abramovici A, Aagaard-Tillery K. Genetic and epigenetic influences associated with intrauterine growth restriction due to in utero tobacco exposure. Pediatr Endocrinol Rev. 2010; 8: 94-102.

69. Maccani MA, Knopik VS. Cigarette smoke exposure-associated alterations to non-coding RNA. Front Genet. 2012; 3: 53.

70. Xiao D, Dasgupta C, Li Y, Huang X, Zhang L. Perinatal nicotine exposure increases angiotensin II receptor-mediated vascular contractility in adult offspring. PLoS ONE. 2014.

71. Breton CV, Byun HM, Wenten M, Pan F, Yang A, Gilliland FD. Prenatal tobacco smoke exposure affects global and gene-specific DNA methylation. Am J Respir Crit Care Med. 2009; 180: 462-467.

72. Li Y, Xiao D, Dasgupta C, Xiong F, Tong W, Yang S, et al. Perinatal nicotine exposure increases vulnerability of hypoxic-ischemic brain injury in neonatal rats: role of angiotensin II receptors. Stroke. 2012; 43: 2483-2490.

73. Li Y, Xiao D, Yang S, Zhang L. Promoter methylation represses AT2R gene and increases brain hypoxic-ischemic injury in neonatal rats. Neurobiol Dis. 2013; 60: 32-38.

74. Giussani DA, Gardner DS, Cox DT, Fletcher AJ. Purinergic contribution to circulatory, metabolic, and adrenergic responses to acute hypoxemia in fetal sheep. Am J Physiol Regul Integr Comp Physiol. 2001; 280: 678-685.

75. Patterson AJ, Chen M, Xue Q, Xiao D, Zhang L. Chronic prenatal hypoxia induces epigenetic programming of PKC{epsilon} gene repression in rat hearts. Circ Res. 2010; 107: 365-373.

76. Zucchi FC, Yao Y, Ward ID, Ilnytskyy Y, Olson DM, Benzies K, et al. Maternal stress induces epigenetic signatures of psychiatric and neurological diseases in the offspring. PLoS One. 2013; 8: 56967.

77. Maccani MA, Avissar-Whiting M, Banister CE, McGonnigal B, Padbury JF, Marsit CJ. Maternal cigarette smoking during pregnancy is associated with downregulation of miR-16, miR-21, and miR-146a in the placenta. Epigenetics. 2010; 5: 583-589.

78. Taki FA, Pan X, Zhang B. Chronic nicotine exposure systemically alters microRNA expression profiles during post-embryonic stage in Caenorhabditis elegant. J Cell Physiol. 2014; 229: 79-89.