The Effects of Nicotine on Development

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Abstract

Recently, there has been a significant increase in the use of noncombustible nicotine–containing products, including electronic cigarettes (e-cigarettes). Of increasing popularity are e-cigarettes that can deliver high doses of nicotine over short periods of time. These devices have led to a rise in nicotine addiction in adolescent users who were nonsmokers. Use of noncombustible nicotine products by pregnant mothers is also increasing and can expose the developing fetus to nicotine, a known teratogen. In addition, young children are frequently exposed to secondhand and thirdhand nicotine aerosols generated by e-cigarettes, with little understanding of the effects these exposures can have on health. With the advent of these new nicotine-delivery systems, many concerns have arisen regarding the short- and long-term health effects of nicotine on childhood health during all stages of development. Although health studies on nicotine exposure alone are limited, educating policy makers and health care providers on the potential health effects of noncombustible nicotine is needed because public acceptance of these products has become so widespread. Most studies evaluating the effects of nicotine on health have been undertaken in the context of smoke exposure. Nevertheless, in vitro and in vivo preclinical studies strongly indicate that nicotine exposure alone can adversely affect the nervous, respiratory, immune, and cardiovascular systems, particularly when exposure occurs during critical developmental periods. In this review, we have included both preclinical and clinical studies to identify age-related health effects of nicotine exposure alone, examining the mechanisms underlying these effects.

In recent years, new nicotine-delivery systems and other noncombustible nicotine–containing products have become increasingly available for recreational purposes and for smoking cessation. Currently, nicotine-containing electronic cigarettes (e-cigarettes), smokeless tobacco (Swedish snuff, pituri, or mishri), and nicotine-replacement therapies (NRTs), such as transdermal patches or chewing gum, are commonly being used by the public.1-4

The use of these noncombustible nicotine products has raised significant concerns about the health effects of nicotine alone on children and vulnerable populations. Most recently, widespread adolescent use and addiction to nicotine has been recognized as a consequence of new e-cigarette technologies.5,6 Among adolescents, the introduction of JUUL in particular has contributed to higher nicotine exposure and greater addiction potential compared with nonpod users.7 The health effects of unintentional or secondhand and thirdhand nicotine exposure from noncombustible nicotine sources are

less understood. It has been recognized, however, that use of these products can expose nonusers to detectable nicotine levels. For instance, nicotine exposure can occur in offspring of mothers who use noncombustible nicotine products during pregnancy and in children exposed to secondhand nicotine-containing aerosols. Breast milk from users of Swedish snuff has been shown to contain high nicotine and cotinine levels, and measurable levels of nicotine have been found in breast milk from mothers who use the nicotine patch for smoking cessation. Elevated levels of nicotine from e-cigarette aerosols have also been detected by air sampling, with measurable levels of nicotine found in nontobacco users attending an e-cigarette convention. In addition, other studies have found that thirdhand nicotine exposure from e-cigarettes can also occur.

Before the widespread acceptance of these noncombustible nicotine products, there has been little focus on the health effects of nicotine alone on childhood health and development, with most studies focused on tobacco smoke exposure. Consequently, current knowledge of the health effects of nicotine alone on childhood health and development come primarily from in vitro and in vivo preclinical studies, maternal in utero smoke exposure, and cross-sectional studies in e-cigarette users. Although several recent clinical studies support an association between nicotine aerosols and a higher likelihood of cardiovascular and respiratory disease in users, no long-term longitudinal studies exist that have addressed the health effects of noncombustible nicotine products on childhood development.

Because of the recent popularity of noncombustible nicotine–containing products, there has emerged an urgent need to inform policy makers and health care providers about the potential health effects of nicotine exposure on childhood development. In this review, we aim to explore the age-related effects of nicotine exposure and the mechanisms underlying these effects using, when available, clinical studies focused on noncombustible nicotine use during development. Because there are few existing human studies examining the effects of pure nicotine exposure, we have included in vivo, in vitro, and human smoke exposure studies in this review to determine the likelihood of nicotine exposure alone in causing adverse health consequences during development.

**NICOTINE AS A LIGAND FOR NICOTINIC ACETYLCHOLINE RECEPTORS**

Nicotinic acetylcholine receptors (nAChRs) are located throughout the central and peripheral nervous system. These receptors are transmembrane pentameric neurotransmitter-gated ion channels that open with ligand binding, enabling fast synaptic transmission.

The neuronal nAChR subunits are composed of α-2 to α-10 subunits and β-2 to β-4 subunits. Although acetylcholine is the endogenous ligand for nAChRs, these receptors can also bind with nicotine. The α-4 and β-2 nAChRs bind nicotine with high affinity, whereas the α-7 nAChRs bind nicotine with less affinity. Animal modeling has revealed that nicotine exposure can cause inappropriate activation or deactivation of nAChRs during critical periods of brain development.

Nicotine addiction causes upregulation of nAChRs. When nicotine binds to nAChRs, the neurotransmitter dopamine is released, reinforcing drug use and feelings of pleasure. Chronic exposure to nicotine can decrease responsiveness of nAChRs in the brain, alter sensitivity to dopamine, and change brain circuits involved in learning, stress, and self-control; this can result in addiction and dependence, characterized by withdrawal symptoms when not using nicotine. Nicotine can also activate the endogenous opioid system through α-7 nAChRs binding. Preclinical studies in knock-out mice have revealed that both β-2 and α-7 subunits are important for nicotine addiction and withdrawal. Other neurotransmitters can also be released when nicotine binds to nAChRs, including norepinephrine, acetylcholine, serotonin, γ-aminobutyric acid, and glutamate.

**NICOTINE METABOLISM**

The development of health issues and propensity toward addiction are likely influenced by nicotine metabolism. Nicotine is primarily metabolized by CYP2A6 in the liver, and age, genetics, sex, and kidney function can contribute to the variability in rates of nicotine metabolism. Nicotine exposure can occur during fetal and early postnatal life. Dempsey et al reported detectable umbilical cord nicotine levels in newborns of smoking mothers. They also found that elimination of nicotine was prolonged in the newborns compared with adults. Nordenstam et al reported that users of snuff had higher levels and slower clearance of nicotine from their breast milk compared with smokers.

Although adolescent use of alternative tobacco products is increasing, most studies on nicotine metabolism have been done in smokers. Nevertheless, genetics likely influences the probability of nicotine addiction in both smokers and noncombustible nicotine users. A study in Mexican mestizo smokers revealed that the number of risk alleles in the CYP2A6 gene correlated with earlier initiation of smoking and greater consumption. Another study in adolescent smokers reported that fast metabolizers of nicotine had greater nicotine withdrawal symptoms.
Nicotine pharmacokinetics can also vary by nicotine-delivery device and likely contributes to addiction potential. In one study, researchers compared plasma nicotine levels in users of cigarettes, snus, and nicotine gum. They found that loose snus had peak plasma nicotine levels at 1 hour, nicotine gum at 45 minutes, and cigarette users at 7 minutes. A small study in adults using nicotine-containing e-cigarettes revealed peak plasma nicotine levels at 5 minutes, with nicotine levels similar to smokers. Another study reported that experienced smokers and e-cigarette users can self-titrate to achieve optimal levels of nicotine. Additional studies are needed to further understand age-related differences in metabolism of noncombustible nicotine in infants, children, and adolescents and how these differences can affect health outcomes.

NICOTINE AND PREGNANCY

Nicotine levels have been detected in offspring of mothers who smoke during pregnancy, and in utero smoke exposure has been associated with some forms of birth defects. This relationship was highlighted in a live-birth cohort study in which smoking during the first trimester increased the likelihood of birth defects, including limb reduction, gastrochisis, and oral clefts. However, determining the effects of nicotine alone on health outcomes is difficult because tobacco smoke contains >4800 different components. Preclinical studies suggest that nicotine alone may interfere with normal development. A study in pregnant mice found that nicotine crosses the placenta into the fetal bloodstream and binds to fetal nAChRs. Another study in pregnant rats revealed a transient reduction in uterine blood flow with nicotine aerosols that could be blocked using a nAChR antagonist. Of increasing concern is the perception that e-cigarette or noncombustible tobacco use is a safe alternative to smoking during pregnancy. The prevalence of e-cigarette use in pregnant women has been estimated to be between 0.6% and 15%. However, to date, studies evaluating birth outcomes in mothers who use nicotine-containing e-cigarette during pregnancy are lacking. A study in the United Kingdom revealed a significant increase in respiratory anomalies (odds ratio [OR]: 4.65) in mothers using NRTs compared with controls.

Cleft Palate

Fetal exposure to maternal smoking during pregnancy is related to the presence of orofacial clefts in the offspring. A case-control study revealed that offspring exposed to prenatal smoke were 1.6 to 2.0 times as likely to have a cleft lip or palate if these defects were not associated with other congenital abnormalities. Separating out the effect of nicotine on birth outcomes, however, can be difficult. Nevertheless, a preclinical study in mice found that persistent exposure to nicotine during pregnancy led to stillbirth, low birth weight, and abnormalities of the palate. Gunnerbeck et al also reported that mothers who used Swedish snuff during pregnancy had a higher adjusted OR (1.19) of delivering a child with an oral cleft compared with nontobacco users. These studies suggest that nicotine alone is associated with abnormal in utero palate development.

Preterm Birth

Maternal smoking during pregnancy is a known risk factor for prematurity. In a study from New Zealand, maternal smoking during pregnancy was related to an independent increase in preterm birth, and in a case-control study from Stockholm, preterm birth was increased in moderate to heavy smokers. A study supporting a nicotine link to preterm birth revealed that mothers who used snuff during pregnancy had an increased OR of 1.58 for premature birth compared with mothers not using tobacco products.

Stillbirth

In a preclinical study in mice, nicotine exposure during pregnancy caused a significant increase in fetal loss. Noncombustible nicotine use and increased risk for stillbirth delivery is supported by several human studies. Mothers who used Swedish snuff during pregnancy had a higher likelihood of having a stillborn infant. Another study revealed that the absolute risks of stillbirth were similar between mothers who smoked or used NRT (5 per 1000 live births) compared with controls (3.5 per 1000 live births); however, the adjusted OR in the NRT group was not significantly different from that of controls.

Intrauterine Growth Restriction

Maternal smoking during pregnancy has been associated with intrauterine growth restriction. Preclinical nicotine studies also support this relationship. A study in pregnant rats revealed fetal growth restriction and reduction in uterine and placental blood flow in nicotine-treated rats, and Rowell and Clark reported that nicotine-treated pregnant mice had decreased placental and fetal weights. The role of nicotine and altered fetal growth is also supported by a study in mothers who used snuff during pregnancy. They had an increased OR of 1.26 for a small-for-gestational-age infant, whereas offspring of mothers who smoked had an increased OR of 2.55.

These preclinical and human studies of pregnant mothers who smoke or use smokeless tobacco support an association between nicotine exposure and adverse pregnancy outcomes.
NICOTINE AND SUDDEN INFANT DEATH SYNDROME

Maternal smoking during pregnancy is a known risk factor for sudden infant death syndrome (SIDS). In a large national case-control study, Mitchell et al., found a relative risk of SIDS of 4.09 (95% confidence interval 3.28–5.11) among infants whose mothers smoked during pregnancy. Preclinical studies in animals support a relationship between nicotine exposure in utero and abnormal respiratory responses in mice. Mouse pups exposed to in utero nicotine can develop abnormal respiratory responses to hypoxia and depressed arousal to intermittent hypoxia. Cohen et al. found that pups lacking functional β-2-containing nAChRs had similar respiratory responses as the nicotine-exposed pups. Slotkin et al. also found that catecholamine responses were impaired in rats exposed to in utero nicotine. Another study in pregnant baboons given nicotine infusions revealed that offspring developed altered serotonergic and nAChR binding in areas of the medulla that regulate cardiorespiratory control. Although no studies were found linking SIDS and infants exposed to noncombustible tobacco products, Nordenstam et al. reported that infants of mothers who used Swedish snuff or smoked during pregnancy had higher low frequency and high frequency ratios at 1 to 2 months of age compared with controls, indicative of lower vagal activity. Taken together, the preclinical animal studies and observations in children exposed to prenatal smoke indicate a possible association between in utero nicotine exposure and increased risk of SIDS.

NICOTINE EXPOSURE AND BEHAVIORAL OUTCOMES

Neuronal nAChRs are expressed during different periods of fetal development and are involved in cell survival, synaptogenesis, and morphogenesis. Inappropriate activation of nAChRs during fetal and early postnatal development by nicotine exposure can disrupt normal brain development. In utero nicotine exposure may also have more long-term effects on behavior. In our murine model, adult mice exposed to nicotine-containing e-cigarette aerosols during late gestation and early postnatal life only demonstrated increased levels of activity in the zero maze and open-field tests compared with controls. In other murine models, prenatal nicotine exposure was associated with behavioral analogs of anxiety and altered sensorimotor integration and deficits in attention and working memory in male mice. In rats, prenatal nicotine exposure was associated with developmental effects on the medial prefrontal cortex, decreased synaptic plasticity, and attention deficit–related deficits in cognitive behavior. In contrast, one study found that adolescent rats had enhanced learning when exposed to nicotine in some settings. Multiple studies in humans exposed to smoke support the preclinical findings. Behavioral and cognitive outcome studies in children with in utero smoke exposure revealed impaired executive function, altered intelligence and auditory functioning, and behavioral problems. A meta-analysis found an association between prenatal smoke exposure and attention-deficit/hyperactivity disorder. In a Finnish national birth cohort study, an association was found between in utero smoke exposure and higher rates of behavioral and emotional disorders. The combination of preclinical and human studies in children exposed to prenatal smoke indicate that in utero nicotine exposure alone likely contributes to adverse behavioral and cognitive outcomes. However, prospective observational studies will be needed to determine the extent by which noncombustible nicotine exposures can affect developmental and behavioral problems during childhood and adolescence.

NICOTINE AND ADDICTION

Nicotine addiction is characterized by mood or performance enhancement and avoidance of withdrawal symptoms, whereas nicotine withdrawal symptoms include irritability, depression, restlessness, anxiety, problems socializing, difficulty with concentrating, increased hunger, insomnia, and craving for tobacco. Preclinical studies suggest that behavioral differences and greater dopamine release in response to nicotine underlie the greater likelihood of addiction occurring in adolescents compared with adults. Among never smokers, adolescents who tried nicotine-containing e-cigarettes were at significantly higher risk for daily use of e-cigarettes (adjusted OR: 2.92), whereas adolescents who tried nonnicotine-containing e-cigarettes were not. In addition, pod products containing high levels of nicotine, such as JUUL, have resulted in widespread acceptance of e-cigarettes among adolescents. In a study of high school students who ever used e-cigarettes, JUUL was the preferred device among ever users of single devices and was associated with the highest nicotine use. Another study revealed that adolescents who were pod e-cigarette users had greater nicotine dependence and higher urinary cotinine levels than nonpod e-cigarette users. Another study emphasized the addictive potential of e-cigarettes in adolescents. Of the adolescents who only used e-cigarettes, 80.3% were still using 12 months later, daily use increased from 14.5% to 29.8%, and tobacco smoking initiation occurred in 28.8%. These studies and others suggest that the widespread use and acceptance of e-cigarettes, particularly the pod devices...
containing high levels of nicotine, will likely increase the number of adolescents addicted to nicotine and increase tobacco smoking initiation in upcoming years.

**NICOTINE AND THE CARDIOVASCULAR SYSTEM**

Maternal smoking is associated with an increased risk of long-term pediatric cardiovascular morbidity in offspring. There is little known, however, regarding the effects of nicotine alone on the development of cardiovascular disease in children and adolescents. Several clinical studies indicate that nicotine-containing e-cigarettes can cause short-term cardiovascular changes in adults. Fritz et al. reported that users of nicotine-containing e-cigarettes or conventional cigarettes had greater arterial stiffness, higher systolic and diastolic blood pressure, and a higher heart rate compared with subjects not exposed to nicotine. In this study, the users of nicotine-containing e-cigarette sustained elevated blood pressure longer than those smoking conventional cigarettes. Although short-term cardiovascular abnormalities may predict long-term cardiovascular abnormalities in users of nicotine-containing e-cigarettes, there are currently no long-term studies. However, a preclinical study from Espinoza-Derou et al. strongly supports a link between nicotine alone and cardiovascular abnormalities. They reported that ApoE/−/− mice exposed to 2.4% nicotine e-cigarettes for 12 weeks had increased atherosclerotic lesions and decreased left ventricular fractional shortening and ejection fraction compared with mice exposed to 0% nicotine e-cigarette aerosols. Another study using ApoE/−/− mice revealed that nicotine promoted autophagy in blood vessels, increased migratory capacity of vascular smooth muscle cells (VSMCs), and promoted the development of atherosclerosis.

Nicotine was also shown to induce VSMC transformation toward a more atherosclerotic phenotype in human VSMCs. Taken together, these studies support the biological plausibility for cardiovascular disease development with the use of nicotine alone.

**NICOTINE AND THE LUNG**

Lung development in utero begins with lung-bud development in the early first trimester and extends up until the late third trimester with the formation of alveoli and surfactant maturation. Subsequently, the majority of postnatal alveolar growth occurs by age 2 years, with more recent evidence suggesting some additional growth into adolescence. Thus, any environmental exposures occurring between conception and adolescence have the potential to affect lung growth. However, parsing the effects of nicotine from those of other constituents in smoke exposure or e-cigarette aerosols in the developing human lung is difficult because the respiratory epithelium is exposed to both.

In utero, nicotine is readily absorbed into the maternal bloodstream and crosses the placenta, with blood levels in the fetus thought to be similar to those in the mother. Mechanisms by which nicotine may affect the developing lung include via nAChRs and through reduction of antioxidant enzyme activity. Animal studies of prenatal nicotine exposure reveal multiple changes within the lung, including narrowing of airways and thickening of their walls, and dysnaptic lung growth with reduced surface area complexity. The resultant effects in rodents include reduced forced expiratory flows in adulthood akin to obstructive lung disease in humans. There are some data suggesting that the pulmonary effects of prenatal nicotine may be ameliorated by antioxidant therapy (vitamin C) in monkeys and melatonin in rats.

The effects of postnatal nicotine exposure on lung development are less well elucidated than those of prenatal exposure. Nicotine and nicotine metabolites have been detected in children exposed to secondhand smoke. There are causal links between smoke exposure and lower respiratory tract illnesses in infants and children, asthma in school-aged children, and reduced childhood lung function, suggesting effects on immune function, airway characteristics, and lung growth. Several cross-sectional studies in adolescent users of e-cigarettes have revealed an association between e-cigarette use and chronic bronchitis symptoms, self-reported doctor diagnosis of asthma, higher rates of respiratory symptoms, and greater school absenteeism due to asthma.

In vitro and in vivo studies examining mucociliary clearance (MCC) in the lung have revealed that nicotine-containing e-cigarettes can impair MCC and decrease airway hydration. Impairment of MCC can alter immune defenses in the lung and increase the likelihood of lower airway infections.

Nicotine exposure in utero or in early childhood may also have respiratory effects throughout the life span of the individual through epigenetic changes, which may be heritable. One study of nicotine-exposed pregnant rats revealed that the offspring of the exposed offspring had potentially epigenetic-induced increased airway resistance and contractility proteins.

Although no long-term studies exist, preclinical and limited clinical studies support an association between exposure to nicotine alone and impaired lung development and altered MCC. Cross-sectional studies in adolescents also suggest an increased risk for respiratory symptoms in adolescent e-cigarette...
users with and without asthma. Prospective observational studies will be needed to fully delineate the effects of nicotine alone on lung function and respiratory outcomes.

NICOTINE AND THE IMMUNE SYSTEM

The mechanisms underlying nicotine’s effect on immune responses is complex. Tobacco smoke exposure can alter immune responses by inducing T helper 2 cytokine production and attenuating interferon-γ responses in children. Young children with mothers who smoked had a higher risk of lower respiratory tract infections, as did children exposed to secondhand smoke. Preclinical studies have revealed that nicotine can alter immune function via nAChRs on lymphocytes or by glucocorticoid hypersecretion. In other animal studies, authors have attempted to parse out the effects of nicotine from tobacco smoke. The authors in a study in mice used nicotine e-cigarette aerosols and found that exposed mice had impaired bacterial clearance of Streptococcus pneumoniae and increased viral titers of influenza A virus compared with controls. Another study in mice revealed that nicotine-activated α-7 nAChRs increased recruitment of T regulatory cells. Other mouse studies reported that nicotine can impede airway clearance by impairing MCC, increasing mucus viscosity and inactivating α-7 nAChRs in the airways.

Taken together, these preclinical and smoke studies indicate that nicotine can alter antimicrobial and inflammatory responses and impact MCC in the airways.

NICOTINE AND MALIGNANCY

It is well known that the use of combustible tobacco products increases the risk for a malignancy; however, nicotine alone may contribute to treatment resistance and cancer progression. An in vitro study using human umbilical cord mesenchymal stem cells treated with nicotine revealed increased migration, enhanced stemness, and increased epithelial-mesenchymal transition (EMT). Consistent with cellular processes that promote tumor progression. In another study, nicotine induced EMT of breast cancer cells and activated fibroblasts, which enhanced EMT and cancer cell migration. A study using human non–small cell lung cancer cells revealed that nicotine induced non–small cell lung cancer cell invasion, migration, and EMT, effects that were mediated by α-7 nAChRs. No studies currently exist linking nicotine-containing e-cigarettes and tumor progression or development in any organ systems. Long-term observational studies will likely answer these questions. Nevertheless, current in vitro studies suggest a link between exposure to nicotine alone and tumor progression and cancer cell migration.

ACUTE NICOTINE INGESTION IN CHILDREN AND ADOLESCENTS

Nicotine is a water-soluble bioactive alkaloid with strong parasympathomimetic properties. Mild acute nicotine intoxication can cause nausea, vomiting, respiratory symptoms, and cardiovascular instability, whereas high levels of systemic nicotine can lead to seizures and cardiorespiratory arrest. The severity of nicotine intoxication depends on dose, duration, frequency of exposure, route of exposure, and formulation. Accidental ingestion of liquid nicotine has been responsible for the deaths of several young children. As a result of these accidental nicotine ingestions in children, the Child Nicotine Poisoning Prevention Act was passed in 2016, resulting in a significant decline in accidental liquid nicotine exposures in the United States.

In addition, suicide rates in adolescents and young adults have been increasing. It has been recently recognized that adolescents who use e-cigarettes are at higher risk for mental health concerns and that suicides and attempts by nicotine ingestion have occurred in teenagers and young adults.
Therefore, health care providers need to be aware that adolescent e-cigarette users may represent a subset of children at increased risk for depression and suicide and that liquid nicotine can be used as a vehicle for suicide attempts.

**GAPS IN KNOWLEDGE**

This review supports biological plausibility for nicotine exposure alone to cause adverse health outcomes in children and adolescents (Table 1, Supplemental Table 2). With the emergence of new devices that deliver noncombustible nicotine and their increasing popularity to youth, there is a growing need to understand the effects of nicotine alone on human health. In addition to preclinical studies, steps are needed to characterize users and their profiles (including trajectories) and to identify those at highest risk for nicotine addiction and nicotine-related health conditions. A more complete understanding of the effects of nicotine exposure on offspring of pregnant women, on infants and children, on adolescents who vape, and on children with chronic health conditions is also needed. In addition, public health interventions that regulate the manufacture, sale, and use of these new nicotine-delivery systems should be implemented to reduce exposure to adolescents and young adults who are at an increased risk for long-term health issues.

**CONCLUSIONS**

Preclinical and clinical studies indicate that nicotine exposure alone has the potential to cause developmental abnormalities, harm childhood health, and addict a new generation of adolescents and young adults. Additional education, studies, and policies are needed to protect children and to mitigate nicotine’s adverse health effects in children and vulnerable populations.

**ABBREVIATIONS**

e-cigarette: electronic cigarette
EMT: epithelial-mesenchymal transition
MCC: mucociliary clearance
nAChR: nicotinic acetylcholine receptor
NRT: nicotine-replacement therapy
OR: odds ratio
SIDS: sudden infant death syndrome
VSMC: vascular smooth muscle cell

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