Cardiorespiratory effects of nicotine exposure during development

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Abstract

Exposure to tobacco smoke is a major risk factor for the sudden infant death syndrome. Nicotine is thought to be the ingredient in tobacco smoke that is responsible for a multitude of cardiorespiratory effects during development, and pre-rather than postnatal exposure is considered to be most detrimental. Nicotine interacts with endogenous acetylcholine receptors in the brain and lung, and developmental exposure produces structural changes as well as alterations in neuroregulation. Abnormalities have been described in sympathicovagal balance, arousal threshold and latency, breathing pattern at rest and apnea frequency, ventilatory response to hyperoxia or hypoxia, heart rate regulation and ability to autoresuscitate during severe hypoxia. This review discusses studies performed on infants of smoking mothers and nicotine-exposed animals yielding varying and sometimes inconsistent results that may be due to differences in experimental design, species and the dose of exposure. Taken together however, developmental nicotine exposure appears to induce vulnerability during hypoxia and a potential inability to survive severe asphyxia.

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1. Introduction

Intrauterine exposure to maternal tobacco smoking is associated with increased morbidity and mortality of the human infant. The magnitude of the problem varies among different countries, but as recently reported by the International Child Care Practices Study, 22% of mothers and 45% of fathers were smoking at a child’s birth in a survey of 21 centers in 17 countries (Nelson and Taylor, 2001). However, the prevalence of smoking might be lower now due to intensive anti-smoking campaigns in many countries. Infants of smoking mothers have lower birth weight, higher prevalence of pulmonary morbidity in infancy and childhood, increased risk of late fetal and early neonatal death as well as an increased risk of the sudden infant death syndrome (SIDS) than compared with unexposed infants.

It is generally believed that nicotine is the major agent in tobacco smoke that acts as a developmental neurotoxicant and is responsible for most of the...
harmful effects (Slotkin, 2004). Furthermore, prenatal exposure is considered to be a major risk factor both for pulmonary disease and SIDS. Nicotine is readily transferred to the fetus, where it binds to nicotinic acetylcholine receptors (nAChR). This article will review recent studies of cardiorespiratory effects of nicotine in the developmental period. Results of these studies have sometimes been inconsistent and often inconclusive, which might be explained partially by the use of various forms of exposure in various species. Furthermore, both the lung and the central nervous system are target organs for prenatal nicotine exposure with alterations of their specific function making interpretation of, e.g., altered breathing patterns and the ventilatory response to hypoxia complex.

2. Smoking and SIDS

Since passive smoking was identified as a risk factor for SIDS, numerous studies have added substantial evidence for this relationship. Large intervention programs successfully reducing the prevalence of prone sleeping, another key risk factor for SIDS, have led to an increased relative importance of passive smoking as a risk factor. The risk for SIDS is increased by both pre- and postnatal exposure, and there is a definite dose–response relationship between SIDS and pre- or postnatal exposure. Maternal smoking of more than 20 cigarettes per day increases the relative risk for SIDS (Mitchell and Milerad, 1999).

Objective measurements of nicotine and its metabolites in victims of SIDS indicate that these infants have been significantly exposed to tobacco smoke both prior to and around the time of death (Milerad et al., 1994; Milerad et al., 1998). High postmortem concentrations of nicotine metabolites are found more frequently in infants who were co-sleeping with parents and in those with focal organ lesions possibly due to unrecognized hypoxic-ischemic insults.

Morphological findings usually regarded as being typical of SIDS include decrease in visceral organ size and delays in their normal pattern of maturation, tissue scarring and alterations in gene activation leading to, e.g., increased release of serotonin from neuroendoctrine cells in the lung (Schuller et al., 2000). Similar organ changes can also be produced by fetal exposure to tobacco products.

3. Methodological considerations regarding maternal smoking and animal nicotine infusion studies

3.1. Maternal smoking

The number of cigarettes smoked by the mothers in the studies reviewed here varies considerably. Most women were reported to be light or moderate smokers, smoking less than 10 or 10–20 cigarettes per day, respectively. The nicotine content of cigarettes varies widely but is usually not specified in these reports. Most mothers smoked both before and after birth of their child. Only some studies have reported whether other persons in the household were smokers. It might be of importance to know whether the control infants were exposed to passive smoking. The use of other drugs is rarely presented. Only a few studies have reported maternal cotinine concentrations.

To confirm presence of nicotine exposure in the study infants and absence thereof in the control infants, levels of cotinine, a slowly eliminated major nicotine metabolite, have been reported in urine (Lewis and Bosque, 1995; Poole et al., 2000; Taladhar et al., 2003; Parsiow et al., 2004; Horne et al., 2002), hair (Sovik et al., 1999) or saliva (Campbell et al., 2001) from the study infants. However, such levels were not reported in other studies, i.e., (Tirosh et al., 1996; Ueda et al., 1999; Franco et al., 1999; Galland et al., 2000; Chang et al., 2003). As Sovik et al. (1999) have pointed out, such levels are essential to show that the results are valid, i.e., that the control and smoke-exposed groups differed. Women claiming to be non-smokers could actually have smoked and women claiming to be smokers could have smoked too little to result in detectable physiological changes in their infants.

3.2. Animal nicotine infusion studies

Most studies of prenatal nicotine exposure have been performed in rats using maternal continuous subcutaneous infusions by osmotic minipumps (Alzet) of nicotine bitartrate, often referred to as nicotine tartrate. However, the dose is often expressed as free base nico-
nicotine, which is 35% of the nicotine bitartrate dose. Sometimes it is not clear whether the dose is based on free base nicotine or nicotine tartrate.

The commonly used dose of approximately 6 mg/kg/day nicotine tartrate, corresponding to 2.1 mg/kg/day free base nicotine, achieves maternal mean nicotine blood levels of approximate 35 ng/ml (Fewell et al., 2001b; Murrin et al., 1987) similar to levels present in heavy smokers smoking 30 cigarettes per day (Benowitz et al., 1982). This dose regimen has not been shown to be associated with effects on fetal growth in rats (Bamford et al., 1996; Huang et al., 2004; Fewell et al., 2001a,b).

Other studies have used 6 mg/kg/day free base nicotine, which would have achieved estimated maternal mean nicotine levels of approximately 80 ng/ml according to the study of Murrin et al. (1987) and calculations by Lichtensteiger et al. (1988). This level exceeds what has been found in most heavy smokers. Using this paradigm, signs of gestational toxicity in the form of reduced maternal weight gain, fetal resorption and intrauterine growth retardation have been described (Navarro et al., 1990; Slotkin et al., 1999; Gauda et al., 2001; Simakajornboon et al., 2004; Bamford and Carroll, 1999). However, Slotkin (1998, 2004) and Robinson et al. (2002) have noted that there are pharmacokinetic differences between rats and man. The plasma half-life of nicotine in the rat is about 54 min while in humans it is 2–2.5 h, and higher doses are generally required to elicit the same effects in the rat.

The plasma half-life of nicotine is 5–7 min in mice, therefore, eight- to 10-fold higher nicotine infusion rates than those used in rats have been employed to achieve similar up-regulation of nicotinic binding in the fetus (Robinson et al., 2002). The maternal dose used by Robinson et al. (2002) in mice was 60 mg/kg/day, resulting in nicotine and cotinine mean concentrations of 233 and 327 ng/ml, respectively without an effect on birth weight. Because the osmotic minipumps used for the majority of these studies infused nicotine for 28 days, the infusion occurred during most of the prenatal period and continued for approximately 10 days after birth exposing the pups to nicotine through their mothers’ milk, which theoretically could have had additional effects. In the study performed by Fewell et al. (2001a), maternal mean nicotine concentrations more than doubled from days 1–2 to days 10–11 postpartum, but nicotine was not detectable in serum of the pups. Thus, the observed effects in the pups were considered to be a result of prenatal exposure rather than of combined pre- and postnatal exposure.

4. Acute cardiovascular effects of smoking on mother and fetus

Studies comparing the effects of tobacco and non-tobacco cigarettes have shown that it is mainly the nicotine content of the cigarettes that seems to affect fetal hemodynamics (Lindblad et al., 1988). Cigarette smoking during pregnancy has been shown to acutely increase fetal heart rate as well as maternal blood pressure and heart rate (Lindblad et al., 1988). Acute repeated smoking has been shown to significantly decrease fetal heart rate variability (Oncken et al., 2002). Attempts to further evaluate the acute effects of maternal smoking on the fetal cardiovascular system with doppler ultrasound have yielded discrepant results. There are studies reporting an increase in the estimated flow in the fetal aorta and umbilical vein after maternal smoking (Pijpers et al., 1984), whereas others have found no effects. A possible reason for these discrepancies may be differences in nicotine levels (Lindblad et al., 1988). The nicotine levels needed in maternal plasma for fetal hemodynamics to be affected have been estimated to be 16–20 ng/ml (Lindblad et al., 1988) corresponding to approximately 20 cigarettes per day (Hill et al., 1983; Oncken et al., 1997).

To evaluate effects on uterine blood flow, studies in animals have employed very high nicotine infusion rates that have exceeded the amount of nicotine obtained by heavy smoking. Monheit et al. (1983) showed that very high doses of nicotine, 1.0 and 1.5 mg/min, administered to pregnant sheep decreased uterine blood flow by 42 and 32%, respectively, possibly mediated by catecholamine-induced vasoconstriction. However, a nicotine infusion rate of 0.5 mg/min resulting in mean peak nicotine concentrations of 130 ng/ml, a value substantially higher than reported in smoking people, did not substantially alter uterine or umbilical vascular hemodynamics. An infusion rate of 10 μg/kg/min of nicotine to pregnant ewes did not impair uterine blood flow and caused no fetal hypoxia (Clark and Ison, 1992). This dose corresponds to
14.4 mg/kg/day, which is still substantially higher than the maternal dose used in most other studies.

In summary, cigarette smoking appears to affect fetal heart rate and variability. However, based on studies in sheep, smoking as practiced by most mothers is unlikely to compromise uterine blood flow or cause fetal hypoxemia. The decrease in birth weight is, therefore, likely to be caused by other factors. Furthermore, as discussed below, the pattern of fetal growth retardation is somewhat different than that observed as a result of placental insufficiency.

5. Effects of perinatal tobacco smoke or nicotine exposure on lung function – implications for breathing regulation

It is beyond the scope of this article to cover this topic in detail. The aim here is to illustrate that lung function in the developmental period can be markedly altered by nicotine exposure. Numerous studies have shown an association between passive smoking and respiratory problems in infants and children, and it is now a generally held view that the main consequences are due to tobacco smoke exposure during fetal life (Tager et al., 1993). Evidence that fetal effects occur prior to the middle of the third trimester was presented by Hoo et al. (1998). They showed that premature infants born at a mean gestational age of 33 weeks to mothers who smoked during pregnancy had altered respiratory mechanics when compared with non-exposed controls of the same gestational age.

Studies evaluating pulmonary mechanics in infants and children of smoking mothers indicate that prenatal exposure alters expiratory flow profiles, reduces respiratory compliance and increases airway resistance (Hanrahan et al., 1992). In a follow-up study, Cunningham et al. (1994) reported reduced expiratory flow rates in 8–12-year-old children whose mothers smoked during pregnancy, providing evidence that the ill-effects of maternal smoking during pregnancy may persist at least into late childhood.

In animal models, maternal nicotine exposure causes a variety of effects on the neonatal lung, e.g., hypoplasia, decreased elastin in the parenchyma and increased alveolar volume indicating emphysema-like changes (Pierce and Nguyen, 2002). On a cellular level, nicotine binds to nAChR, ligand-gated ion channels controlling influx of calcium and sodium into cells. Nicotinic receptors are present not only in cholinergic nerves innervating bronchial smooth muscle and submucosal glands but also in several non-neuronal cell types, e.g., bronchial epithelial and vascular endothelial cells. Acetylcholine acting on non-neuronal nAChR is involved in modulating cell shape and motility, and may also moderate cell proliferation and differentiation. In a series of experiments, Sekhon and coworkers have shown that maternal nicotine exposure increases α7 nAChR subunit expression in airway epithelial cells, increases collagen gene expression and collagen staining in airway and alveolar walls, increases numbers of type II and neuroendocrine cells in newborn rhesus monkeys (Sekhon et al., 2002). Commensurate with the morphological changes, altered pulmonary function characterized by increased airway resistance and decreased expiratory flow rates were found. The altered lung development following prenatal nicotine exposure may also be attributed to stimulation of nAChR resulting in premature onset of cell differentiation at the expense of replication, analogous to what has been demonstrated in the central nervous system of fetal rats exposed to a continuous nicotine infusion (Slotkin, 2004).

Sandberg et al. (2004) exposed fetal sheep during the last trimester to a moderate dose of nicotine tartrate corresponding to 1.5 mg/kg/day of nicotine free base or a low dose of 0.5 mg/kg/day. Lung function studies at an age of 1–7 weeks showed that prenatal nicotine exposure improved gas mixing in distal airways and also reduced specific airway conductance as a sign of airway obstruction in proximal airways, while dynamic compliance ($C_{dyn}$) was unchanged (Sandberg et al., 2004a,b). When these lambs were exposed to acute hypoxia (0.1 FiO2), as is commonly done to evaluate the effect of nicotine on respiratory control, lambs exposed to a moderate maternal nicotine concentration (mean 17 ng/ml), but not a low concentration (6 ng/ml), showed less of the expected increase in $C_{dyn}$ and functional residual capacity together with signs of increased airway reactivity (Sandberg et al., 2004a,b).

In summary, studies in infants and children have shown that prenatal exposure to maternal tobacco smoking alters lung mechanics and increases the risk for wheezing respiratory illness that may persist into late childhood. Animal experiments have strongly linked these effects to nicotine as the respon-
sible agent and have demonstrated that prenatal expo-
sure can induce altered alveolar architecture and pul-
monary hypoplasia, increases collagen deposition and
decreases elastin content in the airways and may lead to
increased airway resistance and hyperreactivity. There-
fore, altered lung mechanics during eupneic breathing
as well as during hypoxemia make interpretation of
respiratory control studies difficult.

6. Effects of smoking and nicotine on neural
networks controlling respiration

Nicotine interacts with endogenous nicotinic acetyl-
choline receptors in the brain, which results in a wide
variety of effects (Slotkin, 1998). Fetal exposure to
tobacco smoke or nicotine produces a number of mor-
phological alterations in brain structures associated
with control of breathing (Kinney et al., 1993, 2001).
In addition to giving rise to structural changes, nicotine
alters neuroregulation through an increased release of
serotonin and nitric oxide as well as biogenic amines
(dopamine and norepinephrine) from synaptic nerve
terminals in the brain and elsewhere (Benowitz et al.,
1990). Through its effects on the release of these neu-
rotransmitters nicotine may interfere with a number
of regulatory mechanisms, many of which have been
investigated only recently.

Dopaminergic neurons regulate a variety of sen-
sory and neuroendocrine functions as well as reward-
seeking behaviors like food intake (Wooten, 1997).
Dopamine neurotransmission is more directly involved
in the control of breathing by affecting oxygen-sensing
mechanisms of the carotid bodies. Prenatal nicotine
exposure may decrease oxygen sensitivity by upreg-
ulating mRNAs involved in the synthesis of dopamine
(Ganda et al., 2001). Dopaminergic mechanisms also
play a major role in modulating the central inhibitory
response to hypoxia (Srinivasan et al., 1989).

Noradrenergic neurons regulate a variety of auto-
nomic functions including cognition and responses
to stress (Page and Valentino, 1994). As described in
detail in the section on autoreexcitation, nicotine
decreases the ability for sympathetic activation in
response to respiratory related stress such as hypox-
emia (Slotkin et al., 1995).

Nicotine exposure during fetal life increases sero-
tonin (5-HT) release by up-regulation of the nicotinic
α7 acetylcholine receptor. The role of serotonin in
mood and anxiety disorders is well known and sero-
tonin modulation is one of the cornerstones of pharma-
cotherapy of depression. Serotonin also has a major role
in the regulation of respiratory activity in that increased
levels of serotonin have mainly stimulatory effects
on respiration. Serotonin receptor agonists stimulate
breathing and can overcome opioid-induced respira-
tory depression (Manzke et al., 2003) while serotonin
receptor antagonists block the long term hyperventi-
latory response to hypoxemia. Furthermore, serotonin
plays a key role in modulation of the plasticity of the
respiratory system in terms of its adaptation to envi-
ronmental influences. In particular, the modulation of
respiratory reflexes and adaptation to hypoxemia are
mediated by serotonergic mechanisms.

Since it is frequently assumed that hypoxic ventila-
tory control is deficient in SIDS infants, it is of interest
to note that SIDS victims seem to have a deficit of 5HT-
receptors in the areas in the medulla oblongata that
regulate escape and defense mechanisms to exogenous
stressors such as asphyxia. Kinney and coworkers have
shown that the arcuate and caudal raphe nuclei, neu-
ronal networks within the reticular activating system
with abundant serotonergic projections to the respira-
tory system, contain decreased serotonergic receptor
binding in the majority of the SIDS victims they exam-
ined and have proposed that this abnormality results in
failure of protective responses to life-threatening stres-
sors (e.g., asphyxia, hypoxia, hypercarbia) (Kinney
et al., 2001). However, it has not been established that
hypoxic ventilatory control is deficient in SIDS victims.
Although Kinney et al. found a significant difference
between SIDS victims and controls, a causal relation-
ship has not yet been found, which should stimulate
further investigation. This group has also shown that
SIDS victims of smoking mothers show a failure to
up-regulate nicotine binding in the arcuate nucleus, a
brain stem area associated with respiratory and cardio-
vascular control and arousal (Nachmanoff et al., 1998).

Nicotine may be regarded as a fetal neuroteratogen
that alters the formation and differentiation of brain
cells and affects cell replication and programmed cell
death (apoptosis) (Slotkin, 2004). The neuronal dam-
age in the brain stem found in many SIDS victims,
i.e., delayed myelination and astrogliosis, has also been
ascribed to prenatal tobacco smoke exposure (Krous
et al., 1981).
Nicotinic receptors also play an important role in the regulation and generation of respiratory pattern both before and after birth (Feldman et al., 2003). The preBożtinger Complex (preBoC) is an area in the ventral medulla believed to be the site for respiratory rhythm generation. Microinjections of nicotine into preBoC and adjacent nuclei in the brain stem increase the frequency of bursts but decrease their amplitude, i.e., changes the respiratory rhythm to a pattern of rapid shallow breathing (Shao and Feldman, 2002). Although the clinical significance remains to be further elucidated, it is of interest that this particular breathing pattern is present in animals chronically exposed to nicotine during fetal life (Hafstrom et al., 2002a).

7. Effects of smoking and nicotine on control of breathing

Active smoking exposure to side stream smoke and nicotine exposure have somewhat differential effects on respiratory control and the route of exposure has to be taken into account when evaluating studies. Tobacco fumes inhaled during active smoking contains very high concentrations of nitric oxide (NO), which relaxes airway tone and dilates the lower airways during acute exposure (Vleeming et al., 2002). At the same time, NO in tobacco smoke depresses the endogenous NO synthesis in the airways, which leads to an increased airway tone during periods of non-smoking. This reduction of NO synthesis requires minute amounts of tobacco fumes and may explain some of the marked pulmonary effects of exposure to environmental tobacco smoke. Nicotine itself rapidly crosses the blood-brain barrier and releases NO from a number of neuronal sites. The endogenously released NO acts both as a cerebral vasodilator and a non-classical neurotransmitter. Endogenous NO in the brain thus decreases the sympathetic outflow from the brain to the periphery and inhibits dopamine reuptake (Vleeming et al., 2002). The likely effects on respiratory control may be a lower central sensitivity to information from oxygen sensing structures and a decreased arousability.

In summary, the central effects on respiratory control may be similar from all routes of exposure, but changes in airway tone and pulmonary mechanics that influence respiratory pattern and timing may depend on whether the subjects have been exposed to tobacco products during fetal life only, exposed to sidestream smoke after birth or exposed to nicotine only.

7.1. Effects on resting respiration from exposure to tobacco smoke

Most investigators have found that minute ventilation \( \left( V_E \right) \) is not affected by maternal smoking, although Ueda et al. (1999) found a decreased respiratory drive as estimated by occlusion pressure \( \left( P_{0.1} \right) \) in 2–24-month-old infants of smoking mothers. An altered breathing pattern with reduced tidal volume and increased respiratory rate \( \left( f_R \right) \) in infants of smoking mothers were reported by Sovik et al. (1999) and Hanrahan et al. (1992). These effects on \( f_R \) or tidal volume \( \left( V_T \right) \) were not consistently found in other studies.

7.2. Effects on resting respiration from exposure to nicotine

St.-John and Leiter (1999) found that \( V_E \) was significantly decreased in 0–4-day-old rat pups exposed to nicotine prenatally, and attributed this to a reduced metabolic rate and/or hypoventilation in the nicotine-exposed newborn. However, Bamford et al. (1996) observed no effects on oxygen consumption during normoxia or hypoxia in prenatally exposed 2–34-day-old rat pups. In a later study, Bamford and Carroll (1999) found an increased variability in oxygen consumption of nicotine-exposed 3-day rats while breathing room air, but there was no significant effect of nicotine exposure on the ability to reduce oxygen consumption in hypoxia at 3 or 8 days.

An increased respiratory rate and smaller tidal volumes were not observed by Bamford et al. (1996) in nicotine-exposed rat pups but were reported in various species by other groups. In prenatally nicotine-exposed rat pups, Huang et al. (2004) observed a higher respiratory rate at 10 days and decreased \( V_T \) at 14 and 18 days, and Simakajornboon et al. (2004) saw an increased \( f_R \) at 5 days. Similar changes in breathing pattern with an increased \( f_R \) and decreased \( V_T \) but without a significant
change in $V_E$ were found at a postnatal age of 5 and 21 days in prenatally nicotine-exposed lambs (Hafstrom et al., 2002a). These lambs also had an increased respiratory drive ($P_{0.1}$) and effective impedance suggesting altered lung function, e.g., increased airway resistance, decreased compliance, or both. The raised inspiratory drive was thus interpreted as a compensatory increase due to increased impedance of the respiratory system. Indeed, specific conductance was found to be decreased in nicotine-exposed lambs in a subsequent study using the same model (Sandberg et al., 2004a,b).

Irregular breathing with more frequent, but not longer, apneas was found in prenatally nicotine-exposed rat pups on postnatal days 1 and 2 (Huang et al., 2004). Also, Robinson et al. (2002) found a higher incidence of apnea during both normoxia and hypoxia in 0–3-day-old mice suggesting that normal developmental changes in breathing pattern are delayed following prenatal nicotine exposure.

8. Effects of smoking and nicotine on chemosensitivity

Evaluation of the oxygen sensitivity of peripheral chemoreceptors and the central integration of their afferent input is most often tested by assessing the magnitude of the ventilatory response to acute hypoxia or hyperoxia.

8.1. Response to hypoxia in infants of smoking mothers

Ueda et al. (1999) found that the ventilatory response to 0.14 FiO$_2$ was significantly blunted in 15 infants of smoking mothers aged 2–12 months during chloral hydrate-induced quiet sleep and that there was no increase in respiratory drive as estimated by $P_{0.1}$. In this study, the infants were not challenged with hypercarbia.

A lower hyperventilatory response has not been found in studies performed during natural sleep without sedation. Lewis and Bosque (1995) found that the ventilatory responses to hypoxia (0.17, 0.15, and 0.13 FiO$_2$) or hypercapnia (0.04, 0.06, and 0.08 FiCO$_2$) were similar in smoke-exposed and non-exposed infants. A recent study showed that maternal smoking did not adversely affect the ventilatory response to 0.15 FiO$_2$ prior to arousal from active or quiet sleep at 2–5 weeks, 1–3 months or 5–6 months (Parsiow et al., 2004).

Sovik et al. (1999) used an alternative method to evaluate sensitivity of oxygen chemoreceptors. They studied 15 infants of smoking mothers and 16 controls during quiet sleep at 1, 3, and 10 days and 10 weeks of age. Challenges for 15 s with alternating 1.0 FiO$_2$ and 0.15 FiO$_2$ were presented in random order. Neither the time-courses nor the magnitudes of O$_2$ responses were affected by maternal smoking. The alternating breath test (alternating two breaths of 40% O$_2$ and two breaths of 0% O$_2$), which presumably tests the sensitivity of the peripheral chemoreceptors, was used by Poole et al. (2000) to evaluate respiratory control during quiet sleep in 40 infants at 10 weeks of age. Seventeen of these were infants of smoking mothers. Exposed and control infants had similar responses for ten respiratory parameters including respiratory drive and timing.

A combined hypoxia and hypercarbia test was used by Campbell et al. (2001) in a large study of 96 smoke-exposed and 97 control infants. The infants were tested during quiet or active sleep in the supine position at 0–4 weeks and 10–14 weeks. Ventilation was measured during exposure to a test gas containing 0.055 FiCO$_2$ and 0.13 FiO$_2$ and the slope of a linear curve fit relating inspired CO$_2$ to the logarithm of ventilation was taken as a quantitative measure of ventilatory asphyxial sensitivity (VAS). Interestingly, VAS was shown to be higher in the smoke-exposed infants compared with controls.

Results of studies where oxygen sensitivity was evaluated by combining hypoxic gas mixtures with inhalation of CO$_2$ have to be interpreted with some caution. Simultaneous CO$_2$ admixture increases peripheral chemoreceptor sensitivity (Mateika et al., 2004), but more importantly there are plenty of free nerve endings and other airway receptors that sense inhaled CO$_2$ and stimulate ventilation. Inhalation of CO$_2$ can therefore not merely be regarded as “replacement” for exhaled CO$_2$ during a respiratory challenge test but has powerful effects of its own that may override other influences on O$_2$ sensitivity.

The divergent results of some of these studies suggest that factors like sleep position, activity state, use of sedation, degree of smoke exposure, and whether hypoxic or combined hypoxic and hypercarbic gas mixtures were used determine the outcome to a large extent.
Animal studies are, therefore, important to standardize the experimental conditions and to test defense mechanisms critical for survival during more severe hypoxia/asphyxia challenges.

8.2. Response to hypoxia in nicotine-exposed animals

A diminished ventilatory response to hypoxia in nicotine-treated animals has been reported by several investigators both during acute postnatal nicotine exposure and after prenatal exposure. Milerad et al. (1995) first reported that the early ventilatory response to hypoxia (0.1 FiO₂) was attenuated during an acute intravenous low-dose nicotine bitartrate infusion (0.5 μg/kg/min) in nicotine-naïve lambs at the ages of 7 and 27 days, possibly through a nicotine-induced inhibition of the oxygen chemoreceptors. Later, Hafstrom et al. (2000) used this model and demonstrated that the early ventilatory response to hypoxia was significantly blunted during quiet sleep but not during wakefulness. A subsequent report by this group showed that a continuous high dose nicotine infusion from birth does not further compromise hypoxia defense mechanisms in prenatally nicotine-exposed lambs at 5 and 21 days (Hafstrom et al., 2000).

Prenatal nicotine exposure in rats was associated with a decreased peak ventilatory response to hypoxia and a reduction in the magnitude of ventilatory roll-off at 15 min in 5-day-old but not in 10–20-day-old pups (Simakajornboon et al., 2004). The authors attributed their findings to an increased expression of certain protein kinase isoforms, i.e., PKC-β and PKC-δ in the caudal brain stem, an area thought to mediate critical components of the hypoxic ventilatory response. A decreased hypoxic ventilatory response was also found in prenatally exposed rat pups on days 0, 1 and 4 (St.-John and Leiter, 1999). In addition, these authors showed that V̇E was significantly reduced in the nicotine-exposed pups compared with controls both during normoxia and during the entire hypoxic challenge.

Hafstrom et al. (2002b) exposed fetal sheep during the last trimester to a low dose of nicotine tartrate corresponding to approximately 0.5 mg/kg/day of nicotine free base resulting in an average nicotine blood level of 7 ng/ml comparable to light smoking. At an age of 5 days, these lambs had a blunted ventilatory response to hypoxia compared with controls during quiet sleep but not during wakefulness. In contrast, other studies of young rats did not find significant differences between control and prenatally nicotine-exposed animals. Slotkin et al. (1997) measured the ventilatory response as respiratory rate and found no effect of prenatal nicotine exposure on the response to 0.05 FiO₂ in 1–2-day-old rat pups anesthetized with urethane. Also Bamford et al. (1996) could not observe that the ventilatory responses to 0.10 FiO₂ or 0.05 FiCO₂ were affected by nicotine at any of the ages tested.

When comparing the results of Bamford et al. (1996) with those reported by St. John and Leiter (1999) it should be noted that these two studies evaluated two different facets of the hypoxic ventilatory response. The newborn ventilatory response to hypoxia is characteristically biphasic; an initial peak in ventilation is followed by a decline until a steady-state is reached. The early ventilatory response to hypoxia is thought to reflect the carotid body stimulation while the steady-state late response, or roll-off, is also influenced by central adaptation. Since Bamford et al. (1996) recorded respiration during steady-state ventilation after 10 min in hypoxia, while St.-John and Leiter (1999) and Hafstrom et al. (2002b) evaluated the peak response during the initial 4–5 min in hypoxia these seemingly different results are complementary rather than contradictory. It would appear that the blunted early response reported by St.-John and Leiter (1999) and Hafstrom et al. (2002b) suggest a nicotine effect on the peripheral chemoreceptors, while the Bamford study failed to reveal major effects on the central modulation.

In a subsequent study, Bamford and Carroll (1999) found that the ventilatory response to mixed hypoxia/hypercarbia (0.05 FiO₂ + 0.05 FiCO₂) in the rat was unaffected by prenatal nicotine exposure. A combined challenge test like this has, however, some limitations, as discussed above.

8.3. Response to hyperoxia

The contribution of the peripheral oxygen chemoreceptors to the respiratory drive is commonly estimated non-invasively by measuring the ventilatory response to hyperoxia. Brief exposure to hyperoxia leads to silencing of the peripheral chemoreceptors and the concomitant decrease in ventilation is used as an estimate
of chemoreceptor activity. During the hyperoxia test, the decline in ventilation is thought to represent withdrawal of baseline peripheral chemoreceptor drive and is, therefore, a measure of the resting tone of the chemoreceptors. Only studies on animals have been reported.

Bamford and Carroll (1999) tested the effects of prenatal nicotine exposure on the ventilatory response to hyperoxia in the rat. Three-day-old nicotine-exposed pups had no significant ventilatory response to hyperoxia indicating a blunted chemoreceptor activity, whereas control pups displayed an expected reduction in ventilation during the test. Ventilatory responses to hyperoxia in 8- and 18-day-old pups were unaffected by nicotine. Bamford and Carroll (1999) also recorded carotid sinus nerve activity during baseline and hypoxia/hypercarbia challenges in these 3–20-day-old rat pups, but found no effect of prenatal nicotine. The latter result would suggest that prenatal nicotine exposure may affect the central integration of peripheral chemoreceptor input rather than alter their sensitivity per se.

Similar to the studies in rats, Hafstrom et al. (2002b) showed that the ventilatory response to hyperoxia was significantly attenuated in prenatally nicotine-exposed 5-day-old lambs during both wakefulness and quiet sleep. However, there was no longer a nicotine effect when these lambs were 11 or 23 days old (unpublished results). The attenuating effect of prenatal nicotine exposure on the response to hyperoxia at 5 days in these lambs appeared to be due to dopamine modulation in the peripheral arterial chemoreceptors (Gaude et al., 2001). Nicotine-induced dopaminergic modulation of the peripheral chemoreceptors was also evaluated by Holger et al. (1995) who delivered a single high dose of nicotine to 3-day-old rat pups. Chemoreceptor activity was assessed by the hyperoxia test and showed that the respiratory responses (ventilation and respiratory rate) were significantly lower after administration of nicotine. This inhibitory effect of nicotine was counteracted by blockade of the dopamine type 2 receptors with domperidone. Furthermore, nicotine reduced dopamine content and increased expression of tyrosine hydroxylase suggesting that nicotine affects chemoreception through a dopaminergic mechanism.

Cohen et al. (2002) have recently showed that the protective response to hypoxia during sleep is partially regulated by a particular nicotinic receptor nAChR in mice. Brief exposure to nicotine significantly reduced breathing drive in sleeping adult wild-type mice, but had no effect in mutants lacking the β2 subunit of the nAChR. The authors proposed that nicotine impairs breathing (and possibly arousal) responses to hypoxia by disrupting functions normally regulated by β2-containing, high-affinity nAChRs.

9. Effects on arousal

An extensive review of influences of maternal smoking on infant arousal has recently been published (Horne et al., 2004). Therefore, this topic will be summarized only briefly.

Infants of mothers who smoked during pregnancy have been shown to have a higher arousal threshold after obstructive apneic events during quiet sleep (Tirosh et al., 1996) and a deficient hypoxia awakening response from quiet sleep (Lewis and Bosque, 1995; Parsiow et al., 2004). However, protective responses (i.e., the combination of ventilatory and awakening responses) to rebreathing during quiet and active sleep have been found to be similar in smoke-exposed and non-exposed infants by (Campbell et al., 2001).

A higher arousal threshold and a reduced likelihood of arousal as a result of auditory stimuli have also been found in infants of smoking mothers (Franco et al., 1999; Chang et al., 2003). Using air jet stimulation, Horne et al. (2002) showed that infants of smoking mothers had fewer spontaneous arousals from quiet sleep and an elevated arousal threshold at 2–3 months of age. In contrast to most other stimuli, Galland et al. (2000) found no effect of maternal smoking on the arousal response to tilting at 1 and 3 months.
A delayed arousal from quiet sleep during acute hypoxia was found in prenatally nicotine-exposed 5-day-old lambs by Hafstrom et al. (2002b). This study in sheep illustrates that arousal as well as the cardiorespiratory response can be influenced by a low maternal nicotine free base dose (0.5 mg/kg/day) resulting in an average maternal nicotine concentration of 7 ng/ml corresponding to smoking approximately 10 cigarettes per day (Hill et al., 1983). The arousal response to hypoxemia is elicited by stimulation of peripheral chemoreceptors, and Hafstrom et al. (1998) showed in these lambs that the effect of prenatal nicotine exposure on arousal, in part, is likely to be a dopamine-mediated effect on the peripheral chemoreceptors. However, since arousal thresholds to a variety of stimuli have been shown to be altered, it has been suggested that the decreased ability to be aroused following prenatal exposure to tobacco smoke may result from the effect of nicotine on brainstem regions associated with the regulation of arousal and cardiorespiratory regulation (Tirosh et al., 1996; Franco et al., 1999; Kinney et al., 1993).

10. Effects of smoke exposure and nicotine on autonomic functions

10.1. Sympathico-vagal balance: heart rate and heart rate variability

Indirect evaluation of autonomic nervous system activity can be made either by challenge tests involving measurements of heart rate and blood pressure responses after stimulation of peripheral chemoreceptors or baroreceptors, or by power spectral analysis of heart rate variability. Two separate frequency bands identified after spectral analysis are frequently used as an index of sympathovagal balance. A high frequency band originates mainly from parasympathetic discharges and a low frequency band originates mainly from sympathetic discharges.

In adults, cigarette smoking increases sympathetic nerve activity as well as circulating catecholamine levels. This leads to an increase in heart rate, blood pressure and the low frequency power band, while baroreceptor sensitivity is decreased. Most of these changes can be reversed by smoking cessation and partly reproduced by transdermal nicotine patches.

Franco et al. (2000) observed similar effects on the resting spectral power pattern of heart rate as a function of sleep stages in infants of smoking mothers. Eighteen infants of smokers and 18 controls were studied at a median postnatal age of 10.5 weeks. During REM sleep, infants of smoking mothers had significantly lower high frequency powers and higher low/high frequency ratios than controls indicating changes in autonomic control and maturation. More subtle changes reminiscent of those observed in adults using nicotine patches were found by Browne et al. (2000). They compared heart rate and blood pressure responses to a passive head-up tilt test in infants of non-smokers and infants of smokers at an age of 2–3 days and again at an age of 3 months. Resting heart rate and heart rate in response to tilting were similar in the two groups and there were no significant differences between groups in power spectral indices of heart beat variability. However, baroreflex sensitivity was affected as evidenced by a significantly higher resting systolic blood pressure at 2–3 days of age in the smoke-exposed infants compared with controls. Also in contrast to controls systolic blood pressure decreased in response to a head-up tilt in the smoke-exposed infants and did not increase above resting levels after return to the flat position.

Other investigators have also been unable to show differences between infants of smoking mothers and control infants with regard to measures of heart rate variability or heart rate responses following head-up tilting (Galland et al., 2000) or following air-jet-induced arousal (Tuladhar et al., 2003). Sovik et al. (2001) used heart rate responses to transient chemoreceptor stimulation to evaluate effects of maternal smoking on infant autonomic function. Twenty-three infants of smoking mothers and 23 controls were repeatedly exposed to 100% O₂, 15% O₂ or 3% CO₂ during quiet sleep from postnatal days 2–82. Increasing number of cigarettes smoked by the mother was correlated with deeper heart rate declines during hyperoxia and smaller heart rate increases during hypoxia. Furthermore, the heart rate response lagged more behind the ventilatory responses in the smoke-exposed group compared with the control group.

Taken together, results of these studies suggest that infants of smoking mothers have an altered autonomic nervous system function reminiscent of but considerably milder than habitual adult smokers.
10.2. Blood pressure

It is now well known that fetal growth retardation is associated with increased blood pressure in adults (Barker et al., 1989). Maternal smoking has also been found to be associated with increased systolic blood pressure in childhood, but this was not wholly attributable to an effect on birth weight (Blake et al., 2000). Furthermore, these authors found that maternal smoking during pregnancy does not account for the acknowledged elevation in blood pressure associated with low birth weight. The number of cigarettes smoked by mothers during pregnancy has been shown to correlate positively with the blood pressure of neonates and infants (Beratis et al., 1996). No significant association between maternal smoking during pregnancy and blood pressure elevation has been observed at school age, but it is not known why the effects diminish with age. A possible explanation could be that growth retardation of individual organ systems is different in fetuses that are growth retarded due to poor placental transfer of nutrients and those who have been exposed to maternal smoking. The main reduction of organ size due to smoking is in abdominal circumference (reflecting size of liver) and peripheral muscle mass (Bernstein et al., 2000). The retarded fetal growth due to maternal smoking occurs early in pregnancy. By contrast, low birth weight infants of non-smoking mothers, who have a reduced ponderal index, have a large liver and are prone to develop “the metabolic syndrome” in adulthood, a lower glucose tolerance, elevated blood pressure and a disturbed lipid metabolism with an increased serum low density lipoproteins. It is not clear whether maternal smoking may lead to similar consequences.

11. Effects on heart rate

Active smoking raises heart rate and blood pressure in both habitual smokers and non-smoking volunteers. These effects are largely mediated by an increased sympathetic activity and altered sensitivity of the aortic baroreflex following nicotine exposure (Mancia et al., 1997).

The effects on heart rate and blood pressure in infants and young animals chronically exposed during fetal life and/or after birth are somewhat different from the acute effects seen in adults and are, to a large extent, a consequence of an altered fetal development of cardiovascular regulation. Hafstrom et al. (2002b) found a higher heart rate but a similar blood pressure in 5-day-old lambs exposed to nicotine during fetal life (maternal nicotine free base dose: 0.5 mg/kg/day) compared with age-matched control animals during the awake state and while asleep. In contrast to the elevated resting heart rate while breathing room air, nicotine-exposed animals did not increase the heart rate in response to hypoxia to the same extent as unexposed controls. Subsequent studies by this group showed that the magnitude of the diminished heart rate responsiveness was both dose- and age-dependent. Lambs exposed prenatally to a moderate nicotine free base dose (1.5 mg/kg/day) had a lower response than controls at an average age of 11 days but not at 25 or 50 days. A low nicotine free base dose (0.5 mg/kg/day) had no significant effect on the heart rate response at these ages (unpublished results). Continued postnatal nicotine infusion after prenatal exposure did not further affect the heart rate response to hypoxia compared with prenatal exposure alone (Hafstrom et al., 2004).

One- to 2-day-old rat pups exposed to a much higher maternal nicotine free base dose (6 mg/kg/day) did not have an elevated heart rate in room air. They exhibited no initial increase in heart rate as expected in response to severe hypoxia (0.05 FIO2), instead heart rate declined precipitously and more rapidly compared with controls (Slotkin et al., 1997).

Slotkin et al. have linked this deficient response to several factors. They showed that prenatally nicotine-exposed 1-day-old rat pups had a deficient adrenomedullary catecholamine release during hypoxemia (Slotkin et al., 1995). Electrocardiographic evaluation showed an impaired sinoatrial reactivity to hypoxia (Slotkin et al., 1997). Receptor binding studies revealed a delayed development of cardiac β-adrenergic receptor binding capabilities, which was associated with a reduced cardiac response to adrenergic stimulation (Navarro et al., 1990). In addition, Slotkin et al. (1999) demonstrated that a prenatal nicotine free base dose of 2 mg/kg/day maximally increased the number of cardiac M2-muscarinic cholinergic receptors and thus could enhance the inhibitory responses mediated by muscarinic cholinergic activation. The combination of lower catecholamine levels,
a reduced cardiac response to adrenergic stimulation and enhanced cholinergic inhibition could, according to Slotkin et al. (1999), explain the impaired cardiac response to hypoxic episodes and the increased perinatal mortality associated with maternal smoking.

A recent in vitro rat brainstem slice study by Neff et al. (2004) provides an additional explanation for the marked rapid bradycardia during severe hypoxia in prenatally nicotine-exposed rat pups observed by Slotkin et al. (1997). Prenatal exposure to nicotine changed the GABAergic response to hypoxia in cardioinhibitory vagal neurons from a biphasic response to a precipitous decrease in spontaneous GABAergic inhibitory postsynaptic current frequency. This exaggerated disinhibition of the activity of brainstem preganglionic cardioinhibitory vagal neurons would induce a more rapid increase in parasympathetic outflow to the heart resulting in bradycardia in vivo. Neff et al. (2004) also propose that this mechanism could explain the exaggerated bradycardia observed before death in some victims of SIDS.

12. Effects on autoresuscitation

12.1. Response to hypoxemia

The escape and defense mechanisms that promotes successful recovery from asphyxia or severe airway obstruction are regulated from specific areas in the brain stem reticular formation and their cortical projections. These defense mechanisms include both arousal and autoresuscitation reflexes such as gasping in response to a distorted blood gas homeostasis. Survival during profound hypoxemia depends on the ability to autoresuscitate by gasping whereby oxygen homeostasis can be restored. Given the association between SIDS and maternal smoking and given that defense mechanisms to asphyxia are thought to be defective in victims of SIDS, several studies have been conducted to test whether prenatal exposure to nicotine may interfere with gasping and survival during profound hypoxemia.

The majority of animal experiments, where maternal smoking during pregnancy has been mimicked by chronic nicotine exposure of the fetus, show some attenuation of defense and survival mechanisms associated with the ability to sustain and recover after asphyxia or hypoxia. The ability to maintain and increase heart rate in the recovery phase appears to be particularly affected. In the experiments by Slotkin et al. (1995) described above, rat pups with deficient adrenomedullary catecholamine release due to prenatal exposure to a maternal nicotine free base dose of 6 mg/kg/day during fetal life have an impaired stress response and would die in experiments that unexposed rat pups or pups exposed to a maternal nicotine free base dose of 2 mg/kg/day would survive.

Fewell and Smith (1998) used a nicotine tartrate dose of 6 mg/kg/day (corresponding to 2.1 mg/kg/day nicotine free base) in pregnant rats to evaluate the effects on gasping in the offspring. First, they investigated the duration of gasping until death during severe hypoxemia (97% N₂/3% CO₂). The duration of gasping in anoxia was not affected by prenatal nicotine treatment at an age of 5 or 6 days. Secondly, they determined the ability to repeatedly autoresuscitate when the animals were allowed to breathe room air after being subjected to the same anoxic gas mixture until a primary apnea occurred. The number of successful autoresuscitations during repeated anoxic exposures was reduced in nicotine-exposed animals.

Fewell et al. (2001b) explored the issue further by determining the threshold level of maternal nicotine tartrate that could impair protective responses of 5- or 6-day-old rat pups to severe hypoxemia. Doses of 3 or 6 mg/kg/day, resulting in maternal nicotine levels comparable to levels seen in moderate or heavy smokers (19 ± 6 and 35 ± 8 ng/ml, respectively), impaired the ability to autoresuscitate from intermittent hypoxia-induced primary apnea, while a dose of 1.5 mg/kg/day had no effect. The same group of investigators (Fewell et al., 2001a) also determined the effect of postnatal age on the ability to autoresuscitate after exposure to prenatal nicotine tartrate at a dose of 6 mg/kg/day. Impaired ability to autoresuscitate from repeated episodes of hypoxia was seen at an age of 1–2 and 5–6 days, but not 10–11 days. A shorter gasping period (decreased time to the last gasp) during a single and prolonged episode of anoxia was seen in 1–2 days old animals only.

A higher nicotine tartrate dose (12 mg/kg/day) did not further compromise gasping time in anoxia (Schuen et al., 1997). The pups were exposed to an anoxic gas mixture (97% N₂/3% CO₂) until gasping ceased at ages between 3 and 26 days. Like Fewell and Smith (1998),
they found no significant effect of prenatal nicotine exposure at any age on duration of gasping, number of gasps or any other of the cardiorespiratory variables recorded.

12.2. Response to laryngeal chemoreflex stimulation

The laryngeal chemoreflex (LCR) allows a standardized testing of recovery responses after apnea and bradycardia and is a common experimental model. Froen et al. (2000) found that sedated, 1-week-old piglets acutely treated with nicotine (5 μg i.v./kg) had more spontaneous apneas and an impaired autoresuscitation after apnea induced by LCR stimulation. In experiments where smoke exposure and infection were mimicked by a combined pretreatment with nicotine and IL-1β, additive adverse effects were found on apnea duration and autoresuscitation. Similar but less marked effects were also seen with combined nicotine and endotoxin treatment.

Sundell et al. (2003) demonstrated that young lambs exposed from birth for 4 weeks to a continuous infusion of nicotine at a dose of 1–2 mg free base/kg/day had a lower ability to recover after LCR-induced apnea and bradycardia. Following LCR stimulation, nicotine-treated lambs had a more pronounced decrease in ventilation, longer reflex apnea and greater reflex bradycardia both in tests performed in room air and mild hypoxia compared to controls. Although nicotine-exposed lambs took more sighs than controls, these sighs were less efficient in restoring heart rate to pretest levels.

There are case-reports clearly linking sudden death in infants to an exaggerated apnea and bradycardia following LCR stimulation (Wennergren et al., 1989). This association may be related to an altered response to LCR stimulation or, perhaps as likely, to a more general defect in mechanisms of autoresuscitation. The specific role of the LCR reflex is to inhibit breathing and, thus, protect the airway from inadvertent aspiration of foreign matter. However, the mechanisms of recovery are not different from those that support recovery from cardiorespiratory arrests due to other causes. A crucial event in the sequence of reflex survival responses known as autoresuscitation is a rise in heart rate. In order to overcome the vagal reflex that maintains bradycardia breathing movements, or rather lung inflations are necessary (Marshall, 1994). In their absence intense stimulation of laryngeal receptors may cause death even in young healthy adults. Fatalities associated with swimming and drowning accidents have been attributed to this mechanism (Daly et al., 1979). In a situation such as asphyxia, young mammals quickly start to inflate the lungs by sighs, which progress to gasping if the initial steps are not effective.

It is, therefore, tempting to view the exaggerated LCR response related to nicotine exposure as a different facet of the decreased ability to autoresuscitate and survive during severe hypoxia as described by Slotkin et al. (1995) and Fewell and Smith (1998). However, in contrast to pure hypoxia, which is not a common situation, the LCR is a physiological and frequently occurring reflex in infants.

13. Summary and discussion of smoking and nicotine effects on cardiorespiratory control

Nicotine binds to receptors present in all organ systems and affects a multitude of autonomic and sensory functions. There is no consensus in the literature as to which nicotine effects specifically target cardiorespiratory control and which are secondary to the extensive effects on brain and synaptic transmission. The general effects of nicotine on neural functions are likely to explain some of the seemingly inconsistent results reported here. The discrepant results seen when human and experimental studies are compared can also be attributed to differences in study design, the doses used, postnatal age of tested subjects and to what extent environmental factors such as activity state were standardized. When the experimental conditions and study protocols are comparable there are also similarities of findings.

Results of animal studies, based on prenatal exposure with moderate doses of nicotine and where respiratory data were collected in the newborn period, are in many respects comparable to results obtained in infants of smoking mothers. A consistent finding across species is that tobacco smoke and prenatal nicotine exposure delay or weaken hypoxic arousal, whether the subjects are 2–3-month-old infants or lambs during the first week of life. The decrease in arousability appears most prominent when hypoxia is the respiratory stimulant, but it is also seen with auditory or tactile
sensory stimulation. Interestingly, hypercarbic arousal seems little affected.

There is also ample evidence from animal studies that the ability to sustain severe hypoxia or anoxia is severely impaired by prenatal nicotine exposure. This vulnerability is most clearly seen during the early postnatal period. The decreased vulnerability appears to be an effect of a deficient sympathetic activation during hypoxic stress leading to a circulatory collapse during prolonged or severe exposure. The observed defect in autoresuscitation does not seem to be related to the frequency or duration of gasping but rather to the fact that gasping in nicotine-exposed animals is less efficient in restoring adequate circulation.

Further proof for a deficit in autoresuscitation is that cardiorespiratory recovery from apnea and bradycardia induced by laryngeal stimulation is delayed in nicotine-exposed animals during the newborn period. However, the relation to nicotine dosage and route of exposure is less clear since the effects on apnea and bradycardia are seen in acute experiments as well as following chronic postnatal exposure. To what extent deficient arousal, decreased ability to overcome apnea and bradycardia and impaired survival are related to deficient oxygen sensitivity is still a matter of controversy. A decreased hypoxic ventilatory response has been observed in sedated, sleeping infants of smoking mothers and nicotine-exposed animals, i.e., unsedated sleeping young lambs and rats less than 6 days old, but not in infants studied during natural sleep or in mice. A nicotine effect on the ventilatory response to combined hypoxic and hypercarbic exposure has not been observed in infants of smoking mothers or in rats. Taken together, it is likely that the hypoxic ventilatory response is only moderately affected by nicotine exposure. It is not clear whether the lower hypoxic ventilatory response is a consequence of altered carotid body chemoreceptors. Carotid body chemoreception is involved as evidenced by a weaker ventilatory response to inhalation of pure oxygen in nicotine exposed subjects. On the other hand, neurophysiologic recordings from the carotid sinus nerve have shown that the response to hypoxia is not affected by nicotine, which would imply an altered integration of carotid body output rather than a lower sensitivity.

To what extent the effects of prenatal nicotine exposure persist beyond infancy has not been clearly established but the observed effects on cardiorespiratory control are most prominent during the newborn period and tend to be less apparent with increased maturational age. The effect on breathing pattern, which is, in turn, an effect of an altered lung development, seems to be most persistent. The long-term consequences are not known.

References


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