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Cigarette smoke exposure effects on the brainstem expression of nicotinic acetylcholine receptors (nAChRs), and on cardiac, respiratory and sleep physiologies

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A B S T R A C T

Cigarette smoking during pregnancy is the largest modifiable risk factor for adverse outcomes in the infant. Investigations have focused on the psychoactive component of cigarettes, nicotine. One proposed mechanism leading to adverse effects is the interaction between nicotine and its nicotinic acetylcholine receptors (nAChRs). Much data has been generated over the past three decades on the effects of cigarette smoke exposure (CSE) on the expression of the nAChRs in the brainstem and physiological parameters related to cardiac, respiration and sleep, in the offspring of smoking mothers and animal models of nicotine exposure. This review summarises this data and discusses the main findings, highlighting that findings in animal models closely correlate with those from human studies, and that the major brainstem sites where the expression level for the nAChRs are consistently affected include those that play vital roles in cardiorespiration (hypoglossal nucleus, dorsal motor nucleus of the vagus, nucleus of the solitary tract), chemosensation (nucleus of the solitary tract, arcuate nucleus) and arousal (rostral mesopontine sites such as the locus coeruleus and nucleus pontis oralis). These findings provide evidence for the adverse effects of CSE during and after pregnancy to the infant and the need to continue with the health campaign advising against CSE.

1. Introduction

Cigarette smoking during pregnancy is the largest modifiable risk factor for adverse outcomes in the infant (Benowitz and Dempsey (2004)). The majority of the information related to smoking during pregnancy comes from developed countries where smoking trends are comparable to those seen in the United States (Murin et al., 2011). In the United States, about 12.8% of women continue to smoke during pregnancy (Tong et al., 2009). In Australia, 13.5% of women were reported smoking during pregnancy in 2010 (Li et al., 2012), which is a decrease from 23% in 2001 and 20% in 2004 (Schneider et al., 2010). Although this decrease is positive, the data is based on self-report and is most likely an under-estimate of the real prevalence (Burstyn et al., 2009) since 25% of pregnant smokers do not disclose information regarding smoking status (Shipton et al., 2009), often due to social stigma (Wigginton and Lee, 2013).

Smoking during pregnancy and postpartum, poses a significant threat to a woman's (Dunn et al., 2000) and child's (American Academy of Pediatrics, 1997) health including:

1 ***obstetric,*** such as placenta previa (Oyelese and Smulian, 2006; US Department of Health and Human Services, 2004), placenta abruption (Oyelese and Ananth, 2006; Services, 2004), stillbirth and ectopic pregnancy (Services, 2004; US Department of Health and Human Services, 2004);
2 ***fetal,*** including growth restriction (US Department of Health and Human Services, 2004), low birth weight (Fantuzzi et al., 2008; Services, 2004; Ventura et al., 2003), preterm birth (Kolas et al., 2000), and birth defects (Hackshaw et al., 2011), and
3 ***infant into childhood,*** such as an increased risk of sudden infant death syndrome (SIDS) (Shah et al., 2006), ear, nose and throat related illnesses (Reviewed in (DiFranza et al., 2004; Ilicali et al., 2001; Strachan and Cook, 1998; Willatt, 1986), respiratory illnesses (Carlsen and Carlsen, 2008) and cognitive deficits (Clifford et al., 2012).

Although, there are thousands of compounds found in cigarette smoke, investigations studying the effects of CSE during pregnancy have focused mainly on the psychoactive component of nicotine (Dani and Harris, 2005). This is because the direct effects of CSE seem to result from the interaction between nicotine with its nicotinic acetylcholine receptors (nAChRs), both in the mother and in the developing fetus. For example, a study conducted by Slotkin et al. (2002), exposed Rhesus monkeys to environmental tobacco smoke (ETS) during late

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gestation and in the early postnatal period and observed selective up-regulation of nAChRs in the brainstem. No changes were seen in muscarinic acetylcholine receptors or β-adrenergic receptors. The lack of change in neurotransmitter receptors unrelated to nicotine supported nicotine exposure as the primary mediator of the effects of ETS in contrast to generalised toxicity from other components of ETS. Limited studies exist looking at other components of cigarettes on the nAChRs. Two in vitro studies in human neuroblastoma cell lines (Ambrose et al., 2007) and fetal pulmonary neuroendocrine cells (Schuller et al., 2000) showed changes in nAChR binding as a result of exposure to the non-nicotine component of tobacco particulate matter and the tobacco specific 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone (NNK) respectively. However, these studies suggested the changes in nAChRs were indirect rather than by binding to the nicotinic receptor site.

nAChRs are expressed in early prenatal development of the fetal nervous systems: central (CNS), peripheral (PNS) and enteric (ENS) (Garza et al., 2009; Winzer-Serhan and Leslie, 1997; Zoli et al., 1995). Activation of nAChRs due to maternal smoking can lead to detrimental effects on the fetal nervous system development during the prenatal stage. These defects may lead to a delayed neurodevelopment in the first few years of life (Chen et al., 2013), decrease in cognitive functioning and negative behavioural outcomes during childhood (Kafouri et al., 2008). Additionally, maternal smoking during pregnancy also has adverse effects to the development and maturation of the cardiovascular and respiratory systems (Carlsen and Carlsen, 2008; Dempsey and Benowitz, 2001; Fu et al., 2009; Maritz, 2008; Maritz et al., 2005; Pausova et al., 2003).

Our laboratory's interest is of SIDS, defined as "the sudden death of an infant < 1 year of age, with onset of the fatal episode apparently occurring during sleep, that remains unexplained after a thorough investigation, including performance of a complete autopsy and review of the circumstances of death and clinical history" (Krous et al., 2004). The mechanism of SIDS is still unknown, although risk factors have been determined with cigarette smoke exposure (CSE) now being the predominant factor (Fleming and Blair, 2007). Prior to the 'Back to Sleep' campaigns, the pooled odds ratio for maternal smoking on SIDS incidence was 2.9 (2.8–3.0) (Mitchell and Milerad, 2006). After the campaigns, these ratios rangedfrom 3.8 to 4.1 (Mitchell, 2009); thus infants with prenatal exposure, have four times greater risk for SIDS. Moreover; postnatal exposure alone (paternal smoking where mother is a non-smoker) is an independent risk with odds Ratio = 1.47(Mitchell and Milerad, 2006). The leading hypothesis for SIDS is that the potential cause combines a developmental insult that leads to an abnormal neuroregulation of the cardiorespiratory control system (Hunt, 1992; Hunt and Brouillette, 1987) and an impaired arousal response to hypoxic conditions (Hunt, 1992). Further, this abnormality is thought to involve alterations in neurotransmitter and receptor systems (Kinney et al., 1995) including nAChRs (Harper et al., 2000; Nachmanoff et al., 1998) within regions that control respiratory and cardiovascular systems and arousal (Harper et al., 2000) as well as those regions that are hypoxic sensitive. As the region housing these control centres, the main brain region of interest is the brainstem. This review thus summarises the data pertaining to the effects of CSE on expression of nAChRs in the brainstem, and the physiological effects related to cardiac, respiratory and sleep/arousal systems.

2. Cigarette smoke, nicotine and nicotinic acetylcholine receptors (nAChRs)

Cigarette smoke contains more than 4800 chemicals according to the American Lung Association (Abbott and Winzer-Serhan, 2012). These major components include carbon monoxide, carbon dioxide, methane and nicotine, with lesser but considerable amounts of acetone, acetylene, formaldehyde, propane, hydrogen cyanide and toluene (Abbott and Winzer-Serhan, 2012). Nicotine, the major psychoactive component (Dani and Harris, 2005) is a poisonous alkaloid that has a low molecular weight and is a highly lipid soluble and an addictive stimulant with a half-life of 1–2 h (Benowitz, 1986). Cotinine is the metabolite of nicotine and has a longer half-life (15–20 h) and is consequently the preferred biomarker for measuring CSE (Benowitz, 1986; Zevin et al., 1998).

The nAChRs belong to the gene superfamily of ligand gated cation channels that include muscle nAChRs, gamma aminobutyric acid ($GABA_A$ and $GABA_C$), glycine and 5-Hydroxytryptamine ($5\text{-}HT_3$) receptors (Changeux and Edelstein, 1998). They are arranged as pentamers of subunits surrounding a central pore (Cooper et al., 1991). Genes encoding a total of 17 subunits (α1-10, β1-4, δ, γ and ε) have been identified to date. All the subunits are of mammalian origin with the exception of α8 (avian origin) (Dani and Bertrand, 2007; Gotti and Clementi, 2004; Hogg et al., 2003). They are present as heteropentamers or homopentamers (α7, α9) throughout the Central Nervous System (CNS), autonomic ganglia and at skeletal muscle neuromuscular junction (Hogg et al., 2003). Although, nAChRs are mainly located at presynaptic or preterminal sites, (where they chiefly regulate neurotransmitter release (Gotti and Clementi, 2004) and are involved in neurogenesis (Zheng et al., 1994)), they are also found on cell bodies or dendrites where they regulate postsynaptic effects (Gotti and Clementi, 2004; Hogg et al., 2003).

The α1, β1, δ, γ and ε are classified as muscle type subunits whereas the rest are classed as neuronal subtypes. The muscle nAChRs are present in two forms of α1, β1, and γ or α1, β1, δ and ε, both in the ratio of 2:1:1:1 (Albuquerque et al., 2009). The neuronal types are a mixture of α and β subunits with the presence of certain subunits determining ligand specificity and affinity, channel gating and cation permeability.

The ligand binding site is a hydrophobic region present at the interface between adjacent subunits. At all times, the "positive" side of the binding site is produced by an α subunit (α1, α2, α3, α4, α6, α7 or α9) as this is where Cys-Cys pair is required, which is essential for the agonist binding region and to carry out the agonist induced receptor motion (Albuquerque et al., 2009). The "negative" side of the agonist-binding site is made of α10, β2, β4, γ or ε subunit. The α5, β1 and β3 are accessory subunits that assemble to form the fifth subunit position in the receptor complex and do not take part in forming the agonist binding site. These have a role in nAChR conformation changes, assembly, desensitisation, cation selectivity and binding of allosteric ligands (Albuquerque et al., 2009).

Endogenously, nAChRs are activated by acetylcholine (ACh), and exogenously, by nicotine, as suggested by the name. The nAChRs carry out a number of roles via the ACh-mediated innervations throughout the CNS and the peripheral nervous system. They regulate processes necessary for network operations through transmitter release, cell excitability and neuronal integration. They also influence physiological processes such as arousal, sleep, fatigue, anxiety, the central processing of pain, and cognitive functions (Gotti and Clementi, 2004; Hogg and Bertrand, 2004; Hogg et al., 2003). Each of the individual subunits contributes to the function of nAChRs, and their roles have been identified through knockout studies as summarised in Table 1.

3. Expression of nAChRs in the developing brainstem

Acetylcholine plays a key role in regulating ontogenesis. The nAChRs are important for the organisation of different structures of the brain during the prenatal period through their roles in cell survival and targeting. These developmental processes are vital in forming the basic neural and sensory circuits and developing catecholamine systems through regulation of neurotransmitter release (Reviewed in Dwyer et al. (2009)).

The brainstem is divided into three main parts, midbrain, pons and medulla, and houses nuclei that regulate autonomic functions that are vital for sleep, arousal, cardiac, respiratory, vasomotor and reflex motor control systems (Kandel et al., 2000). The expression of the nAChRs has

Table 1
Summary of main functional role of nAChR subunits based on animal knockout studies.

Subunit	Physiological Role	References
α2	Maintains the nicotine induced balance between excitation and inhibition, gates Long Term Potentiation (LTP) and directs information flow through the hippocampal circuits.	(Nakauchi et al., 2007)
	Involved in mediating hippocampus-dependent memory	(Kleeman et al., 2016)
α3	Necessary for early postnatal survival as knock out studies demonstrated early neonatal death.	(Xu et al., 1999a)
	Mediates normal function and fast synaptic transmission of the autonomic nervous system, therefore essential for autonomic control of peripheral organs such as bladder and pupil contraction.	
α4	Crucial for nicotine elicited antinociception (possibly associated with β2 nAChR subunit with which it assembles).	(Marubio et al., 1999, 2003)
	Required for high affinity binding with nicotine and epibatidine binding.	(Gotti et al., 2008)
	Required to exert tonic control on striatal basal dopamine release in conjunction with β2 subunit.	
	Essential for nicotine mediated responses in raphe magnus and thalamus.	
	Associated with suppressing anxiety like behaviours.	
α5	Required for cardiac parasympathetic ganglion transmission during high frequency vagal stimulation.	(Wang et al., 2002)
	Affects the affinity and sensitivity to agonists and antagonist in the native receptor hence involved in modifying the pharmacological and biophysical properties of the nAChR.	(Salas et al., 2003)
	Alters sensitivity to nicotine induced seizures and hypolocomotion.	
α6	Necessary to establish nicotine self-administration behaviour.	(Pons et al., 2008)
α7	Essential for the high affinity α-bungarotoxin binding.	(Orr-Urtreger et al., 1997)
	Required for the fast desensitizing currents in the hippocampus.	
α9	Mediates the effects of olivocochlear system- hearing.	(Vetter et al., 1999)
	Suppresses the cochlear responses during efferent fibre activation.	
β1[a]	Predominantly muscle control.	(Reviewed in (Hurst et al., 2013))
	Lethality upon mutation. Causes congenital myasthenic syndromes	(Quiram et al., 1999)
β2	Maturation of the neural circuit pathway involved in auditory processing.	(Horst et al., 2012)
	Regulates the transient phasic activity of non-rapid eye movement (NREM) sleep, and the onset and duration of REM sleep, thus contributing to the organisation of sleep pattern.	(Lena et al., 2004) (Cohen et al., 2005)
	Responsible for the awakening effects of nicotine.	(Marubio et al., 1999)
	Crucial for nicotine elicited antinociception.	(Zoli et al., 1999)
	Neuronal survival and maintenance of cognitive performance.	(Picciotto et al., 1995)
	Plays a role in slowing age related neurodegeneration.	(Picciotto et al., 1998)
	Essential for high affinity nicotine binding and presynaptic activity.	
	Required for the nicotine induced dopamine release.	
β3	Contributes to (striatal) dopamine release and locomotor activity.	(Salminen et al., 2007) (Cui et al., 2003)
β4	Plays a role in the autonomic ganglia transmission.	(Xu et al., 1999b)

Determined through mutation model.
[a] Seemingly no knock out studies performed to date.

been studied extensively in the brainstem of various species (summarised in Tables 2–4). In general, the expression of the nAChRs has been determined at the mRNA, protein, and functional levels by polymerase chain reaction and in-situ hybridisation, immunostaining, and autoradiography, respectively. The common ligands for autoradiography included [^{3}H] nicotine (targets all nAChR subunits), [^{3}H] epibatidine (targets the α2-α4, β2, β4 subunits), [^{3}H] cytisine (targets the α4β2 subunits) and [^{125}I] α-bungarotoxin (targets the α7 subunit) (Jensen et al., 2005).

Baseline human expression studies have shown that many of the subunits (α3, α4, α5, α7, β2, β3 and β4) are first expressed at 4–5 weeks of gestation with wide distribution through the fetal brain (Hellstrom-Lindahl et al., 1998). Expression is high during early-mid gestation, followed by the transient expression during mid gestation - early postnatal periods (Hellstrom-Lindahl and Court, 2000; Hellstrom-Lindahl et al., 1998; Kinney et al., 1993). During the late prenatal stage and early infancy, the expression of nAChRs decreases substantially in different regions of the brain except for the major cerebellar nuclei where nAChR expression remains unchanged (Reviewed in Gotti and Clementi (2004); Hellstrom-Lindahl and Court, 2000; Hellstrom-Lindahl et al., 1998).

In the human brainstem, studies are limited to the fetal and infant age (Tables 2 and 4) with only two studies in the adult brainstem (Breese et al., 1997; Machaalani et al., 2010), to our knowledge. In the fetal brainstem medulla, high ^{3}H Nicotine binding was observed in the tegmental nuclei (nucleus pontis oralis, hypoglossal nucleus, nucleus of the solitary tract) related to cardiopulmonary integration, sleep, arousal, rapid eye movement and somatic motor control of (Kinney et al., 1993), and there was a reduction in binding with increasing postconceptional age (Duncan et al., 2008b). The decline in ^{3}H Nicotine binding from fetal stage to postnatal stage was also noticed in the reticular formation (nucleus centralis, nucleus pontis oralis and nucleus cuneiform), hypoglossal (XII) and nucleus of the solitary tract (NTS) (Kinney et al., 1993). The high expression of nicotine binding in the tegmental nuclei during mid gestation was proposed to reflect the role of the nAChRs in developing the brainstem tegmentum so that once this role is fulfilled the number of nAChRs gradually decline by postnatal age (Kinney et al., 1993). A similar role is thought to be at play during the transition of nAChR expression from the fetal to postnatal stage where they may participate in ontogenesis and developing new structures prenatally, with subsequent decline in expression before the transient upregulation as they participate in maturational processes. The rapidly changing profile of nAChRs delineates developmental vulnerabilities when the infant is sensitive to the detrimental effects of nicotine.

Rats and mice are altricial animals in that their stage of brain development at birth is considerably more immature than that of humans (Reviewed in Gotti and Clementi (2004)). It has been reported that high affinity ^{3}H nicotine binding in the rat takes place in a caudal to rostral pattern with binding seen first at G12 in the spinal cord and caudal medulla, followed by the lower brainstem, mesencephalon and parts of the diencephalon at G14 (Naeff et al., 1992). Two studies that looked at the brainstem expression of the nAChRs across the lifespan showed that (Winzer-Serhan and Leslie, 1997; Tribollet et al., 2004) there was an abundance in neuronal nicotinic receptors in the embryonic and postnatal stage that decreased at later ages.

The similarities of high levels of the nAChRs in key brainstem nuclei in the human and animal brainstem in the prenatal period, that then

Table 2
Summary of studies showing nAChR expression in the brainstem medulla, by species.

nAChR subunit	Species	Age	Experimental Method	Reference
α2, α3, α4, β2,	Rat	Adult	In situ hybridization Autoradiography- [^{3}H] nicotine binding	(Wada et al., 1989)
HA binding nAChRs	Rat	Fetal Infant	[^{3}H] nicotine binding	(Naeff et al., 1992)
α3, α4, β2, β4	Rat	Fetus Infant Adult	In situ hybridization	(Zoli et al., 1995)
α3, β4	Rat	Fetus Infant Adult	In situ hybridisation	(Winzer-Serhan and Leslie, 1997)
α2, α3, α4, α7, β2	Rat	Infant Adult	[^{3}H] nicotine binding [^{3}H] epibatidine binding α-[^{3}H] bungarotoxin binding Ribonuclease protection assay for mRNA	(Miao et al., 1998)
α4, β2	Rat	Infant Adult	[^{3}H] cytisine binding	(Slotkin et al., 1999)
α7, α4, β2	Rat	unspecified	[^{3}H] nicotine binding [^{3}H] methyllycaconitine binding	(Mugnaini et al., 2002)
α3, α4, β2, β4 (α4β2, α3β2, α3β4)	Rat	Adult	[^{125}I] epibatidine 5-[^{125}I] iodo-3-(2-azetidinylmethoxy) pyridine [^{125}I] A-85380) autoradiography	(Perry et al., 2002)
α4, β2, α7	Rat	Infant Adult	[I^{125}] α-bungarotoxin [^{3}H] cytisine binding	(Slotkin et al., 2004)
α4, α7	Rat	Embryonic Infant Adult	Autoradiography	(Tribollet et al., 2004)
α7	Rat	Adult	Immunohistochemistry	(Dehkordi et al., 2004)
α4, α7	Rat	Adult	Immunofluorescence	(Dehkordi et al., 2005)
α3, α4, α7, β2, β4	Rat	Adult	Cytisine binding	(Smith and Uteshev, 2008)
α2, α3, α4, α5, β2	Mouse	Adult	In situ hybridization L-[^{3}H] nicotine binding	(Marks et al., 1992)
α4, α7, β2	Mouse	Infant	[I^{125}] α-bungarotoxin [^{3}H] nicotine binding	(van de Kamp and Collins, 1994)
α4, β2	Mouse	Adult	[^{3}H] nicotine binding In situ hybridization	(Pauly et al., 1996)
α2, α3, α4, α5, α7, α9, β1, β2	Mouse	Infant	Immunohistochemistry	(Vivekanandarajah et al., 2016)
α4, α7	Rabbit	Adult	Immunofluorescence	(Centeno et al., 2004)
α7, β2	Piglet	Infant	Immunohistochemistry	(Browne et al., 2010)
α2, α3, α4, α5, α9, β1	Piglet	Infant	Immunohistochemistry	(Vivekanandarajah et al., 2015)
α4, β2	Monkey	Adult	[^{3}H] cytisine binding	(Slotkin et al., 2002)
α7	Human	Adult	[^{125}I] α-bungarotoxin In situ hybridisation	(Breese et al., 1997)
α3, α4, α5, α7, β2, β3, β4	Human	Fetus	PCR for mRNA [^{3}H] epibatidine binding [^{3}H] cytisine binding	(Hellstrom-Lindahl et al., 1998)
HA binding nAChRs	Human	Fetus Infant	[^{3}H] nicotine binding	(Kinney et al., 1993)
α3, α4, α7, β2	Human	Fetus Adult	RT PCR for mRNA [^{3}H] epibatidine binding [^{3}H] cytisine binding [I] α-bungarotoxin	(Hellstrom-Lindahl and Court, 2000)
Multiple nAChRs	Human	Fetus Infant	Immunocytochemistry [^{3}H] nicotine binding [^{3}H] epibatidine binding [^{3}H] cytisine binding [^{125}I] bungarotoxin binding	(Duncan et al., 2008a)
α7, β2	Human	Infant Adult	Immunohistochemistry	(Machaalani et al., 2010)

Abbreviations: HA: high affinity.

decreases and stabilises in adulthood, supports that these nAChRs regulate both developmental and maturational processes of neuronal pathways and play an important role in the control of autonomic function during the prenatal developmental stage. Disruption of the patterns of expression of nAChRs during this critical developmental period, can lead to abnormal cardiac, respiratory, sleep and arousal physiologies in the infant (discussed in Section 5).

4. Consequences of cigarette smoke/nicotine exposure during development on nAChR expression in the brainstem

The effects of CSE (active or passive), or exposure to nicotine on nAChR expression in the brainstem, has been studied in various animal models (Table 3) and in humans (Tables 4 ,). Although, there are differences between the animal and human studies in that nicotine effects are investigated in lab animals and CSE effects are studied in humans, the advantage of the animal models is that various paradigms can be tested and controlled for such as dosage, age, and period of exposure (pre vs post-natal). Comparing animal and human studies, there is an

Table 3
Summary of animal studies examining cigarette smoke/nicotine exposure effects on nAChR expression in the developing brainstem.

Subunit(s) studied	Species	Exposure period and mode	Nicotine dose	Age of study	Experimental Method	Brain region	Finding	Reference
Prenatal exposure								
α7, α4, β2	Mouse	Maternal infusion at G11-G20-21 followed by subcutaneous injection until age of study	2 mg/kg/hr	At birth P20-30	[I^{125}] α-bungarotoxin [^{3}H] nicotine binding	Cerebellum Hypothalamus Hindbrain (pons medulla) Hippocampus Striatum Midbrain Cortex	↑ [^{3}H] nicotine binding at birth in the hypothalamus, hippocampus and cortex. ↑ [^{3}H] nicotine binding in the hindbrain, hippocampus, striatum, midbrain and cortex at P20-30. Little effect on [I^{125}]- alpha-bungarotoxin binding.	(van de Kamp and Collins, 1994)
Non selective	Rhesus monkey	G45-50 to P70-78 for both mother and offspring by inhalation via smoking chamber	ETS: final concentration of 1 mg/m^3 for 6 h/day, 5days/week from	P70-78	[^{3}H] cytisine binding	Brainstem Caudal portion of cerebral cortex	Selective ↑ nAChRs in the brain.	(Slotkin et al., 2002)
α3/α6β2β3, α7, α4, β2	Mouse	5 week old mice treated over 4/7 weeks orally	Nicotine treatment gradually increased from 50 μg/mL to 300 μg/mL to 500 μg/mL to over different time intervals	9/12 week old mice	[^{3}H] methyllycaconitine binding [^{3}H] Epibatidine binding	Striatum, midbrain, hippocampus and cortex	7-week treatment period: ↑ in [^{3}H] methyllycaconitine binding in the hippocampus, ↑ in [^{3}H] Epibatidine binding was observed in all the areas studied except for the striatum.	(Nuutinen et al., 2005)
α2, α3, α4, α5, α7, β2, β3, β4	Rat	Maternal exposure G3-21 and G8-21 and G15 to 21 via subcutaneous injection	1.5 mg/kg twice daily	Fetal; G21	Quantitative real-time PCR	Forebrain Hindbrain	↑ α2, α4, α7 and β2 mRNA in the fetal forebrain and hindbrain. No change in α3, α5, β3 and β4 expression.	(Lv et al., 2008)
Postnatal exposure								
α2, α3, α4, α5, β2	Mouse	Intravenous infusion between 60 and 90 days of age	4 mg/kg/hr for 10 days	Between 70–100 day old mice	[^{3}H] nicotine binding	Cortex Midbrain Cerebellum	↑ [^{3}H] nicotine binding in the cortex and midbrain. Little effect on the RNA expression of the nAChRs.	(Marks et al., 1992)
LA and HA nicotinic receptors	Rat	Subcutaneous injections for 18 days	2 mg free base /kg treated twice daily for 18 days	Unspecified	[^{3}H] nicotine binding (-) nicotine binding	Cortex Hippocampus Striatum Thalamus Midbrain Cerebellum	↑ HA [^{3}H] nicotine binding in the cortex, hippocampus, midbrain and striatum.	(Zhang et al., 1994)
α4, β2	Mouse	Intravenous infusion 60–90 day old mice	4 mg/kg/hr for 7 days	67–97 day old mice	[^{3}H] nicotine binding In situ hybridization	Several brain regions including telencephalon, diencephalon, mesencephalon, pons and cerebellum.	↑ [^{3}H] nicotine binding in 37 of 46 brain regions investigated.	(Pauly et al., 1996)
α2, α3, α4, α7, β2	Rat	Subcutaneous injections at P1-21, and P8-16	0.1 mg/kg s.c. free base twice per day	P7, P14, P21, P28, P56, P84 and P115.	[^{3}H] nicotine binding [^{3}H] epibatidine binding α-[^{3}H] bungarotoxin binding Ribonuclease protection assay for mRNA	Cortex Hippocampus, Striatum Brainstem Thalamus (including hypothalamus) Cerebellum	Transient ↑ [^{3}H] nicotine binding and [^{3}H] epibatidine binding in most of the brain regions studied in the P1-21 treated rats. Longlasting ↑ [^{3}H] nicotine binding in the cortex, hippocampus and striatum of adult rat treated with nicotine from P8-16. No change in mRNA expression in both groups.	(Miao et al., 1998)

(*continued on next page*)

Table 3 (*continued*)

Subunit(s) studied	Species	Exposure period and mode	Nicotine dose	Age of study	Experimental Method	Brain region	Finding	Reference
α4, β2	Rat	Subcutaneous injections at P1-4, P11-14, P21-24	0.3 or 3 mg/kg, twice daily for 4 days.	P5 P15 P25	[^{3}H] Cytisine binding	Brainstem	↑ nAChRs at P5 following both low and high dose treatment from P1-4 and ↑ nAChRs at P15 following high dose treatment from P11-14.	(Slotkin et al., 1999)
α7 and β2	Piglet	Intraperitoneal insertion of an osmotic minipump at P1 infusing for 14days	2 mg/kg/day for 14 days	Postnatal (P14)	Immunohistochemistry (Protein)	Brainstem medulla	↓ α7 in DMNV. ↑ β2 in the cDMNV, cNSTT and cNTS. .	(Browne et al., 2010)
α2, α3, α4, α5, α9 and β1	Piglet	Intraperitoneal insertion of an osmotic minipump at P1 infusing for 14days	2 mg/kg/day for 14 days	Postnatal (P14)	Immunohistochemistry (Protein)	Brainstem medulla	↓ α3, ↓β1 in XII ↓ α4, ↓β1 in DMNV ↑ α2 ↓β1 in the NTS ↑α2, ↑α3, ↓α4 in the VEST, ↑α9 in the Cun and ↑α2, ↑α4 in the NSTT.	(Vivekanandarajah et al., 2015)
Pre- into postnatal exposure								
α4, β2, α7	Rat	Prenatal osmotic minipump G4-G21 Postnatal subcutaneous injections P1-4, P11-14, P21-24	Prenatal: 6 mg/kg/day Postnatal: 0.3 or 3 mg/kg, twice daily for 4 days.	Neonatal rats (P1-4, 11-14, 21-24)	[I^{125}] α -bungarotoxin [^{3}H] Cytisine binding	Brainstem, forebrain and cerebellum	PN 1-4: Little or no effect on α7 nAChRs PN 11-14 and 21-24: ↓ receptor expression in brainstem and cerebellum and regions containing cell bodies that project to the forebrain.	(Slotkin et al., 2004)
α4, β2	Rat	Prenatal osmotic minipump G4-G21 Postnatal subcutaneous injections P30-47.5	6 mg/kg/day	P45 P50 P60 P75	[^{3}H] Cytisine binding	Cerebral cortex Midbrain	Prenatal nicotine treatment: minor effects on nAChRs. Adolescent nicotine treatment: ↑ nAChR.	(Abreu-Villaca et al., 2004)
α2, α3, α4, α5, α7, α9, β1 and β2	Mouse	Pre-into post-natal exposure via smoking chamber commencing at G0-P20.	2 cigarettes (nicotine ≤ 1.2 mg, CO ≤ 15 mg) twice daily for 6 weeks prior to mating, during gestation and lactation.	Postnatal (P20)	Immunohistochemistry (Protein)	Brainstem medulla	↑α2 in the FAC, ↑α3 in the XII, DMNV, NTS, CUN, NSTT, FAC, ↑α4, ↑α7, ↑α9 in the XII ↑α5, ↑α7, ↑β1 in the DMNV ↓α4, ↑α5, ↓β1 in the NTS ↓α5, ↑β2 in the CUN ↑α7, ↑β1 NSTT ↓ β1 in LRt, ↑β1 in the ION, ↑α7 in the FAC	(Vivekanandarajah et al., 2016)

Abbreviations: ETS: environmental tobacco smoke; CUN: cuneate nucleus; DMNV: dorsal motor nucleus of the vagus; FAC: facial nucleus; G: gestational; HA: high affinity; ION: inferior olivary nucleus; LA: low affinity; LRt: lateral reticular formation; nAChR: nicotinic acetylcholine receptor; NSTT: nucleus of the spinal trigeminal tract; NTS: nucleus of the solitary tract; P: postnatal; PCR: polymerase chain reaction; XII: hypoglossal nucleus.

Table 4
Summary of human studies examining cigarette smoke/nicotine exposure effects on nAChR expression in the developing brainstem.

Subunit(s) studied	Age	Experimental Method	n values of CSE vs non-CSE	Brain region	Finding	Reference
LA and HA nicotinic receptors mainly α4β2	Postnatal (< 1 year)	[^{3}H] nicotine binding	2 vs 3	Midbrain Pons Medulla	No change	Kinney et al., 1993
LA and HA nicotinic receptors mainly α4β2	Postnatal (< 1 year)	[^{3}H] nicotine binding	5 vs 10	Midbrain Pons Medulla	↑ binding in nucleus parabrachialis lateralis, locus coeruleus, nucleus pontis oralis.	Nachmanoff et al., 1998
LA and HA nicotinic receptors mainly α4β2	Prenatal (4–12 weeks of gestation)	[^{3}H] epibatidine binding [^{3}H] cytisine binding	12 with CSE. No mention of n value for non-CSE	Midbrain Pons Medulla	No change in [^{3}H] epibatidine binding. Unspecified result in relation to [^{3}H] cytisine binding due to the low brain tissue sample from smoking mothers for this ligand.	Hellstrom-Lindahl et al., 1998
α4, α7	Prenatal (4-12 weeks of gestation)	PCR	9 vs 8	Pons Medulla	Age-related ↑ in the pons for α4 and α7 Age-related ↑ in the medulla for α7	Falk et al., 2005
LA and HA nicotinic receptors mainly α4β2	Postnatal (< 1 year)	[^{3}H] nicotine binding	4 vs 2	Midbrain Pons Medulla	↓ binding in locus coeruleus, periaqueductal gray, raphe dorsalis.	Duncan et al., 2008b
α7, β2	Postnatal (< 1 year)	Immunohistochemistry	8 vs 14	Pons Medulla	↓ expression in the arcuate nucleus, hypoglossal nucleus, and the nucleus of the solitary tract.	Machaalani et al., 2011

overall increase in the nAChRs following nicotine exposure in the animal models and CSE in human studies, further supporting the main teratological role for nicotine within cigarette smoke.

Animal studies of prenatal chronic exposure have generally found increased nAChR expression (Duncan et al., 2009; Falk et al., 2005; Lv et al., 2008; Slotkin et al., 1987, 2002). Studies of postnatal exposures demonstrate conflicting results. Although, there is generally an increase in nAChR binding in rats (Miao et al., 1998; Slotkin et al., 1999; Zhang et al., 1994) and mice following postnatal CSE, in piglets our group found a decrease protein expression of α4, α7 and β1 in the dorsal motor nucleus of the vagus (DMNV) and decreased α3, β1 in the XII and decreased α4 in the vestibular nucleus (Vivekanandarajah et al., 2016). We found a combination of increased and decreased expression of several nAChR subtypes in the piglet brainstem medulla after a pure postnatal nicotine exposure (Vivekanandarajah et al., 2015). These differences may be due to species variation, treatment period, the mode of treatment, and the time and pattern of exposure. We employed an intraperitoneal osmotic mini pump whereas the other groups have used intravenous infusion (Marks et al., 1992; Pauly et al., 1996) or subcutaneous injections (Zhang et al., 1994; Miao et al., 1998; Slotkin et al., 1999) Miao et al. (1998) exposed rats to nicotine during two different developmental periods; one group aged P1–P21 and the other P8–16. The P1-P21 group had elevated levels of ^{3}H nicotine binding which was transient, returning to normal levels 7 days following nicotine withdrawal. However, the P8–16 group changes were long lasting and remained through adulthood, providing evidence that the second postnatal week in rats is a critical period for development of these receptors.

Studies in the human have aimed to compare expression amongst cohorts with or without CSE. One limitation of post-mortem studies is that there is frequently no analysis of the biological concentration of nicotine or cotinine in the infant's system and information regarding the CSE status of the infant relies on questionnaire data provided by parents, usually from a categorical variable (Yes/No) during the death scene investigation. When stratified based on this reporting, the available studies show conflicting findings. For [^{3}H] nicotine binding, one study found no change (Kinney et al., 1993), another found an increase in several nuclei of the pons (Nachmanoff et al., 1998), while a third found a decrease in similar nuclei of the pons (Duncan et al., 2008b). These studies provide a good example of the complexity of human studies, where without measurable cotinine levels it is unclear whether the differences are due to presence or absence of circulating nicotine at the time of death, or due to the mechanism of death where the studies had differing cohorts of infants who died from varying causes. Regardless, the studies verify that changes in some brainstem nuclei are linked to CSE and these could relate to the abnormal physiologies reported.

5. Physiological consequences of cigarette smoke exposure during prenatal and postnatal development

Smoking during and after pregnancy leads to an increased risk of respiratory and cardiovascular illnesses (Carlsen and Carlsen, 2008) to the infant. Given the brainstem houses nuclei of predominant functions related to cardiac, respiratory and sleep/arousal control, any changes in the normal status of these nuclei due to cigarette smoke exposure would lead to alterations in these functions. These are addressed here and summarized in Tables Table 5 (animal model data) and Table 6 (human infant data).

5.1. Effects on the cardiovascular system

Cardioinhibitory neurons which are normally silent during hypoxia, are excited during hypoxic episodes in rats with prenatal nicotine exposure. This abnormal excitation occurs through cholinergic enhancement of glutamate release onto these neurons. The result is bradycardia during the hypoxic episode that may lead to death (Evans et al., 2005; Huang et al., 2007; Slotkin et al., 1995). This excitatory neurotransmission to the cardiac vagal neurons was absent when α3β4 nAChRs were blocked, suggesting mediation through α3β4 containing nAChRs (Kamendi et al., 2009). Infants of mothers who smoked during pregnancy have also been found to have decreased heart rate during hypoxic conditions (Søvik et al., 2001) along with impaired autonomic cardiac control (Søvik et al., 2001; Thiriez et al., 2009). This is also supported by animal studies; rats (Slotkin et al., 1997) and lambs (Hafstrom et al., 2002) exposed to hypoxic conditions. Impairment of autonomic control is demonstrated by changed systolic blood pressure responses to a passive head-up tilt, which is decreased in 2–3 day old infants with CSE, but unchanged in control infants (Browne et al., 2000).

5.2. Effects on the respiratory system

Smoke exposure during pregnancy affects baseline/resting ventilation, breathing drive, respiratory rate and alters ventilatory drive in animal models and in human infants. Maternal smoking results in

Table 5
Summary of animal studies examining physiological outcomes of cigarette smoke/nicotine exposure during the prenatal and postnatal period.

Species	Age	Exposure period and mode	Nicotine dose	Experimental Method	Physiological Outcome	Reference
Cardiovascular Response						
Rat	P1	Prenatal treatment via maternal exposure. Subcutaneous implantation of an osmotic minipump on G5 to last till the day of parturition (G22).	2 mg/kg/day 6 mg/kg/day	Survival response to hypoxia (5% O_2 balanced with N_2). Adrenal catecholamine release and brainstem/forebrain noradrenergic mechanisms.	6 mg/kg/day: ↑ mortality. ↓ adrenomedullary catecholamine release, an essential component required to maintain cardiac rhythm during hypoxia. Suppressed spontaneous neuronal activity.	(Slotkin et al., 1995)
Rat	P1-2	Prenatal treatment via maternal exposure. Subcutaneous implantation of an osmotic minipump on G4 to last till the day of parturition (G22).	6 mg/kg/day	HR and BP to 10 min. of hypoxia (5% O_2 + 95% N_2).	Absent ↑ in HR. Rapid and precipitous ↓ HR within few minutes of hypoxia exposure.	(Slotkin et al., 1997)
Lamb	P5	Prenatal treatment via maternal exposure. Subcutaneous implantation of an osmotic minipump on G98 of the 147-day gestation.	0.5 mg/kg/day	Ventilatory responses to hypoxia (10% O_2 in N_2) and hyperoxia (100%) during wakefulness and quiet sleep	↓ HR response during both wakefulness and quiet sleep.	(Hafstrom et al., 2002)
Lamb	P5 P28	Postnatal offspring exposure via subcutaneous implantation of an osmotic minipump from P0 to 4 weeks.	1–2 mg/kg/day	laryngeal stimulation on HR.	↑ reflex bradycardia	(Sundell et al., 2003)
Respiratory Response						
Lamb	P7 P17 P27	Offspring lamb (postnatal) exposure Continuous intravenous infusion via chronic instrumentation at P2-4 and studied sequentially during the first 4 weeks after birth.	0.5 μg/kg/min	Activation of peripheral chemoreceptors to hypoxia (10% O_2 in N_2) or hyperoxia (100% O_2).	↓ ventilatory response to hypoxia and hyperoxia at all ages.	(Milerad et al., 1995)
Rat	P3 P8 P18 P34	Maternal exposure via subcutaneous implantation of an osmotic minipump on on G2 that lasted till P7-8.	6 mg/kg/day	Baseline breathing control	No differences	(Bamford et al., 1996)
Rat	P5-6	Pre- into post-natal nicotine exposure. Subcutaneous implantation of osmotic minipump from G6-P5-6.	6 mg/kg/24 h	gasp and autoresuscitation during a single and repeated hypoxia (97% N_2, 3% CO_2)	No effect on last gasp. Blunted autoresuscitation response from primary apnea during repeated hypoxic episodes.	(Fewell and Smith, 1998)
Rat	P3 P8 P18	Pre- into post-natal nicotine exposure via subcutaneous implantation of an osmotic minipump from G2-3 that delivered nicotine for 28 days until P7-8.	6 mg/kg/day for 4 weeks	Ventilatory responses to hypoxia (5% O_2 + 5% CO_2) and to hyperoxia	No differences at P8 and P18. P3: absent ↓ ventilation to hyperoxia and altered oxygen consumption.	(Bamford and Carroll, 1999)
Rat	P0 P1 P4	Prenatal maternal exposure for 28 days. Subcutaneous/intra-peritoneal implantation of osmotic minipump in female rats two days before mating up to 28 days.	7 mg/kg/day to 3 mg/kg/day	Baseline ventilation and respiration.	↓ minute ventilation in room air ↓ hypoxic gas mixtures	(John and Leiter, 1999)
Lamb	P4.6 ± 1.3	Postnatal exposure. Infusion over two consecutive days	0.5 μg/kg/min	Ventilatory responses and to hypoxia (0.1 fraction of inspired O_2)	↓ Haemoglobin O_2 saturation ↓ ventilatory response to hypoxia in quiet sleep.	(Hafström et al., 2000)
Rat	P1-2 P5-6 P10-11	Maternal Exposure via Prenatal and postnatal infusion via subcutaneous implantation of osmotic minipump from G6-7 that lasted for 28 days.	6 mg/kg/day	protective responses that promote survival during a single hypoxic (97% N_2, 3% CO_2) episode and during repeated hypoxic episodes.	↓ in the time to last gasp, ↑ in the total number of gasps in the P1-2 rats. P1-2 and 5-6 nicotine-exposed rats had a ↓ in the number of successful autoresuscitations and disrupted cardiorespiratory events preceding death.	(Fewell et al., 2001a)
Rat	P5-6	Maternal Exposure via subcutaneous implantation of osmotic minipump from pre- into post-natal stage from G6-7 that lasted for 28 days.	1.5 mg/kg/day 3 mg/kg/day 6 mg/kg/day	Threshold level of prenatal nicotine exposure required for the protective responses that promote survival during a single hypoxic (97% N_2, 3% CO_2) and repeated hypoxic episodes.	Did not affect the time to last gasp nor the total number of gasps when pups were exposed to a single hypoxic episode. 3 or 6 mg/kg/day rat pup had a ↓ in the number of successful autoresuscitations to repeated hypoxia.	(Fewell et al., 2001b)
Piglet	P7	Piglet offspring via a single intravenous infusion of postnatal treatment	5 μg/kg	Ventilatory responses and blood gases following induction of apnea by insufflation of 0.1mL of acidified saline in the subglottic space.	↑ spontaneous apneas and prolongation of apneas. Repeated spontaneous apneas resulted in failure to hyperventilate after induced apnea. ↓ SaO_2 2 min. after apnea. Disrupted normal autoresuscitation after apnea.	(Froen et al., 2000, 2002)
Lamb	Average age of P5	Maternal exposure via Subcutaneous implantation of osmotic minipump on G98 of the 147-day gestation.	0.5 mg/kg/day	Ventilatory responses to hypoxia (10% O_2 in N_2) and hyperoxia (100%) during wakefulness and quiet sleep	↓ ventilatory response to 10% oxygen during quiet sleep.	(Hafstrom et al., 2002)

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Table 5 (*continued*)

Species	Age	Exposure period and mode	Nicotine dose	Experimental Method	Physiological Outcome	Reference
		Pumps replaced after 28 days and removed after delivery of the lamb.			↓ ventilatory responses to hyperoxia in both activity states.	
Mouse	P0 P3 P9 P19 P42	Maternal exposure. Subcutaneous implantation of osmotic minipump at G10 for 8 days.	0.5 μL/h for 8 days.	Ventilatory responses to hypoxia (7.4% O_2).	↑ frequency of apnea with increased age in normoxia. initial ↓ in frequency of apnea and then ↑ with prolonged hypoxia.	(Robinson et al., 2002)
Lamb	P5 P28	Postnatal offspring exposure. Subcutaneous implantation of osmotic minipump at P0 that lasted for 4 weeks.	1-2 mg/kg/day	Laryngeal stimulation on HR.	↓ in ventilation, longer reflex apnea and an impaired ability to terminate the stimulated apnea both normoxia and in hypoxia.	(Sundell et al., 2003)
Rat	P5 P10 P15 P20	Pre- into post-natal maternal exposure. Subcutaneous implantation of osmotic minipump at G5 until P9-10.	6 mg/kg/day	Respiratory drive and hypoxic (10% O_2) ventilatory response	↑ baseline respiratory frequency ↓ in peak hypoxic ventilatory response and ventilatory roll-off.	(Simakajornboon et al., 2004)
Rat	P1 P2 P6 P10 P14 P18	Maternal exposure via subdermal implantation of osmotic minipump at G5 for 28 days	6 mg/kg/day	Ventilatory pattern and the frequency and duration of apneas.	P1 and P2: ↑ frequency of apneas. P10: ↑ breathing frequency P14 and P18: ↓ tidal volume.	(Huang et al., 2004)
Mouse	P0 P1 P3 P8	Pre- into post-natal maternal exposure. Subcutaneous implantation of an osmotic minipump at G5-7 for 28 days	60 mg/kg/day at rate of 0.25 μL/h	Response to hypercapnia (10% CO_2 for 20 min.) and hypoxia (inhalation of 0%O2 in 100%N_2 for 20 s) at P0-3. Brainstem – spinal cord slices.	P0-3: ↓ RR and responses to hypercapnia and hypoxia. P0-3: Isolated brainstem-spinal cord preparations demonstrated longer and more irregular respiratory cycles and ↓ response to acidification, indicative of impaired central chemoreception.	(Eugenin et al., 2008)
Rat	P1 P3 P6 P9 P12 P18	Maternal exposure. Subdermal implantation of osmotic minipump at G5 for 28 days	6 mg/kg/day	Ventilatory responses to hypoxia (inspired O_2 at 16, 12 and 10%) and hypercapnia (3, 6 and 9% CO_2, in 50% O_2, balance N_2), combined hypoxia-hypercapnia (12% O_2 /5% CO_2) and hyperoxia (50% O_2, 50% N_2).	P1 and P3: impaired ventilatory response to hypoxia. All ages: impaired ventilatory responses to hypercapnia alone and combined hypoxia-hypercapnia (demonstrated through a blunted tidal volume response).	(Huang et al., 2010)
Arousal response during sleep						
Lamb	P4.3 ± 1.3	Postnatal infusion over 2 consecutive days	0.5 μg/kg/min	Arousal response to hypoxia (0.1 fraction of inspired O_2)	Delayed arousal from quiet sleep.	(Hafström et al., 2000)
Rat	P10 P12-24	Maternal exposure, subcutaneous implantation of osmotic minipump at G4-5 till parturition (P = 0).	2 mg/kg/day 4 mg/kg/day	Sleep/wake ontogenesis	↓ total sleep time ↑ awake time, thus ↓ overall REM sleep. temporary ↑ in sleep continuity.	(Frank et al., 2001)
Lamb	Average age of P5	Maternal exposure, subcutaneous implantation of osmotic minipump on G98 of the 147-day gestation. Pumps replaced after 28 days and removed after delivery of the lamb.	0.5 mg/kg/day	Ventilatory responses to hypoxia (10% O_2 in N_2) and hyperoxia (100%) during wakefulness and quiet sleep	Delayed arousals	(Hafstrom et al., 2002)

Abbreviations: G: gestational; HR: heart rate; P: postnatal; REM; rapid eye movement; RR: respiratory rate.

Table 6
Summary of human infant studies examining physiological outcomes of cigarette smoke/nicotine exposure during the prenatal and postnatal period.

CSE exposure period	Infant age group	Experimental method	Physiological outcome in CSE-exposed infants compared to the non-exposed.	Reference
Cardiovascular response				
Prenatal and postnatal exposure	2–3 days 3 months	Head-up tilt challenge. BP analysis.	↓ Systolic pressure in 2–3-day old smoke-exposed infants. No differences in 3-month old smoke-exposed infants.	(Browne et al., 2000)
Prenatal exposure	6–16 weeks	Sleep study (polygraphic study) and HR analysis (LF related to sympathetic and parasympathetic activities and HF component reflecting parasympathetic tonus).	Lower and normalised HF powers and higher LF/HF ratios detected during REM sleep by EEG signal during the polygraphic studies.	(Franco et al., 2000)
Prenatal and postnatal exposure	10–16 weeks	Head up tilt and side motion test. HR and BP analysis.	Head up tilt test- no differences. Side motion test- ↓HR and BP responses.	(Viskari-Lähdeoja et al., 2008)
Prenatal exposure	3 days	Head-up and -down tilt test. HR analysis.	↓ beat-to-beat heart rate variability in quiet sleep. No differences during the tilt test.	(Fifer et al., 2009)
Prenatal exposure	33–34 weeks post-conceptional age (pre-term infants)	HR analysis through ECG and coarse-graining spectral analysis	↓ heart rate variability	(Thiriez et al., 2009)
Respiratory response				
Prenatal and postnatal exposure	4.2 ± 1.9 weeks	Pulmonary Function test	↓ forced expiratory flow rates ↓ functional residual capacity flow	(Hanrahan et al., 1992)
Prenatal and postnatal exposure	< 1 week 5–29 weeks	Polysomnography (PSG) study	Frequent and longer OSA episodes.	(Kahn et al., 1994)
Prenatal and postnatal exposure	2–3 months	Arousal in hypoxia (17%, 15% and 13%O_2) and hypercapnia (4%, 6% and 8% CO_2)	There was no difference in the ventilatory response to hypoxia and hypercapnia.	(Lewis and Bosque, 1995)
Prenatal and postnatal exposure	2–24 months	Ventilatory response to hypoxia 14% O_2	↓ respiratory drive characterised by a decrease in occlusion pressure ($P_{0.1}$). Impaired ventilatory response to hypoxia. A dose-response relationship was demonstrated between the number of cigarettes smoked by the mother and the severity of the reduced ventilatory response.	(Ueda et al., 1999)
Prenatal and postnatal exposure	1 day 3 days 10 days 10 weeks	Normal baseline parameter measurements of tidal volume and RR.	↓ tidal volumes ↑ respiratory rates during air breathing.	(Søvik et al., 1999)
Prenatal and postnatal exposure	8–12 weeks	Alternating breath test of Inspired O_2 at 40% and 0%. Respiratory drive and time.	No differences.	(Poole et al., 2000)
Prenatal exposure	1 month 3 months	Delivery of asphyxial (hypercapnia/hypoxia) (CO_2 maximum 5% and O_2 minimum 13.5%) gases in the supine sleeping position.	↓ oxygen saturation despite an ↑ in tidal volume.	(Campbell et al., 2001)
Prenatal exposure	Around 36–37 weeks postconceptional age (Preterm infants)	Multichannel PSG study	Increase in the apneic index and increased respiratory events during active sleep mainly due to obstructive apnea.	(Sawnani et al., 2004)
Prenatal and postnatal exposure	2–5 weeks 2–3 weeks 5–6 months	Arousal in hypoxia (15% O_2) during PSG study	There was no effect of maternal smoking on ventilatory responses preceding hypoxia induced arousal at any age in either sleep stage (quiet/active sleep).	(Parsiow et al., 2004)
Arousal response during sleep				
Prenatal and postnatal exposure	2–3 months	Arousal in hypoxia (17%, 15% and 13%O_2) and hypercapnia (4%, 6% and 8% CO_2)	↓ arousal during hypoxia. No differences during hypercapnia.	(Lewis and Bosque, 1995)
Prenatal exposure	Newborns 4–21 weeks	Auditory stimulus to invoke arousals	More intense auditory stimulus was required to induce arousals during REM sleep; thus, ↑ arousal thresholds.	(Franco et al., 1999)
Prenatal and postnatal exposure	2–3 weeks 2–3 months 5–6 months	Spontaneous and air jet stimulus induced arousals in supine and prone position during PSG study.	2–3 months of age: ↑ arousal threshold in quiet sleep in supine position and ↓ spontaneous arousals from quiet sleep in both prone and supine sleeping positions.	(Horne et al., 2002)
Prenatal exposure	8-12 weeks	Audiology stimuli during REM and non-REM sleep during the PSG study.	No differences.	(Chang et al., 2003)

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Table 6 (*continued*)

CSE exposure period	Infant age group	Experimental method	Physiological outcome in CSE-exposed infants compared to the non-exposed.	Reference
Prenatal exposure	Postconceptional age: 33.9 ± 6 weeks (Preterm infants)	PSG study	↓ sleeping time (with ↑ percentage of active sleep and ↓ percentage of quiet sleep). ↑ wakefulness after sleep onset. ↑ nocturnal body movements and thus more disturbed sleep.	(Stephan-Blanchard et al., 2008)
Prenatal exposure	Around 36–37 weeks postconceptional age (Preterm infants)	Multichannel PSG study	↓ arousal index specifically associated with respiratory events.	(Sawnani et al., 2004)
Prenatal and postnatal exposure	2–5 weeks 2–3 weeks 5–6 months	Arousal in hypoxia (15% O_2) in PSG study	5–6 months: ↑ Arousal latency.	(Parsiow et al., 2004)

Abbreviations: BP: blood pressure; ECG: electrocardiogram; EEG: electroencephalogram; HF: high frequency; HR: heart rate; LF: low frequency; OSA: obstructive sleep apnea; PSG: polysomnography; REM: rapid eye movement; RR: respiratory rate.

reduced forced expiratory flow rates and reduced functional residual capacity flow in infants (Hanrahan et al., 1992). Infants whose mothers smoked during pregnancy also have lower tidal volumes and higher respiratory rates than controls during baseline resting ventilation (Søvik et al., 1999). This is supported by animal studies where prenatal maternal smoke exposure decreased minute ventilation in room air (John and Leiter, 1999) and increased baseline respiratory frequency (Simakajornboon et al., 2004) in rats.

Previous studies measuring ventilatory drive in offspring of smoking mothers have demonstrated conflicting results. Although some studies in human infants have reported no difference in resting ventilation or ventilatory response to hypoxia or hypercapnia: (Campbell et al., 2001; Lewis and Bosque, 1995; Parsiow et al., 2004); rats at P8 and P18 (Bamford and Carroll, 1999)) one group demonstrated a decrease in respiratory drive when measured by occlusion pressure ($P_{0.1}$- airway opening pressure 100 ms after occlusion) and an impaired ventilatory response to hypoxia in infants from the smoking group (Ueda et al., 1999). That study also found a dose-response relationship between the number of cigarettes smoked by the mother and the severity of the reduced ventilatory response. The differences between the studies may be attributed to the difference in age, the amount of cigarette smoke exposure and other factors such as sleep position and sleep stage (Sawnani et al., 2010). Several animal studies support impaired ventilatory responses to hypoxia (Lamb- (Hafström et al., 2000; Hafstrom et al., 2002; Milerad et al., 1995); Rat at P3- (Bamford and Carroll, 1999) at P1and P3-(Huang et al., 2010); Mouse at P0-3-(Eugenin et al., 2008)). Nicotine exposure extending from the pre- into the post-natal period in mice led to hypoventilation and reduced responses to hypercarbia and hypoxia at P0-3, and disrupted the respiratory rhythm pattern generator during early postnatal period, causing subsequent vulnerability in breathing and failure to respond to chemosensory demands (Eugenin et al., 2008).

Smoking during pregnancy has been linked to the occurrence of obstructive sleep apnea (OSA) and the arousal threshold to respiratory events. Infants of mothers who smoked heavily during pregnancy had more frequent and longer OSA episodes compared to control and light smoker groups (Kahn et al., 1994). Infants were found to be at greater risk for OSA if both parents smoked, and the risk appeared to be confined to prenatal exposure as CSE in the postnatal period did not increase the risk (Kahn et al., 1994). Similar findings of increased apneas due to prenatal exposures were reported in the rat (Robinson et al., 2002) and mouse (Huang et al., 2004). In piglets, postnatal exposure alone was linked to increased frequency and duration of spontaneous apneas (Froen et al., 2000, 2002).

5.3. Effects on sleep and arousal

The overarching effect of CSE is for delayed arousals following respiratory challenges such as respiratory events, hypoxia or anoxia. A delayed arousal response to hypoxia was seen in lambs from quiet sleep (Hafström et al., 2000; Hafstrom et al., 2002). Infants of smoking mothers at 2–3 months of age had increased arousal thresholds in quiet sleep when they slept in the supine position and fewer spontaneous arousals from quiet sleep in both prone and supine sleeping positions (Horne et al., 2004). Further, preterm infants of smoking mothers had increased frequency of apneas and decreased frequency of arousals with arousal specifically diminished after respiratory events (Sawnani et al., 2004).

6. Mechanisms for the decrease vs increase in nAChR subunit expression and consequences

Summarising the studies in Tables 3 and 4, nAChR expression was either increased or decreased in the various brainstem nuclei as a result of CSE or exposure to nicotine. It is generally accepted that the nicotine-induced effect on nAChRs is posttranscriptional as nicotine exposure

doesn't change mRNA levels in rat and mouse brains (Bencherif et al., 1995; Marks et al., 1992; Miao et al., 1998; Peng et al., 1994). Mechanisms responsible for these changes could include one or more of the following:

1 Altered desensitisation: overall decreased expression of nAChRs in the brainstem may be due to a poorly understood mechanism of alteration in the desensitisation rate of nAChRs (Reviewed in (Buisson and Bertrand, 2002); (Giniatullin et al., 2005)). When a medium to high agonist concentration is introduced, nAChRs are first activated. If the agonist concentration remains high, the receptors then desensitize with subsequent recovery when the agonist is removed. During the desensitised state, the receptors response to a downstream signalling pathway decreases. As a result, down-regulation of the receptor function may occur due to either an increase/decrease in the nAChRs (Buisson and Bertrand, 2002).
2 Alterations in cell surface expression: The full function of nAChRs is primarily dependent on associated proteins such as chaperones, regulators and modulators. This mainly occurs via exocytosis or endoplasmic reticulum (ER) release/retention of the nAChRs and would be relevant to increased or decreased expression levels. Exocytosis involves the transport of the nAChRs from the trans-Golgi network during biosynthesis to increase the surface expression of the receptor (Colombo et al., 2013) and involves structural regulatory proteins. Thus, any change in these regulatory proteins would alter receptor trafficking. Two examples of regulatory proteins linked with nAChRs are visinin-like protein (VILIP-1) (Zhao et al., 2009) and resistance to inhibitors of Cholinesterase 3 (RIC 3) (Alexander et al., 2010). Another example of an associated protein is lynx, a modulator that affects α4β2 subunit stoichiometry by affecting assembly in the ER (Nichols et al., 2014). Furthermore, evidence suggests that nicotine itself is a pharmacological chaperone of nAChRs (Lester et al., 2009), where stabilisation of assembled receptors by nicotine results in an overall increase in α4β2 nAChR expression at the plasma membrane (Srinivasan et al., 2011), promoting subunit assembly of the nAChRs.
3 Internalisation/endocytosis: would be responsible for decreased subunit expression and occurs as a protective mechanism to excessive activation due to increased agonist levels (St John and Gordon, 2001).
4 Compensatory: increased nAChR expression could be a compensatory response (Guyon et al., 1998) whereby the functional loss of nAChRs due to a decrease in nAChR expression or prolonged desensitised state, induces the cell signalling pathway leading to an upregulation of the gene expression itself.
5 Alterations in translation: expression could be altered by changes in mRNA translation to protein (Reviewed in (Vogel and Marcotte, 2012)).

The overall trend is for nicotine exposure to upregulate the nAChRs. Despite increased nAChR expression (increased binding), the receptors are functionally desensitized with chronic nicotine exposure, i.e. there is a temporary functional loss of receptors (Wonnacott, 1990). This compromises the downstream functions of nAChRs.

The consequences of altered nAChR expression at the cellular level can disrupt a range of normal cellular functions as nAChRs control processes such as transmitter release, cell excitability and neuronal integration (reviewed in (Gotti et al., 2006)). They also play a crucial role in cell survival and targeting, the formation of neural and sensory circuits through spontaneous activity and the development of catecholamine systems by regulation of neurotransmitter release (Reviewed in (Dwyer et al. (2009)). For example, nAChRs influence the release of other excitatory (glutamate) and inhibitory (GABA) neurotransmitters, so desensitisation can lead to reduction in the release of other neurotransmitters (Fregosi and Pilarski, 2008).

7. Conclusion

The development of the knock out and knock in models over the last few years has advanced our understanding of the functions of the individual nAChR subtypes. Immunoassays with subunit-specific antibodies has enabled the study of nAChR expression and localisation and new selective ligands have allowed study of the binding patterns of specific nACh receptor complexes. The advancement of technology from intravenous infusion of nicotine, to osmotic minipumps, transdermal patches and smoking chambers has enabled different methods of delivery of cigarette smoke and nicotine to more closely mimic human patterns of exposure. In this review, we correlated findings in animal models with those from human studies. The major brainstem sites where expression levels of the nAChRs are consistently affected include those that play vital roles in cardiorespiration (XII, DMNV, NTS), chemosensation (NTS, arcuate nucleus) and arousal (rostral mesopontine sites such as the locus coeruleus, nucleus pontis oralis). These findings stress how CS during and after pregnancy impacts on the children of those pregnancies.

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