Neurochemistry International 125 (2019) 117–126

Contents lists available at ScienceDirect

Neurochemistry International

journal homepage: www.elsevier.com/locate/neuint

Molecular mechanisms for nicotine intoxication

Tursun Alkam[a,b,**], Toshitaka Nabeshima[a,c,*]

[a] Japanese Drug Organization of Appropriate Use and Research, Nagoya, Japan
[b] Department of Basic Medical Sciences, College of Osteopathic Medicine of the Pacific, Western University of Health Sciences, Pomona, CA, USA
[c] Advanced Diagnostic System Research Laboratory, Graduate School of Health Sciences, Fujita Health University, Toyoake, Japan

ARTICLE INFO

Keywords:
Acute nicotine intoxication
Chronic nicotine intoxication
Tobacco sickness
Nicotine products
Prenatal nicotine exposure
Fetal brain development
Newborn behaviors
Sudden infant death syndrome

ABSTRACT

Nicotine, one of the more than 4700 ingredients in tobacco smoke, is a neurotoxin and once used as pesticides in agriculture. Although its use in agriculture is prohibited in many countries, nicotine intoxication is still a problem among the workers in tobacco farms, and young children as well as adults due to the accidental or suicidal ingestions of nicotine products. Understanding the mechanism of nicotine intoxication is important not only for the prevention and treatment but also for the appropriate regulatory approaches. Here, we review pharmacokinetics of nicotine and the molecular mechanisms for acute and chronic intoxication from nicotine that might be relevant to the central and the peripheral nervous system. We include green tobacco sickness, acute intoxication from popular nicotine products, circadian rhythm changes, chronic intoxication from nicotine through prenatal nicotine exposure, newborn behaviors, and sudden infant death syndrome.

1. Introduction

Nicotine is a water-soluble bioactive alkaloid with potent parasympathomimetic and addictive properties. Nicotine is obtained from the dried leaves and stems of tobacco plant *Nicotiana tabacum* that grows natively in North and South America. Native Americans (e.g., Anishinaabe-Ojibwe people living around Great Lakes region in America and Canada) began using tobacco in many different ways, such as in religious, ceremonial and medicinal practices thousands years ago and continues the tradition till now (Johnston, 1990; Struthers and Hodge, 2004). Christopher Columbus, in 1492, was offered dried tobacco leaves as a ceremonial gift from the Native Americans (Brooks, 1953). Tobacco was then introduced to Europe for its pleasurable effects and some medicinal use (Charlton, 2004).

Nicotiana tabacum is now cultivated in more than 100 countries, and some 5.73 million metric tons dry weight of tobacco were grown worldwide in 2004 (McKnight and Spiller, 2005). The tobacco plants are now grown in China (39.5% of world total production), Brazil (7.2%), India (8.7%), the US (9.0%) as well as other countries, but these four countries obviously occupy 65% or more of total tobacco production (McKnight and Spiller, 2005; Yoo et al., 2014). However, 80% of tobacco smokers live in low-and middle-income countries where the burden of tobacco-related illness and death is heaviest and tobacco regulatory approaches are not well-established (McKnight and Spiller, 2005; The World Health Organization, 2018b).

Although the number of smokers is declining in developed countries, it is increasing significantly in developing countries thanks to population growth (Ng et al., 2014). Approximately 1.1 billion people smoke tobacco worldwide in 2015, more than half of them reside in eight regions or countries - Bangladesh, Brazil, China, the European Union, India, Indonesia, the Russian Federation, and the United States (Prabhat Jha et al., 2015; The World Health Organization, 2018a). Tobacco is mostly smoked in the form of cigarettes, and an estimated 5.9 trillion cigarettes sold globally in 2006 (Prabhat Jha et al., 2015). Based on these estimates, a smoker smokes average 15 cigarettes a day. Nicotine is the main component found in fresh leaves of tobacco, and the average nicotine content ranges from 2% to 6% of the dry weight of leaves (Gonzalez-Coloma et al., 2010).

Each cigarette contains approximately 8–20 mg of nicotine, the average amount in one cigarette being 12 mg, and merely more than 40 mg nicotine intake at a time is needed to kill an adult (Francisco García Calvo-Flores et al., 2017; Mayer, 2014). Tobacco smoke contains more than 4700 toxic and carcinogenic compounds in addition to nicotine (Talhout et al., 2011; Thielen et al., 2008). Although tobacco smoking itself does not cause immediate death, the tobacco plant has probably been responsible for more deaths, when consider deaths from

* Corresponding author. Advanced Diagnostic System Research Laboratory, Graduate School of Health Sciences, Fujita Health University, Toyoake, Aichi, 470-1192, Japan.
** Corresponding author. Department of Basic Medical Science, College of Osteopathic Medicine of the Pacific, Western University of Health Sciences, 309 East Second Street, Pomona, CA, 91766-1854, USA.
E-mail addresses: tursun.alkam@gmail.com (T. Alkam), tnabeshi@ccalumni.meijo-u.ac.jp, tnabeshi@fujita-hu.ac.jp (T. Nabeshima).

https://doi.org/10.1016/j.neuint.2019.02.006
Received 12 October 2018; Received in revised form 28 January 2019; Accepted 12 February 2019
Available online 16 February 2019

the tobacco-related cancers and chronic diseases, than any other plants in the world (Charlton, 2004).

2. Nicotine

Nicotine, 3-(1-methyl-2-pyrrolidinyl) pyridine, is pale yellow and hygroscopic oily liquid. Nicotine was first isolated from tobacco by German chemists Posselt and Reimann in 1828 and named after Jean Nicot, who introduced tobacco to the French court around 1560 (Henningfield and Zeller, 2006; Ujváry, 1999). Nicotine was found to be a powerful neurotoxin to insects and has since been used as a potent insecticide in agriculture and families worldwide. Nicotine is never smoked or ingested alone until recent innovation of electronic cigarette (e-cigarette) and nicotine gum.

From World War II to 1980s, nicotine consumption for insecticide use amounted to more than 2500 tons worldwide with most of it from waste of the tobacco industry (Ujváry, 1999). However, due to its fatal toxicity following accidental ingestion, inhalation, or skin contact, the production and the use of nicotine as insecticide are decreased significantly. Currently, nicotine insecticide is totally prohibited for organic farming in Japan and the United States (Francisco García Calvo-Flores et al., 2017; Ikka et al., 2018).

The lethal dose of nicotine has been estimated to be 40–60 mg (0.8–1 mg/kg) for adults and about 10 mg (1 mg/kg) for children (Goshman, 1985). The severity of nicotine intoxication is dependent on dose, dose duration and frequency, route of exposure, formulation of the nicotine product, and interpersonal variability (National Center for Chronic Disease Prevention and Health Promotion (US) Office on Smoking and Health, 2014). The time course of nicotine accumulation in the brain and other body organs, and the resultant pharmacologic effects, are highly dependent on route and rate of dosing (Benowitz et al., 2009).

3. Pharmacokinetics

The majority (70–80%) of nicotine is metabolized to cotinine in human liver microsomes, and the enzyme cytochrome P450 2A6 (CYP2A6) mediates approximately 90% of this reaction (Benowitz et al., 1994; Nakajima et al., 2006; Nakajima et al., 2002; Nakajima et al., 2001; Nakajima et al., 1996b; Yamanaka et al., 2004). Cotinine is further metabolized by CYP2A6 to trans-3′-hydroxycotinine (Nakajima et al., 1996a; Zhu et al., 2013). Nicotine is also metabolized to nornicotine via *N*-demethylation by CYP2A6 and CYP2B6 at low and high substrate concentrations, respectively (Yamanaka et al., 2005; Yamanaka et al., 2004; Yamazaki et al., 1999). The contributions of CYP2A6 and CYP2B6 in the metabolism of nicotine would be dependent on the expression levels of these isoforms in the human liver (Yamanaka et al., 2005). It has also been reported that the genetic polymorphism of *CYP2A6* gene causes large interindividual differences of nicotine metabolism and smoking behavior (Nakajima et al., 2000; Soeroso et al., 2018; Yamanaka et al., 2004; Yoshida et al., 2002).

Three metabolites of nicotine including cotinine, nornicotine, and norcotinine are identified in the brain (Crooks et al., 1997). Both CYP2B and CYP2A6 are expressed in the brain. Human smokers, rats, and monkeys with chronic nicotine treatment have higher levels of CYP2B in the brain (Lee et al., 2006; Miksys et al., 2000; Miksys et al., 2003). Chronic nicotine exposure increases the protein levels of CYP2B6 in human brain and the activity of CYP2B6, which reduces nicotine levels, in the rat brain (Garcia et al., 2017; Miksys et al., 2003). Chronic nicotine treatment increases CYP2B expression in rat brain but not in the liver (Miksys et al., 2000). In a microdialysis study, after nicotine treatment with intravenous infusion, the intracerebroventricular injection of CYP2B inhibitor C8X increases nicotine levels in the rat brain without altering peripheral levels of nicotine (Garcia et al., 2015).

After chronic continuous infusion of nicotine, blood nicotine, cotinine and nornicotine concentrations remain relatively constant, whereas concentrations of nicotine and nornicotine in brain increase approximately 4-fold (Ghosheh et al., 2001). Nornicotine, like nicotine, increases dopamine in the midbrain (Green et al., 2001; Hoffman and Evans, 2013; Papke et al., 2007). Nornicotine inhibits dopamine transporter function via a nAChR-mediated mechanism (Middleton et al., 2007). Similar to nicotine, nornicotine self-administeration level in rats is significantly above than that of saline control (Bardo et al., 1999). Pre-treatment with nicotine or nornicotine produces a dose-dependent decrease in nicotine self-administration in rats (Green et al., 2000). These reports suggest that nornicotine may contribute to the long-lasting neuropharmacological effects of nicotine.

In humans, nicotine and its metabolites are eliminated from the body via renal excretion (Benowitz et al., 2009); however, only 2–3% of nicotine is excreted as nornicotine in urine (Kyerematen et al., 1990; Yamanaka et al., 2004), suggesting that the metabolism of nicotine to nornicotine would be a relatively minor pathway in the systemic clearance of nicotine (Yamanaka et al., 2005). The brain half-lives of nicotine, cotinine, and nornicotine were 52, 333, and 166 min, respectively (Ghosheh et al., 1999). Peak brain concentrations of nicotine metabolites were 300, 70, and 7 nM for cotinine, nornicotine, and norcotinine, respectively (Ghosheh et al., 1999). The nornicotine concentration in brain is nearly equal to that of nicotine, indicating that nornicotine is a major metabolite of nicotine in the brain (Crooks et al., 1997; Ghosheh et al., 1999).

The elimination half-life of nicotine is around 2 h in non-pregnant adults (Benowitz et al., 1982). The elimination half-life of nicotine from blood during and after pregnancy is 1.6 h and 1.8 h, respectively, while the elimination half-life from breast milk is 1.6 h (Dempsey and Benowitz, 2001). In tobacco smoke-exposed newborns, due to the low activity of CYP2A6, the elimination half-life of nicotine is 3–4 times longer than that in adults (Benowitz et al., 2009; Dempsey et al., 2000).

4. Acetylcholine receptors

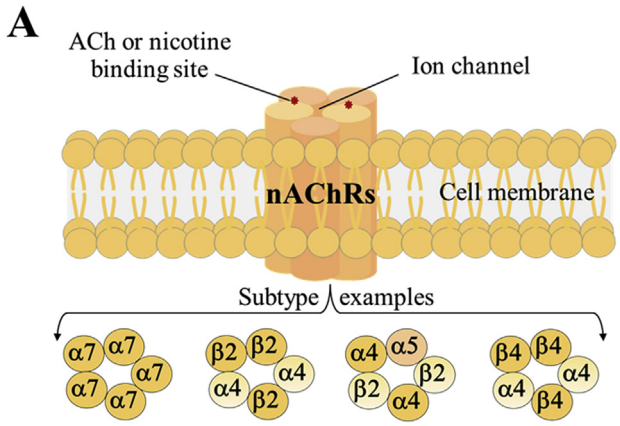
Acetylcholine receptors (AChRs) are classified into nicotinic AChRs (nAChRs) and muscarinic AChRs (mAChRs), according to their relative affinities and sensitivities to different molecules. These two AChRs play important roles in control of cardiac rate and rhythm, respiration, blood pressure, digestion, muscular motion, memeory, addiction, circardian rhythm and many other functions.

4.1. Nicotinic acetylcholine receptors

Nicotine exerts its effects via the stimulation of the ion channel nAChRs (Fig. 1A). The nAChRs are transmembrane polypeptides whose subunits form cation-selective ion channels which are permeable to Ca^{2+}, Na^{+}, and K^{+}. The nAChRs are located on plasma membranes of the central nervous system (CNS) neurons, of postganglionic cells in all autonomic ganglia, and of muscles innervated by somatic motor fibers (Pappano, 2015).

Neuronal nAChRs, which are composed of alpha (α2–α7, α9, and α10) and beta (β2–β4) subunits, are localized in ganglionic cells as well as in non-neuronal cells (Dani, 2015; Paterson and Nordberg, 2000; Posadas et al., 2013). The most abundant nAChR subtypes in the nervous system are homomeric α7 receptor and heteromeric receptors that containing only one type of α and one type of β subunit (Millar and Gotti, 2009). Agonists of nAChRs bind at subunit interfaces and both α and non-α subunits are able to contribute to the agonist binding site (Luetje and Patrick, 1991; Millar and Gotti, 2009; Sine, 2002). Both α4 and β2 subunits contribute to the high affinity nicotine binding sites (Millar and Gotti, 2009). The α4β2 subtype is the most abundant and widely distributed nAChR in mammalian brain, and characterized by its high-affinity for ACh and nicotine (Millar and Gotti, 2009; Posadas et al., 2013).

All heteromeric nAChRs contain at least one α-type subunit which can act as the principal subunit at the agonist binding site, but not all α



B

The half-lives of the two agonists of nAChRs.

Agonists	In the blood circulation	In the synaptic cleft
ACh	< 2 seconds	< 1 second
Nicotine	≈ 2* or 8** hours	Unknown

* In adults. ** In newborns.

Fig. 1. Nicotinic acetylcholine receptors and the half-lives of their two agonists. A: The nAChRs are transmembrane polypeptides whose subunits form cation-selective ion channels. Both ACh and nicotine bind to nAChRs to exert their effects. B: The half-lives of ACh and nicotine in the blood circulation and the synaptic cleft. ACh: acetylcholine. nAChRs: nicotinic acetylcholine receptors.

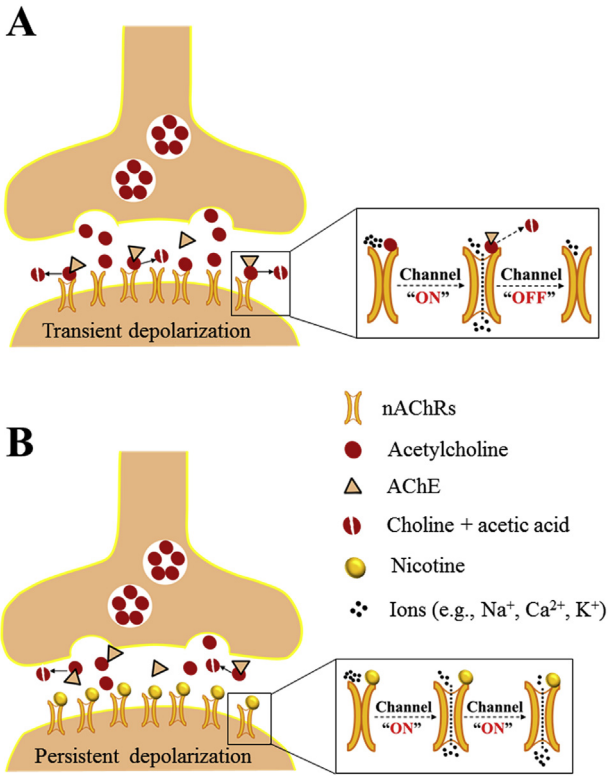


Fig. 2. Acetylcholine and nicotine act via nicotinic acetylcholine receptors. A: ACh exerts its effect by stimulating and opening the cation-selective ion channel nAChRs, which are permeable to Ca^{2+}, Na^{+}, and K^{+}, to cause depolarization of the target cell. The effect is brief, because as soon as ACh binds with nAChRs, AChE in the synaptic cleft hydrolyzes ACh into choline and acetic acid and terminates its function to close the ion channel. B: Nicotine exerts its effect by stimulating and opening the cation-selective ion channel nAChRs to cause depolarization of the target cell. The effect is persistent, because after binding with nAChRs, nicotine cannot be rapidly hydrolyzed to be ineffective like ACh and the ion channel stays open. The persistent stimulation of nAChRs raises the intracellular (depolarizing) positive ion concentration to a pathological level and causes cellular dysfunction. This ultimately leads to desensitized non-conducting conformation of AChRs and causes rapid development of depolarization blockade which results in signal transmission blockade. The persistent stimulation of nAChRs contributes the intoxication from nicotine. ACh: acetylcholine. AChE: acetylcholinesterase. nAChRs: nicotinic acetylcholine receptors.

subunits can perform this role; for example, the α5 and α10 subunits are only able to form nAChRs agonist binding site when co-assembled with another α subunit (Millar and Gotti, 2009). A single α5 subunit may combine as an "accessory" subunit that does not contribute to the agonist-binding site, but its presence modifies the functional properties of the receptor/channel complex (Dani, 2015; Gotti et al., 2009). The α5 subunit is the most common additional subunit but is present in less than 20% of nAChRs in the brain (Brown et al., 2007; Millar and Gotti, 2009).

Peripheral nAChRs, which are composed of α1, β1, γ and δ or ε subunits, are localized in the neuromuscular junction of somatic muscle (Dani, 2015; Posadas et al., 2013). The α3β4 subtypes are commonly found in the peripheral nervous system which have low affinity for nicotine and have much slower desensitization kinetics than α4β2 nAChRs (Dani, 2015; Fenster et al., 1997).

Physiologically, nAChRs are activated by neurotransmitter acetylcholine (ACh) to depolarize neurons in the central nervous system and on target organs throughout the body as part of the parasympathetic autonomic nervous system (Fig. 2A). Through its binding sites on nAChRs, ACh activates the receptors and rapidly changes the three-dimensional structures of the receptors to open the ion channel allowing an influx of cations (Ca^{2+}, Na^{+}, and K^{+}) for a few seconds which results in the rapid depolarization of the cell (Quick and Lester, 2002). Normally, in both the central and peripheral nervous systems, ACh is released through the presynaptic membrane and diffuses across the synaptic cleft where it binds to nAChRs in postsynaptic membrane. But within a second after the release of ACh, acetylcholinesterase (AChE) degrades it into choline and acetic acid with the result of the termination of function (Quick and Lester, 2002). ACh is also an autocrine or paracrine hormone synthesized and secreted by airway bronchial epithelial cells into blood circulation (Proskocil et al., 2004; Slevin et al., 2018). The blood also contains abundant AChE both on the surface of the red cells and in the plasma. As soon as secreted acetylcholine enters the blood circulation it is very rapidly destroyed. The half-life of ACh in blood circulation is less than 2 s (Vane, 1969). Thus, even if acetylcholine leaks into the venous circulation, it is very quickly destroyed and is unlikely to reach the arterial side of the circulation in effective amounts to have a significant role as circulating ACh (Vane, 1969). After a brief stimulation by ACh, nAChRs become desensitized or temporarily inactive. The desensitization by ACh is a readily reversible form of signal plasticity and might be responsible for synaptic efficacy and protection of the cells from uncontrolled excitation (Giniatullin et al., 2005; Quick and Lester, 2002). Interestingly, α7-containing nAChRs desensitize rapidly (in milliseconds), while non-α7 containing nAChRs receptors desensitize slowly (in seconds) in the mammalian nervous system (Giniatullin et al., 2005). Thus, the brief depolarization and the desensitization of nAChRs at subtype-dependent individual speed regulate the normal signal transductions as well as the various physiological functions of the cell.

Nicotine, in the same way as ACh, also activates nAChRs (Fig. 1A). However, since nicotine cannot be rapidly hydrolyzed by AChE like ACh in the synaptic cleft (Fig. 1B), the stimulatory function of nicotine on nAChRs is prolonged (Fig. 2B). The prolonged activation of nAChRs raises the intracellular calcium concentration to pathological levels and

causes cellular dysfunction. Further, this persistent activation ultimately changes the structures of the AChRs to a desensitized non-conducting conformation and causes rapid development of depolarization blockade which results in signal transmission obstruction even when the membrane has repolarized (Krejci et al., 2006; Pappano, 2015).

4.2. Muscarinic acetylcholine receptors

Nicotine modulates the expression and function of mAChRs. Prenatal nicotine exposure (PNE) reduces mAChRs subtypes in developing rat brain, in part, through suppression of the messenger RNA expression (Zhu et al., 1998). Chronic nicotine treatment during gestation and lactation significantly inhibits developmental increase of mAChRs in the brain of rat neonates (Zhu et al., 1996). Adolescent nicotine exposure regulates cardiac autonomic receptors that are involved in the control of heart rate and contractility, the stimulatory β-adrenergic receptors, and inhibitory M2 subtype of mAChRs (Chow et al., 2000). Chronic nicotine exposure induces a significant reduction of M2 subtype of mAChR and a tendency toward initial suppression and subsequent elevation β-receptors in the heart of adolescent rats (Chow et al., 2000). Chronic treatment with nicotine has no effect on mAChR binding sites in the brain of aged rats (Zhang et al., 2002). Chronic administration of nicotine causes an increase in the density of α1-and α2-binding sites in some brain regions, but decrease of the affinity of mAChR binding sites in the brain and in the heart (Yamanaka et al., 1985). Nicotine increases the affinity of brain mAChR for muscarinic agonist, but decreases the affinity of brain mAChR for muscarinic antagonist (Wang et al., 1996). Nicotine improves memory performance when the functions of mAChRs are normal; when the mAChRs are blocked, nicotine does not enhance spatial memory, suggesting that mAChRs are involved in the spatial memory-enhancing effect of nicotine (Liu et al., 2004). However, by activating the nAChR, nicotine attenuated the impairment of short-term memory induced by mAChR blockade (Hefco et al., 2003).

5. Acute nicotine intoxication

Nicotine stimulates both autonomic ganglia (sympathetic ganglion and parasympathetic ganglion) and elicits simultaneous discharges of both the sympathetic and the parasympathetic nervous systems (Pappano, 2015). Nicotine activates nAChRs, with greater affinity for neuronal than for skeletal muscle nAChRs at neuromuscular junctions, to initiate action potentials in postganglionic neurons (Benowitz, 1988).

The acute mild toxicity of nicotine usually occurs as early as 15 min to one hour after ingestion or inhalation and may last up to several hours, while severe toxicity may last up to 3 days (McBride et al., 1998). Historically, most cases of nicotine poisoning have been the result of use of nicotine as an insecticide (McNally, 1922). Currently, the main source of acute nicotine intoxication in young children is accidentally chewing nicotine gum, nicotine patches, and smokeless tobacco. Infants are most susceptible to accidental nicotine ingestion because of their natural curiosity for oral examination of everything. Ingestion of as little as 1 mg of nicotine by a small child can produce acute mild to severe intoxication such as nausea and vomiting, weakness, convulsions, respiratory arrest and death (Connolly et al., 2010). As for the adolescents and adults, tobacco leaves in green tobacco farms (for tobacco farmers) and e-cigarette are an emerging new source of acute nicotine intoxication.

5.1. Mild intoxication

The mild acute intoxication from nicotine causes cholinergic symptoms such as nausea, vomiting, diarrhea, respiratory difficulty, and alternating tachycardia and bradycardia (Table 1).

The most common form of mild intoxication is green tobacco sickness (GTS). GTS is caused by the absorption of nicotine by a variety of routes including the lungs, gastrointestinal tract, and intact skin when farm workers have direct contact with tobacco plants while handling wet tobacco leaves during cultivation and harvesting (Gehlbach et al., 1974; McBride et al., 1998). The nicotine concentration in the workplaces of tobacco farming is very high and poses a great threat for acute nicotine intoxication through skin absorption or inhalation of airborne nicotine among tobacco farmers (Yoo et al., 2014). Tobacco smokers rarely suffer from GTS because of tolerance to the effects of nicotine (Gehlbach et al., 1974), underlie that GTS is an acute intoxication from nicotine.

The initial response to nicotine often resembles simultaneous discharge of both the parasympathetic and the sympathetic nervous systems. In the cardiovascular system, nicotine may induce sympathetic tachycardia, via stimulation of β4 subunit-containing nAChRs, that alternates with a α7-subunit-stimulated bradycardia mediated by vagal discharge (Ji et al., 2002). In the neuromuscular junction, nicotine stimulates the nAChRs on the neuromuscular end plate apparatus and induces immediate depolarization of the end plate. Since nicotine can be not rapidly hydrolyzed in the synaptic cleft like ACh, its persistent stimulation causes rapid development of depolarization blockade which results in transmission blockade even when the membrane has repolarized. This transmission blockade is manifested as weakness, flaccid paralysis in the case of skeletal muscle including respiratory muscle (Pappano, 2015). Nicotine induces bronchoconstriction (Hahn et al., 1992). Thus, the bronchoconstriction and the weakness of respiratory muscles may explain the respiratory difficulty induced by nicotine. The pathophysiology involves in nausea, vomiting, and diarrhea is complex and includes the central nervous system, autonomic nervous system, gastrointestinal tract activity, and genetic susceptibility (Singh et al., 2016; Thomas et al., 2005). Likewise, the exact mechanism by which nicotine induces nausea, vomiting, diarrhea, increased salivation is not yet completely understood.

The rare form of mild intoxication is the hallucination. Acute nicotine intoxication by the ingestion of toxic quantities of tobacco can induce hallucinations (Thomas, 2002), which are fake and involuntary perceptions with seemingly-real quality in the absence of actual stimuli (Alkam and Nabeshima, 2016). Exposure to smoking/nicotine results in a transient decrease in slow-wave and an increase in fast-wave activity of the electroencephalogram, indicating a positive relationship between the amount of smoking and cortical excitability (Harkrider and Champlin, 2001), and affects the afferent and efferent transmission of acoustic information by enhancing cortical excitability in the site of auditory hallucination generation (Fisher et al., 2012; Harkrider and Champlin, 2001).

5.2. Severe intoxication

Severe intoxication can cause seizure, hypotension and respiratory depression which lead to death. Suicidal ingestion of liquid nicotine from e-cigarette in adults and accidental ingestion of nicotine products in children are the leading causes of severe nicotine intoxication (Table 1).

In the past decade a number of alternative e-cigarettes have hit the market, rapidly gaining consumers especially among the younger population (Kaisar et al., 2016; Siqueira et al., 2017). The e-cigarettes are battery-powered devices that aerosolize liquid nicotine by heating a solution of nicotine, glycerol and flavoring agents for inhalation and simulate tobacco smoking. Due to the large amount and the high concentration of nicotine in e-cigarette solution, the direct oral intake of a nicotine solution causes hypoxic brain injury and cardiac death (Bartschat et al., 2015; Chen et al., 2015; Park and Min, 2018). Some acute toxic effects of e-cigarettes on heart rate, blood pressure, and airway resistance are reported (Orellana-Barrios et al., 2015). High but not lethal concentration of nicotine causes seizures, hypotension and respiratory depression (Centers for Disease Control and Prevention (US) et al., 2010). Nicotine at a high toxic dose (4 mg/kg, i.p.) in mice elicits

Table 1
A brief summary of the acute intoxication from nicotine.

Types	Acute Intoxication	
	Mild	Severe
Sources of nicotine and population	Adults: tobacco leaves in green tobacco farms.	Young children: chewing nicotine gum, nicotine patches, and smokeless tobacco. Adults: e-cigarettes.
Causes	Contacting with the tobacco leaves in tobacco farms.	Young children: accidental ingestion of nicotine products; Adults: suicidal ingestion of liquid nicotine in e-cigarettes.
Final outcomes	Green tobacco sickness.	Death.
Symptoms	Tachycardia, bradycardia, respiratory difficulty, nausea, vomiting, diarrhea.	Seizure, hypotension and respiratory depression, and death.
Possible mechanisms learned from animal researches	Nicotine stimulates β4 subunit of nAChRs in sympathetic nerve terminals to induce tachycardia, and α7-subunit to cause bradycardia which is mediated by vagal discharge (Ji et al., 2002). Nicotine-induced bronchoconstriction (Hahn et al., 1992) and weakness of respiratory muscles (Pappano, 2015) may explain the respiratory difficulty. The exact mechanism by which nicotine induces nausea, vomiting, and diarrhea is not yet completely understood, though most likely involve in parasympathetic ganglia and vagal reflex.	Nicotine acts on neuronal nAChRs containing α5- and/or β4-subunits to induce seizure (Kedmi et al., 2004). Nicotine acts on nAChRs in the nucleus tractus solitaries of the brainstem to regulate calcium-calmodulin-endothelial nitric oxide synthase signaling pathways to induce hypotention (Cheng et al., 2011). Nicotine persistently stimulates nAChRs in the neuromuscular end plate and causes depolarization blockade which results in muscle weakness, flaccid paralysis that leads to respiratory (muscle) failure and death (Pappano, 2015).

seizures at 15 min post-injection by activating neurons in amygdala (Iha et al., 2017). The nAChRs containing either α5- (e.g., α4α5β2) or β4 (e.g., α4β4)-subunits are involved in nicotine-induced seizures, while the nAChRs containing α5-subunit regulate the rate of response to high doses of nicotine to induce seizures (Kedmi et al., 2004). Hypotensive and bradycardic effects of nicotine intoxication might be mediated through calcium-calmodulin-endothelial nitric oxide synthase signaling pathways via nAChRs regulation in the nucleus tractus solitaries, which is the primary integrative center for cardiovascular control and other autonomic functions embedded in the medulla oblongata of the brain stem (Cheng et al., 2011).

6. Chronic nicotine intoxication

Chronic intoxication from nicotine in relevance to the nervous system is primarily induced during the fetal brain development by nicotine exposure via by pregnant mother's tobacco smoke or use of nicotine products and/or second-hand smoke after birth (Table 2).

Offspring from women who smoke during pregnancy show behavioral abnormalities, including attentional deficits, impaired learning and memory, lowered IQ, and cognitive dysfunction (Cornelius and Day, 2009; Knopik, 2009). Although more than 80% of the world's smokers live in low-income and middle-income countries, tobacco use in pregnant women in these countries, except Turkey, is low. However, higher prevalence of tobacco smoking in pregnant women have been reported in high-income countries including the USA and the UK from population-based studies, while tobacco smoking during pregnancy has been reported decreasing in Japan (Caleyachetty et al., 2014; Zheng et al., 2016). In addition to the increasing use of the smokeless tobacco and e-cigarette in pregnant women in worldwide (Caleyachetty et al., 2014), pregnant women are also exposed to tobacco smoke at public places, eateries, and even at work places.

Nicotine, obtained from inhaled tobacco smoke or nicotine products, in pregnant mother's blood easily crosses the blood placenta barrier and accumulates in fetal serum and amniotic fluid at a higher concentration than that in maternal serum (Dempsey and Benowitz,

Table 2
A brief summary of the chronic intoxication from nicotine.

Types	Chronic Intoxication	
	Prenatal	Prenatal and/or Postnatal
Sources of nicotine	Pregnant mother's tobacco smoke and second-hand smoke, her use of nicotine products such as nicotine gum, nicotine patch, smokeless tobacco, and e-cigarette.	Fetuses: Pregnant mother's tobacco smoke or her use of nicotine products such as nicotine gum, nicotine patch, smokeless tobacco, and e-cigarette. Infants: second-hand smoke
Causes	Prenatal exposure to nicotine (PNE) via maternal supply.	PNE via maternal supply. Neonatal exposure to nicotine (NNE) in tobacco smoke.
Final outcomes	Brain developmental abnormality, Newborn abnormal neurobehaviors, Cognitive and emotional behavioral abnormalities.	Newborn abnormal neurobehaviors, sudden infant death syndrome (SIDS).
Possible mechanisms learned from animal researches	Persistent stimulation of the nAChRs by nicotine causes disruptions of fetal brain development, which is regulated by ACh-controlled transient and timely stimulation of nAChRs. PNE impairs neurogenesis by suppressing the proliferation of neuronal progenitor cells in the ventricular zone as well as the sub-ventricular zone via α7 subunit of nAChRs (Aoyama et al., 2016). PNE causes deficits in expressions of enzymes such as choline acetyltransferase in the cerebral cortex (Slotkin et al., 2007), tyrosine hydroxylase in the medial prefrontal cortex (PFC), and the synthesis as well as the release of noradrenaline (NA) and dopamine in the PFC Alkam et al., 2013b; Alkam et al., 2017). All of these disruptions may contribute to emotional and cognitive abnormalities, including novel learning and memory, attention-deficit/hyperactivity disorder, which are induced by nicotine intoxication in the fetal brain (Alkam et al., 2013a; Alkam et al., 2013b; Alkam et al., 2017).	PNE and NNE increase serum levels of corticosterone and catecholamine in newborns (Oliveira et al., 2010; Santos-Silva et al., 2011), and impair the auditory information processing in newborns by reducing the sensitivity of cortical nAChRs (Liang et al., 2006). These changes may underlie the excitable, hypertonic, and stressed behaviors in newborns (Bublitz and Stroud, 2012). In the brainstem, PNE disrupts serotoninergic system which plays a critical role in breathing and arousal, both of which are impaired in the SIDS. PNE increases the density of serotonin (5-HT) receptor-1A in the brainstem and decreases CO_2 retention-induced ventilator responses (Cerpa et al., 2015). PNE increases the density of 5-HT transporter in the brainstem (Muneoka et al., 2001) and decreases the turnover rate of NA in the PFC Alkam et al., 2013b) which regulates the arousal in the forebrain. Thus, PNE may lead to the failure of arousal and respiratory regulation which protect against lethal asphyxia in SIDS.

2001). Nicotine can change the development of both α and β subunits of nAChRs in the fetal brain at gene level in association with restriction of fetal brain growth (Lv et al., 2008). Human and animal data support that nicotine exposure during periods of developmental vulnerability causes impairments in fetal brain development and maturation of the cerebral cortex and hippocampus that lasts through adolescents (Cornelius and Day, 2009; England et al., 2015).

6.1. Fetal brain development

Once embryonic neurogenesis is initiated, neurotransmitter signaling plays a critical role in aspects of neurogenesis including proliferation, migration and differentiation in various locations in the central nervous system (Berg et al., 2013). One of the neurotransmitter receptor types involved in embryonic neurogenesis is nAChRs (Itou et al., 2011). The nAChRs are detected in neural progenitors of the early embryonic mouse cerebral cortex as early as embryonic day 10 (Atluri et al., 2001).

Nicotine in the blood of the smoking mother easily crosses placenta and interacts with functional nAChRs in the fetal brain (Dempsey and Benowitz, 2001; Slotkin, 1998). The most significant chronic toxicity of nicotine is due to its persistent over-stimulation of the nAChRs and disruption of neurodevelopmental events that are normally ascribed to the action of ACh at a physiologic concentration (Blood-Siegfried and Rende, 2010). While cholinesterase rapidly hydrolyzes ACh in the synaptic cleft and terminates its function on nAChRs, nicotine cannot be hydrolyzed so rapidly in the synaptic cleft and keeps stimulating nAChRs even when the stimulation is not needed or harmful. Thus, abnormal regulations of nAChRs activity by nicotine result in the disruption of fetal brain development (Navarro et al., 1989).

PNE in animal models mimics the fetal nicotine exposure during pregnancy in humans. Studies using various animal species or strains provided evidence for PNE-induced impairments in neurogenesis, neurochemical, and the various emotional and cognitive behaviors of offspring (Huang et al., 2007; Matta et al., 2007; Slotkin et al., 2007; Slotkin et al., 2005; Vaglenova et al., 2004; Vaglenova et al., 2008; Zhu et al., 2014; Zhu et al., 2012; reviewed in Alkam and Nabeshima, 2019a, 2019b). We have also reported that PNE during different time-windows of fetal brain development impairs neurogenesis, disrupts neurotransmitters systems, induces abnormalities in emotional and cognitive behaviors in mice offspring (Alkam et al., 2013a; Alkam et al., 2013b; Alkam et al., 2017; Aoyama et al., 2016).

PNE during gestational day 14 (G14)-postnatal day 0 (P0) is found to impair neurogenesis by suppressing the proliferation of neuronal progenitor cells (NPCs) in ventricular zone as well as the sub-ventricular zone, on gestational day 14 (G14), G15, and G16 in mice (Aoyama et al., 2016). These impairments result in fewer glutamatergic neurons in the medial prefrontal cortex on P70-P84 in offspring. The anti-neurogenic effects of PNE are blocked by pretreatment with a nAChRs α7 antagonist methyllycaconitine, but not with a nAChRs α4β2 antagonist dihidro-β-erythroidine (Aoyama et al., 2016). These results suggest that α7 nAChRs-mediated decrease in the proliferation of neuronal progenitors during prenatal period induced by PNE is critical to behavioral dysfunctions of offspring observed during adolescent and adult life (Alkam et al., 2013a; Alkam et al., 2013b; Alkam et al., 2017; Aoyama et al., 2016). PNE with postnatal nicotine exposure during G6-P21 suppresses the late-stage differentiation of NPCs in rat offspring on P21, but this suppression disappears on P77 (Ohishi et al., 2014).

PNE leads to significant deficits in choline acetyltransferase, an enzyme that is present at the presynaptic ends of axons and synthesizes excitatory neurotransmitter ACh, in the cerebral cortex in offspring (Slotkin et al., 2007). PNE reduces 5-HT_{1A} receptor binding, while 5-HT2 receptor binding showed significant overall increases in the cerebral cortex of offspring (Slotkin et al., 2007). PNE reduces the number of tyrosine hydroxylase (TH)-positive varicosities in the medial prefrontal cortex and in the core as well as the shell of nucleus accumbens examined on P70 (Alkam et al., 2017). Consistently, PNE reduces the content and turn-over rate of noradrenaline (NA) and dopamine (DA) in the frontal cortex on P56 (Alkam et al., 2013b; Ribary and Lichtensteiger, 1989). Thus, the chronic toxicity of nicotine in fetal brain lasts even long after the birth.

6.2. Infant neurobehaviors

Tobacco smoke during pregnancy has strong association with early and long-term neurobehavioral deficits in infants (Bublitz and Stroud, 2012). The tobacco-exposed infants are found more excitable, hypertonic, and stressed that require more handling compare to unexposed infants (Law et al., 2003).

In animal studies, neonatal nicotine exposure (NNE) weakens the function of cortical nAChRs and impairs the auditory information processing as well as auditory learning in adult rats (Liang et al., 2006). PNE or NNE through lactation increases serum leptin, serum corticosterone, and adrenal catecholamine content on postnatal day 15 (P15) and P21 (Oliveira et al., 2010; Santos-Silva et al., 2011). In the same rat model, nicotine increases DA receptor 1 (DR1) and DR2 but decreases DA transporter (DAT) in the nucleus accumbens during lactation on P15 and induces anxiety-like behavior during P15-20 (Pinheiro et al., 2015). Nicotine injection twice daily (1 or 2 mg/kg) during P8 –14 prolongs the durations of excitatory postsynaptic potentials in auditory cortex in electrophysiological study, suggesting disruption of synaptic development of glutamate synapses and N-methyl-D-aspartate (NMDA) receptor -mediated synaptic transmission (Aramakis et al., 2000). NNE diminishes the function of cortical nAChRs and impairs nicotinic enhancement of central auditory processing and auditory learning in adult rats (Liang et al., 2006). In in vitro studies, cerebellar granule and glial cells are cultured from 7 day-old rat pups with PNE or NNE. PNE increases the basal glutamate uptake in the glial cells, and NNE increases the NMDA-induced release of glutamate in the granule cells prepared from 7 days old rat pups (Lim and Kim, 2001; Lim et al., 2000). Thus, pathologic modulation glutamatergic and dopaminergic systems by nicotine may explain abnormal neurobehaviors of infants born from smoking mothers.

6.3. Sudden infant death syndrome

Sudden infant death syndrome (SIDS), also known as crib death, is the sudden death of an infant less than one year of age and typically associated with sleep. SIDS usually remains unexplained after a thorough case investigation, including performance of a complete autopsy, examination of the death scene, and review of the clinical history (Willinger et al., 1991).

The functional abnormalities of brainstem prior to death are regarded as the main pathology in infants dying suddenly and unexpectedly in both safe and unsafe sleep environments (Randall et al., 2013). Analyses of brain tissue from infants died of SIDS have consistently revealed a high prevalence of abnormalities in the brainstem serotoninergic system including an increased number of serotonergic neurons, a higher proportion of serotonergic neurons displaying immature morphology, decreased tissue levels of serotonin (5-HT) and its synthetic enzyme, tryptophan hydroxylase 2, and altered 5-HT receptor binding intensity both in serotonergic nuclei themselves and in several nuclei that are important in cardiorespiratory control (Bright et al., 2018; Li et al., 2018).

The brainstem plays a critical role in respiratory and autonomic regulation, sleep, and arousal, but these physiological processes become abnormal in SIDS infants; this abnormality can lead to the failure of arousal to protect against lethal asphyxia by lifting the head and turning to escape asphyxiating environments to gain fresh air (Kinney et al., 2001).

Victims of SIDS are more often and more heavily exposed to tobacco smoke doses before death than infants who have sudden infectious

deaths nicotine (Milerad et al., 1998). Accidental death in infancy and childhood is often associated with a significant exposure to nicotine (Milerad et al., 1998).

Tobacco smoke exposure by pregnant mother's tobacco smoke or use of nicotine products and/or second-hand smoke after birth has been shown to be a risk factor for SIDS (Bajanowski et al., 2008; Mitchell et al., 1993). Infants from mothers who smoked during pregnancy have deficient hypoxic awakening responses, which may contribute to the increased risk of SIDS in infants from smoking mothers (Lewis and Bosque, 1995). Reviews of clinical data suggest that medullary serotonergic network deficiency is responsible for SIDS which results from a failure of protective responses to life-threatening stressors (e.g. asphyxia, hypoxia, hypercapnia) during sleep (Kinney et al., 2001).

Investigations in animal models of PNE have demonstrated that nicotine significantly diminishes resting ventilatory activity and responses to hypoxia in neonatal rats (St-John and Leiter, 1999). PNE increases the parasympathetic control of heart rate in baboon fetuses. These changes in heart rate are associated with increased 5-HT-1A receptor binding in the raphe obscurus (ROb) and increased nicotinic receptor binding in the ROb and vagal complex (Duncan et al., 2009). Prenatal-perinatal nicotine exposure decreases the carbon dioxide (CO_2) retention (hypercapnia)-induced ventilatory responses of newborn mouse, reduces both the number of activated Rob neurons during eucapnic normoxia and their hypercapnia-induced recruitment. In the same study, PNE increases the density of 5-HT-1A receptor in ROb neurons and reduces the spontaneous firing frequency of ROb neurons without affecting their CO_2 sensitivity or their passive and active electrical properties in neonatal mice (Cerpa et al., 2015). PNE increases the density of 5-HT transporter (5-HTT) in the brainstem (Muneoka et al., 2001), but decreases the density of 5-HTT in the cerebral cortex (Xu et al., 2001). Obviously, PNE-induced disruption of the respiratory network through reorganization of neurotransmitter systems and remodeling of neural circuits (Campos et al., 2009) may underlie the mechanism of developmental nicotine exposure-induced SIDS in infants.

6.4. Circadian rhythm

Circadian rhythm is the 24-h internal clock in the brain that regulates cycles of alertness and sleepiness by responding to light changes in the environment (Reddy and Sharma, 2018). The development of the circadian system occurs in mammals postnatally (Reddy and Sharma, 2018). Therefore, PNE has no effects on circadian rhythm of the fetus. However, tobacco smoke or nicotine exposure during any stages of life from infancy affects circadian rhythm.

Tobacco smoking or secondhand tobacco smoking disrupts circadian clock function (Gentner and Weber, 2012; Hwang et al., 2014; Olff et al., 2006). Nicotine exposure in smokers is a chronic intermittent process, with episodic intake during wakefulness and abstinence during sleep resulting in circadian fluctuation of blood nicotine levels (Shao et al., 2018). Sleep disorders linked to the circadian rhythm are often overlooked and can have detrimental effects on the human body (Reddy and Sharma, 2018).

Nicotine advances the phase of the circadian neuronal activity rhythm in rat suprachiasmatic nuclei explants (Trachsel et al., 1995). Nicotine causes phase shifts in the circadian rhythms of rats by delays in the early subjective night and advances in the late subjective night (O'Hara et al., 1998). Effects of the oral intake of nicotine solution and/or forced administration of nicotine at a fixed time-of-day on circadian rhythm of ambulatory activity and drinking in rats are observed under various conditions (Umezu et al., 1992). Rats show nocturnal pattern under the light-dark cycle (light period 6:00–18:00). When the rats are given 15–150 mg/ml of nicotine solution under the restricted feeding condition (only for 1 h per day during 10:00–11:00), they demonstrate a marked phase-shift in the circadian rhythm in the concentration-dependent manner. Interestingly, the free-running rhythms of rats under the constant red dim light condition (CRDL) are not modified by the intake of nicotine solution of 50–150 mg/ml. However, when nicotine (1.5 mg/kg, po), but not tap water, is administered at 10:00 every day under the CRDL condition, it also produces phase-shift which is similar to that induced by the nicotine ingestion at a fixed time-of-day (Umezu et al., 1992). Chronic oral nicotine administration affects the circadian rhythm of DA and 5-HT metabolism in the striatum of mice, and thus may affect the functions regulated by these transmitters (Pietila et al., 1995).

While nicotine modulates circadian rhythm, the sensitization and tolerance to nicotine are influenced by circadian timing cues (Shao et al., 2018). The episodic and circadian dynamics of nicotine exposure present a significant challenge to understand its long-term effects; studies using chronic exposure, such as with osmotic pumps that deliver continuous amounts of nicotine, likely miss critical aspects of the effects of episodic nicotine, such as related to the time-dependent activation and desensitization/resensitization of receptors, as well as any circadian effects (Shao et al., 2018).

7. Future directions

Currently available research findings greatly improve our understandings about the molecular mechanisms of intoxication from nicotine. Nicotine is mainly degraded by enzymes in the liver and its half-life is around 2 h (Benowitz et al., 2009; Benowitz et al., 1982). Nicotine exerts its various toxicities through different subunits of nAChRs, which are located in the pre- or post-synaptic membranes. The membrane-bound nAChRs are degraded by membrane internalization as well as intracellular lysosomal degradation, and the half-life is up to 10 days (Bezakova et al., 2001; Bruneau and Akaaboune, 2006; Engel and Fumagalli, 1982). Nicotine increases the expression and the half-life of surface membrane nAChRs (Kuryatov et al., 2005; Nashmi et al., 2003). However, the process or mechanism involved in the degradation or the elimination of nAChRs-binding or free nicotine in the synaptic cleft, as well as its half-life, is not clearly known. The specific involvement of nAChRs subunits in nicotine intoxication at the different nervous systems has not been well clarified. Therefore, future studies should answer questions such as synaptic nicotine degradation and specific subunits of nAChRs that involved in the various toxicity of nicotine. Understanding these unknowns may help identifying the molecular targets for better treatment strategies for nicotine intoxication.

Acknowledgment

This study was supported by Grants-in-Aid for Scientific Research C (grant number 24590219, 26460240, 15K08218, 16K08421), B (grant number 17H04252) and the Private University Research Project from the Ministry of Education, Culture, Sports, Science and Technology of Japan and Smoking Research Foundation Grant for Biomedical Research (SRF).

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.neuint.2019.02.006.

References

Alkam, T., Nabeshima, T., 2016. Chapter 4 - Modeling the Positive Symptoms of Schizophrenia. In: In: Pletnikov, M.V., Waddington, J.L. (Eds.), Handbook of Behavioral Neuroscience, vol. 23. Elsevier, pp. 39–54.

Alkam, T., Nabeshima, T., 2019a. Chapter 6-Prenatal nicotine exposure and neuronal progenitor cells. In: Preedy, V. (Ed.), Neuroscience of Nicotine: Mechanisms and Treatment, 1st Edition. Elsevier (in Press, to be released on March 20, 2019).

Alkam, T., Nabeshima, T., 2019b. Chapter 24-Prenatal nicotine exposure and impact on the behaviors of offspring. In: Preedy, V. (Ed.), Neuroscience of Nicotine: Mechanisms and Treatment, 1st Edition. Elsevier (in Press, to be released on March 20, 2019).

Alkam, T., Kim, H.C., Hiramatsu, M., Mamiya, T., Aoyama, Y., Nitta, A., Yamada, K.,

Nabeshima, T., 2013a. Evaluation of emotional behaviors in young offspring of C57BL/6J mice after gestational and/or perinatal exposure to nicotine in six different time-windows. Behav. Brain Res. 239, 80–89.
Alkam, T., Kim, H.C., Mamiya, T., Yamada, K., Hiramatsu, M., Nabeshima, T., 2013b. Evaluation of cognitive behaviors in young offspring of C57BL/6J mice after gestational nicotine exposure during different time-windows. Psychopharmacology (Berl) 230 (3), 451–463.
Alkam, T., Mamiya, T., Kimura, N., Yoshida, A., Kihara, D., Tsunoda, Y., Aoyama, Y., Hiramatsu, M., Kim, H.C., Nabeshima, T., 2017. Prenatal nicotine exposure decreases the release of dopamine in the medial frontal cortex and induces atomoxetine-responsive neurobehavioral deficits in mice. Psychopharmacology (Berl) 234 (12), 1853–1869.
Aoyama, Y., Toriumi, K., Mouri, A., Hattori, T., Ueda, E., Shimato, A., Sakakibara, N., Soh, Y., Mamiya, T., Nagai, T., Kim, H.C., Hiramatsu, M., Nabeshima, T., Yamada, K., 2016. Prenatal nicotine exposure impairs the proliferation of neuronal progenitors, leading to fewer glutamatergic neurons in the medial prefrontal cortex. Neuropsychopharmacology 41 (2), 578–589.
Aramakis, V.B., Hsieh, C.Y., Leslie, F.M., Metherate, R., 2000. A critical period for nicotine-induced disruption of synaptic development in rat auditory cortex. J. Neurosci. 20 (16), 6106–6116.
Atluri, P., Fleck, M.W., Shen, Q., Mah, S.J., Stadfelt, D., Barnes, W., Goderie, S.K., Temple, S., Schneider, A.S., 2001. Functional nicotinic acetylcholine receptor expression in stem and progenitor cells of the early embryonic mouse cerebral cortex. Dev. Biol. 240 (1), 143–156.
Bajanowski, T., Brinkmann, B., Mitchell, E.A., Vennemann, M.M., Leukel, H.W., Larsch, K.P., Beike, J., Lingua::EN::Titlecase, S.I.D.G., 2008. Nicotine and cotinine in infants dying from sudden infant death syndrome. Int. J. Leg. Med. 122 (1), 23–28.
Bardo, M.T., Green, T.A., Crooks, P.A., Dwoskin, L.P., 1999. Nornicotine is self-administered intravenously by rats. Psychopharmacology (Berl) 146 (3), 290–296.
Bartschat, S., Mercer-Chalmers-Bender, K., Beike, J., Rothschild, M.A., Jubner, M., 2015. Not only smoking is deadly: fatal ingestion of e-juice-a case report. Int. J. Leg. Med. 129 (3), 481–486.
Benowitz, N.L., 1988. Drug therapy. Pharmacologic aspects of cigarette smoking and nicotine addiction. N. Engl. J. Med. 319, 1318–1330.
Benowitz, N.L., Jacob 3rd, P., Jones, R.T., Rosenberg, J., 1982. Interindividual variability in the metabolism and cardiovascular effects of nicotine in man. J. Pharmacol. Exp. Therapeut. 221, 368–372.
Benowitz, N.L., Jacob 3rd, P., Fong, I., Gupta, S., 1994. Nicotine metabolic profile in man: comparison of cigarette smoking and transdermal nicotine. J. Pharmacol. Exp. Therapeut. 268, 296–303.
Benowitz, N.L., Hukkanen, J., Jacob III, P., 2009. Nicotine chemistry, metabolism, kinetics and biomarkers. Handb. Exp. Pharmacol. 29–60.
Berg, D.A., Belnoue, L., Song, H., Simon, A., 2013. Neurotransmitter-mediated control of neurogenesis in the adult vertebrate brain. Development 140 (12), 2548–2561.
Bezakova, G., Rabben, I., Sefland, I., Fumagalli, G., Lømo, T., 2001. Neural agrin controls acetylcholine receptor stability in skeletal muscle fibers. Proc. Natl. Acad. Sci. Unit. States Am. 98 (17), 9924–9929.
Blood-Siegfried, J., Rende, E.K., 2010. The long-term effects of prenatal nicotine exposure on neurologic development. J. Midwifery Wom. Health 55 (2), 143–152.
Bright, F.M., Vink, R., Byard, R.W., 2018. Brainstem Neuropathology in Sudden Infant Death Syndrome. In: Duncan, J.R., Byard, R.W. (Eds.), SIDS Sudden Infant and Early Childhood Death: The Past, the Present and the Future, Adelaide (AU).
Brooks, J.E., 1953. The mighty leaf: Tobacco through the centuries. Little, Brown and Company, Boston.
Brown, R.W., Collins, A.C., Lindstrom, J.M., Whiteaker, P., 2007. Nicotinic alpha5 subunit deletion locally reduces high-affinity agonist activation without altering nicotinic receptor numbers. J. Neurochem. 103, 204–215.
Bruneau, E.G., Akaaboune, M., 2006. The dynamics of recycled acetylcholine receptors at the neuromuscular junction in vivo. Development 133, 4485–4493.
Bublitz, M.H., Stroud, L.R., 2012. Maternal smoking during pregnancy and offspring brain structure and function: review and agenda for future research. Nicotine Tob. Res. 14 (4), 388–397.
Caleyachetty, R., Tait, C.A., Kengne, A.P., Corvalan, C., Uauy, R., Echouffo-Tcheugui, J.B., 2014. Tobacco use in pregnant women: analysis of data from demographic and health surveys from 54 low-income and middle-income countries. Lancet Glob Health 2 (9), e513–e520.
Calvo-Flores, Francisco García, Isac-Garcia, Joaquin, Dobado, Jose A., 2017. Emerging Pollutants: Origin, Structure, and Properties. John Wiley & Sons.
Campos, M., Bravo, E., Eugenin, J., 2009. Respiratory dysfunctions induced by prenatal nicotine exposure. Clin. Exp. Pharmacol. Physiol. 36 (12), 1205–1217.
Centers for Disease Control and Prevention (US), National Center for Chronic Disease Prevention and Health Promotion (US), Office on Smoking and Health (US), 2010. How Tobacco Smoke Causes Disease: The Biology and Behavioral Basis for Smoking-Attributable Disease: A Report of the Surgeon General. Centers for Disease Control and Prevention (US), Atlanta (GA).
Cerpa, V.J., Aylwin, M.d.l.L.O., Beltran-Castillo, S., Bravo, E.U., Llona, I.R., Richerson, G.B., Eugenin, J.L., 2015. The alteration of neonatal raphe neurons by prenatal-perinatal nicotine. Meaning for sudden infant death syndrome. Am. J. Respir. Cell Mol. Biol. 53 (4), 489–499.
Charlton, A., 2004. Medicinal uses of tobacco in history. J. R. Soc. Med. 97 (6), 292–296.
Chen, B.C., Bright, S.B., Trivedi, A.R., Valento, M., 2015. Death following intentional ingestion of e-liquid. Clin. Toxicol. 53 (9), 914–916.
Cheng, P.W., Lu, P.J., Chen, S.R., Ho, W.Y., Cheng, W.H., Hong, L.Z., Yeh, T.C., Sun, G.C., Wang, L.L., Hsiao, M., Tseng, C.J., 2011. Central nicotinic acetylcholine receptor involved in Ca(2+) -calmodulin-endothelial nitric oxide synthase pathway modulated hypotensive effects. Br. J. Pharmacol. 163 (6), 1203–1213.
Chow, F.A., Seidler, F.J., McCook, E.C., Slotkin, T.A., 2000. Adolescent nicotine exposure alters cardiac autonomic responsiveness: β-adrenergic and m2-muscarinic receptors and their linkage to adenylyl cyclase. Brain Res. 878 (1–2), 119–126.
Connolly, G.N., Richter, P., Aleguas Jr., A., Pechacek, T.F., Stanfill, S.B., Alpert, H.R., 2010. Unintentional child poisonings through ingestion of conventional and novel tobacco products. Pediatrics 125 (5), 896–899.
Cornelius, M.D., Day, N.L., 2009. Developmental consequences of prenatal tobacco exposure. Curr. Opin. Neurol. 22 (2), 121–125.
Crooks, P.A., Li, M., Dwoskin, L.P., 1997. Metabolites of nicotine in rat brain after peripheral nicotine administration. Cotinine, nornicotine, and norcotinine. Drug Metab. Dispos. 25, 47–54.
Dani, J.A., 2015. Neuronal nicotinic acetylcholine receptor structure and function and response to nicotine. Int. Rev. Neurobiol. 124, 3–19.
Dempsey, D.A., Benowitz, N.L., 2001. Risks and benefits of nicotine to aid smoking cessation in pregnancy. Drug Saf. 24 (4), 277–322.
Dempsey, D., Jacob 3rd, P., Benowitz, N.L., 2000. Nicotine metabolism and elimination kinetics in newborns. Clin. Pharmacol. Ther. 67 (5), 458–465.
Duncan, J.R., Garland, M., Myers, M.M., Fifer, W.P., Yang, M., Kinney, H.C., Stark, R.I., 2009. Prenatal nicotine-exposure alters fetal autonomic activity and medullary neurotransmitter receptors: implications for sudden infant death syndrome. J. Appl. Physiol. 107 (5), 1579–1590 1985.
Engel, A.G., Fumagalli, G., 1982. Mechanisms of acetylcholine receptor loss from the neuromuscular junction. In: Ciba Found Symp, pp. 197–224.
England, L.J., Bunnell, R.E., Pechacek, T.F., Tong, V.T., McAfee, T.A., 2015. Nicotine and the Developing Human. Am. J. Prev. Med. 49 (2), 286–293.
Fenster, C.P., Rains, M.F., Noerager, B., Quick, M.W., Lester, R.A.J., 1997. Influence of subunit composition on desensitization of neuronal acetylcholine receptors at low concentrations of nicotine. J. Neurosci. 17 (15), 5747–5759.
Fisher, D.J., Grant, B., Smith, D.M., Borracci, G., Labelle, A., Knott, V.J., 2012. Nicotine and the hallucinating brain: effects on mismatch negativity (MMN) in schizophrenia. Psychiatr. Res. 196 (2–3), 181–187.
Garcia, K.L.P., Coen, K., Miksys, S., Le, A.D., Tyndale, R.F., 2015. Effect of Brain CYP2B Inhibition on Brain Nicotine Levels and Nicotine Self-Administration. Neuropsychopharmacology 40 (8), 1910–1918.
Garcia, K.L.P., Le, A.D., Tyndale, R.F., 2017. Brain CYP2B induction can decrease nicotine levels in the brain. Addict. Biol. 22 (5), 1257–1266.
Gehlbach, S.H., Williams, W.A., Perry, L.D., Woodall, J.S., 1974. Green-tobacco sickness. An illness of tobacco harvesters. J. Am. Med. Assoc. 229 (14), 1880–1883.
Gentner, N.J., Weber, L.P., 2012. Secondhand tobacco smoke, arterial stiffness, and altered circadian blood pressure patterns are associated with lung inflammation and oxidative stress in rats. Am. J. Physiol. Heart Circ. Physiol. 302 (3), H818–H825.
Ghosheh, O., Dwoskin, L.P., Li, W.K., Crooks, P.A., 1999. Residence times and half-lives of nicotine metabolites in rat brain after acute peripheral administration of [2'-(14)C] nicotine. Drug Metab. Dispos. 27, 1448–1455.
Ghosheh, O.A., Dwoskin, L.P., Miller, D.K., Crooks, P.A., 2001. Accumulation of nicotine and its metabolites in rat brain after intermittent or continuous peripheral administration of [2'-(14)C]nicotine. Drug Metab. Dispos. 29, 645–651.
Giniatullin, R., Nistri, A., Yakel, J., 2005. Desensitization of nicotinic ACh receptors: shaping cholinergic signaling. Trends Neurosci. 28 (7), 371–378.
Gonzalez-Coloma, A., Reina, M., Diaz, C.E., Fraga, B.M., 2010. 3.09 - Natural Product-Based Biopesticides for Insect Control. In: Liu, H.-W., Mander, L. (Eds.), Comprehensive Natural Products II. Elsevier, Oxford, pp. 237–268.
Goshman, L.M., 1985. Clinical Toxicology of Commercial Products. J. Pharmaceut. Sci. 74 (10), 1139 5th ed.
Gotti, C., Clementi, F., Fornari, A., Gaimarri, A., Guiducci, S., Manfredi, I., Moretti, M., Pedrazzi, P., Pucci, L., Zoli, M., 2009. Structural and functional diversity of native brain neuronal nicotinic receptors. Biochem. Pharmacol. 78 (7), 703–711.
Green, T.A., Phillips, S.B., Crooks, P.A., Dwoskin, L.P., Bardo, M.T., 2000. Nornicotine pretreatment decreases intravenous nicotine self-administration in rats. Psychopharmacology (Berl) 152 (3), 289–294.
Green, T.A., Crooks, P.A., Bardo, M.T., Dwoskin, L.P., 2001. Contributory role for nornicotine in nicotine neuropharmacology: nornicotine-evoked [3H]dopamine overflow from rat nucleus accumbens slices11Abbreviations: DA, dopamine; and DHβE, dihydro-β-erythroidine. Biochem. Pharmacol. 62 (12), 1597–1603.
Hahn, H.L., Lang, M., Bleicher, S., Zwerenz, S., Rausch, C., 1992. Nicotine-induced airway smooth muscle contraction: neural mechanisms involving the airway epithelium. Functional and histologic studies in vitro. Clin. Investig. 70, 252–262.
Harkrider, A.W., Champlin, C.A., 2001. Acute effect of nicotine on non-smokers: III. LLRs and EEGs. Hear. Res. 160 (1–2), 99–110.
Hefco, V., Yamada, K., Hefco, A., Hritcu, L., Tiron, A., Olariu, A., Nabeshima, T., 2003. Effects of nicotine on memory impairment induced by blockade of muscarinic, nicotinic and dopamine D2 receptors in rats. Eur. J. Pharmacol. 474 (2–3), 227–232.
Henningfield, J.E., Zeller, M., 2006. Nicotine psychopharmacology research contributions to United States and global tobacco regulation: a look back and a look forward. Psychopharmacology (Berl) 184 (3–4), 286–291.
Hoffman, A.C., Evans, S.E., 2013. Abuse potential of non-nicotine tobacco smoke components: acetaldehyde, nornicotine, cotinine, and anabasine. Nicotine Tob. Res. 15 (3), 622–632.
Huang, L.Z., Liu, X., Griffith, W.H., Winzer-Serhan, U.H., 2007. Chronic neonatal nicotine increases anxiety but does not impair cognition in adult rats. Behav. Neurosci. 121 (6), 1342–1352.
Hwang, J.W., Sundar, I.K., Yao, H., Sellix, M.T., Rahman, I., 2014. Circadian clock function is disrupted by environmental tobacco/cigarette smoke, leading to lung inflammation and injury via a SIRT1-BMAL1 pathway. FASEB J. 28 (1), 176–194.
Iha, H.A., Kunisawa, N., Shimizu, S., Tokudome, K., Mukai, T., Kinboshi, M., Ikeda, A., Ito, H., Serikawa, T., Ohno, Y., 2017. Nicotine elicits convulsive seizures by activating

amygdalar neurons. Front. Pharmacol. 8, 57.
Ikka, T., Yamashita, H., Kurita, I., Tanaka, Y., Taniguchi, F., Ogino, A., Takeda, K., Horie, N., Hojo, H., Nanjo, F., Morita, A., 2018. Quantitative validation of nicotine production in tea (Camellia sinensis L.). PLoS One 13 e0195422.
Itou, Y., Nochi, R., Kuribayashi, H., Saito, Y., Hisatsune, T., 2011. Cholinergic activation of hippocampal neural stem cells in aged dentate gyrus. Hippocampus 21 (4), 446–459.
Ji, S., Tosaka, T., Whitfield, B.H., Katchman, A.N., Kandil, A., Knollmann, B.C., Ebert, S.N., 2002. Differential rate responses to nicotine in rat heart: evidence for two classes of nicotinic receptors. J. Pharmacol. Exp. Therapeut. 301 (3), 893–899.
Johnston, B., 1990. Ojibway Heritage. Bison Books, Nebraska, US.
Kaisar, M.A., Prasad, S., Liles, T., Cucullo, L., 2016. A decade of e-cigarettes: Limited research & unresolved safety concerns. Toxicology 365, 67–75.
Kedmi, M., Beaudet, A.L., Orr-Urtreger, A., 2004. Mice lacking neuronal nicotinic acetylcholine receptor β4-subunit and mice lacking both α5- and β4-subunits are highly resistant to nicotine-induced seizures. Physiol. Genom. 17 (2), 221–229.
Kinney, H.C., Filiano, J.J., White, W.F., 2001. Medullary serotonergic network deficiency in the sudden infant death syndrome: review of a 15-year study of a single dataset. J. Neuropathol. Exp. Neurol. 60 (3), 228–247.
Knopik, V.S., 2009. Maternal Smoking During Pregnancy and Child Outcomes: Real or Spurious Effect? Dev. Neuropsychol. 34 (1), 1–36.
Krejci, E., Valenzuela, I. M.-P. y., Ameziane, R., Akaaboune, M., 2006. Acetylcholinesterase dynamics at the neuromuscular junction of live animals. J. Biol. Chem. 281 (15), 10347–10354.
Kuryatov, A., Luo, J., Cooper, J., Lindstrom, J., 2005. Nicotine acts as a pharmacological chaperone to up-regulate human alpha4beta2 acetylcholine receptors. Mol. Pharmacol. 68, 1839–1851.
Kyerematen, G.A., Morgan, M.L., Chattopadhyay, B., deBethizy, J.D., Vesell, E.S., 1990. Disposition of nicotine and eight metabolites in smokers and nonsmokers: identification in smokers of two metabolites that are longer lived than cotinine. Clin. Pharmacol. Ther. 48 (6), 641–651.
Law, K.L., Stroud, L.R., LaGasse, L.L., Niaura, R., Liu, J., Lester, B.M., 2003. Smoking during pregnancy and newborn neurobehavior. Pediatrics 111 (6), 1318–1323.
Lee, A.M., Miksys, S., Palmour, R., Tyndale, R.F., 2006. CYP2B6 is expressed in African green monkey brain and is induced by chronic nicotine treatment. Neuropharmacology 50 (4), 441–450.
Lewis, K.W., Bosque, E.M., 1995. Deficient hypoxia awakening response in infants of smoking mothers: possible relationship to sudden infant death syndrome. J. Pediatr. 127 (5), 691–699.
Li, A., Darnall, R.A., Dymecki, S., Leiter, J.C., 2018. Animal Models: Illuminating the Pathogenesis of Sudden Infant Death Syndrome. In: Duncan, J.R., Byard, R.W. (Eds.), SIDS Sudden Infant and Early Childhood Death: The Past, the Present and the Future, Adelaide (AU).
Liang, K., Poytress, B.S., Chen, Y., Leslie, F.M., Weinberger, N.M., Metherate, R., 2006. Neonatal nicotine exposure impairs nicotinic enhancement of central auditory processing and auditory learning in adult rats. Eur. J. Neurosci. 24 (3), 857–866.
Lim, D.K., Kim, H.S., 2001. Changes in the glutamate release and uptake of cerebellar cells in perinatally nicotine-exposed rat pups. Neurochem. Res. 26 (10), 1119–1125.
Lim, D.K., Park, S.H., Choi, W.J., 2000. Subacute nicotine exposure in cultured cerebellar cells increased the release and uptake of glutamate. Arch Pharm. Res. (Seoul) 23 (5), 488–494.
Liu, Y., Wang, Y., Sun, X., Wang, H., 2004. Evidence that muscarinic receptors are involved in nicotine-facilitated spatial memory. Pharmacol. Biochem. Behav. 78 (4), 775–779.
Luetje, C., Patrick, J., 1991. Both alpha- and beta-subunits contribute to the agonist sensitivity of neuronal nicotinic acetylcholine receptors. J. Neurosci. 11 (3), 837–845.
Lv, J., Mao, C., Zhu, L., Zhang, H., Pengpeng, H., Xu, F., Liu, Y., Zhang, L., Xu, Z., 2008. The effect of prenatal nicotine on expression of nicotine receptor subunits in the fetal brain. Neurotoxicology 29 (4), 722–726.
Matta, S.G., Balfour, D.J., Benowitz, N.L., Boyd, R.T., Buccafusco, J.J., Caggiula, A.R., Craig, C.R., Collins, A.C., Damaj, M.I., Donny, E.C., Gardiner, P.S., Grady, S.R., Heberlein, U., Leonard, S.S., Levin, E.D., Lukas, R.J., Markou, A., Marks, M.J., McCallum, S.E., Parameswaran, N., Perkins, K.A., Picciotto, M.R., Quik, M., Rose, J.E., Rothenfluh, A., Schafer, W.R., Stolerman, I.P., Tyndale, R.F., Wehner, J.M., Zirger, J.M., 2007. Guidelines on nicotine dose selection for in vivo research. Psychopharmacology (Berl) 190 (3), 269–319.
Mayer, B., 2014. How much nicotine kills a human? Tracing back the generally accepted lethal dose to dubious self-experiments in the nineteenth century. Arch. Toxicol. 88 (1), 5–7.
McBride, J.S., Altman, D.G., Klein, M., White, W., 1998. Green tobacco sickness. Tobac. Contr. 7 (3), 294–298.
McKnight, R.H., Spiller, H.A., 2005. Green tobacco sickness in children and adolescents. Publ. Health Rep. 120 (6), 602–605.
McNally, W.D., 1922. A report of seven cases of nicotine poisoning. J. Lab. Clin. Med. 8, 83–85.
Middleton, L.S., Crooks, P.A., Wedlund, P.J., Cass, W.A., Dwoskin, L.P., 2007. Nornicotine inhibition of dopamine transporter function in striatum via nicotinic receptor activation. Synapse 61 (3), 157–165.
Miksys, S., Hoffmann, E., Tyndale, R.F., 2000. Regional and cellular induction of nicotine-metabolizing CYP2B1 in rat brain by chronic nicotine treatment. Biochem. Pharmacol. 59 (12), 1501–1511.
Miksys, S., Lerman, C., Shields, P.G., Mash, D.C., Tyndale, R.F., 2003. Smoking, alcoholism and genetic polymorphisms alter CYP2B6 levels in human brain. Neuropharmacology 45 (1), 122–132.
Milerad, J., Vege, A., Opdal, S.H., Rognum, T.O., 1998. Objective measurements of nicotine exposure in victims of sudden infant death syndrome and in other unexpected child deaths. J. Pediatr. 133 (2), 232–236.
Millar, N.S., Gotti, C., 2009. Diversity of vertebrate nicotinic acetylcholine receptors. Neuropharmacology 56 (1), 237–246.
Mitchell, E.A., Ford, R.P., Stewart, A.W., Taylor, B.J., Becroft, D.M., Thompson, J.M., Scragg, R., Hassall, I.B., Barry, D.M., Allen, E.M., et al., 1993. Smoking and the sudden infant death syndrome. Pediatrics 91, 893–896.
Muneoka, K., Ogawa, T., Kamei, K., Mimura, Y., Kato, H., Takigawa, M., 2001. Nicotine exposure during pregnancy is a factor which influences serotonin transporter density in the rat brain. Eur. J. Pharmacol. 411 (3), 279–282.
Nakajima, M., Yamamoto, T., Nunoya, K., Yokoi, T., Nagashima, K., Inoue, K., Funae, Y., Shimada, N., Kamataki, T., Kuroiwa, Y., 1996a. Characterization of CYP2A6 involved in 3'-hydroxylation of cotinine in human liver microsomes. J. Pharmacol. Exp. Therapeut. 277, 1010–1015.
Nakajima, M., Yamamoto, T., Nunoya, K., Yokoi, T., Nagashima, K., Inoue, K., Funae, Y., Shimada, N., Kamataki, T., Kuroiwa, Y., 1996b. Role of human cytochrome P4502A6 in C-oxidation of nicotine. Drug Metab. Dispos. 24, 1212–1217.
Nakajima, M., Yamagishi, S., Yamamoto, H., Yamamoto, T., Kuroiwa, Y., Yokoi, T., 2000. Deficient cotinine formation from nicotine is attributed to the whole deletion of the CYP2A6 gene in humans. Clin. Pharmacol. Ther. 67 (1), 57–69.
Nakajima, M., Kwon, J.T., Tanaka, N., Zenta, T., Yamamoto, Y., Yamamoto, H., Yamazaki, H., Yamamoto, T., Kuroiwa, Y., Yokoi, T., 2001. Relationship between interindividual differences in nicotine metabolism and CYP2A6 genetic polymorphism in humans. Clin. Pharmacol. Ther. 69 (1), 72–78.
Nakajima, M., Kuroiwa, Y., Yokoi, T., 2002. Interindividual differences in nicotine metabolism and genetic polymorphisms of human CYP2A6. Drug Metab. Rev. 34 (4), 865–877.
Nakajima, M., Fukami, T., Yamanaka, H., Higashi, E., Sakai, H., Yoshida, R., Kwon, J., McLeod, H., Yokoi, T., 2006. Comprehensive evaluation of variability in nicotine metabolism and CYP2A6 polymorphic alleles in four ethnic populations. Clin. Pharmacol. Ther. 80 (3), 282–297.
Nashmi, R., Dickinson, M.E., McKinney, S., Jareb, M., Labarca, C., Fraser, S.E., Lester, H.A., 2003. Assembly of α4β2 Nicotinic Acetylcholine Receptors Assessed with Functional Fluorescently Labeled Subunits: Effects of Localization, Trafficking, and Nicotine-Induced Upregulation in Clonal Mammalian Cells and in Cultured Midbrain Neurons. J. Neurosci. 23 (37), 11554–11567.
National Center for Chronic Disease Prevention and Health Promotion (US) Office on Smoking and Health, 2014. The Health Consequences of Smoking—50 Years of Progress: A Report of the Surgeon General. Centers for Disease Control and Prevention (US), Atlanta (GA) Available from: https://www.ncbi.nlm.nih.gov/books/NBK294308/#.
Navarro, H.A., Seidler, F.J., Eylers, J.P., Baker, F.E., Dobbins, S.S., Lappi, S.E., Slotkin, T.A., 1989. Effects of prenatal nicotine exposure on development of central and peripheral cholinergic neurotransmitter systems. Evidence for cholinergic trophic influences in developing brain. J. Pharmacol. Exp. Therapeut. 251, 894–900.
Ng, M., Freeman, M.K., Fleming, T.D., Robinson, M., Dwyer-Lindgren, L., Thomson, B., Wollum, A., Sanman, E., Wulf, S., Lopez, A.D., Murray, C.J.L., Gakidou, E., 2014. Smoking prevalence and cigarette consumption in 187 countries, 1980-2012. J. Am. Med. Assoc. 311 (2), 183–192.
O'Hara, B.F., Edgar, D.M., Cao, V.H., Wiler, S.W., Craig Heller, H., Kilduff, T.S., Miller, J.D., 1998. Nicotine and nicotinic receptors in the circadian system. Psychoneuroendocrinology 23 (2), 161–173.
Ohishi, T., Wang, L., Akane, H., Shiraki, A., Itahashi, M., Mitsumori, K., Shibutani, M., 2014. Transient suppression of late-stage neuronal progenitor cell differentiation in the hippocampal dentate gyrus of rat offspring after maternal exposure to nicotine. Arch. Toxicol. 88 (2), 443–454.
Olff, M., Meewisse, M.L., Kleber, R.J., van der Velden, P.G., Drogendijk, A.N., van Amsterdam, J.G.C., Opperhuizen, A., Gersons, B.P.R., 2006. Tobacco usage interacts with postdisaster psychopathology on circadian salivary cortisol. Int. J. Psychophysiol. 59 (3), 251–258.
Oliveira, E., Pinheiro, C.R., Santos-Silva, A.P., Trevenzoli, I.H., Abreu-Villaca, Y., Nogueira Neto, J.F., Reis, A.M., Passos, M.C.F., Moura, E.G., Lisboa, P.C., 2010. Nicotine exposure affects mother's and pup's nutritional, biochemical, and hormonal profiles during lactation in rats. J. Endocrinol. 205 (2), 159–170.
Orellana-Barrios, M.A., Payne, D., Mulkey, Z., Nugent, K., 2015. Electronic cigarettes-a narrative review for clinicians. Am. J. Med. 128 (7), 674–681.
Papke, R.L., Dwoskin, L.P., Crooks, P.A., 2007. The pharmacological activity of nicotine and nornicotine on nAChRs subtypes: relevance to nicotine dependence and drug discovery. J. Neurochem. 101 (1), 160–167.
Pappano, A.J., 2015. Cholinoceptor-Activating & Cholinesterase-Inhibiting Drugs. In: Katzung, B.G., Trevor, A.J. (Eds.), Basic & Clinical Pharmacology, 13e. McGraw-Hill Medical, New York, NY.
Park, E.J., Min, Y.G., 2018. The emerging method of suicide by electronic cigarette liquid: a case report. J. Kor. Med. Sci. 33 (11), e52.
Paterson, D., Nordberg, A., 2000. Neuronal nicotinic receptors in the human brain. Prog. Neurobiol. 61 (1), 75–111.
Pietila, K., Laakso, I., Ahtee, L., 1995. Chronic oral nicotine administration affects the circadian rhythm of dopamine and 5-hydroxytryptamine metabolism in the striata of mice. Naunyn-Schmiedeberg's Arch. Pharmacol. 353, 110–115.
Pinheiro, C.R., Oliveira, E., Manhaes, A.C., Fraga, M.C., Claudio-Neto, S., Younes-Rapozo, V., Lotufo, B.M., Moura, E.G., Lisboa, P.C., 2015. Exposure to nicotine increases dopamine receptor content in the mesocorticolimbic pathway of rat dams and offspring during lactation. Pharmacol. Biochem. Behav. 136, 87–101.
Posadas, I., Lopez-Hernandez, B., Cena, V., 2013. Nicotinic receptors in neurodegeneration. Curr. Neuropharmacol. 11 (3), 298–314.
Prabhat Jha, MacLennan, Mary, Chaloupka, Frank J., Yurekli, Ayda, Ramasundarahettige,

Chintanie, Krishna, Palipudi, Zatońksi, Witold, Asma, Samira, Gupta, Prakash C., 2015. Chapter 10 - Global hazards of tobacco and the benefits of smoking cessation and tobacco taxes. In: third ed. In: Gelband, H., J, P., Sankaranarayanan, R. (Eds.), Cancer: Disease Control Priorities, vol. 3 Washington (DC): The International Bank for Reconstruction and Development/The World Bank. Available from: https://www.ncbi.nlm.nih.gov/books/NBK343639/.

Proskocil, B.J., Sekhon, H.S., Jia, Y., Savchenko, V., Blakely, R.D., Lindstrom, J., Spindel, E.R., 2004. Acetylcholine is an autocrine or paracrine hormone synthesized and secreted by airway bronchial epithelial cells. Endocrinology 145 (5), 2498–2506.

Quick, M.W., Lester, R.A.J., 2002. Desensitization of neuronal nicotinic receptors. J. Neurobiol. 53 (4), 457–478.

Randall, B.B., Paterson, D.S., Haas, E.A., Broadbelt, K.G., Duncan, J.R., Mena, O.J., Krous, H.F., Trachtenberg, F.L., Kinney, H.C., 2013. Potential asphyxia and brainstem abnormalities in sudden and unexpected death in infants. Pediatrics 132 (6), e1616–e1625.

Reddy, S., Sharma, S., 2018. Physiology, Circadian Rhythm, StatPearls, Treasure Island (FL).

Ribary, U., Lichtensteiger, W., 1989. Effects of acute and chronic prenatal nicotine treatment on central catecholamine systems of male and female rat fetuses and offspring. J. Pharmacol. Exp. Therapeut. 248, 786–792.

Santos-Silva, A.P., Oliveira, E., Pinheiro, C.R., Nunes-Freitas, A.L., Abreu-Villaca, Y., Santana, A.C., Nascimento-Saba, C.C., Nogueira-Neto, J.F., Reis, A.M., Moura, E.G., Lisboa, P.C., 2011. Effects of tobacco smoke exposure during lactation on nutritional and hormonal profiles in mothers and offspring. J. Endocrinol. 209 (1), 75–84.

Shao, X.M., Liu, S., Lee, E.S., Fung, D., Pei, H., Liang, J., Mudgway, R., Zhang, J., Feldman, J.L., Zhu, Y., Louie, S., Xie, X.S., 2018. Chronic intermittent nicotine delivery via lung alveolar region-targeted aerosol technology produces circadian pharmacokinetics in rats resembling human smokers. J. Appl. Physiol. 125 (5), 1555–1562.

Sine, S.M., 2002. The nicotinic receptor ligand binding domain. J. Neurobiol. 53 (4), 431–446.

Singh, P., Yoon, S.S., Kuo, B., 2016. Nausea: a review of pathophysiology and therapeutics. Therap Adv Gastroenterol 9 (1), 98–112.

Siqueira, L.M., Committee On Substance, U.S.E., Prevention, 2017. Nicotine and Tobacco as Substances of Abuse in Children and Adolescents. Pediatrics 139.

Slevin, M., Iemma, R.S., Zeinolabediny, Y., Liu, D., Ferris, G.R., Caprio, V., Phillips, N., Di Napoli, M., Guo, B., Zeng, X., AlBaradie, R., Binsaleh, N.K., McDowell, G., Fang, W.-H., 2018. Acetylcholine Inhibits Monomeric C-Reactive Protein Induced Inflammation, Endothelial Cell Adhesion, and Platelet Aggregation; A Potential Therapeutic? Front. Immunol. 9.

Slotkin, T.A., 1998. Fetal nicotine or cocaine exposure: which one is worse? J. Pharmacol. Exp. Therapeut. 285, 931–945.

Slotkin, T.A., Seidler, F.J., Qiao, D., Aldridge, J.E., Tate, C.A., Cousins, M.M., Proskocil, B.J., Sekhon, H.S., Clark, J.A., Lupo, S.L., Spindel, E.R., 2005. Effects of prenatal nicotine exposure on primate brain development and attempted amelioration with supplemental choline or vitamin C: neurotransmitter receptors, cell signaling and cell development biomarkers in fetal brain regions of rhesus monkeys. Neuropsychopharmacology 30 (1), 129–144.

Slotkin, T.A., MacKillop, E.A., Rudder, C.L., Ryde, I.T., Tate, C.A., Seidler, F.J., 2007. Permanent, Sex-Selective Effects of Prenatal or Adolescent Nicotine Exposure, Separately or Sequentially, in Rat Brain Regions: Indices of Cholinergic and Serotonergic Synaptic Function, Cell Signaling and Neural Cell Number and Size at 6 Months of Age. Neuropsychopharmacology 32 (5), 1082–1097.

Soeroso, N.N., Zain-Hamid, R., Sinaga, B., Sadewa, A., Syafiuddin, T., Syahruddin, E., Tann, G., Mutiara, E., 2018. Genetic polymorphism of CYP2A6 and its relationship with nicotine metabolism in male bataknese smokers suffered from lung cancer in Indonesia. Open Access Maced J Med Sci 6 (7), 1199–1205.

St-John, W.M., Leiter, J.C., 1999. Maternal nicotine depresses eupneic ventilation of neonatal rats. Neurosci. Lett. 267 (3), 206–208.

Struthers, R., Hodge, F.S., 2004. Sacred tobacco use in Ojibwe communities. J. Holist. Nurs. 22 (3), 209–225.

Talhout, R., Schulz, T., Florek, E., van Benthem, J., Wester, P., Opperhuizen, A., 2011. Hazardous compounds in tobacco smoke. Int. J. Environ. Res. Public Health 8 (2), 613–628.

The World Health Organization, 2018a. The World Health Organization: Global Health Observatory data - Prevalence of tobacco smoking. Web address: http://www.who.int/gho/tobacco/use/en/, Accessed date: 28 September 2018.

The World Health Organization, 2018b. The World Health Organization: Tobacco-Fact Sheet. Web address. http://www.who.int/news-room/fact-sheets/detail/tobacco, Accessed date: 28 September 2018.

Thielen, A., Klus, H., Muller, L., 2008. Tobacco smoke: unraveling a controversial subject. Exp. Toxicol. Pathol. 60 (2–3), 141–156.

Thomas, B., 2002. "Mushroom Madness" in the Papua New Guinea Highlands: A Case of Nicotine Poisoning? J. Psychoact. Drugs 34 (3), 321–323.

Thomas, G.A., Rhodes, J., Ingram, J.R., 2005. Mechanisms of disease: nicotine–a review of its actions in the context of gastrointestinal disease. Nat. Clin. Pract. Gastroenterol. Hepatol. 2 (11), 536–544.

Trachsel, L., Heller, H.C., Miller, J.D., 1995. Nicotine phase-advances the circadian neuronal activity rhythm in rat suprachiasmatic nuclei explants. Neuroscience 65 (3), 797–803.

Ujváry, I., 1999. Nicotine and Other Insecticidal Alkaloids. In: Izuru, Y., Casida, J.E. (Eds.), Nicotinoid insecticides and the nicotinic acetylcholine receptor. Springer, Tokyo.

Umezu, T., Kuribara, H., Tadokoro, S., 1992. [Effects of nicotine on circadian rhythm of ambulatory activity and drinking in rats]. Yakubutsu Seishin Kodo 12, 113–120.

Vaglenova, J., Birru, S., Pandiella, N.M., Breese, C.R., 2004. An assessment of the long-term developmental and behavioral teratogenicity of prenatal nicotine exposure. Behav. Brain Res. 150 (1–2), 159–170.

Vaglenova, J., Parameshwaran, K., Suppiramaniam, V., Breese, C.R., Pandiella, N., Birru, S., 2008. Long-lasting teratogenic effects of nicotine on cognition: gender specificity and role of AMPA receptor function. Neurobiol. Learn. Mem. 90 (3), 527–536.

Vane, J.R., 1969. The release and fate of vaso-active hormones in the circulation. Br. J. Pharmacol. 35 (2), 209–242.

Wang, H., Cui, W.Y., Liu, C.H., 1996. Modulation by nicotine on binding of cerebral muscarinic receptors with muscarinic agonist and antagonist. Zhongguo Yaoli Xuebao 17, 497–499.

Willinger, M., James, L.S., Catz, C., 1991. Defining the sudden infant death syndrome (SIDS): deliberations of an expert panel convened by the National Institute of Child Health and Human Development. Pediatr. Pathol. 11 (5), 677–684.

Xu, Z., Seidler, F.J., Ali, S.F., Slikker Jr., W., Slotkin, T.A., 2001. Fetal and adolescent nicotine administration: effects on CNS serotonergic systems. Brain Res. 914 (1–2), 166–178.

Yamanaka, K., Oshita, M., Muramatsu, I., 1985. Alteration of alpha and muscarinic receptors in rat brain and heart following chronic nicotine treatment. Brain Res. 348 (2), 241–248.

Yamanaka, H., Nakajima, M., Nishimura, K., Yoshida, R., Fukami, T., Katoh, M., Yokoi, T., 2004. Metabolic profile of nicotine in subjects whose CYP2A6 gene is deleted. Eur. J. Pharm. Sci. 22 (5), 419–425.

Yamanaka, H., Nakajima, M., Fukami, T., Sakai, H., Nakamura, A., Katoh, M., Takamiya, M., Aoki, Y., Yokoi, T., 2005. CYP2A6 and CYP2B6 are involved in nornicotine formation from nicotine in humans: interindividual differences in these contributions. Drug Metab. Dispos. 33, 1811–1818.

Yamazaki, H., Inoue, K., Hashimoto, M., Shimada, T., 1999. Roles of CYP2A6 and CYP2B6 in nicotine C-oxidation by human liver microsomes. Arch. Toxicol. 73 (2), 65–70.

Yoo, S.J., Park, S.J., Kim, B.S., Lee, K., Lim, H.S., Kim, J.S., Kim, I.S., 2014. Airborne nicotine concentrations in the workplaces of tobacco farmers. J Prev Med Public Health 47 (3), 144–149.

Yoshida, R., Nakajima, M., Watanabe, Y., Kwon, J.T., Yokoi, T., 2002. Genetic polymorphisms in human CYP2A6 gene causing impaired nicotine metabolism. Br. J. Clin. Pharmacol. 54 (5), 511–517.

Zhang, X., Tian, J.Y., Svensson, A.L., Gong, Z.H., Meyerson, B., Nordberg, A., 2002. Chronic treatments with tacrine and (-)-nicotine induce different changes of nicotinic and muscarinic acetylcholine receptors in the brain of aged rat. J. Neural. Transm. 109 (3), 377–392.

Zheng, W., Suzuki, K., Tanaka, T., Kohama, M., Yamagata, Z., Okinawa Child Health Study, G., 2016. Association between maternal smoking during pregnancy and low birthweight: effects by maternal age. PLoS One 11 e0146241.

Zhu, J., Takita, M., Konishi, Y., Sudo, M., Muramatsu, I., 1996. Chronic nicotine treatment delays the developmental increase in brain muscarinic receptors in rat neonate. Brain Res. 732 (1–2), 257–260.

Zhu, J., Taniguchi, T., Konishi, Y., Mayumi, M., Muramatsu, I., 1998. Nicotine administration decreases the number of binding sites and mRNA of M1 and M2 muscarinic receptors in specific brain regions of rat neonates. Life Sci. 62 (12), 1089–1098.

Zhu, J., Zhang, X., Xu, Y., Spencer, T.J., Biederman, J., Bhide, P.G., 2012. Prenatal nicotine exposure mouse model showing hyperactivity, reduced cingulate cortex volume, reduced dopamine turnover, and responsiveness to oral methylphenidate treatment. J. Neurosci. 32 (27), 9410–9418.

Zhu, A.Z., Zhou, Q., Cox, L.S., Ahluwalia, J.S., Benowitz, N.L., Tyndale, R.F., 2013. Variation in trans-3'-hydroxycotinine glucuronidation does not alter the nicotine metabolite ratio or nicotine intake. PLoS One 8, e70938.

Zhu, J., Lee, K.P., Spencer, T.J., Biederman, J., Bhide, P.G., 2014. Transgenerational transmission of hyperactivity in a mouse model of ADHD. J. Neurosci. 34 (8), 2768–2773.