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Unique Effects of Nicotine Across the Lifespan

Michelle Ren, M.S.^{1,*}, Shahradd Lotfipour, Ph.D.^{1,2,3}, Frances Leslie, Ph.D.¹

¹Department of Pharmaceutical Sciences, School of Pharmacy and Pharmaceutical Sciences, University of California, Irvine, Irvine, CA, USA

²Department of Emergency Medicine, School of Medicine, University of California, Irvine, Irvine, CA, USA

³Department of Pathology and Laboratory Medicine, School of Medicine, University of California, Irvine, Irvine, CA, USA

Abstract

Smoking remains the leading cause of preventable death in the United States. Although combustible cigarettes are largely being replaced by tobacco-free products, nicotine use continues to increase in vulnerable populations, including youth, adolescents, and pregnant women. Nicotine exerts unique effects on specific brain regions during distinct developmental periods due to the dynamic expression of nicotinic acetylcholine receptors (nAChRs) throughout the lifespan. Nicotine exposure is a health concern not only for adults but also has neurotoxic effects on the fetus, newborn, child, and adolescent. In this review, we aim to highlight the dynamic roles of nAChRs throughout gestation, adolescence, and adulthood. We also provide clinical and preclinical evidence of the neurodevelopmental, cognitive, and behavioral consequences of nicotine exposure at different developmental periods. This comprehensive review highlights unique effects of nicotine throughout the lifespan to help elucidate interventions and public health measures to protect sensitive populations from nicotine exposure.

Keywords

nicotinic acetylcholine receptors; developmental nicotine exposure; prenatal; perinatal; adolescence; aging

1. Introduction

Use of nicotine products is an unrelenting public health concern, as smoking is the leading cause of preventable death in the United States (U.S.) (Centers for Disease Control and Prevention, 2021). Although the rate of smoking combustible cigarettes has decreased in the last decade, nicotine exposure has risen substantially due to the increased popularity of tobacco-free, electronic nicotine delivery systems (e.g. electronic cigarettes, vaping), primarily among youth and teenagers (Miech et al., 2019). Additionally, pregnant and lactating women are increasingly replacing tobacco products with e-cigarettes even though

*Correspondence should be addressed to: Michelle Ren, M.S., 303 Medical Surge II, Irvine, CA, 92617, renm1@uci.edu.

these may not be safer for the developing offspring (Kim and Oancea, 2020; Wagner et al., 2017). Nicotine, the primary psychoactive component of tobacco, exerts unique effects on specific brain regions during distinct developmental periods (Dwyer et al., 2009). Nicotine exposure is thus not only a health concern for adults but also has neurotoxic effects on the fetus, newborn, child, and adolescent.

Nicotine binds to nicotinic acetylcholine receptors (nAChRs), which regulate various aspects of brain development. The effects of nicotine are highly dependent on timing of exposure, with detrimental effects of drug exposure more pronounced prior to adulthood due to the incomplete maturation of neural circuitry in the developing brain. Various animal studies (i.e. lambs, rats, and mice) reveal that gestational nicotine exposure contributes to reduced pulmonary function, auditory processing defects, and impaired cardiorespiratory function during infancy, as well as cognitive and behavioral deficits later in life (Bamford and Hawkins, 1990; Franke et al., 2007, 2008; Huang et al., 2007; Karlsson et al., 2004; Neff et al., 2003; Paz et al., 2007). Further, adolescent nicotine exposure may cause deficits in working memory and attention, and alterations in reward processing that increase the potential for subsequent drug abuse and addiction (Ren and Lotfipour, 2019; Leslie, 2020; Fleming et al., 1989; Lai et al., 2000; Nkansah-Amankra et al., 2016).

In this review, we aim to highlight the dynamic roles of nAChRs throughout the lifespan and provide clinical and preclinical evidence of the neurodevelopmental, cognitive, and behavioral consequences of nicotine exposure at different developmental periods. This comprehensive review highlights unique effects of nicotine throughout the lifespan to help elucidate interventions and public health measures to protect sensitive populations from nicotine exposure.

2. Materials and Methods

We conducted a systematic search of the literature related to developmental nicotine exposure published before July 2021. We used the electronic databases of PubMed and Google Scholar for research articles published in English between January 1971 and July 2021. Articles or book chapters were included in the review if they discussed nicotine exposure during gestation, childhood, adolescence, or aging. We grouped studies together according to their methodological similarities, so findings without substantial support or reproducibility (i.e., fewer than 5 comparable studies) were excluded. Following exclusion and careful analysis of studies based on key results, limitations, suitability of the methods to test the initial hypothesis, and quality and interpretation of the results obtained, 156 references were selected. The use of three reviewers and two extensive electronic databases allows for a widespread range of research articles, which maximizes scientific credibility and minimizes potential bias.

3. Results

3.1 Pharmacology

Nicotine is the primary psychoactive constituent in tobacco products and binds to nAChRs, which are pentameric ligand-gated ion channels composed of α and β subunits (α 1–7, 9–10;

$\beta 1-4$). nAChRs are widely distributed throughout the human and rodent brain and periphery and are critical in the processes of the neuromuscular junction, neurotransmitter release, brain maturation, reward processing, and cognition (Broide and Leslie, 1999; Campbell et al., 2010; Gotti et al., 2006; Gotti and Clementi, 2004; McGehee, 1999; Pentel et al., 2006; Zoli et al., 1995). Nicotine can both activate and desensitize nAChRs that mediate the physiological effects of acetylcholine (Dani, 2001). A developmental regulation of nAChR function occurs in the brain, with differing modulation of neurotransmitter release from gestation through adulthood (O'Leary and Leslie, 2003). This shift in nAChR regulation is dependent on the properties of nAChRs across the lifespan. A comprehensive review of nAChR regulation of developing catecholamine systems and its implications for numerous disease states has been provided previously (Azam et al., 2006). Notably, age-dependent changes in nAChR pharmacology are important in the development of the cerebellum and sensory cortices, as well as dopamine release from the ventral midbrain and norepinephrine release from the hippocampus.

3.2 Prenatal and early postnatal development

Prenatal nicotine exposure continues to be a concern for pregnant women who have increasingly replaced smoking with electronic nicotine products or patches due to the misconception of a safer smoking alternative (Baeza-Loya et al., 2014). Nicotine readily crosses the placental barrier and can be found in the amniotic fluid and umbilical cord of neonates (Luck et al., 1985). Nicotine exposure during pregnancy results in increased high affinity nAChR binding in the fetal and neonatal brain, providing evidence that nicotine reaches the fetal brain and upregulates nAChRs as it does in adult rats (Navarro et al., 1989; Nguyen et al., 2003; Pentel et al., 2006; Slotkin et al., 1987). Numerous reports in humans have revealed the toxic properties of nicotine exposure during pregnancy on the offspring's brain and behavior (Lotfipour et al., 2014; McGrath-Morrow et al., 2020).

nAChRs are involved in critical early developmental processes, including neurite outgrowth, cell survival, proliferation, differentiation, and neurogenesis (Dani, 2001). Activation and/or desensitization of nAChRs via nicotine exposure during gestation may disrupt brain programming and plasticity into postnatal life (Slotkin et al., 1987). Furthermore, use of e-cigarettes (Regan et al., 2021) or combustible cigarettes (Kyrklund-Blomberg et al., 2005; Mitchell and Milerad, 2006; Ozturk et al., 2016; Perry et al., 2019; US Department of Health and Human Services, 2014) during pregnancy is associated with pregnancy complications, risks of preterm delivery, lower birth weight, cleft palate, and sudden infant death syndrome.

In utero nicotine exposure in both humans (Ernst et al., 2001; Eskenazi et al., 1995; Regan and Pereira, 2021) and rodents (Paulson et al., 1993; Roy and Sabherwal, 1994; Slotkin et al., 1987) adversely affects prenatal and postnatal growth and increases the risk of fetal mortality and morbidity. Prenatal nicotine exposure affects cardiovascular and lung function and growth of the developing mouse fetus, as nicotine adversely affects fetal hemodynamics acutely and chronically in early pregnancy, potentially leading to fetal tissue hypoxia and intrauterine growth restriction (Aoyagi et al., 2020). Prenatal nicotine also interferes with male testosterone production during the perinatal surge in humans (Fried et al., 2001) and

rodents (Sarasin et al., 2003), and these acute endocrine effects of nicotine during gestation may be long-lasting (Lichtensteiger and Schlumpf, 1985).

Gestational nicotine exposure also impacts the developing brain at doses that do not delay general growth (Slotkin, 1998), which can be observed through motor, sensory, cognitive, and behavioral deficits in infants and toddlers (Ernst et al., 2001; Fergusson et al., 1998; Fuentes-Cano et al., 2020; Gusella and Fried, 1984; Lichtensteiger et al., 1988; Weissman et al., 1999; Zeid et al., 2018). Smoking during pregnancy is now considered to be the primary cause of sudden infant death syndrome, resulting from compromised development of cardiac and respiratory brainstem centers (Slotkin and Seidler, 2011; Vivekanandarajah et al., 2019; Zhang and Wang, 2013). Additionally, *in utero* exposure to nicotine produces decreased synaptic plasticity and developmental effects on the medial prefrontal cortex and nucleus accumbens in rodents, which is observed through attention-deficit/hyperactivity disorder, conduct problems, depression, anxiety, externalizing behavior, and substance use in the offspring (Table 1; Franke et al., 2008; Dwyer et al., 2019).

The prenatal period in humans refers to the entire duration of human gestation (3 trimesters or 9 months). However, because rodents are born at an earlier stage of brain maturation than humans, prenatal nicotine exposure in rats or mice only translates to exposure during the first two trimesters of human gestation (Bayer et al., 1993; Quinn, 2005). The first twelve days of rodent development are comparable to the third trimester of human gestation (Quinn, 2005), so nicotine exposure during the early postnatal period in rodents is also studied for a comprehensive understanding of human prenatal nicotine exposure. During this time, the brain is rapidly growing, and development of the cortex, hippocampus, and cerebellum are just beginning (Bayer et al., 1993; Dobbing, 1971). There is a transient appearance of cholinergic markers, including nAChRs, during the postnatal development of these regions (Broide and Leslie, 1999; Clos et al., 1989; Winzer-Serhan and Leslie, 2005). Disruption of the cholinergic system during this period via early postnatal nicotine exposure impairs development of the cortex and hippocampus, and produces permanent changes in cortical circuitry that result in deficiencies in somatosensory, auditory and cognitive processing (Aramakis et al., 2000; Heath et al., 2010; Hsieh et al., 2002; Huang et al., 2007; Liang et al., 2006). Human studies have also shown similar deficiencies in central auditory processing in school age children prenatally exposed to cigarette smoke (McCartney et al., 1994).

3.3 Adolescence

Adolescence is characterized by significant hormonal, psychosocial, and neural changes in rodents (postnatal day (PND) 28–42) and humans (12–18 years of age) (Spear, 2000). During this sensitive maturational period, the brain is remarkably vulnerable to the harmful effects of nicotine, which is especially critical given that adolescence is also the age of peak onset of nicotine use (Miech et al., 2019).

Animal studies consistently demonstrate the unique effects of nicotine exposure on the adolescent brain, including increased number and activity of nAChRs in reward-related brain regions (Doura et al., 2008; Kota et al., 2007), as well as increased nicotine-induced dopamine release in limbic regions (Azam et al., 2007; Corongiu et al., 2020). Behaviorally,

adolescents exposed to nicotine display increased rewarding effects of drugs of abuse (Leslie, 2020; Ren and Lotfipour, 2019; Yuan et al., 2015), decreased attention and other learning/memory deficits (Counotte et al., 2009, 2011; Holliday and Gould, 2016; Kutlu et al., 2018; Portugal et al., 2012), and emotional dysregulation (Adriani et al., 2004; Holliday and Gould, 2016; Iniguez et al., 2009; Jobson et al., 2019; Slawecki et al., 2003; Smith et al., 2006). This is due largely in part by increased activity in reward-related centers in the brain via dopaminergic, serotonergic, cholinergic, and inflammatory mechanisms (Table 1). The increased reward induced by nicotine may lead to subsequent abuse of other drugs, including nicotine itself, alcohol, cocaine, methamphetamine, and fentanyl (Alajaji et al., 2016; Cardenas et al., 2021; Cole et al., 2019; Collins and Izenwasser, 2004; Collins et al., 2004; Dao et al., 2011; Linker et al., 2020; McQuown et al., 2009, 2007; Pipkin et al., 2014; Reed and Izenwasser, 2017; Thomas et al., 2018). These nicotine-induced changes in the brain and behavior are long-lasting into adulthood.

Adolescent nicotine exposure is predictive of nicotine dependence in adulthood, as adolescent rodents show increased nicotine reward (Adriani et al., 2003; Torres et al., 2008), reduced aversion (O'Dell et al., 2006; Shram et al., 2006; Torres et al., 2008), and enhanced sensitivity to withdrawal effects (Dierker and Mermelstein, 2010; DiFranza and Lew, 1995; Zhan et al., 2012) as compared to adults. There is significant clinical evidence supporting that individuals who begin smoking during adolescence are more likely to have trouble quitting than those who start as adults (Breslau and Peterson, 1996; Cengelli et al., 2012; Chen and Millar, 1998; DiFranza and Lew, 1995; Kandel and Chen, 2000; Khuder et al., 1999). This is further reinforced by the report that 90 percent of adult smokers started before age 18 (Substance Abuse and Mental Health Services Administration, 2014; US Department of Health and Human Services, 2014). Teen e-cigarette users are more likely to report dependence signs and be daily users if they use high nicotine content pods, such as Juul (Boykan et al., 2019).

Further, nicotine exposure differentially impacts males and females during adolescence. Females are more vulnerable to tobacco use than males, as female versus male adolescent rodents self-administer greater amounts of oral or intravenous nicotine (Chen et al., 2007; Klein et al., 2004; Lynch, 2009; Sanchez et al., 2014), show impaired rearing and locomotor activity following adolescent nicotine exposure (Trauth et al., 2000), and are more sensitive to behavioral deficits and hippocampal cell damage from nicotine withdrawal (Xu et al., 2003). Sex differences in nicotine responses may be due to gonadal steroid-mediated sexual differentiation of the brain, as nAChRs and major neurotransmitter systems are modulated by different sex hormones throughout development (Azam et al., 2007; Cross et al., 2016; Pogun and Yararbas, 2009; Slotkin et al., 2007).

3.4 Aging

The adult brain is no longer considered to be developing; rather, the aging brain experiences a gradual loss of neural circuits and synaptic plasticity that is associated with an age-dependent decline in cognitive function (Yankner et al., 2008). Clinical and preclinical data support a neuroprotective effect of nicotine during adulthood and senescence, preventing the onset of degenerative neurological disorders, such as Alzheimer's dementia and Parkinson's

Disease (Ferrea and Winterer, 2009). Nicotine use in humans also positively influences learning, memory, and attention, and improves mood, stress regulation, and anxiety (Feldner et al., 2007; Foulds et al., 1996; Gehricke et al., 2007; Grobe et al., 1998; Marshall et al., 2008; Metcalfe et al., 2003; Xu et al., 2005). However, the potential benefits of nicotine use in either cigarettes or e-cigarettes are greatly outweighed by its negative consequences, including risk of addiction, cancer, heart disease, high blood pressure, respiratory infections, and gastrointestinal distress (Mishra et al., 2015; US Department of Health and Human Services, 2014). The debate against nicotine's neuroprotective versus neurotoxic effects is complex and appears to involve regulation mechanisms of nAChRs and interactions between nicotine and other central nervous system neurotransmitters.

The observation of lower rates of dementia in smokers has prompted further investigation into the role of nicotinic effects in neurodegenerative diseases (Table 1). Alzheimer's disease is characterized by an aggregation and precipitation of amyloid precursor proteins (APP) in the form of plaques, which are a result of overproduction and/or altered metabolism of APP- β . $\alpha 7$ -containing nAChRs are present in the plaques, and nicotine prevents the conversion of APP- α to APP- β and lowers the secretion of APP- β (Gutala et al., 2006; Utsuki et al., 2002). The proposed mechanism is a central role of $\alpha 4\beta 2$ and $\alpha 7$ nAChRs in enhancing the release of neuroprotective APP- α and lowering APP- β production (Mousavi and Hellström-Lindahl, 2009).

A U.S. government-funded veteran's study found that smoking reduced Parkinson's deaths by 64 percent (Dorn, 1959). Nicotine promotes neuron survival and partially protects from Parkinson's by suppressing SIRT6 in mice (Nicholatos et al., 2018). The neuroprotective effects of nicotine have been observed particularly in the hippocampus, entorhinal cortex, and neocortex (Perry et al., 2000; Zeid et al., 2018). In contrast, nicotine has been shown to have neuroinflammatory effects in adolescence that switch to neuroprotection in adulthood (Linker et al., 2020). These findings may suggest interventions using neuronal nAChRs as novel targets for inflammation and neuroprotection in adults (Bencherif, 2009), with a strong contraindication at younger ages.

3.5 Vaping Versus Smoking

Replacing traditional combustible cigarettes with e-cigarettes (vaping) reduces the exposure to tobacco's carcinogens and is substantially less harmful than smoking (George et al., 2019; McNeill et al., 2018, 2020; National Academies of Sciences, Engineering, and Medicine 2018). However, vaping also carries significant health risks, including addiction, metal exposure, inhalation of toxic solvents, and vaping-associated lung injury (Perrine et al., 2019; Schmidt, 2020). Furthermore, its effectiveness in reducing or eliminating smoking is controversial (Dai and Leventhal, 2019; El Dib et al., 2017). Clinical data suggest that smokers vape to maintain their habit instead of quitting entirely and have increased total daily nicotine use despite a reduction in cigarette smoking (Hajek et al., 2019; Martinez et al., 2020; Rehan et al., 2018). Although vaping may promote harm reduction for smoking, nicotine exposure is a concern in the youth, and adolescents have demonstrated an increased attraction to electronic cigarettes due to vape flavors, belief that vaping is harm-free, self-help, and societal pressure (Leventhal et al., 2019; Newcombe et al., 2021). There is

increasing evidence in humans and animals that e-cigarette use is harmful to youth and the unborn child (Pierce et al., 2021; Regan et al., 2021).

4. Conclusion

Due to the dynamic expression of the cholinergic system throughout the lifespan, chronic and acute nicotine exposure differentially affect brain structure, function, and behavior in the perinatal period, adolescence, and adulthood. The patterns of expression and pharmacological and physiological properties of nAChRs are unique to the developmental period. Nicotine exposure during the perinatal period disrupts general growth, cardiovascular and lung function, the endocrine system, motor function, reward, and attention. Adolescent nicotine exposure enhances susceptibility to addiction, impulsivity, and mood disorders. While nicotine exposure during adulthood may not have the apparent adverse consequences on the brain seen in earlier critical developmental windows, the health risks associated with tobacco and nicotine use are equally destructive. The potential neuroprotective effects of nicotine in senescence comprise an interesting field of research to explore further.

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Highlights

- Nicotine's impacts on the brain and behavior are dependent on timing of exposure
- Nicotinic acetylcholine receptors have dynamic expression throughout the lifespan
- Gestational nicotine impairs offspring somatosensory, auditory, and cognitive processing
- Adolescent nicotine disrupts working memory, attention, and reward processing
- Nicotine may provide a neuroprotective effect during adulthood and senescence

Table 1:

Summary of behavioral findings and molecular mechanisms of prenatal, adolescent, or adult nicotine exposure in rodents, and relevant human studies.

Nicotine Exposure (dose, route of administration, duration)	Rat/Mouse, Strain, and Age of Exposure	Behavioral Findings and Age of Evaluation	Molecular Mechanisms	Reference(s)	Relevant Human Studies
<i>Prenatal exposure</i>					
3 mg/kg/day, s.c., 2 weeks	Sprague-Dawley rats, prenatal (G4–18)	Increased cocaine self-administration in nicotine-exposed vs. saline-exposed offspring (P32–37)	Increased cocaine-induced c-fos mRNA expression in the nucleus accumbens	Franke et al., 2008	Lotfipour et al., 2014
		Increased cocaine-induced locomotor activity in nicotine-exposed vs. saline-exposed offspring (P32)	Altered corticolimbic dopamine system development (increased dopamine in prefrontal cortex)	Dwyer et al., 2019	
<i>Adolescence: drug-related behavior</i>					
60µg/kg, i.v., 4 days	Sprague-Dawley rats, adolescence (P28–31)	Increased self-administration of cocaine in adolescent rats pretreated with nicotine vs. saline-treated adolescents and both saline- and nicotine-treated adults (P32)	5HT1A receptor activation	Dao et al., 2011	Fleming et al., 1989; Lai et al., 2000; Nkansah-Amankra et al., 2016
		Increased self-administration of nicotine, cocaine, methamphetamine, ethanol, and fentanyl in adolescent rats pretreated with nicotine vs. saline-treated adolescents and both saline- and nicotine-treated adults (P32)	D2 receptors, microglia (CX3CL1 receptor) activation	McQuown et al., 2007, 2009; Linker et al., 2020; Cardenas et al., 2021	
0.4 mg/kg/day, i.p., 10 days	Sprague-Dawley rats, adolescence (P34–43)	Exposure to nicotine during periadolescence, but not a similar exposure in the postadolescent period, increased intravenous self-administration of nicotine (P75+)	Increase in gene expression of the DA neuron-specific subunits ($\alpha 5$ and $\alpha 6$) and of the $\beta 2$ subunit from adolescent nicotine exposure	Adriani et al., 2003	
0.16 or 0.64 mg/kg, s.c., 2 weeks	Sprague-Dawley rats, adolescence (P35–50)	Increased methamphetamine intake in adulthood	None evaluated	Pipkin et al., 2014	
0.4 mg/kg nicotine/day, i.p., 7 days	Sprague-Dawley rats, adolescence (P30–36)	Long-term increase in cocaine reinforcement, lack of sensitization to nicotine's locomotor-activating effects (P37); opposite findings in adults	Adolescent nicotine treatment increased dopamine transporter densities and decreased serotonin transporter densities; in adults, no change in dopamine transporter, dopamine D1 or D2 receptor, or serotonin transporter densities	Collins and Izenwasser 2004; Collins et al., 2004; Reed and Izenwasser, 2017	
0.1, 0.5, or 1 mg/kg, s.c., 2/daily for either 1 (acute) or 7 (repeated) days	CD-1 mice, adolescence (P28–34 or P50–56)	Adults exposed to nicotine during early but not late adolescence had increased preference for cocaine, morphine,	Accumulation of deltafosB in the nucleus accumbens	Alajaji et al., 2016	

Nicotine Exposure (dose, route of administration, duration)	Rat/Mouse, Strain, and Age of Exposure	Behavioral Findings and Age of Evaluation	Molecular Mechanisms	Reference(s)	Relevant Human Studies
		and amphetamine during adulthood (P70+)			
0.4 mg/kg, i.p., 14 days	Long-Evans rats, adolescence (P28–42)	Adults exposed to nicotine during adolescence had increased ethanol self-administration compared to adolescent and adult saline exposure and adult nicotine exposure	Altered GABA transmission and chloride homeostasis in the ventral tegmental area	Thomas et al., 2018	
<i>Adolescence: attention</i>					
0.4 mg/kg, s.c., 3/ daily for 10 days	Wistar rats, adolescence (P34–43)	Impaired measures of attention in adulthood (P70+)	Reduced mGluR2 protein and function on presynaptic terminals of PFC glutamatergic synapses, enhanced releasability of dopamine in the mPFC	Counotte et al., 2009; Counotte et al., 2011	Foulds et al., 1996; Grobe et al., 1998; Xu et al., 2005
<i>Adolescence: mood and anxiety</i>					
0.03, 0.1, or 0.3 mg/kg/day, i.p., 10 days	CD-1 mice, adolescence (P36–48 or P49–61)	Acute nicotine administration had opposite effects on anxiety in adolescents (P48) and adults (P61)	A dose-dependent reduction of GluR2/3 immunoreactivity in the striatum and hippocampus 2 months after a pretreatment with nicotine during mid-adolescence	Adriani et al., 2004	Newcombe et al., 2021
0, 0.16, 0.32, or 0.64 mg/kg, s.c., 2x/day for 15 consecutive days 0.4 mg/kg, s.c., 3x/day for 10 consecutive days	Sprague-Dawley rats, adolescence (P30–44, P34–44)	Increased depression-like and anxiety-like behaviors in adulthood (P70+)	Prefrontal cortical neuronal hyperactivity, selective PFC downregulation of D1R expression levels, increased phosphorylation of ERK 1–2	Iniguez et al., 2009; Jobson et al., 2019	
<i>Aging</i>					
100 µg/ml in 2% saccharin, oral, 14 days 1 or 8 mg/kg/day, 14 days	C57BL/6J mice, adulthood (P60+)	Nicotine prevents the conversion of APP-α to APP-β and lowers the secretion of APP-β	Nicotine treatment enhances expression of APP and APLP2 proteins in SH-SY5Y cells The proposed mechanism is a central role of α4β2 and α7 nAChRs in enhancing the release of neuroprotective APP-α and lowering APP-β production	Gutala et al., 2006; Utsuki et al., 2002	Dorn, 1959
Mouse fibroblasts stably transfected with chick cDNA coding the α4 and β2 nAChR subunit	Human neuroblastoma SH-SY5Y cells and M10 cells	Treatment with nicotine increased release of sAPPα and at the same time lowered Aβ levels in both SH-SY5Y and SH-SY5Y/APP ^{sw} cells expressing α3 and α7 nAChR subtypes	Nicotine-induced attenuation of β-amyloidosis is mediated by nAChRs and not by a direct effect of nicotine	Mousavi and Hellström-Lindahl, 2009	
200 µg/ml in drinking water, 3 weeks	Immortalized WT and SIRT6 null fibroblasts Conditional SIRT6 overexpressing mice (C57BL/6J)	Reduced abundance and secretion of TNFα in a SIRT6-dependent manner, promoting neuron survival	Suppression of SIRT6 increases AKT signaling and reduces the secretion of TNFα, both of which likely mediate the impact of SIRT6 on DA neuron survival and PD pathology	Nicholatos et al., 2018	

Nicotine Exposure (dose, route of administration, duration)	Rat/Mouse, Strain, and Age of Exposure	Behavioral Findings and Age of Evaluation	Molecular Mechanisms	Reference(s)	Relevant Human Studies
	background), Adulthood (P60+)				

G: Gestational day, P: Postnatal day, i.p.: intraperitoneal, i.v.: intravenous, s.c.: subcutaneous.

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