Neurotoxicology of nicotine and tobacco

Edward D. Levin*
Professor of Psychiatry and Behavioral Sciences, Duke University Medical Center, Durham, NC, United States
*Corresponding author: e-mail address: edlevin@duke.edu

Contents

1. Introduction

Nicotine is the primary psychoactive ingredient in tobacco. Nicotine-driven tobacco addiction is the cause of substantial toxicity, including neurotoxicity, much of which is due to the wide variety of other toxic chemicals in tobacco. However, nicotine itself can also cause neurotoxic effects. The primary determinant of nicotine neurotoxicity is developmental phase during which exposure occurs. Nicotine has long been well-characterized as a developmental neurotoxicant because cholinergic systems play critical roles controlling neurodevelopment (Abbott and Winzer-Serhan, 2012; Slikker et al., 2005; Slotkin, 2004). A great number of experimental studies have demonstrated the persisting neural and behavioral toxicity of nicotine in animal models primarily in mice and rats, but also in other species including zebrafish and monkeys. The vulnerability to nicotine neurotoxicity extends to adolescence. In adulthood there is less evidence for neurotoxicity of nicotine apart from nicotine-driven tobacco addiction and more recently addiction to e-cigarettes. There is less evidence

Advances in Neurotoxicology
ISSN 2468-7480
https://doi.org/10.1016/bs.ant.2022.06.003

of addiction to other forms of nicotine delivery such as gum or skin patches. In fact, there is evidence for potential therapeutic efficacy for nicotine in the treatment of cognitive impairments seen with attention deficit hyperactivity disorder (ADHD), Down's syndrome, schizophrenia and aging related cognitive impairments including Alzheimer's disease. These studies have primarily used nicotine skin patches as the delivery device. Because nicotine neurotoxicity varies so substantially over the life span, this discussion is organized by life stage. Particular neurotoxic risks are caused by nicotine during prenatal and neonatal development as well as during adolescence compared with adult and aging life phases.

2. Prenatal and neonatal development

A substantial number of studies have shown that nicotine exposure during early development causes long-term neural and behavioral toxicity (Levin and Abreu-Villaça, 2018). Prenatal nicotine in mice caused significant locomotor hyperactivity (Ajarem and Ahmad, 1998). Prenatal nicotine exposure disrupts connectivity between the thalamus and neocortex (Heath et al., 2010; King et al., 2003). Prenatal nicotine exposure in mice significantly altered the glutamate/GABA balance in the lateral dorsal tegmental nucleus which is the source of cholinergic projections controlling activity of ventral tegmental dopamine neurons (Polli and Kohlmeier, 2019). The concentration of nicotinic receptors in the brains of mice peaks during the neonatal period with a preponderance of high affinity sites and declines over the rest of the lifespan with a diversification of nicotinic binding to include both low and high affinity sites (Zhang et al., 1990).

In rats, our studies have shown that chronic nicotine exposure during gestation causes neural and behavioral dysfunction that persists into adulthood even with low levels of exposure modeling exposure to second-hand tobacco smoke. Fig. 1 shows that nicotine administered together with the complex mixture of tobacco smoke extract (TSE) produces significant locomotor hyperactivity in the offspring compared to vehicle controls as well as compered to the same dose of nicotine given alone (Hall et al., 2016). Fig. 2 shows the persisting working and reference memory impairment in the 16-arm radial maze of female offspring of dams exposed to TSE during the second half of gestation (Cauley et al., 2018). Prenatal TSE exposure also caused persistently altered cholinergic and serotonergic transmitter systems in the offspring (Slotkin et al., 2017).

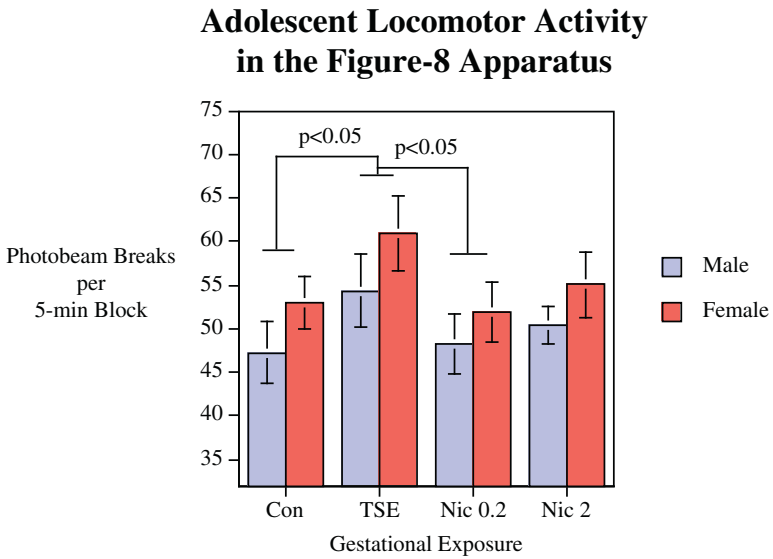

Fig. 1 Comparison of the effects of maternal exposure to nicotine alone vs nicotine in tobacco smoke extract (TSE) on offspring locomotor activity in the figure-8 maze (mean ± SEM). Low dose (0.2 mg/kg/day) nicotine in TSE caused significant locomotor hyperactivity relative to controls as well as the same dose of nicotine alone (Hall et al., 2016).

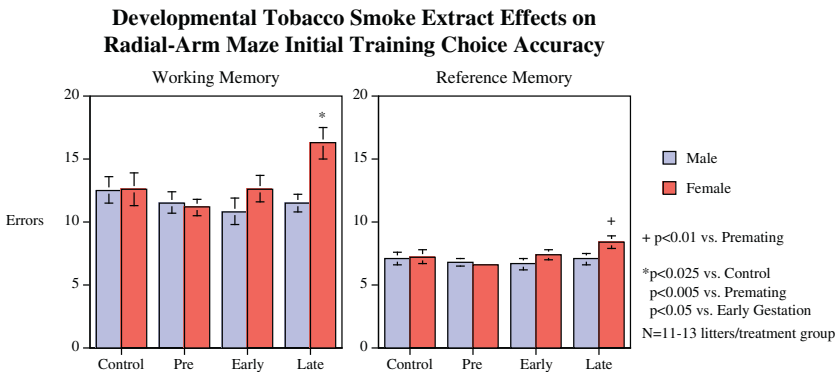

Fig. 2 Tests of effects of maternal pre-mating vs early or late gestation exposure to tobacco smoke extract (TSE) on offspring choice accuracy in the 16-arm radial maze showed that late gestational TSE exposure significantly increased both working and reference memory errors in female offspring (mean ± SEM) (Cauley et al., 2018).

The developmental neurotoxicity of nicotine generalizes beyond mammals. Complementary species can be useful in the study of developmental nicotine neurotoxicity. In zebrafish our studies have found that exposure to nicotine during the first 5 days after fertilization significantly increased

startle response in adulthood (Crosby et al., 2015). Sea urchin and chick embryos are also sensitive to the developmental toxicity of nicotine (Buznikov et al., 2003; Yanai et al., 2010).

3. Adolescence

Adolescence is also a period for enhanced neurotoxicity with nicotine exposure (Korpi et al., 2015; Kwan et al., 2020; Ren et al., 2022; Slotkin, 2004). Slotkin and co-workers have demonstrated that nicotine exposure during adolescence causes persisting neurotoxic effects in rats (Slotkin, 2004). Chronic nicotine administration causes an increase in nicotinic receptor number in adult rats (Marks et al., 1983; Schwartz and Kellar, 1983). This effect is prolonged with chronic nicotine exposure in adolescent rats (Trauth et al., 1999). Adolescent male and female rats self-administered greater amounts of nicotine than rats that started in young adulthood. During adolescence males showed a greater increase than females, but females showed a more persisting increase in nicotine self-administration than males as the rats continued self-administration into adulthood (Levin et al., 2003, 2007, 2011). This may be related to the increase in impulsiveness with nicotine in adolescence (DeBry and Tiffany, 2008).

4. Adulthood

Compared to younger ages there is much less evidence of nicotine neurotoxicity in adulthood. Nicotine can at higher doses cause convulsions (Broide et al., 2002; Damaj et al., 1999; Yamamoto et al., 1966). The main neurotoxic concern of nicotine in adults is the fact that nicotine is the principal driving force underlying tobacco addiction by which other neurotoxic chemicals are self-administered. Chronic nicotine administration does temporally increase the concentrations of nicotinic acetylcholine receptors in adults (Marks et al., 1983; Schwartz and Kellar, 1983).

There have been studies of the use of nicotine skin patches to alleviate the cognitive impairments seen in adults with ADHD (Conners et al., 1996; Levin et al., 1996a), Down's syndrome (Seidl et al., 2000) and schizophrenia (Levin et al., 1996b).

5. Aging

Nicotine has been investigated as a possible therapeutic agent in aging-related cognitive impairments such as, age-associated memory impairment,

mild cognitive impairment and Alzheimer's disease (Newhouse et al., 2012; White and Levin, 1999, 2004) as well as the motor dysfunction of Parkinson's disease (Tizabi et al., 2021) and symptoms of depression (McClernon et al., 2006). There is evidence for the efficacy of nicotine for improving cognition in aging (Newhouse et al., 2012; White and Levin, 1999, 2004), though further research is needed. Few adverse effects of acute or chronic nicotine skin patch treatments have been seen in chronic experimental human studies (Newhouse et al., 2012; White and Levin, 1999, 2004).

6. Future directions

The neurotoxic risks of nicotine and the complex mixture of tobacco including nicotine have been well characterized with differential effects seen over the lifespan. Of course, further research is needed for better understanding of nicotine's neurotoxicity. Paternal nicotine exposure prior to conception (2 mg/kg/day for 56 days via sc osmotic minipump) has been shown to alter sperm DNA methylation (Schrott et al., 2020) and cause long-term neurobehavioral alterations including locomotor activity and impaired habituation (Hawkey et al., 2019). Specifically, paternal nicotine exposure caused locomotor hyperactivity in male offspring, reversing the typical sex difference in locomotor activity in the figure-8 maze (Fig. 3).

Exposure to nicotine is never alone with tobacco use. Tobacco contains thousands of other compounds, some like benzo[a]pyrene (BaP) that are known neurotoxicants. We have found that prenatal exposure to nicotine + BaP causes greater persisting neural and behavioral impairments than either alone. In addition to BaP there are other polycyclic aromatic hydrocarbons that remain understudied. In addition, neurotoxic heavy metals such as cadmium are also found in tobacco (Satarug and Moore, 2004). Many studies have documented the neurotoxic effects of cadmium (Wang and Du, 2013; Wright and Baccarelli, 2007).

E-cigarettes have a much simpler chemistry, but they also can present neurotoxic risk (Ruszkiewicz et al., 2020). They contain nicotine and other potentially neurotoxic chemicals that could exacerbate the neurotoxicity of nicotine (Clapp and Jaspers, 2017; DeVito and Krishnan-Sarin, 2018). Lead has been found in the vapor output of some e-cigarettes (Eshraghian and Al-Delaimy, 2021). Of course, the neurotoxic effects of lead are very well characterized, especially with exposure during development (Grandjean and Landrigan, 2014). The interactive neurotoxic potential of nicotine + other chemicals in e-cigarettes needs further study.

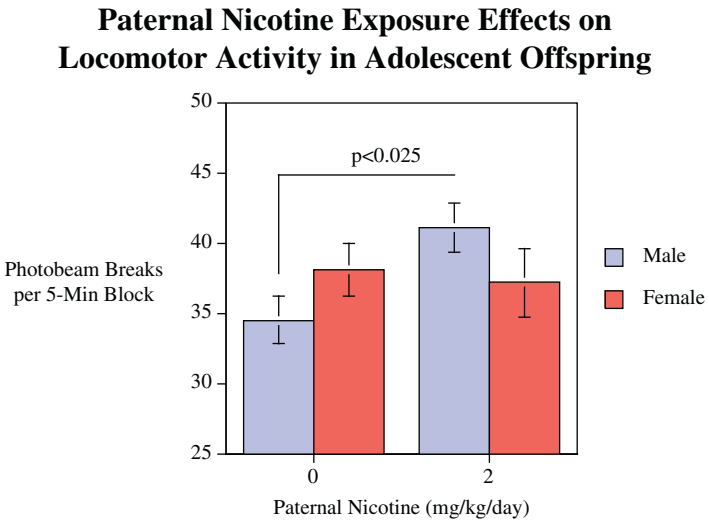

Fig. 3 Paternal pre-mating nicotine significantly increases locomotor activity in their male offspring (mean ± SEM) (Hawkey et al., 2019).

Pesticides have been found in tobacco (López Dávila et al., 2020). Pesticide neurotoxicity, especially with exposure during development, is very well characterized (Abreu-Villaça and Levin, 2017, 2018). Pesticide plus nicotine interactions have not been well enough studied. The rest of the very complex mixture of tobacco remains to be studied regarding its potentiation of nicotine's neurotoxicity. In initial studies our studies have found that nicotine together in the complex mixture of tobacco smoke extract produced greater neural and behavioral impairment than the same dose of nicotine alone (Hall et al., 2016). However, this tobacco smoke extract did not include the gaseous chemicals present in tobacco smoke. Carbon monoxide (CO) is of particular concern, given its known neurotoxic effects. There has been some earlier study of CO which also causes developmental neurotoxicity (Mactutus, 1989). However, the combined neurotoxicity of nicotine and CO and other constituents of tobacco smoke should be further studied.

In addition to the complex chemical exposure of nicotine from tobacco and e-cigarettes, nicotine is often taken together with other known neurotoxic drugs of abuse such as alcohol, opiates, stimulants and cannabis which is itself a complex mixture. How nicotine neurotoxicity might be exacerbated by these co-exposures needs further study.

Nicotine exposure might change neurotoxicity of other exposures later in life. Slotkin and colleagues found that prenatal nicotine altered neurotoxic changes to noradrenergic, serotonergic and cholinergic systems caused by later exposure to the organophosphate insecticide chlorpyrifos (Slotkin et al., 2015a,b; Slotkin and Seidler, 2015).

Nicotine is not the only nicotinic chemical that causes neurotoxicity. Neonicotinoid insecticides are becoming more widely used. Despite some research that did not find significant neurotoxicity from neonicotinoid insecticide exposure (Sheets et al., 2016) there is experimental evidence that neonicotinoid pesticide exposure like nicotine can cause long-lasting neurobehavioral toxicity after developmental exposure in zebrafish (Crosby et al., 2015) as well as neurotoxic effects in primary neural cultures from developing mice (Kimura-Kuroda et al., 2012) and lasting cognitive impairment after neonatal exposure in rats (Kara et al., 2015). Potential neurotoxic risks of neonicotinoid insecticides for potential neurotoxicity especially with early developmental exposure should be further investigated.

7. Summary and conclusions

Nicotine has proven neurotoxicity with exposure during development, both in pre and postnatal periods as well as during adolescence. The neurobehavioral toxicity caused by prenatal developmental nicotine/tobacco causes locomotor hyperactivity as well as cognitive impairment. Nicotine neurotoxicity during adulthood and aging periods of life appears to be less and there are potential therapeutic uses as a cognitive enhancer that are being investigated.

Primarily, nicotine has been characterized as a developmental neurotoxin. Nicotine exposure during prenatal development causes persisting neural and behavioral dysfunction. The rodent models shed light on the causative impact of nicotine and mechanisms of behavioral impairment. Adolescence is also a vulnerable period for nicotine neurotoxicity. Nicotinic receptor increases with chronic exposure are prolonged in adolescents and they show increased nicotine self-administration vs adults.

Acknowledgment

This research was supported by grants from the National Institutes of Health (ES022831), the U.S. Environmental Protection Agency (83543701) and the March of Dimes.

References

Abbott, L.C., Winzer-Serhan, U.H., 2012. Smoking during pregnancy: lessons learned from epidemiological studies and experimental studies using animal models. Crit. Rev. Toxicol. 42, 279–303.

Abreu-Villaça, Y., Levin, E.D., 2017. Developmental neurotoxicity of succeeding generations of insecticides. Environ. Int. 99, 55–77.

Abreu-Villaça, Y., Levin, E.D., 2018. Developmental neurobehavioral neurotoxicity of insecticides. In: Wang, C., Paule, M., Slikker W. Jr., (Eds.), Handbook of Developmental Neurotoxicology. Academic Press, San Diego, pp. 453–466.

Ajarem, J.S., Ahmad, M., 1998. Prenatal nicotine exposure modifies behavior of mice through early development. Pharmacol. Biochem. Behav. 59 (2), 313–318.

Broide, R.S., Salas, R., Ji, D., Paylor, R., Patrick, J.W., Dani, J.A., De Biasi, M., 2002. Increased sensitivity to nicotine-induced seizures in mice expressing the L250T alpha 7 nicotinic acetylcholine receptor mutation. Mol. Pharmacol. 61 (3), 695–705.

Buznikov, G.A., Slotkin, T.A., Lauder, J.M., 2003. Sea urchin embryos and larvae as biosensors for neurotoxicants. Curr. Protoc. Toxicol. Chapter 1, Unit 1.6.

Cauley, M., Hall, B.J., Abreu-Villaça, Y., Junaid, S., White, H., Kiany, A., Slotkin, T.A., Levin, E.D., 2018. Critical developmental periods for effects of low-level tobacco smoke exposure on behavioral performance. Neurotoxicology 68, 81–87.

Clapp, P.W., Jaspers, I., 2017. Electronic cigarettes: their constituents and potential links to asthma. Curr. Allergy Asthma Rep. 17 (11), 79.

Conners, C.K., Levin, E.D., Sparrow, E., Hinton, S.C., Erhardt, D., Meck, W.H., Rose, J.E., March, J., 1996. Nicotine and attention in adult attention deficit hyperactivity disorder (ADHD). Psychopharmacol. Bull. 32 (1), 67–73.

Crosby, E.B., Bailey, J.M., Oliveri, A.N., Levin, E.D., 2015. Neurobehavioral impairments caused by developmental imidacloprid exposure in zebrafish. Neurotoxicol. Teratol. 49, 81–90.

Damaj, M.I., Glassco, W., Dukat, M., Martin, B.R., 1999. Pharmacological characterization of nicotine-induced seizures in mice. J. Pharmacol. Exp. Ther. 291, 1284–1291.

DeBry, S.C., Tiffany, S.T., 2008. Tobacco-induced neurotoxicity of adolescent cognitive development (TINACD): a proposed model for the development of impulsivity in nicotine dependence. Nicotine Tob. Res. 10 (1), 11–25.

DeVito, E.E., Krishnan-Sarin, S., 2018. E-cigarettes: impact of E-liquid components and device characteristics on nicotine exposure. Curr. Neuropharmacol. 16 (4), 438–459.

Eshraghian, E.A., Al-Delaimy, W.K., 2021. A review of constituents identified in e-cigarette liquids and aerosols. Tob. Prev. Cessat. 7, 10.

Grandjean, P., Landrigan, P.J., 2014. Neurobehavioural effects of developmental toxicity. Lancet Neurol. 13, 330–338.

Hall, B.J., Cauley, M., Burke, D.A., Kiany, A., Slotkin, T.A., Levin, E.D., 2016. Cognitive and behavioral impairments evoked by low-level exposure to tobacco smoke components: comparison with nicotine alone. Toxicol. Sci. Off. J. Soc. Toxicol. 151 (2), 236–244.

Hawkey, A.B., White, H., Pippen, E., Greengrove, E., Rezvani, A.H., Murphy, S.K., Levin, E.D., 2019. Paternal nicotine exposure in rats produces long-lasting neurobehavioral effects in the offspring. Neurotoxicol. Teratol. 74, 106808.

Heath, C.J., King, S.L., Gotti, C., Marks, M.J., Picciotto, M.R., 2010. Corticothalamic connectivity is vulnerable to nicotine exposure during early postnatal development through alpha4/beta2/alpha5 nicotinic acetylcholine receptors. Neuropsychopharmacology 35 (12), 2324–2338.

Kara, M., Yumrutas, O., Demir, C.F., Ozdemir, H.H., Bozgeyik, I., Coskun, S., Eraslan, E., Bal, R., 2015. Insecticide imidacloprid influences cognitive functions and alters learning performance and related gene expression in a rat model. Int. J. Exp. Pathol. 96 (5), 332–337.

Kimura-Kuroda, J., Komuta, Y., Kuroda, Y., Hayashi, M., Kawano, H., 2012. Nicotine-like effects of the neonicotinoid insecticides acetamiprid and imidacloprid on cerebellar neurons from neonatal rats. PLoS One 7 (2), e32432.

King, S.L., Marks, M.J., Grady, S.R., Caldarone, B.J., Koren, A.O., Mukhin, A.G., Collins, A.C., Picciotto, M.R., 2003. Conditional expression in corticothalamic efferents reveals a developmental role for nicotinic acetylcholine receptors in modulation of passive avoidance behavior. J. Neurosci. 23 (9), 3837–3843.

Korpi, E.R., den Hollander, B., Farooq, U., Vashchinkina, E., Rajkumar, R., Nutt, D.J., Hyytiä, P., Dawe, G.S., 2015. Mechanisms of action and persistent neuroplasticity by drugs of abuse. Pharmacol. Rev. 67 (4), 872–1004.

Kwan, L.Y., Eaton, D.L., Andersen, S.L., Dow-Edwards, D., Levin, E.D., Talpos, J., Vorhees, C.V., Li, A.A., 2020. This is your teen brain on drugs: in search of biological factors unique to dependence toxicity in adolescence. Neurotoxicol. Teratol. 81, 106916.

Levin, E.D., Abreu-Villaça, Y., 2018. Developmental neurotoxicity of nicotine and tobacco. In: Wang, C., Paule, M., Slikker W. Jr., (Eds.), Handbook of Developmental Neurotoxicology. Academic Press, San Diego, pp. 439–452.

Levin, E.D., Conners, C.K., Sparrow, E., Hinton, S.C., Erhardt, D., Meck, W.H., Rose, J.E., March, J., 1996a. Nicotine effects on adults with attention-deficit/hyperactivity disorder. Psychopharmacology 123 (1), 55–63.

Levin, E.D., Wilson, W., Rose, J.E., McEvoy, J., 1996b. Nicotine-haloperidol interactions and cognitive performance in schizophrenics. Neuropsychopharmacology 15 (5), 429–436.

Levin, E.D., Rezvani, A.H., Montoya, D., Rose, J.E., Swartzwelder, H.S., 2003. Adolescent-onset nicotine self-administration modeled in female rats. Psychopharmacology 169, 141–149.

Levin, E.D., Lawrence, S., Petro, A., Horton, K., Rezvani, A.H., Seidler, F.J., Slotkin, T.A., 2007. Adolescent vs. adult-onset nicotine self-administration in male rats: duration of effect and differential nicotinic receptor correlates. Neurotoxicol. Teratol. 29, 458–465.

Levin, E.D., Slade, S., Wells, C., Cauley, M., Petro, A., Vendittelli, A., Johnson, M., Williams, P., Horton, K., Rezvani, A.H., 2011. Threshold of adulthood for the onset of nicotine self-administration in male and female rats. Behav. Brain Res. 225 (2), 473–481.

López Dávila, E., Houbraken, M., De Rop, J., Wumbei, A., Du Laing, G., Romero Romero, O., Spanoghe, P., 2020. Pesticides residues in tobacco smoke: risk assessment study. Environ. Monit. Assess. 192 (9), 615.

Mactutus, C.F., 1989. Developmental neurotoxicity of nicotine, carbon monoxide, and other tobacco smoke constituents. Ann. N. Y. Acad. Sci. 562, 105–122.

Marks, M.J., Burch, J.B., Collins, A.C., 1983. Effects of chronic nicotine infusion on tolerance development and nicotine receptors. J. Pharmacol. Exp. Ther. 226, 817–825.

McClernon, F.J., Hiott, F.B., Westman, E.C., Rose, J.E., Levin, E.D., 2006. Transdermal nicotine attenuates depression symptoms in nonsmokers: a double-blind, placebo-controlled trial. Psychopharmacology 189 (1), 125–133.

Newhouse, P.A., Kellar, K., Aisen, P., White, H., Wesnes, K., Coderre, E., Pfaff, A., Wilkins, H., Howard, D., Levin, E.D., 2012. Transdermal nicotine treatment of mild cognitive impairment: a six-month double-blind pilot clinical trial. Neurology 78, 91–101.

Polli, F.S., Kohlmeier, K.A., 2019. Alterations in NMDAR-mediated signaling within the laterodorsal tegmental nucleus are associated with prenatal nicotine exposure. Neuropharmacology 158, 107744.

Ren, M., Lotfipour, S., Leslie, F., 2022. Unique effects of nicotine across the lifespan. Pharmacol. Biochem. Behav. 214, 173343.

Ruszkiewicz, J.A., Zhang, Z., Gonçalves, F.M., Tizabi, Y., Zelikoff, J.T., Aschner, M., 2020. Neurotoxicity of e-cigarettes. Food Chem. Toxicol. 138, 111245.
Satarug, S., Moore, M.R., 2004. Adverse health effects of chronic exposure to low-level cadmium in foodstuffs and cigarette smoke. Environ. Health Perspect. 112 (10), 1099–1103.
Schrott, R., Rajavel, M., Acharya, K., Huang, Z., Acharya, C., Hawkey, A., Pippen, E., Lyerly, H.K., Levin, E.D., Murphy, S.K., 2020. Sperm DNA methylation altered by THC and nicotine: vulnerability of neurodevelopmental genes with bivalent chromatin. Sci. Rep. 10 (1), 16022.
Schwartz, R.D., Kellar, K.J., 1983. Nicotinic cholinergic binding sites in the brain: in vivo regulation. Science (New York, N.Y.) 220, 214–216.
Seidl, R., Tiefenthaler, M., Hauser, E., Lubec, G., 2000. Effects of transdermal nicotine on cognitive performance in Down's syndrome. Lancet 356 (9239), 1409–1410.
Sheets, L.P., Li, A.A., Minnema, D.J., Collier, R.H., Creek, M.R., Peffer, R.C., 2016. A critical review of neonicotinoid insecticides for developmental neurotoxicity. Crit. Rev. Toxicol. 46 (2), 153–190.
Slikker W., Jr., Xu, Z.A., Levin, E.D., Slotkin, T.A., 2005. Mode of action: disruption of brain cell replication, second messenger, and neurotransmitter systems during development leading to cognitive dysfunction—developmental neurotoxicity of nicotine. Crit. Rev. Toxicol. 35 (8-9), 703–711.
Slotkin, T.A., 2004. Cholinergic systems in brain development and disruption by neurotoxicants: nicotine, environmental tobacco smoke, organophosphates. Toxicol. Appl. Pharmacol. 198 (2), 132–151.
Slotkin, T.A., Seidler, F.J., 2015. Prenatal nicotine alters the developmental neurotoxicity of postnatal chlorpyrifos directed toward cholinergic systems: better, worse, or just "different?". Brain Res. Bull. 110, 54–67.
Slotkin, T.A., Skavicus, S., Levin, E.D., Seidler, F.J., 2015a. Prenatal nicotine changes the response to postnatal chlorpyrifos: interactions targeting serotonergic synaptic function and cognition. Brain Res. Bull. 111, 84–96.
Slotkin, T.A., Skavicus, S., Seidler, F.J., 2015b. Prenatal drug exposures sensitize noradrenergic circuits to subsequent disruption by chlorpyrifos. Toxicology 338, 8–16.
Slotkin, T.A., Stadler, A., Skavicus, S., Card, J., Ruff, J., Levin, E.D., Seidler, F.J., 2017. Is there a critical period for the developmental neurotoxicity of low-level tobacco smoke exposure? Toxicol. Sci. Off. J. Soc. Toxicol. 155 (1), 75–84.
Tizabi, Y., Getachew, B., Aschner, M., 2021. Novel pharmacotherapies in Parkinson's disease. Neurotoxicity Res. 39 (4), 1381–1390.
Trauth, J.A., Seidler, F.J., McCook, E.C., Slotkin, T.A., 1999. Adolescent nicotine exposure causes persistent upregulation of nicotinic cholinergic receptors in rat brain regions. Brain Res. 851 (1–2), 9–19.
Wang, B., Du, Y., 2013. Cadmium and its neurotoxic effects. Oxid. Med. Cell Longev. 2013, 898034.
White, H.K., Levin, E.D., 1999. Four-week nicotine skin patch treatment effects on cognitive performance in Alzheimer's disease. Psychopharmacology 143 (2), 158–165.
White, H.K., Levin, E.D., 2004. Chronic transdermal nicotine patch treatment effects on cognitive performance in age-associated memory impairment. Psychopharmacology 171 (4), 465–471.
Wright, R.O., Baccarelli, A., 2007. Metals and neurotoxicology. J. Nutr. 137 (12), 2809–2813.
Yamamoto, I., Otori, K., Inoki, R., 1966. Pharmacological studies on antagonists against nicotine-induced convulsions and death. Jpn. J. Pharmacol. 16 (4), 402–415.

Yanai, J., Brick-Turin, Y., Dotan, S., Langford, R., Pinkas, A., Slotkin, T.A., 2010. A mechanism-based complementary screening approach for the amelioration and reversal of neurobehavioral teratogenicity. Neurotoxicol. Teratol. 32 (1), 109–113.

Zhang, X., Wahlstrom, G., Nordberg, A., 1990. Influence of development and aging on nicotinic receptor subtypes in rodent brain. Int. J. Dev. Neurosci. 8 (6), 715–721.