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Neurotoxicity of e-cigarettes

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Abstract

It appears that electronic cigarettes (EC) are a less harmful alternative to conventional cigarette (CC) smoking, as they generate substantially lower levels of harmful carcinogens and other toxic compounds. Thus, switching from CC to EC may be beneficial for smokers. However, recent accounts of EC- or vaping-associated lung injury (EVALI) has raised concerns regarding their adverse health effects. Additionally, the increasing popularity of EC among vulnerable populations, such as adolescents and pregnant women, calls for further EC safety evaluation. In this state-of-the-art review, we provide an update on recent findings regarding the neurological effects induced by EC exposure. Moreover, we discuss possible neurotoxic effects of nicotine and numerous other chemicals which are inherent both to e-liquids and EC aerosols. We conclude that in recognizing pertinent issues associated with EC usage, both government and scientific researchers must address this public health issue with utmost urgency.

Keywords

e-cigarette; electronic cigarette; vaping; neurotoxicity; brain; neurodevelopment

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Declaration of interests

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1. E-cigarettes as an alternative to conventional tobacco products

Tobacco smoking is considered the most preventable disease cause worldwide (Samet, 2013). The association between tobacco smoking and pathological conditions, such as cancer, cardiovascular diseases or neurodevelopmental diseases is well established (Burns, 2003; Lagiou and Lagiou, 2017; Nguyen et al., 2018; Sales et al., 2019). Although the consumption of conventional cigarettes (CC) has decreased, alternatives such as electronic cigarettes (EC, widely known as e-cigarettes, e-cigs or vaping) emerged, and their usage in the last decade has increased (Dai and Leventhal, 2019).

EC are battery-operated devices designed to release vapors of nicotine and/or other substances to be inhaled in aerosolized form, intended to provide an analog sensation to tobacco smoking, absent actual smoke (Haddad et al., 2019; Tegin et al., 2018). The EC basic structure consists of a battery, a heating element, and a liquid containing cartridge. The increase in the airflow activates the heating element which is in contact with the liquid (e-liquid or e-juice). This results in liquid vaporization and formation of aerosol, which is released and inhaled by the user. When heated, some constituents in the e-liquid (e.g. particular solvents) can generate a vapor that closely resembles tobacco smoke. However, no burn or flame is generated, which means that carbon monoxide and many other toxic combustion products are not present in the aerosol (Hatsukami et al., 2019; Kaisar et al., 2016; Patil et al., 2019; Stone and Marshall, 2019; Zhang et al., 2018a).

Thus, EC are considered less harmful than smoking regular tobacco cigarettes (Amrock et al., 2015; Farsalinos and Polosa, 2014), and are marketed as an alternative, safe and effective form of smoking-cessation therapy. A recent randomized clinical trial has shown a higher rate (18%) of sustained (1 year) abstinence from CC when EC were used, whereas standard nicotine replacement therapies were less effective (9.9%) (Hajek et al., 2019). Other studies have shown weak, or negative effect of EC in encouraging smoking cessation (Kalkhoran and Glantz, 2016; Patil et al., 2019; Worku and Worku, 2019).

Even though EC are free of many hazardous substances generated by CC, they contain other chemicals that may be toxic (Farsalinos and Polosa, 2014; Gupta et al., 2019; Zulkifli et al., 2018). Moreover, an increasing number of cases of severe EC-linked lung injury (CDC, 2020) challenges the idea that EC are a safe alternative to CC.

2. Major health concerns associated with e-cigarettes

Since the primary patent filing in 2003 and further launch on the Chinese (2004), European (2006) and the US (2007) markets, the use of EC is continuously growing, especially among young individuals (MacDonald and Middlekauff, 2019; McCubbin et al., 2017; Tegin et al., 2018). Recent prevalence of EC consumption has been estimated at 3.5–5.5% in the general population, where most of the EC users were also recognized as CC smokers (Dai and Leventhal, 2019; Yoong et al., 2018). Of importance, during recent years (2014–2018) the prevalence of EC smoking in the general population has slightly declined or remained stable, but increased significantly (46.2%) among young adults (age 18–24), making EC the most common nicotine product used by young adults (data from the US) (Dai and Leventhal,

2019). An analogous trend has been observed for adolescents – an increased use from 0.6% in 2011 to 4.9% in 2018 among middle school students, and from 1.5% to 20.8% among high school students in the same period (Gentzke et al., 2019). Similar trends have also been described in Great Britain, Hong Kong, and Taiwan (Bauld et al., 2017; Chang et al., 2017; Chen et al., 2019; SAHM, 2020).

There are advantages to EC usage. For instance, it has been shown that abstaining from CC smoking by using EC may improve respiratory outcomes among ex-CC smokers (Campagna et al., 2016; Cibella et al., 2016; Polosa et al., 2014; Polosa et al., 2016a; Polosa et al., 2016b). Nonetheless, several cross-sectional surveys of adolescents have shown that EC use is associated with increased risks of respiratory and asthma symptoms and asthma-related school absenteeism (Cho and Paik, 2016; Choi and Bernat, 2016; McConnell et al., 2017; Wang et al., 2016). The association of EC use and self-reported chronic respiratory disorders has been also reported in adults (Perez et al., 2019; Wang et al., 2018; Wills et al., 2019). Clinical studies focusing on pulmonary changes following EC exposure have shown mixed results, with some studies reporting impaired respiratory outcomes (Chaumont et al., 2019; Marini et al., 2014; Meo et al., 2019; Vardavas et al., 2012) and others showing no significant changes (Boulay et al., 2017; Ferrari et al., 2015; Flouris et al., 2013; Polosa et al., 2017). However, increased incidence (recognized recently in the US as a nationwide outbreak) of EC or vaping product use-associated lung injury (EVALI) has raised significant concern. As of January 14, 2020, there were 2,668 hospitalized EVALI cases (including 60 deaths) and nearly half the patients required intensive care to treat respiratory failure (CDC, 2020). Most patients diagnosed with EVALI were younger than 35 years-of-age and have reported the use of EC products containing tetrahydrocannabinol (THC) (82%) acquired primarily from informal sources (78%). Therefore, the outbreak has been linked to EC products containing THC, although the precise cause of the disease remains unknown (see section 4.2.) (Blount et al., 2019; CDC, 2020; Ellington et al., 2020; King et al., 2020).

Another significant health hazard associated with EC usage is cardiovascular diseases (Benowitz and Fraiman, 2017). A cross-sectional analysis by the National Health Interview Survey revealed that daily EC use was linked to increased odds of myocardial infarction (Alzahrani et al., 2018). Several studies have examined the acute effects of EC on vascular function using biomarkers such as flow-mediated dilation (Carnevale et al., 2016), circulating endothelial progenitor cells (Antoniewicz et al., 2016), pulse wave velocity (Vlachopoulos et al., 2016), and others (Chaumont et al., 2018; Franzen et al., 2018), providing evidence for EC-induced vascular damage. Notably, the transient abnormalities of these biomarkers may represent pharmacological effect of nicotine (Benowitz and Burbank, 2016; Benowitz and Fraiman, 2017). Similarly, the main hemodynamic changes following acute EC exposure, such as increase in heart rate and blood pressure (Middlekauff et al., 2014; Vansickel and Eissenberg, 2013; Yan and D'Ruiz, 2015), or the acute cardiac sympathetic activation (Moheimani et al., 2017) were also associated with the presence of nicotine in EC aerosols.

The nicotine delivered EC systems may also have a detrimental effect on juveniles. EC are particularly popular among youngsters (Dai and Leventhal, 2019; Gentzke et al., 2019). The central nervous system (CNS) remains under continuous development and is associated with

intense experience-dependent plasticity in the prefrontal cortex, which regulates cognition, emotion, and decision-making (Bernheim et al., 2013; Dwyer et al., 2009; Yuan et al., 2015). The neuronal nicotinic acetylcholine receptors (nAChRs) are critical regulators of brain development, which exhibit higher expression pattern during CNS formation and maturation (Dwyer et al., 2008; Dwyer et al., 2009; Ehlinger et al., 2016). Therefore, nicotine is able to increase neuronal activity with a greater effect in the adolescent brain when compared to the adult (Ehlinger et al., 2016; Shram et al., 2007). Furthermore, chronic nicotine exposure during adolescence has long-term consequences on cognitive behavior associated with diminished cognitive function, which could lead to reduced attention span and enhanced impulsivity in adults (Counotte et al., 2011; Counotte et al., 2009; Trauth et al., 2000). EC associated nicotine exposure during adolescence leads to aberrant activation of nAChRs, and further lifelong changes in neuronal signaling, influencing behaviors such as addiction, cognition and emotional regulation (Tobore, 2019; Yuan et al., 2015). In fact, a strong negative association of white matter integrity with tobacco use by adolescents has been attributed to the increasing popularity of EC (Thayer et al., 2020). EC use has been linked to illicit drug use, mental health problems, and impulsivity in university students (Grant et al., 2019). EC have been shown to have greater addictive potential when compared to CC in educated young adults (Jankowski et al., 2019) (the mechanism behind nicotine addiction and neurotoxicity has been further elaborated in section 6.1). Vaping also potentiates some neurological conditions, such as increased frequency of epileptic seizures (Wharton et al., 2019).

A risk upon use of EC during pregnancy has also emerged (Scherman et al., 2018). One of the pioneering (US population-based) studies reported that the prevalence of daily EC use among pregnant women was relatively low (0,6 %; 2 of 326); however, it revealed numerous misconceptions about EC among pregnant women, for example, approx. 30% of pregnant women did not realize that EC contained nicotine or could be addictive (Mark et al., 2015). Moreover, several studies reported higher rate of EC usage among pregnant woman: 4.9% (Kurti et al., 2017), 6.8% (Cardenas et al., 2019a), 6,5–8.5% (Wagner et al., 2017), 7.0% (Kapaya et al., 2019), probably due to the common perception of EC as a safer alternative to CC. The detrimental effects of nicotine and other CC-derived chemicals on fetal development are well established (Bruin et al., 2010; Faber et al., 2017). However, the perception among pregnant women of EC as a minor or moderate health hazard (Ashford et al., 2016; McCubbin et al., 2017) might impair this positive trend. Although human studies investigating the impact of maternal vaping on offspring’s health are missing (Cardenas et al., 2019b; NAS, 2018), it is likely that nicotine and other toxicants released by EC present a health risk to the developing fetus. Indeed, EC use during pregnancy increased the risk of smallness-for-gestational-age (Cardenas et al., 2019a). Additionally, animal studies have shown that exposure to EC during early development impairs major organ system development and function. For instance, pregnant rats exposed to EC containing nicotine showed a marked decrease in blood flow in both maternal uterine and fetal umbilical circulation, which led to a reduction in offspring weight (Orzabal et al., 2019). Maternal EC exposure in mice has been shown to impair embryo implantation and cause weight reduction in female offspring (Wetendorf et al., 2019). Maternal exposure to EC has also been shown to negatively affect the offspring’s cardiac (Palpant et al., 2015), lung (Chen et al., 2018a)

and kidney (Li et al., 2019) development. The general impact of EC exposure on animal pregnancy and early development has been recently reviewed elsewhere (Greene and Pisano, 2019; Orzabal and Ramadoss, 2019), and known neurodevelopmental effects will be discussed in section 3.

Numerous studies suggest health hazards subsequent to EC usage especially in teenagers and pregnant women. This is due to the increasing popularity of EC with these groups, and simultaneously the higher vulnerability to nicotine and other chemicals present in EC vapors, affecting in particular the developing brain. Therefore, in this paper, we provide an overview of current findings regarding EC impact to the brain and we also discuss neurotoxic effects of chemicals found in both e-liquids and EC vapors (Figure 1).

3. E-cigarettes exposure affects the brain (animal studies)

3.1. Neurotoxicity of EC aerosols

Despite growing awareness of the potential hazard of EC usage, little is known about their neurotoxic effect. To date, only a few studies have addressed the neurotoxicity of EC, particularly during neurodevelopment. The impact of maternal exposure to EC aerosols on offspring cognitive performance has been evaluated in Balb/c mice. Dams were exposed during and after pregnancy to ambient air, EC aerosols with, or without nicotine. The study showed deficits in short-term memory, reduced anxiety and hyperactivity in offspring following maternal EC exposure (Nguyen et al., 2018). Interestingly, in human maternal CC exposure, particularly heavy smoking (>20 cigarettes/day) has been associated with increased anxiety and other internalizing behaviors in young children (Moylan et al., 2015). Memory deficits were likely caused by nicotine (stronger effect), while reduced anxiety (elevated plus maze tests) was observed in both groups exposed to EC aerosols with and without nicotine, which suggests the neurotoxic effect of other EC constituents. Moreover, exposure to nicotine-free EC aerosols significantly increased global DNA methylation soon after birth, affected histone acetyltransferases, and induced changes within genes linked to neurological activity (Nguyen et al., 2018). The effect of switching from a CC to EC during pregnancy has been also evaluated. One group of Balb/c female mice was exposed to tobacco CC smoke before gestation, during gestation and lactation, while another group was exposed to cigarette smoke before gestation, followed by EC aerosols during gestation and lactation. Continuous tobacco cigarette smoke exposure resulted in marked neurological deficits in the offspring, whereas switching to EC during pregnancy reduced neurological deficits, as compared to CC; however, some neurological damage was still observed. The offspring from mothers switching to EC exhibited normal exploration activity, but showed epigenetic changes – a decrease in global DNA methylation, aurora kinase (Aurk) A and B gene expression (important for cellular division), and a reduction in neuronal cell numbers in the hippocampus, as compared to the control (Nguyen et al., 2019). In a similar study, investigating the replacement of CCs to EC during gestation and lactation, the effect of nicotine, as well as L-carnitine (as a neuroprotectant) were evaluated. CC-induced upregulation of mRNA expression of neuropeptide Y (NPY), NPY Y1 receptor, proopiomelanocortin downstream components, and inducible nitric oxide synthase (iNOS), were normalized in Balb/c offspring due to replacement by EC (with nicotine), but only

partially normalized due to L-carnitine supplementation. Interestingly, nicotine-free EC exposure significantly increased mRNA expression of brain NPY and iNOS in pups (Chen et al., 2018b). Epigenetic changes were also observed in offspring of C57BL/6 mice dams exposed to aerosols from EC (with and without nicotine) during gestation and lactation. A comparison of global gene expression changes in the frontal cortex of EC-exposed offspring (one-month-old) revealed that the nicotine-free group (both males and females) had the highest number of unique gene expression changes. Transcriptome alterations in both sexes and treatment groups (with and without nicotine) were all significantly associated with downstream adverse neurobiological outcomes (based on ingenuity pathway analysis, IPA) (Lauterstein et al., 2016). In EC-exposed C57BL/6 mice pups, hippocampal gene expression of neurotrophins, nerve growth factor receptor and brain-derived neurotrophic factor (Bdnf), and serum levels of inflammatory markers, interleukin (IL): IL-1β, IL-2, and IL-6 were significantly reduced irrespective of nicotine presence (Zelikoff et al., 2018). Moreover, exposure to EC aerosols without nicotine enhanced expression of calcium-binding adaptor molecule 1, a specific marker of activated microglia, in the cornus ammonis 1 region of the hippocampus, but not in other brain regions. Analysis of genes associated with the CNS inflammation using frontal cortex transcriptome data revealed, that male offspring exposed early in life to EC aerosols without nicotine had 27 altered genes that overlapped with the IPA “affects inflammation of the CNS” molecule list, while females from the same group had 24 altered genes that fall into that criteria. For pups exposed to EC containing nicotine, in males 6 genes and in females 13 genes (from the list) were altered (Zelikoff et al., 2018). This effect might be due to the dual function of nicotine as both a developmental neurotoxicant and neuroprotectant (see section 4.1). Acute EC vapor exposure (without nicotine) for three days increased reactive oxygen species (ROS) formation in the frontal cortex and down-regulation (mRNA and protein) of a neuronal nitric oxide synthase NOS (nNOS) in whole brain of the adult C57BL/6 mice. Many of these changes were prevented by genetic deletion of phagocytic NADPH oxidase (NOX2), suggesting that EC vapors induce NOX2-dependent prooxidative and inflammatory milieu in the brain (Kuntic et al., 2019). Again, these studies demonstrate that EC components other than nicotine can cause damage to the brain. When the neurological effects of EC vapor *vs.* CC smoke exposure (three 30-min sessions/day for 7 weeks, producing similar nicotine exposure of 16.8 mg/day) was evaluated in young (one-month-old) male Balb/c mice, both EC and CC led to similarly elevated brain cotinine and nicotine levels, as well as urine cotinine levels. Moreover, both exposures caused the up-regulation of α4β2-containing nAChRs in different brain areas. Mice exposed to CC smoke showed a wide range of behavioral alterations, related to the withdrawal symptoms (locomotor activity, episodic memory, and emotional responses) 24 h after cessation, while mice exposed to EC showed less severe outcomes (Ponzoni et al., 2015). Adult male C57BL/6 mice exposed for 6 months to EC vapors containing nicotine (24 mg/ml) showed altered homeostasis of several neurotransmitters in the mesocorticolimbic areas: levels of dopamine decreased in the striatum, γ-aminobutyric acid (GABA) decreased in the frontal cortex, glutamate increased in the striatum, glutamine increased in both the striatum and frontal cortex, whereas no changes in serotonin levels were observed, suggesting that chronic EC use may result in the development of nicotine dependence (Alasmari et al., 2019). Exposure of adult male C57BL/6J mice to EC vapor (24 mg/ml nicotine) for 1 week decreased brain glucose uptake and glucose transporters

(GLUT) GLUT1 and GLUT3 expression under normoxic and ischemic conditions (Sifat et al., 2018). Similarly, 2 weeks exposure to EC (24 mg/ml nicotine) lead to the oxidative stress, loss of blood-brain barrier (BBB) integrity, neurovascular inflammation, and worsening of post-ischemic brain injury at the rate analogous to CC (Kaisar et al., 2017), which suggest that EC usage could enhance ischemic brain injury and/or stroke risk. EC exposure has also been shown to alter brain lipid profiles. Adult Sprague Dawley rats exposed to EC vapors (18mg/ml nicotine) for 4 or 8 weeks showed a significant increase in saturated fatty acids and decrease in cholesterol and oxysterols levels in the brain, which as authors suggest, could contribute to the development of neurodegenerative diseases (Cardenia et al., 2018).

3.2. Neurotoxicity of EC liquids

Besides vapor exposure, there is also a risk related to the ingestion of e-liquids – a few fatal, or near-fatal cases from purposeful or incidental e-liquid exposures have been reported (Belkoniene et al., 2019; Chen et al., 2015; Hua and Talbot, 2016; Ordonez et al., 2015; Payne et al., 2017; Thornton et al., 2014). Thus, the potential neurotoxicity of e-liquids should be also considered. When e-liquid (28 μl/kg of body weight) with, or without nicotine (0.5 mg/kg), has been intraperitoneally injected to adult rats for 4 weeks, it altered cognitive functions of animals, with the more pronounced effect in nicotine-free group, which corresponded larger decrease in hippocampal cell viability, when compared to nicotine-containing group. Yet, e-liquid treatment did not affect motor function and cortical cell viability in both groups (Golli et al., 2016). Toxicity of 35 commercially available EC refills at concentrations 0.001–1% has been compared *in vitro* in mouse neural stem cells (mNSC) and other cell types – human embryonic stem cells (hESC) and human pulmonary fibroblasts (hPF). Overall, hESCs and mNSCs were more sensitive to refill solutions than hPF. Refill products varied from non-cytotoxic to highly cytotoxic, demonstrating variability and the importance of evaluating multiple marketed samples. Interestingly, cytotoxicity was not correlated with nicotine levels, but with the number and concentration of flavor chemicals. Of note, doses applied in the study were 100 times lower (maximum concentration of 1%) than a potential dose of human exposure (Bahl et al., 2012). The possible molecular mechanism behind EC neurotoxicity was revealed in the recent *in vitro* study. In mNSCs, EC liquid and aerosol exposures (up to 24h, 0.3–1%) altered mitochondrial dynamics and mitochondrial membrane potential, caused mitochondrial hyperfusion and swelling (Zahedi et al., 2019). Moreover, EC induced increased production of mitochondrial superoxide levels, protein oxidation, mitochondrial DNA aggregation, and impaired autophagy clearance. Observed mitochondrial damage was likely due to impaired calcium homeostasis and attributed mostly to the nicotine presence. Despite excessive mitochondrial damage, mNSCs exposure to e-liquids and aerosols did not lead to mitophagy in most scenarios, except for the treatment with 1% menthol-containing EC group (Zahedi et al., 2019).

Taken together, exposure to EC aerosols and liquids may cause developmental delays, neurobehavioral changes and cognitive deficits, which imply their neurotoxic potential. On a molecular level, EC-induced changes in the brain were associated with massive epigenetic alterations, mitochondrial damage, oxidative stress, inflammation, calcium and

neurotransmitter dyshomeostasis (Figure 1). Interestingly, many detrimental effects of EC exposure were observed regardless of nicotine presence, suggesting either the neuroprotective role of nicotine or neurotoxicity of other EC constituents.

4. Neurotoxicity of e-liquid and EC aerosol constituents

ECs are generally considered safer than CC – the mainstream cigarette smoke delivered about 1500 times more harmful and potentially harmful constituents than EC aerosols (Tayyarah and Long, 2014). Albeit, the EC emission is not free from dangerous chemicals. Despite the absence of combustion products and toxicants such as carbon monoxide, and very low levels of tobacco-specific nitrosamines, EC may increase exposure to other toxic or potentially toxic compounds, some of them are not present in conventional tobacco smoke. Typically, EC liquid contains solvent carriers (>75%) – usually propylene glycol (PG) and/or vegetable glycerin (VG), water (20%), flavoring chemicals (10%), and nicotine (2%), and similar proportions of these constituents are found in EC-derived aerosols (Tayyarah and Long, 2014). Moreover, EC aerosols contain additional substances, such as formaldehyde and acrolein (Kaisar et al., 2016; Sleiman et al., 2016), and numerous trace substances, such as heavy metals, phenolic compounds, polycyclic aromatic hydrocarbons, and other, potentially harmful chemicals. The neurotoxic properties of common EC constituents have been reviewed.

4.1. Nicotine

Nicotine is the most studied constituent of EC exhibiting neurotoxic properties. The nicotine levels in e-liquids vary widely among products, with a range from 0 to 87.2 mg/ml (NAS, 2018). Actual nicotine intake is only partially dependent on the nicotine concentration in e-liquid. Other factors, such as device characteristics (e.g., generations/models, heat/power settings) and user behavior (e.g., experience, puff topography) are also important determinants of systemic nicotine exposure (DeVito and Krishnan-Sarin, 2018). There is substantial evidence that nicotine intake from EC among experienced users is equivalent to that from CC (NAS, 2018). A study measuring urinary and salivary nicotine equivalents in chronic EC users found that long-term use of EC is associated with roughly similar daily nicotine intake compared with CC users (Shahab et al., 2017). EC can deliver nicotine rapidly to the human brain, although brain nicotine accumulation from EC was smaller than that from CC in both males (24%) and females (32%) (Solingapuram Sai et al., 2019). Yet the effects of EC use on resting state functional brain connectivity and withdrawal symptoms were similar to those observed for CC, and other forms of nicotine administration, suggesting analogous addictive properties (Hobkirk et al., 2018). As described earlier (section 3), many neurological and neurodevelopmental effects observed in animals exposed to EC may be attributed to the nicotine neurotoxicity and its addictive properties (Alasmari et al., 2019; Javadi-Paydar et al., 2019; Li et al., 2018).

4.1.1. Neurotoxic effect of nicotine and mechanisms of nicotine addiction—

Developmental neurotoxicity of nicotine is well established – prenatal exposure of the fetus to nicotine is likely to disturb the balance of cholinergic transmission and hence result in various behavioral and developmental impairments in the offspring, as well as perinatal

morbimortality (Bruin et al., 2010; Cauley et al., 2018; Slikker et al., 2005; Slotkin and Seidler, 2015). General nicotine toxicity related to cholinergic overstimulation (Lott and Jones, 2019). Many psychopharmacological effects of nicotine are related to their addictive properties. Nicotine delivered by non-tobacco mode (EC) can be as popular or addictive as a CC. This is evidenced by the recent use of EC that are devoid of tobacco, but allegedly, provide pure nicotine (Alasmari et al., 2019). Nicotine as an addictive substance stimulates the central reward pathway, believed to be primarily driven by a select dopaminergic trajectory emanating from the ventral tegmental area (VTA) and terminating in nucleus accumbens (NACC), is commonly referred to as “mesolimbic reward pathway”. The significance of this pathway in conferring “pleasure” or “reward” by natural stimuli such as food or sex, or various addictive drugs was established decades ago (NIDA, 2016; Wise, 1996). More recently it has been demonstrated that deficits in this circuit is likely the cause of social interaction impairment in children with autism (Supekar et al., 2018).

The actions of nicotine are primarily mediated through nicotinic receptors. These receptors are ligand-gated ion channels that were first described at the neuromuscular junction and were extensively investigated due to their abundance in electric ray also called torpedo fish (Changeux, 2012; Keesey, 2005). Nicotinic receptors are also abundant in the autonomic ganglia and the CNS. However, the subunit structure of nicotinic receptors at these three sites differ from each other. Thus, at the neuromuscular junction, nicotinic receptors are either in the embryonic form, composed of α1, β1, γ, and δ subunits or in the adult form composed of α1, β1, δ, and ε subunits. In the autonomic ganglia, these receptors are primarily composed of α3–β4 subunit combination whereas in the CNS, the homomeric (all one type of subunit, e.g. α7) or heteromeric (at least one α and one β subunit combination) are the most abundant (Dani, 2015; Gotti et al., 2019). Currently, 12 different neuronal nicotinic receptor subunits (α2–α10 and β2–β4) have been identified. Neuronal nicotinic receptors, primarily composed of α4β2 subunit and strategically located in the VTA and NACC, are critically involved in mediating the rewarding effects of nicotine as well as dependence and addiction to it (Dani, 2015; Gotti et al., 2019). It has been demonstrated that α4 β2 and also α6-containing subunits in VTA and NACC are not only involved in addictive behavior of nicotine, but also other drugs, such as alcohol (Gotti et al., 2019; Mineur and Picciotto, 2008; Rahman et al., 2016; Tolu et al., 2017). Moreover, a recent study implicates α6 in nicotine-induced structural plasticity in mouse and human induced pluripotent stem cells -derived dopaminergic neurons (Collo et al., 2018).

4.1.2. Nicotine as a neuroprotectant and cognitive enhancer—In addition to their role in nicotine addiction, nAChRs have also been implicated in various neurological diseases such as Parkinson’s (PD), Alzheimer’s (AD), epilepsy, as well as neuropsychiatric disorders such as schizophrenia and depression (Brown et al., 2013; De Biasi, 2015; Dineley et al., 2015; Hurley and Tizabi, 2013; Tizabi, 2016; Tizabi and Getachew, 2017; Tizabi et al., 2010). Although in many studies, nicotine is presented as a neuroprotectant (Tizabi, 2016). In regard to depression, an antidepressant effect of nicotine has been well established by preclinical (Djuric et al., 1999; Kalejaiye et al., 2013; Semba et al., 1998; Tizabi et al., 2009; Tizabi et al., 2010; Tizabi et al., 1999; Tizabi et al., 2000), as well as few clinical studies (Cook et al., 2007; McClernon et al., 2006; Pomerleau and Pomerleau, 1992; Salin-Pascual

et al., 1995). Moreover, high incidence of smoking among depressed patients may be considered as an attempt at self-medication with nicotine, which also contributes to the difficulty in quitting smoking by such population (Cook et al., 2007; Edwards and Kendler, 2011; Moreno-Coutino et al., 2007; Spring et al., 2008). The antidepressant effects of nicotine are believed to be primarily mediated by α4-β2 and to some extent by α7 subtypes (Alzarea and Rahman, 2019; Barreto et al., 2014; Picciotto et al., 2015; Rahman, 2015). Neuroprotective effects of nicotine and its applicability to neurological disease, particularly PD has been documented (Hoskin et al., 2019; Tizabi and Getachew, 2017). In cellular models of substantia nigra neurons, nicotine has been shown to protect against salsolinol and aminochrome that selectively damage the dopaminergic cells (Copeland et al., 2007; Das and Tizabi, 2009; Munoz et al., 2012; Ramlochansingh et al., 2011). Nicotine protection against toxicity induced by iron (Fe) and manganese (Mn), excess of which has been implicated in PD, were also recently reported (Getachew et al., 2019). Earlier studies verified the protection of nicotine in PD-like symptoms induced by 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridin in various animal studies, including non-human primates (Quik et al., 2015; Quik et al., 2006). Postulated mechanisms of nicotine action include inhibition of astrocyte activation and hence inflammatory suppression (Bagdas et al., 2018; Liu et al., 2012; Patel et al., 2017), modulation of synaptic plasticity *via* interaction with the neurotrophic mediators, especially Bdnf (Bagdas et al., 2018; Edwards and Kendler, 2011; Hoskin et al., 2019; Liu et al., 2012; Patel et al., 2017; Quik et al., 2015). The latter mechanism may also be at least partially responsible for the antidepressant effects of nicotine (Bagdas et al., 2018; Liu et al., 2012; Patel et al., 2017; Quik et al., 2015). It is noteworthy that nicotine activation of presynaptic receptors on various neuronal networks can enhance the release of a number of neurotransmitters such as dopamine, norepinephrine, serotonin, and glutamate, all of which have been implicated in mood regulation (Gotti et al., 2019; Liu et al., 2018; Miller, 2019). Curiously, there exists a substantial co-morbidity between PD and depression, which poses a further challenge in treatment options as depression itself may be an indication of latent neurodegeneration, particularly in late life (Baquero and Martin, 2015; Burgut et al., 2006; Hurley and Tizabi, 2013). In addition, nicotine role in inflammatory processes, apoptosis, oxidative stress, protein aggregation, and neuroplasticity, may also extend its beneficial effects to other CNS diseases, such as autism schizophrenia, epilepsy or Tourette syndrome (De Biasi, 2015; Dineley et al., 2015; Tizabi, 2016; Tizabi et al., 2019).

Cognitive enhancing effects of nicotine have also been amply verified, as reviewed by (Besson and Forget, 2016). This contention is supported by a number of animal studies showing that nicotine can block or reverse the cognitive impairment induced by chronic stress (Andreasen et al., 2011; Shang et al., 2017); glutamate N-methyl-D-aspartate (NMDA) receptor antagonist (Andre et al., 2011; Jacklin et al., 2012); lipopolysaccharide (Wei et al., 2015) and methamphetamine (Vieira-Brock et al., 2015), as well a clinical study showing beneficial effects of nicotine patch in mild cognitive impairment (Newhouse et al., 2012).

In summary, nicotine is a neurotoxicant and highly addictive drug, but with great therapeutic potential in various neurodegenerative and neuropsychiatric disorders. However, beneficial,

neuroprotective effects of nicotine exposure may be easily nullified due to the presence in EC liquids and vapors, other harmful and neurotoxic compounds.

4.2. Solvents

The most common solvents and simultaneously the primary ingredients (>75%) of e-liquids are PG and/or VG (Tayyarah and Long, 2014). Additionally, other solvents in lower concentrations have been detected in commercial e-liquids (Hutzler et al., 2014), e.g. ethylene glycol (WHO, 2002). Both PG and VG are generally recognized as safe (GRAS) and approved by the Food and Drug Administration (FDA) by ingestion. Results of ninety-day rat study (funded by the tobacco industry) revealed low toxicity of inhaled PG/VG mixtures in a number of endpoints (measured in blood, lung, and liver), and only the addition of nicotine produced adverse effects (Phillips et al., 2017). Nevertheless, other studies provide evidence that at certain conditions PG/VG may produce adverse health effects. For glycerin and its pure form glycerol, animal studies have shown relatively low toxicity both in acute (Becker et al., 2019) and chronic exposures (Gad et al., 2006), also *via* inhalation (Renne et al., 1992), and toxic effects have been observed only due to dramatic overdose (Andresen et al., 2009; Traudt et al., 2014). For PG, a solvent widely applied in the pharmaceutical, cosmetic and food industry, an airway and ocular irritability from occupational exposure have been reported (Varughese et al., 2005; Wieslander et al., 2001). PG exposure has been associated with toxic effects on the peripheral system (LaKind et al., 1999; Levy et al., 1995) and the CNS disturbances, such as drowsiness and confusion (Arulanantham and Genel, 1978; Lim et al., 2014). There is a limited, but consistent evidence, that very high doses of PG administered orally or intravenously produce toxic effects in humans, related to osmotic changes in the blood, and lactic acid formation, secondary to the PG metabolism (Zosel et al., 2010). For example, PG is a common solvent for intravenous phenobarbitals used for the treatment of neonatal convulsions, thus such treatment may lead to PG levels exceeding safety thresholds (millimolar levels) (Pouwels et al., 2019), resulting in the developing brain damage. Single intraperitoneal injection of PG (2–10 ml/kg) induced widespread apoptosis in the brain of developing C57BL/6 mice at the rate similar to the damage induced by ethanol (Lau et al., 2012). High dose (70% and 35%) PG injections caused axonal degeneration and intraneural inflammation in the sciatic nerve of young female CD1 mice (Belavy et al., 2013), and low dose (0.5–5%) exposure stimulated release of calcium from mitochondrial stores in cerebrocortical synaptosomes isolated from Wistar rats (Satoh et al., 2004). Cytotoxicity of solvents depends on theirs concentrations – liquids containing PG and VG solutions up to 1% were not cytotoxic to mNSCs and other stem cells (Bahl et al., 2012), and aerosols produced from such liquids did not affect mitochondria integrity (Zahedi et al., 2019). However, when 80% PG/ 20% water mixture was aerosolized at 5V, it produced significant cytotoxicity in peripheral cell lines (Behar et al., 2018). When female Balb/c mice were exposed for 2 weeks to EC vapors from three different e-liquids containing PG 70%/glycerol 30%, PG 100%, or glycerol 100%, they showed altered expression of circadian molecular clock genes in the brain and other organs (e.g. liver or kidney). Considering the role of the circadian molecular clock in biological homeostasis and disease, these alterations could potentially facilitate the onset of adverse neurological conditions (Lechasseur et al., 2017). On the other hand, developmental

exposure to PG 100% vapors from EC in C57BL/6J mice reduced pups' body weight, but had no effect on neurobehavioral outcomes (Smith et al., 2015).

The toxicity of EC solvents may also reflect their pyrolytic properties. When heated in EC device (150–350°C), both PG and VG produce mist which contains numerous toxic carbonyls, such as acrolein, acetaldehyde, and formaldehyde in levels which may reach similar to those found in tobacco smoke (Conklin et al., 2018; Goniewicz et al., 2014; Hutzler et al., 2014; Jensen et al., 2015; Rubinstein et al., 2018; Sleiman et al., 2016). For example, formaldehyde is a well-established environmental neurotoxicant linked to neurodegeneration (Songur et al., 2010; Tulpule and Dringen, 2013). Additionally, during vaping at high voltage (5V) formaldehyde reacts with EC solvents and forms potentially toxic formaldehyde hemiacetal (Jensen et al., 2015; Salamanca et al., 2017). Acrolein is also a ubiquitous environmental pollutant linked to neurodegeneration, due to its pro-inflammatory and pro-oxidative properties (Wang et al., 2017). Analogously, acetaldehyde has been shown to be neurotoxic *via* oxidative stress (Yan et al., 2016), calcium dyshomeostasis (Cui et al., 2019) and NMDA receptor activation (Wan et al., 2000). Many other products of solvents pyrolysis found in EC vapor exhibit hazardous properties. These include: glycidol (Sleiman et al., 2016), which is a developmental neurotoxicant (Akane et al., 2014; Kawashima et al., 2017), and glyoxal and methylglyoxal (Sleiman et al., 2016), which are potent glycating agents mediating the formation of advanced glycation end-products , linked to neurodegeneration (Wetzels et al., 2017).

Another potentially toxic chemical used as solvent in EC is vitamin E acetate (α-tocopherol acetate; ester of α-tocopherol and acetic acid), which has recently been detected in the majority of THC-containing products and samples of lung fluid from EVALI patients (Blount et al., 2019; Lewis et al., 2019; Taylor et al., 2019), suggesting a possible link to this vaping-related illnesses. The FDA reports that most outbreak-associated THC products contain vitamin E acetate, at an average concentration of 50% (23– 88%) (it is used as THC solvent because of similar viscosity) (FDA, 2020). Vitamin E acetate is commonly used in the dietary supplements and in cosmetics as a precursor of vitamin E (Desmarchelier et al., 2013), and to date has not been associated with adverse health outcomes, and is recognized as GRAS (FDA, 2019) for ingestion only. Although the safety profile (including neurotoxicity) of vitamin E acetate inhalation is not known. In rats, unlike vitamin E, vitamin E acetate inhalation does not attenuate the inflammatory response to bacterial lipopolysaccharide toxicity in lungs (Hybertson et al., 2005). Additional studies to examine the effects of inhaling aerosolized vitamin E acetate are required.

4.3. Flavor chemicals

Numerous studies demonstrated that flavoring is an important factor for EC users (Audrain-McGovern et al., 2016; Nonnemaker et al., 2016). Flavoring is particularly appealing to youth and inexperienced smokers, which are more likely to initiate vaping through flavored products (Harrell et al., 2017; Krusemann et al., 2019; Schneller et al., 2019; Soneji et al., 2019; Zare et al., 2018). Moreover, recent data suggest that popular flavor chemicals may trigger a reward mechanism in mice (Avelar et al., 2019). Therefore, flavorings in EC are

currently one of the major targets for regulatory authorities, alarmed by an outbreak of EVALI and fatal cases particularly among young EC users (Layden et al., 2019).

Hundreds of different flavor chemicals have been detected in e-liquids, with several chemicals present in the majority of commercial products (Hua et al., 2019; Omaiye et al., 2019b). Although flavorants detected in EC are usually considered as GRAS in food products, they have not been safety tested for exposure routes other than ingestion and for chronic exposures, thus their perniciousness when aerosolized and inhaled is often unrecognized (Barrington-Trimis et al., 2016). In fact, numerous flavorings, e.g. menthol, menthone, maltol, ethyl maltol, vanillin, ethyl vanillin, cinnamaldehyde, ethyl cinnamate, benzyl alcohol, benzaldehyde, eugenol, p-anisaldehyde, triacetin, and 2,5-dimethypyrazine, have been effectively transferred to EC aerosols that may cause cytotoxicity, mostly to the respiratory system (Behar et al., 2018; Hickman et al., 2019; Hua et al., 2019; Kosmider et al., 2016; Omaiye et al., 2019a; Sassano et al., 2018; Sherwood and Boitano, 2016). Multiple studies have implied that the high number and concentration of flavor chemicals are critical for cellular and CNS toxicity of e-liquids (Behar et al., 2018; Cervellati et al., 2014; Hua et al., 2019; Otero et al., 2019). Nonetheless, no difference between various flavors of e-liquids was observed in eliciting neurobehavioral outcomes in mice (Nguyen et al., 2018), and to date, no other study has addressed neurotoxicity of EC-derived flavoring chemicals. Therefore, there is a huge gap in understanding the effect of flavorants delivered through the EC vapors on the brain, which urgently needs to be evaluated.

Yet, the possible neurotoxic effect of these substances can be predicted based on toxicity evoked in other conditions. For instance, Kaur *et al.* reviewed data on the toxicity of flavoring chemicals in tobacco and non-tobacco products in the context of pulmonary diseases, and discussed possible pathomechanisms associated with oxidative stress, inflammation and DNA damage (Kaur et al., 2018). Diacetyl and acetyl propionyl, found in the majority of commercial e-liquids and aerosols in levels exceeding the safety limits (Farsalinos et al., 2015a), have been linked to the occupational “popcorn” lung disease (Holden and Hines, 2016). Menthol and ethyl maltol have been found in some commercial EC refill fluids in levels respectively 30 and 100 times their cytotoxic concentration, while one refill product contained 34% of cinnamaldehyde, which was more than 100,000 times its cytotoxic level (Omaiye et al., 2019b). Menthol is a flavorant commonly found in CC. It is of low toxicity and is often used as a natural medicine for cold or pain. However, a case of fatal occupational exposure (Kumar et al., 2016), and a nearly fatal case of chronic exposure through menthol-rich cough droplets (Baibars et al., 2012) have been reported. Moreover, menthol may produce some powerful neurological effects (Henderson et al., 2017; Thompson et al., 2018) – it has been shown to affect cigarette smoking-related behaviors, and at the molecular level, to modulate nAChRs and alter nicotine metabolism, as reviewed in (Wickham, 2015). The other popular chemical flavorant in EC – farnesol has also been shown to produce reward-related behavior in male mice, associated with the upregulation of α6* nAChRs; it enhanced locomotor activity and affected dopaminergic and GABAergic transmissions (Avelar et al., 2019). Maltol toxicity has been shown in neuroblastoma cell lines derived from mouse (Neuro 2a) and human (IMR 32), and in primary murine fetal hippocampal neurons (Hironishi et al., 1996), although this flavorant can also act as neuroprotectant, attenuating oxidative stress and nuclear factor-κB (NF-κB)-dependent

signaling pathway (Mi et al., 2018; Song et al., 2015). Cinnamaldehyde is one of the most frequent flavorant in EC (Omaiye et al., 2019b), and cinnamaldehyde-containing e-liquids and aerosols have been shown to produce cytotoxicity, genotoxicity and adversely affect cellular functions at low concentrations in peripheral tissues (Clapp et al., 2017; Hickman et al., 2019; Sassano et al., 2018). For instance, at sub-cytotoxic concentrations, cinnamaldehyde decreased cell growth, attachment and spreading, altered cell morphology, motility, and increased DNA strand breaks in hPF (Behar et al., 2016). Cinnamaldehyde in e-liquids has been shown to alter mitochondrial function (respiration, glycolysis), reduce adenosine triphosphate (ATP) levels, and suppress ciliary beat frequency in bronchial epithelial cells (Clapp et al., 2019).

Several flavor chemicals may pyrolyze or react with other components of EC liquids and produce new, potentially harmful chemicals. For instance, flavor aldehydes, including benzaldehyde, cinnamaldehyde, citral, ethyl vanillin and vanillin rapidly react with PG after mixing, producing aldehyde PG acetals, detected in many commercial e-liquids (Erythropel et al., 2019). Up to 40% of flavor aldehyde content was converted to acetals, with 50–80% preservation in EC vapors, and these acetals were shown to activate aldehyde-sensitive irritant receptors and aldehyde-insensitive irritant receptors in human embryonic kidney cells HEK-293T (Erythropel et al., 2019). Interestingly, several flavor-derived chemicals may have protective properties. For example, sweeteners, such as sucrose, glucose, and sorbitol in EC yielded a significant amount of 5-hydroxymethylfurfural and furfural (Abraham et al., 2011; Adams et al., 1997; Soussy et al., 2016), which exhibit neuroprotective and antioxidant effect *via* activation of the nuclear factor erythroid 2-related factor 2 (Nrf2)/ antioxidant response element (ARE) signaling pathway (Ya et al., 2017), and apurinic/ apyrimidinic endonuclease/ redox factor-1 (Zhang et al., 2015). In addition, vanillin exhibits antioxidant activity beneficial in cancer therapy (Bezerra et al., 2016) and neuroprotection at a high dose (Ho et al., 2011; Yan et al., 2017).

4.4. Other organic compounds

Additional organic compounds exhibiting neurotoxic properties have been detected in e-liquids, e.g. toluene, p,m-xylene, ethyl acetate, benzene, ethanol, and methanol, with some exceeding safety limits (Lim and Shin, 2017). Benzene was detected in EC aerosols generated from different liquids and devices, reaching maximal levels of 5000 $\mu g/m^3$, which are significantly lower than from CC (200,000 $\mu g/m^3$), but still may produce adverse health effects, especially due to repeated exposures (Pankow et al., 2017). The increase in many toxic volatile organic chemicals has also been detected in the urine of adolescent EC users; however at levels lower than in CC/EC dual users (Rubinstein et al., 2018). Xylene, N,N-dimethylformamide (dimethylfuran), and acrylonitrile levels were higher in the urine of EC users than non-smokers (Lorkiewicz et al., 2019). Moreover, some cancerogenic tobacco-specific nitrosamines, e.g. N-nitrosonornicotine and 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone) have been detected in EC aerosols (Goniewicz et al., 2014) and in EC users (Bustamante et al., 2018; Kotandeniya et al., 2015), although at levels orders of magnitude lower than produced by CC. Potential carcinogenic and neurotoxic phthalates, diethyl phthalate and diethylhexyl phthalate , have been also found in e-liquids (Oh and Shin, 2015).

4.5. Heavy metals and other trace elements

Several neurotoxic heavy metals, such as arsenic (As), cadmium (Cd), lead (Pb), manganese (Mn), zinc (Zn), nickel (Ni), aluminum (Al), tin (Sn), chromium (Cr) and copper (Cu) have been found in EC vapors (Gaur and Agnihotri, 2019; Goniewicz et al., 2014; Halstead et al., 2019; Hess et al., 2017; Mikheev et al., 2016; Olmedo et al., 2018; Williams et al., 2015; Zhao et al., 2019). These metals mostly originate from components of EC atomizer (metallic coil), but may also be present in e-liquids (Beauval et al., 2016). Although the majority of studies have shown significantly lower concentrations of metals in EC vapors than in CC smoke (Goniewicz et al., 2014; Palazzolo et al., 2016), some of them were at similar, or even higher level, e.g. Ni (Halstead et al., 2019; Palazzolo et al., 2016; Williams et al., 2013), Cu (Lerner et al., 2015a), Cr (Halstead et al., 2019), Al and Pb (Williams et al., 2013), raising concerns about their health effect (Halstead et al., 2019; Olmedo et al., 2018). Although risk assessment analyses have shown that inhalation exposures to these metals in EC users are unlikely to exceed safety limits (Farsalinos and Rodu, 2018; Farsalinos et al., 2015b), EC-derived metals can contribute to the overall increase of the internal dose, as has been demonstrated for Cr, Ni (Aherrera et al., 2017), Cd and Pb (Jain, 2019). EC users showed also higher serum levels of selenium (Se), silver (Ag), vanadium (V), lanthanides and other rare earth elements (Badea et al., 2018). Thus, the use of EC may increase exposure to hazardous metals affecting human health (Gaur and Agnihotri, 2019). Moreover, mixtures of different metals and other components, even at levels that are considered below the individual the lowest-observed-adverse-effect level (LOAEL) can have additive or synergistic effects (Andrade et al., 2017; Karri et al., 2016). Albeit numerous metals detected in EC vapors exhibit neurotoxic properties when inhaled (Lebedova et al., 2018; Lucchini et al., 2012; Mate et al., 2017; Wallin et al., 2017), to date no study has specifically addressed the effects of EC-derived metals on the brain

4.6. Nanoparticles

The aerosol emitted by EC contains a high concentration of nanoparticles , which despite the small size (<100 nm), display a significant toxicological impact (Zoroddu et al., 2014). Nanoparticles have a bigger surface area per unit mass, increasing their catalytic potential when compared to larger particles. Moreover, small size allows easier penetration and transport through cellular barriers to various organs, including the brain. Nanoparticle exposure has been linked to developmental neurotoxicity (Umezawa et al., 2018; Wu et al., 2015; Zhang et al., 2018b) and other brain disorders (Engin and Engin, 2019; Mushtaq et al., 2015; Sharma and Sharma, 2012; Teleanu et al., 2019).

Typical EC generates high concentrations of nanoparticles and fewer bigger particles (<10 μm) when compared to CC smoke (Schripp et al., 2013). One puff of aerosol emitted from one type of EC device contained approximately 2×10^6 nanoparticles/cm^3 (<100 nm), particularly of toxic metals, such as Sn, Cr and Ni (Williams et al., 2013). In another study, emission from different e-liquids contained 10^7–10^8 nanoparticles/cm^3 (5–50 nm), with metals representing approximately 10% of the total nanoparticle mass, while the rest were unknown chemicals (Mikheev et al., 2016). Interestingly, the emission of nanoparticles was dependent on the flavor – it was significantly higher for tobacco-flavored EC than for menthol-flavored EC (Lee et al., 2017). The chemical content and subsequent health hazards

of EC-derived nanoparticles require further investigation. Yet one conclusion can be drawn – the smaller the particle size, the higher its ability to produce free radicals (Abdal Dayem et al., 2017), which are additional harmful components of aerosols emitted by EC.

4.7. Free radicals

Many EC constituents, like metallic coil, metals, solvents, flavorings and other components of e-liquids, trigger the generation of harmful free radicals and ROS (Tobore, 2019). Thus, EC users may be exposed to ROS, which in excess cause oxidative stress, a key factor contributing to aging and many diseases, including neurodevelopmental (Dowell et al., 2019; Rock and Patisaul, 2018) and neurodegenerative disorders (Carvalho et al., 2017; Singh et al., 2019). Smoking-related cerebral oxidative stress is a potential mechanism promoting neurodegeneration and increased risk for neurodegenerative diseases (Durazzo et al., 2016).

Activating the EC heating element and aerosolizing the e-liquid produce ROS which may be inhaled and circulate in the body. The amount of ROS produced by EC is generally lower than in CC smoke (10–1000 times) (Goel et al., 2015; Ito et al., 2019; Shein and Jeschke, 2019; Son et al., 2019; Zhao et al., 2018), although considering different usage patterns, the daily exposure could be of comparable levels (Son et al., 2019). Moreover, several conditions (Lerner et al., 2015a) and the new generation of high power EC devices (Haddad et al., 2019) promote the generation of ROS levels analogous to CC. In addition to device settings, e-liquid composition affects the amount of ROS produced – higher ROS emission in EC vapors is dependent on concentration of VG (Haddad et al., 2019; Son et al., 2019) and flavors (Lerner et al., 2015b; Son et al., 2019), but not nicotine (Haddad et al., 2019). Moreover, the age and stage of the EC heating element can affect ROS emission (Lerner et al., 2015b).

EC vapors induce ROS production *in vitro* in the respiratory system (Anderson et al., 2016; Chatterjee et al., 2019; Ganapathy et al., 2017; Lee et al., 2019; Putzhammer et al., 2016; Scott et al., 2018; Zhao et al., 2018) and other cell types (Di Biase et al., 2018; Shaito et al., 2017). EC-induced oxidative stress is linked to the toxicity of EC vapors in mice lungs (Lerner et al., 2015b), liver (Espinoza-Derout et al., 2019), and rat testicles (Vivarelli et al., 2019). Moreover, increased ROS production and other oxidative stress markers are found in the serum of young healthy individuals using EC for a short time (acute exposure) (Chatterjee et al., 2019). The effect of EC and CC aerosol extracts on cerebrovascular function was evaluated in mouse brain microvascular endothelial cells (mBMECs). Both extracts showed similar properties – increased intracellular ROS levels as well as the expression of Nrf2 and its downstream effector (Sivandzade and Cucullo, 2019). Moreover, both extracts decreased BBB integrity and increased permeability, however, the effect was stronger for CC exposure (Sivandzade and Cucullo, 2019). Similarly, EC and CC treatment promoted ROS-associated mitochondrial depolarization in the vascular endothelial cell line bEnd.3, but only CC induced mitochondrial depolarization in mBMECs, and both exposures upregulated the transmembrane Fe exporter Slc40a1, which is crucial for maintaining cellular Fe and redox homeostasis (Kaisar et al., 2018).

5. Conclusions and perspectives

To date, no published study has evaluated the effects of EC exposure on brain function, and only a few studies have addressed this issue in animals. For instance, mice studies revealed that EC exposure during pregnancy affects neurobehavioral outcomes in offspring, characterized by deficits in short-term memory or anxiety. At the molecular level, EC exposure induced broad epigenetic alterations, mitochondrial dysfunction, inflammation, oxidative stress, calcium, and neurotransmitter dyshomeostasis, all of which may account for the EC associated neurotoxic effects (Figure 1). In addition to nicotine, numerous neurotoxic chemicals, particles, and radicals have been found in EC liquids and aerosols. Some of them may pose a potential hazard for EC users due to their presence at levels exceeding safety limits (e.g. flavorants diacetyl and acetyl propionyl). Others, which are present at low concentrations (e.g. heavy metals), may seem harmless, but due to the cumulative, synergistic effects of various factors that exhibit analogous properties, and target toxic pathways such as induction of oxidative stress, mitochondrial impairment, or inflammation, may also contribute to the neurological outcomes observed following EC exposure. However, studies are limited and oftentimes do not adequately reflect real-life scenarios; for instance, little is known about the long-term effects of EC use. One of the major difficulties in studying EC toxicity is a broad heterogenicity in the composition of e-liquids available on the market. The lack of regulation governing e-liquid formulations has led to a situation when dozens of different solvents, hundreds of flavorants, and great variability in nicotine concentrations may be found in such products. That makes it extremely difficult to determine the composition and levels of chemicals released in aerosols, and subsequently, identify the possible cause of health problems related to EC exposure (e.g. EVALI). This causes also barrier for standardization of experimental designs or comparison of the experimental outcomes.

Another important public health issue related to EC is its increasing popularity among adolescents and pregnant women. Modern design, attractive flavoring, and common belief that EC are a safe alternative to conventional tobacco products, make EC appealing particularly to younger generations. And that may have severe consequences on the health of these vulnerable populations. Additional research is needed in order to fully estimate both the overall safety of EC usage and its specific effects on the brain. Although from the data available we can already conclude that EC should not be ignored as a potential health hazard, and current guidelines regarding EC use should be carefully reconsidered. Future studies should be profitably directed at the aforementioned issues. Ultimately, a balance should be struck between science and technology development, while recognizing pertinent issues associated with EC usage, with government and scientific researchers addressing this public health in an urgent manner.

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Abbreviations

AD	Alzheimer’s disease
Ag	silver
Al	aluminum
ARE	antioxidant response element
As	arsenic
ATP	adenosine triphosphate
Aurk	aurora kinase
BBB	blood-brain barrier
Bdnf	brain-derived neurotrophic factor
CC	conventional cigarettes
Cd	cadmium
CNS	central nervous system
Cr	chromium
Cu	copper
EC	electronic cigarettes
EVALI	electronic cigarette or vaping product use-associated lung injury
FDA	Food and Drug Administration
Fe	iron
GABA	γ-aminobutyric acid
GLUT	glucose transporters
GRAS	generally recognized as safe
hESC	human embryonic stem cells
hPF	human pulmonary fibroblasts
iNOS	inducible nitric oxide synthase
IL	interleukin
IPA	ingenuity pathway analysis
LOAEL	lowest-observed-adverse-effect level
mBMECs	mouse brain microvascular endothelial cells

Mn	manganese
mNSC	mouse neural stem cells
NACC	nucleus accumbens
nAChRs	nicotinic acetylcholine receptors
Ni	nickel
NMDA	N-methyl-D-aspartate
NOX2	NADPH oxidase
NF-κB	nuclear factor-κB
nNOS	neuronal nitric oxide synthase
NPY	neuropeptide Y
Nrf2	nuclear factor erythroid 2-related factor 2
Pb	lead
PD	Parkinson’s disease
PG	propylene glycol
ROS	reactive oxygen species
Se	selenium
Sn	tin
THC	tetrahydrocannabinol
V	vanadium
VG	vegetable glycerin
VTA	ventral tegmental area
Zn	zinc

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Highlights

- Electronic cigarettes (EC) are marketed as alternatives to conventional cigarette (CC) smoking
- However, recent accounts of EC- or vaping-associated lung injury (EVALI) have raised concerns regarding their adverse health effects.
- The increased popularity of EC among vulnerable populations, such as adolescents and pregnant women, calls for further safety evaluation.
- EC may have neurotoxic effects due to nicotine and other chemicals inherent both to e-liquids and EC aerosols.

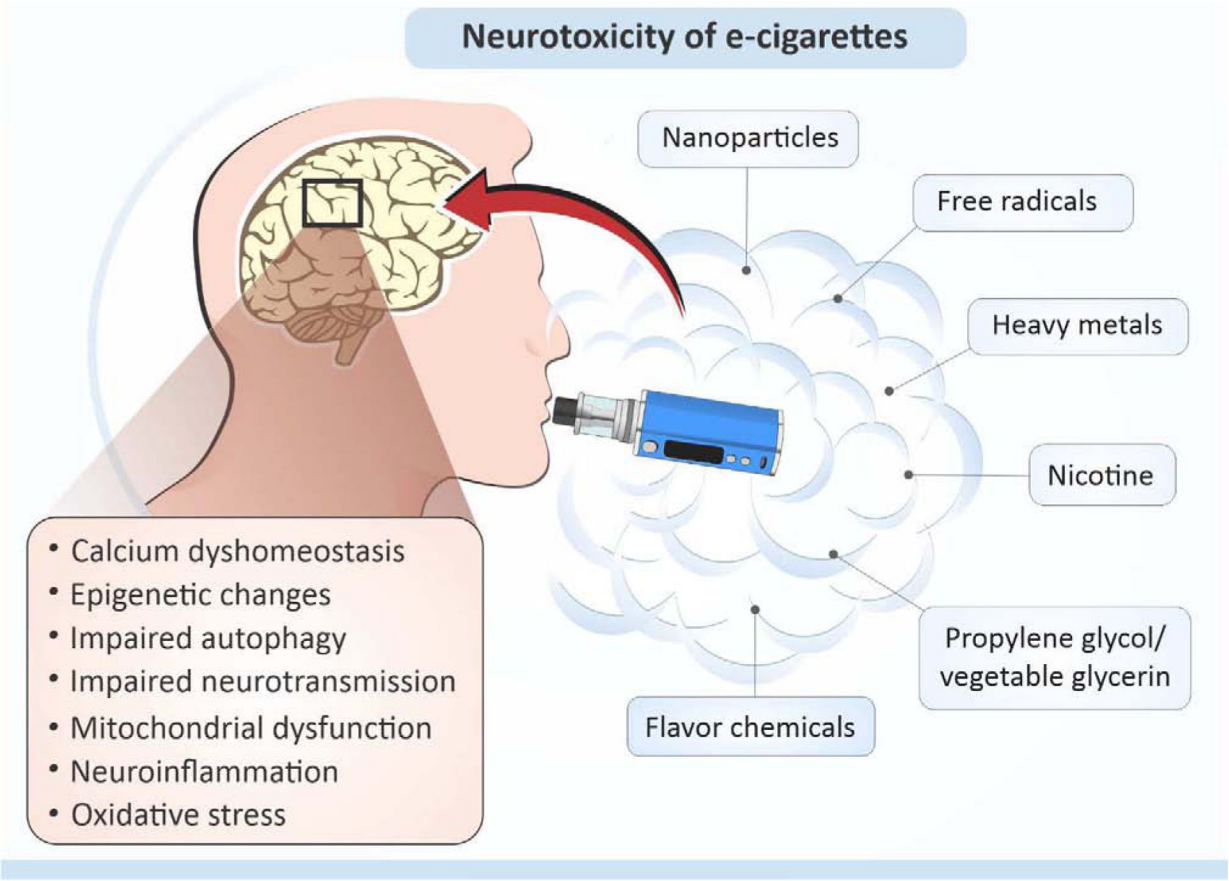

Figure 1.
Neurotoxic effects of compounds found in e-cigarettes (see text for details).