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Recent Findings in the Pharmacology of Inhaled Nicotine: Preclinical and Clinical In Vivo Studies

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Abstract

Introduction: The rise of vaping in adolescents, the recent entrance of new inhaled nicotine products such as iQOS on the market and e-cigarette or vaping product use-associated lung injury cases has created concern for the use of inhaled non-combustible nicotine products. This narrative review discusses recent experimental in vivo studies that utilize human, rat and mouse models to understand the pharmacological impact of nicotine from non-combustible products.

Methods: The search engine PubMed was utilized with the following search terms: inhaled nicotine, nicotine e-cigarette, heated tobacco products, iQOS, electronic cigarette, nicotine inhaler, nicotine vaping. This review highlights recent primary in vivo studies of inhaled nicotine administration experimental paradigms that occurred in laboratory settings using human and rodent (rats and mice) models that have been published from January 2017-December 2019.

Results: The pharmacokinetics of nicotine via e-cigarettes is influenced by the PG/VG and flavor constituents in e-liquids, the presence of nicotine salts in e-liquids, puff topography of nicotine and tobacco product users and the power of the e-cigarette device. The pharmacodynamic impact of inhaled nicotine has cardiovascular, pulmonary and central nervous system implications.

Conclusion: The articles reviewed here highlight the importance of both animal and human models to fully understand the impact of inhaled nicotine pharmacology There is a need for more rodent pharmacokinetic inhaled nicotine studies to understand the influences of factors such as flavor and nicotine salts. Additionally, consensus on nicotine measurement in both human and rodent studies is greatly needed.

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1. Introduction

Nicotine, the alkaloid found in the tobacco plant, is the primary mediator of rewarding effects in tobacco and nicotine products (De Biasi and Dani, 2011). These products include inhaled combustible products (cigarettes, cigarillos, cigars), orally administered products (nicotine gum snus, chewing tobacco), and inhaled non-combustible products (electronic cigarettes, heated tobacco). Of the multiple forms of nicotine delivery, inhaled non-combustible products are a recent concern with e-cigarette use in adolescents being considered an epidemic (Cullen et al., 2019), the rise of e-cigarette or vaping product use-associated lung injury (EVALI) cases (Perrine et al., 2019) and the onset of sales of newer inhaled non-combustible products such as the heated tobacco system IQOS(Mallock et al., 2019). There are reviews focusing on e-cigarette respiratory effects(Gotts et al., 2019; Javed et al., 2017), e-cigarette cardiovascular effects(Benowitz and Burbank, 2016; Buchanan et al., 2020; MacDonald and Middlekauff, 2019; Qasim et al., 2017), pharmacokinetics of nicotine(Caldwell et al., 2012; Fearon et al., 2018; Schroeder and Hoffman, 2014) and characteristics of e-cigarettes that influence inhaled nicotine exposure(Breland et al., 2017; Devito and Krishnan-Sarin, 2018).

However, given the constantly evolving landscape of inhaled nicotine products that are available on the market, this review will highlight recent findings in inhaled nicotine administration experiments. The search engine PubMed was utilized with the following search terms: inhaled nicotine, nicotine e-cigarette, heated tobacco products, iQOS, electronic cigarette, nicotine inhaler, nicotine vaping. These terms are used to described inhaled nicotine products in the NIH and FDA collaborative national survey, Population Assessment of Tobacco and Health study(NIH) and the CDC (CDC). English language abstracts or full text publications were reviewed. Publications were excluded from this review that covered: 1) only in vitro studies, 2) had subjects other than mice, rats, humans, 3) epidemiological studies or 4) studies only with an observational exposure design where participants used nicotine and tobacco products outside of the laboratory, 5) and studies that only conducted secondary analyses of clinical experimental studies. Additionally, since there have been reviews that have focused on the characteristics that influence nicotine exposure with the inhaled nicotine product e-cigarettes (Breland et al., 2017; Devito and Krishnan-sarin, 2018), to prevent overlap, only articles published from January 2017-December 2019 were included. The articles selected in this narrative review were primary in vivo studies of inhaled nicotine administration experimental paradigms (e-cigarettes, nicotine aerosol, nicotine inhalers and heated tobacco products) that occurred in laboratory settings using human and rodent (rats and mice) models published between January 2017-December 2019. This review is divided into two main sections: Pharmacokinetics and Pharmacodynamics. In both sections animal and human studies will be discussed if available. The pharmacokinetic section mostly consists of human studies because there is a lack of inhaled nicotine pharmacokinetic studies conducted in animals. The pharmacokinetic section is divided by nicotine devices. The pharmacodynamic section mostly consists of animal studies because there are a lack of recent inhaled nicotine pharmacodynamic studies conducted in humans. Pharmacodynamics is defined as the impact a drug has on the body, therefore, the

pharmacodynamics section was organized into biological systems (i.e. pulmonary, cardiovascular, etc.).

2. Pharmacokinetics

Pharmacokinetics (a component of pharmacology) is defined as the movement of drugs throughout the body and is composed of 4 steps: absorption, distribution, metabolism and excretion(Benet and Zia-Amirhosseini, 1995). The studies highlighted in this section will focus on nicotine absorption in human and animal models. In inhalation nicotine exposure experiments nicotine assessment in biological samples is used to validate nicotine administration compared to placebo (DeVito et al., 2019; Espinoza-derout et al., 2019; Krishnan-Sarin et al., 2017; Shi et al., 2019),examine the impact of variables (propylene glycol/vegetable glycerin levels, flavor constituents, puff topography, etc.) on nicotine absorption(Crotty Alexander et al., 2018; Hiler et al., 2017; Laube et al., 2017; Maloney et al., 2019; Montanari et al., 2019; Phillips et al., 2018; Shao et al., 2017; Spindle et al., 2018; St.Helen et al., 2017; Voos et al., 2019b),compare differences with inhaled vs other routes of nicotine administration on absorption (Javadi-paydar et al., 2019; Lefever et al., 2017) or compare different nicotine and tobacco products (Breland et al., 2019; Maloney et al., 2019; Nabavizadeh et al., 2018; Phillips et al., 2019, 2018; St. Helen et al., 2019; Teichert et al., 2018). The following are studies that assessed nicotine in biological samples to validate nicotine administration compared to placebo. In humans, it has been shown that under directed puffing bout conditions (1 puffing bout=10 puffs, 3 sec each, 30 sec puff interval) with e-cigarettes, 12mg/ml nicotine e-liquids resulted in higher salivary nicotine levels than 6mg/ml(Krishnan-Sarin et al., 2017). Additionally, plasma nicotine assessment has been used to validate nicotine exposure where plasma nicotine levels increased in participants post exposure of 24mg/ml of nicotine in e-cigarettes in comparison to the 0mg/ml nicotine condition (DeVito et al., 2019). Apolipoprotein-E knockout mice (model of atherosclerosis) were shown to have an increase in plasma cotinine levels after exposure to 12 weeks of e-cigarette aerosol containing 2.4% nicotine compared to saline aerosol exposure(Espinoza-Derout et al., 2019). Furthermore, C57BL/6 mice demonstrated higher plasma cotinine levels after exposure to 24mg/ml nicotine aerosol for 14 days compared to air exposed mice (Shi et al., 2019).

There are multiple variables that have been shown to impact nicotine pharmacokinetics. This section will highlight the impact of factors influencing e-cigarette pharmacokinetics [propylene glycol/vegetable glycerin (solvents used in nicotine delivery of e-cigarettes)], flavor constituents, puff topography behaviors, e-cigarette device power, the form of nicotine administered (freebase nicotine vs nicotine salts), the nicotine inhaler device and heated tobacco products. The pharmacokinetic section mostly consists of human studies because there is a lack of inhaled nicotine pharmacokinetic studies conducted in animals.

2.1. E-cigarettes

E-cigarettes are inhaled nicotine delivery systems that also contain flavors and other constituents(Breland et al., 2017). The below factors will be discussed that alter nicotine pharmacokinetics with e-cigarettes.

2.1.1. Propylene glycol/ Vegetable glycerin levels—E-cigarettes utilize e-liquids that contain propylene glycol(PG) and vegetable glycerin(VG) (Devito and Krishnan-sarin, 2018). PG is thought to enhance the throat irritation or “throat hit” of e-liquids (Smith et al., 2019) and VG increases the exhaled aerosol (Li et al., 2016). There are various combinations of PG and VG ratios found in e-liquids on the market (Breland et al., 2017) but little is known about the impact of these components on nicotine absorption in e-cigarettes. A study in humans demonstrated that when e-cigarette users administer 10 directed puffs (30 sec interpuff interval) of an e-cigarette that contains 18mg/ml of nicotine with various PG:VG ratios (2PG:98VG, 20PG:80VG, 55PG:45VG, 100PG), there were higher plasma nicotine levels from the PG based e-liquids compared to the VG based e-liquids (Spindle et al., 2018).

2.1.2 Flavor Constituents—Flavor additives in inhaled non-combustible nicotine products such as e-cigarettes have been reported to increase the liking and rewarding effects of these products (Camenga et al., 2017; Devito et al., 2019; Kong et al., 2015; Leventhal et al., 2019; Villanti et al., 2017). The addition of flavor additives in e-liquids may be added to counteract the effects of nicotine. Nicotine in e-cigarettes increase perceived irritation and bitterness in humans (Pullicin et al., 2019). Clinical experimental studies have shown that menthol partially reduces the self-reported aversiveness of 24mg/ml nicotine in smokers undergoing directed puffing bouts (3 puffs per flavor, 4 sec each) (DeVito et al., 2019). In addition, compared to tropical fruit and cream e-liquid flavors, menthol in combination with 36mg/ml of nicotine reduced cigarette smoking urges using a two puffing bout e-cigarette exposure procedure (1 puffing bout=10 puffs)(Cobb et al., 2019).

Furthermore, menthol additive has also been shown to increase the liking of the 12mg/ml of nicotine (Krishnan-Sarin et al., 2017). Menthol and fruit flavor was also preferred compared to tobacco flavor with an e-cigarette paradigm where never smokers and current smokers were exposed to 2 puffs per flavor (1 puff = 4 second inhalation, 1 second hold, 2 second exhale) (Leventhal et al., 2019). Flavor additives have also been shown to have an impact on nicotine intake. It has been shown that 180 min. after a directed puffing bout (15 puffs) strawberry flavor in combination with 19.9mg/ml of nicotine had a significantly higher area under the curve (AUC) in participants compared to tobacco flavor in combination with 19.3mg/ml of nicotine in e-liquids. In addition, the 90 min. ad lib e-cigarette exposure session in this study demonstrated that strawberry e-liquid exposure produced higher nicotine levels than tobacco flavored e-liquids (St. Helen et al., 2017). In another study nicotine delivery of 24mg/ml of nicotine was investigated in combination with cherry, tobacco, menthol, expresso, and vanilla flavors in a directed puffing experiment (20 puffs total every 30 sec). The cherry-flavored e-liquid delivered the highest Cmax (median = 21.2 ng/ml), while vanilla delivered the lowest Cmax (median = 9.73 ng/ml). In this study, there was no restriction on puffing duration and it was shown that puffing duration was shortest for tobacco but longest for menthol flavor(Voos et al., 2019b). Additionally, during an ad-lib session, subjects puffed more from fruit flavored e-liquids than menthol flavored (DeVito et al., 2019).

2.1.3 Puff Topography—Puffing behaviors or topography differs depending on the tobacco or nicotine product an individual consumes (Evans and Hoffman, 2014; Jesus et al., 2013; Pickworth et al., 2017) and on their experience with tobacco and nicotine products such as e-cigarettes (Devito and Krishnan-sarin, 2018; Vansickel et al., 2018). Puff topography measurements such as puff duration, interpuff interval, puff volume and the number of puffs have been shown to be related to nicotine exposure (Behar et al., 2015; Lopez et al., 2016; St.Helen et al., 2016). A directed puffing and ad-lib e-cigarette study found that experienced e-cigarette users had larger puff volumes, longer puff durations and interpuff intervals during the ad-lib session compared to the directed puffing bout session with 12mg/ml nicotine e-liquid (Spindle et al., 2017). Additionally, puff topography differs based on the power of the e-cigarette device. A recent study where participants underwent a 30 min. e-cigarette exposure ad-lib session shows that the number of puffs and puff duration was lower when the e-cigarette device was set at 10W compared to 6W when using the participants' own nicotine-containing e-liquids (Farsalinos et al., 2018). It has also been demonstrated that participants take shorter puffs when exposed to 100% PG e-liquid solutions with 18mg/ml of nicotine compared to other e-liquid conditions (20PG:80VG, 55PG:45VG, 2PG:98VG), but still had the highest total nicotine exposure when administering PG based e-liquids (Spindle et al., 2018). During another study with a directed e-cigarette two puffing bout procedure, experienced e-cigarette users (self-reported e-cig use for ≥ 3 months) took longer puffs and had significantly higher plasma nicotine levels compared to e-cigarette naïve smokers (≥ 10 cigarettes per day, < 5 ECIG uses lifetime) when consuming the same e-liquid nicotine concentration(Hiler et al., 2017). Participants took longer and larger puffs and had an increase in the number of puffs with 3mg/ml nicotine in e-liquids during a 60 min ad-lib session compared to 8mg/ml nicotine e-liquids(Hiler et al., 2019).

2.1.4. E-cigarette Device Power—There are multiple e-cigarette device types available on the market. There are early e-cigarette devices (cig-a-likes) that look like cigarettes and contain a fixed amount of nicotine, vape-pens, modifiable devices or mods that allow users to change device power, nicotine concentrations, and other constituents of e-liquids including flavors (Barrington-Trimis et al., 2017; Krishnan-Sarin et al., 2019; Yingst et al., 2015). There are newer devices known as "pod devices," which are small devices that generate discreet vapor and are typically lower powered devices(DeVito and Krishnan-sarin, 2018). Pod e-cigarette devices are among the most popular device types used currently(Barrington-Trimis and Leventhal, 2018; Krishnan-Sarin et al., 2019; Tan et al., 2019). Studies have demonstrated that during a fixed puffing bout schedule, advanced e-cigarette devices such as pod e-cigarette devices produced higher blood nicotine levels compared to earlier e-cigarette devices in humans(Hajek et al., 2018, 2017; Rüther et al., 2018; Yingst et al., 2019b, 2019a). Given that devices vary by power (measured in watts) [voltage^2/ heating coil resistance (ohms or Ω)], it is important to understand the impact of device power on nicotine delivery. In a recent study, e-cigarette users used their own e-cigarette devices and nicotine e-liquids and participated in a directed puffing bout session (10 puffs, 30 sec puff interval) .Comparisons were made between those who used third generation e-cigarette devices with higher power and lower nicotine concentrations (i.e. mods) and those who used second generation e-cigarette devices with lower power and

higher nicotine concentrations(eGO tank-style systems). Users of third generation e-cigarette devices achieved higher plasma nicotine concentrations during the directed puffing bout and the 2 hr. ad-lib session (Wagener et al., 2017). A study that used six different e-cigarette devices [2 cigalikes (disposable, rechargeable), 2 later-generation (eGO, mod), and 2 niche devices (e-Cigar, e-Pipe)] found that 120 min. after undergoing a directed puffing bout (20 puffs, 30 sec interval) smokers achieved significantly greater AUC nicotine with mod devices (29.9mg/ml nicotine in e-liquid, W=14.1) compared to disposable [11.7mg/ml nicotine in e-liquid, Watts (W)=5.41], rechargeable (19.4mg/ml in e-liquid, nicotine, W=4.31) and e-Cigar (15.5mg/ml nicotine in e-liquid, W=14.4) devices (Voos et al., 2019a). However, this study did not control for nicotine concentration used in each device so it is unclear the impact of e-cigarette device power in the results (Voos et al., 2019a). In another study where participants received either 3 or 8mg/ml nicotine in an e-cigarette device that differed in coil resistance (0.5 Ω, 40.5 W or 1.5 Ω, 13.5 W), plasma nicotine levels were higher in the 8mg/ml nicotine, 0.5 Ω, 40.5 W condition and lowest in the 3mg/ ml nicotine,1.5 Ω, 13.5 W condition in a directed puffing bout and ad-lib session (Hiler et al., 2019). 8mg/ml of nicotine in combination with a 0.5 Ω, 40.5 W e-cigarette device also produced the largest reduction in abstinence symptoms (Hiler et al., 2019). When dual users (e-cigarette and cigarette users) used their own e-cigarette devices over a 24 hour period adlibitum, those who used variable-power tank devices had higher nicotine exposure than those who used cigalikes or fixed power devices (Harvanko et al., 2019)

2.1.5. Nicotine Salts—Nicotine can be found in its freebase form or its salted form (monoprotonated or diprotonated). Nicotine salts are formed by the reaction of nicotine with a suitable acid such as benzoate or lactate (Caldwell et al., 2012). Freebase nicotine is volatile and can result in higher buccal absorption rates but because nicotine salts are less volatile, more nicotine reaches the lungs and participates in pulmonary absorption (Benowitz et al., 2009; Bowen and Xing, 2015; Caldwell et al., 2012). Nicotine salts may increase the amount of nicotine exposure (Bowen and Xing, 2015) and it has been hypothesized that they can be administered at higher doses of nicotine with less throat irritation in comparison to freebase nicotine (Chen, 1976; Duell et al., 2018). E-cigarette pod devices contain nicotine salts (Goniewicz et al., 2018) opposed to freebase nicotine which is used in e-liquids of earlier generations of e-cigarettes(Duell et al., 2019). The utility of nicotine salts instead of freebase nicotine in inhaled non-combustible products is thought to produce a nicotine delivery similar to cigarettes(Duell et al., 2019). A study comparing nicotine delivery of Myblu™ brand e-cigarettes (freebase nicotine and nicotine lactate) to cigarettes showed that compared to cigarettes, 25mg/ml of nicotine lactate nicotine exposure was 60 % lower than cigarettes while 25mg/ml of nicotine freebase exposure was 70% lower than cigarettes after directed puffing bouts(O'Connell et al., 2019).

2.2. Nicotine inhaler

Another inhaled nicotine device is the nicotine inhaler. Compared to e-cigarettes, nicotine inhalers do not contain PG/VG and the FDA has approved a nicotine inhaler to be used as nicotine replacement therapy (West et al., 2000). In a directed puffing bout experiment, plasma nicotine levels and abuse liability of a nicotine inhaler (10mg nicotine) and e-cigarettes (0mg/ml or 36mg/ml nicotine) were investigated. It was demonstrated that plasma

nicotine concentrations were higher in the e-cigarette 36mg/ml nicotine exposure session compared to exposure with 0mg/ml nicotine e-cigarettes and the nicotine inhaler. The nicotine inhaler (10mg) produced higher plasma nicotine levels than the 0mg/ml nicotine concentration e-cigarette condition and both e-cigarettes (0mg/ml and 36mg/ml nicotine) were rated as more reinforcing than the nicotine inhaler (Maloney et al., 2019). Similarly, the nicotine inhaler (10mg) produced a lower plasma nicotine concentration than the highest nicotine concentration used in an e-cigarette and higher plasma nicotine concentrations compared to 0mg/ml nicotine e-cigarette (Breland et al., 2019). The nicotine inhalator (15mg nicotine) administered under directed puffs (80 total, 15 sec puff interval ,for 20 min.) produced a lower plasma nicotine concentration(Cmax) than another inhaled nicotine product, the P3L(contains only nicotine and lactate), that was used for only 12 total puffs (30 sec puff interval, over 6 min) at multiple aerosol nicotine concentrations (50, 80, and 150 μg/puff) (Teichert et al., 2018). The P3L is a nicotine delivery device that consists of a pen-sized holder and a charger unit. Inside of the holder there is a cartridge that contains nicotine and the acid in separate compartments. This device has heating capabilities and through a ventilation mechanism is able to control the amount of nicotine salt delivered. This device does not contain PG or VG (Teichert et al., 2018). Additionally the nicotine inhalator(30 min) in this study took a longer time to reach Cmax compared to the P3L device (7 min) (Teichert et al., 2018). Nicotine from nicotine inhalers are absorbed in the oral cavity opposed to in the lungs which may account for differences in nicotine plasma concentrations in these studies (Lunell et al., 2000).

2.3. Heated Tobacco products

Another category of inhaled nicotine products is the electrically-heated tobacco product with one of the newest products from this category being the IQOS(Glantz, 2018). There is limited data on heated tobacco products, however, it is important to discuss information that is currently available in order to inform future studies. IQOS mostly contains nicotine in a salt form (Meehan-atrash et al., 2019) and was shown to produce minimal or no carbon monoxide(Adriaens et al., 2018; Caponnetto et al., 2018) and reduce cigarette withdrawal symptoms in cigarette smokers during a 5 min ad-lib session (Adriaens et al., 2018). In anesthetized Sprague Dawley rats who were passively exposed (nose only) to 10 cycles of 5 sec exposure+ 25 sec break had post exposure serum nicotine levels higher in IQOS exposed-condition than the cigarette-exposed condition (~4.5-fold higher) even though cigarette delivered more nicotine into the aerosol compared to iQOS(Nabavizadeh et al., 2018).

3. Pharmacodynamics

Pharmacodynamics can be defined as the physiological and biophysical effects of drugs on the body (Felmlee et al., 2012). This section will focus on nicotine's impact on the following biological systems: cardiovascular, pulmonary, central nervous system and other effects of nicotine. The pharmacodynamic section mostly consists of animal studies because there are a lack of recent inhaled nicotine pharmacodynamic studies conducted in humans. Nicotine induces its pharmacodynamic effects through nicotinic acetylcholine receptors (nAChRs) (Changeux et al., 1998) which belong to the Cys-loop receptor family and are ligand gated

ion channels that form pentamers arranged around a water-filled pore (Albuquerque et al., 2009; Le Novère and Changeux, 1995). These receptors are permeable to both Na^+ and Ca^{2+} and can form homomeric and heteromeric receptors (Millar and Gotti, 2009). Nicotinic subunits can assemble in different combinations resulting in a diversity of functions of nAChR subtypes. nAChRs are located throughout the central and peripheral nervous system, tissues and organs of the body (Dani and Bertrand, 2007; Haass and Kubler, 1996; Wang and Hu, 2018).

3.1. Cardiovascular

Nicotine administration increases heart rate, blood pressure (Haass and Kubler, 1996) and has a negative impact on cardiovascular physiology (Benowitz and Burbank, 2016; Buchanan et al., 2020; MacDonald and Middlekauff, 2019; Qasim et al., 2017). One clinical study demonstrated that exposure using a standard puffing paradigm [30 puffs (3 sec duration)] with e-cigarettes containing 19mg/ml nicotine, compared to those containing 0 mg/ml over a 30 min period increased heart rate, arterial stiffness and increase in blood pressure (Antoniewicz et al., 2019). Similarly, other human studies have also observed that nicotine exposure via e-cigarettes produced increases in heart rate (Chaumont et al., 2018; Franzen et al., 2018; Hiler et al., 2017; Spindle et al., 2018, 2017). Preclinical evidence also suggests an influence of nicotine aerosol on cardiovascular parameters. For example, pregnant Sprague-Dawley rats exposed to inhaled nicotine aerosol demonstrated a reduction in uterine artery blood flow (Orzabal et al., 2019) and cardiac arrhythmia (Shao et al., 2017). Vascular endothelial function was impaired in anesthetized Sprague Dawley rats who were passively exposed (nose only) acutely to iQOS aerosol (0.67 ± 0.02 mg nicotine in particle phase of aerosol) and cigarette smoke (1.07 ± 0.05 nicotine in particle phase of smoke) comparably (Nabavizadeh et al., 2018). Further, apolipoprotein-E knockout mice (mouse model of atherosclerosis) exposed to 12 weeks of nicotine aerosol (0 or 24% nicotine) (24 vaping episodes 12 hr. per day; 1 vaping episode=8 puffs) displayed signs of cardiomyopathy and atherosclerotic lesions (Espinoza-Derout et al., 2019). Additionally, nicotine aerosol exposure in C57BL/6 female mice (3month, 5 days/week,4 sec puff duration, 20 sec interval, 60 min/day) and CD-1 female mice (6month, 5 days/week,4 sec puff duration, 20 sec interval, 60 min/day) decreased heart rate and increased blood pressure (Crotty Alexander et al., 2018). This study demonstrated heart rate decrease instead of heart rate increase which may be the result of chronic nicotine exposure. Additionally, this study only used female mice; therefore, it would be important to understand sex differences with this exposure paradigm with the utilization of male mice. In another study, C57BL/6 female and male mice passively exposed to 24mg/ml nicotine aerosol (3 h/day for 14 days) during a whole body exposure procedure displayed increased angiogenesis in heart tissue(Shi et al., 2019). Furthermore, an increase in arterial stiffness has also been demonstrated in C57BL/6 female mice after chronic exposure to 18mg/ml of nicotine aerosol (Olfert et al., 2018). There are cardiovascular disorders that are thrombosis-dependent. Thus, to understand the impact of nicotine-containing e-cigarettes on thrombosis, a study exposed C57BL/6J male mice to 200 puffs of 18mg/ml nicotine aerosol for 5 days (whole body exposure). Compared to clean air exposed mice, e-cigarette exposed mice had a shorter occlusion time in a thrombosis model (Qasim et al., 2018).

3.2. Pulmonary

Inhaled nicotine may have negative implications for the pulmonary system (Javed et al., 2017). Occasional tobacco users who inhaled 30 puffs (3 sec duration) of e-cigarettes (0, 19mg/ml nicotine) during a 30 min period had increased obstruction of airways with 19mg/ml of nicotine exposure compared with 0 mg/ml of nicotine (Antoniewicz et al., 2019). After 15 puffs of a nicotine-containing e-cigarette (18mg/ml), spirometry measurements were assessed and participants showed no change in forced expiratory volume in 1 s, forced vital capacity but a reduction in peak expiratory flow (Kerr et al., 2019). Anesthetized Sprague Dawley rats exposed to nose-only nicotine aerosol (5, and 10%) for 15 min experienced pulmonary edema and an increase in inflammatory markers in the lungs (Ahmad et al., 2019). Proinflammatory markers were also increased in the lungs of C57BL/6J mice after passive exposure to 2 hours daily for 3 days (2 puffs/min, 3.3. sec duration) of 25mg/ml nicotine aerosol(Wang et al., 2019). This increase in lung inflammation was also seen in another study that utilized C57BL/6J mice (Glynos et al., 2018). Additionally, a study demonstrated that after acute nicotine-containing e-cigarette exposure, participants had elevated plasma endothelial microparticles levels and altered transcriptome of the small airway epithelium (site of lung abnormalities in smokers) and alveolar macrophages (phagocytes of the lower respiratory tract)(Staudt et al., 2018). However, evidence of changes in lung biomarkers have not been consistently found in all studies. For example, in C57BL/6 mice exposed to 4% nicotine aerosol for 3 weeks (4 hours/day, 30 sec puff interval, a 3-se puff duration) there were no significant microscopic changes in the respiratory tract (Lee et al., 2019). A heated tobacco product, the carbon heated tobacco product 1.2 (CHTP1.2) which is a disposable single-use device that resembles a cigarette but has a carbon heating source that is thought to not cause combustion (Phillips et al., 2018), produced low or no inflammatory or cellular responses in the lungs of Sprague Dawley rats after 90 days of exposure (6 hours/day, 5 days/week) testing multiple nicotine concentrations (15 ug/L, 23 ug/L, 50 ug/L) (Phillips et al., 2018; Titz et al., 2018). Additionally, after chronic nicotine aerosol exposure in C57BL/6 mice there were increased inflammatory markers in the larynx, the structure air passes through in route to the lungs(Ha et al., 2019).

3.3. Central Nervous System

Brain nicotine concentrations have been shown to increase after a single puff of an e-cigarette containing nicotine (Sai et al., 2019). One of the most abundant nicotinic receptors found in the mammalian brain are the high affinity heteromeric α4β2-containing nAChRs (Hill et al., 1993). Smokers exposed to cigarette smoking have the majority of their brain high affinity β2-containing nAChRs occupied (Brody et al., 2006; Staley et al., 2005). β2-containing nAChRs are also upregulated in postmortem brains of smokers (Breese et al., 1997) and animals (Alsharari et al., 2015) after chronic nicotine administration. In addition, preclinical studies showed that the β2 subunit is required for nicotine reward, reinforcement, and some aspects of withdrawal (Jackson et al., 2009, 2008; Orejarena et al., 2012; Picciotto et al., 1998). There are limited studies on the occupancy of nicotinic receptors after exposure to non-combustible tobacco products. One human study exposed e-cigarette users to different nicotine concentrations (0,8,36 mg/ml nicotine) under a directed puffing procedure [one puff every 30 sec for 5 min (10 puffs total)], and observed that the average β2-

containing-nAChR occupancy was higher after 36 mg/ml of nicotine compared to 8 mg/ ml. Of interest, both nicotine concentrations were sufficient to reduce drug cravings (Baldassarri et al., 2018). The insula, prefrontal cortex and the nucleus accumbens are brain regions that are related to nicotine dependence(Dani et al., 2011; Naqvi et al., 2014). Exposure to nicotine(10mg) from a nicotine inhaler (two-second inhaler puffs every 10 s over the course of 20 min for a total of 120 inhalations) was shown to contralaterally decrease resting state functional connectivity between the anterior insula and nucleus accumbens(Perry et al., 2019) in humans. Similarly, after directed puffing exposure with e-cigarettes, participants demonstrated decreased resting state functional connectivity in the right insula and prefrontal cortex (Hobkirk et al., 2018). C57BL/6 mice exposed to 6 months (4 s every 20 s, for 1 h/day, for 5 days/week) of nicotine aerosol (24mg/ml) displayed homeostatic alterations in the mesolimbic pathway (rewarding system of the brain) indicated by increase in glutamate in the striatum but a decrease of dopamine in the striatum and GABA levels were decreased in the frontal cortex(Alasmari et al., 2019). In addition, 6 month nicotine aerosol exposure (24mg/ml) in female CD-1 mice increased expression of the homomeric α7 nAChR in the frontal cortex and the striatum but not in the hippocampus(Alasmari et al., 2017). The α7 nAChR has been shown to play a role in nicotine dependence (Jackson et al., 2019, 2018, 2017).

3.4. Other effects

Inhaled nicotine has been shown to have other pharmacodynamic effects. Male and female ICR mice exposed passively to 5 min of nicotine aerosol (0, 12, 24, 30 mg/ml) demonstrated a decrease in body temperature and locomotor activity (Lefever et al., 2017). Similarly, in male Sprague Dawley rats, inhaled nicotine (30mg/ml) increased locomotor activity and decreased body temperature after four 15-min vapor exposure sessions separated by an hour (Javadipaydar et al., 2019). In addition, increased locomotion was also exhibited in apolipoprotein-E knockout mice after chronic administration of e-cigarette aerosol containing nicotine (2.4%)(Shao et al., 2019). Male Wistar rats exposed to nicotine vapor (20, 40, 80 mg/mL) for 11 days (60 min/session/day; 3-s puff ,2 min puff interval, 30 puffs total) experienced spontaneous and mecamylamine-precipitated signs of nicotine withdrawal (Montanari et al., 2019). The female offspring of C57BL/6 mice exposed to 24mg/ml nicotine vapor (5 days/week, 3 h/day, 2 puffs per min) during pregnancy weighed significantly less than their control non-exposed counterparts (Wetendorf et al., 2019). Also, male and female C57BL/6 mice exposed to aerosolized nicotine exhibited increases in nicotine-like responding in the drug discrimination assay (Lefever et al., 2019).

4. Discussion

The collection of articles reviewed here demonstrate that the pharmacological characterization of inhaled non-combustible nicotine exposure has mainly focused on e-cigarettes. It has been shown that pharmacokinetics of nicotine via e-cigarettes is influenced by the PG/VG, flavor constituents, nicotine salts, puff topography and the power of the e-cigarette device used in human subjects. The pharmacodynamic impact of inhaled nicotine has mainly utilized nicotine aerosol or nicotine from e-cigarette devices and focused on cardiovascular, pulmonary and central nervous system effects in rodents.

It is recommended that studies focus on adolescent subjects. Most human e-cigarette experimental studies that have been conducted mainly recruited participants over 21 years of age. Considering the exponential rise in use of e-cigarettes among adolescents(Cullen et al., 2019) and the well-known differences in nicotine sensitivity and toxicity between adult and adolescent animals (Yuan et al., 2015) there is a dire need to understand the impact of these products in human adolescents. However, there are many potential ethical hurdles that make such studies very hard to conduct. Given these hurdles, adolescent e-cigarette exposure studies using rodents could provide insight on inhaled nicotine exposure in youth. Additionally, details such as power, resistance, PG/VG levels in e-liquids, form of nicotine (salt or freebase) and wattage should be provided for each device used in studies to fully understand the impact of nicotine.

Based on the reviewed articles, there are important recommendations for rodent studies to allow for a better understanding of the pharmacology of inhaled nicotine. Rodent models have provided crucial contributions to nicotine and tobacco research(Smith et al., 2017). Currently there are significant gaps in our understanding of inhaled nicotine that could be addressed using rodent models especially as it pertains to the impact of flavors, PG/VG levels and nicotine salts on the pharmacokinetics of nicotine. All the rodent studies reviewed utilized passive administration of nicotine aerosol but there is a need to create a self-administration nicotine aerosol procedure to mimic inhaled nicotine use behaviors in humans. Furthermore, in rodent studies, the procedure for nicotine aerosol exposure varies (whole body vs nose-only exposure, length of duration, etc.) and there is no consensus on an exposure protocol to mimic human behavior. Additionally, rodent studies should strive to include equal numbers of both male and female subjects.

There are shared recommendations for both human and rodent studies. Throughout the human and rodent studies, the measurement of nicotine was not consistent (measured in aerosol, mg/ml from e-liquid label, measured per puff, measured in e-liquid, mg/ml, %). This limits the interpretation of results and makes it difficult to compare across studies. Also, many rodent and human studies compared findings to the well-studied tobacco product, cigarettes(De La Garza et al., 2019; Glynos et al., 2018; Larcombe et al., 2017; Phillips et al., 2018; Rüther et al., 2018; Van Heel et al., 2017). Comparing non-combustible inhaled nicotine products to cigarettes may minimize the understanding of their effects and limit our understanding of new pharmacological implications for inhaled nicotine products that are non-combustible. All future studies should include a negative control (saline/vehicle condition) to fully understand the impact of inhaled nicotine on outcome measures. Furthermore, given the entrance of newer non-combustible inhaled nicotine products such as the iQOS, further studies should seek to understand these products in humans and rodents.

In sum, the articles reviewed here highlight the importance of both animal and human models to fully understand the impact of inhaled nicotine pharmacology. Animal models highlight the molecular impact of inhaled nicotine in a controlled manner. For example, unlike in human subjects, experimenters have control of the drug exposure history of animals, have control over nicotine access of animals and the genetics of animals can easily be manipulated to understand the impact of specific receptors or enzymes. It is especially important to understand the molecular effects of inhaled nicotine on the pulmonary and

cardiovascular system using animals given the rise of EVALI cases (Perrine et al., 2019). This narrative review serves as an update to the pharmacology of inhaled nicotine literature and a call to action to address important gaps.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Highlights:

- Human and rodent inhaled nicotine experiments
- E-cigarettes, heated tobacco products, nicotine inhaler
- Pharmacodynamics and pharmacokinetics nicotine studies