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Review

A computerized exposure system for animal models to optimize nicotine delivery into the brain through inhalation of electronic cigarette vapors or cigarette smoke

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ABSTRACT

Pre-clinical studies investigated the effects of chronic exposure to nicotine on lungs, kidneys and brains using animal models. Most of these studies delivered nicotine into the circulatory and central nervous systems (CNS) through intraperitoneal injection or oral consumption methods. Few studies used inhalation machine system for nicotine delivery into brains in rodents to mimic human exposure to cigarettes. However, finding a more accurate and clinically relevant method of nicotine delivery is critical. A computerized inhalation machine has been designed (SciReq) and is currently employed in several institutions. The computerized machine delivers electronic (e)-cigarette vapor as well as tobacco smoke to rodents using marketed e-cigarette devices or tobacco cigarettes. This provides evidence about clinical effects of nicotine delivery by traditional methods (combustible cigarettes) and new methodologies (e-cigarettes) in physiological systems. Potential neurobiological mechanisms for the development of nicotine dependence have been determined recently in mice exposed to e-cigarette vapors in our laboratory using SciReq system. In this review article, the discussion focuses on the efficiency and practical applicability of using this computerized inhalation exposure system in inducing significant changes in brain protein expression and function as compared to other nicotine delivery methods. The SciReq inhalation system utilized in our laboratory and others is a method of nicotine delivery to the CNS, which has physiological relevance and mimics human inhalant exposures. Translation of the effects of inhaled nicotine on the CNS into clinical settings could provide important health considerations.

Contents

Abbreviations: α-7nAChR, alpha-7 nicotinic acetylcholine receptor; CNS, central nervous system; e-cigarette, electronic cigarette; GLT-1, glutamate transporter-1; xCT, cystine/glutamate exchanger.

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1. Introduction

Parenteral routes of nicotine administration have been the standard methods used in pre-clinical nicotine delivery methods for decades (Nadal et al., 1998; Tizabi et al., 2002; Knackstedt et al., 2009; Fowler and Kenny, 2011; Wang et al., 2014). These parenteral routes include intraperitoneal, intravenous and intracerebral injections. Oral nicotine consumption is a method utilized in several studies to examine the behavioral effects of nicotine in animals (Sparks and Pauly, 1999; Adriani et al., 2002; Sari et al., 2016). However, these delivery methods have less desirable clinical and pharmacokinetic properties as compared to inhalation of nicotine (For review see (Le Houezec, 2003)). Laboratories have designed a computerized system for nicotine or tobacco smoke inhalation to investigate their effects in the body organs, including the brain.

The use of inhalation system for nicotine or tobacco cigarette smoke delivery in an animal model can provide novel evidence about the long-term effects of these chemicals on several neurotransmitters. It is important to note that exposure to nicotine through intra-striatal or subcutaneous routes of nicotine administration upregulated nicotinic acetylcholine receptors (nAChRs) in the mesocorticolimbic areas (Auta et al., 2000; Buisson and Bertrand, 2001; Alsharari et al., 2015). In addition, intravenous self- administration of nicotine via base/infusion for 21 days reduced one of the major glial glutamate transporters such as glutamate transporter 1 (GLT-1) in central reward brain regions (Knackstedt et al., 2009). These effects on the central nervous system (CNS) induced by nicotine exposure using non-clinical nicotine exposure methods may or may not be clinically relevant. Thus, using a nicotine delivery system reflective of human exposure routes is important to confirm or refute these findings. Thus, this will define addictive behavioral and neurobiological effects that may be induced by inhaled nicotine, which may mediate alterations in the function and expression of certain brain proteins. In this review article, we compared and contrasted the inhalation route with other routes of nicotine exposure on mediation of addictive effects.

Inhalation has been associated with a fast rate of nicotine absorption as compared to other routes of delivery of nicotine (For review see (Le Houezec, 2003)). In addition, bioavailability of nicotine in the brain has been reported to be higher after inhalation of cigarettes as compared to parenteral routes of nicotine delivery (Benowitz, 1990). Alterations in pharmacokinetic parameters occurred in subjects exposed to chronic inhalation of cigarette smoke-containing nicotine compared to other methods of nicotine delivery (Benowitz, 1990; Le Houezec, 2003). These differences in pharmacokinetics provide evidence that chronic nicotine inhalation may mediate alterations in key proteins involved in the development of nicotine dependence to a different extent, and in a different pattern than other routes of nicotine administration.

The inhalation exposure system (computerized inExpose machine) of nicotine has been found to be associated with several modifiable characteristics. Different electronic cigarette (e-cigarette) and tobacco cigarette brands can be used in the system (Hwang et al., 2016), and this could be clinically relevant when testing the most marketed e-cigarette and tobacco cigarette products (Fig. 1). In addition, the exposure period and duration to cigarettes can be controlled by the experimenters to mimic the actual human exposure duration and frequency to cigarettes (Hwang et al., 2016) (Fig. 1). Interestingly, other drugs of abuse can also be applied using the inhalation exposure machine, which may provide potential evidence about the effects of inhaled drugs of abuse on the body. We here shed light on the main characteristics of using the computerized inhalation exposure system in animal models compared to other routes of nicotine delivery.

2. Comparisons of nicotine inhalation to other delivery routes

Several studies investigated the effects of nicotine on nicotinic receptors, dopaminergic and glutamatergic systems in the CNS. These studies found that nicotine exposure was able to upregulate subtypes of nAChRs in mesocorticolimbic brain regions (Buisson and Bertrand, 2001; Alsharari et al., 2015). In addition, intraperitoneal injection of nicotine increased dopamine release in part by stimulation of nAChRs (Tizabi et al., 2002; Tizabi et al., 2007). Moreover, nicotine self-administration upregulated ionotropic glutamate receptors (Wang et al., 2007; Kenny et al., 2009; Alasmari et al., 2016). In addition, intravenous self-administration of nicotine was found to reduce the expression of GLT-1 in the nucleus accumbens (Knackstedt et al., 2009). The alterations in dopaminergic and glutamatergic systems as well as nicotinic receptors following different nicotine exposure methods have been suggested to mediate the development of nicotine dependence. However, little is known about the effects of chronic exposure to nicotine exposure using inhalation of e-cigarette vapor or tobacco smoke-containing nicotine on dopaminergic system, glutamatergic system and nicotinic receptors.

A recent study from our laboratory reported that chronic inhalation of e-cigarettes vapor containing-nicotine induced alterations in the glutamatergic system in the brain of female CD1 mice (Alasmari et al., 2017). This study found that inhalation of e-cigarette vapor containing-nicotine for six months upregulated alpha 7 nAChR (α-7 nAChR) in frontal cortex and striatum in CD1 mice (Alasmari et al., 2017). It is important to note that α-7 nAChR regulates glutamate release from pre-synaptic glutamatergic neurons (Konradsson-Geuken et al., 2009). In addition, chronic inhalation of e-cigarette vapor induced downregulation of cystine/glutamate exchanger (xCT) in striatum and hippocampus as compared to a group exposed to air (Alasmari et al., 2017). xCT is an important glial protein that regulates glutamate homeostasis (Baker et al., 2002). Moreover, chronic exposure to e-cigarette vapor induced significant decrease in GLT-1 expression in the striatum. GLT-1 is glial glutamate transporter that clears the majority of extracellular glutamate (Danbolt, 2001). The reduction in the expression of GLT-1 and xCT is suggested to be associated with increase in extracellular glutamate concentration as it was found in animal model of alcohol dependence (Nemmar et al., 2013). Alterations of these proteins have been suggested previously to be involved in part in the development of nicotine dependence (For review see (Alasmari et al., 2016)).

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