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Review

Impact of Tobacco Regulation on Animal Research: New Perspectives and Opportunities

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Abstract

Introduction: The Family Smoking Prevention and Tobacco Control Act in the United States and the World Health Organization Framework Convention on Tobacco or Health ratified by over 170 countries render scientific investigations into the abuse liability, harm, and effects of tobacco more critical than ever. A key area to explore relates to the potential regulation of nicotine content in cigarettes. Determining the nicotine content per cigarette below which smokers reliably reduce their consumption of and dependence on cigarettes, an idea proposed almost 20 years ago (Benowitz & Henningfield, 1994), could be a powerful approach to reduce the abuse liability and consequent harm from cigarettes. However, this approach is laden with potentially complex issues. Many of these complications can be studied using animal models, but they require a particular perspective.

Methods: Herein, we review several challenges for animal researchers interested in nicotine reduction as examples of how this perspective dictates new approaches to animal research. These include defining the threshold nicotine dose for maintaining self-administration, evaluating the differential impact of various implementation strategies, assessing the factors that could interact with nicotine to alter the reinforcement threshold, describing the role of cues in maintaining low dose nicotine self-administration, and examining individual differences in response to nicotine reduction.

Conclusions: Researchers who study tobacco using animal models have the opportunity to play a central role in the regulatory science of tobacco and conduct studies that directly inform policy decisions that could impact the lives of millions.

Introduction

New tobacco control measures are urgently needed. As of 2010, 19.3% of adults in the United States continue to smoke, and about half of those smokers are expected to die prematurely from illnesses related to their use of tobacco (CDC, 2002, 2011). The United States Food and Drug Administration (FDA) was recently given the authority to regulate tobacco products under the Family Smoking Prevention and Tobacco Control Act (FSPTCA; U.S. Congress, 2009). This legislation provides a powerful tool for reducing the harm associated with smoking at the policy level. One important implication of this law is that cigarettes—the most lethal tobacco product of all—will now be evaluated with respect to the public health consequences of use. This increased authority to regulate tobacco in the United States echoes a global change. Article 9 of the World Health Organization Framework Convention on Tobacco Control (WHO FCTC), ratified by over 170 countries, states that the countries agree to establish shared guidelines for evaluating and regulating the content and emission of tobacco products (WHO, 2003). The FSPTCA and WHO FCTC render scientific investigations into the abuse liability, harm, and effects of tobacco more critical than ever.

With this changing landscape, researchers who study tobacco using animal models have the opportunity to conduct studies that could impact regulatory decisions. This type of work—regulatory science—strives to contribute to the development of standards that regulatory agencies can use to assess the performance of the products they regulate (IOM, 2011). These efforts go beyond the basic science purpose of elucidating the mechanisms and enhancing the understanding for various phenomena; rather, they serve to provide the empirical basis

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for policy decisions that may impact the lives of many. The demand for this information places responsibility on nicotine and tobacco scientists with a wide range of expertise to answer critical questions related to the FSPTCA and WHO FCTC (Hatsukami et al., 2010).

A key area for investigators to explore relates to the potential regulation of nicotine content. In the United States, the FSPTCA enables the FDA to establish tobacco product standards, including limits on the constituents in tobacco products (U.S. Congress, 2009). The FSPTCA does not allow nicotine levels to be decreased to zero, although the FDA does have the authority to reduce nicotine to very low levels that may be nonaddicting. Determining the threshold dose of nicotine per cigarette below which smokers reliably reduce their consumption of and dependence on cigarettes, an idea proposed nearly two decades ago (Benowitz & Henningfield, 1994), is a critical consideration for the FDA. However, this seemingly simple concept of reducing nicotine content to reduce the abuse liability and consequent harm from cigarettes is laden with complications. Many of these complications can be studied within the context of animal research, but they require a particular perspective. Herein, we review several challenges for animal researchers interested in nicotine reduction as examples of how this perspective will dictate new approaches to animal research. These include defining the threshold nicotine dose for maintaining self-administration, evaluating the differential impact of various implementation strategies, assessing the factors that could interact with nicotine to alter the reinforcement threshold, describing the role of cues in maintaining low dose nicotine use, and examining individual differences in the response to nicotine reduction to help identify subpopulations that could be put at risk given any policy change.

This article focuses predominantly on rodent models of nicotine self-administration. Although other methods and procedures are also useful tools (see Discussion), the primary mechanism by which one would expect reduced nicotine content to reduce the harm of tobacco is through changes in nicotine reinforcement and dependence. Intravenous nicotine self-administration models, in which animals receive a dose of nicotine contingent upon a specified behavior (e.g., lever press, nose poke), are the gold standard for studying the reinforcing effects of nicotine. Rats are most frequently utilized for these studies (Rose & Corrigall, 1997) and will be the focus here, although other animal models may provide unique opportunities (e.g., genetic manipulations in mouse models).

The Role of Animal Research in the Regulatory Science of Tobacco

The primary role of animal research in tobacco regulatory science is to address issues that are difficult or impossible to study in humans for ethical, safety, or logistical reasons. In this regard, animal research has several distinct advantages. First, controlled, experimental manipulations can be done in animals to examine factors that may influence initiation of tobacco use. Although longitudinal studies in humans are informative, such approaches provide limited information about the causal relationship between nicotine and behavior. Second, animal research allows the study of the effects of nicotine or other constituents in isolation from factors related to "product appeal" or "product attractiveness" (e.g., sensory variables, advertising, promotion; Henningfield, Hatsukami, Zeller, & Peters, 2011). This specificity is essential to understanding the extent to which changes in the abuse liability of a product are attributable to changes in nicotine content per se. Third, animal studies can evaluate constituents across a wide range of doses that may not be appropriate for clinical studies or feasible, given the current products available to clinical researchers. Fourth, animal research allows control over the history of nicotine and other drug intake. Fifth, animal research allows experimental analysis of neural mechanisms underlying changes in product use, which may be helpful in selecting or developing medications to assist smokers in reducing or quitting within the context of reduced nicotine. Finally, potential undesired consequences of nicotine reduction (e.g., compensation, discomfort, and dysfunction) and their underlying mechanisms can be easily studied in animals. In addition to these advantages, animal research can also serve to help shape clinical research by highlighting critical determinant of behavior following nicotine reduction.

However, the translation of information from animal models to the human experience has an important constraint. Animal models should not be used to specify precise quantities of nicotine or other constituents to apply in policy development. Despite similarities between animals and humans in the intravenous nicotine doses that are self-administered, and even the plasma nicotine levels attained, the goal of animal research should not be to specify a threshold reinforcing nicotine dose or develop specific standards for other constituents. Translating a specific nicotine dose across species is inherently problematic because of pharmacokinetic, pharmacodynamic, neurobiological, and behavioral differences between species. Indeed, the range of parameters that can alter the dose–response relationship even within species (e.g., strain), is striking. Animal models also fail to capture the rich array of contextual and social variables related to smoking. Instead, functional relationships between key variables, dose, and behavior should be emphasized. Animal research can help describe what factors result in shifts in the dose–response curve and alter the nicotine reinforcement threshold rather than what nicotine level should be targeted.

What Is the Reinforcement Threshold for Nicotine Self-Administration in Rats?

Dose–Response Curves for Acquisition and Maintenance

The acquisition and maintenance phases of intravenous nicotine self-administration are key processes to study in animals because they correspond to the primary phenomena targeted by a nicotine reduction policy, initiation, and persistence of use. Numerous studies have examined dose–response relationships for intravenous nicotine self-administration in rats (representative studies summarized in Table 1). These studies vary across a number of potentially important parameters and few were specifically designed to measure the reinforcement threshold for nicotine (i.e., the lowest dose that engenders or maintains self-administration). Nonetheless, they provide valuable information regarding the range of doses that likely encompass the reinforcement

Table 1. A Representative Summary of Studies Evaluating the Impact of Dose on Acquisition and Maintenance of Nicotine Self-Administration

Citation	Phase	Strain	Sex	Age	Previously trained	Doses (μg/kg/infusion)	Cue	Response	Session duration	Largest subthreshold dose	Lowest nicotine dose supporting behavior
Chaudhri et al., 2007	ACQ	SD	M	Adult	Y	10,30,90	Y	LP	1h	N/A	10
Chaudhri et al., 2007	ACQ	SD	M	Adult	Y	10,30,90	N	LP	1h	30	90
Chen et al., 2007	ACQ	LE	M	Adol	N	7.5,15,30	Y	LP	23h	7.5	15
Chen et al., 2007	ACQ	LE	F	Adol	N	7.5,15,30,60	Y	LP	23h	7.5	15
Cox et al., 1984	ACQ	WI	F	Adult	N	0,3,10,30	N	LP	23h	10	30
Donny et al., 1998	ACQ	SD	M	Adult	Y	10,30,60	Y	LP	1h	10	30
Donny et al., 1999	ACQ	SD	M	Adult	Y	20,30,60,90	Y	LP	1h	N/A	20
Donny et al., 2000	ACQ	SD	M&F	Adult	Y	20,30,60,90	Y	LP	1h	N/A	20
Liu et al., 2008	ACQ	SD	M	Adult	Y	0,15,30,60	Y	LP	1h	N/A	15
Lynch 2009	ACQ	SD	M&F	Adol	Y	5,10	Y	LP	20 inf	N/A	5
O' Dell et al., 2007	ACQ	WI	M	Adult	Y	15,30,60	Y	NP	23h	N/A	15
Peartree et al., 2012	ACQ	SD	M	Adult	N	0,15,30,60	N	LP	2h	15	30
Shoaib et al., 1997	ACQ	SD,LE	M	Adult	N	15,30,60 (LE&SD)	Y	NP	2h	N/A	15
Shram et al., 2008	ACQ	LE,WI	M	Adult	N	15,30	Y	LP	2h	15 (W) N/A (LE)	30 (W) 15 (LE)
Shram et al., 2008	ACQ	LE,WI	M	Adol	N	15,30	Y	LP	2h	15	30
Sorge & Clark, 2009	ACQ	LE	M	Adult	N	0,1,3,10,30,60	Y	LP	2h	1	3
Valentine et al., 1997	ACQ	HO	M	Adult	N	3.75,7.5,15,30	Y	LP	22/23h	N/A	3.75
Brower et al., 2002	MAIN	LE,HO	M	Adult	N	0.9(L),1.8,2.75,7.5(L&H)	Y	LP	23h	N/A	0.9 (L); none (H)
Clemens et al., 2010	MAIN	SD	M	Adult	N	0,7.5,15,30,60	Y	LP/NP	2h	N/A	7.5
Corrigall & Coen, 1989	MAIN	LE,WI	M	Adult	Y	3,10,30,60	Y	LP	1h	N/A	3
Cox et al., 1984	MAIN	WI	F	Adult	N	0,3,30	N	LP	23h	N/A	3
DeNoble & Mele, 2006	MAIN	LE	M	Adult	N	0,8,16,32,64	Y	LP	24h	N/A	8
Donny et al., 1995	MAIN	SD	M	Adult	Y	3,30,60	Y	LP	1h	N/A	3
Shoaib et al., 1997	MAIN	SD,LE	M	Adult	N	0,2,4,8,15,30,60,120	Y	NP	2h	N/A	~4-15
Watkins et al., 1999	MAIN	WI	M	Adult	Y	3,10,30,60,0	Y	LP	3h	N/A	3

Note. ACQ = acquisition; MAIN = maintenance; SD = Sprague-Dawley; LE = Long Evans; WI = Wistar; HO = Holtzman; LE = Lewis; FI = Fisher 344; M = male; F = female; Adol = adolescent; LP = lever press; NP = nose poke. Threshold dose defines as dose not significantly greater than saline or in which less than 50% of the animal met acquisition criteria. Studies without direct comparison to saline or inactive responding are omitted.

threshold in rats and highlight several variables to be discussed in the following sections, which may be important determinants of self-administration at low doses of nicotine.

Acquisition dose–response curves have been generated by assigning different groups of animals to different nicotine doses. On average, the dose–response curve for acquisition of intravenous nicotine self-administration under small fixed ratio (FR) schedules (fixed number of responses required per infusion) has a biphasic inverted-U shape. The peak of the curve is around 20–30 μg/kg, with acquisition commonly observed at this dose in several species, including rats, dogs, monkeys, and humans (Harvey et al., 2004; Matta et al., 2007). At lower unit doses (3.75–10 μg/kg) on the ascending limb of the dose–response curve, mean response rates increase with dose. In this range, there is considerable individual variability in response rates and a lower proportion of rats acquire nicotine self-administration (i.e., responding greater than saline control and/or inactive operandum; Cox, Goldstein, & Nelson, 1984; Shram, Li, & Le, 2008). As such, the ascending limb of the group curve may be an averaging artifact, resulting from increasing proportions of animals acquiring, and not reflect intermediate responding by the majority of individuals. In most studies, the average rate of self-administration for doses at or less than 10 μg/kg is not significantly different from saline (Chen, Matta, & Sharp, 2007; Cox et al., 1984; Donny et al., 1998); however, some studies utilizing different strains and longer duration of access report self-administration at doses as low as 3.75 μg/kg (Valentine, Hokanson, Matta, & Sharp, 1997). Although acquisition rates (i.e., latency to stable responding) tend not to improve significantly as the unit dose increases above 30 μg/kg with the majority of animals acquiring the behavior (Donny et al., 1998; 2000; Shoaib, Schindler, & Goldberg, 1997), infusion rates decrease with dose in this range, resulting in the descending limb of the curve. Because the decrease in infusion rate is not proportional to the increase in dose, an increase in nicotine intake is observed as dose increases (Donny et al., 1999).

Similar to acquisition, the peak of the dose–response curve obtained during maintenance of nicotine self-administration is typically between 10 and 30 μg/kg (Brower, Fu, Matta, & Sharp, 2002; Corrigall & Coen, 1989; Denoble & Mele, 2006; Donny, Caggiula, Knopf, & Brown, 1995; Shoaib et al., 1997; Watkins, Epping-Jordan, Koob, & Markou, 1999). Nicotine self-administration decreases and variability increases when unit doses less than 10 μg/kg are substituted for a higher training dose (e.g., 30 μg/kg). Similar to acquisition, the rate of nicotine self-administration decreases across unit doses more than 30 μg/kg and changes in infusion rate are not proportional to dose, so that intake increases with dose. The threshold reinforcing unit dose of nicotine at the low end of the dose range is rarely determined (see Table 1), but doses as low as 3 μg/kg have been shown to maintain nicotine self-administration rates above those for saline in both limited and extended access studies (Brower et al., 2002; Corrigall & Coen, 1989; Cox et al., 1984; Shoaib et al., 1997; Watkins et al., 1999).

Cross-study comparisons suggest that the ascending limb of the dose–response curve during maintenance of nicotine self-administration may span a wider range and result in a lower reinforcement threshold than that for acquisition. Consistent with that observation, some research has shown that preexposure to nicotine can affect acquisition of nicotine self-administration (Adriani et al., 2003; Hanson, Ivester, & Morton, 1979; Shoaib et al., 1997). Within-subject designs that employ an ascending dose–response procedure for acquisition or reacquisition of nicotine self-administration in addition to assessing the dose–response curve for dose reduction using the same testing parameters would help clarify this issue. One variable to be particularly mindful of is the influence of response-contingent cues, which may account for sustained responding (see Data Analysis Considerations section). Regardless, the lack of data directly addressing whether the threshold for acquisition and maintenance are the same, a fundamental issue facing nicotine reduction strategies, is striking and highlights how a change in perspective illuminates gaps in the literature.

The data available to date, however, provide relatively little direct evidence about the threshold for nicotine reinforcement and nicotine reduction strategies for several reasons. First, studies have typically examined a limited range of doses (e.g., 3–4), often failing to identify a subthreshold dose. Second, it is not clear that the range of doses used have been sufficient to fully characterize the dose–response curve in every subject. Quantifying and understanding individual variability is essential to deriving estimates of the reinforcement threshold and to anticipate and overcome limitations to a nicotine reduction policy (see the following sections). Third, procedures that can influence the dose–response curve vary widely across studies along parameters that may directly impact the threshold for reinforcement. Fourth, studies have not been designed to mimic specific policy scenarios. For example, maintenance doses have often been tested in random order within subjects. It is possible that the dose–response function would differ from that in previous studies if doses were tested in a descending order within subjects (cf. Brower et al., 2002; Chen et al., 2007; Shoaib et al., 1997), which would more closely approximate a potential nicotine reduction policy.

Indeed, consideration of how a nicotine reduction policy might be implemented raises important questions about the temporal aspects of reduction (e.g., gradual versus abrupt reduction). Benowitz and Henningfield (1994) originally recommended a reduction in nicotine levels of all cigarettes over the course of 10–15 years, although recent studies have demonstrated that immediate reduction is also successful in decreasing smoking and even dependence (Donny, Houtsmuller, & Stitzer, 2007; Hatsukami et al., 2010). While arguments could be made for either reduction strategy, the rate of reduction may substantially impact the level to which nicotine content would need to be reduced. Although no studies to date have addressed this issue, early work on nicotine self-administration did find that rats switched to saline extinguished more slowly if they received an intermediate dose reduction prior to saline substitution (Cox et al., 1984). Future animal research should directly assess the impact of different temporal parameters to better determine whether the reinforcement threshold depends on the rate at which nicotine is reduced and other interacting variables (e.g., cues).

Other Outcome Measures

Compensation

One major concern about a nicotine reduction policy is that smokers might compensate for reduced nicotine levels by smoking more cigarettes and/or smoking more intensely as

the nicotine content in products is reduced. Consequently, exposure to tobacco toxins would be, at least transiently, increased. Compensation is commonly observed when smokers switch to cigarettes with a lower nicotine and tar yield or reduce the number of cigarettes they smoke per day (Hecht et al., 2004; Scherer, 1999). A marked degree of variability between subjects is evident in many of these studies, ranging from no compensation to near complete compensation. Understanding the mechanisms underlying these individual differences in compensation is critical for predicting which populations are at greatest risk for compensation and in need of interventions to minimize it.

Despite the importance of compensatory smoking in humans, this phenomenon has received little direct attention in animal nicotine self-administration models. Numerous studies have shown that modest compensatory increases in nicotine self-administration occur when the unit dose is reduced from a relatively high training dose (60 μg/kg; Shoaib et al., 1997; Watkins et al., 1999). As in human smokers, individual differences in compensation are observed in rats self-administering nicotine; however, few have paid specific attention to factors that moderate individual differences in compensation (Harris, Burroughs, Pentel, & LeSage, 2008; Harris, Pentel, Burroughs, Staley, & Lesage, 2011; Harris, Pentel, & LeSage, 2009). Individual differences in nicotine pharmacokinetics and severity of withdrawal as indicated by elevations in intracranial self-stimulation thresholds have not been found to predict the magnitude of compensation. However, baseline nicotine self-administration infusion rate has been consistently inversely related to degree of compensation, such that less compensation occurs in rats with higher baseline infusion rates (Harris et al., 2008, 2009, 2011). Because these studies did not conduct complete dose–response determinations, the maximum magnitude and individual variability in compensation was not fully characterized. Furthermore, compensation, and predictors of individual levels of compensation, has not been thoroughly assessed at the low end of the dose–response curve. Studies of this sort might provide important information about how subpopulations of smokers might be differentially affected by a nicotine reduction policy.

Behavioral Economics

The concepts of behavioral economics have proven useful for understanding how variables such as drug dose and response requirements to obtain a drug interact to control overall consumption of drugs of abuse (Hursh, 1980, 1991). This approach focuses on the relationship between the unit price of a drug and the demand for that commodity (i.e., drug intake). Unit price is expressed as a cost–benefit ratio of response requirement (e.g., FR value) divided by reinforcer magnitude (e.g., unit dose of drug). A fundamental concept is the demand curve, the function describing the consumption of a drug (y-axis) across a range of unit prices of that drug (x-axis). Generally, a demand curve shows that as the unit price of a commodity increases, consumption decreases. The primary outcome of interest in the demand curve analysis is the "elasticity" of demand for a drug. Demand is inelastic if consumption declines slowly (i.e., proportionally less) as unit price increases, or elastic if consumption declines rapidly (i.e., proportionally greater) as unit price increases. Elasticity of demand provides an index of the reinforcing or motivational efficacy of a drug, the extent to which an organism will defend a level of consumption as unit price increases (Bickel, Marsch, & Carroll, 2000; Hursh, Galuska, Winger, & Woods, 2005).

From a behavioral economic perspective, nicotine reduction policies involve increases in the unit price of nicotine (response cost/dose) by decreasing nicotine yield. As such, their effects on nicotine consumption are ideally suited to a demand curve analysis. In fact, DeGrandpre, Bickel, Hughes, and Higgins (1992) applied demand curve analysis in a meta-analysis of 17 nicotine reduction studies examining the effects of nicotine yield on smoking behavior. They found that the relationship between nicotine intake and unit price (i.e., nicotine yield) was well described by a nonlinear demand function, accounting for over 95% of the variance in nicotine intake both within and between studies. Behavioral economic analysis therefore has provided a precise method of characterizing the effects of nicotine reduction on smoking behavior. It has been useful for examining the effects of behavioral (e.g., access to alternative reinforcers) and pharmacological (e.g., NRT) treatments on the reinforcing efficacy of cigarette smoke and for investigating the nicotine and non-nicotine factors that contribute to smoking (Bickel, Madden, & DeGrandpre, 1997; Johnson & Bickel, 2003; Johnson, Bickel, & Kirshenbaum, 2004; Shahan, Bickel, Madden, & Badger, 1999; Shahan, Odum, & Bickel, 2000). Despite its frequent use in human smoking studies as well as its utility in animal studies examining the reinforcing efficacy of other drugs of abuse, very few animal studies have examined the elasticity of demand for nicotine (Diergaarde, van Mourik, Pattij, Schoffelmeer, & De Vries, 2011). Increasing the study of behavioral economic outcomes in animal nicotine self-administration research is important for several reasons. First, behavioral economic analysis is specifically intended for modeling drug abuse policies in animals (Hursh, 1991). Second, it would provide a conceptual framework to facilitate translation of findings between preclinical studies, clinical trials, and public policy concerned with nicotine reduction. Third, it provides unique information that can complement the analysis of nicotine reinforcement thresholds by elucidating the behavioral mechanisms mediating changes in such thresholds. For instance, a decrease in threshold could reflect an increase in potency, an increase in the reinforcing efficacy of nicotine, or both. Normalized demand curve analysis can measure changes in reinforcing efficacy per se independent of dose and potency, allowing analysis of the relative contribution of these two factors and facilitating comparison of demand across species (Hursh et al., 2005). Finally, demand curve analysis provides a simple and precise quantitative approach to measuring changes in reinforcing efficacy across a wide range of conditions (Hursh et al., 2005).

Models of Relapse

Reduced nicotine content cigarettes could also reduce the health burden of tobacco by facilitating cessation amongst those who initially continue to smoke (cf. Hatsukami et al., 2010). That is, some individuals may not stop smoking as a direct result of nicotine reduction, possibly because the nicotine content in cigarettes remains above their individual threshold for reinforcement. However, they may be more likely to achieve abstinence when they make an active quit attempt. Animal models of reacquisition and reinstatement, as well as other models pertinent to cessation (e.g., withdrawal, punished behavior), may be useful for assessing this effect (Panlilio, Thorndike, & Schindler, 2005; Shaham, Shalev,

Lu, De Wit, & Stewart, 2003). For example, the ability of cues to reinstate behavior might decline as a result of a history of nicotine reduction. Whether this effect occurs, differs across individuals, or is affected by the pattern of reduction is unknown. Hence, animal models of relapse may be useful for understanding the variables that moderate the impact of nicotine reduction on cessation.

Model Considerations

Common parameters of the nicotine self-administration model have been criticized for not adequately modeling certain features of tobacco use. For example, animal studies typically use rapid (e.g., <3 s) infusions (Bardo, Green, Crooks, & Dwoskin, 1999; Corrigall & Coen, 1989; Donny et al., 1995; Kenny & Markou, 2006; LeSage, Burroughs, & Pentel, 2006; Shoaib et al., 1997). This has been based on the assumption that each cigarette puff delivers a bolus of nicotine to the brain within 10 s. However, the distribution kinetics of nicotine after the puff of a cigarette are actually considerably slower, with arterial nicotine concentrations peaking at approximately 30 s and brain nicotine concentrations peaking at around 2 min (Rose, Behm, Westman, & Coleman, 1999). Sorge and Clark (2009) directly compared nicotine self-administration in slow versus fast infusion models. They found that robust acquisition and maintenance of nicotine self-administration can be achieved if low nicotine doses (e.g., 3 μg/kg), which are normally ineffective when delivered rapidly (3 s), are delivered more slowly (30 s). In addition, dopamine antagonists that normally increase nicotine self-administration for fast infusions of high unit doses decreased nicotine self-administration for slow infusions of low doses. These findings highlight a need for further study of the role of infusion parameters and nicotine distribution kinetics in animal nicotine self-administration models. These studies may also be useful models for understanding how other changes in cigarette design that alter nicotine delivery could impact low-dose nicotine reinforcement.

Numerous other features of the self-administration model are known to influence the reinforcing effects of nicotine and vary widely across studies. These include, among others, the response topography (e.g., lever press vs. nose-poke), schedule of reinforcement, duration of daily access, access to alternative reinforcers, level of food restriction, pharmacological history, sex, and strain (Caille, Clemens, Stinus, & Cador, 2012; Clemens, Caille, & Cador, 2010; Lesage, 2009). For brevity, we have omitted a detailed discussion of the literature pertaining to these variables; however, each could impact the threshold for nicotine reinforcement. Moreover, several variables have not been manipulated in animal models of nicotine self-administration but are known to alter the reinforcing effects other drugs of abuse (e.g., access to exercise, environmental enrichment). Finally, as discussed in detail in the next section, most studies of nicotine self-administration assess nicotine in the absence of other tobacco constituents. This approach may be a poor proxy for the effects of nicotine reduction in cigarettes. The potential impact of these various parameters on behavior in models of low dose nicotine self-administration should be explored. Moreover, these parameters need to be carefully controlled to facilitate comparison and integration of findings across studies within and between laboratories.

A primary question raised by the prospect of nicotine regulation is whether reducing nicotine delivery below the reinforcement threshold in established adult smokers would be sufficient to prevent the development of nicotine addiction in nicotine naive individuals. Almost invariably, smoking starts during adolescence. Therefore, research is needed to examine the extent to which adolescents would initiate and continue using nicotine at doses below those that maintain behavior in adults. Research on the differential effects of nicotine in adolescents compared with adults is mixed. Several studies suggest that adolescent rats self-administer more nicotine (30 μg/kg) and acquire stable behavior faster than adults (Chen et al., 2007; Levin, Rezvani, Montoya, Rose, & Swartzwelder, 2003; Levin et al., 2011). However, relatively little attention has been given to acquisition of self-administration at low doses. Compared with rats in early adolescence (starting PND 31), adult male rats are more likely to acquire nicotine self-administration at a low dose (15 μg/kg; Shram et al., 2008). These data are limited, however, both in terms of the age of initiation and the exclusive focus on males. Several studies have reported sex differences in the acquisition of nicotine self-administration during adolescence (Chen et al., 2007; Levin et al., 2011), including a greater likelihood of females acquiring at a low dose (5 μg/kg; Lynch, 2009). Likewise, other work has suggested that adolescents may be more sensitive to the potentiating effects of acetaldehyde (a tobacco constituent discussed in the Could Other Constituents of Tobacco Impact the Threshold for Self-administration? section) on nicotine self-administration (Belluzzi, Wang, & Leslie, 2005). Clearly, much work remains to be done determining the potential impact of nicotine reduction on adolescent initiation of nicotine self-administration.

Data Analysis Considerations

Animal researchers typically analyze nicotine self-administration dose response data via statistical comparisons of group mean response rates for a given nicotine dose to that for saline. Accordingly, the nicotine reinforcement threshold would be the lowest dose that maintains a significantly higher mean rate of responding when compared with saline. However, threshold estimates based on group averages may be of limited use for setting nicotine performance standards. Regulatory agencies will likely be more interested in knowing the proportion of individuals showing different patterns of behavior (e.g., how many individuals fail to change or even increase use) at a given nicotine dose (Hatsukami et al., 2010). This is consistent with the FDA's current practice of setting the acceptable daily intake or tolerable daily intake for other regulated substances (e.g., artificial sweeteners, melamine; Crump, 1984; Hsieh, Chiang, Chiang, & Wen, 2009; Renwick, 1990). From this perspective, the nicotine reinforcement threshold would be the dose at which less than a specified percentage of animals acquire or maintain nicotine self-administration. This requires researchers to adopt a different approach to analyzing dose–response curves, which focuses more on the distribution of individuals in large samples of animals and less on the average response of a relatively small group.

How Will Non-nicotine Stimuli Impact Behavior During Reduction?

Smoking does not take place in a vacuum. Smokers administer nicotine in the context of many environmental stimuli that are

paired with both nicotine and self-administration behavior (e.g., location of smoking, cigarette appearance and taste, other people or activities usually combined with smoking, taste and effects of alcohol). These stimuli (i.e., cues) can serve multiple functions in both Pavlovian and operant associative processes. Cues are most commonly discussed for their involvement in Pavlovian conditioning as conditioned stimuli. Any stimulus that regularly precedes nicotine (an unconditioned stimulus) and therefore also regularly precedes the pharmacological effects of nicotine (unconditioned responses), whether or not it precedes smoking behavior, can come to function as a conditioned stimulus causing reflexive conditioned responses (Pavlov, 1927). These responses can be similar to those elicited by nicotine (e.g., increased heart rate) and may contribute to subjective feelings of craving and withdrawal in the presence of cues. In addition to cues becoming conditioned stimuli by virtue of preceding the drug effect, when the cues also precede smoking behavior, they can serve as discriminative stimuli (i.e., occasion setters) signaling that engaging in smoking behavior will result in nicotine reinforcement (Skinner, 1953). As a result, their presence increases the probability of engaging in smoking behavior. Finally, the frequent pairing of stimuli with the reinforcing effects of nicotine can cause them to become conditioned reinforcers that can reinforce smoking behavior in their own right (e.g., the taste of a cigarette).

Interestingly, researchers have also suggested a nonassociative mechanism through which environmental stimuli may be involved in maintaining smoking behavior (Chaudhri et al., 2006; Donny et al., 2003; Palmatier, Liu, Matteson, Donny, Caggiula, et al, 2007). According to the dual-reinforcement model, smoking behavior is not maintained simply by the unconditioned reinforcing effects of nicotine and the consequent conditioned effects of nicotine-associated stimuli; nicotine also increases the reinforcing value of other non-nicotine reinforcing stimuli in the environment through nonassociative mechanisms. This alternative relationship between nicotine and other reinforcers is important to consider when evaluating the outcome of nicotine reduction for several reasons. First, the reinforcement-enhancing effects are known to impact responding for nicotine-associated conditioned reinforcers. Animals responding to stimuli that have previously been paired with nicotine do so more rigorously if they are concurrently exposed to nicotine even noncontingently (Palmatier, Liu, Matteson, Donny, Caggiula et al., 2007). Second, chronic treatment and subsequent withdrawal from nicotine leads to a decrement in reinforced behaviors, which may provide an additional motive for use of even low levels of nicotine (Epping-Jordan, Watkins, Koob, & Markou, 1998; LeSage et al., 2006; Skjei & Markou, 2003; Weaver et al., 2012). Finally, the dose–response curve for the primary reinforcing and reinforcement-enhancing effects of nicotine may differ. Although studies have described each effect across a range of doses (Chaudhri et al., 2007; Corrigall and Coen, 1989; Donny et al., 1995; Harrison, Gasparini, & Markou, 2002), and these studies differ on a number of parameters (e.g., strain, route of administration, and history of nicotine exposure) and none of the studies has directly compared the curves for these two effects of nicotine. In sum, both effects should be considered in evaluating the impact of nicotine reduction on behavior.

While it is difficult to identify which of these functions a specific cue serves, likely because each cue serves multiple functions, it is clear that environmental stimuli are important and likely contribute to the maintenance of smoking. With regard to a nicotine reduction policy, it is important to consider how the continued presence of these cues will affect behavior as nicotine is reduced. Indeed, if nicotine was reduced below the threshold for nicotine reinforcement, cues that have been paired with nicotine may be a primary determinant of continued smoking. Smokers have long, complicated, unknown, and largely variable histories with their smoking cues and manipulating cues experimentally in humans is fraught with challenges (Conklin & Tiffany, 2002). These difficulties make questions about smoking cues ripe for the animal self-administration paradigm.

Considerable evidence from animal models supports the hypothesis that cues play a role in self-administration behavior and that their continued presence alters behavior when nicotine is removed (i.e., extinction; Caggiula et al., 2001; Cohen, Perrault, Griebel, & Soubrie, 2005). In one study, responding was maintained by cues in the absence of nicotine for the entirety of the sessions tested (55–60 sessions). Once cues were removed, responding began to slowly decline (Cohen et al., 2005). These results indicate that once cues have a history of being paired with nicotine, they may be critically involved in the maintenance of behavior. The cues are likely maintaining behavior in part because they have established conditioned reinforcing value through associative processes involving their repeated pairing with the unconditioned reinforcer of nicotine. Over time, it is likely that the association would weaken and the cues would lose their reinforcing value, but the timeline for this decline and the determinants of the rate of change are unknown. Notably, the method of nicotine reduction (immediate vs. gradual) might be expected to affect the speed of extinction of these conditioned reinforcing effects. Indeed, animal research on oral cocaine consumption suggests that cues are more likely to maintain behavior in a gradual, compared with an abrupt, reduction approach (Falk & Lau, 1995). Additionally, it is not known how behavior would be changed by the continued presence of cues if nicotine was reduced but not eliminated. Indeed, if low doses of nicotine enhance the value of nicotine-associated reinforcers (Palmatier, Liu, Matteson, Donny, Caggiula et al., 2007), then even small amounts of nicotine could have marked effects on behavior.

Given the critical role cues may play in attenuating decreases in behavior in the absence of primary reinforcement from nicotine, individual differences in the underlying mechanisms driving cue effects are of the utmost importance. Some researchers suggest that the variability of drug outcomes, and specifically in cue effects, can be explained by the degree that the drug cues are "wanted" (Berridge & Robinson, 2003). According to this theory, all drug users learn about the cues through associative processes, but the degree to which organisms will engage in behavior to obtain access to the cues may be a trait of the individual (Flagel, Watson, Akil, & Robinson, 2008). Some individuals may be more susceptible to the ability of a cue to elicit attraction or engagement, occasion search for their paired unconditioned rewards, and serve as a conditioned reinforcer for new instrumental behaviors. Accordingly, researchers have described two behavioral phenotypes. One of the phenotypes, called sign-tracking, describes rats that approach and engage cues that predict reward, while the other, called goal-tracking, describes rats that immediately approach the location of the reward when the cue is presented

(i.e., the cue itself is not "attractive"). Sign-tracking has been shown to be related to several drug outcomes including higher break points for cocaine on progressive-ratio schedules (generally considered to be an indicator of motivation to obtain drug; Saunders & Robinson, 2011), the development of cocaine-paired conditioned place preference (Meyer, Ma, & Robinson, 2011), greater cocaine sensitization upon repeat treatment (Flagel et al., 2008), and greater cue-induced reinstatement (Yager & Robinson, 2010). While research has yet to examine sign-tracking in relation to nicotine outcomes, this new paradigm may provide an important insight into the variability observed in nicotine self-administration and the role of cues following nicotine reduction.

If nicotine is reduced to low levels, over time, the conditioned effects of nicotine-associated stimuli should extinguish. Current theories of extinction emphasize that the relationship between a cue and nicotine is not unlearned, but instead, a new relationship between the cue and the unavailability of nicotine dominates. This new learning is context dependent (Bouton, Todd, Vurbic, & Winterbauer, 2011; Bouton, Westbrook, Corcoran, & Maren, 2006); extinction learning in a new context tends not to generalize back to the original learning context (Wing & Shoaib, 2008). Not surprisingly then, treatments targeting the extinction of drug cues by presenting smoking cues repeatedly without the drug in a controlled setting have had little success (Conklin & Tiffany, 2002). One of the advantages of a nicotine-reduction policy is that people continuing to smoke would do so in the same contexts in which they had always smoked. Additionally, extinction of multiple conditioned stimuli at one time has been shown to be more effective than extinction of each cue individually when the cues were together paired with nicotine in the past (Rescorla, 2006). If nicotine content were reduced, conditioned stimuli that had always been paired together would be extinguished together.

Extinguishing the conditioned effects of nicotine-associated cues may also help prevent relapse after cessation (Becker, Rose, & Albino, 2008). The most common animal model of relapse processes is reinstatement. In this paradigm, self-administration behavior is extinguished by no longer presenting nicotine infusions or cues contingent upon behavior. After behavior has decreased below some experimenter-defined criterion, cues (or nicotine) are again presented contingent upon behavior. Nicotine-seeking behavior is considered to be reinstated when self-administration behavior increases significantly following cue presentation (Fowler & Kenny, 2011; Liu et al., 2006; Paterson, Froestle, & Markou, 2005). One would predict blunted cue-induced reinstatement following reduction as the cues would be presented in the absence of the primary reinforcing effects of nicotine; however, little is known about how reinstatement might differ when animals are "extinguished" with low doses of nicotine. Furthermore, few studies have examined the role of context in reinstatement (Wing and Shoaib, 2008). Cues may continue to reinstate behavior in contexts that were not encountered during reduction.

Animal research may be useful for identifying novel approaches to addressing potential challenges related to the different contexts associated with nicotine use. As implied previously, contexts that are infrequently encountered may take longer to extinguish and, therefore, result in renewed behavior. In addition, contexts associated with high doses of nicotine (e.g., chain smoking) may be more resistant to extinction given the stronger value of the unconditioned stimulus. One possibility for facilitating extinction would be the introduction of a novel cue paired with extinction. This novel cue would function to signal that nicotine was no longer available and no longer paired with previous smoking cues. The cue would transcend various environmental contexts, such that extinction learning in one context might be generalized to other contexts. Indeed, basic behavioral work has shown that pairing extinction with a novel cue helped transfer extinction learning from one context to another context in which extinction learning had not yet taken place but in which the cue had previously been paired with the reinforcer (Brooks & Bouton, 1993). Such animal research might suggest the utility of introducing a novel cue to cigarettes or cigarette packaging paired with nicotine reduction to bolster extinction across contexts.

Could Other Constituents of Tobacco Impact the Threshold for Self-Administration?

For years, research on the addictive properties of a cigarette has focused on nicotine; however, there are over 4,000 chemicals in a cigarette, some of which are hypothesized to contribute to cigarette addiction. Although limited, evidence suggests that a number of non-nicotine compounds in cigarettes have their own reinforcing properties and/or potentiate the reinforcing value of nicotine (Bardo et al., 1999; Belluzzi et al., 2005; Castagnoli et al., 2002; Clemens, Caille, Stinus, & Cador, 2009; Green, Phillips, Crooks, Dwoskin, & Bardo, 2000; Guillem et al., 2005, 2006; Villegier, Lotfipour, Belluzzi, & Leslie, 2007; Villegier, Lotfipour, McQuown, Belluzzi, & Leslie, 2007). Thus, studies focused on nicotine in isolation may significantly underestimate the abuse liability of cigarettes. Research related to the regulation of nicotine must consider the potential role of non-nicotine compounds in cigarette smoke. Animal research is well-suited to examine the role of other tobacco constituents because complex interactions with nicotine across a range of doses can be evaluated in ways that are currently unfeasible in humans.

On August 30, 2010, the Tobacco Products Scientific Advisory Committee (TPSAC) for the FDA released a list of potentially harmful non-nicotine constituents, including several compounds that are believed to be addictive (TPSAC, 2010). There are four compounds or classes of compounds for which evidence exists that they possess either reinforcing properties or are able to potentiate the reinforcing properties of nicotine: (1) minor tobacco alkaloids, (2) monoamine oxidase inhibitors (MAOIs), (3) acetaldehyde, and (4) β-carbolines (harman and norharman). Although there are data to suggest these four types of constituents may be important, the data are quite limited. Furthermore, key questions related to the complex interactions between nicotine and a mix of various compounds, as found in cigarette smoke, have not been addressed.

Nicotine is the primary alkaloid found in the tobacco leaf, accounting for approximately 95% of the total alkaloid content. The remaining portion is composed of the minor tobacco alkaloids, including nornicotine, anabasine, anatabine, cotinine

and myosmine, each exhibiting a similar chemical structure to nicotine (Hukkanen, Jacob, & Benowitz, 2005). TPSAC included anabasine and nornicotine on the list of potentially harmful cigarette smoke constituents; anatabine and myosmine were initially on the list but were removed because of lack of sufficient data. A few studies have evaluated how these minor alkaloids impact nicotine self-administration in rats. In an important study, Clemens and colleagues (2009) demonstrated a significantly higher level of responding in rats self-administering 30 μg/kg nicotine plus a mixture of these five minor alkaloids (at doses indexed to their concentration, relative to nicotine, in cigarette smoke) compared with rats responding for infusions of nicotine alone, the minor alkaloids alone, or saline alone. The solution of minor alkaloids alone had no effect relative to saline. Nornicotine has been shown to support self-administration by itself, but higher doses are required and lower response rates are attained (Bardo et al., 1999). Conversely, large doses of nornicotine administered to rats prior to a nicotine self-administration session also inhibited nicotine self-administration (Green et al., 2000; Stairs et al., 2007). Additional studies not utilizing self-administration also suggest that the minor alkaloids may have actions relevant to reward (Dwoskin et al., 1995; Green, Brown, Phillips, Dwoskin, & Bardo, 2002; Papke, Dwoskin, & Crooks, 2007). Nevertheless, with the exception of the Clemens study, the critical question of whether these compounds interact with nicotine has not been addressed.

Monoamine oxidase is partially inhibited (~30%–40%) in brains of cigarette smokers (Berlin & Anthenelli, 2001; Fowler, Volkow, Wang, Pappas, Logan, MacGregor, et al., 1996; Fowler et al., 1998; Fowler, Volkow, Wang, Pappas, Logan, Shea, et al., 1996; Leroy et al., 2009; Volkow, Fowler, Ding, Wang, & Gatley, 1999) and this decreased MAO activity may be relevant to the addictive properties of cigarettes. Although it is currently unknown what cigarette smoke constituents result in this MAO inhibition, describing the impact of MAO inhibition is an important step for understanding the addictive potential of cigarettes. One approach to study this in rodents is to examine the impact of known MAO inhibitors that are not in tobacco on nicotine self-administration, as well as interactions with other non-nicotine constituents of cigarette smoke. Guillem and colleagues (2005) pretreated rats with the nonselective MAO inhibitors tranylcypromine and phenelzine and observed a significant increase in nicotine self-administration, compared with rats pretreated with saline. Several aspects of this study deserve comment. First, this study used doses of MAO inhibitors that likely resulted in near complete MAO inhibition (McManus & Greenshaw, 1991; Todd & Baker, 1995), compared with the 30%–40% inhibition typically associated with cigarette smoking. Second, subsequent work by these researchers have questioned whether the effects of these MAO inhibitors resulted from MAO inhibition or other actions of these drugs independent of, or in addition to, their effects on MAO (Lotfipour et al., 2011). Third, Guillem et al. (2005) examined the impact of these drugs across a range of nicotine doses and observed the potentiation of nicotine self-administration selectively at the lower doses of nicotine; studying just large doses of nicotine would have missed the effect. Fourth, this study also classified rats based on locomotor activity in a novel environment, and the impact of these drugs on nicotine self-administration was greater in the rats with high locomotor activity in a novel environment. This highlights the complexity of these studies and the importance of looking at group variability and individual animal differences, rather than the standard approach of just looking at the mean of a group.

Acetaldehyde is a component of cigarette smoke, although there are many other sources of this compound. Acetaldehyde has several biological activities that may contribute to interactions with nicotine, including either directly or indirectly inhibiting MAO (Talhout, Opperhuizen, & van Amsterdam, 2007). Rats self-administer acetaldehyde alone (Takayama & Uyeno, 1985), consistent with research showing that it can activate reward-related circuits in the brain (Foddai, Dosia, Spiga, & Diana, 2004). However, the doses of acetaldehyde used in these studies are likely higher than what would be relevant to cigarette smoke. Belluzzi and colleagues (2005) found that an acetaldehyde dose proportional to the concentration found in cigarette smoke (micrograms/cigarette) increased nicotine self-administration in adolescent rats, but not adult rats. However, as with most studies, this only looked at the interaction between nicotine and one other constituent and only evaluated a limited range of nicotine doses. Still, this study by Belluzzi and colleagues (2005) clearly highlights the potential difference between studying nicotine self-administration in adolescence, the time most relevant to smoking initiation in humans, and nicotine self-administration in adults, the time at which most experimental studies are conducted. Unpublished data also indicate that lower doses of acetaldehyde synergistically interact with nicotine to enhance self-administration in adult rats (DeNoble & Mele, 1983).

Harman and norharman are additional biologically active components of cigarette smoke (Pfau & Skog, 2004), although there is very little research on their interaction with nicotine. These compounds are MAO inhibitors (Herraiz, 2004) and may contribute to the MAO inhibition observed in smokers at the concentrations present in cigarette smoke (Rommelspacher, Meier-Henco, Smolka, & Kloft, 2002). However, they also appear to have actions independent of MAO inhibition (Arib et al., 2010; Rommelspacher et al., 2002; Touiki, Rat, Molimard, Chait, & de Beaurepaire, 2005). Large doses of norharman enhance responding for nicotine in rats on a progressive ratio, but not an FR, schedule of reinforcement (Guillem et al., 2006). Thus, while the data on harman and norharman are quite limited, they illustrate the potential contribution of β-carbolines and highlight the need to consider the nature of the behavioral paradigm (see Behavioral Economics section) in evaluating nicotine reinforcement.

Taken together, research has clearly demonstrated that non-nicotine constituents play an important role in nicotine reinforcement. The role of these constituents as determinants of behavior related to nicotine reduction, however, is nearly entirely unknown. Studies must address how these constituents impact both acquisition and maintenance of low dose nicotine self-administration. Furthermore, it is important to recognize that cigarette smoke contains all of the constituents, and studies must therefore examine them as a group, rather than as isolated constituents in individual experiments. Even a combination of all constituents studied to date does not represent the thousands of other constituents in tobacco smoke that may enhance further or attenuate the effects observed with isolated constituents. Use of smoke exposure or administration of extracts from commercial tobacco products may be useful for addressing this issue (Harris, Stepanov, Pentel, & Lesage, 2012;

Small et al., 2010). Ultimately, understanding these interactions will be critically important for considering policies to reduce the addictive potential of cigarettes. Animal models provide the ideal tools for assessing the impact of these pharmacological interactions and determining which other constituents must be addressed in a comprehensive nicotine reduction strategy.

How Might Comorbid Psychiatric Disorders, Such as Schizophrenia and Depression, Impact the Response to Nicotine Reduction?

The heterogeneity of the current smoking population may make anticipating the response to nicotine reduction difficult. Multiple factors, including age, sex, smoking history, nicotine dependence severity, and psychiatric disorder comorbidity likely contribute to differences in smoking behavior. Certain populations have smoking rates that greatly exceed those of the overall population, display particular difficulty by establishing consistent abstinence during quit attempts, and manifest greater negative side effects during smoking cessation (Hyland et al., 2006; Vangeli, Stapleton, Smit, Borland, & West, 2011). Based on these observations, one might expect the consequences of nicotine reduction to vary dramatically across subgroups. Here, we focus on individuals with comorbid psychiatric disorders, and specifically schizophrenia and depression, as examples of the importance of considering subgroups in the context of research on nicotine reduction.

Smoking rates in individuals with schizophrenia have been reported to be as high as 80%, compared with about 20% in the general population (de Leon et al., 1995; Hughes, Hatsukami, Mitchell, & Dahlgren, 1986). Smokers with schizophrenia tend to consume more cigarettes per day (Ziedonis, Kosten, Glazer, & Frances, 1994) and display higher rates of nicotine dependence than the general population (Aguilar, Gurpegui, Diaz, & de Leon, 2005). There is a wealth of evidence suggesting that patients with schizophrenia may smoke for reasons other than, or in addition to, those of the general population. These include smoking for improvement in symptoms of schizophrenia, in particular cognitive enhancement (Adler et al., 1998; George et al., 2006; Gonzalez-Burgos, Fish, & Lewis, 2011; Sacco et al., 2005). Studies demonstrate nicotinic receptor antagonists worsen these symptoms (Tandon, 1999), as does smoking abstinence (George et al., 2002), with symptom improvement upon resumption of smoking behavior (Sacco et al., 2005). Furthermore, preclinical evidence points to the potential utility of nicotinic agonists for alleviating the cognitive deficits associated with schizophrenia, further highlighting how nicotine may ameliorate some symptoms (D'Souza & Markou, 2012). Smoking may also decrease medication-induced side-effects, specifically, extrapyramidal symptoms (Goff, Henderson, & Amico, 1992) that may contribute to a lack of adherence (Tandon, 2011). Despite these data suggesting that nicotine reduction could have detrimental effects on smokers with schizophrenia, research specifically evaluating the short-term (i.e., single session) effects of very low nicotine cigarettes has shown reductions in smoking behavior, withdrawal symptoms, and craving in patients with schizophrenia with no change in psychiatric symptoms (Tidey, Rohsenow, Kaplan, Swift, & Ahnallen, 2012). Hence, although smokers with schizophrenia might be expected to experience greater dysfunction upon nicotine reduction and may continue to smoke even low nicotine content cigarettes to alleviate this dysfunction, more research is clearly needed.

While no animal model can completely mimic the complex symptoms and deficits associated with a disease such as schizophrenia, several models have been able to reproduce core schizophrenia-like symptoms (Dawe, Hwang, & Tan, 2009). One of the most well-studied, the neonatal rat ventral hippocampal lesion (NHVL) model, produces animals with cognitive-like symptoms (attentional and working memory deficits), negative-like symptoms (e.g., social withdrawal), and positive-like symptoms (e.g., stereotypy or hyperlocomotion), in addition to sensory gating deficits (Chambers, 2009; Dawe et al., 2009). Initial studies have demonstrated that acute nicotine treatment may reduce some of these symptoms in NHVL rats (Chambers, 2009; Moss et al., 2009). However, these studies have not taken into consideration the important issues raised earlier, such as contingency, nicotine history, and dose. Of particular interest are potential differences in the threshold dose of nicotine required to maintain self-administration behavior between NHVL rats and normal controls when both groups have a history of nicotine self-administration. Other potential effects of nicotine reduction, such as increased anxiety and agitation, which has been documented upon smoking cessation in patients with schizophrenia (Tidey, Rohsenow, Kaplan, Swift, & Adolfo, 2008), could be evaluated in NHVL animals, and potential treatments for such symptoms could be assessed for their efficacy in NHVL animals. Finally, an examination of the interactions between nicotine and pharmacological agents used to treat schizophrenia, along with possible use of antidepressants or anxiolytic medications, would be possible in these studies.

It may be particularly important to consider contextual factors that could moderate the effects of nicotine reduction in NVHL rats to better evaluate whether differential motives for nicotine use could drive differential self-administration behavior. One useful approach would be to examine the range of nicotine doses that can alleviate symptoms and whether this ameliorative effect can motivate low dose self-administration. Whether NHVL rats self-administer nicotine at a lower dose than control rats if that dose improved their performance on a concurrently administered cognitive task would represent a highly novel and clinically informative contribution to the literature on nicotine reduction.

Cigarette use is also disproportionately high in people with depression compared with the general population (Ziedonis et al., 2008). The smoking rate in people with a lifetime history of depression is 60% (Lasser et al., 2000), while in patients currently diagnosed with depression, rates are as high as 30% (Grant, Hasin, Chou, Stitson, & Dawson, 2004). Importantly, studies have demonstrated decreased long-term abstinence after quit attempts in smokers with a history of depression (Covey, 2004). Further, smoking cessation may trigger or exacerbate depressive symptoms (Tsoh et al., 2000), suggesting that people

with depression may be particularly vulnerable to nicotine reduction.

Numerous studies have begun to elucidate the potential biological, psychological, and environmental mechanisms that likely contribute to the association between depression and smoking (for review, see Ziedonis et al., 2008). One potential mechanism involves the role of cholinergic system in depression, and how nicotine may interact with disrupted cholinergic function in depressed patients (Mineur & Picciotto, 2010). Procedures similar to those suggested previously for schizophrenia could also be used to examine the interactions between depression and nicotine reduction at the preclinical level. Animal models of depression could be combined with nicotine self-administration to examine this relationship. For example, the learned helplessness model of depression involves exposure of rats to an uncontrollable, inescapable aversive foot shock, which results in a decreased tendency to escape the same foot shock at later time points when escape is possible. This model has been cited as having high translational validity to depressive disorders (Pryce et al., 2011). Evidence suggests that nicotine may have antidepressant effects in the learned helplessness model of depression (Semba, Mataki, Yamada, Nankai, & Toru, 1998), as well as in other animal models of depression (Picciotto, Brunzell, & Caldarone, 2002; Andreasen, Henningsen, Bate, Christiansen, & Wiborg, 2011); however, these studies have generally used subcutaneous nicotine, often acute noncontingent, which limits their relevance to cigarette smoking and cessation in the depressed individual. Combined use of animal models of depression and self-administration can examine issues such as the initial response to nicotine, the nicotine threshold in rats displaying depression-like symptoms, the impact of nicotine self-administration on the signs of depression, the impact of nicotine history on threshold in these rats compared with controls, the emergence or worsening or depressive and/or withdrawal symptoms after nicotine reduction, and interactions between antidepressants and different doses of nicotine.

Clearly, there are many complex questions regarding the potential impact of nicotine reduction on different portions of the population, with particular concern for those with psychiatric disorders. While these questions must be investigated in patients, the variability in patient disease state, symptom severity, current and history of medications, compliance, and ethical issues regarding the potential negative impact of such studies limit what can feasibly be accomplished in the patient population. Animal models can be a valuable complimentary approach. Beyond those established for schizophrenia and depression, animal models exist that reproduce symptoms of multiple diseases, including anxiety, another widespread psychiatric disorder in the general population that is prevalent among tobacco users. Overall, animal models could provide information on the potential impact of nicotine dose reduction on self-administration behavior and symptom severity in these and other subpopulations of concern.

Discussion

Reducing the harm caused by cigarettes remains a critically important goal. The regulation of tobacco could be a powerful tool in this effort. The prospect of lowering the nicotine content of cigarettes as a means of reducing harm is particularly encouraging given the central role that nicotine is thought to play in initiating and maintaining smoking behavior (USDHHS, 1988). If nicotine levels were reduced below the point at which the cigarette functions as a reinforcer, both the initiation of new smoking and the persistence of current smoking would be expected to decline, and decreases in the harmful effects of cigarettes should follow.

Policy decisions such as those addressing the regulation of nicotine in cigarettes must rely on the available science. A critical step in building up the science of nicotine reduction starts with knowledge of the questions that will be asked when evaluating this approach (Hatsukami et al., 2010). This requires moving beyond the basic and well-justified conclusion that nicotine is necessary for maintaining smoking behavior and toward addressing specific and complex issues pertaining to nicotine regulation per se. In this review, we elaborated on some of these issues as they pertain to animal research with the overarching view that animal models can and will be an important component of the regulatory science of nicotine reduction.

Preclinical Abuse Liability Research in Light of Nicotine Reduction

The central construct underlying research into nicotine reduction is a familiar one—abuse liability. Animal research related to abuse liability assessments range from in vitro characterization of the pharmacological actions of compounds to behavioral models of reinforcement. Herein, we focused on animal models of nicotine reinforcement, primarily nicotine self-administration, given the assumption that the primary way in which nicotine reduction strategies would reduce harm is through reduced product use. From that perspective, animal models directly evaluating nicotine reinforcement are central to efforts aimed at informing tobacco product regulation. Nevertheless, these models have caveats that must be acknowledged and, if possible, addressed to maximize their utility.

One limitation noted previously is that animal research errs on the side of isolating variables. This bias is driven, at least in part, by the goal of describing the mechanisms underlying complex behaviors (discussed in detail in Challenging the Expectation That Research Must Be Mechanistic section). However, as animal researchers, we must recognize a large disconnect between this approach and the human conditions we are trying to model. Nicotine use almost invariably occurs in a complex pharmacological environment. Cigarette smoke contains thousands of compounds, many of which have significant pharmacological effects. Yet, the primary model we utilize to understand smoking behavior is self-administration of isolated nicotine (Corrigall & Coen, 1989; Donny et al., 1995; Palmatier, Evans-Martin, Hoffman, Caggiula, Chaudhri et al., 2006; Shoaib et al., 1997; Sorge & Clarke, 2009). One might ask "why should the default model assess nicotine in isolation?" This model serves to answer questions related to nicotine reinforcement, but may be less than optimal for addressing questions related to nicotine reduction in cigarettes, which have thousands of other constituents. The same argument could be made for environmental factors that could alter nicotine reinforcement and the consequences of nicotine reduction. Consider the potential impact of cues for reduction strategies. Assessing the impact of gradual versus immediate reduction in nicotine content in the absence of cues might yield a different conclusion than

if nicotine is assessed with a rich set of associated stimuli (Falk & Lau, 1995). Finally, there may be critical interactions across the different types of variables. For example, other constituents of tobacco might alter the role of conditioned stimuli without affecting behavior reinforced by nicotine alone. Likewise, other tobacco constituents or nicotine-associated cues might be more important for certain subgroups of the smoking population.

Second, current approaches to nicotine self-administration, including our own work, generally fail to capture the heterogeneity of behavior which, as noted earlier, is a defining feature of the ascending limb of the dose–response curve for nicotine self-administration and a critical concern of nicotine reduction strategies. The lack of attention to heterogeneity is evident in the methods commonly used. Most studies utilize sample sizes in the range of 8–12 rats per group, which are simply insufficient for understanding within group variance. Furthermore, the analytic methods we rely on describe group effects, not individual differences. Consequently, research on the acquisition of nicotine self-administration describes average acquisition curves that may poorly represent what happens at the individual level. Statistical approaches that examine within group variance support the assumption that the heterogeneity is significant and meaningful (Donny et al., 2004; Lanza, Donny, Collins, & Balster, 2004). Relatedly, as a field, we have not taken full advantage of the experimental models of specific individual-level risk factors known to be related to smoking, particularly psychiatric conditions. These models can be combined with the self-administration and other approaches for assessing the effects of nicotine to better describe how nicotine reduction might impact behavior across multiple segments of the population.

Third, current animal models of nicotine self-administration are relatively underdeveloped as indices of the behavioral consequences of nicotine addiction. Nicotine reduction would impact all types of smokers including initial users, light and intermittent smokers, current heavy, dependent smokers, and ex-smokers. These individuals differ not just in the history of use, but in the neurobiological and behavioral consequences of addiction. While self-administration models using other drugs of abuse have been developed to capture various signs of the addiction process (Ahmed & Koob, 1998; Deroche-Gamonet, Belin, & Piazza, 2004; Vanderschuren & Everitt, 2004), similar signs of addiction to nicotine in rats have not been reported. Development of these models would be ideal; however, even better integration of other approaches and measures of dependence (Epping-Jordan et al., 1998; Kenny & Markou, 2005), such as assessing disruptions in brain reward function during nicotine dose reduction (Harris et al., 2011), would provide valuable insight and maximize the relevance of animal models of nicotine reduction.

One could argue that other effects of nicotine besides reinforcement are only relevant insofar as they contribute to the reinforcing effects of nicotine. While it is true that change in use behavior is the primary target of interest, other assays may prove important in at least three ways. First, they may provide higher throughput models to quickly highlight factors that should be studied in models of reinforcement. One could imagine, for example, assessing the effects of potential MAO inhibitors in tobacco on the neurobiological effects of low doses of nicotine as a screen prior to assessing the potential impact of these constituents on nicotine self-administration. Second, other assays will be needed to shed light on the possible consequences of nicotine reduction, even if those consequences do not alter the probability of nicotine use. For example, one might argue that reducing nicotine content will lead to an increase in psychiatric symptoms. Even if individuals do not smoke for this reason (i.e., smoking is not driven by self-medication with nicotine), regulatory agencies will want to consider how best to mitigate these adverse consequences. Finally, this work might help identify areas of concern for human researchers. For example, if research demonstrates that nicotine reduction leads to cognitive impairments in adolescents, but not adults, then clinical research would need to consider the potential impact on smoking behavior in this subpopulation. Given the fundamental limitation of animal models (they represent aspects of, but do not replicate, the condition of interest), this type of translational research could prove vital.

Challenging the Expectation That Research Must Be Mechanistic

Animal research is heavily mechanistic, an approach that has resulted in many important advances in our understanding of nicotine addiction. However, we must be careful not to confuse the importance of mechanistic work with the expectation that animal research needs to be mechanistic to be important. The goals of regulatory science do not necessarily require mechanistic understanding. For example, if a tobacco constituent lowers the nicotine dose necessary for maintaining self-administration, even if we do not know how or why, that information would be critically important. Similarly, behavioral studies aimed at evaluating different nicotine reduction schedules could be useful even if not particularly informative about the etiology or pathophysiology of nicotine addiction. The potential bias that could result from misplaced expectations about what animal research can and should contribute may be most harmful in the grant review process. One could argue that the innovation related to studying nicotine reduction is low; we already know a lot about the dose–effect relationships, so studying the effects of nicotine as dose is reduced (as opposed to varied randomly, for example) may seem trivial. On the other hand, the potential significance of work related to nicotine reduction strategies is enormous. Indeed, a mathematical modeling evaluation of this approach suggested that the reduction in smoking prevalence could be dramatic (e.g., reduced to 5%), and the subsequent effect on death and disease could be equivalent to the impact of sanitation policies (Tengs, Ahmad, Savage, Moore, & Gage, 2005). Both reviewers and applicants will need to be particularly mindful of the value of animal research aimed at informing regulatory decisions despite any perceived shortcomings in elucidating mechanisms.

Moving Targets: The Evolution of Products and Policy

Both tobacco products and tobacco product regulation are likely to evolve rapidly. As animal researchers, we are accustomed to studying the effects of nicotine and assuming our findings are relevant to understanding cigarette use within the context of a relatively stable marketplace. However, cigarettes will evolve, particularly under the pressure created by tobacco regulation. The FDA has authority to regulate new tobacco products (i.e., products that are not considered substantially equivalent

to products that existed on February 15, 2007); therefore, evidence related to the evaluation of the abuse liability of new products will be important. For example, one concern about nicotine regulation is that the industry could develop products that continue to promote initiation and maintenance of tobacco use despite reduced nicotine content by altering the manufacturing of cigarettes. Research on the abuse potential of other non-nicotine constituents is imperative to develop our understanding of existing products and for premarket screening of new products. Furthermore, although cigarettes have constituted the predominant form of nicotine and tobacco use for almost a century, other products have begun to emerge (e.g., snus, dissolvables, hookah, e-cigarettes) and may be of concern in their own right or in the context of co-use with cigarettes. As animal research shifts to consider evaluating the abuse liability of nicotine within the context of cigarettes, it will also become important to determine how these other products can be evaluated in animal models.

Like the products themselves, tobacco product regulation will evolve with new questions and concerns emerging as new data, clinical observations, surveillance of tobacco product use, legal interpretations, policies, and legislation surface. These changes will shape research priorities. Currently, there is little infrastructure for translating these changes into guidelines for animal research efforts. Animal researchers are often distant from these public health, legal, and policy considerations. Greater integration of animal researchers into these discussions will likely generate creative and innovative research with more direct impact on tobacco regulation.

Conclusions

The passage of the FSPTCA (U.S. Congress, 2009) and the emphasis on tobacco product regulation by the WHO (WHO, 2007) creates a new research agenda for nicotine and tobacco researchers. Moving forward, a primary goal for animal researchers should be to provide regulatory authorities with the data needed to make well-informed policy decisions. More than ever, this requires an integrated approach that starts with a thoughtful consideration of the potential impact of tobacco product regulation, as well as the ever-changing tobacco market, and aims to translate these considerations into novel approaches to understanding the role of nicotine in tobacco use.

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