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Sex differences in nicotine self-administration in rats during progressive unit dose reduction: Implications for nicotine regulation policy

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ABSTRACT

Reducing the nicotine content in tobacco products is being considered by the FDA as a policy to reduce the addictiveness of tobacco products. Understanding individual differences in response to nicotine reduction will be critical to developing safe and effective policy. Animal and human research demonstrating sex differences in the reinforcing effects of nicotine suggests that males and females may respond differently to nicotine-reduction policies. However, no studies have directly examined sex differences in the effects of nicotine unit-dose reduction on nicotine self-administration (NSA) in animals. The purpose of the present study was to examine this issue in a rodent self-administration model. Male and female rats were trained to self-administer nicotine (0.06 mg/kg) under an FR 3 schedule during daily 23 h sessions. Rats were then exposed to saline extinction and reacquisition of NSA, followed by weekly reductions in the unit dose (0.03 to 0.00025 mg/kg) until extinction levels of responding were achieved. Males and females were compared with respect to baseline levels of intake, resistance to extinction, degree of compensatory increases in responding during dose reduction, and the threshold reinforcing unit dose of nicotine. Exponential demand-curve analysis was also conducted to compare the sensitivity of males and females to increases in the unit price (FR/unit dose) of nicotine (i.e., elasticity of demand or reinforcing efficacy). Females exhibited significantly higher baseline intake and less compensation than males. However, there were no sex differences in the reinforcement threshold or elasticity of demand. Dose–response relationships were very well described by the exponential demand function (r^2 values > 0.96 for individual subjects). These findings suggest that females may exhibit less compensatory smoking in response to nicotine reduction policies, even though their nicotine reinforcement threshold and elasticity of demand may not differ from males.

1. Introduction

Progressive reduction of the nicotine content in tobacco products to render them non-addictive has been advocated by scientists and considered by policy makers for many years (Benowitz and Henningfield, 1994; Kessler, 1994; Henningfield et al., 2004; Hatsukami et al., 2010b). This approach has received increasing attention since the introduction of the Family Smoking Prevention and Tobacco Control Act (FSPTCA) to Congress in 2007 (http://www.govtrack.us/-congress/bills/110/hr1108). Passed in 2009, the FSPTCA provides the FDA regulatory authority over myriad aspects of tobacco products, including the performance standards of specific constituents in tobacco itself and tobacco smoke (www.gpo.gov/fdsys/pkg/PLAW-111publ31/pdf/PLAW-111publ31.pdf). As such, the FDA now has the power to enforce a nicotine reduction policy as a population-wide strategy to reduce initiation of tobacco use in adolescents and promote cessation of use in current tobacco users.

Although, the public health benefits of a nicotine reduction policy could be vast (Tengs et al., 2005), there are significant knowledge gaps, conceptual issues, and ethical concerns that must be addressed to anticipate fully the feasibility and public health consequences of nicotine reduction (see Hatsukami et al., 2010b; Donny et al., 2012; Sofuoglu and LeSage, 2012; Benowitz and Henningfield, 2013 for review). For example, the threshold (i.e., lowest) nicotine content in tobacco products that engenders or maintains tobacco addiction is unknown. In addition, it is not clear to what extent a compensatory increase in smoking would be observed as cigarette nicotine content is reduced (Scherer, 1999), which is one of many potential adverse side effects of a nicotine reduction policy (Hatsukami et al., 2010b). Given that thousands of people die every week from tobacco-related disease (CDC, 2008), the FDA is in urgent need of research on these issues (see recent FOAs at http://www.fda.gov/tobaccoproducts/default.htm).

Understanding individual differences in response to nicotine reduction will be critical to anticipating the relative risk of addiction and

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adverse side effects (e.g., compensatory smoking) in subpopulations of smokers. Such knowledge will be vital to developing safe and effective policies, as well as clinical interventions to support those policies. For example, animal and human research suggests that there are sex differences in the addiction-related behavioral effects of nicotine. Female rats have been shown to acquire nicotine self-administration more rapidly (Donny et al., 2000; Lynch, 2009), work harder to self-administer nicotine (Donny et al., 2000; Lynch, 2009; Li et al., 2012), and exhibit greater cue-induced enhancement of nicotine self-administration (Chaudhri et al., 2005). In humans, women have shown less sensitivity to the discriminative stimulus effects of nicotine (Perkins et al., 1994), less change in subjective and reinforcing effects with changes in the nicotine content of a cigarette (Perkins et al., 1999), greater responsiveness to smoking-paired cues (Perkins, 1996), and less success in quitting smoking (for review, see Perkins, 2001). These findings suggest that males and females may respond differently to nicotine-reduction policies and may be at differential risk for side effects of such policies.

Animal research is vital to developing the science base to support FDA policy (for detailed discussion, see Donny et al., 2012). While there are a plethora of published studies in animals that have shown a dose–response relationship for nicotine's reinforcing effects (i.e., self-administration, for review see Matta et al., 2007; Donny et al., 2012), very few have been designed in a way that models aspects of a nicotine reduction policy like that being considered by the FDA (e.g. Denoble and Mele, 2006; Smith et al., 2013). Specifically, doses have usually been manipulated between groups rather than within subjects; or in random order within subjects rather than in a strictly descending order as would be stipulated by a nicotine reduction policy. The range and number of doses has also typically been limited within a single study. Moreover, operationally defining and quantifying individual differences in the nicotine reinforcement threshold and the magnitude of compensation during repeated reductions in unit dose have not been a primary focus. Although some studies have demonstrated compensation in rats following within-subject reductions in unit dose (e.g., Corrigall and Coen, 1989; Shoaib et al., 1997; Denoble and Mele, 2006), few have specifically examined individual differences in compensation (Harris et al., 2009, 2011; Smith et al., 2013).

To our knowledge, only three studies have examined changes in NSA during progressive reductions in the unit dose (Shoaib et al., 1997; Denoble and Mele, 2006; Smith et al., 2013). None of these studies operationally defined and measured nicotine reinforcement thresholds for individual subjects, and it is not clear whether the dose range was wide enough to do so. In one study, a saline phase was not included in the repeated dose-reduction protocol to allow calculating a reinforcement threshold for maintenance of NSA in individuals (Smith et al., 2013). However, the lowest nicotine dose (0.001875 mg/kg) did not maintain infusion rates above those in a separate group of rats with access to saline, suggesting that the dose range in the progressive reduction protocol encompassed a reinforcement threshold for nicotine. Nonetheless, the nicotine solutions used in this study included a cocktail of several tobacco constituents known to alter the reinforcing effects of nicotine (Clemens et al., 2009), and the concentration of the cocktail remained constant over the course of nicotine dose reduction. While this provides vital face validity for modeling nicotine reduction policy in animals, it didn't allow measurement of the nicotine reinforcement threshold per se and how non-nicotine constituents may have altered it.

The purpose of the present study was to examine sex differences in response to nicotine reduction using a rodent self-administration model. The study was specifically designed to model a nicotine reduction policy by arranging progressive decreases in the unit dose of nicotine to the point of extinction of self-administration in every subject. This approach is somewhat analogous to human studies that have examined progressive reduction of cigarette nicotine yield or content (e.g., Benowitz et al., 2007, 2009, 2012). However, in those studies, extinction of smoking behavior was not achieved in all subjects to allow measurement of individual reinforcement thresholds and sex differences were not examined. In the present study, the primary measures of interest, determined in individual rats, were the nicotine reinforcement threshold and magnitude of compensation.

Because changing the unit dose also changes the unit price of nicotine (response requirement/unit dose, Hursh, 1991), the present study was well suited to a behavioral economic analysis. This approach utilizes the concept of a demand curve; the function describing the consumption of a commodity (e.g., nicotine, y-axis) versus the unit price of that commodity (i.e., responses per unit dose, x-axis). Generally, a demand curve shows that as the price of a commodity increases, consumption decreases. The primary purpose of demand curve analysis is to characterize 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. Commodities for which demand is more inelastic are considered to have greater reinforcing efficacy or "essential value" (Hursh and Silberberg, 2008). In the present study, demand curve analysis provided a way to examine sex differences in the elasticity of demand for, or relative reinforcing efficacy of, nicotine in the context of a nicotine reduction model. Behavioral economics provides a conceptual and methodological framework commonly used in human laboratory, clinical, and epidemiological research (DeGrandpre et al., 1992; Emery et al., 2001; Tauras and Chaloupka, 2001; Bidwell et al., 2012; Mackillop et al., 2012a, 2012b), but seldom used in animal models of nicotine addiction (Diergaarde et al., 2011). As such, the use of a behavioral economic approach in the present study addresses an important knowledge gap in animal research and may facilitate the prediction of findings in human laboratory studies, clinical trials, and policy surveillance studies that utilize similar behavioral economic measures.

2. Methods and materials

2.1. Animals

Eight male and eight female Holtzman rats (Harlan, Indianapolis, IN) weighing 300–325 g and 225–250 g, respectively, at arrival were maintained under a restricted feeding regimen (18–20 g/day). Rats were fed daily during the 1-h interval between experimental sessions (see below). This strain was chosen to extend our previous studies that used the same strain to examine individual differences in compensatory NSA following unit dose reduction (Harris et al., 2008, 2009). Upon arrival, all rats were individually housed in a temperature- and humidity-controlled colony room with unlimited access to food and water under a reversed 12 h light/dark cycle (lights off at 11:00 h) for approximately one week. Rats were then moved to operant conditioning chambers and placed on food restriction in a separate room under the same light/dark cycle following recovery from catheter implantation for NSA (see below). Protocols were approved by the Institutional Animal Care and Use Committee of the Minneapolis Medical Research Foundation in accordance with the 1996 NIH Guide for the Care and Use of Laboratory Animals and the Guidelines for the Care and Use of Mammals in Neuroscience and Behavioral Research (National Research Council 2003).

2.2. Apparatus

Each operant conditioning chamber (29 cm × 26 cm × 33 cm; Coulbourn Instruments, Allentown, PA) was made of aluminum and Plexiglas walls, an aluminum ceiling, and a stainless steel grid floor. Two response levers were located on the front wall 10 cm above the chamber floor on either side of an aperture for delivery of food pellets (not used in this study) located 2 cm above the floor. LED stimulus lights were located 2 cm above each response lever. Water was continuously available via a spout mounted on the back wall of the chamber. Each chamber was placed inside a