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The effect of sazetidine-A and other nicotinic ligands on nicotine controlled goal-tracking in female and male rats

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ABSTRACT

Nicotine is the primary addictive component of tobacco products and its complex stimulus effects are readily discriminated by human and non-human animals. Previous research with rodents directly investigating the nature of the nicotine stimulus has been limited to males. The current study began to address this significant gap in the literature by training female and male rats to discriminate 0.4 mg/kg nicotine from saline in the discriminated goal-tracking task. In this task, access to sucrose was intermittently available on nicotine session. On interspersed saline session, sucrose was not available. Both sexes acquired the discrimination as evidenced by increased head entries into sucrose receptacle (goal-tracking) evoked by nicotine; the nicotine generalization curves were also similar between females and males. The pharmacological profile of the nicotine stimulus was assessed using substitution and targeted combination tests with the following ligands: sazetidine-A, PHA-543613, PNU-120596, bupropion, nornicotine, and cytisine. For females and males, nornicotine fully substituted for the nicotine stimulus, whereas sazetidine-A, bupropion, and cytisine all evoked partial substitution. Female and male rats responded in a similar manner to interaction tests where a combination of 1 mg/kg of sazetidine-A plus nicotine or nornicotine shifted the nicotine dose-effect curve to the left. The combination of sazetidine-A plus bupropion or cytisine failed to do so. These findings begin to fill a significant gap the in scientific literature by studying the nature of the nicotine stimulus and response to therapeutically interesting combinations using a model that includes both sexes.

1. Introduction

Smoking is the leading preventable cause of death in the United States, responsible for approximately 443,000 deaths annually (CDC, 2008). In spite of well-known health risks, nearly 70 million Americans continue to use tobacco products (NIDA, 2012). Most smokers, almost 70%, report that they desire to quit smoking (CDC, 2011). Gender can play an important role in this tenacious addiction, as well as in the success of smoking cessation treatments. Though fewer women smoke than men, the quit attempts of women are less likely to be successful compared to male counterparts, and there is increased sensitivity to social and behavioral factors related to tobacco use among women [for reviews see Perkins (2008) and Schnoll et al. (2007)]. There is no doubt that socio-environmental factors are likely the cause of some of these sex differences. However, the potential import of biological factors cannot be ignored (Arnold, 2009; Beery and Zucker, 2011; Cahill, 2006; Wetherington, 2007). These include the widespread effect of gonadal hormones early in development on the organization of the physiology including the nervous system, the differential impact of circulating gonadal hormones that vary across the lifespan of the individual, and the differential expression of X and Y genes in women and men (i.e., sex chromosome effects).

Preclinical models with rodents have also identified sex differences in the effects of nicotine further suggesting a biological mechanism for at least some of the differences. For example, females were more sensitive than males to the acute locomotor effects of nicotine (Harrod et al., 2004; Kanýt et al., 1999). This sex difference in the stimulant effects of nicotine was reduced in gonadectomized females (Booze et al., 1999; Kanýt et al., 1999). Further, female rats have higher rates of nicotine self-administration in comparison to males (Donny et al., 2000). Adult

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female rats also appear to be more sensitive to the reward-enhancing effects of nicotine and they will take more nicotine than males when a weak sensory reinforcer also follows lever pressing (Chaudhri et al., 2005). Consistent with this observation, in a place conditioning tasks, adult female rats were more sensitive than male rats to the conditioned rewarding effects of nicotine; evidence of conditioned reward was abolished in ovariectomized females (Torres et al., 2009). In the present study, we sought to extend the work on sex differences by investigating whether the nature of the nicotine stimulus differed between female and male rats.

Over the years, a variety of tasks have been developed to study the interoceptive stimulus effects of drugs in rodents and primates (Murray et al., 2011; Stolerman et al., 2009; Wooters et al., 2009). These drug discrimination tasks have served as powerful tools for understanding the behavioral and neuropharmacological processes of psychoactive substances. For the present study, we used the drug discriminated goal-tracking (DGT) task (Besheer et al., 2004) to study the interoceptive stimulus effects of nicotine. In the DGT task, rats have intermittent access to non-contingent liquid sucrose deliveries when given nicotine before the session. On intermixed saline sessions, sucrose is not available. A discrimination between nicotine and saline develops as evidenced by nicotine differentially evoking goal-tracking [i.e., "anticipatory" head entries into the site where sucrose was delivered; see Boakes (1977) and Farwell and Ayres (1979)]. This discrimination is specific to the pharmacological effect of nicotine and does not reflect a drug vs no drug discrimination (Besheer et al., 2004; Murray and Bevins, 2009).

Sex differences involving interoceptive conditioning with the nicotine stimulus have not been studied in the DGT task. Further, after an extensive search of the two-lever drug discrimination literature (cf. Stolerman et al., 2009; Wooters et al., 2009), we could not find a published paper with rodents that used nicotine as the training stimulus and examined potential sex differences (cf. Bevins and Charntikov, 2015). The only published sex difference involving the nicotine stimulus in rodents that we found was that reported in Jung et al. (2000). In that report, male and female rats were trained to discriminate pentylenetetrazol from saline. In substitution tests, nicotine prompted less pentylenetetrazol-like responding in females than males. Albeit limited, this outcome, combined with the work from Perkins and colleagues in humans (Perkins, 1999; Perkins et al., 1996), indicates the need to better understand the nature of the nicotine stimulus in both sexes.

With this need in mind, the goal of the present study was to begin to fill this gap in the scientific literature on nicotine drug discrimination. Table 1 lists the ligands we used to better understand the nature of the nicotine stimulus in female and male rats, as well as the purported mechanism(s) of each ligand. The ligands were selected because of their action on nicotinic acetylcholine receptors [nAChR (e.g., sazetidine-A)] and/or their use in smoking cessation (e.g., bupropion). As detailed in the Methods section, we investigated the substitution pattern of bupropion, cytisine, nornicotine, sazetidine-A, PNU-120596, and PHA-543613 in the DGT task. Based on the results of our substitution tests, we used interaction tests to further inform us about pharmacological profile of selected nicotine-like ligands. Because there is a significant gap in understanding pharmacology associated with sazetidine-A's nicotine-like stimulus effect, we focused our interaction tests on

Table 1
Drug Information.

Test Type	Drug	Doses (mg/kg)	IPI	Route	Mechanism
Generalization-1[1]	Nicotine	0, 0.025, **0.05**, 0.1, 0.2, 0.4	5 min	SC	α4β2 > α3β4 > α3β2 > α7 (Wooters et al, 2009)
Generalization-(2[1], 3[2], 4[2])	Nicotine	**0, 0.025, 0.05, 0.1, 0.4**			
Substitution[1] Interaction[1,2]	Sazetidine-A	0, 0.3, **1**, 3	10 min	SC	α4β2 partial agonist (Xiao et al, 2006)
Substitution[1] Interaction[2]	PHA-543613	0, 1, 3, 10	10 min	SC	α7 nAChR agonist (Wishka et al, 2006)
Substitution[1] Interaction[2]	PNU-120596†	**0, 10, 30**	10 min	SC	α7 nAChR positive allosteric modulator (Hurst et al, 2005)
Substitution[2] Interaction[2]	Bupropion	**0, 5, 10, 20, 30, 60**	15 min	IP	DAT and NET inhibitor, nAChR antagonist (Dwoskin et al, 2006)
Substitution[2] Interaction[2]	Nornicotine	**0, 0.3, 1, 3, 5.6**	15 min	SC	α6/3β2β3 > α7 > α4β2 > α3β4 > α3β2hα5 > α3β2β3 > α3β2 (Papke et al, 2007)
Substitution[2] Interaction[2]	Cytisine	**0, 0.1, 0.3, 1**	15 min	SC	α4β2 > α3β4 > α7 (Smith et al, 2007)

†All drugs, except PNU-120596, were administered at 1 mg/ml volume and were diluted in saline; PNU-120596 was administered at 0.5 mg/ml and was dissolved in 10% Tween prepared in H_2O. [1]Denotes tests on the first subset of rats. [2]Denotes tests using the second subset of rats. Interaction tests are indicated by the brackets (interaction **doses** in bold; also cf. Figure 1).