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Nicotine intake and problem solving strategies are modified during a cognitively demanding water maze task in rats

Tanseli Nesil [a,1,2], Lutfiye Kanit [a,b,2], Sakire Pogun [a,*]

[a] Ege University, Center for Brain Research, Bornova, Izmir, Turkey
[b] Ege University, School of Medicine, Department of Physiology, Bornova, Izmir, Turkey

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ABSTRACT

Background: Nicotine is the major addictive component in tobacco, and despite well-established adverse health effects of tobacco addiction, some smokers have difficulty quitting. The acute cognitive enhancement and/or the amelioration of the cognitive disruption during withdrawal that some smokers experience after smoking are among important factors that hinder quit attempts. The animal model presented in the current study is comparable to the human smoking condition although nicotine intake routes are different. Rats were exposed to a free choice of oral nicotine starting at adolescence, and given a water maze (WM) task as adults. This design allowed us to see if rats alter their nicotine intake during the WM task and if nicotine preference and intake modify abilities and strategies rats use for problem solving.
Methods: Male and female rats were exposed to a free choice of oral nicotine/water for 24 weeks, starting at five weeks of age. After this period, they were selected based on their nicotine intake and, together with control animals that received only water, were subjected to a place-learning task in the WM. Free-choice nicotine exposure continued during WM testing. Following acquisition, the probe trial presented the rats with a choice between using two different strategies for problem solving.
Results: Nicotine supported acquisition and rats increased their nicotine intake during WM testing; this effect was more pronounced in male rats with minimum nicotine preference and intake. Furthermore, nicotine modified the "female type" strategy in solving the place-learning task and nicotine treated female rats, unlike control females, behaved like males.
Conclusions: The increase in nicotine intake during mental engagement, and the sexually dimorphic effect of nicotine on problem solving strategies that we have observed in rats, may suggest that implementing sex-specific smoking cessation approaches, especially under stressful and cognitively demanding conditions, may be useful in helping smokers quit.

1. Introduction

Nicotine/tobacco addiction continues to be a serious health problem despite clearly demonstrated adverse effects on health. Smoking is reinforced by the pharmacological effects produced by nicotine, a drug of abuse, absorbed from inhaled smoke. Non-pharmacological, psychological factors also contribute to the maintenance of smoking (Robinson et al., 1992). On the other hand, nicotine also has positive, cognition-enhancing properties in humans (Colrain et al., 1992, Levin, 1992, Mangan and Golding, 1983, Newhouse et al., 2004, Peeke and Peeke, 1984, Rezvani and Levin, 2001, Robinson and Pritchard, 1992, Warburton, 1992) and in rodents (Levin, 1992, Levin et al., 2006, Puma et al., 1999), which may in themselves be of importance in the decision whether to continue smoking. One of the reasons that hinder successful quitting is apparently the effect of nicotine on cognitive function. After binding to nicotinic acetylcholine receptors (nAChRs), nicotine influences sensory, motor, attentional processing and impacts executive functions, learning and memory (Reviewed in (Evans and Drobes, 2009)). Nicotine deprivation impairs attention and cognitive function in smokers, and smoking a cigarette or taking another form of nicotine reverses this decline (Heishman, 1999); subsequently, some smokers believe that quitting smoking may deteriorate their performance. There may also be psychological factors operating in smokers (Levin et al., 1991) or animals (Caggiula et al., 2001, 2002, Chaudhri et al., 2006, Levin et al., 1991) self-administering nicotine. Associations between the tactile, olfactory, and visual cues and smoking a cigarette in humans, and environmental cues during nicotine self-administration in animals accompany the pharmacological effects of nicotine (Le Foll and Goldberg, 2006). Nonpharmacological influences are apparent in

* Corresponding author at: Ege University, Center for Brain Research, Bornova 35100, Izmir, Turkey.
E-mail addresses: sakire.pogun@ege.edu.tr, sakirepogun@gmail.com (S. Pogun).
[1] Present address: University of Virginia, Department of Psychiatry and Neurobehavioral Sciences, Charlottesville, VA, USA.
[2] The contribution of TN and LK are equal and therefore they are co-first authors.

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studies that report placebo effects of smoking or nicotine intake in other forms (Perkins et al., 2003).

Cognitive effects of nicotine vary in a complex way as a function of a number of factors that include the type of task, the hypothalamic–pituitary–adrenal axis (HPA) activity, as well as the sex of the subject. Laboratory-based information about the nature and extent of cognitive benefits will aid in this cost-benefit decision to quit smoking by optimizing smoking cessation interventions.

Place learning in a water maze (WM), developed by Morris (Morris, 1984), is a widely used preparation to test cognitive functioning in rodents, and is considered to be cognitively demanding (Jankowsky et al., 2005, Sweet et al., 2014, Wass et al., 2008). Animals find the water aversive and therefore learn to find the platform to escape. The platform is located in a circular tank, either above or below the water level, and rats use different strategies to find the platform, such as using visual cues, navigational cues, response learning, or thigmotaxis. The WM task can be designed to force the animal to use only one strategy, or to present more than one option thereby offering the rats a choice between using different strategies (McDonald and White, 1994). Sex of the subjects, pharmacological manipulations, developmental stage or hormones are among factors that may influence the preferred cognitive style. In our laboratory, a large number of studies demonstrated that there are sex differences in strategies that rodents use to solve a place learning problem in a WM. Specifically, male rats prefer spatial/navigational cues while female rats prefer visual cues to locate a platform in the WM even when there are no sex differences in abilities assessed during acquisition (Kanit et al., 2005, Kanit et al., 2003, Kanit et al., 1998a, Kanit et al., 2000, Kanit et al., 1998b, Kant et al., 2000). Additionally we had shown that when rats are treated with s.c. nicotine, this sexually dimorphic pattern is reversed in nicotine treated females; they behave like males and start using a spatial strategy (Kanit et al., 1998a). Although we have shown that nicotine injections modify place learning strategies in rats, it is not known if problem solving strategies and abilities in a WM place learning task are affected by chronic nicotine exposure using an experimental design where the nicotine intake of rats is not forced but is dependent on the nicotine preference of rats.

Another important effect that needs to be considered in WM studies is the stress of being forced to swim in water. If rats continue to regulate their nicotine intake during the WM study, stress should also be considered as one of the plausible factors that modify intake.

Others and we have been using oral self-administration as an alternative to nicotine injections or IV self-administration (Collins et al., 2012, Nesil et al., 2011). Most of the orally applied nicotine is metabolized in the liver during the first-pass, therefore, compared to intravenous (i.v.) route in rodents or inhalation in humans, the rate of entry to the brain is slower and the quantities are lower. However, there are important advantages: animals are not food deprived, can be exposed to nicotine for up to 24 h a day for extended periods, environmental cues and learning does not interfere with self-administration of nicotine (reviewed in Collins et al., 2012). Oral nicotine self-administration using the two-bottle free choice method is specifically suitable to assess individual differences in nicotine preference and intake. The results of studies using this method of nicotine delivery are similar to previous reports using the intravenous route in rats and to smoking in humans (Glick et al., 1996, Maehler et al., 2000, Matta et al., 2007). The addictive potential of oral nicotine application has been demonstrated in studies showing the acquisition of drug-taking behavior (Galli and Wolffgramm, 2011), dependence (Locklear et al., 2012), tolerance(Grabus et al., 2005), or withdrawal (Gaddnas et al., 2000, Nesil et al., 2015b) in animal models. Oral nicotine has also been used in studies to study stress responses in rats (Keser et al., 2013, Vieyra-Reyes et al., 2008).

We have demonstrated significant individual variation in the nicotine preference and intake of rats when oral nicotine is administered in a two-bottle free choice design (Nesil et al., 2011). Others and we have accepted the amount of nicotine intake by rats who had free access to a choice between nicotine and water to reflect the nicotine preference of individual rats (Biondolillo et al., 2009, Glick et al., 1996, Keser et al., 2013, Locklear et al., 2012, Nesil et al., 2011, Nesil et al., 2015a, Nesil et al., 2015b). In the current study, we pre-selected Sprague Dawley rats based on their nicotine intake and preference, and then tested their performance in a WM place-learning task. This experimental paradigm is comparable to the human smoking condition and therefore may have translational value in understanding the cognitive effects of chronic nicotine exposure.

The aim of the present study is to evaluate place-learning strategies employed by adult male and female rats, which had free access to uninterrupted oral nicotine starting at adolescence, compared with controls under similar conditions. Nicotine exposure continued during behavioral testing. The novelty of the current study is not only preselecting rats based on their nicotine preference and intake as adults, but also giving the rats the possibility to modify their nicotine intake during WM testing. This experimental approach would answer two interrelated questions: 1) Do rats modify their nicotine intake during the WM task? 2) Does nicotine preference and intake modify abilities and strategies rats use to solve a WM place-learning problem?

Our results may aid in understanding the modification of cognitive styles by nicotine in smokers, and also hint at possible changes in smoking patterns under stressful conditions involving mental engagement.

2. Methods

2.1. Laboratory animals

Male and female adult Sprague Dawley rats, obtained from Ege University Laboratory Animal Breeding Facility, were bred in our laboratories. Male and female offspring (n = 88, 46 F) were subjected to oral nicotine self -administration for 24 h/day continuously for 24 weeks (two-bottle free choice, 5–28 weeks of age). Rats were housed singly after weaning (4 weeks), kept under standard laboratory conditions (20–22 °C, 12–12 h light–dark cycle), fed *ad libitum* (standard rat food pellets) and received their drinking solutions from two bottles at all times. We have previously shown that nicotine preference and intake changes through development and overall, intake is reduced: Adolescent intake is greater than adult intake (Collins et al., 2012, Nesil et al., 2011). Therefore, we selected rats with high or low nicotine preference as adults (5–6 months of age). Selection was based on average nicotine intake during weeks 17–18 of nicotine exposure. After 18 weeks of nicotine self-administration, the highest [Maximum (Max)] and lowest [Minimum (Min)] nicotine consuming/preferring male and female rats (n = 12 for each group) were selected and transferred to another room. Only the 12 highest and 12 lowest nicotine consuming male and female rats (total n = 48) were included in the study. Control (Cont) rats (total n = 17, 9 F) were under the same conditions, but received water from both bottles. Oral nicotine self-administration continued during the WM study. Rats were handled for four days before the WM experiments began.

The animals were treated under the prescriptions for animal care and experimentation of the pertinent European Communities Council Directive (86/609/EEC), and the Institutional Animal Ethics Committee of Ege University approved all the procedures.

2.2. Measurement of voluntary nicotine intake behavior

Oral nicotine self-administration was performed as described earlier (Nesil et al., 2011). Briefly, singly housed rats were given access to either nicotine in water [Sigma, (−) nicotine hydrogen tartrate] or water using a two bottle free-choice method. Nicotine concentration used was comparable to published reports using similar protocols in rats (Adriani et al., 2004, Adriani et al., 2002, Halder et al., 2013, Nesil et al., 2011, Smith and Roberts, 1995). The concentration of nicotine