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Cigarette smoke exposure during adolescence enhances sensitivity to the rewarding effects of nicotine in adulthood, even after a long period of abstinence

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ABSTRACT

Adolescence is a period of enhanced vulnerability to the motivational properties of tobacco/cigarette smoking. Several studies have suggested that smoking initiation during this period will more likely lead to long-lasting cigarette or nicotine addiction. In the present study, we investigated the influences of adolescent cigarette smoke or nicotine exposure on the rewarding effects of nicotine, particularly whether these influences persist even after a long period of abstinence. Towards this, adolescent and adult Sprague–Dawley rats were repeatedly exposed to cigarette smoke or nicotine, for 14 days, and then were subjected to a 1-month abstinence period. Thereafter, the rewarding effects of nicotine were evaluated through the conditioned place preference (CPP) and self-administration (SA) tests. Even after a 1-month abstinence period, rats pre-exposed to either nicotine or cigarette smoke demonstrated enhanced CPP for the higher dose (0.6 mg/kg) of nicotine. Notably, cigarette smoke-preexposed adolescent rats, now adults, showed CPP for both 0.2 and 0.6 mg/kg dose of nicotine. Moreover, only these rats (pre-exposed to cigarette smoke during adolescence) showed significant acquisition and maintenance of nicotine (0.03 mg/kg/infusion) SA. These results suggest that cigarette smoke exposure during adolescence enhances sensitivity to the rewarding effects of nicotine in adulthood, even after a long period of abstinence. This may be a factor in the high rates of nicotine addiction and dependence observed in smokers who started during adolescence. More importantly, our findings highlight the enduring consequences of adolescent-onset cigarette smoking and the need to protect this vulnerable population.

1. Introduction

Cigarette/tobacco smoking is a major health problem and considered as one of the leading causes of preventable diseases and deaths worldwide (WHO, 2011). This habit typically starts during adolescence (Chen and Kandel, 1995; Lantz, 2003), in fact, about 80% of current smokers started smoking during this stage (USDHHS, 2012). Adolescence has been regarded as a critical period of vulnerability to drug use, abuse, and addiction (Spear, 2011). Moreover, substantial evidence suggests that adolescents are highly sensitive to the motivational/addictive effects of nicotine, the primary psychoactive substance in tobacco and tobacco products (Adriani et al., 2003; Buchmann et al., 2013; DiFranza et al., 2007; Dwyer et al., 2009; Levin et al., 2003). Enhanced sensitivity to the rewarding effects of nicotine during adolescence may account for the high incidence of smoking initiation during this period.

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Recent studies have shown that early smoking initiation will more likely lead to long-lasting or even life-long cigarette/nicotine addiction (Buchmann et al., 2013; Grimshaw et al., 2006; Kendler et al., 2013; USDHHS, 2012). Nicotine exposure during adolescence causes acute and persistent effects in the developing brain which may result in an increased probability of smoking continuation and relapse, even after long periods of abstinence (Lydon et al., 2014). Indeed, higher rates of unsuccessful quit attempts and/or relapse were observed in smokers who started smoking during adolescence (Abdolahinia et al., 2012; Khuder et al., 1999). In addition, young smokers are at greater risk of developing smoking-related disorders (USDHHS, 2012). Due to the enormity of this problem, efforts are being made in order to better understand and ultimately prevent the consequences of cigarette smoking on the developing adolescent brain.

In the present study, we investigated the influences of adolescent cigarette smoke exposure on the addictive/rewarding effects of nicotine, particularly whether these influences persist even after a long period of abstinence. We hypothesized that adolescent cigarette smoke or nicotine exposure renders an individual hypersensitive to the addictive effects of nicotine, which may persist even after long periods of abstinence; a possible factor in the high rates of nicotine addiction observed in this particular population. Towards this, adolescent and adult rats were exposed to nicotine or cigarette smoke, for 14 days, and then were subjected to a 1-month abstinence period. Thereafter, the rewarding effects of nicotine were evaluated through two of the most widely used animal models of drug addiction, the conditioned place preference (CPP) and self-administration (SA) tests.

2. Materials and methods

2.1. Animals

Male Sprague–Dawley rats were obtained from Hanlim Animal Corporation (Hwasung, Korea) and housed 4 per cage (46 × 26 × 26 cm) in a controlled vivarium [temperature (22 ± 2 °C), humidity (50 ± 5%), and 12-h light/dark cycle (lights on at 7:00 a.m.)]. Food and water were available *ad libitum*. Adolescent (PND 21-60) (O'Dell et al., 2006; Spear, 2011) and adult (>PND60) rats were used in this study. All procedures were performed in accordance with the Principles of Laboratory Animal Care (NIH Publication No. 85-23, revised 1985) and the Animal Care and Use Guidelines of Sahmyook University, Korea.

2.2. Cigarette smoke or nicotine exposure

After a 1-week acclimatization, adolescent (PND 28) and adult (PND 63) rats were exposed to cigarette smoke or nicotine, as previously described (de la Peña et al., 2014) (Fig. 1). Briefly, cigarette smoke was generated by burning 3R4F reference cigarettes (University of Kentucky, College of Agriculture, Reference Cigarette Program, Lexington, KY) through a microprocessor-controlled smoking machine (Scitech, Korea). The smoke was then transported to an exposure chamber, where animals were placed in cages. A standardized smoking procedure was followed: 35 cm^3 puff volume, 1 puff/minute, 2 s/puff (Small et al., 2010). Rats were exposed to cigarette smoke for 2 h (12 cigarettes), two times a day (morning and afternoon), for 14 days. Average carbon monoxide and total particulate matter levels were 94 mg/m^3 and 376 ppm, respectively.

For nicotine exposure, rats were implanted with osmotic pumps (Alzet®, Cupertino, CA, USA) filled with nicotine (nicotine hydrogen tartrate salt; Sigma, Seoul, South Korea), calculated to deliver 3.2 mg/kg/day for 14 days. This dose sufficiently induces nicotine dependence in rats (Cohen and George, 2013; Hamilton et al., 2010; Matta et al., 2007). All nicotine doses were reported as free base. The cigarette smoke and nicotine exposure protocol employed herein produced stable and comparable blood nicotine levels (see de la Peña et al., 2014), which are within the range observed in human smokers (Matta et al., 2007). The drug-naïve group was implanted with sham pumps.

2.3. Conditioned place preference (CPP) test

CPP tests were performed in two-compartment boxes with distinct visual and tactile cues, separated by a wall with a guillotine door (de la Peña et al., 2012). A biased conditioning procedure was followed (Le Foll and Goldberg, 2005). Each test has three phases: habituation and pre-conditioning (3 days), conditioning (6 days), and post-conditioning (1 day). For the first two days, rats were allowed free access to both compartments for 15 min, once a day (habituation). On the third day, the time spent in each compartment was measured (Ethovision System; Noldus IT, The Netherlands) to determine the preferred and non-preferred compartment of each rat (pre-conditioning). The conditioning phase followed wherein rats were subcutaneously injected with nicotine (0.2 or 0.6 mg/kg) and confined to their non-preferred compartment, or given saline and placed on their preferred side for 30 min. These dosages were selected based on previous studies in adolescent and adult rats (Ahsan et al., 2014; de la Peña et al., 2014; Le Foll and Goldberg, 2005). Control groups received saline every day. The post-conditioning phase followed where animals were drug-free and, similar to pre-conditioning, the time spent in each compartment was recorded.

2.4. Self-administration (SA) test

The methods for the SA experiments were outlined in detail in our previous studies (de la Peña et al., 2014; de la Peña et al., 2012). SA tests were performed in standard operant chambers (Coulbourn Instruments, Allentown, Pennsylvania, USA). Rats were first trained

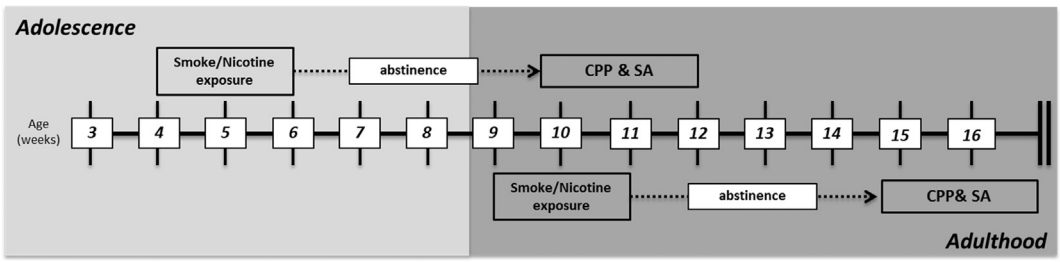

Fig. 1. The experimental schedule. Adolescent and adult Sprague–Dawley rats were exposed to cigarette smoke or nicotine for 14 days. Then, rats were subjected to a 1-month abstinence period. Thereafter, the rewarding effects of nicotine were assessed in the conditioned place preference (CPP) and self-administration (SA) tests.