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Mini-Review

Rodent models of nicotine reward: What do they tell us about tobacco abuse in humans?

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ABSTRACT

Tobacco products are widely abused in humans, and it is assumed that nicotine is the key substrate in these products that produces addiction. Based on this assumption, several pre-clinical studies have utilized animal models to measure various aspects of nicotine addiction. Most of this work has focused on behavioral measures of nicotine and how other variables contribute to these effects. Here we discuss the most commonly used animal models including, self-administration (SA), place conditioning (PC), and the intracranial self-stimulation (ICSS) paradigms in rodents. The strengths, limitations and procedural variables of these models are reviewed, followed by a discussion of how the animal models have been used to study factors such as age, sex, stress, and the effects of tobacco products other than nicotine. These factors are discussed in light of their influences on human tobacco abuse. The rodent models are evaluated in the context of face, predictive, and construct validity, and we propose that inclusion of factors such as age, sex, stress and other constituents of tobacco aside from nicotine can increase the utility of these animal models by more closely mimicking human tobacco abuse.

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1. Introduction

Tobacco use is a major health and economic concern. Although over 4800 chemical compounds have been identified in tobacco, the addictive nature of tobacco products is largely due to one compound,

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nicotine, a major alkaloid component (Stolerman and Jarvis, 1995). The seven main features of nicotine dependence have been formally described in the Diagnostic and Statistical Manual (DSM-VI). These include: tolerance, withdrawal, increasing use over a longer period than intended, unsuccessful efforts to discontinue use, large amounts of time spent obtaining drug, loss of social and occupational functioning, and continued use despite realization of harmful consequences. The DSM-VI requires a person to meet at least 3 of these criteria to be considered dependent and neither tolerance nor withdrawal alone is sufficient for a diagnosis of nicotine dependence.

Much pre-clinical work has focused on studying the neural mechanisms that mediate the rewarding effects of nicotine. Although, it is not possible to mimic all aspects of nicotine dependence as indicated by the DSM-VI criteria, animal models have attempted to mimic aspects of dependence including, tolerance, withdrawal, and possibly continued use and inability to discontinue use. The three most commonly used animal models to study the rewarding effects of nicotine include the self-administration (SA), place conditioning (PC) and intracranial self-stimulation (ICSS) paradigms.

The goal of this review is to provide a discussion of the most commonly used rodent models of nicotine addiction and to provide an evaluation of the validity of these models in measuring different aspects of tobacco abuse in humans. Our discussion includes a description of the methodology, parameters, and findings from studies using the SA, PC, and ICSS rodent models. We also include a discussion of how these models have been used to assess nicotine dependence and withdrawal since these are contributing factors to tobacco abuse in humans. An important aspect of our review is a consideration of these animal models with respect to the degree to which they assess face, predictive, and construct validity. Finally, we discuss how the inclusion of variables such as age, sex, environmental stressors, and additional tobacco ingredients in these rodent models can potentially increase the utility of these models by providing a better understanding of the mechanisms that mediate tobacco abuse in humans.

2. Animal models assessing the rewarding effects of nicotine

2.1. Nicotine SA

The SA paradigm is based on reinforcement principles involving strengthening of a behavioral response by presentation of nicotine after the operant response is performed. The operant behavior typically involves lever pressing, but often includes nose poke behavior in mouse preparations. Although oral nicotine SA has been established, this review will focus on the intravenous (IV) route of administration given that this route is more commonly used in animal studies and more closely mimics the rapid drug distribution of nicotine to the brain via inhalation.

Nicotine IVSA was first demonstrated in non-human primates (Goldberg et al., 1981), and subsequent reports using rodents focused on optimizing the parameters of nicotine IVSA. Using limited access schedules, manipulations such as a fast infusion delivery (approximately 1 s), and a pH of the drug at physiological levels have emerged as important variables that facilitate reliable nicotine IVSA in rats (Corrigall and Coen, 1989). Several laboratories have also reported that nicotine IVSA using limited access conditions (e.g. 1–2 h access) is facilitated by pre-training with food reinforcement and by maintaining animals on a food-restricted diet (approximately 80% of free feeding weight). The critical role of secondary reinforcers (i.e., cues predictive of nicotine) in maintaining nicotine IVSA in rats has also been examined. Indeed, when rats are permitted to make responses for nicotine in the absence of such cues, the operant response then extinguishes (Caggiula et al., 2002). Thus, it appears that a number of experimental manipulations (food pre-training, food-restriction, and the presence of secondary reinforcers) are important for rats to acquire and maintain nicotine IVSA. It is noteworthy, that such manipulations are not needed, or at least not needed to a great extent, for IVSA of other drugs of abuse such as cocaine. Thus, the need for such manipulations in order for rats to self-administer nicotine may call into question the validity of the IVSA paradigm in rats (at least under limit-access conditions) and whether nicotine really serves as a positive reinforcer on its own.

More recent studies have avoided food restriction procedures by giving the animals extended access to nicotine IVSA. For the extended procedures, animals are given up to 23 h of access to nicotine IVSA in a chamber where they are also able to respond for food and water delivery. Most studies using extended access procedures have employed the use of secondary reinforcers, indicating that the use of stimulus lights may also be necessary for the maintenance of nicotine intake in extended access procedures. However, to our knowledge no one has determined whether cues are as critical in extended access procedures as they have been shown to be in limited access procedures. The extended access paradigm is believed to model continuous availability of tobacco in humans. These studies have shown that rats display increased nicotine IVSA during the active/dark phase of the light cycle, and that the average daily nicotine intake is 0.18–1.5 mg/kg/day which approximates the levels of nicotine intake observed in human smokers (LeSage et al., 2003). Lastly, it has been demonstrated that rats given extended access to nicotine display physical signs of withdrawal and an increase in nicotine intake following abstinence from nicotine IVSA (O'Dell and Koob, 2007). This "nicotine deprivation effect" is believed to reflect the increase in tobacco use that is seen during relapse in abstinent smokers.

Although nicotine IVSA has been observed in mice, there are fewer studies in mice as compared to rats. In the initial studies, the tail vein was used as the IV portal due to the small size of the jugular vein in mice (Martellotta et al., 1995). Since the tail of the mouse is secured during the entire session to avoid disruption of drug delivery, it has been suggested that these studies may be limited with regard to modeling nicotine use in humans. Nicotine IVSA in mice has also been examined in animals that were trained initially to press for cocaine (Picciotto et al., 1998). This procedure may model how tobacco is commonly used in combination with other drugs of abuse. Also, there is a report of extended (12 h) access to nicotine in mice whereby animals SA nicotine during the active phase of their light cycle, which more closely mimics extended use of nicotine in humans during their active wake period (Stolerman et al., 1999).

2.2. Nicotine-induced PC

The PC paradigm assesses the motivational properties of a drug by means of Pavlovian conditioning. The drug is administered in a distinct environment and after several pairings the environment (conditioned stimulus=CS) becomes associated with the effects of the drug (unconditioned stimulus=UCS), thereby acquiring incentive-motivational properties. The environment contains cues that elicit either approach (i.e., conditioned place preference; CPP) or avoidance (i.e., conditioned place aversion; CPA) depending on whether rewarding or aversive properties of the drug were associated with the cues during conditioning.

There are some methodological issues to be considered when conducting PC studies with nicotine. Perhaps, the most important factor in regards to measuring nicotine reward is whether a *biased* or *unbiased* PC design is used. In a *biased* PC procedure, the animal receives repeated drug administration in their initially non-preferred environment (if examining the rewarding effects of a drug), or the preferred side (if examining the aversive effects of a drug). In an *unbiased* PC design, the animals are randomly assigned without regard to initial bias for either side of the conditioning apparatus.

In rats, nicotine has been reported to produce CPP, CPA, or no effect depending on the dose of nicotine that is used. In general, previous studies using a dose of nicotine within a 0.2–0.6 mg/kg dose range report CPP, whereas studies using a dose within a 0.8–1.2 mg/kg dose range report