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REVIEW

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Nicotine as a typical drug of abuse in experimental animals and humans

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Abstract *Rationale and background:* Tobacco use through cigarette smoking is the leading preventable cause of death in the developed world. Nicotine, a psychoactive component of tobacco, appears to play a major role in tobacco dependence, but reinforcing effects of nicotine often are difficult to demonstrate directly in controlled laboratory studies with animal or human subjects. *Objective:* To review the major findings obtained with various procedures developed to study dependence-related behavioral effects of nicotine in experimental animals and humans, i.e., drug self-administration, conditioned place preference, subjective reports of nicotine effects and nicotine discrimination, withdrawal signs, and ratings of drug withdrawal. *Results:* Nicotine can function as an effective reinforcer of drug-seeking and drug-taking behavior both in experimental animals and humans under appropriate conditions. Interruption of chronic nicotine exposure produces withdrawal symptoms that may contribute to relapse. Difficulties encountered in demonstrating reinforcing effects of nicotine under some conditions, relative to other drugs of abuse, may be due to weaker primary reinforcing effects of nicotine or to a more critical contribution of environmental stimuli to the maintenance of drug-seeking and drug-taking behavior with nicotine than with other drugs of abuse. Further experiments are also needed to delineate the role other chemical substances inhaled along with nicotine in tobacco smoke play in sustaining smoking behavior. *Conclusion:* Nicotine acts as a typical drug of abuse in experimental animals and humans.

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Introduction

Tobacco smoking is presently estimated to cause 20% of all deaths in developed countries. As with other types of drug dependence, tobacco dependence is described as a chronic, relapsing disorder in which compulsive drug-seeking and drug-taking behavior persist despite negative consequences and the motivation to quit. The high addictive properties of tobacco are exemplified by the great difficulty in quitting smoking. Although most smokers want to stop, only a small percent succeed. It is now becoming clear that continued tobacco use induces adaptive changes in the central nervous system that lead to drug dependence (American Psychiatric Association 2000). Nicotine, the major psychoactive component of tobacco, is thought to play a critical role in tobacco dependence through its actions as a reinforcer of drug-seeking and drug-taking behavior (Fiore et al. 2000; Goldberg et al. 1981a,b; Henningfield and Goldberg 1983a,b; Le Foll et al. 2005b; Stolerman and Shoaib 1991). Nevertheless, tobacco contains several hundred other chemical substances, some of which have psychoactive effects or may enhance the psychoactive effects of nicotine, and these other substances may contribute to the reinforcing effects of tobacco smoking (Fowler et al. 1996a,b). Indeed, reinforcing effects of nicotine have often been difficult to demonstrate directly in past controlled laboratory studies with both animals and humans as experimental subjects. As a result, there has been a controversy in the literature about the validity of previous findings that nicotine can produce reinforcing effects in experimental animals or human subjects (Dar and Frenk 2002, 2004; Robinson and Pritchard 1992).

A variety of laboratory animal models are available to study the cardinal features of drug dependence (Deroche-Gamonet et al. 2004; Everitt and Robbins 2000; Goldberg 1975; Goldberg et al. 1975, 1979, 1981a,b; Katz and

Goldberg 1988; Le Foll and Goldberg 2005a,b; Markou et al. 1993; Schindler et al. 2002; Schuster and Woods 1968; Spealman and Goldberg 1978; Vanderschuren and Everitt 2004). The effects of nicotine have been evaluated using animal models for studying the reinforcing effects of drug injections [intravenous drug self-administration and conditioned place preference (CPP) procedures], the subjective responses to administered drugs (drug discrimination), and the withdrawal states, including behavioral disturbances, that are associated with abrupt termination of chronic drug exposure (smoking cessation or administration of selective antagonists after chronic exposure) and relapse phenomena (reinstatement of extinguished drug-seeking behavior induced by stress, drug-associated cues, or drug priming). Most of these experimental studies have used rodents (rats and mice) as subjects, but results are available from studies using other animal species (monkeys and dogs) and human volunteers as subjects. We will first summarize the main experimental procedures used to assess these effects of nicotine and then review the preclinical and clinical findings obtained with nicotine using these procedures. Since previous review articles already provide detailed comparisons of the effects of nicotine in animals and humans (Henningfield and Goldberg 1983a,b; Rose and Corrigall 1997; Stolerman 1999), we focus here on the most recent important findings obtained with nicotine in animals and humans.

Experimental procedures for studying nicotine dependence

Intravenous drug self-administration

Natural rewards, such as water or food, and drugs of abuse may serve as positive reinforcers under appropriate conditions. For example, to assess the reinforcing effects of food, a food-deprived animal can be placed in a sound-attenuating chamber containing stimulus lights, response levers, and a device for dispensing food pellets. Lever-pressing responses will occur with increasing frequency when they result in delivery of food pellets, which, therefore, serve as positive reinforcers under these conditions. With intravenous drug self-administration proce-

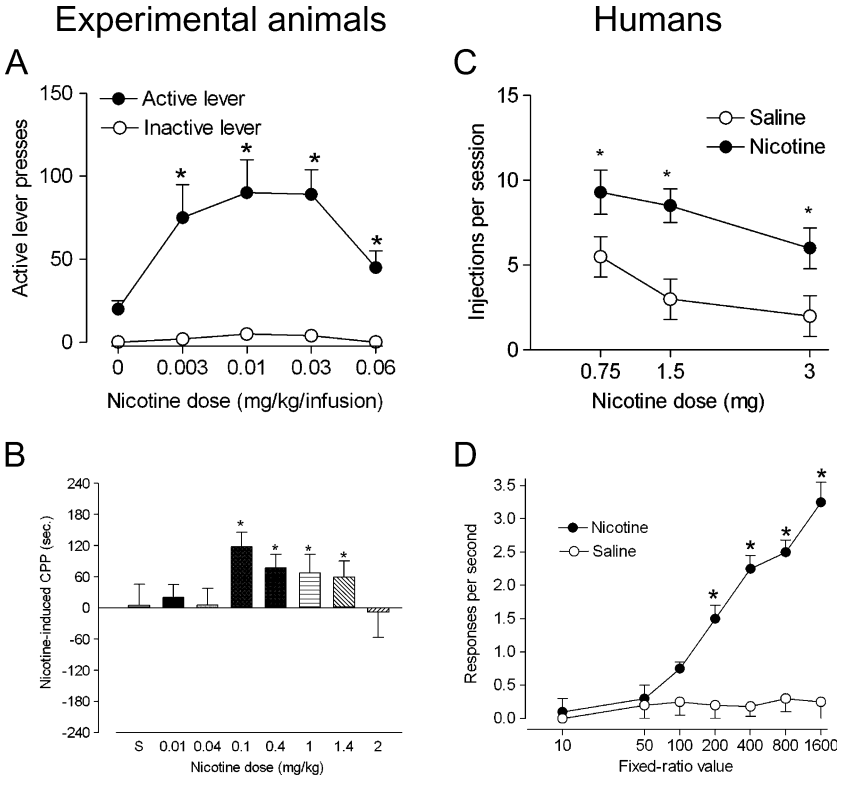

Fig. 1 Reinforcing effects of nicotine in experimental animals (**a**, **b**) and humans (**c**, **d**). **a** During repeated sessions, rats learned to press a lever to self-administer intravenous injections of nicotine, and light stimuli were paired with each drug infusion. Results are expressed as mean (±SEM) of number of responses on the active and inactive lever. Responding was higher on the active lever compared to the inactive lever. From Corrigall and Coen (1989). **b** Nicotine-induced CPP over a large range of doses in rats. Over repeated sessions, rats are either injected with nicotine and then placed in one environment, or injected with saline and placed in the other environment. In a nicotine-free state, the animal is then allowed access to both environments during a test session without injection, and the amount of time spent in each environment is recorded. From Le Foll and Goldberg (2005a). **c** Human subjects learned to respond on levers to intravenously self-administer nicotine or saline. A light stimulus was paired with each injection. The number of self-administered nicotine injections was consistently higher than the number of self-administered saline injections (**c**) and rate of responding was significantly higher for nicotine than for saline when the number of responses needed to produce an injection was high (**d**). Results are expressed as mean (±SEM) of number of injections per session (**c**) or as a function of the number of responses required for each injection of nicotine or saline (fixed-ratio value) (**d**). From Harvey et al. (2004)

dures, a catheter implanted in a jugular vein allows the animal to intravenously self-administer a small amount of drug by pressing a lever. The administration of drug constitutes the event that positively reinforces the lever-pressing behavior, and reward is inferred if the frequency of responding subsequently increases (thus, defining reinforcement) (Fig. 1). With these behavioral procedures, stimuli such as a light or tone are often associated with delivery of the reinforcer. It has been argued that, in many instances, these stimuli are not neutral, but themselves have the potential to produce weak reinforcing effects, and there is accumulating evidence that nicotine exposure can increase their motivational value, i.e., they may become more effective reinforcers (Chaudhri et al. 2005). These stimuli, or "cues," can also progressively gain motivational value by Pavlovian conditioning and associative learning processes. In either case, environmental stimuli can acquire the ability to facilitate the maintenance of drug-seeking and drug-taking behavior and also reinstate drug-seeking behavior that has been extinguished (Arroyo et al. 1999; de Wit and Stewart 1981; Goldberg 1975; Goldberg et al. 1975, 1983; Le Foll and Goldberg 2005b; Meil and See 1996; Self and Nestler 1988; Stewart 1983), and may become critical determinants of reinforcement of drug-taking behavior by nicotine administration.

Various schedules of reinforcement have been employed to study drug self-administration behavior. Two of the most commonly used are fixed-ratio and progressive-ratio schedules of intravenous drug injection. Under a fixed-ratio schedule of intravenous drug injection, the subject must make a fixed number of responses (lever press or pull or nose-pokes) in order to obtain each injection of drug [e.g., one lever press for a fixed-ratio 1 (FR1) schedule]. In contrast, under a progressive-ratio schedule of intravenous drug injection, the number of responses the subject must make to obtain successive drug injections (the ratio value) increases progressively until the subject fails to make the required number of responses (Hodos 1961). The highest ratio (the "breaking point") reached before responding ceases is thought to reflect the reinforcing effectiveness of the drug. Intravenous self-administration studies have repeatedly shown that most drugs considered to be addictive in humans can serve as positive reinforcers for laboratory rats and monkeys, whereas nonaddictive drugs have given negative results in the great majority of cases (Balster 1992; Katz and Goldberg 1988). Once an animal has learned to intravenously self-administer a drug, the influences of drug priming, stressors or presentation of drug-associated stimuli on drug self-administration behavior, or relapse to extinguished drug-seeking behavior provide useful measures for studying the behavioral aspects of drug dependence (see Shalev et al. 2002 for a review).

Drug-induced conditioned place preferences

Another experimental animal model for exploring the reinforcing effects of drugs of abuse is the CPP procedure. A distinctive environment (e.g., one compartment of a two- or three-compartment apparatus) is paired repeatedly with administration of a drug, and a different environment is repeatedly associated with administration of vehicle. CPP occurs when repeated administration of a drug in this particular environment results in the ability of that environment to elicit approach behavior and increased time contact (place preference) in the absence of the previously administered drug. It has been argued that CPP, like drug self-administration and a number of related phenomena, is an example of dopamine-mediated incentive learning and that the approach behavior and increased time spent by animals in a drug-paired environment can be considered a measure of drug-seeking behavior and the reinforcing effects of drugs (Bardo and Bevins 2000; Le Foll and Goldberg 2005b,c). CPP has been demonstrated for most drugs of abuse, as well as for natural reinforcers such as food. The acquisition of a drug-induced CPP is likely to be correlated with other reinforcing effects of abused drugs, whereas its expression reflects the influence on behavior of environmental stimuli previously associated with a drug's effects.

Drug discrimination

Humans exposed to psychoactive drugs report characteristic subjective effects, and drug-discrimination procedures in rats and monkeys are extensively used as animal models of these subjective reports of drug effects in humans. The ability to perceive and identify the characteristic interoceptive effects of abused drugs is thought to play a critical role in drug-seeking, encouraging the development of this behavior and directing it towards one substance rather than another, on the basis of relative potencies and subjective effects (Colpaert 1999; Stolerman and Shoaib 1991). These interoceptive subjective effects of drugs are most frequently assessed in humans through the use of subject-rating scales, and correlated changes in behavior are frequently assessed using performance-assessment tasks. In animals, the interoceptive effects of drugs can serve as discriminative stimuli to indicate how to obtain a reinforcer such as a food pellet or how to avoid an electric shock. For example, animals can be trained under a discrete-trial schedule of food-pellet delivery or stimulus-shock termination to respond on one lever after an injection of a training dose of nicotine and on the other lever after an injection of vehicle. Once animals learn to reliably make this discrimination, the discriminative effects of different drugs or different nicotine doses can be compared and the modulation of subjective effects of nicotine by various pharmacological treatments can be measured (Le Foll and Goldberg 2004; Le Foll et al. 2005b). This procedure works well with nicotine in rats (Rosecrans 1979; Stolerman 1989) (Fig. 2a), mice (Shoaib et al. 2002; Stolerman et al. 1999), and squirrel monkeys (Takada et al. 1988) and has also been used in human subjects by using nasal sprays containing either nicotine or placebo (Perkins et al. 1996).

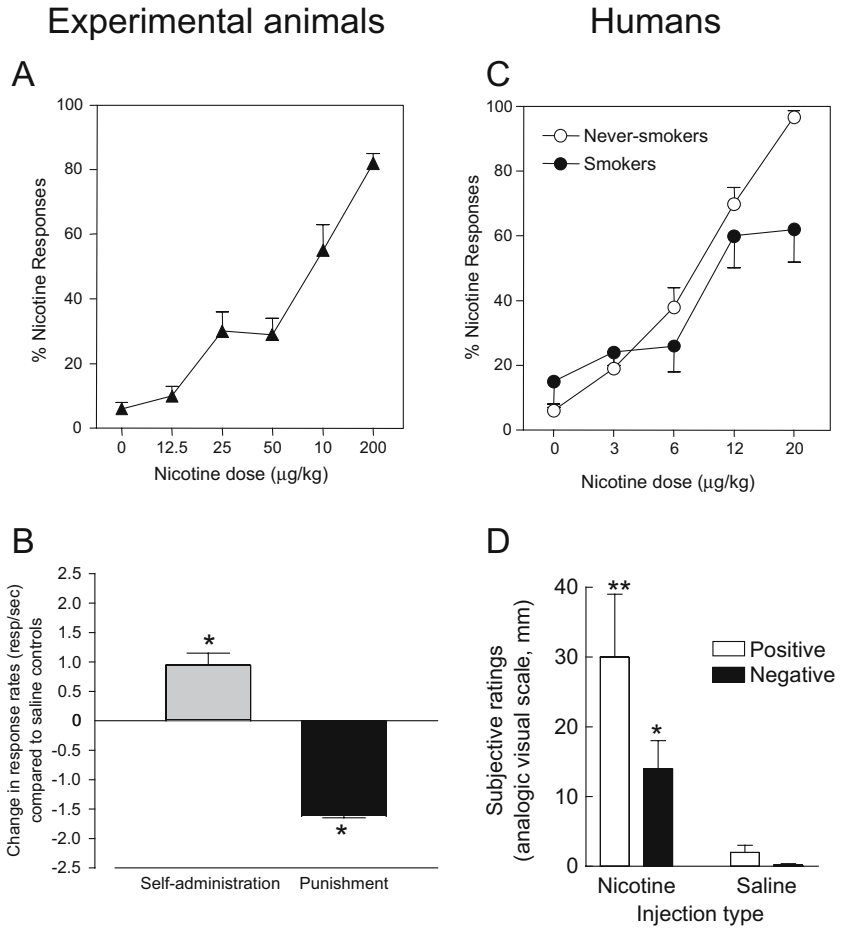

Fig. 2 Subjective and discriminative-stimulus effects of nicotine in experimental animals (**a**, **b**) and humans (**c**, **d**). **a** Dose–effect functions for the discriminative-stimulus effects of nicotine in rats (n=8) trained to discriminate 200 µg/kg s.c. nicotine from saline. The percentage of responses on the lever associated with nicotine administration is shown as a function of dose (microgram per kilogram) during tests with various nicotine doses. Adapted from Chance et al. (1977). **b** In squirrel monkeys, intravenous injections of nicotine (10.5 µg/kg) maintain i.v. self-administration behavior (adapted from Goldberg et al. 1981a,b), but also act like a punisher to suppress food-maintained behavior (adapted from (Goldberg and Spealman 1983). **c** Dose–effect functions for the discriminative-stimulus effects of nicotine in humans (smokers or nonsmokers) trained to discriminate 20 µg/kg nicotine administered by nasal spray from placebo spray. From Perkins et al. (1997). **d** Reported positive and negative effects of nicotine injections in human subjects. Mean (+SEM) ratings of positive or negative effects (in millimeter) after injection of nicotine or saline on a 100-mm visual analog scale (VAS). * negative ratings were significantly greater for nicotine than saline. ** positive ratings for nicotine were significantly greater than negative ratings for nicotine and significantly greater than positive ratings for saline. *, ** P<0.05, from Harvey et al. (2004)

Measurement of withdrawal disturbances

Abrupt cessation of exposure to most drugs of abuse leads to withdrawal signs and symptoms in humans (American Psychiatric Association 2000), and these can be measured in humans by reports by subjects using standardized rating scales and by reports of trained observers (Hughes et al. 1991). Animal models have been developed to evaluate the physical signs, as well as the behavioral consequences of inferred emotional disturbances following cessation of exposure to drugs of abuse. In these procedures, the animals are frequently implanted chronically with mini-pumps delivering the drug continuously, and cessation is produced either by the removal of the pump or by injection of specific antagonist (Malin et al. 1992; Watkins et al. 2000).

Effects of nicotine in experimental animals and humans

Reinforcing effects of nicotine in experimental animals

Intravenous self-administration of a psychoactive drug is generally considered to be the most direct measure of a drug's reinforcing effects. Although intravenous drug self-administration procedures generally work well with psychostimulants and opioids over a relatively wide range of conditions, the conditions under which nicotine maintains nicotine self-administration behavior appear to be more limited. Several factors have now been identified that strongly affect the ability of nicotine to initiate and maintain intravenous self-administration behavior (Le Foll and Goldberg 2005b; Rose and Corrigall 1997).

First, the choice of the animal species appears crucial. In rodents, the rate of responding maintained by nicotine is higher in rats (Corrigall and Coen 1989; DeNoble and Mele 2005; Donny et al. 1995) than in mice (Martellotta et al. 1995; Paterson et al. 2003; Rasmussen and Swedberg 1998; Stolerman et al. 1999) (Fig 1a), although this might be related to the greater number of experiments that have been conducted with rats and, thus, the better information about appropriate experimental conditions that is available. High rates of responding maintained by nicotine self-administration have also been reported in dogs (Risner and Goldberg 1983) and squirrel monkeys (Goldberg et al. 1981a,b; Sannerud et al. 1994), but rates of responding maintained by nicotine in rhesus monkeys and baboons have usually been quite low (Ator and Griffiths 1983; Deneau and Inoki 1967; Goldberg et al. 1981a,b; Slifer and Balster 1985; Wakasa et al. 1995). Moreover, findings have not been consistent across or within studies with rats (Brower et al. 2002; Shoaib et al. 1997), where strain differences are likely (Brower et al. 2002; Shoaib et al. 1997), and studies with animals are difficult to compare since procedural details, such as nicotine injection speed (Samaha and Robinson 2005; Wakasa et al. 1995), or environmental factors associated with nicotine injection (Le Foll and Goldberg 2005b) can strongly influence the acquisition and subsequent maintenance of nicotine-reinforced self-administration behavior. The reinforcing effects of nicotine appear to be particularly pronounced in squirrel monkeys (Le Foll and Goldberg 2005b). Persistent self-administration behavior can be obtained in this species under fixed-interval (Spealman et al. 1981) and second-order schedules of intravenous nicotine injection (Goldberg et al. 1981a,b), and squirrel monkeys respond at rates as high as one response per second for intravenous injections of nicotine under fixed-ratio schedules (Sannerud et al. 1994).

Although the first studies clearly demonstrating the reinforcing effects of nicotine in experimental animals used fixed-interval and second-order schedules (Goldberg et al. 1981a,b; Spealman and Goldberg 1982), more recent studies have mainly employed fixed-ratio and progressive-ratio schedules (Donny et al. 1999; Paterson et al. 2004; Risner and Goldberg 1983; Sannerud et al. 1994). Intravenous nicotine self-administration is usually studied under conditions where availability of injections is restricted by timeout periods ranging from several seconds to several minutes between injections and with daily sessions of short duration (Corrigall and Coen 1989) or under conditions of prolonged access to nicotine (Valentine et al. 1997). In contrast to cocaine, where intake progressively increases after prolonged access to the drug (Ahmed and Koob 1998; Paterson and Markou 2003), no escalation in intake has been found after prolonged access to nicotine (Paterson and Markou 2004). Several studies suggest that rates of responding maintained by nicotine may be less than rates of responding maintained by cocaine when the amount of work required to obtain injections is increased in animals using progressive-ratio schedules (Goldberg and Henningfield 1988; Rasmussen and Swedberg 1998; Risner and Goldberg 1983) or that speed of acquisition of self-administration behavior may be slower than that with other drugs of abuse (Shoaib et al. 1997). However, some investigators have reported similar rates of responding for nicotine and other drugs of abuse in rodents (Paterson et al. 2004; Paterson and Markou 2003) and squirrel monkeys (Spealman and Goldberg 1982). Nevertheless, existing studies that have directly compared in the same animals the reinforcing effects of nicotine to those of cocaine using progressive-ratio or choice schedules clearly suggest that the reinforcing effects of nicotine are weaker under progressive-ratio schedule of reinforcement (Manzardo et al. 2002; Risner and Goldberg 1983) and that animals tend to prefer cocaine over nicotine when given access to both drugs during the same session (Manzardo et al. 2002).

The ability of nicotine to induce CPP has also been frequently studied (Fig. 1). In the CPP procedure, animals are tested in a drug-free state to determine whether they prefer an environment associated with the effects of nicotine as compared to an environment previously associated with the effects of saline vehicle. Thus, this procedure relies on the capacity of stimuli associated with nicotine's effects to elicit approach responses and increased time spent in the environment associated with nicotine's effects and is used as a measure of reinforcing effects. Nicotine has been shown to induce CPP across a large range of doses in some experiments (Fig. 1b), but the magnitude of the effect is generally small and affected by environmental stimuli (Le Foll and Goldberg 2005c), suggesting that the reinforcing effects of nicotine may be weaker that those of other drugs of abuse.

Several experimental variables may determine the reinforcing effects of nicotine both in the intravenous self-administration and the CPP procedures (Le Foll and Goldberg 2005b,c). It appears, for example, that adolescent rats, food-deprived animals, and rats previously exposed to nicotine are more likely to acquire intravenous nicotine self-administration behavior or to develop nicotine-induced CPP (Adriani et al. 2003; Belluzzi et al. 2004a,b; Corrigall and Coen 1989; Shoaib et al. 1994, 1997; Vastola et al. 2002). However, the most important variable appears to be environmental stimuli that are repeatedly associated with each nicotine injections or marginally reinforcing stimuli whose effects are facilitated by nicotine exposure.

An extensive literature suggests that Pavlovian associative conditioning processes are implicated in the acquisition of motivational value by initially neutral stimuli that are repeatedly paired with drugs-of-abuse effects. In an early paper with monkeys published in 1981, it was first suggested that environmental stimuli associated with nicotine administration are critical for the maintenance of nicotine-seeking behavior (Goldberg et al. 1981a,b). During these experiments, a light stimulus was repeatedly paired with nicotine delivery. Although responding ultimately depended on injections of nicotine, the brief light stimulus associated with injections played an important role in the maintenance of persistent responding since rates

of responding were about twice as high when the brief light was presented as when it was absent (Goldberg et al. 1981a,b).

The critical role played by environmental stimuli in the reinforcing effects of nicotine has recently been demonstrated in rodents (see Caggiula et al. 2002 and Le Foll and Goldberg 2005b for detailed analysis). In those experiments, discontinuing presentation of environmental stimuli associated with intravenous nicotine injection decreased self-administration behavior almost as effectively as the removal of nicotine itself, indicating their critical role in sustaining drug-taking behavior (Caggiula et al. 2001, 2002; Donny et al. 2003). Moreover, in some experiments with rats, the responding maintained by nicotine-associated light stimuli was equal to the responding maintained by nicotine itself (Cohen et al. 2005). In addition, the contingent presentation of environmental light stimuli was able to maintain responding for up to 3 months, demonstrating their persistent nature and their high motivational value (Cohen et al. 2005). Finally, the use of behavioral procedures that do not have environmental stimuli directly paired with nicotine delivery has been reported to result in very low levels of drug-taking behavior in experiments with drug-naive mice (Paterson et al. 2003) and rats (Donny et al. 2003).

Nicotine, like other psychostimulant drugs (Hill 1970), also produces unconditioned effects that increase the ability of nondrug environmental stimuli to serve as reinforcers independent of any direct temporal association between nicotine administration and stimulus presentation (Caggiula et al. 2002; Olausson et al. 2003, 2004). It is still unclear whether both processes occur concurrently in smokers, magnifying the role of associated environmental stimuli in nicotine self-administration and tobacco dependence or whether one process predominates. Interestingly, these conditioning processes may also occur with sensorimotor stimuli of tobacco smoke (Rose et al. 2000, 2003a), and this could explain the reduction in subjective reports of tobacco craving, desire to smoke, and tobacco withdrawal that are produced by placebo cigarettes in smokers (Butschky et al. 1995; Robinson et al. 2000).

Reinforcing effects of nicotine in humans

Critical variables determining whether or not nicotine functions effectively as a reinforcer of drug-seeking and drug-taking behavior in the laboratory are recently becoming clear. In human subjects studied under controlled laboratory conditions, reliable evidence that nicotine, by itself, can serve as an effective reinforcer of drug-taking behavior has until recently been primarily indirect. For example, cigarette smoke intake varies as a function of various manipulations affecting nicotine exposure, and pure nicotine medications (e.g., gum, nasal spray, or patch) can be used as temporary or long-term substitutes to facilitate smoking cessation (Fiore 2000; Le Foll et al. 2005b). However, the persistent use of nicotine replacement therapy (NRT) provides only indirect evidence for the reinforcing effects of nicotine in humans since NRT use may be maintained by the knowledge of the subjects that it helps smoking cessation outcome. Nevertheless, in this situation, smokers will self-administer nicotine spray more than placebo over several days after quitting smoking (Perkins 2004). However, the reinforcing effects of nicotine gum in smokers are highly dependent on instructions given to them, suggesting that pharmacological effects are not the only factors involved in the maintenance of use of NRT (Hughes 1989).

A recent analysis of laboratory experiments evaluating self-administration of nicotine by intravenous injection or by nasal spray in human cigarette smokers concluded that clear differences between voluntary responding for nicotine injections and saline injections had not yet been demonstrated (Dar and Frenk 2004), although these conclusions have been disputed (Perkins 2004). Nevertheless, nicotine has now been shown to act as an effective reinforcer of intravenous self-administration behavior in human smokers (Harvey et al. 2004) (Fig. 1c–d) in experiments conducted with male cigarette smokers who had been smoking an average of 1.5 packs of cigarettes per day for an average of 13.4 years. Before each session, a catheter was inserted in a forearm vein for delivery of nicotine or saline. During experimental sessions, subjects sat in a chair in a test room facing a test panel with two levers and a stimulus light over each lever. When the subject pulled either lever, there was an audible click, and a response was recorded. Pulling one lever repeatedly produced intravenous injections of nicotine, while pulling the other lever produced injections of saline. Note that each delivery of nicotine was associated with the presentation of a stimulus light. The number of lever-pull responses required to produce an injection varied between sessions from 10 to as high as 1,600. As the response requirement increased, response rates on the nicotine lever increased substantially, while rates on the saline lever remained low (Fig. 1d). The number of injections per session was markedly and significantly greater for nicotine than saline (Fig. 1c) and varied as a decreasing function of the dose of nicotine (Harvey et al. 2004). These findings clearly demonstrate that nicotine, by itself and in the absence of other constituents of tobacco smoke, can serve as an effective reinforcer of intravenous drug-taking behavior in human cigarette smokers. Furthermore, in these experiments, subjects adjusted their responding to increasing response requirements in a way that maintained relatively constant levels of nicotine injections per session.

The earlier difficulties in obtaining reliable intravenous nicotine self-administration and nicotine-induced CPPs across species and laboratories suggest that the reinforcing effects of nicotine, by itself, may be lower than the reinforcing effects of other drugs of abuse under many experimental conditions. These findings contrast with the apparently high reinforcing effects of tobacco smoke in human smokers. These discrepancies could be explained in part by different reinforcing effects of nicotine between species or by the influence of non-nicotine stimuli associated with smoking. An additional possibility is that

the reinforcing properties of nicotine in tobacco smoke may be enhanced by other constituents of tobacco smoke. Recently, it has been shown that behavioral sensitization to nicotine, which has been implicated in drug dependence (Robinson and Berridge 1993, 2001), becomes long-lasting when nicotine is administered after treatment with a monoamine-oxidase inhibitor (Villegier et al. 2003), and tobacco smoke is known to contain many compounds, some of which are monoamine-oxidase inhibitors (Fowler et al. 1996a,b). Recently, the potentiation of the effects of nicotine by acetaldehyde has also been demonstrated in rodents (Belluzzi et al. 2004a,b). Further experiments are needed to clarify the implication of other constituents of tobacco smoke than nicotine in the reinforcing effects of tobacco.

Subjective effects of nicotine in humans and discriminative and aversive effects in animals

Discriminative-stimulus effects of nicotine in experimental animals

The discriminative-stimulus effects of nicotine, which are extensively used as an animal correlate of subjective reports of nicotine effects in humans, are mainly mediated by neuronal nicotinic acetylcholine receptors (nAChR) since discrimination of nicotine can be blocked by mecamylamine, a nicotinic receptor antagonist that penetrates the blood-brain barrier, but not by the nicotinic receptor antagonist hexamethonium, which does not readily enter the brain (Kumar et al. 1987; Pratt et al. 1983; Stolerman 1999; Stolerman et al. 1984). These discriminative effects are mainly mediated by high-affinity nicotinic receptors (Shoaib et al. 2002; Stolerman et al. 1997). Nevertheless, a dopaminergic component may also be involved (Desai et al. 2003) (see also Corrigall and Coen 1994; Le Foll et al. 2005c). The areas of the brain that appear to be most strongly implicated in the mediation of nicotine's discriminative-stimulus effects are the prefrontal cortex and the ventral striatum, but the hippocampus may also be involved (Ando et al. 1993; Miyata et al. 1999, 2002; Rosecrans and Meltzer 1981).

Aversive effects of nicotine in experimental animals

It has long been known that nicotine can produce both reinforcing and aversive effects, sometimes at the same dose, depending on the experimental conditions and the subject's history (Goldberg and Spealman 1982; Goldberg et al. 1983; Henningfield and Goldberg 1983a,b). In agreement, the same dose of nicotine may produce either positive or aversive motivational effects in rats using CPP procedure (Laviolette and Van Der Kooy 2003; Le Foll and Goldberg 2005c). Similarly, squirrel monkeys will learn to repeatedly press a lever in order to obtain intravenous injections of nicotine (Fig. 2b) (Goldberg et al. 1981a,b). However, ongoing lever-press responding for food is completely suppressed (punished) when lever presses produce intravenous injections of the same dose of nicotine that can maintain self-administration behavior under other conditions (Fig. 2b) (Goldberg and Spealman 1983). Further, monkeys will learn to press a lever to avoid programmed injections of nicotine (Spealman 1983). Aversive effects of nicotine have also been demonstrated in rats using the conditioned taste aversion procedure with systemic nicotine injections (Reavill et al. 1986; Shoaib and Stolerman 1995; Stolerman 1988) and with intracranial infusions of nicotine (Laviolette and Van Der Kooy 2003; Shoaib and Stolerman 1995).

Discriminative-stimulus and aversive effects of nicotine in humans

Human subjects can be trained to discriminate the effects of inhaled nicotine administered by nasal spray (Perkins et al. 1997) (Fig 2c). Interestingly, subjects reported both positive and negative effects following intravenous nicotine self-administration, although the positive effects were more pronounced (Fig. 1c) (Harvey et al. 2004). A recent review of the literature on subjective effects of nicotine in human subjects indicated that, across various delivery forms, nicotine increased ratings of positive effects in smokers, such as high, liking, and euphoria (Kalman 2002). Studies involving intravenous nicotine administration have reported similar positive effects, but have also shown that nicotine can elicit concurrent reports of negative effects, such as tension, jitteriness, and dysphoria (Garrett and Griffiths 2001; Henningfield et al. 1985; Jones et al. 1999; Soria et al. 1996). It is likely that subjective effects and reinforcing effects of drugs of abuse can be dissociated and that drugs of abuse may function as highly effective reinforcers even when they produce measurable reports of negative effects (Ettenberg and Geist 1991). In addition, drugs of abuse may continue to function as highly effective reinforcers when dose is reduced to the point that measurable reports of positive effects are absent (Lamb et al. 1991; Panlilio et al. 2005).

Nicotine withdrawal signs in experimental animals

A wide range of behavioral signs (e.g., teeth chattering, chewing, gasping, writhing, head shakes, body shakes, tremors) have been noted upon cessation of chronic nicotine exposure in experimental animals (Epping-Jordan et al. 1998; Isola et al. 1999; Malin et al. 1992; Paterson and Markou 2004; Suzuki et al. 1996). Generally, rats or mice are chronically implanted with minipumps that deliver nicotine continuously, and withdrawal signs are seen after either removal of the pump or injection of a nicotinic antagonist (Malin et al. 1992; Watkins et al. 2000). To monitor physical signs of withdrawal, the number of occurrences of each sign is counted, and the subject's overall withdrawal score is the number of signs cumulated across all categories (Malin et al. 1992). These

behavioral withdrawal signs have been termed "somatic abstinence signs" or "somatic behavioral signs".

These physical signs of nicotine withdrawal often are accompanied by behavioral disturbances indicating emotional correlates, such as increased startle responses (Helton et al. 1993) and higher electrical thresholds for intracranial self-stimulation (ICSS), suggesting hypoactivity of brain reward pathways and, thus, a depression-like state (Epping-Jordan et al. 1998). Interestingly, with mild nicotine withdrawal, indications of emotional disturbance are more likely to appear than are the behavioral somatic signs listed above. Nicotine withdrawal is also associated with avoidance behavior. Rats will avoid a compartment associated with mecamylamine-precipitated nicotine abstinence using a CPP procedure (Suzuki et al. 1996). Nicotine also has antidepressant-like effects in the forced-swim test (Tizabi et al. 1999, 2000) in Flinders-sensitive rats, a strain of rat that has been proposed as an animal model of depression (Overstreet 1995; Overstreet et al. 1995).

Nicotine-withdrawal signs and symptoms in humans

Tobacco withdrawal induces a wide range of signs and symptoms in human smokers (Hughes et al. 1991; Hughes and Hatsukami 1986). For tobacco users trying to quit, symptoms of withdrawal from nicotine are unpleasant and stressful, but temporary. Since NRT strongly decreases the intensity of withdrawal symptoms (Hughes et al. 1984; West et al. 1984a), it is assumed that the decrease in nicotine levels is responsible for the tobacco withdrawal symptoms in humans. Reducing the nicotine content of cigarettes can also result in a withdrawal syndrome (West et al. 1984b), as well as ceasing the use of nicotine gum (Hughes et al. 1986; West and Russell 1985). Signs and symptoms of nicotine withdrawal include any or all of the following: headache, nausea, constipation or diarrhea, falling heart rate and blood pressure, fatigue, drowsiness and insomnia, irritability, difficulty concentrating, anxiety, depression, increased hunger and caloric intake, increased pleasantness of the taste of sweets, and tobacco cravings. Most withdrawal signs and symptoms peak 48 h after quitting tobacco smoking and are completely gone in 6 months (Le Foll et al. 2005b). Slowing of heart rate and weight gain are the distinguishing features of tobacco withdrawal, compared to other drugs of abuse (Hughes et al. 1994).

Interestingly, cessation of tobacco use increases the risk of depression (Glassman et al. 1990), and this vulnerability persists for several months (Glassman et al. 2001). There is also some evidence that nicotine itself may possess antidepressant properties in humans (Salin-Pascual and Drucker-Colin 1998; Salin-Pascual et al. 1996; see Picciotto et al. 2002 for a review), but these results have not yet been validated in placebo-controlled clinical trials (Thorsteinsson et al. 2001). Furthermore, tobacco smoke contains chemical substances other than nicotine that may have antidepressant effects, possibly through the prolonged inhibition of monoamine oxydase A and B in the brain (Berlin and Anthenelli 2001; Fowler et al. 1996a,b). The increased risk of depression following smoking cessation may be related to factors other than nicotine. Nevertheless, withdrawal symptoms that occur following smoking cessation may contribute to difficulties in quitting smoking.

Relapse models: influence of stress, drug priming, and presentation of cues

"Relapse" in experimental animals

The animal model most frequently used to study relapse phenomena is reinstatement of extinguished drug self-administration behavior (see Epstein and Preston 2003; Katz and Higgins 2003; Shaham et al. 2002 for reviews and discussions on the limitations of the reinstatement model in animals to study relapse in humans). Only limited research has been conducted with nicotine, as compared to other drugs of abuse. Various factors thought to trigger relapse in humans appear to be able to reinstate nicotine seeking in laboratory animals. Studies in rats have shown that noncontingent administration of nicotine during extinction of nicotine self-administration behavior reinstates responding previously reinforced by nicotine (Andreoli et al. 2003; Chiamulera et al. 1996; Lindblom et al. 2002; Shaham et al. 1997). However, the effect of nicotine priming is weak in some studies as compared to other drugs of abuse (Erb et al. 1996; Shaham et al. 1996), and effects are not found consistently (Lesage et al. 2004). Exposure to drug-paired stimuli also appears to be effective in reinstating extinguished nicotine-seeking behavior (Lesage et al. 2004) and in facilitating the reacquisition of nicotine self-administration behavior after a period of extinction (Caggiula et al. 2001). However, some investigators have found no effect of exposure to nicotine-paired stimuli on nicotine-seeking behavior (Andreoli et al. 2003). Exposure to stressors is also able to reinstate extinguished nicotine-seeking behavior (Buczek et al. 1999). Although all these experiments are not entirely consistent (see above), it appears that extinguished nicotine-seeking behavior generally can be reinstated by all factors that are effective in reinstating extinguished cocaine- or heroin-seeking behavior.

The existing treatments available to treat human smokers have only recently been evaluated in animal models of nicotine dependence. The major findings are listed in Table 1. This table also reports the results obtained with drugs that have been tested both in animals and humans (for more extensive reviews see Cryan et al. 2003a,b; George and O'Malley 2004). It appears that NRT and bupropion are able to affect nicotine self-administration behavior, but the results have not been consistent across studies with bupropion (perhaps due to the role of bupropion metabolites in the therapeutic efficacy of this drug). NRT and bupropion also are effective in attenuating nicotine withdrawal signs and symptoms. These drugs have not been evaluated in animal models of nicotine relapse. Varenicline (a nicotinic receptor partial agonist) is also a promising agent to treat

tobacco dependence (Sands et al. 2005). Recent evidence suggests that innovative approaches such as the blockade of cannabinoid CB_1 receptors (Cohen et al. 2005; Le Foll and Goldberg 2004, 2005a) or blockade of dopamine D_3 receptors (Andreoli et al. 2003; Le Foll et al. 2003a, 2005a,c), which are over-expressed in the brain of nicotine-treated animals (Le Foll et al. 2003a,b), decreases the influence of nicotine-associated stimuli or nicotine priming on nicotine-seeking behavior (Le Foll and Goldberg 2005a; Sokoloff et al. 2005).

Relapse in humans

Tobacco seeking, craving, and relapse in humans are well known to be triggered by environmental stimuli, or cues,

Table 1 Summary of effects of different drugs that have been tested both in experimental animals and human smokers

Experimental animals		Human subjects	
Nicotine			
Continuous nicotine infusion decreases intravenous nicotine self-administration in rats with 23 h/day access to nicotine (no effect on cocaine self-administration).	(LeSage et al. 2002, 2003)	Increased rates of smoking cessation in controlled clinical trials using nicotine replacement therapy	(Fiore et al. 2000; Le Foll et al. 2005a; Silagy et al. 2000)
Repeated nicotine administration decreases discriminative stimulus effect of nicotine in rats.	(Robinson et al. 2005)	Nicotine exposure attenuates discriminative effects of nicotine in women.	(Perkins et al. 2001)
Nicotine withdrawal after chronic exposure through osmotic pumps or intravenous self-administration produces withdrawal symptoms.	(Epping-Jordan et al. 1998; Malin et al. 1992; Paterson and Markou 2004)	Nicotine replacement therapy attenuates nicotine withdrawal symptoms.	(Hughes et al. 1984; West et al. 1984a),
Bupropion			
Bupropion at low doses (10–30 mg/kg) had no effect or increased intravenous self-administration of nicotine, whereas higher dose of bupropion (30–78 mg/kg) decreased nicotine self-administration under a fixed-ratio schedule. Bupropion (20–40 mg/kg) had no effect on intravenous self-administration of nicotine under a progressive-ratio schedule.	(Bruijnzeel and Markou 2003; Rauhut et al. 2003; Shoaib et al. 2003)	Bupropion increased smoking cessation rate in controlled clinical trials.	(Fiore et al. 2000; Le Foll et al. 2005b; Tashkin et al. 2001)
Bupropion produced nicotine-like discriminative effects in two out of three studies.	(Shoaib et al. 2003; Wiley et al. 2002; Young and Glennon 2002)	Bupropion decreased reports of craving and reactivity to nicotine-associated stimuli and decreased withdrawal symptoms.	(Brody et al. 2004; Hurt et al. 1997; Jorenby et al. 1999; Shiffman et al. 2000a,b)
Bupropion enhances brain reward function and reverses the affective and somatic aspects of nicotine withdrawal in the rat.	(Cryan et al. 2003a,b)	Bupropion decreased tobacco withdrawal symptoms.	(Brody et al. 2004; Hurt et al. 1997; Jorenby et al. 1999; Shiffman et al. 2000b)
Rimonabant (cannabinoid CB_1 antagonist)			
Rimonabant decreased intravenous self-administration of nicotine under a fixed-ratio schedule, decreased responding maintained by nicotine-associated stimuli, and blocked nicotine-induced conditioned place preference in rats.	(Cohen et al. 2002, 2005; Le Foll and Goldberg 2004, 2005a)	Rimonabant increased rate of smoking cessation in the STRATUS-US trial.	(Anthenelli and Despres 2004)
Rimonabant did not produce nicotine-like discriminative stimulus effects and did not alter the discriminative-stimulus effects of nicotine	(Cohen et al. 2002; Le Foll and Goldberg 2004)	Subjective effects of rimonabant are rated identical as those of placebo.	(Huestis et al. 2001)
Varenicline (a nicotinic receptor partial agonist)			
Varenicline blocks the discriminative-stimulus effect of nicotine and the dopamine-releasing effect of nicotine.	(Sands et al. 2005)	Varenicline seems to increase smoking cessation rates in smoking cessation trials.	(Sands et al. 2005)

Table 1 (continued)

Experimental animals		Human subjects	
Mecamylamine (a nicotinic receptor antagonist)			
Mecamylamine decreased intravenous nicotine self-administration under various procedures in rats and monkeys.	(Goldberg et al. 1981a,b; Corrigal and Coen 1989; Donny et al. 1999)	Although acute mecamylamine increases nicotine self-administration and smoking, prolonged mecamylamine treatment has shown some interest for smoking cessation.	(Pomerleau et al. 1987; Rose et al. 1994, 2001, 2003b)
Mecamylamine blocks the discriminative-stimulus effect of nicotine in rats	(Stolerman et al. 1997)	Mecamylamine blocks the discriminative-stimulus effect of nicotine in humans.	(Perkins et al. 1999; Rose et al. 1989)
Mecamylamine produces withdrawal symptoms in rats chronically exposed to nicotine.	(Epping-Jordan et al. 1998; Malin et al. 1992)	Mecamylamine produces some withdrawal symptoms in smokers.	(Rose et al. 2001)

that have acquired motivational salience through repeated associations with self-administered nicotine (O'Brien 2003; Shiffman et al. 1986, 2000a,b), but may also be triggered by withdrawal symptoms and tobacco smoking in abstinent subjects. NRT and bupropion, the two medications currently available for smoking cessation, are effective in increasing smoking cessation rates (i.e., the decrease relapse rates) and are partly effective in reducing reports of craving for cigarettes in abstinent smokers (Jorenby 2002). NRT and bupropion may both act primarily by attenuating tobacco withdrawal symptoms (Shiffman et al. 2000a,b) (Table 1). Continuous NRT by skin patches seems relatively ineffective in attenuating reports of craving produced by smoking-associated stimuli (cues) in smokers (Tiffany et al. 2000; Waters et al. 2004). Interestingly, nicotine gum has recently been shown to be efficacious in reducing cue-induced craving for cigarettes (Shiffman et al. 2003). These differences may be due either to the tolerance occurring with continuous exposure to nicotine through skin patches or to the failure to specifically evaluate effects of the skin patches in the subgroup of subjects displaying a high degree of cue-reactivity. Recent imaging studies suggest that reports of craving and brain activation induced by environmental stimuli (cues) associated with tobacco smoking are related to limbic brain areas (Brody et al. 2002; Due et al. 2002) and are reduced by bupropion (Brody et al. 2004). Rimonabant also seems effective in preventing relapse to tobacco use in abstinent smokers (Anthenelli and Despres 2004) (Table 1). Although Rimonabant appears to decrease the reactivity to nicotine-associated stimuli in animals, parallel experiments have not yet been conducted in humans.

Conclusions

The two procedures most widely used to assess reinforcing effects of drugs in experimental animals, intravenous drug self-administration procedures and CPP procedures, have recently been used to demonstrate a major influence of environmental stimuli on the reinforcing properties of nicotine (Caggiula et al. 2002; Goldberg et al. 1981a,b; Le Foll and Goldberg 2005b). As dependence develops, environmental stimuli that are repeatedly associated with episodes of smoking behavior acquire the ability through Pavlovian associative conditioning processes to elicit brain activation and reports of craving for tobacco in dependent subjects and may trigger relapse in ex-smokers (Due et al. 2002). The high rate of relapse observed in smokers may be related to these conditioning factors, which are long-lasting and resistant to behavioral and pharmacological interventions. Therefore, a tobacco control approach aimed at limiting the environmental situations that can be associated with smoking behavior and restricting the opportunity to engage in smoking behavior in public places may be helpful in reducing tobacco dependence. In addition, innovative pharmacological treatment approaches such as the use of dopamine D_3 antagonists (Le Foll et al. 2000, 2005a) or cannabinoid CB_1 antagonists (Le Foll and Goldberg 2005b) are under development and show promise of being able to selectively block the influence of these conditioned factors.

In conclusion, nicotine functions as an effective reinforcer of drug-seeking and drug-taking in both humans and experimental animals. In intravenous drug self-administration studies, nicotine can serve as a prototypical drug of abuse under certain conditions, maintaining very high levels of operant responding that are clearly distinguishable from responding maintained by saline placebo in both experimental animals and human smokers. Nicotine is also able to induce significant CPP in rodents. Thus, the reinforcing effects of nicotine have now been clearly demonstrated across procedures and across different experimental species. Analysis of the discriminative effects of nicotine in experimental animals and reports of subjective effects of nicotine in humans reveal a complex global effect with both positive and negative components. Both the positive and negative effects of nicotine are affected by environmental conditions and the context of the experiments, factors that may explain the difficulties in obtaining reliable results with nicotine in the past. As with other drugs of abuse, cessation of nicotine exposure induces a withdrawal syndrome that is associated with both physical and emotional signs and symptoms. Nicotine usage may be continued by some subjects to prevent or relieve these withdrawal symptoms and, perhaps, also to prevent

depression that may occur following smoking cessation. As with other drugs of abuse, nicotine priming and exposure to nicotine-associated stimuli or stressors produce reinstatement or relapse both in experimental animals and humans. Medications that are effective in humans for increasing smoking cessation rates also appear effective in reducing either intravenous nicotine self-administration, nicotine withdrawal signs and/or the effects of presentation of environmental stimuli on behavior, demonstrating again a strong analogy between responding of experimental animals and humans. All of these findings indicate that nicotine can act like a typical drug of abuse both in animals and humans.

Smoking behavior by humans results in many associations between the tactile, olfactory, and visual stimuli that accompany smoking of a cigarette and the pharmacological effects of inhaled nicotine. Moreover, the fact that these stimuli cannot be avoided by most smokers (situations such as the home, the workplace, etc.) may explain the very high rate of relapse observed in ex-smokers, as compared to subjects dependent on other drugs of abuse. Nicotine's reinforcing effects in animals appear to be less pronounced than the reinforcing effects of tobacco smoke in humans. This could be due, in part, to the critical role played by environmental factors in nicotine dependence. Without associated environmental influences, recent evidence suggests that nicotine is relatively ineffective in animal models of reinforcement. This could also be due to more pronounced reinforcing effects of nicotine in human and nonhuman primates compared to rodents, and there may be a potentiation of the reinforcing effects of nicotine by other substances in tobacco smoke. Further studies that directly compare the effects of nicotine and tobacco smoke both in animals and humans will allow elucidating these uncertainties in the future.

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