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REVIEW

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# Nicotine self-administration in animals and humans: similarities and differences

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**Abstract** Studies of nicotine self-administration in animal and human subjects are discussed with respect to the behavioral paradigms employed, the effects of nicotine dose manipulations and nicotinic agonist/antagonist pretreatment, and the role of neurochemical processes mediating reinforcement. Animal models have focused on intravenous nicotine self-administration, while most studies in human subjects have studied cigarette smoking behavior. Despite procedural differences, data from both animal and human studies show an inverted-U function relating nicotine dose to self-administration behavior, with maximal rates of responding occurring at intermediate doses of nicotine. Moreover, nicotine supplementation via non-contingent nicotine administration suppresses nicotine self-administration behavior in both animal models and human cigarette smokers. Nicotine antagonist treatment also reduces responding, although human studies usually find a transient increase in smoking, which is interpreted as an attempt to compensate for nicotinic receptor blockade. Amongst the neurochemical systems which have been examined, most emphasis has been given to dopamine. The mesolimbic dopamine pathway has been implicated in nicotine reward based on animal studies, and research with humans suggests a role for dopaminergic processes as well. However, dopaminergic blockade appears to increase cigarette smoking behavior in humans, while in animals nicotine self-administration is attenuated. Future research should exploit the complementary aspects of animal models and human paradigms to provide a coherent understanding of nicotine reinforcement. Animal models allow for analysis of anatomical and physiological mechanisms underlying nicotine self-administration; human studies validate the relevance to tobacco dependence and smoking cessation treatment.

**Key words** Nicotine · Self-administration · Dopamine · Reinforcement

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## Introduction

The study of nicotine dependence, like other drug dependencies, profits from animal models. Animal paradigms offer the possibility to examine the mechanisms of dependence at a depth not possible with human studies, and to investigate the risk factors for addiction and potential treatment interventions at a preclinical stage. On the other hand, human studies are necessary to validate the animal models; more importantly human studies are the clinical endpoint in research to develop tools to augment treatment efficacy. The objective of this article is to compare nicotine self-administration in animal models with self-administration of the drug by humans through the inhalation of tobacco smoke. Comparisons have been made along three dimensions in which there is sufficient data to draw conclusions.

The first dimension is the dose-effect relationship in nicotine self-administration. For animals, nicotine self-administration is typically achieved with intravenous (IV) delivery of the drug. Models for nicotine self-administration have developed more slowly than similar paradigms for the study of other drugs, and the diffusion and acceptance of these models has been slow until recently. Nonetheless, the availability of such models does permit comparison of dose ranges and other parameters of nicotine self-administration across animal species. Furthermore, a limited amount of data for IV self-admin-

istration in humans illuminates this comparison. Conclusions can be drawn about the similarity, or lack thereof, between these data from IV self-administration of nicotine and the dose-effect relationship for tobacco smoking.

Secondly, we have compared animal and human data with respect to the neurochemical elements which appear to support nicotine reinforcement. The bulk of contemporary research with nicotine self-administration in animals has been designed to further our understanding of the mechanisms in the central nervous system by which nicotine reinforces this behavior. By its very nature, the work has focused on processes at a level which is not possible with human subjects; indeed, that is the strength of the animal approach. One of the results of such research is the generation of detailed knowledge that supports the development of therapeutics to assist in smoking cessation. One of the main outcomes of the mechanistic studies done with rodents to date has been the demonstration that the mesolimbic dopamine system plays a significant role in IV nicotine self-administration. This conclusion is compared to observations from studies of tobacco smokers treated with dopaminergic compounds. These comparisons, and a lesser amount of data with respect to other neurochemical systems, form the second part of the manuscript.

The third comparison is driven by emerging knowledge from human subjects treated with nicotinic agonists and antagonists in smoking cessation studies. In particular, there is a growing literature describing studies using the nicotinic antagonist mecamylamine which allows intriguing comparisons to be made between the time course of extinction of nicotine self-administration in animal and human paradigms.

## Description of behavioral paradigms

### Animal research

Drug abuse consists of a constellation of behaviors. One particular dimension of abuse is the ability of the drug to act as a reinforcer of behavior, that is, to initiate and sustain addictive patterns of use. Research spanning several decades has established that the reinforcing properties of drugs can be studied with self-administration techniques in animals (e.g., Johanson and Schuster 1981; Collins et al. 1984). Data from such paradigms provide a reliable measure of the addictive liability of many psychoactive agents in humans (Griffiths et al. 1980) and figure prominently in preclinical medication development strategies (Witkin 1994).

Successful paradigms generally rely on restricted access to the drug, and allow a within-session access controlled by a schedule in which the animal must respond a certain number of times or within a certain time window for the drug. For rodents, schedules which have relied on small fixed ratios have been used successfully, and detailed technical aspects of this approach have been reviewed (Corrigall 1992). For primates, more complex second-order schedules have been used (e.g., see Goldberg et al. 1981). In general in all of these studies, infusions are followed by a time-out period to control access to the drug. A number of studies in a range of species have now shown that animals will reliably acquire and maintain nicotine self-administration behavior (e.g., Corrigall and Coen 1989; Risner and Goldberg 1983; Goldberg and Henningfield 1996a).

### Human studies

Although some studies have examined intravenous self-administration of nicotine in human subjects (Henningfield et al. 1983; Goldberg and Henningfield 1996a), most studies of nicotine self-administration in humans have focused on cigarette smoking behavior. Short-term laboratory studies have assessed ad libitum smoking over minutes to hours by monitoring indices of smoking topography, such as the number of puffs and rate of puffing, puff volume and inhalation depth, and biochemical indices of smoke absorption, including plasma nicotine or cotinine concentrations. These measures have been used to characterize smoking behavior and its response to cigarette deprivation, to variations of nicotine dose or nicotine pre-loads, as well as to other pharmacologic manipulations such as nicotinic or dopaminergic receptor blockade. Chronic studies of smoking behavior over weeks to months have also been conducted with smokers whose brand of cigarette has been changed to vary nicotine delivery and with smokers who have been exposed to pharmacologic agents affecting nicotine reinforcement. The third major paradigm for studying human nicotine self-administration has been in the context of smoking cessation treatment. In these studies various types of nicotine replacement and, more recently, nicotine blockade, have been evaluated and found to facilitate abstinence from smoking.

## Comparisons across human and animal studies

### Patterns of nicotine intake

Nicotine has been shown to serve as a reinforcer in intravenous drug self-administration paradigms with a range of animal species, including primates (Goldberg et al. 1981; Sannerud et al. 1994), dogs (Risner and Goldberg 1983) and rodents (Corrigall and Coen 1989). The latter observation, that rodents self-administer nicotine, has recently been validated by others (Donny et al. 1995; Tessari et al. 1995), and broadened by the examination of several strains (Shoaib et al. 1997). There is remarkable consistency between the original study and these replications with respect to the doses of nicotine which are effective in maintaining self-administration. Even more striking is the consistency across the range of animal species in the doses of nicotine that have been reported to maintain self-administration behavior.

However, comparison of the doses which support IV nicotine self-administration in animals with the doses of nicotine which are effective reinforcers in humans is not straightforward since the comparison must be made between different routes of administration. This difference in route theoretically could be overcome by comparing plasma nicotine levels in animals during IV self-administration with those in humans during cigarette smoking; to date, however, no studies of nicotine self-administration in animals have measured plasma nicotine levels to provide this comparison. An alternative benchmark is the dose range used for studies in which human subjects self-administer nicotine IV in a laboratory environment (Henningfield et al. 1983; Goldberg and Henningfield 1996b). In this research, IV self-administration of nicotine occured at doses ranging between approximately 10 and 45 μg/kg per infusion, a range which accords well with studies in animals, as described below. It should be noted, however, that the dose range in humans has not been extended to higher values due to concerns with side effects.

The dose-effect curve for IV nicotine self-administration has both similarities and differences to dose-effect relationships for other drugs. As is the case for other drugs, the lower end of the dose-effect curve for nicotine self-administration is determined by the reinforcing properties of the drug, and probably dependent upon the schedule of reinforcement. For example, if the schedule had no time-out period, it may be that lower doses of the drug would maintain greater self-administration behavior, because the animals would be able to achieve sufficient additivity in repetitive doses administered in rapid succession. At the upper end of the dose-effect curve, responding may be limited by several factors. One is the aversive effects of nicotine. For example, doses at the upper end of the range of self-administration (100 μg/kg) can produce emesis in monkeys (Goldberg et al. 1983) and seizures in rats (Corrigall, unpublished observations). Research with primates has also established that the same doses of nicotine which will maintain self-administration behavior will also serve as a negative reinforcer; in other words, monkeys will respond to terminate a scheduled infusion of nicotine over a dose range similar to that which maintains self-administration behavior (Spealman and Goldberg 1982). The upper end of the dose-effect curve may also be influenced by the accumulated intake of the drug over the session; this inference is drawn from the observation in rodents that the total session intake tends to reach a plateau at doses of 30 and 60 μg/kg. These data are consistent with human studies in which smokers typically inhale 15–30 μg/kg per cigarette and smoke one or two cigarettes per hour (Benowitz et al. 1990).

The overall shape of the dose-effect curve for IV nicotine self-administration in animals certainly differs from that for cocaine or opiates (Dai et al. 1989; Corrigall and Coen 1991a). Although the dose-effect curve for all of these drugs is, broadly speaking, an inverted U-shape, self-administration of nicotine appears to occur

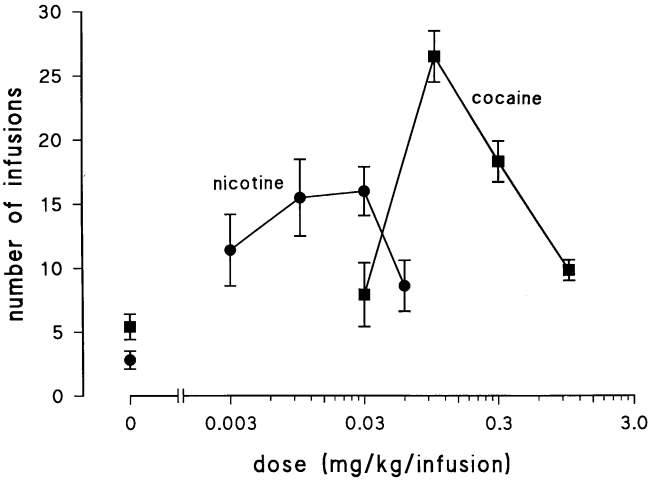


**Fig. 1** Self-administration of nicotine and of cocaine in separate groups of animals. The schedule of reinforcement was the same in each case, and consisted of a fixed ratio 5 schedule with a 1-min time-out period following each infusion

with little compensation as the dose is changed over the middle range. Figure 1 shows the dose-effect curve for IV nicotine self-administration in rodents, and compares this with IV cocaine self-administration. With cocaine self-administration maintained on the same schedule of reinforcement as used in nicotine, there is more pronounced regulation of intake as the dose of the drug available to the animals is decreased. These changes are not so large that they compensate fully for the change in dose; that is, there is not a titration to a given amount of intake, but they are regular and show that the animals attempt to adjust for the alteration in dose. For nicotine, changes in responding with dose are restricted to the low- and high-dose ends of the curve. This pattern of partial compensation, with a middle range of doses over which responding is insensitive to dose, appears to be a characteristic of nicotine self-administration across animal species, and interestingly, seems to occur whether the schedule of reinforcement is a fixed ratio, fixed interval, or progressive ratio (Goldberg et al. 1981; Risner and Goldberg 1983; Corrigall and Coen 1989). This pattern bears a strong resemblance to descriptions of tobacco smoking in terms of boundaries on intake, an upper one which the smoker tries not to exceed, and a lower one below which the smoker does not want his nicotine levels to go (Kozlowski and Herman 1984; Russell 1987). Within these boundaries the dose of nicotine appears to be less relevant to humans.

In studies of tobacco smoking by humans, the dose of nicotine has most often been manipulated experimentally by altering the nicotine delivery of smokers' usual brands of cigarette. Many studies have shown that smokers generally increase their rate of smoking in response to a reduction in cigarette nicotine yield from their customary brand and decrease their rate of smoking in response to increases in cigarette nicotine yield (McMorrow and Foxx 1983). While these studies have clearly demonstrated compensatory changes in smoking topog-

raphy in response to nicotine dose manipulations, the degree of nicotine regulation or “titration” is usually quite crude. Typically, smokers compensate to an extent that reduces the difference in obtained nicotine dose to about 50% of the nominal change in cigarette nicotine yield (Russell 1990).

In a related paradigm, an exogenous source of nicotine is added to supplement that which is obtained from cigarettes. Nicotine supplementation, whether delivered orally from capsules (Jarvik et al. 1970), intravenously (Lucchesi et al. 1967) intra-nasally (Perkins et al. 1992b) or through nicotine skin patches (Foulds et al. 1992), generally produces a suppression of smoking behavior. As in nicotine titration studies, the suppression is not necessarily proportional to dose. For example, in a study reported by Benowitz and Jacob (1990) smokers received an intravenous infusion of nicotine equal to the total dose self-administered from cigarettes in a previous session. Instead of resulting in a complete suppression of smoking behavior, subjects continued to smoke at approximately 75% of their baseline rate. Similarly, supplementation of nicotine via skin patches delivering 21 mg/24 h, leads to a suppression in smoke intake by 25–50% (Foulds et al. 1992; Rose et al. 1994b).

Some of the insensitivity of ad libitum smoking to dose manipulations may be related to non-nicotine conditioned reinforcing factors which may play a major role in the maintenance and regulation of smoking behavior. It is clear that smoking cigarettes is far more rewarding than receiving nicotine by alternative forms of delivery such as nicotine gum, patches or nasal spray (Henningfield et al. 1983; Perkins et al. 1992a; Pomerleau et al. 1992; Sutherland et al. 1992). Most smokers who are actively trying to quit eventually relapse to cigarettes even when provided with these alternative nicotine delivery systems (Fagerström 1988; Palmer et al. 1992; Sutherland et al. 1992; Hughes and Glaser 1993). Although these alternative forms of nicotine delivery can effectively relieve certain smoking withdrawal symptoms, they only partially alleviate craving for cigarettes during the initial days of smoking abstinence (Abelin et al. 1989; Rose et al. 1990). While the rate of nicotine delivery could clearly be a factor, smokers report missing the behavioral and sensory components of the act of smoking (Rose et al. 1990, 1994b). The pleasurable sensations accompanying smoking, including the taste, aroma, and especially the respiratory tract sensations from each puff of smoke, provide a rich set of cues which presumably become reinforcing through their association with the pharmacologic effects of nicotine (Rose 1988; Rose and Levin 1991b). These results are analogous to those seen with eating behavior; the caloric nourishment ultimately received from a meal may be reinforcing, but greater pleasure is obviously associated with the behavior of eating a meal versus IV feeding. In addition to providing added reinforcement for smoking cigarettes, the sensory and behavioral cues may also provide a chain of stimulus-response associations that facilitate the conditioning of smoking behavior in response to situational cues. In several published studies Rose and colleagues have shown that subjects report enjoying respiratory tract sensations elicited by cigarette smoke or nicotine, and that these sensations are especially important in relieving craving for cigarettes and facilitating smoking abstinence (Rose 1988; Westman et al. 1995). The importance of sensory factors in the regulation of smoke intake (Rose et al. 1993) has also been demonstrated in a laboratory study in which smokers were allowed to smoke ad libitum one of three types of smoke: high nicotine smoke which was also rated high in sensory intensity, diluted smoke low in nicotine and low in sensory intensity, and a smoke-like aerosol low in nicotine delivery but which produced intense airway sensations due to the aerosol particle size and composition (Behm et al. 1990). Smokers displayed compensatory increases in puffing when exposed to the dilute smoke condition, but did not increase their smoking when puffing the low-nicotine, high sensory smoke. A similar result was obtained when low tar and nicotine cigarettes were enriched with capsaicin to enhance their sensory impact; compensatory increases in smoking were prevented that otherwise occurred when subjects smoked low-yield cigarettes (Behm and Rose 1994).

Investigators have also used de-nicotinized tobacco cigarettes to explore non-nicotine determinants of smoking. These cigarettes resemble normal cigarettes in taste, but have a nicotine delivery less than one tenth of conventional popular brands of cigarette. Several studies have confirmed that non-nicotine factors modulate subjective responses such as craving for cigarettes (Hasenfratz et al. 1993; Butschky et al. 1995; Rose and Behm 1995). However, measurements of ad libitum smoking behavior have thus far produced mixed results. In one study, Hasenfratz et al. (1993) found no acute compensatory increases in smoking when subjects used de-nicotinized cigarettes after overnight abstinence. However, Rose and Behm (1995) reported that smokers did increase their smoking of de-nicotinized cigarettes during a 3-h session after overnight abstinence from smoking. Moreover, a nicotine skin patch abolished this compensatory increase in smoking behavior. One salient difference in procedure between the two studies was that subjects in the Hasenfratz study had more prior exposure to the cigarettes and any initial compensatory smoking may have extinguished prior to the measurement of ad libitum smoking in the laboratory. If compensatory smoking behavior does occur using de-nicotinized cigarettes, then this would imply that the immediate perception of the CNS effects of nicotine is not adequate to account fully for the regulation of smoking behavior, and suggests that conditioning factors are also important.

It should be noted that non-nicotine cigarettes duplicate only a portion of the sensory aspects of cigarette smoking, because nicotine itself stimulates peripheral receptors in the respiratory tract (Ginzel and Eldred 1977). Thus, differences between nicotine and non-nicotine cigarettes cannot be attributed definitively to the CNS actions of nicotine alone. Studies using peripheral nicotinic antagonists, discussed below, are valuable in addressing this issue.

As in humans, animal behavior can become conditioned by administration of a drug, and this has been shown to be the case for nicotine self-administration. For example, monkeys trained to self-administer nicotine on a second-order schedule responded less for the drug during intervals in which a stimulus complex, previously associated with drug delivery, was absent (Goldberg et al. 1981). This observation suggests that cues associated with the drug contribute to the maintenance of high rates of drug-taking behavior for nicotine. Other studies have aimed to examine the conditioned effects of nicotine by means of the place preference technique. In this type of experiment, animals experience experimenter-administered drug in a distinctive environment, and are subsequently tested for a preference for that environment compared with another which has been paired with the vehicle solution only. The rationale for this Pavlovian conditioning task is that preference for the environment paired with the drug is a measure of the rewarding effects it produces. For nicotine, several studies have examined place preference effects following systemic administration, but the results as a whole have been equivocal (e.g. Fudala et al. 1985; Clarke and Fibiger 1987). Although preference experiments for nicotine have relied on routes of administration other than the IV one, other drugs such as cocaine, amphetamine and mu-selective opioids typically produce a place preference with SC or IP administration. Nicotine may require a larger number of drug-environment pairings than other substances. A recent investigation suggests that it is chronic treatment rather than increased pairing which is the important feature in demonstrating conditioned place preferences for nicotine (Shoaib et al. 1994), but it may be that the numerous drug-environment pairings which occur during smoking behavior in humans or IV self-administration in animals contribute to conditioned effects.

In summary, evidence shows that smokers are sensitive to manipulations of nicotine dose, although the extent of regulation is often less than proportional. In animals, alterations in dosage are also not accompanied by marked compensatory changes in responding, and in fact there is less compensation in responding for IV nicotine than is observed for the IV self-administration of other drugs. The underlying reason for this dose-response relationship is unknown, and discovery of the processes involved should be a challenge to the behavioral neuroscientist. It is tempting to speculate that the mechanism of receptor desensitization may contribute, but while there is evidence that such processes may alter transmitter release in circuitry involved in reinforcement (Benwell et al. 1995), there is as yet no direct evidence for the role of desensitization in self-administration per se. Whatever the reason, data from both humans and animals suggest that the dose of nicotine may not be critical, and that a range of doses may be acceptable. In addition, in humans, sensory cues likely play a prominent role in smoking topography and behavior.

## Response to treatment with a nicotinic antagonist

In either animals or humans, the effects of nicotinic antagonists would be expected to resemble a reduction in nicotine dose. In view of the inverted U-function relating responding, or measures of cigarette smoking, to dose, treatment with an antagonist theoretically might be expected to lead either to an increase or to a decrease in self-administration depending on the baseline level of nicotine intake.

Treatment of animals trained to self-administer nicotine with nicotinic antagonists has been carried out at mid-range doses of nicotine and as expected theoretically there is a decrease in responding following such treatments. Data supporting this statement include the effects of systemically administered mecamylamine on nicotine self-administration in a range of animals and in a variety of schedules of drug access (Goldberg et al. 1981; Spealman and Goldberg 1982; Risner and Goldberg 1983; Corrigall and Coen 1989). One exception to this statement is a study of nicotine self-administration by rodents on a CRF schedule in which the first of a series of mecamylamine treatments produced an increase in responding, but subsequent treatments were without effect (Hanson et al. 1979). In this study, baseline intake of nicotine was very low. Nicotine antagonists have also been used to discover which sites in the CNS are involved in nicotine reinforcement (Corrigall et al. 1994); in this research, nicotine self-administration has also been reduced by intracranial micro-infusions of nicotinic antagonists (see Discussion below).

A perhaps surprising observation about the effects of nicotine antagonists on nicotine self-administration in animals is the absence of a transient increase in responding in that period immediately following treatment. This increase is often observed in self-administration of other drugs when the dose is reduced or treatment with an antagonist occurs, and is also observed in studies of human smokers receiving mecamylamine treatment (see below). Possibly, responding is affected both by an aversive drive state, which is produced by nicotine deprivation and which motivates responding, and by the incentive value or positive reinforcing efficacy of the drug. Animals that are not dependent on nicotine may have less motivation to obtain nicotine and thus be less prone to exhibit an extinction burst of responding after nicotine blockade or after a reduction in nicotine dose than is exhibited by nicotine-dependent human smokers.

Given that smokers generally show increases in smoking when the nicotine yield of their usual cigarette is reduced, a logical expectation would be that mecamylamine would acutely cause smokers to increase their nicotine self-administration. Indeed, in the first published experimental study of nicotinic antagonists in human smokers, Stolerman et al. (1973) reported that mecamylamine acutely increased smoking behavior. Subsequent studies confirmed that the immediate effect of mecamylamine is to increase nicotine intake from cigarettes (Po-

merleau et al. 1987). Moreover, in a subsequent study Rose et al. (1988) showed that mecamylamine increased subjects' preference for nicotine when allowed to control selectively the nicotine content of each puff of smoke.

The chronic effects of mecamylamine may be different from these acute effects. Instead of producing compensatory increases in smoking, mecamylamine, administered in one study at a dose of 5 mg twice a day, led to a gradual reduction in smoking over a 4-week period (see Fig. 3 below). Note the greater cigarette consumption in the mecamylamine-only condition relative to the other conditions for the first 2 days. It is not clear why smoking decreases over time after mecamylamine blockade whereas a nicotine dose reduction as is obtained in brand-switching studies usually produces a sustained increase in rates of smoking (Frost et al. 1995). Possibly, the dose of mecamylamine used was sufficient to virtually completely block the reinforcing effects of nicotine. When the dose of nicotine approaches zero, one might expect extinction to take place rather than continued compensation. Some support for this interpretation is provided by assessments of nicotine discriminability collected in a different study (unpublished data) with 28 smokers who received mecamylamine at a dose of 5 mg twice a day (producing plasma mecamylamine levels of approximately 15 ng/ml). Subjects were asked to rate the perceived strength of high versus low nicotine-containing puffs of smoke at baseline and after 2 weeks of mecamylamine treatment. As shown in Fig. 2, mecamylamine was found effectively to abolish the discriminability of nicotine (as assessed by ratings of perceived "strength" of the cigarettes smoked). Thus, it is not surprising that the effects on behavior might be a transient increase followed by diminished smoking rather than the sustained upward compensation accompanying a partial reduction in dose typically studied in brand-switching experiments.

The effects of mecamylamine on smoking behavior have been assumed to be mediated mainly through blockade of nicotinic receptors in the central nervous system. In the Stolerman study (Stolerman et al. 1973), pentolinium, a peripheral nicotinic antagonist that does not effectively cross the blood-brain barrier, did not affect smoking topography. Similarly, in animals, pentolinium (Hanson et al. 1979) and hexamethonium (Corrigall and Coen 1989) do not alter intravenous nicotine self-administration. However, some of the effects of inhaled nicotine in humans can be blocked by peripheral nicotinic antagonists; for example, Lee et al. (1993) reported that hexamethonium attenuated the perception of nicotine irritation in the respiratory tract. Moreover, recent work in one of our laboratories (J.E.R.) has shown that the peripheral nicotinic antagonist trimethaphan significantly attenuates smoking satisfaction (Rose et al., unpublished data). Rose et al. (1988) had previously reported that mecamylamine attenuated respiratory tract sensations produced by nicotine in cigarette smoke, which likely resulted from its action at peripheral receptors. In

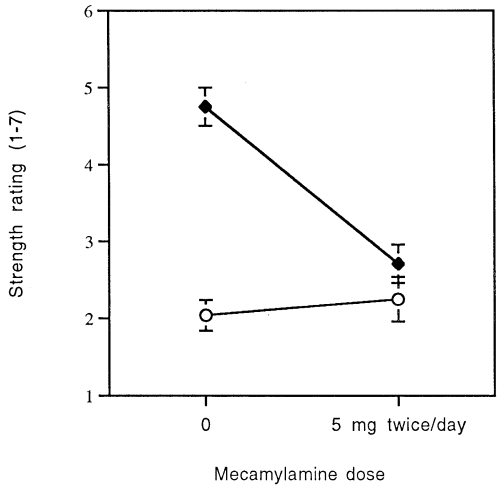


**Fig. 2** Ratings of the strength of high versus low nicotine puffs of cigarette smoke (mean ± SEM), before and 2 weeks after receiving mecamylamine orally at a dose of 5 mg twice per day. The high nicotine cigarette (—◆—) had a nicotine yield of approximately 1.5 mg and the low nicotine cigarette (—○—) yielded 0.75 mg

view of the important role of the sensory aspects of smoking in regulating smoke intake, the role of peripheral nicotine actions in human nicotine self-administration cannot be ruled out.

In summary, while not identical, there are similarities in the effects of nicotinic antagonists on IV self-administration by animals and on cigarette smoking behavior. With animals and humans, responding for nicotine decreases over time in the presence of a nicotinic antagonist. The principle difference between the results of animal and human studies is that human smokers show a transient increase in smoking which might be due to the motivational effects relating to their dependence on nicotine.

## Nicotine-mecamylamine combination in treatment of smoking

Controlled studies of smoking behavior have been useful in developing smoking-cessation interventions. As with treatment of other addictions (e.g. opiate addiction), two of the main pharmacologic treatment strategies explored have been substitution and blockade (Jarvik and Henningfield 1988). Nicotine substitution, as can be achieved clinically using skin patches, gum, nasal spray or inhaler, has been shown to relieve tobacco withdrawal symptoms and to promote abstinence from smoking. Limited clinical work has also been conducted using the nicotine antagonist mecamylamine. Some initial promising results were reported by Tennant et al. (1984), but side effects from the high doses used (averaging more than 25 mg/day), which included constipation, cramps and weakness, caused a substantial number of subjects to drop out of treatment. Rose and Levin (1991a) proposed

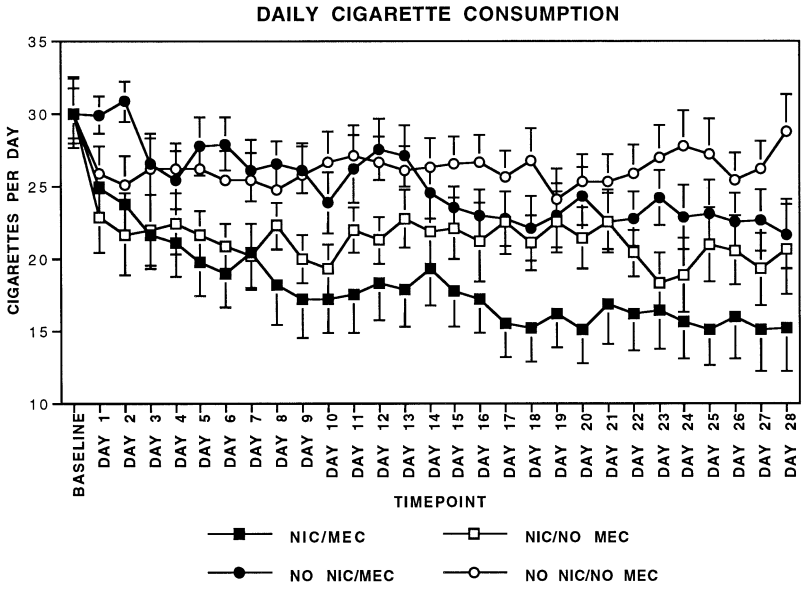


**Fig. 3** Ad libitum smoking rates (mean ± SEM) from study described in Rose et al. (1996). Data depict smoking behavior during 28 days of receiving nicotine alone (*nic/no mec*), mecamylamine alone (*no nic/mec*), nicotine+mecamylamine (*nic/mec*) or neither drug (*no nic/no mec*). Least square means have been plotted, adjusting for baseline levels of self-reported smoking

that the problems of mecamylamine therapy could be solved by the use of lower doses and by combining the paradigms of nicotine substitution and nicotine blockade. In recent work, Rose et al. (1996) have shown that concurrent administration of nicotine with mecamylamine produces greater suppression of ad libitum smoking behavior than either agent alone (see below). Although the value of a nicotine/mecamylamine combination may initially seem counterintuitive, nicotine and mecamylamine both "occupy" receptors that would otherwise be acted upon by nicotine from cigarettes [even though the two drugs bind to different sites in the receptor-ion channel complex (Martin et al. 1989)]. Therefore, nicotine and mecamylamine administered in combination would be expected to occupy more receptors than either drug alone, thereby reducing the number of available receptors to respond to nicotine from cigarettes, attenuating smoking reward and facilitating extinction of the smoking habit. This theory was supported in three previous studies. In one study, the effect of the combination of nicotine and mecamylamine on subjective responses to cigarette smoking was evaluated in a laboratory setting (Rose et al. 1994a). Subjects participated in four conditions, presenting nicotine (1.1 mg) or de-nicotinized smoke, and mecamylamine (10 mg) or placebo capsules, in a 2×2 factorial design. Following this, subjects inhaled a controlled dose of nicotine-containing cigarette smoke (1.1 mg nicotine), which they rated for satisfaction and other characteristics.

Smoking satisfaction and liking were significantly reduced by mecamylamine across blocks of cigarette puffs. Pre-exposure to nicotine-containing smoke also reduced subsequent smoking satisfaction. Thus, rather than counteracting each other, nicotine and mecamylamine had additive effects in reducing subsequent smoking satisfaction. This laboratory study supported the hypothesis that the combination of nicotine and mecamylamine might have promise for smoking cessation treatment.

A subsequent clinical trial compared mecamylamine (2.5–5 mg b.i.d.) plus nicotine skin patch treatment to the nicotine patch alone (Rose et al. 1994b). The primary outcome of interest was continuous smoking cessation, based on a self-report of absolutely no smoking since the previous session, and an expired CO measurement of ≤8 ppm. Continuous abstinence rates were significantly higher among subjects receiving nicotine+mecamylamine treatment at 7 weeks ($P$=0.015), 6 months ($P$=0.046) and at a 12-month follow-up ($P$=0.004).

In a recent follow-up study (Rose et al. 1996), 80 subjects received 4 weeks of pre-cessation treatment with either: nicotine/mecamylamine (21 mg/24 h nicotine patch, 5 mg b.i.d. oral mecamylamine), nicotine alone, mecamylamine alone, or placebo. The post-cessation treatment was the same for all groups, and included concurrent nicotine/mecamylamine administration for 6 weeks. A significant reduction in the rate of relapse to smoking produced by pre-cessation treatment with mecamylamine was confirmed using survival analysis ($P$=0.019). After the target quit-smoking date, the treatment was the same for all groups and hence the differential abstinence is attributable to the pre-cessation treatment with mecamylamine. Our interpretation is that blockade of smoking reward promoted extinction of smoking behavior and facilitated subsequent abstinence from cigarettes, which was supported by the finding that reported enjoyment of smoking was reduced by mecamylamine.

Interestingly, ad libitum smoking prior to the target quit-smoking date showed a significantly greater suppression by concurrent nicotine/mecamylamine treatment relative to nicotine alone, mecamylamine alone or placebo conditions (see Fig. 3). Mecamylamine and transdermal nicotine had additive effects in suppressing ad libitum smoking during the 28 days leading up to the target quit-smoking date. The marked reduction in smoking in the combined nicotine/mecamylamine treatment condition was corroborated by measurements of expired

air carbon monoxide as well as by plasma nicotine and cotinine analyses.

In summary, mecamylamine, with or without concurrent nicotine administration, reduces the rewarding effects of cigarette smoking, promotes smoking abstinence and reduces ad libitum smoking. The effect on ad libitum smoking is markedly enhanced by concurrent nicotine supplementation. Mecamylamine may be promoting extinction of the rewarding value of nicotine, whereas nicotine supplementation could be suppressing smoking primarily through affecting the level of nicotine deprivation. Whether nicotine and mecamylamine are acting at the same anatomical sites or instead work cooperatively through action at different loci can best be answered using animal models.

### Neurochemical mechanisms in nicotine reinforcement

The role of several neurochemical systems in nicotine reinforcement have been examined in both humans and animals. Studies with animal paradigms have addressed the question of neurochemical mechanisms at two levels. At one level, the effect of agonists and antagonists to specific neurochemical systems have been examined in animals trained to self-administer nicotine. These animal studies have a direct parallel in experiments in which similar compounds are tested for their ability to alter smoking by human subjects; comparisons can be made and conclusions need recognize only that different factors may be involved in smoking and intravenous self-administration. At this level there are data to compare animals and humans with respect to several neurochemical systems. At another level of analysis, the real strength of an animal paradigm for nicotine self-administration is that it can be used to discover the neurobiological mechanisms that control reinforcement processes. In this latter vein, the dopamine mechanisms have received the most attention.

## Dopamine

This section summarizes the substantial evidence which shows that dopamine cells in the midbrain are critical elements of the circuitry which supports nicotine self-administration in animals, and compares this knowledge with the limited data from smokers tested with the dopamine antagonist haloperidol.

It has been logical to test if a dopaminergic mechanism might be involved in nicotine reinforcement in animals, since there is a large body of evidence that dopamine, and in particular the mesolimbic dopamine projection, plays a part in other drug reinforcement and motivated behavior (Wise and Bozarth 1987; Robinson and Berridge 1993). In addition, the concept of a dopaminergic substrate to nicotine reinforcement is supported by a variety of anatomical, biochemical and electrophysiological data about nicotinic effects on this neuronal pathway. It is useful to summarize these data as an introduction to studies which directly examine the role of mesolimbic dopamine neurons in nicotine reinforcement.

Neuroanatomical studies have shown that mesolimbic dopamine neurons possess nicotinic receptors on their cell bodies and/or dendrites in the ventral tegmental area (VTA) as well as in mesolimbic terminal synaptic fields in the nucleus accumbens (Clarke and Pert 1985). Nicotinic compounds do appear to be active at each of these receptor populations. In the dopamine synaptic fields, nicotinic agonists potentiate the release of dopamine from mesolimbic terminals in vitro (e.g., Rowell et al. 1987; Rapier et al. 1988), and infusions of nicotine delivered directly into accumbens in situ via a microdialysis probe augment dopamine release (Mifsud et al. 1989). On the other hand, electrophysiological data have shown that nicotine acts directly on dopamine cells in the VTA (Calabresi et al. 1989). Recent microdialysis experiments which have studied dopamine overflow in the nucleus accumbens (Benwell et al. 1993; Nisell et al. 1994) also support the idea that nicotine acts in the VTA rather than in the accumbens to modulate dopamine neurotransmission.

The mechanism of nicotine action on mesolimbic dopamine cells has in addition been studied using behavioral activation. Systemically administered nicotine produces a locomotor stimulant effect which depends on dopaminergic mechanisms (Corrigall and Coen 1991c; O'Neill et al. 1991) and on the integrity of the mesolimbic projection (Clarke et al. 1988). This behavioral effect appears to depend on a VTA site of action; focal microinfusions of nicotinic agonists into the VTA produce locomotor activation, whereas similar infusions into other sites, including the nucleus accumbens, are ineffective (Museo and Wise 1990; Reavill and Stolerman 1990; Welzl 1990 #36). Microdialysis studies have also shown good positive correlations between the activity of the mesolimbic dopamine system in response to nicotine, and behavioral activation (Benwell and Balfour 1992). In addition, both neurochemical measurements and behavioral activation show similar desensitization responses to nicotine (Benwell et al. 1995).

These same dopamine cells appear to be critical elements of the neuronal circuitry maintaining self-administration behavior. First, dopamine antagonists attenuate nicotine self-administration (Corrigall and Coen 1991c). In this study, animals trained to self-administer nicotine were treated prior to their operant sessions on test days with a range of doses of either the $D_1$-selective antagonist SCH23390, the $D_2$-selective antagonist spiperone, or haloperidol. The antagonists produced dose-dependent decreases in nicotine self-administration; since nicotine-maintained responding does not show extinction bursts when the dose of the drug is reduced, decreases in self-administration following dopamine antagonist treatments are consistent with an effect on nicotine reinforcement. Temporal patterns of responding during the treatment sessions show that there were doses of each antagonist at which overt motor impairment did not occur. These ob-

servations provided preliminary evidence that nicotine reinforcement is dependent on a dopaminergic substrate.

A subsequent study examined whether the mesolimbic projection from the VTA to the nucleus accumbens is the dopamine system involved (Corrigall et al. 1992). Lesions of the dopaminergic neurons in this projection were produced with the neurotoxin 6-hydroxydopamine in animals trained to self-administer nicotine. These lesions, which resulted in a 92% reduction in the dopamine content of the mesolimbic projection, attenuated nicotine self-administration markedly compared to sham-treated animals for the 3-week test period. The dopamine content of the adjacent striatum was decreased by less than 20%, an amount smaller by far than that usually associated with effects on motor performance. Nonetheless, lesions of this kind do have effects on a range of reinforced behaviors, and interpretations need to be made with caution.

A third study, therefore, confirmed the role of the mesolimbic dopamine system in nicotine reinforcement using an approach that does not involve direct manipulations of the dopamine system. To this end, focal microinfusions of a nicotinic antagonist were made into each of the VTA and nucleus accumbens (Corrigall et al. 1994). The antagonist chosen for these studies was dihydro-β-erythroidine (DHβE). Animals trained to self-administer nicotine were prepared under surgical anesthesia with chronic guide cannulae directed toward the nucleus accumbens or VTA. Following recovery from surgery and re-establishment of baseline self-administration, micro-infusions of DHβE were made into each of these nuclei 10 min prior to self-administration sessions. When infused into the VTA, DHβE produced a significant and dose-related decrease in nicotine self-administration; the same doses delivered into the nucleus accumbens were without effect (Corrigall et al. 1994). In control experiments, focal administration of DHβE into the VTA was found to be without effect on spontaneous locomotor activity after saline treatment, on cocaine self-administration, and on responding maintained by delivery of food. DHβE is therefore without obvious behaviorally disruptive consequences after intra-VTA infusions, but does attenuate nicotine self-administration.

These data argue very strongly that the mesolimbic dopamine system is a substrate in nicotine reinforcement, and that nicotine activates this system through the VTA. One would expect therefore that dopaminergic compounds would alter the smoking behavior of humans.

Unfortunately, data regarding the effects of dopaminergic manipulations in human smokers are limited. Dawe et al. (1995) recently described the effects of haloperidol administration in light-to-moderate smokers. In this study there was no difference between placebo and haloperidol on self-report measures of smoking satisfaction, nicotine withdrawal, or its relief by smoking; however, plasma nicotine levels were significantly higher in the haloperidol treatment both immediately after a test cigarette and after 1 h of ad libitum smoking. During debriefing, many subjects maintained that the treatment did not alter their smoking behavior. Measures of smoking behavior were also increased in a study of schizophrenia patients who smoke (McEvoy et al. 1995).

Therefore there is consistency between animal studies of nicotine reinforcement and the small amount of data from humans that dopaminergic mechanisms appear to be involved in both behaviors. However, it is puzzling that dopamine blockade leads to a reduction in nicotine self-administration in animal studies, whereas smokers seem to show compensatory increases after receiving haloperidol treatment. The reasons for the different directions of the effects of dopamine antagonists on smoking behavior and nicotine self-administration are not known. It would be valuable to know the effects of dopamine antagonists on IV self-administration of nicotine by humans; the animal-human differences may result from the different routes of administration including other factors that attend inhalation of tobacco smoke such as sensory cues, for example. Another potential explanation for the apparent difference between human and animal findings is that smokers, in contrast to animals self-administering nicotine, may increase their nicotine intake in order to counteract the cognitive impairment that can be produced by dopamine receptor blockade. Levin et al. (1996) have recently found that nicotine indeed offsets the cognitive performance decrement produced by haloperidol in patients with schizophrenia. Human smokers may be dependent on other effects of nicotine that lead to greater compensatory efforts in response to neurochemical blockade than may be exhibited by nondependent animals. Finally, different behavioral outputs are required to increase nicotine levels in IV self-administration (lever pressing for an additional quantal drug delivery) versus inhalation of tobacco smoke (greater depth of inhalation, longer smoke retention, etc.).

Alternatively, one might question the direction of changes in responding produced by dopamine antagonists on nicotine self-administration in animals, since they appear to be different in direction from effects on the self-administration of other drugs such as cocaine. It is useful to explore the effects of dopamine antagonists on cocaine self-administration in animals. When cocaine is self-administered at moderate-to-high doses, treatment with dopamine antagonists produces compensatory increases in responding, resulting in an increase in the number of infusions obtained (see Corrigall and Coen 1991a). At lower doses of cocaine, however, the effects of the dopamine antagonists are very different. Rather than causing a compensatory increase in responding, they cause decreases in both rats (Corrigall and Coen 1991a) and primates (Glowa and Wojnicki 1996). The direction of the response of nicotine self-administration to treatment with dopamine antagonists is therefore similar to the direction observed in treatment of cocaine self-administration at low doses. In terms of the underlying mechanism for nicotine action described above, this is perhaps reasonable. Nicotine's action at the dopamine cell body or vicinity (Corrigall et al. 1994) would be ex-

pected to result in the release of dopamine in the nucleus accumbens in typical physiological concentrations. To this extent, its effects mimic those of cocaine, which acts directly at the terminal region to reduce the re-uptake of dopamine into terminals. However, a normally functioning re-uptake system might be expected to be able to accommodate a large part of the increased dopamine release caused by action of nicotine in the VTA region. Therefore, the net effect might be comparable to a low dose of cocaine, which produces only modest increases in peri-synaptic dopamine because it results in only small effects on the re-uptake system.

## Opioids

Unlike the situation for dopamine, greater attention has been paid to the potential role of opioids in studies of tobacco smoking than in animal self-administration research. Research with smokers has focused largely on the effects of the antagonist naloxone on smoking behavior and subjective effects, in a variety of designs. An early positive report by Karras and Kane (1980) found that naloxone decreased smoking and produced a reduction in the desire to smoke. A subsequent report that plasma beta-endorphin levels correlated with plasma nicotine levels strengthened the speculation that opioid mechanisms might be involved in smoking (Pomerleau et al. 1983). However, two subsequent studies which examined non-deprived smokers found that naloxone produced no effect on intake measures and little-to-no effect on indices of satisfaction from smoking (Palmer and Berens 1983; Nemeth-Coslett and Griffiths 1986). Another study which examined the effects of naloxone on smoking after a period of abstinence reported a small effect in cigarette consumption but no effect on the desire to smoke and other subjective measures (Gorelick et al. 1989). Sutherland et al. (1995) have examined the effect of the longer-lasting antagonist naltrexone in heavy smokers, and found that there were no effects of the antagonist on biochemical or behavioral measures of intake or satisfaction on either the first cigarette smoked after an abstinence period, or during ad libitum smoking.

To the extent that these studies generally point to the absence of an effect of these opioid antagonists on smoking, there is consistency with the animal literature. However, this literature consists of a single animal study only (Corrigall and Coen 1991b) in which animals trained to self-administer nicotine were treated with a range of doses of naloxone or naltrexone prior to operant sessions. There was no effect of either of these antagonists on the rate or pattern of self-administration. Amongst the many locations of mu-type opioid receptors which are potential sites of action for naloxone and naltrexone is the VTA, where it appears that mu receptors are located on GABAergic interneurons which inhibit dopamine cells. There are of course numerous sites at which naloxone and naltrexone could act, but given the clear role for dopamine mechanisms in nicotine reinforcement, it is reasonable to speculate that these antagonists likely do not block an endogenous opioid mechanism within the VTA. Of course this requires confirmation with local microinfusions of opioid antagonists to rule out the possibility that the effects of systemically administered antagonists at several sites cancel each other.

## Other systems

The only other neurochemical system to have received attention in both human and animal studies of nicotine reinforcement is serotonin, and in particular the 5-$HT_3$ receptor subsystem. In the single animal study which has been done, the 5-$HT_3$ selective antagonists MDL72222 and ICS 205–930 had no effect on the rate or pattern of nicotine self-administration (Corrigall and Coen 1994). These findings are consistent with a study by Zacny et al. (1993) in which regular smokers, defined as smokers of 15 or more cigarettes a day for at least 2 years were treated with the 5-$HT_3$ selective antagonist ondansetron. Ondansetron produced no effects on 24-h cigarette consumption, expired-air carbon monoxide, plasma nicotine or cotinine levels, or the smokers' mood.

## Conclusions

Animal and human models have provided complementary insight into the nature of the reinforcing mechanisms maintaining nicotine self-administration. Considerable overlap in the findings is indicated by studies manipulating nicotine dose, which reveal an intermediate dose range over which self-administration is maintained, and crude regulation of overall nicotine intake. Results from nicotinic blockade studies clearly show that reinforcement is attenuated by centrally active nicotinic antagonists in both animals and humans. However, peripheral blockade merits further analysis in human smokers in view of the prominent role of sensory cues in the regulation of ad libitum smoking and the peripheral sensory effects of nicotine. Animal and human studies are also in accord in implicating dopaminergic neurotransmission as a factor affecting nicotine self-administration; however, the direction of the effect appears to be opposite in humans and animals. Research which clarifies the effects of dopaminergic antagonists on sensory and other effects in tobacco smoking, which are not a part of IV nicotine self-administration, may clarify these differences in direction.

By examining the studies that have been conducted, one can find gaps in human or in animal research where parallel studies have not been done, and which suggest areas for fruitful cross-fertilization between animal and human research domains. For example, an analysis of the effects of pharmacologic agents on IV nicotine self-administration has been carried out exclusively with animals. Alternatively, some experimental paradigms, such as supplemental nicotine administration, and concurrent

nicotine agonist/antagonist administration, have thus far been explored to a greater extent in human studies. In the future, these procedures might be applied profitably in the context of animal self-administration paradigms.

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