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REVIEW

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Nicotine and nonnicotine factors in cigarette addiction

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Abstract *Rationale:* A great deal of research supports the role of nicotine in cigarette addiction. However, the effectiveness of nicotine replacement therapy (NRT) as a smoking cessation treatment has fallen short of initial hopes. A key reason may be that NRT does not address nonnicotine components of smoking reinforcement. These include constituents that provide reinforcing sensory stimulation, components that minimize excessive irritation from inhaled nicotine and other pharmacologically active compounds in cigarette smoke. *Objective:* Studies using various paradigms to dissociate nicotine from other components of smoking are summarized. *Results:* Nonnicotine components provide many rewarding effects, often surpassing the direct effects of nicotine. Substitutes for the sensory effects of smoking may be effective in relieving craving for cigarettes and in facilitating smoking cessation. Moreover, techniques for devaluing smoking-related cues may decrease craving and enhance subsequent abstinence. Promising approaches for devaluing smoke cues include extinction-based treatments employing denicotinized cigarettes and the use of nicotinic agonist and/or antagonist treatment during the weeks leading up to a quit attempt. Recent studies suggest that incorporating these approaches into a treatment program may significantly increase smoking abstinence rates. Preliminary findings also suggest that replacement of the effects of monoamine oxidase inhibitors contained in cigarette smoke may enhance quit rates. *Conclusions:* While current NRT methods have been the mainstay of smoking cessation treatment and will likely continue to serve a useful role, the next stage of progress will likely entail the development of tools designed with recognition of the importance of nonnicotine components of cigarette smoking.

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Introduction

There has been substantial progress in analyzing the pharmacologic basis of tobacco addiction and in delineating the role of nicotine in its acquisition and maintenance. The recognition of the critical role played by nicotine has led to the development of several useful treatments to assist cigarette smokers to quit, i.e., nicotine replacement therapy (NRT) in the form of gum, patch, nasal spray, inhaler, and lozenge (Fiore et al. 2000). Although the identification of nicotine as a reinforcing agent for smoking behavior has been an important step forward, much remains to be done in terms of elucidating the role of other components of smoking behavior. The role of nonnicotine factors will be the focus of this article, and evidence will be reviewed suggesting that an appreciation of the role of these factors may lead to further advances in smoking cessation treatment.

Nicotine is not enough; the insufficiency of nicotine replacement in smoking cessation treatment

When NRT was first introduced more than 20 years ago, there existed a widespread belief that the problem of tobacco addiction might yield fairly quickly to a solution. After all, if smokers are smoking primarily to obtain nicotine, and one supplies them with an alternative source of nicotine, then it might be a relatively straightforward manner for smokers to make the transition from cigarettes to NRT, and ultimately to be weaned off of NRT. Unfortunately, this optimistic prediction has not materialized, and success rates in treatment, while demonstrably higher than placebo by a factor of approximately 2, nonetheless remain low in absolute terms. In real-world settings, use of NRT in the absence of intensive behavioral support, typically yields

long-term (6–12 months) success rates of less than 20% (Bohadana et al. 2000; Croghan et al. 2003; Stapleton et al. 1995). What accounts for the modest success of NRT? In part, the low success rates may be due to aversive stimuli accompanying some forms of NRT, such as local irritant effects of nicotine (nasal spray) or its unpleasant taste (gum), which leads to underutilization of NRT. In addition, the absence of a rapid bolus delivery with most forms of NRT, in comparison with the rapid pulmonary absorption afforded by cigarette smoking, may make NRT an imperfect substitute for cigarette smoke. However, the nicotine nasal spray is quite rapid and yet does not appear to be substantially more effective than other forms of NRT (Croghan et al. 2003). On the other hand, even nicotine nasal spray does not provide a series of puffs, each delivering a transient peak in arterial nicotine concentrations as does smoking.

In an attempt to directly evaluate the importance of nicotine absorption rate, our research team has conducted a series of studies comparing the effects of intravenous (IV) nicotine administration with the effects of cigarette smoking. We developed a procedure for mimicking the puff-by-puff nicotine bolus delivery of cigarette smoke using IV administration (Westman et al. 1996). The main results of these studies are summarized below, along with other studies that attempt to parcel out the nonnicotine effects of cigarette.

Dissociating nicotine from nonnicotine components of smoking

To separate nicotine and nonnicotine effects, a procedure for delivering nicotine independently from cigarette smoke and with similar pharmacokinetics of inhaled nicotine is needed. We have employed IV nicotine administration to achieve this end. To match the dose of IV nicotine to that of each smoker's preferred brand of cigarette, we first measured the puff volume, number of puffs, and interpuff intervals when participants smoked one of their usual brands of cigarettes ad libitum. Reproducing these smoking parameters in the laboratory and capturing the smoke particulate matter for subsequent analysis allowed an estimation of the nicotine delivery per puff. In one study, we directly measured arterial nicotine concentrations attained after inhaling successive puffs of cigarette smoke and after receiving IV injections of puff-sized doses of nicotine, and found that the IV administration procedure produced very similar arterial nicotine concentrations as did cigarette smoke (Rose et al. 1999a,b). Moreover, while there was a striking within-subject consistency in the pattern of arterial nicotine concentrations over time, there were marked interindividual differences, with many smokers showing relatively small and shallow arterial peaks. We suggested that the lung served as an initial depot for nicotine, smoothing out the arterial peaks for most smokers; a subsequent study conducted by Brewer et al. (2004) using an animal model in which radiolabeled nicotine was injected directly into the right ventricle of the heart confirmed that a substantial fraction of nicotine remains in the lung for more than 40 s after each injection, resulting in a slower rise in nicotine concentration in the arterial blood and brain, than might otherwise be expected.

Having validated the IV administration procedure as a method of recapturing the pharmacokinetics of inhaled cigarette smoke, we assessed the rewarding properties in comparison to cigarette smoke. Although subjective measures are not a substitute for behavioral measures of reinforcing efficacy, they are widely used in abuse liability assessments (e.g., Houtsmuller et al. 2003; Henningfield et al. 1985), and we have collected subjective ratings as one strategy for assessing the importance of nicotine and other smoke constituents. Previous research had suggested that, under some circumstances, IV nicotine administration has subjective rewarding effects. However, in these studies, extremely rapid, high doses of nicotine were administered (up to 3 mg in 10 s). In several studies, using a more realistic dosing regimen that matched the dose of IV nicotine per injection to the dose of nicotine inhaled in each puff of cigarette smoke, the subjective enjoyment of IV nicotine appears to be minimal (Rose et al. 2000, 2003; Westman et al. 1996). However, some effects, such as relief of craving for cigarettes, were detected, and were of a similar magnitude as those provided by conventional NRT. Hence, inadequate pharmacokinetics does not provide a convincing explanation for the limited success of NRT in smoking cessation treatment.

A more plausible account for the modest effects of NRT was suggested by the results of experimental conditions that delivered the nonnicotine components of smoking, including sensory and motor components, without significant doses of nicotine. Administering smoke without the usual doses of nicotine, such as with denicotinized cigarettes, consistently provides a significant degree of subjective satisfaction (Brauer et al. 2001a; Butschky et al. 1995; Pickworth et al. 1999; Westman et al. 1996). Moreover, several investigators have shown that denicotinized cigarettes relieve craving and other smoking withdrawal symptoms, including negative affect (Gross et al. 1997; Pickworth et al. 1999; Baldinger et al. 1995; Butschky et al. 1995). However, the effect of denicotinized cigarettes on craving appears to be more robust (Buchhalter et al. 2005; Rose and Behm 2004a,b). Two factors have been suggested that may account for different results across studies in the degree of craving and/or withdrawal symptom relief provided by denicotinized cigarettes. One factor is the degree of dependence, as assessed with the Fagerström Test for Nicotine Dependence (FTND) questionnaire. Smokers scoring higher on this measure exhibit more favorable response to denicotinized cigarettes (Brauer et al. 2001a,b), suggesting that they are more dependent on nonnicotine smoke components as well as nicotine. A second factor is the degree to which stressful task demands may create a more important role for nicotine enhancement of cognitive performance (Baldinger et al. 1995) or relief of anxiety.

To assess the effects of denicotinized smoke presentation on craving as well subsequent ad libitum smoking, Dallery et al. (2003) conducted a study involving paced smoking

(normal pace vs rapid smoking) of nicotine-containing and denicotinized cigarettes. Craving was suppressed equally in all conditions, and the latency to smoke after the period of paced cigarette presentation was only slightly influenced by the high-dose nicotine condition (i.e., rapid smoking of nicotine cigarettes).

Similar findings were reported in a study (Rose et al. 2003) that compared the ability of cigarette smoke and IV nicotine to satiate smokers who were allowed concurrent access to their usual brands of nicotine-containing cigarettes. Satiation consisted of programmed puffs of either subjects' usual brands of cigarettes or denicotinized smoke presented over 4 h, accompanied by IV infusions of nicotine or saline. The volume of satiation puffs was controlled using a device that metered a fixed volume of air to the cigarette (Levin et al. 1989). Puff volume, interpuff interval, and number of puffs were individually tailored for each subject and were set equal to the values assessed during a baseline session in which the usual brands of cigarettes were smoked ad libitum. IV nicotine was administered either as a series of doses in 2-s injections, with each dose equal to that of a single puff the usual brand, or as a slow continuous infusion, in which the rate of administration was set equal to the total nicotine dose divided by total session time (4 h). Subjects were allowed free access to their usual brands of cigarettes beginning 1 h after the programmed satiation was initiated, and continuing for 3 h. Cumulative smoke intake was monitored with a cigarette holder containing a pressure transducer that measured flow rate.

Figure 1 depicts the amount of smoke that subjects took from their usual brands of cigarettes in the various conditions that presented concurrent IV nicotine (vs saline) and puffing (usual brand vs denicotinized cigarettes vs no smoking) conditions.

The results indicated that IV nicotine had only a small effect in terms of suppressing ad libitum smoking behavior. In contrast, presentations of denicotinized smoke markedly reduced ad libitum smoke intake from participants' usual brands of cigarettes. The combination of denicotinized smoke and IV nicotine recaptured the satiating effect of the usual-brand cigarettes. The relatively small influence on ad libitum smoking of IV nicotine, when dissociated from cigarette smoke, is reminiscent of previous findings of other laboratories, in which IV nicotine administration produced only slight suppression of smoking behavior (Benowitz et al. 1990; Lucchesi et al. 1967) or, in one study, no suppression at all (Kumar et al. 1977).

In a subsequent study (unpublished data), subjects were allowed to self-administer nicotine vs saline injections (dose/injection equal to that of one puff of smoke from subjects' habitual brands of cigarettes) by pressing a response key once for each injection and to choose puffs of denicotinized cigarette smoke vs sham puffs, from two cigarette holders. Sham puffs consisted of air drawn from a lit cigarette, using a holder that blocked mainstream smoke. When all four alternatives were concurrently available in 10-min preference test periods, subjects self-administered significantly more puffs of denicotinized smoke than any of the other options (see Fig. 2). These studies and others support the conclusion that smoke components other than nicotine play a role in cigarette addiction, and that the failure of current modes of NRT to address these factors is a significant shortcoming that may account for their limited effectiveness in smoking cessation treatment.

The question naturally arises as to which nonnicotine component, if any, is most important. One component comprises the constellation of sensory and behavioral cues accompanying the act of smoking The sensorimotor cues can be logically subdivided into sensory components (taste,

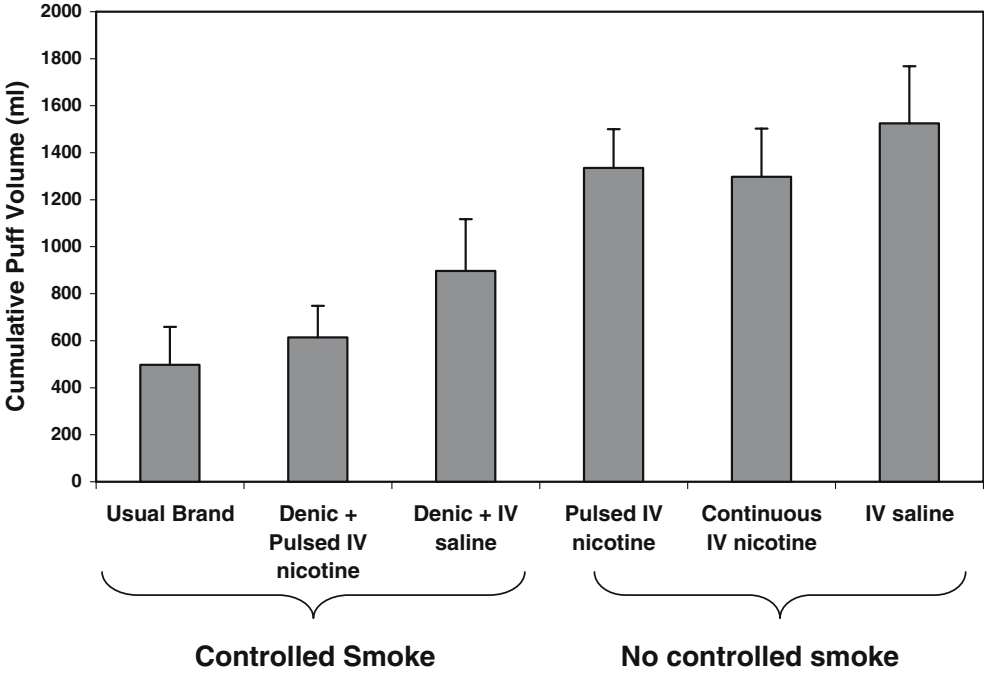

Fig. 1 Cumulative puff volume (mean±SEM) taken from subjects' usual brands of cigarettes during a 3-h ad libitum smoking period, while concurrently receiving controlled inhalations of puffs from the usual-brand cigarettes vs denicotinized cigarettes vs no smoking, and receiving IV infusions of nicotine (in pulsed bolus injections delivering puff-sized doses of nicotine or as a continuous infusion over the entire session) vs saline infusion. Adapted from Rose et al. (2003)

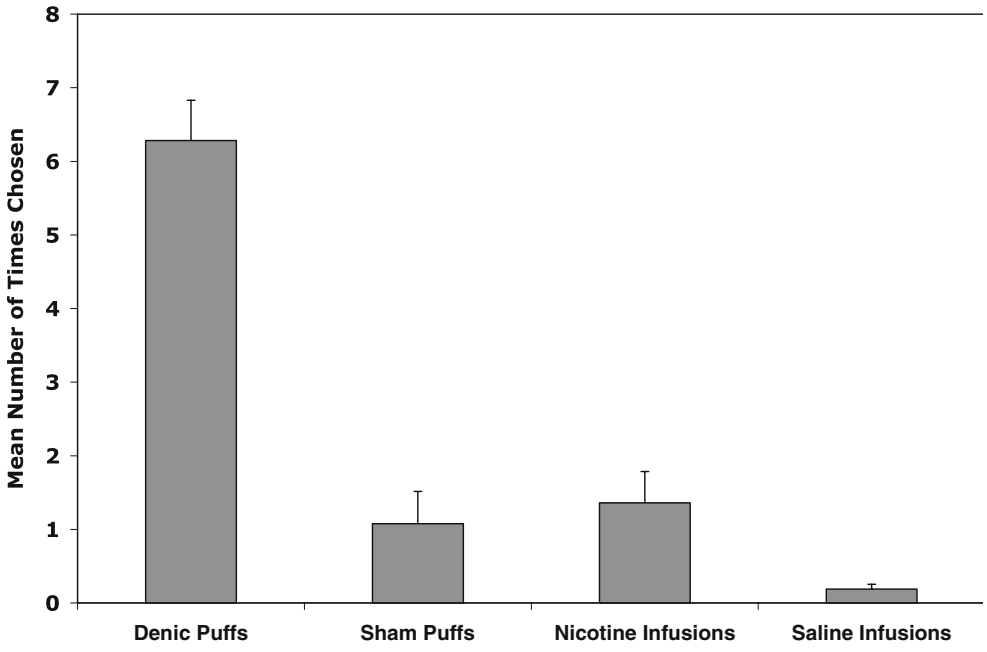

Fig. 2 Mean (±SEM) number of puffs selected in a 10-min preference assessment period during which following alternatives were concurrently available: (1) puffs of denicotinized cigarette smoke ("Denic Puffs"), (2) sham puffs, (3) IV nicotine infusions, or (4) saline infusions

aroma, tracheobronchial sensations) and motoric components (handling, puffing, inhaling). The motoric components without the sensory components do not seem to be capable of eliciting a significant degree of satisfaction, based on studies in which we presented sham smoking involving unlit cigarettes (e.g., Breland et al. 2002; see also Fig. 2) or that used inhalers that delivered inactive vehicle (see below). We do not know whether the sensory components, in the absence of motoric components, are sufficient to provide significant reward, but the available evidence does suggest that sensory factors are critically important for smoking satisfaction. Varying these sensory components, while holding the motoric components constant, yields robust effects on measures of smoking reward. Thus, local anesthesia of the airways, which blunts oral, pharyngeal, and tracheobronchial sensory cues, significantly attenuates smoking satisfaction (Rose et al. 1984, 1985). In one study, the sensory components were examined in more detail, using temporary local anesthesia of successively greater portions of the respiratory tract, by means of mouth rinses, gargling, and inhalations of lidocaine. Subjects reported a linear decrease in craving for cigarettes in response to anesthesia of the mouth, pharynx, and tracheobronchial airways (Rose et al. 1984). In a similar vein, Perkins et al. (2001) showed that attenuating the olfactory/taste cues of smoking diminished the enjoyment and behaviorally reinforcing effects of cigarette smoke, particularly in female smokers.

Sensory cues can also be classified in terms of which constituents in smoke elicit rewarding sensory effects. Cigarette smoke contains thousands of constituents, but nicotine has received the most attention due to its pharmacologic properties. Interestingly, nicotine also appears to contribute significantly to the sensory aspects of smoking. This has been demonstrated by comparing the sensory effects of nicotine-containing and denicotinized cigarettes; nicotine-containing cigarettes are consistently rated as stronger in terms of perceived respiratory tract sensations (Kao and Lee 1991; Lee et al. 1993; Rose and Behm 2004a,b). In addition, nicotine aerosol inhalation elicits strong irritant effects, which can be blocked with the peripheral nicotinic antagonist hexamethonium (Lee et al. 1993), and even IV nicotine infusions can elicit respiratory tract sensations (Henningfield and Goldberg 1983; Rose et al. 2000). These findings as well as other evidence suggest that neuronal nicotinic receptors are expressed in the respiratory tract on nerve endings and offer a mechanism by which nicotine can directly stimulate sensory pathways (Alimohammadi and Silver 2000; Undem and Carr 2001). Moreover, nicotinic receptors containing the alpha-3 subunit have been found on nucleus tractus solitarius neurons innervated by vagal pathways conveying inputs from bronchopulmonary sensory receptors (Ferguson et al. 2000). In a study of smokers who were administered the peripheral nicotinic antagonist trimethaphan to block nicotine-related airway sensations, puffs of subjects' usual brands of cigarettes were rated weaker and less desirable (Rose et al. 1999a,b). Interestingly, trimethaphan attenuated the excessive irritation of a nicotine-injected cigarette, tending to increase its desirability (see Fig. 3).

Aside from nicotine, many other constituents of smoke may contribute to the sensory qualities, including flavorings such as honey, cocoa, and licorice (Baker et al. 2004; Gaworski et al. 1999). In addition, some of the components of "tar" interact with nicotine in the sense that they dampen the excessive harshness that is associated with nicotine aerosol or vapor inhalation, i.e., the tar/nicotine ratio is a key determinant of the overall harshness of smoke (Rose and Behm 1987; Rose et al. 1999a,b). Only a handful of laboratory studies have attempted to administer a nicotine aerosol capable of providing lung delivery of doses of nicotine relevant to smokers, without other components of smoke (Herxheimer 1967; Lux and Frecker 1988).

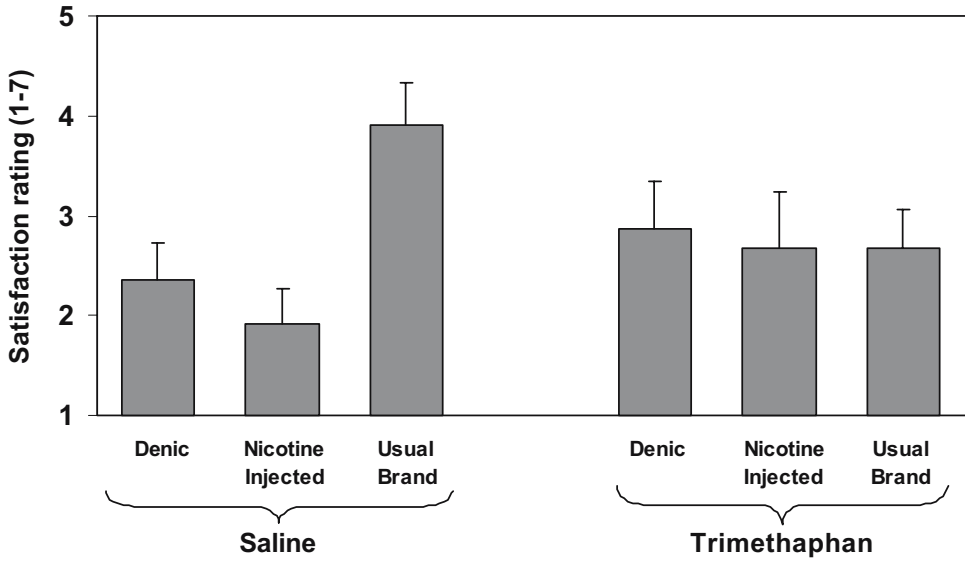

Fig. 3 Self-reported smoking satisfaction (mean±SEM) after smoking either a denicotinized cigarette ("Denic"), a denicotinized cigarette into which nicotine was injected to raise the delivery to that of the usual-brand cigarettes ("Nicotine Injected"), or the usual-brand cigarette ("Usual Brand"), during infusions of trimethaphan (dose titrated to induce a 5–10 mmHg decrease in systolic blood pressure) vs saline. Adapted from Rose et al. (2000)

Although not often mentioned in publications, it is widely acknowledged among researchers who have worked on the problem that nicotine in itself is so irritating and unpalatable that a pure nicotine (base) inhaler would not be acceptable to smokers. Thus, the sensory "package" consisting of appealing flavors in the tar and/or vapor phase of the smoke, together with a sufficient amount of nicotine sensory impact (while avoiding excessive harshness), characterizes cigarettes and their mass appeal.

Nonnicotine smoke components may also have direct pharmacologic effects on the brain or interact with nicotine's reinforcing effects. For example, acetaldehyde has been shown to potentiate the reinforcing effects of nicotine in animal models, especially in adolescence (Belluzzi et al. 2005). It has also been suggested that the ammonia content of tobacco can increase the proportion of unprotonated nicotine in cigarette smoke and lead to more rapid or efficient absorption of nicotine (Henningfield et al. 2004).

Another ingredient in tobacco that may interact with nicotine is menthol. Although cigarettes are commonly referred to a "mentholated" or "nonmentholated", even nonmentholated brands contain some menthol. Menthol serves as a sensory cue, which is preferred by users of mentholated brands (Rose and Behm 2004a,b). Menthol, by virtue of its local anesthetic properties, may also attenuate some of the irritant effects of nicotine (Galeotti et al. 2001). Moreover, menthol increases the permeability of biological membranes (Shojaei et al. 1999), which could conceivably influence nicotine absorption. Ferris Wayne and Connolly (2004) report an analysis of tobacco industry documents supporting the view that menthol alters the perception of tobacco smoke via cooling, smoothing, and anesthetic effects, increases sensory impact through stimulation of trigeminal receptors, and interacts with nicotine, controlling its perception, delivery, and uptake.

Finally, a class of smoke constituents having potentially important pharmacologic effects consists of monoamine oxidase (MAO) inhibitors. Cigarette smoke contains substances that inhibit both isoforms of MAO (MAO-A and MAO-B), resulting in an inhibition of approximately 28% of the brain activity of MAO-A and 40% of the activity of MAO-B (Fowler et al. 1996a,b). It has been hypothesized that these substances may exert antidepressant effects in their own right, or, by increasing the lifetime of neurotransmitters such as dopamine, after their release is evoked by nicotine, they may potentiate the reinforcing effects of nicotine. In one study, administration of MAO inhibitors to rats self-administering nicotine increased response rates substantially (Guillem et al. 2005). In a study of cigarette smokers, the intensity of cigarette withdrawal symptoms was positively correlated with the extent of MAO-B inhibition at baseline (as assessed by platelet MAO-B activity; Rose et al. 2001). Positive findings have also been reported for the use of MAO inhibitors in smoking cessation treatment (Berlin et al. 1995; George et al. 2003). A growing body of evidence thus supports the potential role of MAO inhibitors present in cigarette smoke as modulators of dependence.

Primacy of nicotine

The findings summarized above, which implicate nonnicotine factors as potentially important contributors to cigarette addiction, do not negate the primary reinforcing role of nicotine (US Department of Human and Health Services 1988). Thus, sensory cues have likely become reinforcing due to the Pavlovian association with nicotine (Rose and Levin 1991a,b) or via sensitization of their incentive value by nicotine-mediated dopamine release (see below). The components of tar that diminish the irritation of nicotine or facilitate its uptake may similarly have indirect effects mediated ultimately by nicotine. MAO inhibitors may also derive their impact through amplifying the reinforcing effects of nicotine. Thus, many of the factors discussed here may work by potentiating the positive effects and ameliorating the negative effects of nicotine.

Implications for smoking cessation treatment

The conclusion that nonnicotine components of smoking are important helps reconcile the results that NRT does not yield higher success rates and has additional therapeutic implications. For example, if a substitute could be developed that does provide a significant portion of the sensorimotor reward associated with cigarette smoking, perhaps it could serve as an adjunct to smoking cessation treatment. Moreover, if the sensorimotor cues presented in smokers' preferred brands of cigarettes could be devalued, smoking cessation may be facilitated. In addition, devaluing smoke cues might promote acceptance of alternative forms of NRT, inasmuch as there would be less of a negative contrast in comparison to cigarettes.

Treatment approaches involving devaluation of sensorimotor cues

Methods for devaluing sensorimotor cues associated with smoking have been explored in several studies. Four main approaches could be characterized as means of devaluing smoke cues: (1) rapid smoking or satiation, (2) supplemental nicotine administration during smoking, (3) nicotinic antagonist administration, and (4) use of very low-nicotine-content cigarettes (e.g., denicotinized cigarettes). These techniques will be briefly summarized.

Rapid smoking, a treatment developed in the 1970s (Lichtenstein 2002), entails having smokers puff so rapidly from cigarettes that smoke cues, which are normally pleasant, become aversive. Several studies have reported successful results of this method in smoking cessation treatment, although doubts have been raised about its efficacy (Hajek and Stead 2004). In addition, the aversiveness of the treatment is a drawback for patients as well as treatment providers, and the approach has not achieved widespread popularity.

Recently, studies have explored the use of concurrent NRT, while subjects are still smoking during the weeks leading up to a target quit-smoking date. For example, in one study, smokers wore skin patches delivering 21 mg/24 h nicotine while continuing to smoke ad libitum for 2 weeks. Subsequently, they quit smoking entirely while continuing nicotine patch treatment. Results were encouraging, with success rates being approximately double that of conventional (postcessation only) nicotine patch treatment (Schuurmans et al. 2004). One rationale for concurrent nicotine administration is that smoking may be less rewarding when superimposed on a background level of nicotine (Levin et al. 1994), indirectly diminishing the rewarding effects sensorimotor cues accompanying smoking (Rose and Levin 1991a,b). Nicotine patch treatment was well tolerated when concurrent smoking was allowed, but concerns remain about the possible toxic effects of excessive nicotine intake; however, a recent study in our program found that precessation nicotine patch treatment enhanced quit-smoking rates even when subjects switched to smoking a low-nicotine brand of cigarettes (Rose et al. in press). Cotinine measurements showed that in the latter condition, nicotine intake remained relatively constant during the 2 weeks in which smoking occurred in conjunction with nicotine patch treatment. Thus, the use of a brand-switch manipulation in conjunction with nicotine replacement might achieve the therapeutic benefit of precessation nicotine administration without exceeding the usual nicotine intake to which smokers have become accustomed.

A related, but distinct, pharmacologic approach to devaluing cigarette cues involves administration of the nicotinic antagonist mecamylamine. Mecamylamine is a noncompetitive antagonist at nicotinic receptors and attenuates many of the behavioral and physiological effects of nicotine. Although acute administration of mecamylamine increases smoking behavior (Pomerleau et al. 1987; Rose et al. 1988; Stolerman et al. 1973), this effect is transient, and continued administration leads to a diminution in the smoking behavior as well as the rewarding effects of smoking and related sensorimotor cues (Rose and Behm 2004a,b; Rose et al. 1998). Several studies have shown that mecamylamine treatment, initiated prior to a target quit-smoking date, significantly increases rates of smoking abstinence relative to placebo, (e.g., Rose et al. 1994, 1998).

The two previous approaches, concurrent nicotine administration and mecamylamine administration, are not mutually exclusive. In fact, concurrent nicotine/mecamylamine administration, while smoking is continued for a 2-week period before a target quit-smoking date, significantly increases success rates beyond nicotine alone or mecamylamine alone. In a recent phase III trial conducted by Elan Corp., a total of 1,191 smokers were randomized to receiving, for 2 weeks prior to the target quit-smoking date and for 6 weeks after the quit-date, either nicotine + mecamylamine (Nic/Mec, n=447), nicotine alone (Nic, n=446), mecamylamine alone (Mec, n=149), or placebo (Placebo, n=149), using transdermal patches to deliver the various treatments. Smoking cessation rates, based on a continuous 4-week abstinence, were 30% for Nic/Mec, 23.5% for Nic (p=.023 vs Nic/Mec), 17.4% for Mec (p=.001 vs Nic/Mec), and 6% for Placebo (p<.001 vs Nic/Mec). The rationale for concurrent nicotine/mecamylamine treatment is that, while binding to different sites on the nicotinic receptor (Webster et al. 1999), both agents attenuate the reinforcing effects of cigarettes and together achieve an effect greater than either drug alone (Rose and Levin 1991a,b). In a recent study, Rose and Behm (2004a,b) examined concurrent administration of nicotine, mecamylamine, or the combination vs placebo, administered for 2 weeks before a target quit-smoking date. The dose of nicotine patch was 21 mg/24 h and the mecamylamine dose was 5 mg b.i.d., which reduced to 2.5 mg b.i.d. in the event of intolerable side effects (primarily constipation). Subjects were presented with controlled puffs of test cigarettes, including their usual brands, in weekly laboratory sessions held after overnight abstinence from smoking. All three

active pharmacologic treatments were found to diminish the subjective reward ratings of usual-brand test cigarettes over weeks, as shown in Fig. 4.

A final method to be considered for devaluing cigarettes involves the removal of nicotine from tobacco. While different from pharmacologic treatment using mecamylamine or concurrent nicotine reinforcement with supplemental nicotine administration, the approach can be considered functionally similar. However, instead of attempting to block the reinforcing effects of nicotine inhaled in cigarette smoke, nicotine reinforcement is eliminated by simply removing the nicotine itself. Two main techniques for manufacturing low-nicotine-content tobacco have been tested—extraction of nicotine (Robinson et al. 2000) and genetic modification of the tobacco plant so that the synthetic pathway for nicotine is disrupted (Conkling et al. 2002). A critical distinction between these low-nicotine-content cigarettes and traditional "low tar and nicotine" or "ultralight" cigarettes is that the latter contain tobacco that actually has a high nicotine content (Benowitz et al. 1983); ventilation holes in the filter effect a low nicotine and tar yield when the cigarettes are smoked by machines, but human smokers frequently compensate by taking larger or more frequent puffs (Kolonen et al. 1991) or by covering the ventilation holes in the filter (Kozlowski et al. 1988), thus tending to maintain nicotine intake. In contrast, smokers generally do not appear to compensate when smoking cigarettes that maintain overall tar delivery, with its attendant sensory cues, while reducing nicotine yield (Nil and Battig 1989; Pickworth et al. 1999; Robinson et al. 2000; Rose and Behm 2004a,b). However, some studies have reported compensation when smokers are given cigarettes with low nicotine but normal tar yields. For example, Herning et al. (1981) measured increases in puff volume when cigarette nicotine yield was reduced even when nonnicotine factors were held constant. In another study, Rose and Behm (1991) found that subjects had higher expired air CO levels when they smoked denicotinized cigarettes while wearing placebo nicotine patches than when wearing 21-mg nicotine patches or when smoking their usual brands of nicotine-containing cigarettes. These results suggest that nicotine deprivation or withdrawal symptoms can drive compensatory behavior with low-nicotine-content cigarettes. Whether compensation will occur in a given situation may depend on the balance between the influence of positive incentive factors and withdrawal relief. That is, if smoking is primarily driven by nicotine withdrawal symptoms, compensatory smoking may be more likely to occur; in contrast, if the positive sensory qualities of smoking predominate, the less appealing characteristics of low-nicotine-content smoke may discourage compensation. Indeed, previous research has shown that nicotine-related sensations are part of the enjoyment of smoking (Jones et al. 2002; Pritchard et al. 1996; Rose et al. 1999a,b). The time frame over which compensation is measured is likely to be important, too. As extinction progresses due to the removal of nicotine reinforcement, the sensory characteristics of smoke lose some of their initial hedonic value (Rose and Behm 2004a,b), diminishing the tendency to compensate. A reduction in nicotine dependence and withdrawal symptoms over time would also be expected to further decrease the motivation to compensate.

Clinical trials have been initiated to evaluate the efficacy of low-nicotine-content cigarettes in smoking cessation treatment. In a recent study of denicotinized cigarettes and other treatments, it was suggested that a particularly promising method may be to use low-nicotine-content cigarettes in conjunction with NRT (Rose et al. in press). Concurrent NRT improved compliance with adhering to the brand-switch manipulation (presumably by preventing nicotine withdrawal symptoms) but did not appear to compromise the efficacy of the cigarettes in terms of reducing the rewarding effects of smoke cues (Rose and Behm 2004a,b). An important implication is that receiving nicotine by alternative routes may not maintain dependence on cigarettes to the extent that continued smoking maintains dependence. In other words, the act of smoking is no longer contingently reinforced by inhaling nicotine when smokers wear a nicotine skin patch—nicotine is

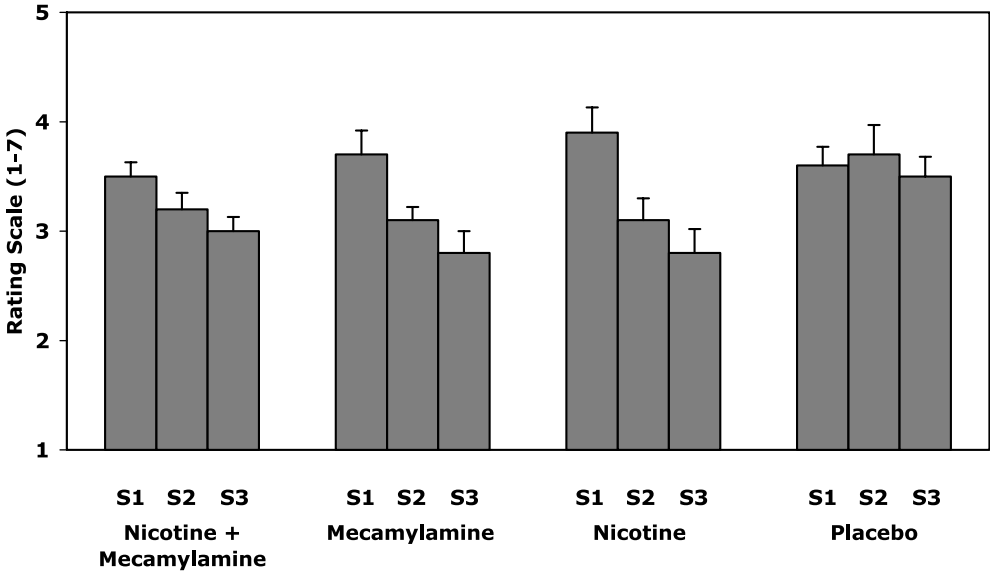

Fig. 4 Mean (±SEM) subjective reward ratings of usual-brand test cigarettes smoked in three weekly test sessions (conducted after overnight abstinence from smoking). Session 1 (*S1*) was conducted before drug treatment, and session 2 (*S2*) and session 3 (*S3*) were held after initiation of treatment with nicotine + mecamylamine ("Nicotine + mecamylamine"), mecamylamine (Mecamylamine"), nicotine ("Nicotine"), or placebo ("Placebo"). Adapted from Rose and Behm (2004a,b)

present continuously before, during, and after a cigarette is smoked and is therefore probably not an effective reinforcer for smoking behavior.

Treatment approaches involving replacement of sensorimotor cues

In addition to devaluing smoke-related sensorimotor cues to facilitate cessation, the use of temporary substitutes to alleviate craving or other withdrawal symptoms may be a worthwhile strategy. An approach that has been studied is the use of inhaled citric or ascorbic acid, which, in small quantities, simulates some of the respiratory tract sensations accompanying cigarette smoking (Levin et al. 1990, 1993). In an initial laboratory study (Rose and Hickman 1987), it was shown that smokers rated the respiratory tract sensations of a citric acid mist more enjoyable than puffs from low tar and nicotine cigarettes, when taste and olfactory cues were minimized and filter ventilation hole-blocking was prevented. Subsequent clinical trials found an enhancement in smoking abstinence among heavy smokers using a metered dose inhaler delivering citric acid vs a vehicle-only placebo inhaler (Behm et al. 1993), or when a cigarette-sized dry powder inhaler was used in conjunction with nicotine patch treatment after the quit-smoking date (Westman et al. 1995).

Other approaches that have been studied include the delivery of pepper constituents, e.g., capsaicin (Behm and Rose 1994) and smoke-based aerosols that deliver minimal amounts of "tar" yet provide enhanced sensory impact due to manipulations of particle size or nicotine/tar ratio (Behm et al. 1990; Rose and Behm 1987). However, no fully satisfactory substitute has thus far been developed.

An existing means for providing replacement of the nonnicotine components of smoking, which was alluded to above in the context of extinction treatment, is denicotinized or genetically modified low-nicotine-content tobacco cigarettes. These cigarettes have been shown to be effective in providing short-term relief of craving for cigarettes (Pickworth et al. 1999; Rose and Behm 2004a,b). Use of these cigarettes in a cessation paradigm may offer two advantages—a means of coping with early craving and possibly other smoking withdrawal symptoms, while at the same time devaluing cues by the removal of contingent nicotine reinforcement.

Conclusions and future research directions

The above review highlights some of the nonnicotine factors likely to play a role in cigarette addiction. However, many important questions remain unresolved, which should be the focus of future investigations. First, it will be important to further clarify the relative importance of nicotine and nonnicotine components, using paradigms that manipulate each factor selectively. This can be achieved either by subtracting a specific constituent from smoke (as with denicotinized cigarettes) or by adding components to an NRT or behavioral treatment paradigm (e.g., adding an MAO inhibitor to nicotine patch treatment). Studies should address the role of different smoke components across the natural history of a smoker, i.e., in the acquisition phase, in maintenance of ongoing smoking behavior, and in facilitating or impeding smoking cessation. A specific issue that merits further research is whether smoke constituents such as MAO inhibitors, acetaldehyde and ammonia, suggested to modulate nicotine reinforcement in animal models, also play a significant role in human smoking behavior. Importantly, research needs to assess whether substitutes for the effects of these compounds might have clinical utility in smoking cessation treatment.

An analysis of the relative importance of smoke components for different subpopulations of smokers should also be undertaken. For example, some of the work cited above suggests that female smokers respond to a greater extent than males to the sensory cues in cigarette smoke. In contrast, it might be hypothesized that certain groups of smokers, such as individuals with schizophrenia, might be especially dependent on nicotine's direct central nervous system (CNS) effects, to self-medicate their psychiatric symptoms (Kumari and Postma 2005; Leonard et al. 1996). Gene variants might be identified that predict which smokers derive reinforcement from the various components of smoke or their interactions, as well as predicting response to treatments (Lerman et al. 2005). These findings may in turn yield strategies for tailoring smoking cessation treatments for different populations.

Several questions also need to be addressed with respect to denicotinized cigarettes. Individual subject characteristics (e.g., dependence) and environmental variables (e.g., stressful tasks) that determine the extent to which denicotinized cigarettes are efficacious in terms of relieving craving and withdrawal symptoms should be identified. The issue of compensation for reduced nicotine delivery also deserves further investigation, in view of the somewhat surprising finding that smokers often do not smoke more intensively when nicotine yield is reduced, when the delivery of nonnicotine components is maintained. The conditions under which compensation may occur should be delineated. The hypothesis that positive or negative sensory qualities as well as withdrawal symptom intensity influence attempts to compensate should be evaluated empirically.

More research is also needed to determine how low the nicotine dose in a "denicotinized" cigarette must be in order to be pharmacologically inactive. The extremely high affinity of some nicotinic receptor subtypes for nicotine (Lippiello and Fernandes 1986) raises uncertainty about the levels of receptor occupancy in human smokers using denicotinized cigarettes, and what functional significance this may have. It is likely that such effects are minimal when standard doses of NRT are used concurrently with these cigarettes; however, in the absence of other nicotine intake, the possibility that very small doses of nicotine present in denicotinized cigarettes affect nicotinic receptor function should be examined.

A number of intriguing issues regarding the specific role of sensory cues in smoking behavior are as yet unresolved. These cues are presumably conditioned reinforcers whose value has been acquired as a result of pairing with nicotine (Rose and Levin 1991b). However, laboratory studies of rats self-administering IV nicotine have shown that the cues accompanying nicotine intake become reinforcing even without direct pairing. That is, noncontingent injections of nicotine also enhance the reinforcing value of cues presented during training sessions (Caggiula et al. 2002; Donny et al. 2003). In the case of human smoking behavior, the sensory cues presented by cigarette smoking possibly do provide at least a mild positive reward initially, and this positive valence may be conducive to the amplification of the rewarding properties of the cues by nicotine. As mentioned above, a number of desirable flavor additives are present in tobacco, which may thus optimize the subsequent amplification of reward value. Thus, further studies of the role of initial reward valence on the course of conditioning need to be conducted. In this connection, a possibility that deserves further examination is that the peripheral actions of nicotine on sensory nerve endings in the lung might have intrinsic rewarding effects. Ginzel and Eldred (1977) showed that injection of nicotinic agonists into the right ventricle of the heart (in cats) caused vagal stimulation that elicited skeletal muscle relaxation. Such a mechanism might also underlie some of the "relaxing" effects of cigarette smoking in humans.

More work is needed to elucidate in detail the brain mechanisms whereby conditioning occurs, and conversely, extinction learning takes place. Is dopamine a common mediator of the rewarding effects of sensorimotor cues associated with cigarette smoking as well as the rewarding effects of nicotine? Animal models have established a role for dopamine, including its modulation by glutamatergic and GABAergic synapses (Pidoplichko et al. 2004), in mediating the direct reinforcing effects of nicotine (Corrigall et al. 1992; Di Chiara 2000; Pich et al. 1997). The potentiation of the positive rewarding effects of cues by noncontingent nicotine administration is also thought to be mediated via stimulation of dopamine release by nicotine, which then lends "incentive salience" to the cues (Balfour et al. 2000; Robinson and Berridge 2001; Wyvell and Berridge 2001). Some studies of human smokers have found behavioral effects of dopaminergic manipulations, such as antagonist (haloperidol) or agonist (bromocriptine) administration (Brauer et al. 2001b; Caskey et al. 2002; Dawe et al. 1995). Moreover, cigarette smoking acutely increases dopamine concentrations in the ventral striatum/nucleus accumbens (Brody et al. 2004). What other neurotransmitter systems are critically involved? What molecular changes underlie neuronal plasticity accompanying conditioning by nicotine? These and other questions about the neural circuitry modifications resulting in the establishment of tobacco dependence, as well as those that may lead to its interruption, have not been fully answered, and yet answers may yield important clues for developing more effective therapies.

A greater understanding of the processes that mediate extinction or loss of reward value when nicotine is discontinued (or its reinforcing effects blocked, as with a nicotinic receptor antagonist) may have important treatment implications. For example, research on extinction has suggested that the original learning is not "erased" over the course of nonreinforced cue presentations, but rather is inhibited by new learning. The original response is prone to reoccur, a process termed "spontaneous recovery" (Pavlov 1927) or, in a situation involving change of contextual cues, "renewal" (Bouton and King 1983). Repeated extinction in a variety of contexts may thus be the most fruitful approach to reducing the rewarding effects of cigarette cues. Procedures for implementing this approach are being developed, using, e.g., denicotinized cigarettes, which can be smoked in all of the usual situations that have been previously associated with smoking.

A related question is whether the beneficial effects of treatments designed to devalue the rewarding properties of cigarettes, including precessation use of NRT, or nicotinic antagonist treatment, or smoking denicotinized cigarettes, in fact result from a disruption of the association between cues and nicotine reinforcement. An alternative hypothesis is that these treatments reduce the degree of nicotine dependence, which indirectly attenuates the value of cues, analogous to the process whereby satiety, by reducing hunger, reduces the positive value of food-related cues (Cardinal and Everitt 2004).

Yet another direction for future clinical research and development will entail devising effective nonnicotine cigarette replacements. As mentioned above, some encouraging results were found using nonnicotine substances (e.g., citric acid) to delivery airway sensations reminiscent of smoking. More effective methods of replacing the missing sensory "impact" of nicotine could prove useful in smoking cessation treatment.

In summary, our view of tobacco addiction has evolved substantially over the decades—cigarette smoking can no longer be viewed in simplistic terms as an addiction to nicotine without regard to nonicotine factors. Instead, the complexity of the interaction of nicotine with sensorimotor cues and perhaps other pharmacologically active substances in smoke needs to be recognized and addressed in cessation treatments. By going beyond a one-factor model of tobacco addiction, dramatically higher success rates in treatment may ultimately be reached.

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