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The reinforcement-enhancing effects of nicotine: implications for the relationship between smoking, eating and weight

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Abstract

Concerns about body weight represent an important barrier to public health efforts aimed at reducing smoking. Epidemiological studies have found that current smokers weigh less than non-smokers, smoking cessation results in weight gain, and weight restriction is commonly cited as a reason for smoking. The mechanisms underlying the relationship between smoking and weight are complex and may involve a number of factors including changes in caloric intake, physical activity, metabolic rate, and lipogenesis. Amongst these possible mechanisms, nicotine-induced enhancement of food reinforcement may be particularly important. In this paper, we first review data from our laboratory that highlight two distinct ways in which nicotine impacts reinforced behavior: 1) by acting as a primary reinforcer; 2) by directly (non-associatively) enhancing the reinforcing effects of other stimuli. We then elaborate on the reinforcement-enhancing effects of nicotine as they pertain to behaviors and stimuli related to food. Data from both laboratory animals and humans support the assertion that nicotine enhances the reinforcing efficacy of food and suggest that the influence of these effects on eating may be most important after nicotine cessation when nicotine's effects on satiety subside. Finally, we discuss the theoretical and clinical implications of this perspective for understanding and addressing the apparent tradeoff between smoking and weight gain. Better understanding of the mechanisms underlying the reinforcement-enhancing effects of nicotine broadly, and the effects on food reinforcement *per se*, may aid in the development of new treatments with better long term outcomes.

Keywords

nicotine; anorexia; satiety; weight; feeding; reinforcement

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1.0 Introduction

Concerns about body weight represent an important barrier to public health efforts aimed at reducing smoking. Epidemiological studies have found that current smokers weigh less than non-smokers and weight restriction is commonly cited as a reason for smoking among adolescents [1–3]. Furthermore, following smoking cessation, ex-smokers typically gain weight. Often, the weight gain is less than 6 kg, although a significant minority gain as much as 7–11 kg [4–7]. Regardless, even the potential for weight gain after cessation is a motive for continued smoking [8, 9].

The mechanisms underlying the relationship between smoking and weight are complex and may involve a number of factors including changes in caloric intake, activity, metabolic rate, and lipogenesis [10]. Despite this complexity, much attention has focused on the effects of nicotine on food consumption. In free-feeding rats, nicotine produces anorectic effects, decreasing total food intake and meal size [11–16]. However, although a common perception is that nicotine reduces eating behavior in humans, these effects are often not observed in smokers. In fact, although smokers generally weigh less than non-smokers, they tend to eat either the same amount or more [17]. Withdrawal from nicotine in chronically treated rats increases food consumption [18, 19]. Likewise, numerous studies have reported increases in caloric intake during smoking cessation that account for a substantial portion of the variance in weight gain [20–23].

Much like the determinants of body weight, multiple behavioral processes and neurobiological mechanisms that could be differentially affected by cigarette smoking underlie eating behavior. One determinant of food intake that may be particularly important is the reinforcing efficacy of food [24]. Indeed, individual differences in food reinforcement predict food intake amongst smokers enrolled in a cessation trial [25], suggesting that the effects of cigarette smoking on the incentive and reinforcing properties of food and food-related stimuli should be a focal point in efforts to understand the relationship between smoking, eating, and weight [26]. Furthermore, of the thousands of constituents in tobacco, substantial data suggest that nicotine, the primary psychoactive constituent, is of central concern [17].

The hypothesis that the effect of cigarette smoking on food intake may be mediated by the impact of nicotine on the reinforcing efficacy of food is consistent with a growing literature describing the effects of nicotine on reinforced behavior. The reinforcement-related effects of nicotine include the widely acknowledged ability of nicotine to act as a primary reinforcer capable of establishing conditioned reinforcers, and a second, powerful ability of nicotine to non-associatively enhance other reinforcers in the environment. In this paper, we first review data from our laboratory that highlights these distinct ways in which nicotine impacts reinforced behavior. We then elaborate on the reinforcement-enhancing effects of nicotine, focusing on behaviors and stimuli related to food. Finally, we discuss the theoretical and clinical implications of this perspective for understanding and addressing the apparent tradeoff between smoking and weight gain.

2.0 Nicotine and reinforced behavior

Nicotine, like other drugs of abuse, functions as a primary reinforcer. Numerous studies have shown that nicotine is self-administered by a variety of animal species [27–30]. Self-administration of nicotine varies as a function of dose and schedule of reinforcement, extinguishes when nicotine is replaced by saline or pharmacologically blocked by a nicotinic antagonist, and, in the absence of other reinforcing stimuli, is dependent on nicotine delivery being response-contingent [27–29, 31–35]. Furthermore, environmental stimuli associated with nicotine delivery impact nicotine self-administration. In humans, nicotine-associated

stimuli contribute to the reinforcing effects of smoking, trigger cravings for cigarettes, and increase the probability of subsequent smoking in otherwise abstinent individuals [28, 36–40]. Likewise, in experimental animals, these stimuli can facilitate acquisition of nicotine self-administration, retard extinction of behavior previously maintained by nicotine, induce reinstatement of responding following extinction, and act as conditioned reinforcers capable of reinforcing new behavior [27, 41–45].

While the primary reinforcing effects of nicotine and the consequent conditioned reinforcing effect of nicotine-associated stimuli are clearly important, the effects of nicotine on operant behavior extend beyond associative learning processes. As will be described more below, nicotine also directly changes ongoing behavior supported by other reinforcing stimuli in a manner that is non-associative in nature. Together, these two effects – nicotine acting as a primary reinforcer and nicotine directly enhancing the reinforcing effects of other stimuli - constitute what we have previously referred to as the "dual-reinforcement" model [46–48]. Below we summarize the research conducted to date that forms the foundation of this model of nicotine's actions.

In our laboratory, we often utilize a compound visual stimulus (VS: the onset of a 1-sec cue light and the offset of a chamber light for 1-min) as the "cue" associated with nicotine delivery. Our early work found this "cue" to be remarkably important for nicotine self-administration. When nicotine was removed responding decreased, but this decrease was attenuated by the continued response-dependent presentation of the VS [44]. Conversely, when the VS was removed while animals were self-administering nicotine, responding for nicotine was greatly reduced [44]. In fact, several studies suggested that the combination of the VS and nicotine produced synergistic increases in behavior; response rates maintained by the combination of nicotine and the VS that were more than the sum of responding maintained by either nicotine or the VS alone [44–46, 49, 50]. An important question raised by these studies was - *what is the nature of the synergism between these stimuli and NIC?*

Although our initial assumption was that the VS was acting as a conditioned reinforcer, close inspection of the data revealed that this may not adequately explain the observations. Importantly, the VS was also functioning as a modest primary reinforcer; even in the absence of a history of pairing the VS with nicotine, the VS maintained responding [46]. This observation was reminiscent of an older literature demonstrating that sensory stimuli can act as unconditioned reinforcers [51–53]. Hence, one possibility was that nicotine altered the reinforcing properties of the VS, not via Pavlovian conditioning, but instead through a non-associative mechanism.

To test this possibility, we dissociated nicotine delivery from both the animal's behavior and the presentation of the VS using a yoking design [46]. Lever pressing in one group of animals was reinforced by intravenous infusions of nicotine paired with the VS. Responding in the other two groups was reinforced only with the VS; however, these groups received infusions of either nicotine or saline yoked to the self-administration animal. Therefore, we controlled the number and pattern of infusions across the groups, but removed the possibility that the VS could acquire any conditioned reinforcing properties by an association with nicotine. Remarkably, yoked nicotine enhanced responding for the VS to levels that were statistically indistinguishable from self-administered nicotine. Subsequent studies have shown that this "reinforcement-enhancing" effect of nicotine is robust and generalizable. It is observed with different routes of nicotine administration [46, 49, 54], under different schedules of reinforcement [55], in both males and females [56], in adolescent and adult rats (unpublished observations), and for reinforcers other than the VS [42](see below). Indeed, this effect is similar to the effects of other stimulants on both intra-cranial self-stimulation [57, 58] and behavior reinforced with conditioned stimuli [47, 59, 60]. In sum, nicotine can

enhance the reinforcing properties of other stimuli by a mechanism that does not require a discrete temporal relationship with either the stimuli or the behavior.

3.0 Effects of nicotine on operant behavior associated with palatable reinforcers

Although much of the preclinical literature supports the notion that nicotine has anorectic effects, this work is based largely on conditions in which food is freely available [18, 61–63]. Free access conditions (or rich schedules of reinforcement) are insensitive measures of reinforcing efficacy, particularly when motivation can be reduced through consumption. Hence, a better assessment of the effects of nicotine and nicotine withdrawal on the reinforcing efficacy of food would derive from lean schedules of reinforcement that are less likely to be impacted by satiation. Likewise, methods that assess the conditioned reinforcing effects of food-associated stimuli may provide useful insight into food reinforcement without the potential masking effect of satiation. The literature on the effects of nicotine and nicotine withdrawal using these approaches is described below.

The preclinical literature supports the hypothesis that nicotine enhances the reinforcing efficacy of food and food-associated stimuli. For example, Popke and colleagues examined responding for 45 mg food pellets on a progressive ratio schedule of reinforcement in male rats maintained at 80–85% of the free feeding weight [64]. Pretreatment with intraperitoneal nicotine across a wide range of doses increased response rate with significant increases in break point observed at several doses. Likewise, Wing and Shoaib found that nicotine increased responding for both a food-associated conditioned stimulus and the unconditioned food reward in rats maintained on a second order schedule of reinforcement [65]. Raiff and Dallery have also reported nicotine-induced increases in reinforcement related to food and food-associated stimuli using an observing response procedure [66]. Similar effects of nicotine have also been observed in mice [67]. These reinforcement-enhancing effects also extend to reinforcement related to sucrose and sucrose-associated stimuli. In a series of studies by Palmatier and colleagues, animals pretreated with subcutaneous nicotine demonstrated increased break points for sucrose on a progressive ratio schedule of reinforcement, although no effect of nicotine was observed under rich schedules of reinforcement (M. Palmatier, personnel communication). Finally, we have shown that nicotine enhances responding for a sucrose-associated stimulus more than it did for the same stimulus when it was explicitly unpaired with sucrose [68]. In sum, substantial data suggest that despite the anorectic effects of nicotine in free feeding animals, nicotine administration enhances the reinforcing efficacy of food.

Much less is known about the effects of chronic nicotine exposure and withdrawal on food reinforced behavior in laboratory animals. Jias and Ellison examined the effects of continuous exposure to nicotine via subcutaneous pellets [69]. Initial exposure to nicotine reduced ad libitum food intake. After food intake returned to control levels, animals were provided limited access (2 hours) to a sucrose solution. Nicotine treatment increased sucrose consumption during these tests despite similar ad libitum food intake. Furthermore, when pellets were removed after 22 days of nicotine exposure, the increase in intake of sucrose remained when assessed three days later. More recently, LeSage and colleagues reported that spontaneous withdrawal in animals chronically treated with nicotine produced an initial decrease in responding for sucrose on a progressive ratio (1 day post-nicotine) that was followed by an increase in responding after 4–5 days of abstinence relative to baseline [70]. Finally, Mannucci and colleagues found that nicotine injected four times a day for 14 days produced little change in total food intake, but increased food consumption in the 2 hours following 24 hour food deprivation [71]. Interestingly, these effects lasted for at least 120 days after nicotine withdrawal, consistent with the increase reported by LeSage and

colleagues [70]. Together, these data suggest that nicotine may continue to facilitate food and sucrose reinforcement during chronic exposure and during subsequent abstinence after an initial, short-lived attenuation. Additional research is needed to verify these initial observations.

Clinical research also suggests that nicotine might facilitate the reinforcing efficacy of food. In fasting smokers, nicotine administration increases, not decreases, caloric intake [17]. Abstinence from nicotine in regular smokers also appears to enhance the incentive and relative reinforcing property of food. For example, Spring and colleagues [72] found that nicotine deprivation in female smokers resulted in an increase in the effort exerted to earn snack foods. Similarly, Lerman and colleagues found that abstinent smokers were willing to forgo more money to earn food, although this effect was genotype specific [26](see below for further discussion). Finally, work by Epstein and colleagues suggests that abstinent smokers also respond differently to food-related cues [73]. Specifically, abstinent smokers fail to habituate to food cues, suggesting that these stimuli retain their incentive properties when they would normally be reduced by sensory-specific satiety. The number of human studies that can speak to the relative reinforcing effects of food are limited; nevertheless, the available data are consistent with the preclinical observations and support the hypothesis that nicotine enhances the incentive and/or reinforcing effects of food and food-related stimuli.

4.0 Theoretical and Clinical Implications

Comparison of the effects of nicotine on behavior reinforced by food and food-related stimuli with its effects on non-food reinforcers, reveals both similarities and differences. Acutely, nicotine appears to produce similar enhancing effects on behaviors related to a wide range of reinforcing stimuli, including sensory reinforcers, food, sucrose, and conditioned reinforcers associated with food, sucrose, and nicotine [46, 49, 64–66, 68]. The effects of nicotine on food reinforcement seem to persist even when nicotine is delivered continuously, suggesting little tolerance [69]. In contrast, the persistence of the reinforcement-enhancing effects on other, non-food, stimuli is less clear with some evidence of tolerance in rats (unpublished observations). The most notable differences between food and other reinforcers in previous studies are during withdrawal. Both preclinical and clinical data point to potentially long-lasting enhancing effects of nicotine on food-related rewards, but withdrawal from continuous nicotine delivered via osmotic minipump in rats reduces the reinforcing effects of brain stimulation (increases intracranial self-stimulation thresholds [74]) and decreases responding for a reinforcing visual stimulus (VS; unpublished observations). This discrepancy may be related to the nature of the reinforcer, but could also be a function of duration of abstinence. The reinforcing efficacy of food is temporarily decreased after withdrawal of nicotine in rats much like the reinforcing efficacy of the VS. Little work has examined whether the initial decline in reinforcement observed for non-food reinforcers may be replaced by an increase as was observed for food by LeSage et al [70]. In support of this possibility, long-lasting decreases in the threshold for intracranial self-stimulation have been reported in animals with a history of short (1 hour per day) and long (12 h per day) access nicotine self-administration [75]. Likewise, long-lasting effects of nicotine on Pavlovian discriminative approach behavior associated with water have been reported in non-dependent rats [76].

An important observation is that nicotine has different effects on food consumption in free-feeding compared to food-restricted individuals. Based on the current literature, our working hypothesis is that this pattern of results arises from two distinct effects with different temporal dynamics. First, nicotine may increase satiety after eating, reducing meal size [11, 12]. This effect may be tied to the acute pharmacological actions of nicotine [13, 16],

although some data suggest that under some nicotine treatment conditions these effects may resurface occasionally for 2 weeks after cessation in rats [11, 12]. Second, nicotine may facilitate the reinforcing properties of food and this effect may persist long after the individual has stopped taking the drug. This hypothesis assumes that the ability of nicotine to enhance food reinforcement is at least partially masked when food is freely available and unmasked when satiation does not suppress consumption. Indeed, the available clinical data demonstrate that anorectic effects of nicotine are observed in humans when assessments follow a small breakfast, but not overnight fasting [77, 78]. A similar moderating effect of food deprivation has been reported for mice [71]. Furthermore, this hypothesis suggests a relatively greater influence of enhanced food reinforcement after cessation of nicotine exposure. Although some studies fail to observe increased total food intake during nicotine withdrawal [71], most do report increases in ad libitum consumption [18, 19, 79] as would be predicted by the hypothesis outlined above.

It is important to note that our data do not allow us to specify what biobehavioral process or processes underlie the effects of nicotine on other reinforcers. Indeed, multiple factors influence the regulation of reinforced behavior and nicotine could be interacting with one or more of those factors. For example, the literature on feeding behavior has emphasized the distinction between hedonic (i.e., reward-related) and homeostatic (need-related) eating. In contrast, a common distinction that dominates much of the drug literature, is between the hedonic properties of stimuli (defined as “liking”) and the incentive properties of stimuli (defined as “wanting”), both of which are “reward-related” processes. Indeed, the hedonic and incentive properties of stimuli appear to be behaviorally and neurobiologically dissociable for both drugs of abuse and food [80–82] as do hedonic and homeostatic eating [83]. Clearly, many of the studies demonstrating that nicotine enhances food reinforcement were conducted in food-restricted animals, suggesting that nicotine might alter homeostatic feeding. However, until studies are conducted with motivated animals that are not food restricted and high incentive stimuli (e.g., with highly palatable foods), it will be difficult to distinguish between the effects of nicotine on homeostatic vs. incentive-based feeding. In terms of future directions, more can also be done to address significant gaps between the preclinical findings, which form the bulk of the data supporting the hypothesis that nicotine can enhance food reinforcement, and clinical studies. Besides obvious species differences, there are at least two notable parameters to consider in this regard. First, with few exceptions, humans administer nicotine via tobacco. Tobacco contains thousands of other constituents besides nicotine, some of which are pharmacologically and behaviorally active [84–86]. Preclinical studies that examine these additional constituents in combination with nicotine could shed new light on the effects of tobacco on eating behavior. Conversely, clinical studies that deliver tobacco with little nicotine (e.g., with very low nicotine cigarettes)[37] and/or delivery nicotine via other routes of administration [78], would help to isolate, whether non-nicotine factors might complicate the translation of animal studies on nicotine to obervations of human tobacco use. Second, humans self-adminster tobacco, but most or all of the animal studies to date examine the effects of experimenter-administered nicotine on feeding behavior. Given that response-contingent and response-independent drug administration often leads to different effects [87–89], it is important to examine the relationship between nicotine and food reinforcement within the context of nicotine self-administration. Interestingly, this would also allow for studies that incorporate the choice between nicotine and food, an interesting situation given the hypothesis that nicotine alters food reinforcement and that feeding conditions alter nicotine self-administration in animals [32] and smoking in humans [90].

The effect of nicotine on food reinforcement may be related to an interaction between cholinergic and dopaminergic systems. Hoebel and colleagues proposed that acetylcholine and dopamine may play opposing roles in the basal ganglia in regards to approach

behaviors. Specifically, they suggest that dopamine may enable an individual to initiate a behavior in response to cues while acetylcholine may facilitate cessation of that response under various conditions [91]. In the case of normal feeding behavior, accumbens dopamine appears to be involved in the effort to obtain food [92] while accumbens acetylcholine influences satiety, predominantly through muscarinic receptors [91]. Data suggest that nicotine infused directly into the nucleus accumbens increases extracellular dopamine and acetylcholine [93] and nicotine may specifically alter phasic striatal dopamine release that is associated with reward [94]. Hence, the effects of nicotine on dopamine function in the striatum may be an important determinant of the reinforcement-enhancing effects of nicotine including the effects of nicotine on food reinforcement [47]. Notably, precipitated withdrawal from chronic nicotine increases acetylcholine, but decreases dopamine levels in the accumbens [95], making it unclear how such neurochemical changes relate to the increased incentive properties of food following cessation.

Accordingly, individual differences in the neural mechanisms underlying food reinforcement could represent an important source of risk for increased food consumption following smoking cessation. Indeed, Lerman and colleagues found that abstinence-induced increases in food reward were only observed in carriers of the A1 allele of the Taq1 polymorphism and these changes were related to weight gain at the 6 month follow-up [26]. The A1 allele of the Taq1 polymorphism is associated with reduced availability of D2 dopamine receptors [96], further indicating that the effect of nicotine on food reinforcement may be mediated through dopamine systems and highlighting the need to consider inter-individual variation at both the neurobiological and behavioral level.

Two other potentially important moderating factors should also be mentioned. Both sex/gender and dietary restraint have been shown to change the relationship between nicotine and eating. For example, Grunberg and colleagues found that nicotine decreased ad libitum food consumption in female, but not male, rats [14]. Gender differences in humans appear to be closely related to dietary restraint (i.e., the tendency to restrict food intake to control body weight). In a laboratory assessment, only women high in dietary restraint (not women low in restraint or men) consumed less food on smoking compared to abstinent days [97]. Women high in dietary restraint also demonstrated elevated salivary response to food cues and disrupted habituation of this response over repeated trials following a brief meal during smoking abstinence [98]. These effects were interpreted as indicative of greater effects of nicotine on satiation in women with high dietary restraint. Other studies suggest that dietary restraint has little effect on food reinforcement in male smokers [99]. Together, these data point a potential influence of gender and dietary restraint on the effects of nicotine on satiation; however, to our knowledge, little data suggest differences in the reinforcing effects of food *per se*.

Several current pharmacotherapies have a beneficial effect on the weight gain during smoking cessation. Both nicotine replacement therapy and bupropion have been shown to reduce the weight gain associated with smoking cessation, although their effects are typically lost once medication is discontinued [10, 100–102]. Our own data suggest that these medications replace the reinforcement-enhancing effects of nicotine for non-food stimuli, and in the case of bupropion, might add to these effects in the presence of nicotine [54]. Indeed, in rats tested on a progressive ratio schedule of reinforcement, bupropion increases the reinforcing efficacy of food [103]. Hence, an important question is why medications that should enhance the reinforcing effects of food suppress weight gain during a cessation attempt. One possibility is that, like nicotine (and presumably nicotine replacement therapy), bupropion prolongs satiation during treatment. Consistent with this hypothesis, bupropion has known anorectic effects in free feeding rats and reduces responding for food on simple fixed ratio schedules of reinforcement [103, 104]. To our

knowledge, no preclinical study has assessed whether termination of bupropion treatment increases food intake as a result of a loss of its satiety effects combined with a persist enhancement of food reinforcement, as suggested above for nicotine.

It is also possible that individual differences play an important role in determining the effects of pharmacotherapy. Lerman and colleagues found that bupropion only attenuated the effects of abstinence on food reward in A1 carriers of the Taq1 polymorphism, abolishing the degree to which abstinence-induced increases in food reward predicted subsequent weight gain [26]. Much remains to be determined about the relationship between pharmacotherapy, food reinforcement, and weight gain amongst smokers attempting to quit. Future work should focus on the behavioral and neurobiological mechanisms that might underlie risk in individuals vulnerable to cessation-related changes in food reinforcement, satiation, and weight gain.

5.0 Conclusions

This review highlights an apparent paradox between the proposed ability of nicotine to enhance food reinforcement on one hand and the known weight suppressing effects of smoking on the other. As noted above, both weight and feeding behavior are likely to be controlled by multiple mechanisms. Under some conditions (e.g., food restriction), the ability of nicotine to enhance reinforcement may dominate the effects on caloric intake. However, under other conditions (e.g., satiation), other effects of nicotine may overshadow any reinforcement-enhancing effect. This complexity underscores the importance of future work aimed at understanding the conditions under which some processes dominate over others.

The relationship between nicotine, eating and weight likely contributes to both the initiation and persistence of cigarette smoking. Amongst the possible underlying mechanisms, nicotine-induced enhancement of food reinforcement may be particularly important for explaining this relationship. The effects of nicotine on food-related behavior are similar to the effects of nicotine on a wide range of reinforced behavior, suggesting that these effects are not entirely specific to food. Better understanding of the neurobiological mechanisms underlying the reinforcement-enhancing effects of nicotine broadly, and the effects on food reinforcement *per se*, may aid in the development of new treatments with better long term outcomes.

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