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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; and 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.

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## 1. 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].

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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. 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-s 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. 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

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