Chapter 7
Altering the Motivational Function of Nicotine through Conditioning Processes

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Introduction

The collection of chapters in this 55th Nebraska Symposium on Motivation Volume clearly highlights that effective strategies for reducing compulsive tobacco use will require a multi-faceted approach in which genetic, neurobiological, individual, and cultural factors are considered. It is difficult, if not impossible, to predict where the next important breakthrough will come from (Bevins & Bardo, 2004; Dethier, 1966; Laidler, 1998). Accordingly, further research that extends and challenges current theory and practice at each of these levels of analysis is needed. The continuing focus of our research program, and the topic of the present chapter, is on the role of Pavlovian conditioning processes involving nicotine. Theoretical and empirical approaches to nicotine dependence that include Pavlovian conditioning processes have lead to important advances in our understanding and treatment of chronic tobacco use (e.g., see Rose, Chapter 8 and Tiffany, Warthen, & Goedecker, Chapter 10 in current Volume). These approaches conceptualize the drug as an unconditioned stimulus (US) or reinforcer. That is, the pharmacological effects of the drug (e.g., reward, analgesia, psychomotor stimulation) enter into an association with stimuli that reliably co-occur with these effects (e.g., paraphernalia, situational cues). Later exposure to these conditioned stimuli (CSs) can evoke conditioned responses (CRs) that increase the chances an individual will seek drug.

Recently, we have suggested that the interoceptive stimulus effects of nicotine might also serve as a CS for other appetitive non-drug outcomes (i.e., USs) and/or a stimulus that occasions whether other CS–US associations will or will not occur (i.e., an occasion setter or facilitator; see Bevins & Palmatier, 2004). We have further suggested that such an associative learning history could impact the tenacity of nicotine addiction—e.g., shorten the time between experimentation and dependence, increase the difficulty of quitting, make sustaining abstinence more difficult, etc. At the current time these suggestions are speculative. With this in

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mind, the present chapter will review the research in this area, as well as high-light some historical precursors and suggest some possible future directions for research. In doing so, hopefully the reader will gain an appreciation on how this approach might lead to further insight into how Pavlovian conditioning processes can alter the motivational function of nicotine in a manner that contributes to chronic tobacco use.

Nicotine as a Reinforcer

Most of the research examining the impact of conditioning processes with nicotine has conceptualized nicotine as a reinforcer. For the current discussion we mean rein-forcer in the same sense as used by Pavlov (1927) and Skinner (1938). According to Pavlov (1927), reinforcer was used interchangeably with unconditioned stimulus, which is shown by an example . "Tactile stimulation of the skin is used as a condi-tioned stimulus for acid. The conditioned stimulus is allowed to act for a period of 3 min and is then *reinforced*, being still continued so as to overlap the action of the acid" [p. 93 (italics added)]. According to this framework, exteroceptive cues that occur in close temporal and spatial relation with tobacco use have the potential to function as conditional stimuli and enter into an association with nicotine (i.e., the reinforcer or US). As a result of this conditioning, a CS acquires the ability to evoke or modify a response. The nature of this CR tends to be more readily predicted from a behavior systems/evolutionary approach to associative learning (cf. Domjan, 2005; Timberlake, 1994). In general terms, stimuli paired with an appetitive US tend to produce approach and search related CRs along with more US-specific behaviors. In contrast, stimuli paired with an aversive US will come to evoke avoid-ance and/or anti-predator behaviors. Translated to smoking, stimuli such as throat irritation and smell of cigarette smoke, sight of the cigarette, lighter and ashtray, smoking/work break areas, and/or smoking companions reliably co-occur with the physiological effects of the nicotine US. In smokers, these stimuli come to control changes in reported cravings and urges, as well as a variety of changes in more physiological measures such as heart rate and galvanic skin response (e.g., Geier, Mucha, & Pauli, 2000; Lazev, Herzog, & Brandon, 1999; Pritchard, Robinson, Guy, Davis, & Stiles, 1996; Rose & Levin, 1991; see Tiffany et al., Chapter 10, in this Volume).

To study the necessary and sufficient conditions for acquisition and expression of nicotine conditioned responding, researchers have developed several preclinical animal models (see Bevins & Palmatier, 2004 for a review). Perhaps the two most widely studied tasks are locomotor conditioning (Bevins, Besheer, & Pickett, 2001; Bevins & Palmatier, 2003; Bevins, Eurek, & Besheer, 2005; Palmatier & Bevins, 2002; Walter & Kuschinsky, 1989) and place conditioning (Grabus, Martin, Brown, & Damaj, 2006; Le Foll & Goldberg, 2005; Shoaib, Stolerman, & Kumar, 1994; see Brunzell & Picciotto, Chapter 3, in this Volume). As an example, in the locomotor conditioning task rats (and less often mice) receive a distinct environment (i.e., a context CS) paired with the psychomotor effect of nicotine. After repeated pairings

of the context CS with the nicotine US, the context CS, in the absence of nicotine (i.e., CS-alone test) evokes an increase in activity relative to controls that receive equal exposure to the nicotine and the context in an unpaired fashion. Although a detailed review of this research is tangential to the goal of the present article, we know that acquisition of conditioned hyperactivity is sensitive to nicotine dose (US magnitude), temporal relation between the CS and US (interstimulus interval), and presentation of other excitatory CSs (Bevins et al., 2001; Bevins & Palmatier, 2004; Bevins et al., 2005). Notably, Pavlov (1927) reported that acquisition of conditioned salivation was affected by similar behavioral factors.

For Skinner (1938), "The operation of reinforcement is defined as the presentation of a certain kind of stimulus in a temporal relation with either a stimulus or response. A reinforcing stimulus is defined as such by its power to produce the resulting change" (p. 62). This definition encompasses that of Pavlov's stimulus–reinforcer relations and extends it to include behavior–reinforcer relations. Current behavioral researchers, albeit not exclusively, tend to use the term reinforcer or reinforcement to refer to the latter relation. As discussed in detail by Caggiula and colleagues in this Volume (Chapter 6) the direct positive reinforcing effects of nicotine, in conjunction with its reinforcer enhancing properties, are important for acquisition and maintenance of tobacco use (see also Chapter 5 by Markou and colleagues that provides a thoughtful discussion of how the removal or avoidance of a withdrawal state (negative reinforcement) also contributes to continued tobacco use).

An instrumental response (e.g., lever press) followed by intravenous (IV) nicotine can maintain and/or increase the frequency of that response (Corrigall & Coen, 1989; Donny, Caggiula, Mielke, Jacobs, Rose, & Sved, 1998). This preclinical self-administration model is one of the most widely used to study the reinforcing effects of abused drugs, including nicotine. In our laboratory, we have recently established nicotine self-administration in rats. Briefly, rats were surgically prepared with an IV catheter following a lever press autoshaping protocol with sucrose designed to engender a high operant level on both levers before starting the self-administration phase. The initiation of daily 1 h self-administration session was signaled by onset of the houselights and insertion of both levers. If the rat pressed the active lever, the levers were immediately withdrawn and nicotine was infused across 1 s; illumination of the cue lights above each lever signaled the infusion. After a 60-s timeout, the levers were reinserted. Notably, the house light remained on during the timeout. Inactive lever presses were recorded, but did not have any programmed consequence. Rats were started on 0.06 mg base/kg/infusion of nicotine and then switched to 0.03 mg base/kg/infusion. Figure 7.1 shows the active and inactive responses for each rat across the acquisition phase. All rats pressed more on the active than the inactive lever by the end of training with the 0.06 mg/kg dose of nicotine. This difference was enhanced when the dose was dropped to 0.03 mg/kg nicotine suggesting that rats were sensitive to the dose of nicotine in this protocol (Fig. 7.1). This point was further supported by each rat's behavior during a subsequent extinction phase where saline replaced nicotine as the infused solution; all remaining procedural details remained the same. That is, all rats increased presses
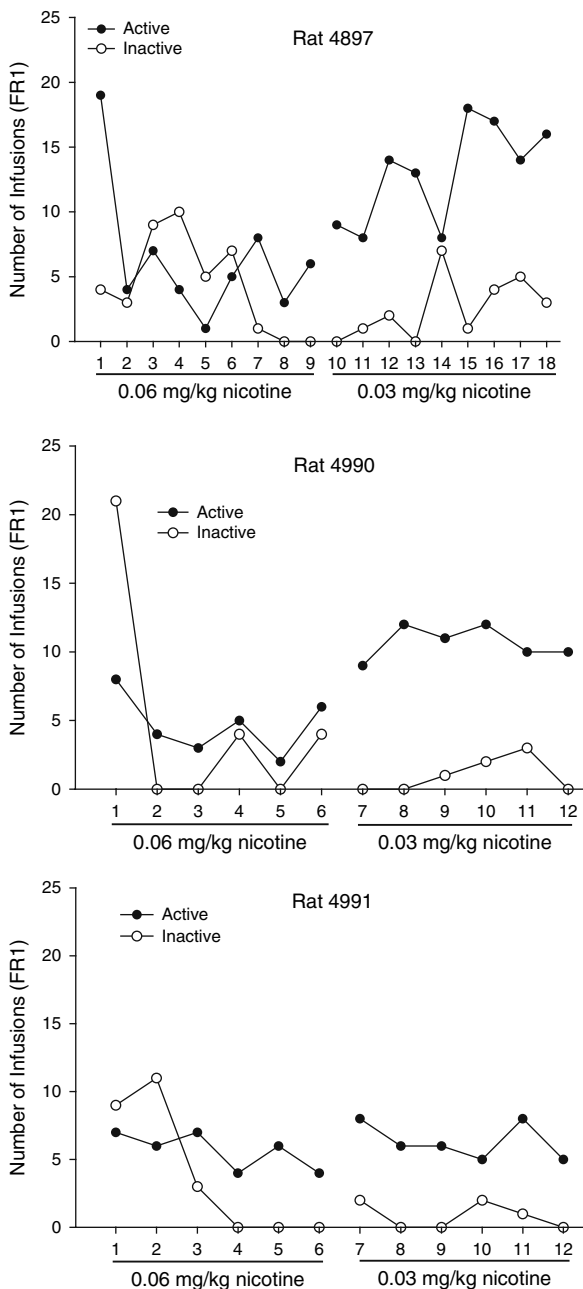
Fig. 7.1 Each panel shows data for a rat in a nicotine self-administration experiment conducted by Jennifer Murray in my laboratory. The main narrative includes a description of the procedures. All rats readily self-administered nicotine as indicated by more responding on the active (nicotine) than inactive lever

on the inactive lever on the first day of extinction (3 to 23, 0 to 10, and 0 to 3 for rats 4897, 4990, and 4991, respectively; data not shown). Additionally, active lever responding on average decreased across repeated extinction sessions.

Nicotine as a Discriminative Stimulus

As described in the previous section, nicotine is clearly able to function as reinforcer. This conceptualization and its theoretical extensions have lead to many important advances in our understanding of the addictive qualities of nicotine involved in tobacco addiction. Also contributing to our understanding of tobacco use and addiction is the research on the discriminative stimulus (S^D) effect of nicotine. That is, the pharmacological action of nicotine on the nervous system has perceptible interoceptive effects that can gain stimulus control over instrumental responding. Studying nicotine as a S^D has provided important insight into behavioral and neuropharmacological processes underlying the subjective effects of nicotine (e.g., Damaj, Creasy, Grove, Rosecrans, & Martin, 1994; Damaj, Creasy, Welch, Rosecrans, Aceto, & Martin, 1995; Perkins, DiMarco, Grobe, Scierka, & Stiller, 1994; Stolerman, 1989; see Perkins, Chapter 9, in this Volume).

Of interest for the present discussion is the two-lever operant drug discrimination task widely used by behavioral pharmacologists to study the S^D effects of nicotine in rodents (Fig. 7.2A). In this example, on sessions (days) when nicotine is administered presses on the right lever will be reinforced with a food pellet after a fixed-ratio (FR) 25 schedule is completed. At the same time, nicotine occasions nonreinforcement (i.e., extinction) of left lever presses. On saline sessions, the schedules are reversed. Left lever presses are reinforced on an FR25 and right lever presses are under extinction. With sufficient training, nicotine functions as a S^D/S^Δ as evidenced by better than 80% responding on the drug-appropriate lever before any reinforcer is delivered—right lever for nicotine sessions and left lever for saline sessions.

In contrast to neuropharmacological processes, potential behavioral (conditioning) processes involved in this discrimination have not been well studied. As described in the previous paragraph, the interoceptive effects of nicotine simultaneously function to occasion responding (S^D) as well as inhibit responding (S^Δ). Figure 7.2B diagrams some of the additional associative structures that could be of empirical and theoretical interest. For simplicity sake this diagram just shows a nicotine session and does not include the instrumental response (i.e., only stimuli are diagramed). Notably, the S^D and S^Δ function of nicotine are associated with different stimuli such as spatial location of the right versus left lever. Thus, on nicotine sessions exteroceptive and proprioceptive stimuli affiliated with the right lever are paired with food; stimuli associated with the left lever are not. Further, the interoceptive stimulus effects of nicotine are paired with intermittent access to food. From a broadly defined conditioning perspective, a glance at these potential associative structures described in Fig. 7.2B prompts several important questions. For example, does nicotine function as a contextual stimulus and acquire conditioned reinforcing value by being paired with food pellets? If so, does this contribute to
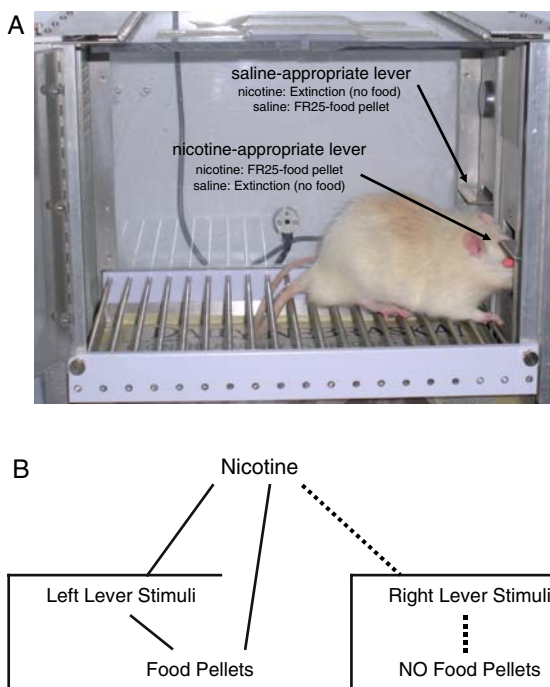
Fig. 7.2 Panel A shows a typical conditioning chamber set up to conduct two-lever operant drug discrimination. The text associated with each *arrow* describes the response contingency in force under a prototypical drug discrimination experiment using nicotine and saline as the injected solutions to be discriminated. **Panel B** shows hypothetical stimulus associations that are imbedded within the response contingencies of an operant drug discrimination study. Although only a nicotine session is shown for simplicity sake, it is clear that there are many direct and higher-order associations possible (see narrative for more detail)

discrimination performance? Alternatively, perhaps nicotine functions as a negative and/or positive facilitator (occasion setter) that disambiguates the stimulus relation between the lever stimuli and availability of food. On this latter point, observations of a well-trained rat will reveal that it engages in many food-related behaviors such as gnawing, licking, and/or nosing the lever while performing the instrumentally trained response (Bevins, 2001; Peterson, Ackil, Frommer, & Hearst, 1972; see also Kintsch & Witte, 1962). They also display goal-tracking behavior such as orienting and moving to the food trough or dipper (Bevins, 2001; Farwell & Ayres, 1979). Such behaviors indicate acquisition of a lever CS–food US association and suggest that the pharmacological effects of nicotine are likely occasioning that the lever stimuli will be paired with food.

The discussion in the previous paragraph is not meant to imply that the response–reinforcer relation is not an important variable in operant drug discrimination with nicotine or any other drug. Indeed, the schedule of reinforcement has been shown to alter acquisition and generalization in a two-lever drug discrimination task with

nicotine (e.g., Stolerman, 1989). Rather, this discussion is meant to highlight that there are many relatively complex stimulus–stimulus and stimulus–reinforcer (i.e., Pavlovian) relations embedded in the task that could also affect the functioning of nicotine as an interoceptive stimulus. In fact, Pavlovian relations co-vary with the response–reinforcer relations and might as readily account for changes in the discriminative qualities of nicotine with changes in the reinforcement schedule. Given the importance of Pavlovian conditioning processes in nicotine addiction prescribed by theorists and researchers (e.g., Bevins & Palmatier, 2004; Conklin & Tiffany, 2002; Geier et al., 2000; Henningfield, Schuh, & Jarvik, 1995; Lazev et al., 1999; Rose & Levin, 1991; see Tiffany et al., Chapter 10, in this Volume), there is surprisingly little research investigating the interoceptive stimulus effects of nicotine from this theoretical perspective.

Interoceptive Pavlovian Conditioning: A Historical Framework

There has been a long history in the Pavlovian conditioning field of studying interoceptive stimuli as CSs. The early research was interested in stimulation of the viscera (stomach, intestine) or brain as the CS (Bykov, 1957; Doty, 1961; Loucks, 1938). For example, Bykov prepared a dog surgically so that water flowed in and then out of the stomach (i.e., the interoceptive CS). This irrigation of the stomach, which produced very little salivation alone, was then paired with access to meat powder and bread US. As described by Bykov (1957), "After several such combinations we found that if water was allowed to flow into the stomach 20 seconds in advance of the reinforcement, the irrigation alone caused the dog to start licking its lips and turning its head to the food box while there was a copious salivary secretion" (p. 249). This example is especially notable given our interest in Pavlovian appetitive conditioning using interoceptive stimuli produced by drug states (see later). That is, Bykov's dog displayed food-related CRs to the interoceptive CS that included licking lips and salivation (Pavlov, 1927), as well as sign/goal tracking (i.e., turning toward food box).

The study of interoceptive stimuli was later extended to the peripheral administration of ligands (e.g., Cook, Davidson, Davis, & Kelleher, 1960). Of particular relevance to the present discussion is the extension of this research to the pharmacological effects of abused drugs. This type of research can be categorized as either drug–drug conditioning or drug–non-drug US conditioning. A recent example of drug–drug conditioning comes from Shepard Siegel's laboratory (e.g., Kim, Siegel, & Patenall, 1999; Sokolowska, Siegel, & Kim, 2002) investigating the ability of the early pharmacological effects of morphine (early onset cues) to serve as a CS for its later, more profound, analgesic effects in rats (for similar research with ethanol see Greeley, Lê, Poulos, & Cappell, 1984). Other drug–drug conditioning research has used one drug as the CS for the later delivery of a different drug (e.g., Revusky, Davey, & Zagorski, 1989). In drug–non-drug US conditioning, the drug state serves as the CS for delivery of a non-pharmacological US. A well-controlled example of this under studied area was conducted by Bormann and Overton (1993). In that

conditioned suppression experiment rats had an IP injection of morphine repeatedly paired with a foot-shock US. Relative to controls, the morphine CS came to evoke a conditioned fear response as measured by drink suppression. Turner and Altshuler (1976) reported a similar result in rats using amphetamine as the CS and a decrease in lever pressing as the measure of conditioned fear.

Nicotine as an Interoceptive CS

Until recent research from our laboratory (see also Troisi, 2006), there has been very little research directly assessing the role of nicotine as a CS. A notable exception to this statement is a study in humans by Clements, Glautier, Stolerman, White, and Taylor (1996). Clements and colleagues, inspired by some of the early drug–drug conditioning research with rats, sought to test whether nicotine could function as a CS for an ethanol US. In that study, one set of smokers received eight conditioning sessions. On half the sessions, a subcutaneous (SC) injection of nicotine (0.6 mg) into the upper arm was followed by a drink containing 9.4% alcohol. For the remaining sessions, a saline injection was followed by a placebo drink that used the same base as in the nicotine sessions (i.e., red angostura). Measures of conditioning included skin conductance, inter-beat interval of the heart, as well as mood/urge ratings. In summarizing their results Clements et al. (1996) concluded that "the study provided inconclusive evidence for the ability of one drug to act as a CS for the presentation of another in human subjects" (p. 94).

In retrospect, the lack of evidence for conditioning to the nicotine CS was not surprising for several reasons. For example, Clements and colleagues acknowledged the route and dose of nicotine may not have been sufficiently salient, or the proper temporal dynamics, to function as a CS. This point is especially notable given that the participants were smokers. That is, from a Pavlovian conditioning perspective, the CS effects of nicotine likely already have a rich conditioning history that might make it difficult to see any effect of a few conditioning trials in the laboratory. As an example, the individuals in this study smoked an average of 15.3 cigarettes per day. Although the duration of smoking is not reported, it is probably an underestimate to say that the participants with a mean age of 27 (range = 21–44) years were smoking at this rate for at least 9 years (i.e., since they were 18 years old). If so, the average number of cigarettes consumed by an individual is estimated at just over 50,000. Thus, in this example there were *at least* 50,000 potential conditioning trials in which the interoceptive stimulus effects of nicotine could have been paired with other appetitive stimuli (e.g., alcohol, food, socialization, work break, peer acceptance, etc.). The four conditioning trials used by Clements et al. (1996) seem few in comparison to an individual's experience before entering the experiment.

We do not mean to imply that the CS effects of a drug cannot be studied in the laboratory situation with human participants. Rather, experiments will simply need to take such history into account. Indeed, in a more recent and cleverly designed study Alessi, Roll, Reilly, and Johanson (2002) clearly demonstrated the feasibility of studying a drug state as CS capable of entering into an association with a reward.
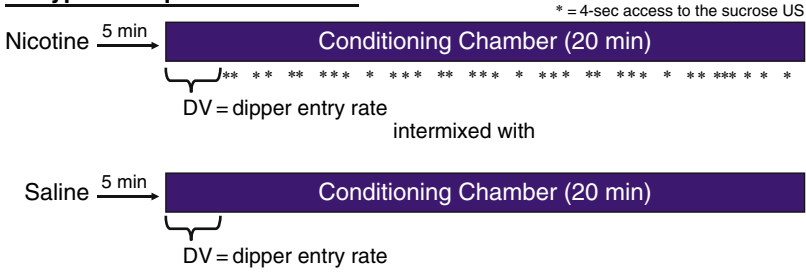
Briefly, human participants had a non-preferred drug (typically diazepam) paired with increased pay during a subsequent computer task. The monetary outcome (US) induced a preference for the interoceptive effects of diazepam (CS). Or, in the word of the authors "drug (diazepam) may have acquired the properties of a conditioned reinforcer as a result of its association with money" (p. 81).

More recently, we have developed a preclinical animal model to study the ability of the pharmacological effects of nicotine to serve as an interoceptive contextual CS for a non-drug appetitive US (i.e., sucrose) in rats (Besheer, Palmatier, Metschke, & Bevins, 2004; Bevins and Palmatier, 2004; Bevins, Penrod, & Reichel, 2007; Murray & Bevins, 2007a, 2007b; Reichel, Linkugel, & Bevins, 2007; Wilkinson, Murray, Li, Wiltgen, Penrod, Berg, & Bevins, 2006). In this Pavlovian appetitive conditioning task, rats received a SC injection of nicotine (i.e., the CS) paired with intermittent access to liquid sucrose (i.e., the US) across a 20-min session. Intermixed with these nicotine sessions were saline sessions in which rats were injected with saline, placed into the same conditioning chambers, but sucrose was withheld (Fig. 7.3A for procedural schematic). Relative to saline (no drug), nicotine evokes differential approach and head entry into the dipper receptacle (Fig. 7.3B). This increase in behaviors directed at the location where the reinforcer has occurred in the past has been referred to as 'goal tracking' (Boakes, 1977; Farwell & Ayres, 1979) and is a widely used measure of Pavlovian conditioning (e.g., Bouton & Sunsay, 2003; Delamater, 1995; Rescorla, 2006).

Ongoing research in the laboratory has focused on neuropharmacological and behavioral processes underlying nicotine's ability to function as an interoceptive context CS in this appetitive drug discrimination procedure. For instance, Wilkinson et al. (2006) found that the magnitude of the goal-tracking CR increased with the number of nicotine CS–sucrose US pairings and that this more robust CR was more resistant to extinction (i.e., more nicotine CS presentations without sucrose to decrease the CR toward control). The CR magnitude also increased with higher concentrations of sucrose (unpublished data). A nicotine dose as low as 0.1 mg/kg can serve as a CS using a fading-dose procedure (Bevins & Palmatier, 2004) or as the dose used from the initiation of training (Murray & Bevins, 2007a, 2007b). Although acquisition rate is similar with lower (0.1 and 0.2 mg/kg) and higher (0.4 mg/kg) doses of nicotine, resistance to extinction increased with nicotine CS dose (Murray & Bevins, 2007b). Importantly, nicotine's ability to evoke this appetitive CR does not reflect state-dependent learning (Bevins et al., 2007).

Besheer et al. (2004) established that the CS effects of nicotine were blocked by pretreatment with the central and peripheral nicotinic acetylcholine receptor (nAChR) antagonist mecamylamine, but not the mostly peripheral nAChR antagonist hexamethonium, suggesting a role of central nervous system (CNS) receptors. Additional neuropharmacological research published or in progress in our laboratory has implicated the α4β2* nAChR, the dopamine and norepinephrine transporter, the glutamatergic N-methyl D-aspartate (NMDA) receptor, and the cannabinoid CB1 receptor in the CS effects of nicotine. Dopamine D1, D2, and D3 receptors, as well as the metabotropic glutamate receptor subtype 5 receptor and the α7* nAChR appear to have minimal role in nicotine's ability to

A. Typical Acquisition Protocol

* = 4-sec access to the sucrose US

Nicotine $\xrightarrow{\text{5 min}}$ | Conditioning Chamber (20 min)

** ** ** *** * *** ** *** * *** ** *** * ** *** * *

DV = dipper entry rate

intermixed with

Saline $\xrightarrow{\text{5 min}}$ | Conditioning Chamber (20 min)

DV = dipper entry rate
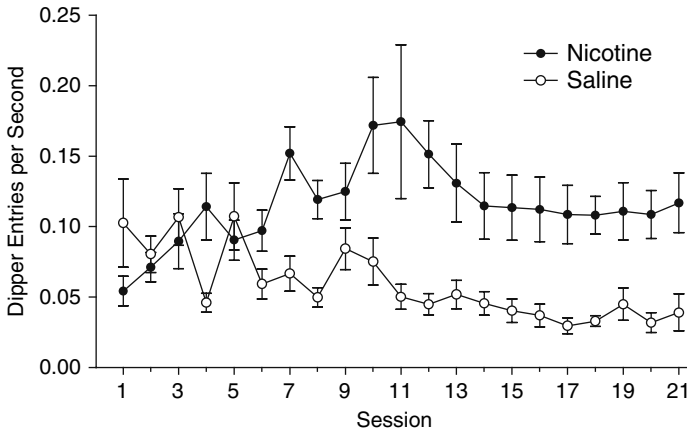
B. Acquisition of the Discrimination

Fig. 7.3 Panel A shows a schematic of a typical protocol used to train the interoceptive stimulus effects of nicotine as an excitatory conditioned stimuli (CS). In brief, nicotine sessions are intermixed with saline session. On nicotine sessions, rats receive intermittent access to sucrose in a dipper receptacle; sucrose is withheld on saline sessions. **Panel B** shows acquisition of conditioned responding (i.e., dipper entries before first sucrose delivery or equivalent time in saline sessions) to the nicotine CS. In this study conducted by Jill Rosno in my laboratory, the nicotine CS dose was (0.4 mg base/kg, SC) and the unconditioned stimulus (US) was 26% sucrose. In a given nicotine session, There were 36 separate 4-s deliveries of the sucrose US

function as a CS (Murray & Bevins, 2007a; unpublished data from experiments in progress; see Chapters 2, 3, and 4 of present Volume (Placzek & Dani; Brunzell & Picciotto; Dwoskin, Pivavarchyk, Joyce, Neugebauer, Zheng, Zhang, Bardo, & Crooks, respectively) for a discussion of nAChRs). In sum, the specificity exemplified by the agonist and antagonist research just described, along with the consistency of the behavioral manipulations with past learning research highlights the utility of this Pavlovian drug discrimination task for studying the underlying behavioral and neural processes of the interoceptive conditional stimulus effects of nicotine.

In more "standard" Pavlovian discrimination tasks, auditory and visual stimuli are often used as CSs. These type of discrete stimuli—versus situational or static apparatus cues—can be readily turned on and off during a conditioning session. Further, several presentations can be programmed in each session allowing one to track acquisition of conditioned responding trial-by-trial. To date, all our published research on the CS effects of nicotine has used SC injections of nicotine. As such, our empirical efforts have employed manipulations comparable to those used with exteroceptive contextual or static apparatus cues. Recent advances in our laboratory, however, have extended this conceptualization of the CS effects of nicotine to include more discrete stimulus properties. Those advances are based on pairing a low dose of nicotine infused IV with brief access to sucrose in long daily sessions. More specifically, food restricted male Sprague Dawley rats were dipper trained for 3 days and then surgically prepared with IV catheters. Acquisition training followed the surgical recovery period. For acquisition, rats received ten IV infusions of nicotine (0.01 mg base/kg) in a 2-h session. Each 1-s nicotine infusion (i.e., the CS) was followed 30 s later by 4-s access to 26% (w/v) sucrose (i.e., the US); nicotine infusions were separated by an average of 11 min. This protocol was repeated daily for 12 days. The last day of acquisition was followed 24 h later by the first of seven extinction sessions in which the nicotine CS was still infused, but the sucrose US was withheld.

Figure 7.4 shows the results from this study examining the ability of IV nicotine to function as a CS. The main dependent measure is number of dipper entries in the 30 s following the nicotine infusion (CS period) minus number of entries in the 30 s before the infusion (pre-CS period). A positive value indicates an increase in dipper entries; 0 indicates no change. Nicotine readily acquired control of conditioned responding (i.e., goal tracking). Further, this conditioned responding decreased
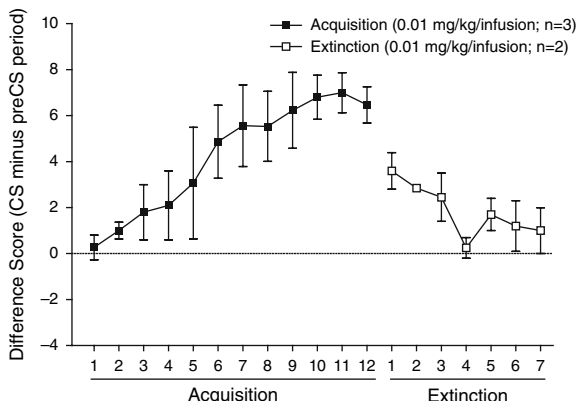

Fig. 7.4 This figure shows results of an experiment conducted by Jennifer Murray in my laboratory using a 1-s intravenous administration of 0.01 mg base/kg nicotine as the conditioned stimuli (CS); 4-sec access to the sucrose unconditioned stimulus (US) followed 30 s later. Intravenous nicotine acquired control over conditioned responding and this conditioning was susceptible to extinction

systematically across sessions when sucrose was withheld (i.e., extinction). These findings are notable for several reasons. First, they demonstrate that a dose of nicotine on the lower end of the self-administration dose-effect curve has sufficient stimulus properties to function as a CS. Second, after acquisition training, dipper entries increased after each nicotine infusion (trial-by-trial data not shown) suggesting that IV nicotine can be used in a manner more similar to a discrete cue. Finally, in the extinction phase nicotine infusions continued, but there was a progressive decrease in dipper entries across sessions. Because nicotine was infused to the same extent in acquisition and extinction, a psychomotor stimulant account of the increased dipper entries in the acquisition phase is untenable. That is, a psychomotor account predicts that the pattern of responding should not change in the extinction phase; this obviously did not occur. Accordingly, the increase in dipper entries in acquisition reflects a conditioned association between nicotine and sucrose. Indeed, we recently conducted an unpaired control group in which nicotine and sucrose occurred in the same session, but their presentations were separated by at least 4 min. This unpaired control did not display an increase in dipper entries immediately following nicotine infusion (data not shown). This result indicates that temporal contiguity between the nicotine and sucrose is required; a conclusion consistent with the extinction results and the implication of conditioning processes (Pavlov, 1927; Wasserman & Miller, 1997).

Nicotine as an Interoceptive Occasion Setter

The research examining the ability of nicotine to function as a CS assumes that the interoceptive effects of nicotine enter into a direct association with the sucrose US. Differential control of a goal-tracking CR by nicotine provides evidence for this conditioned association (see later discussion). A natural extension of this associative analysis is that the nicotine drug state should also be able to serve as a positive or negative occasion setter (i.e., also termed 'facilitator' or 'modulator' in the Pavlovian conditioning literature). A positive occasion setter is a stimulus that sets the occasion upon which each presentation of a CS will be paired with the US; a negative occasion setter indicates that presentations of the CS will not be reinforced (see Schmajuk & Holland (1998) and Swartzentruber (1995) for reviews). Research from our laboratory has shown that nicotine can function in both capacities (Bevins, Wilkinson, Palmatier, Siebert, & Wiltgen, 2006; Palmatier, Peterson, Wilkinson, & Bevins, 2004; Palmatier, Wilkinson, & Bevins, 2005; Palmatier & Bevins, 2007). For example, as a positive drug feature (i.e., occasion setter) nicotine disambiguated the relation between a brief light cue and sucrose delivery. That is, the discrete light CS was paired with the sucrose US when nicotine was administered before the start of the session. In contrast, on saline sessions the same light CS was present, but access to sucrose was withheld. As a negative feature, the interoceptive effects of nicotine indicate that the light CS will not be followed by the sucrose US. Rather, the light CS will be paired with sucrose on saline (no drug) sessions.

Although we have not conducted nearly the amount of neuropharmacological research within this nicotine occasion setting task as with the CS task, the Pavlovian discrimination is quickly acquired, mediated by central nicotinic acetylcholine receptors, and is pharmacologically specific (Bevins et al., 2006; Palmatier et al., 2004; Palmatier et al., 2005). Rather, our empirical efforts in this area have focused more on the underlying behavioral processes mediating nicotine's ability to modulate responding. For the positive occasion setting research, this has entailed asking whether nicotine (or other drug states such as chlordiazepoxide) facilitate conditioned responding to a CS through simple excitatory processes such as a direct association with the US or, is it necessary to infer a non-associative or higher-order associative process to account for its modulatory control over conditioned responding. One account of occasion setting suggests that the discrete CS (e.g., light in our situation) acquires weak excitatory strength from being paired with the sucrose US on half the sessions. Although this excitation is not sufficient to evoke conditioned responding alone, when the CS is combined with the 'occasion setter' that has also been paired with the US on half the sessions, excitation passes some threshold and conditioned responding is observed (cf. Rescorla, 1986). Note that this explanation assumes that the CS and the occasion setter enter into separate excitatory associations with the US that will 'summate' when the two are presented together. This summation account predicts that nicotine will lose its ability to modulate (facilitate) responding to the CS after extensive presentation of the nicotine occasion setter without the sucrose US—i.e., procedural extinction.

We recently tested this account using nicotine as the occasion setter (Experiment 1 in Palmatier & Bevins, 2007). Briefly, nicotine was trained as a positive occasion setter as described earlier. In a subsequent phase, nicotine was presented repeatedly without the discrete CS or sucrose US. This phase was meant to decrease excitation controlled directly by nicotine. Then, the light was re-introduced. Even though there were as many nicotine extinction sessions as there were original nicotine training sessions, conditioned responding to the discrete CS was still facilitated by the nicotine. A similar pattern was observed when amphetamine or chlordiazepoxide functioned as the occasion setter (Palmatier & Bevins, 2007). Combined, this research strains any summation type account. Further, it suggests that the nicotine drug state is modulating responding to the CS via a higher order associative or non-associative process. Currently unpublished research from our laboratory has confirmed this assumption. That is, nicotine trained as an occasion setter for one discrete CS (e.g., light) was able to transfer its modulatory control to a completely separate and distinct CS (e.g., white noise) that has been separately trained with chlordiazepoxide as the occasion setter. Notably, the pharmacological effects of chlordiazepoxide do not substitute for a nicotine occasion setter in the absence of this associative training. Additionally, a novel drug state (amphetamine) did not prompt conditioned responding to either of the discrete CS indicating that training two Pavlovian occasion setting discriminations within subject does not merely result in a drug versus no drug discrimination where the default is to respond when in a drug state. Thus, we are left to conclude that transfer of modulatory control of conditioned responding between nicotine and chlordiazepoxide reflects a common underlying

higher-order associative or non-associative processes that allows for generalization. That is, related conditioning histories allows for functional substitution (versus pharmacological substitution) by drug states (Palmatier, 2004; see Bonardi & Hall, 1994 for comparable results with exteroceptive stimuli).

Implications for the Motivational Function of Nicotine

We suggest that a more complete analysis of nicotine dependence will also include nicotine in the role of a CS. An explicit assumption in our research is that nicotine's ability to control a CR reflects an acquired excitatory association with the sucrose US (Bevins & Palmatier, 2004). Although the inferred nature of the association may vary with one's theoretical preference, this assumption of acquired excitation is held in some form by most Pavlovian conditioning theorists (Bouton 2002; Domjan, 2005; Konorski, 1948; Miller & Escobar, 2002; Pavlov, 1927; Pearce, 1987; Rescorla 1988; Timberlake, 1994; Wagner & Brandon, 2001) and is supported by the research described in this chapter. If nicotine acquires additional appetitive properties by virtue of its conditioning history, then not only are the stimulus properties of the drug changed as evidenced by its control of a CR, but its ability to function in other capacities (e.g., reward, reinforcer, US, etc.) might also be changed. Such changes in the motivational function of nicotine for the smoker could affect the trajectory of nicotine dependence and suggest modifications to current intervention strategies. In less technical and more speculative terms, if the "meaning" of nicotine is altered by an individual's experiences while using nicotine, these associated experiences could alter the progression to dependence, affect the tenacity of the addiction, change the difficulty of quitting, alter the likelihood of relapse, and/or change the magnitude and duration of the relapse. Although in our current research and in the present proposal we focus on positive or appetitive experiences which would change these addiction outcomes for the worse, there is a clear prediction that negative or aversive experiences could also change the trajectory for dependence (e.g., prevent further experimentation and hence development of dependence, decrease likelihood of relapse, etc.).

The research reviewed in this chapter clearly establishes that interoceptive effects of nicotine function as a CS that comes to evoke an appetitive CR. However, the possibility that the motivational impact of nicotine would change as a function of conditioning history has not been directly assessed. Widely studied phenomena such as second-order conditioning (Bevins, Delzer, & Bardo, 1996; Holland & Rescorla, 1975; Pavlov, 1927), counterconditioning (Brooks, Hale, Nelson, & Bouton, 1995; Lovibond & Dickinson, 1982; Pearce & Dickinson, 1975), and revaluation (Holland & Straub, 1979; Molina, Bannoura, Chotro, McKinzie, Arnold, & Spear, 1996; Yin & Knowlton, 2002) support the idea that a cue paired with a biologically relevant outcome will acquire additional appetitive or aversive properties depending on the nature of the US. Additionally, there are a few scattered but important published reports more directly related to this suggestion. Perhaps the most directly relevant is a very clever experiment by Molina et al. (1996). In that study, they reported

that a tactile aversion conditioned by an ethanol US was reversed if ethanol was later paired with sucrose. That is, 10-day-old rat pups had a distinct tactile CS paired with intragastrically administered ethanol (2 g/kg, 16.8% v/v). Relative to unpaired controls, this conditioning history produced a clear aversion for the tactile CS. If rat pups had this same dose of ethanol subsequently paired with 10 min of a sucrose solution (15.3% w/v) infused through an intra-oral cannula then they did not display this tactile aversion. Merely exposing the pups to unpaired ethanol and sucrose or providing an alternative learning history was not sufficient to alter the previously acquired tactile aversion. In the authors' words, "after pups in the present experiments acquired an aversion to the texture as a consequence of its pairing with alcohol US properties, the pup's representation of these properties was changed (devalued) during Phase 2 by pairing the state of alcohol intoxication with an appetitive sucrose infusion" (p. 130). Notably, ongoing research in our laboratory indicates that an appetitive conditioning history with nicotine as a CS appears to enhance its rewarding US effects as measured in a place conditioning task.

We also suggest that a more complete analysis of nicotine dependence will include nicotine in the role of an occasion setter. As such, nicotine disambiguates when other stimuli will be paired with a US. Although functioning as an occasion setter does not preclude also serving as a CS, it will be of interest to determine if some conditions are more likely to encourage higher-order associations rather than direct associations with nicotine. The motivational impact of Pavlovian conditioning history where nicotine serves as an occasion setter was highlighted by the functional substitution research described earlier (Palmatier, 2004). In that research, a drug pharmacologically distinct from nicotine (i.e., chlordiazepoxide), facilitated conditioned responding to the CS (e.g., light) that was paired with sucrose only in the nicotine state. This substitution occurs only when chlordiazepoxide is trained as an occasion setter for a different CS (e.g., white noise). That is, transfer of motivational function was based on learning histories and not on an overlap in the pharmacological effects of the drugs. This functional substitution could have important implications for smoking relapse. Seemingly unrelated stimuli could prompt craving, urges, and/or drug seeking because they share a common conditioning history with nicotine.

Finally, better intervention and prevention programs for nicotine dependence will require a multi-faceted and translational approach in which genetic, neurobiological, individual, and cultural factors are considered. In the present chapter we have focused on interoceptive Pavlovian conditioning processes in which nicotine's motivational function could be altered by conditioning history. Such conditioning history could significantly affect nicotine addiction. Albeit speculative, alterations in nicotine's effects resulting from Pavlovian conditioning could speed the transition between experimentation and dependence, make quitting more difficult, and/or contribute to the high relapse rate. Clearly, more research is required to test these possibilities, as well as to better understand interoceptive Pavlovian conditioning processes with nicotine. This understanding will no doubt enhance the effectiveness of intervention and prevention programs for tobacco use.

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