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Both nicotine reward and withdrawal are enhanced in a rodent model of diabetes

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Abstract

Rationale—It is presently unclear whether diabetic rats experience greater rewarding effects of nicotine and/or negative affective states produced by nicotine withdrawal.

Objective—The present study utilized a rodent model of diabetes to examine the rewarding effects of nicotine and negative affective states and physical signs produced by withdrawal.

Methods—Separate groups of rats received systemic administration of either vehicle or streptozotocin (STZ), which destroys insulin-producing beta cells in the pancreas and elevates glucose levels. Place conditioning procedures were utilized to compare the rewarding effects of nicotine (conditioned place preference; CPP) and negative affective states produced by withdrawal (conditioned place aversion; CPA) in vehicle- and STZ-treated rats. CPA and physical signs of withdrawal were compared after administration of the nicotinic receptor antagonist mecamylamine to precipitate withdrawal in nicotine-dependent rats. A subsequent study utilized elevated plus maze (EPM) procedures to compare anxiety-like behavior produced by nicotine withdrawal in vehicle- and STZ-treated rats.

Results—STZ-treated rats displayed greater rewarding effects produced nicotine and a larger magnitude of aversive effects and physical signs produced by withdrawal as compared to vehicle-treated controls. STZ-treated rats also displayed higher levels of anxiety-like behavior on the EPM during nicotine withdrawal as compared to controls.

Conclusion—The finding that both nicotine reward and withdrawal are enhanced in a rodent model of diabetes implies that the strong behavioral effects of nicotine promote tobacco use in persons with metabolic disorders, such as diabetes.

Keywords

smoking; tobacco; streptozotocin; reward; abstinence; metabolic disorder; diabetic; aversion; anxiety

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Introduction

Diabetes is a complex metabolic disorder that causes a multiplicity of negative health outcomes (Holt et al., 2010). As the disease progresses, persons with diabetes have to learn how to apply various pharmacological tools in an optimal manner to manage different negative health consequences. This might increase vulnerability to experiment with and ultimately abuse an array of addictive substances, including nicotine in tobacco products (Ghitza et al., 2013; Ng et al., 2004). Indeed, tobacco products are appealing for persons with diabetes to control appetite and cope with stress. Also, tobacco products may improve cognitive processes in persons with diabetes. Lastly, tobacco use is maintained by a balance between experiencing the rewarding effects of nicotine and avoiding the aversive effects of withdrawal. However, it is presently unclear whether enhanced rewarding effects of nicotine and aversive effects of withdrawal contribute to the enhanced vulnerability to tobacco use observed in persons with metabolic disorders, such as diabetes.

Recent pre-clinical studies in our laboratory have examined the rewarding effects of nicotine in rodent models of diabetes. Our first study in this area utilized a rodent model of diabetes involving streptozotocin (STZ) administration. STZ is a drug that is taken up by glucose transporters that are concentrated on the insulin-producing beta cells of the pancreas. Since STZ is toxic to these cells, it produces a decrease in insulin production (hypoinsulinemia) and a concomitant increase in blood glucose levels (hyperglycemia), which represent the etiology of Type 1 or advanced stages of Type 2 diabetes in humans (Bell and Hye, 1983). This model was used to compare intravenous self-administration (IVSA) of nicotine in rats that received vehicle or STZ administration. The results revealed that STZ-treated rats displayed higher levels of nicotine IVSA as compared to controls across escalating doses of nicotine (O'Dell et al., 2014). A subsequent study compared conditioned place preference (CPP) produced by nicotine in rats that were fed a regular or high-fat diet (HFD) regimen. The results revealed that the rewarding effects of nicotine were uniquely exacerbated in rats that received the HFD regimen and also displayed insulin resistance (Richardson et al., 2014). Based on these studies, we recently hypothesized that strong rewarding effects of nicotine help promote tobacco use in persons with diabetes (for a review see O'Dell and Nazarian, 2016).

In addition to the strong rewarding effects of nicotine, it is conceivable that other aspects of tobacco use, such as aversive effects of nicotine withdrawal, may also be magnified by diabetes. To address this question, the present study utilized place-conditioning procedures to compare both the rewarding effects of nicotine (CPP) and the aversive effects of nicotine withdrawal (conditioned place aversion; CPA) in vehicle- and STZ-treated rats. The unique advantage of place-conditioning procedures is that they assess both rewarding properties and aversive states in the same experimental procedure. The CPA procedure also allows concomitant assessment of physical signs of withdrawal during conditioning. However, a limitation of the CPA procedure is that the explicit nature of the avoidance behavior is not clear. Thus, a subsequent study utilized elevated plus maze (EPM) procedures to compare anxiety-like behavior produced by nicotine withdrawal in vehicle- and STZ-treated rats.

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Materials and Methods

Overall design

This experiment consisted of 3 studies that were conducted in separate cohorts of rats. Study 1 compared the rewarding effects of nicotine using CPP procedures in vehicle- and STZ-treated rats. Study 2 compared the aversive effects of nicotine withdrawal using CPA procedures in vehicle- and STZ-treated rats. The physical signs of withdrawal were also assessed on the final days of withdrawal conditioning in both groups of rats. An additional group of STZ-treated rats that did not receive nicotine exposure was conditioned in the CPA procedure in order to examine the effects of mecamylamine alone in STZ-treated rats. Study 3 compared anxiety-like behavior produced by nicotine withdrawal in vehicle- and STZ-treated rats.

Subjects

Male Wistar rats were obtained from an out-bred stock of animals (Envigo, Inc., Indianapolis, IN). Each experimental group consisted of rats from distinct litters that were housed in a humidity- and temperature-controlled (22°C) vivarium on a 12-hour light/dark cycle (lights off at 8:30 am). The rats were group-housed with 2–3 same sex littermates. The rats began the experiment between post-natal day 52–60 and their weights fell within a range of 250–300 g. The rats had *ad libitum* access to food and water throughout the experiment except during conditioning and testing. The rats were handled for 4–5 days prior to any experimental manipulations. The UTEP Institutional Animal Care and Use Committee approved all procedures prior to experimentation.

Drugs

The drugs used were: (−) nicotine hydrogen tartrate salt, mecamylamine, and STZ (Sigma Inc., St Louis, MO). Nicotine and mecamylamine were dissolved in 0.9% sterile saline and administered subcutaneously in a volume of 1 ml/kg. STZ was dissolved in citrate buffer (0.1 M citric acid and 0.1 M Na citrate) and fresh solutions were delivered subcutaneously within 15 min of preparation for each cohort of animals. The range of nicotine and mecamylamine doses were selected based on previous research in our laboratory comparing CPP produced by various doses of nicotine (Torres et al., 2008) and physical signs of withdrawal produced by various doses of mecamylamine (O'Dell et al., 2006 and 2007) in adult male rats. The STZ dose was chosen based on previous work demonstrating that this drug produces an increase in glucose levels within 5 days of STZ administration (O'Dell et al., 2014).

Diabetes induction and glucose monitoring

In each study, the rats first received vehicle or STZ (45 mg/kg; expressed as salt) administration. Glucose levels were then monitored every other day at approximately 10 am. Briefly, a 22 g needle was used to nip the tip of the tail to excise a small drop of blood that was expressed on a test strip. The blood glucose levels were then measured using a glucometer that is appropriate for rodent blood plasma (AlphaTRAK, Abbott Laboratories, Inc.). STZ-treated rats had to display an increase in glucose levels of at least 250 mg/dL

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within the first 3–5 days after STZ administration in order to proceed in the study. The rats were conditioned and/or tested approximately 2 weeks after vehicle or STZ administration, during which time they remained in their home cage. Animals that displayed glucose levels higher than 650 mg/dL during the pre-test, post-test, or EPM test were eliminated from the study. Approximately 10 rats were eliminated on the basis of the high glucose criterion on the test days. Glucose monitoring was done after behavioral testing to avoid any potential aversive effects produced by the bleeding procedure. We observed that vehicle-treated rats displayed glucose levels in a range of approximately 115–200 mg/dL during the test days, as indicated in Table 1.

Nicotine dependence induction

Study 2 and 3 compared the effects of withdrawal in vehicle- and STZ-treated rats that received nicotine exposure for 7–14 days. The rats were anesthetized with an isoflurane/oxygen mixture (1–3% isoflurane) and were prepared with osmotic pumps (model 2ML2; Alzet, Inc.) that were placed subcutaneously on the back of the animal parallel to the spine. Extensive work in our laboratory has revealed that this pump model delivers nicotine continuously for 16 days. The pumps contained a dose of nicotine (3.2 mg/kg/day; expressed as base) that produces reliable dependence in adult rats within a 7–day period of nicotine exposure (Watkins et al., 2000). Prior to surgical implantation of the pump, the concentration of nicotine was adjusted according to the rats' weight. The surgical wound was closed with 9-mm wound clips and treated topically with antibiotic ointment. Following surgery, all rats received subcutaneous administration of the analgesic flunixin (2.5 mg/kg; expressed as salt).

General conditioning procedures

Our conditioning chambers consisted of 2 distinct compartments of equal proportions (76 × 24 × 30 cm) that were separated by a removable solid partition. There were 1-way mirrors on the front walls to allow for behavioral observations. One compartment had black walls with pine bedding beneath a smooth Plexiglas® floor with small holes. The other compartment had black and white stripped walls with a mixture of pine bedding and blue paper chips beneath a textured Plexiglas® floor with small holes. Both compartments were equally illuminated, and continuous white noise (0–20 kHz) was used to minimize any disturbances from outside the test area.

This study employed a biased procedure that consisted of 3 phases: an initial pre-test, 8 conditioning days, and a final post-test. A biased conditioning design was used because these procedures have been shown to be more sensitive at detecting mild subjective effects produced by nicotine and withdrawal from this drug (O'Dell and Khroyan, 2009). In order to test for preference behavior, the solid partition that separated the compartments was removed and replaced with a partition that had an opening in the center (8 × 8 cm high). The rats were allowed to shuttle freely between the compartments for 15 min. Four rats that displayed an initial preference of greater than 65% were eliminated from the study. This criterion is based on previous work in our laboratory showing that it is difficult to establish CPP in rats that display a strong initial preference for either compartment, particularly when using a drug like nicotine that produces mild subjective effects.

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Five days after the initial pre-test, an 8-day conditioning procedure was initiated using 30-min sessions. Conditioning was delayed for 5 days after the pre-test in order to minimize latent inhibition that could attenuate the association between the subjective effects of nicotine and the environmental cues. The conditioning phase consisted of 4 drug pairings and 4 saline pairings. The day after the last conditioning session, the rats were re-tested for shifts in preference behavior for 15 min. In each study, the order of drug treatment was counterbalanced within treatment groups such that some rats received drug on the first day of conditioning and the other half of rats received drug on the second day of conditioning.

Somatic signs of withdrawal measures

In Study 2, somatic signs of withdrawal were recorded following each animal's last injection of mecamylamine during the final days of conditioning. The occurrence of the following signs was recorded for 10 min: eye blinks, body shakes, gasps, writhes, headshakes, ptosis, and teeth chattering. Multiple successive counts of any sign required a distinct pause between episodes. If present continuously, ptosis was counted only once. The same observer scored all of the withdrawal signs and was blind to the animal's drug treatment.

EPM procedures

The EPM apparatus consists of 4 arms (10×50 cm) that are elevated to a height of 50 cm above the ground. The closed arms of the EPM have 40 cm high walls around them, and the open arms do not. The EPM apparatus was located in the middle of the testing room beneath a red light. Fourteen days after vehicle or STZ administration, the rats were implanted with osmotic pumps that delivered nicotine, as described above. The rats were first acclimated to the testing room in a rectangular Plexiglas® cage for 10 min. They then received saline or mecamylamine administration, and 10 min later they were placed in the center of the EPM facing the open arm. Time spent in the closed versus open arms was recorded for 5 min. The apparatus was thoroughly cleaned with 70% ethanol and then water between each test.

Specific details of each study

Study 1 compared the rewarding effects of nicotine using CPP procedures in vehicle- and STZ-treated rats. During conditioning, separate groups of rats received saline (n=7 vehicle; n=5 STZ) or various doses of nicotine (0.1 [n=6 vehicle; n=6 STZ], 0.2 [n=10 vehicle; n=8 STZ], 0.4 [n=8 vehicle; n=11 STZ], or 0.8 [n=7 vehicle; n=5 STZ] mg/kg; expressed as base).

Study 2 compared negative affective states produced by withdrawal using CPA procedures in vehicle- and STZ-treated rats. Twelve days after vehicle or STZ administration, the rats were implanted with a nicotine pump, as described above. An additional group of STZ-treated rats were given a sham surgery and did not receive nicotine exposure in order to examine the effects of mecamylamine alone in STZ-treated rats. Two days after surgery, the rats were tested for their initial preference behavior. Five days later, separate groups of rats received saline (n=14 vehicle; n=8 STZ) or mecamylamine (1.5 [n=13 vehicle; n=7 STZ] or 3.0 [n=12 vehicle; n=7 STZ] mg/kg; expressed as salt) during conditioning. An additional group of STZ-treated rats did not receive nicotine pumps and were conditioned with mecamylamine (1.5 [n=7 STZ] or 3.0 [n=7 STZ] mg/kg; expressed as salt).

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Study 3 compared anxiety-like behavior produced by withdrawal using EPM procedures in vehicle- and STZ-treated rats. Fourteen-days after vehicle or STZ administration, the rats were implanted with osmotic pumps that delivered nicotine, as described above. Following 7 days of nicotine exposure, separate groups of vehicle- or STZ-treated rats received either saline (n=15 vehicle; n=9 STZ) or mecamylamine (1.5 [n=9 vehicle; n=9 STZ] or 3.0 [n=9 vehicle; n=9 STZ] mg/kg; expressed as salt).

Statistics

For the conditioning studies, difference scores were computed to reflect the amount of time spent in the initially non-preferred (Study 1) or preferred (Study 2) compartment after conditioning minus before conditioning. CPP was operationally defined as a significant increase in time spent on the initially non-preferred side after conditioning, whereas CPA was defined as a decrease in time spent on the initially preferred compartment after conditioning. Difference scores were analyzed using 2-way ANOVAs with dose (nicotine or mecamylamine) and state (vehicle or STZ) as between-subject factors. In our experience, significant interactions are not typically observed in conditioning procedures involving nicotine (O'Dell et al., 2007; Torres et al., 2008 and 2009). This is because the shifts in preference behavior produced by nicotine or withdrawal from this drug are small, and the effects are similar across doses of nicotine and mecamylamine. For this reason, the present study reports significant main effects for CPP and CPA between vehicle- and STZ-treated rats. This analysis is also in line with our goal of comparing the behavioral effects of nicotine in healthy and diabetic rats.

In Study 2, we calculated mean total signs of withdrawal following mecamylamine administration in vehicle- and STZ-treated rats. Withdrawal signs were analyzed using a 2-way ANOVA with dose of mecamylamine and state (vehicle or STZ) as between-subject factors. In Study 3, percent time spent in the open versus closed arms of the EPM was compared in vehicle- and STZ-treated rats. Anxiety-like behavior was operationally defined as a significant increase in time spent in the closed versus open arms of the EPM as compared to controls. Percent time was analyzed using a 2-way ANOVA with dose of mecamylamine and state (vehicle or STZ) as between-subject factors. For each study, glucose levels were also compared using a 2-way ANOVA with dose (nicotine or mecamylamine) and state (vehicle or STZ) as between subject-factors. Wherever significant interaction effects were observed, post-hoc comparisons were conducted between dose conditions and vehicle- and STZ-treated rats.

Results

Glucose levels in each study

Table 1 reflects glucose levels immediately after the preand post-tests of preference behavior and EPM testing. Our analysis revealed a significant main effect of state [Study 1 [$F_{(1,146)}$ = 628.12, $*p \leq 0.05$], Study 2 [$F_{(1,110)}$ = 619.86, $*p \leq 0.05$], and Study 3 [$F_{(1,108)}$ = 430.02, $*p \leq 0.05$], with STZ-treated rats displaying a significant increase in glucose levels regardless of nicotine or mecamylamine doses.

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CPP results from Study 1

Figure 1 depicts difference scores in vehicle- and STZ-treated rats at individual doses (left panel) and collapsed across doses (right panel) of nicotine. Our analysis of the left panel revealed a significant main effect of dose [$F_{(4,63)} = 2.7$, $*p \leq 0.05$] and state [$F_{(1,63)} = 10.2$, $\dagger p \leq 0.002$], with STZ-treated rats displaying a larger upward shift in time spent in their initially non-preferred side as compared to controls. Given the main effect of state, the panel on the right collapsed across nicotine doses in order to illustrate that this drug produced a larger shift in preference behavior in STZ-versus vehicle-treated rats ($\dagger p \leq 0.05$).

CPA results from Study 2

Figure 2 depicts difference scores in vehicle- and STZ-treated rats at individual doses (left panel) and collapsed across doses (right panel) of mecamylamine. Our analysis of the left panel revealed a significant main effect of dose [$F_{(2,55)} = 4.8$, $\dagger p \leq 0.01$] and state [$F_{(1,55)} = 4.8$, $*p \leq 0.04$], with STZ-treated rats displaying a larger decrease in time spent in their initially preferred side as compared to controls. Given the main effect of state, the panel on the right collapsed across mecamylamine doses in order to illustrate that this drug produced a larger place aversion in STZ-versus vehicle-treated rats ($\dagger p \leq 0.05$). A separate control group of STZ-treated rats were included that did not receive nicotine exposure (data not shown). In the absence of nicotine, mecamylamine did not produce a decrease in time spent in the initially preferred compartment (1.5 mg/kg dose of mecamylamine pre-test value != 506.6±16.7 and post-test value != 476.0±45.0; 3.0 mg/kg dose of mecamylamine pre-test value != 529.0±16.0 and post-test value != 526.8±55.1). These data show that the effects of mecamylamine in STZ-treated rats are uniquely exacerbated following nicotine exposure.

Somatic signs of withdrawal results from Study 2

Figure 3 reflects the somatic signs of nicotine withdrawal in vehicle- and STZ-treated rats. Our analyses revealed a significant interaction between dose and state [$F_{(2,56)} = 3.63$, $p \leq 0.001$], indicating that the somatic signs of withdrawal were dose-dependently higher in STZ-versus vehicle-treated rats. Specifically, a significant increase in signs was observed in vehicle-treated rats following administration of 3.0 mg/kg dose of mecamylamine and STZ-treated rats that received the 1.5 and 3.0 mg/kg dose of mecamylamine as compared to saline controls ($*p \leq 0.05$). Importantly, the magnitude of this effect was larger in STZ-treated rats that received the 1.5 and 3.0 mg/kg dose as compared to vehicle-treated controls ($\dagger p \leq 0.01$). A separate control group of STZ-treated rats were included that did not receive nicotine exposure (data not shown). In the absence of nicotine, STZ-treated rats did not elicit somatic signs of withdrawal following mecamylamine administration (1.5 mg/kg dose of mecamylamine, != 4.9±1.06; 3.0 mg/kg dose of mecamylamine, != 3.6±0.92).

EPM results from Study 3

Figure 4 reflects the percent time spent in the closed arms of the EPM. Our analyses revealed a significant interaction between state and dose [$F_{(2,54)} = 7.5$, $p \leq 0.001$], indicating that STZ-treated rats displayed a dose-dependent increase in time spent in the closed arms of the EPM. Indeed, a significant increase in time spent in the closed arms was observed in vehicle-treated rats that received the 3.0 mg/kg dose and STZ-treated rats that received the

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1.5 and 3.0 mg/kg dose of mecamylamine as compared to their respective saline controls (*$p \leq 0.01$). Importantly, the magnitude of this effect was larger in STZ-treated rats that received the 1.5 mg/kg dose of mecamylamine as compared to vehicle-treated controls (†$p \leq 0.01$).

Discussion

To summarize, the major finding of this report is that STZ-treated rats experience greater rewarding effects of nicotine and aversive effects of withdrawal as compared to vehicle-treated controls. A larger upward shift in preference behavior produced by nicotine was observed in STZ-versus vehicle-treated rats. Also, a larger downward shift in aversion produced by nicotine withdrawal was observed in STZ-versus vehicle-treated rats. Our EPM data suggest that the explicit nature of the aversive effects of withdrawal may be related to an increase in anxiety-like behavior in STZ-versus vehicle-treated rats. Together, our results suggest that diabetes enhances both the rewarding effects of nicotine and negative affective states and somatic signs produced by withdrawal.

Our results revealed that nicotine produced rewarding effects in a pattern and dose range consistent with previous work in our laboratory and others (Fudala et al., 1985; Janhunen et al., 2005; Le Foll and Goldberg 2005; Torres et al., 2009). Importantly, nicotine produced a larger upward shift in CPP in STZ-versus vehicle-treated rats. This finding suggests that the rewarding effects of nicotine are enhanced in a rodent model of diabetes. Consistent with the latter suggestion, previous work in our laboratory demonstrated that STZ-treated rats display higher levels of nicotine intake in extended IVSA procedures as compared to vehicle-treated controls (O'Dell et al., 2014). Also, previous studies revealed that rats that were fed a HFD regimen and were insulin-resistant displayed CPP at a dose of nicotine that did not produce this effect in rats that were not insulin-resistant (Richardson et al., 2014). Together, these results suggest that diabetes enhances the rewarding effects of nicotine.

Our results revealed that nicotine withdrawal produced aversive effects in a dose range that is consistent with previous results from our laboratory and others (O'Dell et al., 2007; Shram et al., 2008). Importantly, mecamylamine produced a larger downward shift in CPA in STZ-versus vehicle-treated rats. Also, the somatic signs of withdrawal were greater in STZ-versus vehicle-treated rats. The latter effect was observed only in STZ-treated rats that were exposed to nicotine. Our EPM results revealed that nicotine withdrawal produced anxiety-like behavior that was greater in STZ-versus vehicle-treated rats. These results suggest that diabetes enhances the negative affective states and physical signs produced by nicotine withdrawal.

Taken together, our findings suggest that both the rewarding effects of nicotine and the aversive effects of withdrawal are enhanced in a rodent model of diabetes. With regard to a potential mechanism, we recently suggested that enhanced tobacco use vulnerability in persons with diabetes is likely mediated via a suppression of dopamine signaling in the mesolimbic pathway (O'Dell and Nazarian, 2016). Although our physiology is motivationally programmed to experience pleasurable stimuli, recent theories suggest that deficits in dopamine systems may weaken inhibitory control of excessive pleasure seeking (George et al., 2011). Thus, compulsive behaviors are believed to overcompensate for a

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reward deficiency syndrome that is rooted in suppressed dopaminergic functioning (Blum et al., 2001, 2008; Fineberg et al., 2010). We suggest that diabetes is another condition by which dopamine systems are suppressed, and this reward deficiency syndrome leads to enhanced susceptibility to compulsive tobacco use to facilitate dopamine transmission. Indeed, previous work in our laboratory has shown that STZ-treated rats display lower baseline dopamine levels as well as a reduction in ability of nicotine to increase nucleus accumbens (NAcc) dopamine levels (O'Dell et al., 2014). Thus, it is possible that individuals with dopaminergic deficits self-medicate with substances that activate dopamine, such as nicotine in tobacco products. With regard to the underlying mechanisms of withdrawal, dopamine levels are decreased in the NAcc of healthy rats experiencing precipitated nicotine withdrawal (Balfour, 2002; Natividad et al., 2010; Zhang et al., 2012). One might postulate that suppressed dopamine systems in STZ-treated rats may contribute to a larger decrease in NAcc dopamine levels during nicotine withdrawal.

There are several clinical implications from the present study. First, our results suggest that persons with metabolic disorders, such as diabetes experience stronger rewarding effects of nicotine and heightened sensitivity to nicotine withdrawal during smoking abstinence. Thus, both of these factors may promote tobacco use in persons with diabetes. Clinical reports have shown individuals with diabetes display reduced cessation rates and readiness to quit smoking (Fan et al., 2013; Solberg et al., 2004) as well as higher levels of negative affect, depression, and stress compared to non-diabetic smokers (Haire-Joshu et al., 1994; Spangler et al., 2001). Thus, intense aversive states could promote tobacco use during the maintenance and abstinence phases of tobacco dependence in persons with diabetes. Lastly, persons with diabetes may display dopamine deficits that are self-medicated with substances that increase dopamine, such as nicotine in tobacco products. As a result, treatment strategies that normalize dopamine transmission may be more effective for smoking cessation in this population. Future studies are needed to examine these hypotheses and to elucidate the underlying mechanisms by which diabetes promotes nicotine reward and withdrawal. Lastly, another interpretation of our behavioral findings is that diabetes may exaggerate the pharmacologic effects of nicotine, and future studies are also needed to examine whether diabetes enhances the pharmacological effects of drugs of abuse. This work in rodent models will follow in the footsteps of Dr. Athina Markou, who contributed to a deeper understanding of the mechanisms that modulate nicotine dependence during her prolific career.

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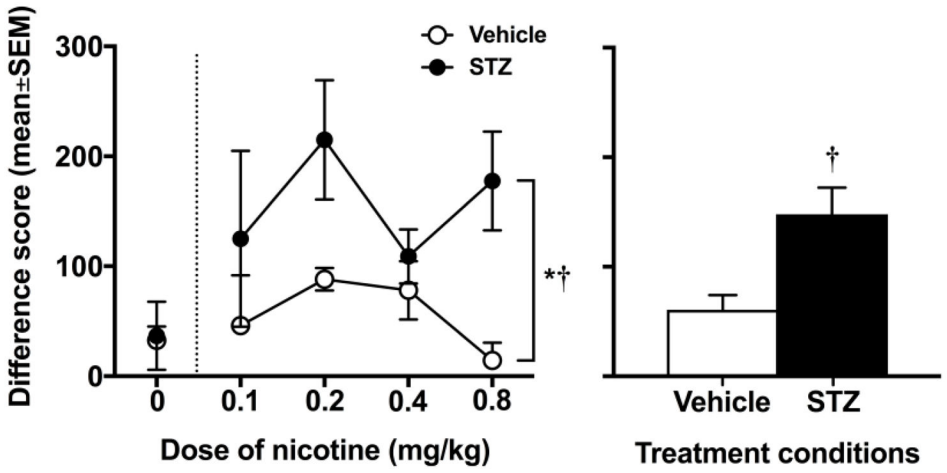

Figure 1.

These data depict difference scores (mean±SEM) in vehicle- and STZ-treated rats at individual doses (left panel) or collapsed across all doses (right panel) of nicotine. Difference scores reflect time spent in the initially non-preferred compartment after conditioning minus before conditioning, such that values above 0 represent a positive shift in preference. The asterisk (*) denotes a significant main effect of dose, and the daggers (†) denote a main effect of state ($p < 0.05$).

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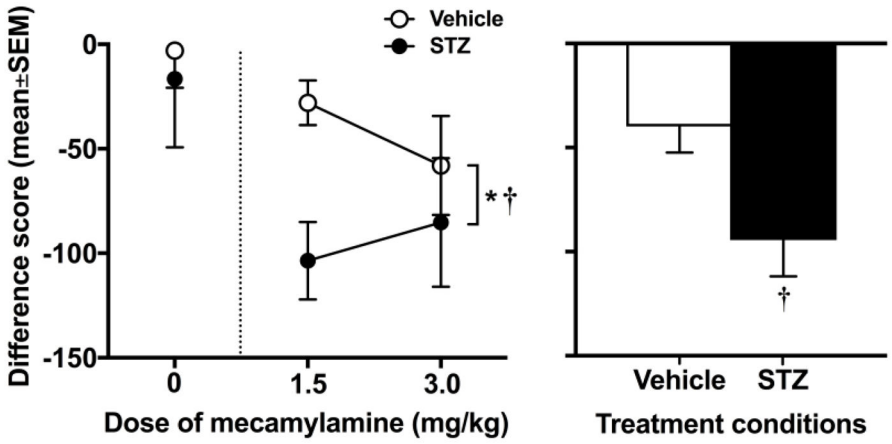

Figure 2.

These data depict difference scores (mean±SEM) in vehicle- and STZ-treated rats at individual doses (left panel) or collapsed across all doses (right panel) of mecamylamine. Difference scores reflect time spent in the initially preferred compartment after conditioning minus before conditioning, such that values below 0 represent a negative shift in preference. The asterisk (*) denotes a significant main effect of dose, and the daggers (†) denote a main effect of state ($p < 0.05$).

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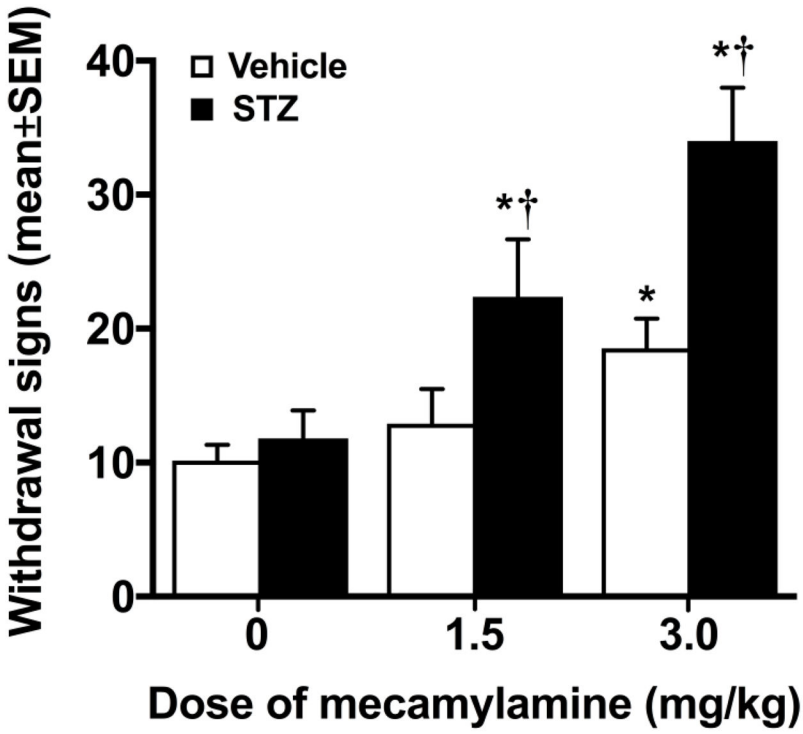

Figure 3.

These data depict total somatic signs of withdrawal (mean±SEM) in vehicleand STZ-treated rats on the last day of mecamylamine administration during conditioning. The asterisks (*) denote a significant difference from saline controls, and the daggers (†) denote a difference from vehicle-treated controls ($p < 0.05$).

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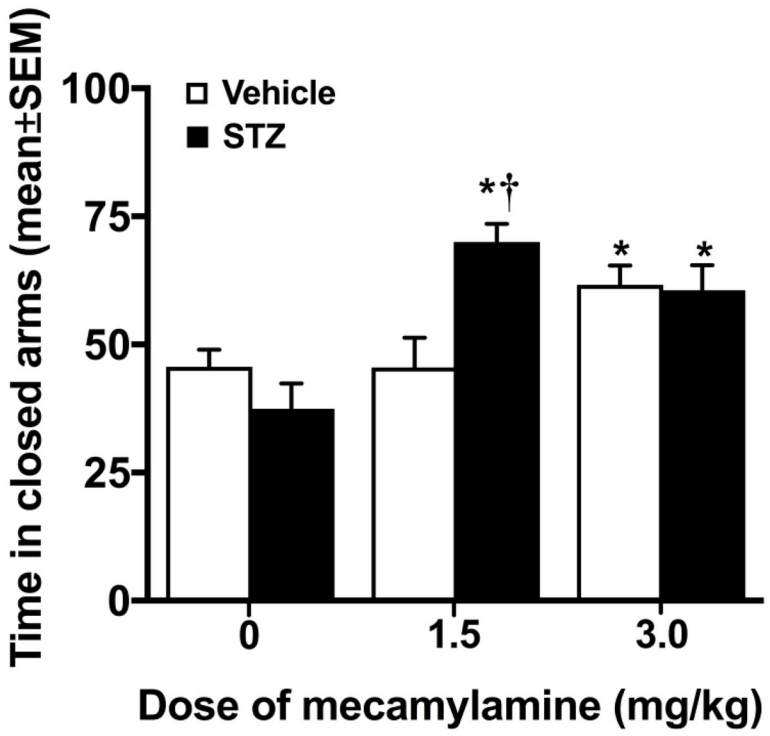

Figure 4.

These data depict percent time spent in the closed arms of the EPM (mean±SEM) in vehicle- and STZ-treated rats. The asterisks (*) denote a significant difference from saline controls, and the dagger (†) denotes a difference from their respective vehicle-treated controls ($p < 0.05$).

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Table 1

Plasma glucose levels (mg/dL)

	Prior to testing		Following testing	
Study 1: Nicotine doses	**Vehicle**	**STZ**	**Vehicle**	**STZ**
0.0 mg/kg	150.1 ± 9.1	470.6 ± 55.9*	152.0 ± 9.3	459.8 ± 28.0*
0.1 mg/kg	134.4 ± 5.1	520.5 ± 39.6*	118.3 ± 3.4	466.1 ± 39.2*
0.2 mg/kg	151.8 ± 14.2	488.0 ± 42.4*	144.9 ± 12.0	492.2 ± 35.2*
0.4 mg/kg	150.5 ± 5.5	516.6 ± 50.0*	126.6± 6.1	476.6 ± 14.0*
0.8 mg/kg	135.1 ± 6.6	414.4 ± 73.0*	124.8 ± 7.2	494.0 ± 27.5*
Study 2: Mecamylamine doses				
0.0 mg/kg	143.6 ± 3.3	489.5 ± 51.3*	137.5 ± 5.5	468.3 ± 17.8*
1.5 mg/kg	153.8 ± 6.2	561.5 ± 42.3*	156.5 ± 6.2	444.1 ± 24.8*
3.0 mg/kg	141.1 ± 5.2	374.4 ± 54.4*	151.0 ± 7.3	334.4 ± 29.8*
Study 3: Mecamylamine doses				
0.0 mg/kg	139.6 ± 4.6	394.7 ± 50.5*	134.8 ± 4.7	469.0 ± 38.1*
1.5 mg/kg	130.6 ± 3.7	542.2 ± 51.9*	125.3 ± 5.0	429.9 ± 16.3*
3.0 mg/kg	173.6 ± 26.7	522.9 ± 45.7*	146.8 ± 6.9	525.1 ± 39.8*

The asterisks (*) denote a significant difference between vehicle- and STZ-treated rats ($p \leq 0.01$).