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Self-administered nicotine increases fat metabolism and suppresses weight gain in male rats

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Abstract

Rationale—The ability of nicotine to suppress body weight is cited as a factor impacting smoking initiation and the failure to quit. Self-administered nicotine in male rats suppresses weight independent of food intake, suggesting that nicotine increases energy expenditure.

Objective—The current experiment evaluated the impact of self-administered nicotine on metabolism in rats using indirect calorimetry and body composition analysis.

Methods—Adult male rats with ad libitum access to powdered standard rodent chow self-administered intravenous infusions of nicotine (60 μg/kg/infusion or saline control) in daily 1-h sessions in the last hour of the light cycle. Indirect calorimetry measured respiratory exchange ratio (RER), energy expenditure, motor activity, and food and water consumption for 22.5 h between select self-administration sessions.

Results—Self-administered nicotine suppressed weight gain and reduced the percent of body fat without altering the percent of lean mass, as measured by Echo MRI. Nicotine reduced RER, indicating increased fat utilization; this effect was observed prior to weight suppression. Moreover, nicotine intake did not affect motor activity or energy expenditure. Daily food intake was not altered by nicotine self-administration; however, a trend in suppression of meal size, a transient suppression of water intake, and an increase in meal frequency was observed.

Conclusion—These data provide evidence that self-administered nicotine suppresses body weight via increased fat metabolism, independent of significant changes in feeding, activity, or energy expenditure.

Keywords

Indirect calorimetry; Energy expenditure; Respiratory exchange ratio; Oxymax

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Conflict of interest The authors declare that have no conflict of interest.

Introduction

Cigarette smoking is the largest cause of preventable death worldwide (Centers for Disease and Prevention 2013; World Health Organization Study Group on Tobacco Product 2015). Smokers weigh less than non-smokers and former smokers (Audrain-McGovern and Benowitz 2011). Many smokers, and more recently, electronic cigarette users, cite weight loss as a reason for smoking, and the fear of weight gain as a reason for relapse or the inability to quit (Morean and Wedel 2017; Pomerleau et al. 2001; Rosenthal et al. 2013; Veldheer et al. 2014). Although the weight-suppressive effects of smoking are clear, the mechanisms underlying this phenomenon are relatively poorly understood.

The weight-suppressive effects of cigarette smoke are often attributed to reductions in food intake, despite evidence that smokers and non-smokers have equal daily caloric intake (Perkins et al. 1990, 1992). Results of the impact of smoking on energy expenditure and metabolism, in humans, are mixed (Perkins 1992; Perkins et al. 1990, 1996). Poor cardiovascular or respiratory health in smokers may impact measurements of basal metabolism, which rely on respiration. Thus, intravenous self-administration animal models may be useful in the study of the impact of smoking on body weight and energy expenditure, where the pharmacological effects of drugs can be studied without the confound of the health impact of smoke inhalation.

Nicotine, the primary psychoactive constituent in cigarettes, suppresses weight gain and is putatively responsible for the weight-suppressive effects of smoking (Perkins 1992; Rupprecht et al. 2016; Zoli and Picciotto 2012). The impact of nicotine on energy balance has been studied extensively in rodents, typically using experimenter, non-contingent administration. Results of studies using experimenter-administered nicotine have shown reduced food intake, increased physical activity, increased thermogenesis, and increased basal metabolism (Bellinger et al. 2010; de Morentin et al. 2012; Zoli and Picciotto 2012). Typically, doses of non-contingent nicotine delivered to rodents to test parameters related to energy balance are larger than an animal would self-administer (Donny et al. 2000), and experimenter- and self-administered nicotine differentially impact blood pressure and heart rate, which contribute to energy balance (Donny et al. 2011). How self-administered nicotine suppresses body weight has, until recently, been largely ignored.

We have recently demonstrated that self-administered nicotine in male rats during 1-h daily sessions results in suppression of body weight independent of food intake (Rupprecht et al. 2016). This suggests that the impact of nicotine on body weight suppression results primarily from increased energy expenditure. The goal of these experiments was to measure whole-body energy expenditure following 1-h nicotine self-administration sessions in male rats using indirect calorimetry. Understanding the effect of self-administered nicotine on energy balance and weight gain may allow for better weight-related health outcomes in smokers attempting to quit and, potentially, for the development of pharmacotherapies for the treatment of obesity.

Materials and methods

Subjects

Male Sprague-Dawley rats (n = 16) (Envigo, Livermore, CA) weighing between 275 and 300 g upon arrival were housed in a temperature (20–22° C) and humidity (45–55%)-controlled facility with artificial lighting (12-h/12-h reverse light-dark cycle, lights off at 10:00AM). Rats were pair-housed in tub cages with a plastic divider separating the rats with ad libitum access to powdered Purina Rat chow 5001 and water, unless noted otherwise. All animal procedures met the guidelines of the National Institutes of Health and were approved by The Scripps Research Institute Institutional Animal Care and Use Committee.

Drugs

Nicotine hydrogen tartrate salt (MP Biomedicals, Solon, OH) was dissolved in 0.9% saline. Doses are expressed as free-base. Methohexital (Sigma, St. Louis, MO) was used at the dose 5 mg/kg to test catheter patency. All self-administered solutions were passed through a 0.22-μm filter to ensure sterility.

Intravenous catheterization—After at least 5 days of habituation to the facility, rats were anesthetized with isoflurane (2–3% in 100% O_2) and implanted with catheters into the right jugular vein, as described previously (Donny et al. 1995). All necessary actions were taken to minimize suffering of the animals. Rats were allowed to recover for a minimum of 5 days before the beginning of the self-administration procedures. Following surgery, catheters were flushed with 0.1 ml sterile saline containing heparin (30 U/ml), gentamicin (1 mg), and streptokinase (9333 U/ml). Thereafter, catheters were flushed with 0.1 ml heparinized saline (10 U/ml) and heparinized saline (30 U/ml) containing gentamicin (1 mg) prior to and following the self-administration sessions, respectively.

Self-administration—Self-administration sessions were conducted in standard sound-attenuating ventilated operant conditioning chambers (Med Associates, St. Albans, VT, USA) equipped with a houselight and two retractable levers located in the front panel. An infusion pump located outside of each chamber delivered intravenous infusions during self-administration sessions through tubing connected to each rat's catheter. The tubing was protected in a metal encasing and allowed for relatively unrestricted movement. One lever was available for the duration of the 1-h self-administration session. A single response on the lever resulted in one infusion of 0.1 ml of nicotine or saline control. Although fixed ratio (FR)-1 is not optimal for demonstrating self-administration behavior, the low effort schedule minimized effort required and behavioral differences between saline and nicotine groups. Infusions were accompanied by the illumination of a white stimulus light above the lever for 1 s, followed by a 30-s timeout period during which the white houselight was extinguished. This is a modified visual stimulus presentation, which is expected to be mildly reinforcing (Caggiula et al. 2009; Rupprecht et al. 2015). No infusions were delivered during the 30-s timeout, but responses on the active lever were recorded. Self-administration sessions occurred during the last hour of the light cycle (9:00AM) so that calorimetry and feeding measurements occurred at the onset of the dark cycle, when feeding is typically initiated in rats. Intravenous infusions were delivered in approximately 1 s (0.1 ml/kg/infusion).

Following experiments, the patency of the intravenous catheters was tested by IV injections of methohexital (5 mg/kg). Patency was confirmed if physical signs of ataxia were displayed within 5 s of intravenous injections. No subjects were lost to failed catheter patency.

Indirect calorimetry: Oxymax comprehensive laboratory animal monitoring system—Prior to surgery, body composition was analyzed by Echo MRI-900 (Houston, TX) to measure lean and fat mass. Rats were then implanted with intravenous catheters and assigned to saline ($n = 8$) or nicotine (60 μg/kg/infusion, $n = 8$) groups, matched for body weight. This dose of self-administered nicotine has been previously shown to suppress weight gain in 1-h daily sessions (Rupprecht et al. 2016, 2017). Rats were allowed to respond for drug infusion under a 1-h fixed ratio (FR-1) schedule of reinforcement for 14 consecutive days. Following sessions 1, 2, 7, 8, 13, and 14 of operant behavior, rats were placed in comprehensive laboratory animal monitoring system (CLAMS) units (Columbus Instruments, Columbus, OH) for open-circuit indirect calorimetry for 22.5 h (beginning at dark onset) and were removed for the next self-administration session. Each clear chamber (32 × 20 × 19 cm) was equipped with a water sipper, chow tray connected to a balance, plastic-mesh floor, and 24 photobeams (2.5 cm apart, 9 and 14 cm above the floor). Thus, food intake, drinking, and locomotor activity were measured concurrently during indirect calorimetry sessions (Frihauf et al. 2016). Chamber exhaust was sampled every 10 min for 50 s through O_2 and CO_2 sensors, from which oxygen consumption $\left(\dot{V}o_2\right)$ and carbon dioxide production $\left(\dot{V}co_2\right)$ were estimated. Sensors were pre-calibrated with a mixture of known concentrations of O_2, CO_2, and N_2 (Praxair, Danbury, CT). Respiratory exchange ratio (RER) was calculated as the ratio of carbon dioxide production (VCO_2) to oxygen consumption (VO_2). Typical physiological range for RER is considered between 0.7 and 1.0; a lower value indicates fat metabolism and a higher value indicates carbohydrate metabolism. Energy expenditure (heat formation [(3.815 + 1.232 × RER) × VO2 (in liters)]) was corrected for estimated metabolic mass by analysis of covariance (ANCOVA), co-varying for lean mass (Arch et al. 2006; Zorrilla and Conti 2014).

Rats were habituated to the CLAMS chambers for 22.5 h, immediately before the first self-administration session. Food and water were freely available at all times, except during the 1-h self-administration session. Eight CLAMS units were available, and so the experiment was conducted as two cohorts of 8 ($n = 4$ of each drug treatment within each cohort) staggered by 5 days. After removal from the CLAMS units on the final day of experimentation (Day 14), rats were euthanized with CO_2, catheter pedestals were removed, and a final Echo MRI body composition analysis was conducted.

Meal pattern analyses were performed following the end of the study. An individual meal was defined as at least 0.25 g of food consumed, with at least 10 min between meals (Mietlicki-Baase et al. 2013).

Statistics—Data are expressed as means ± SEM. All statistical analyses were performed using SPSS. Comparisons between drug group and session (body weight and self-administration session) or hour of the CLAMS session were analyzed by mixed-design and repeated measures ANOVA tests to account for the within-subjects design (time and session)

of the experiments while testing for between-subject effects of nicotine dose groups. Planned post-hoc comparisons between drug groups were assessed at each day for body weight data or each light cycle phase for CLAMS parameters using repeated measures and one-way ANOVA. Data are reported for the second day of each CLAMS exposure (Days 2, 8, and 14; i.e., treating the preceding day as an acclimation day), so that the potential impact of the stress of changing housing conditions on energy expenditure data was reduced. The α-level for all tests was set at 0.05.

Results

Body weight and self-administration

Self-administered nicotine suppressed body weight gain (Fig. 1a). The ANOVA showed a significant effect of time ($p < 0.001$), group ($p = 0.002$), and time × group interaction ($p = 0.04$). Post-hoc comparisons using one-way ANOVA revealed statistical significance between groups beginning on Day 8 of self-administration (Fig. 1a). Absolute body weights at the end of the experiment were saline 344.4 ± 6.5 g; nicotine 325.7 ± 8.5 g. Rats received an Echo MRI prior to jugular catheter surgery and following the final day in the CLAMS units. Over that time period, nicotine significantly reduced fat mass gain ($p = 0.003$) with a non-significant trend toward reduction in total lean mass (Fig. 1b). Following the final session in the CLAMS units, there was a significant reduction in the percentage of fat mass in the nicotine group ($p = 0.005$; Fig. 1c) with no difference between groups in the percentage of lean mass ($p = 0.967$; Fig. 1d). There were no differences in free water ($p = 0.853$) or total water ($p = 0.153$) weight after the final day of CLAMS, as measured by Echo MRI (data not depicted). There were no significant differences in infusions taken between nicotine and saline groups ($p = 0.08$). Average daily nicotine intake was 0.27 ± 0.03 mg/kg/day.

Respiratory exchange ratio

Following Day 2 of self-administration, there was a significant effect of time ($p < 0.001$) and group ($p = 0.005$) on RER, but no time × group interaction (Fig. 2a). Planned 2-way ANOVA comparisons between drug groups in each phase of the light cycle revealed a significant effect of time ($p < 0.003$), group ($p < 0.038$), but no interaction during the dark and light cycles on Day 2. Following Day 8, there was a significant effect of time ($p < 0.001$), a non-significant trend for a group effect over the 22-h session ($p = 0.057$), and no time × group interaction (Fig. 2b). There was a significant effect of time ($p = 0.018$) but no effect of group or interaction during the dark cycle. During the light cycle, there was a significant effect of time ($p = 0.002$) and group ($p = 0.047$). Due to an equipment error, inaccurate measurements for RER were recorded on the final 2 days for the first cohort. Therefore, data are presented for the final cohort only on Day 14. There were no differences in baseline parameters, nicotine self-administration, or CLAMS parameters between the first and second cohort. After the final day of self-administration, there was a significant effect of time ($p < 0.001$) and group ($p = 0.004$), and time × group interaction ($p = 0.001$) on RER (Fig. 2c). There was a significant effect of time ($p = 0.002$), but no effect of group or interaction during the dark cycle. During the light cycle, there was a significant effect of

time (p = 0.001) and group (p = 0.003), but no significant interaction. Overall, results showed that nicotine decreased RER compared to saline primarily during the light cycle.

Energy expenditure

There was no impact of group on energy expenditure on any day during either the light of dark phase of the light cycle (Fig. 3a–c). There was a significant effect of time (p's < 0.002) on every day tested, during both phases of the light cycle. There was no significant time × group interaction.

Locomotor activity

There was no significant impact of drug group on horizontal (x plane) total activity counts (p's > 0.164) or vertical (z plane; data not shown) total activity counts (p's > 0.075) on any day during either phase of the light cycle (Fig. 4a–c). There was a significant effect of time (p's < 0.005) on every day tested in both planes, during both phases of the light cycle.

Feeding and drinking behavior

Self-administered nicotine had no marked impact on total food intake (Fig. 5a, b). Repeated measured ANOVA revealed a significant effect of time (p's < 0.001), but no impact of group or interaction on food intake on all days, when expressed as absolute food intake (Fig. 5a) or when corrected for body weight (Fig. 5b). Planned comparisons between drug groups in each light cycle revealed that self-administered nicotine suppressed absolute food intake during the light cycle on Day 8 only (Fig. 5a).

Self-administered nicotine transiently suppressed water intake (Fig. 5c). On each day, there was a significant effect of time (p's < 0.002) on water intake. On Days 2 and 8, there was a significant effect of group (p's < 0.032), but no significant time × group interaction on any day. Planned post-hoc comparisons isolating each light phase individually revealed water intake was significantly suppressed over 22 h on days 2 and 8 (p's < 0.032) and during the light cycle on day 8 (p = 0.049).

There was no impact of drug on the latency to feed following placement into the CLAMS chambers on any day (p's > 0.362; Fig. 5d). There was no impact of self-administered nicotine on meal size over the course of 22 h (p's > 0.057; Fig. 5e), though meal size was significantly reduced by nicotine during the dark cycle on Day 14 (Table 1). The number of meals consumed over 22 h was significantly increased in the nicotine group (Fig. 5f) on Days 2 (p = 0.026) and 14 (p = 0.012), which was driven primarily during the light cycle (Table 1). Meals were briefer on Day 14 (p = 0.001; Fig. 5g). There was no impact of self-administered nicotine on the mean duration of intermeal intervals (Fig. 5h), with the exception of the light cycle on Day 2 (Table 1).

Discussion

Despite the weight-suppressive effects of smoking and nicotine being studied extensively, the mechanism by which nicotine acts to suppress body weight remains poorly understood. The results of the present study demonstrate that self-administered nicotine can shift RER to

reflect an increase in fat utilization, without changes in total food intake, activity, or energy expenditure. Changes in RER preceded nicotine-induced suppression of weight gain, which was observed as suppressed body fat gain, suggesting that increased fat utilization may cause weight reduction following nicotine self-administration. Very low nicotine intake (0.12 mg/kg on Day 2) was sufficient to suppress RER, consistent with recent data demonstrating that very low doses of self-administered nicotine suppress body weight gain independent of food intake (Rupprecht et al. 2016). It has been hypothesized that cumulative nicotine intake over many days may be directly correlated with body weight suppression (Rupprecht et al. 2016). This may explain the increased magnitude of reduction in RER on Day 14, when total cumulative nicotine intake was highest.

Nicotine reduced RER most substantially during the light phase, many hours after the nicotine self-administration session. As the half-life of nicotine in a rat is approximately 1 hour (Kyerematen et al. 1988), this suggests that increased fat utilization occurs following nicotine clearance. This result suggests that persistent activation of nicotinic acetylcholine receptors (nAChR) is not necessary for increased fat utilization following nicotine self-administration. There are several likely explanations for the present data. First, a nicotine metabolite with a longer half-life may be responsible for reductions in RER following self-administration. Cotinine is the primary metabolite of nicotine, with a half-life of approximately 8 hours in the rat (Kyerematen et al. 1988). Intravenous infusions of cotinine to overnight abstinent smokers fail to produce change in heart rate and other physiologic effects (Benowitz et al. 1983; Hatsukami et al. 1997). Further, chronic injection of cotinine to mice has been shown to increase weight gain (Riah et al. 1999). Therefore, it is unlikely that cotinine or its metabolites act to decrease RER and weight gain.

A second possibility is that nicotine may induce a more chronic increase in lipolysis, despite a lack of ongoing activation by nicotine itself (Andersson and Arner 2001; Friedman et al. 2012; Sztalryd et al. 1996). Evidence supports two parallel pathways by which nicotine could impact lipolysis. First, nicotine has been shown to cause the release of circulating catecholamines, which may in part contribute to increased lipolysis (Cryer et al. 1976). The release of glycerol in subcutaneous fat by intravenous infusion of low-dose nicotine to non-smokers is attenuated by local beta-adrenergic and nAChR blockade (Andersson and Arner 2001), indicating that nicotine results in lipolysis by catecholamine release and local action at adipose tissue. Complicating this idea is evidence demonstrating that while non-contingent intravenous infusion of nicotine causes adrenaline release in rats and humans, there is no impact of self-administered nicotine on adrenaline release in rats, when measured acutely (Donny et al. 2000). Therefore, it may be unlikely that increased catecholamine release explains the results in the present experiment. Current evidence suggests that reduced RER by nicotine, long after nicotine self-administration sessions concluded, is likely driven by lipolysis locally in adipose tissue. The α7 nAChR is expressed in white adipose tissue and the channel is opened by relatively low levels of nicotine, but is rapidly desensitized (Somm 2014). An agonist of α7 nAChR has been demonstrated to decrease weight gain in obese, but not normal weight mice (Marrero et al. 2010). Therefore, it is possible that nicotine acts to increase lipolysis via α7 nACh receptors, and the activation of intracellular processes following nAChR activation acts to increase fat utilization after nicotine clearance. Further, nicotine can activate brain PPARα via an α7-dependent mechanism (Jackson et al.

2017). PPARα in the periphery is known to promote liver uptake and beta oxidation of fatty acids and decrease RER. Nicotine has been shown to activate PPARδ expression in other peripheral tissues (Sun et al. 2009), and PPARδ similarly promotes beta oxidation in skeletal muscle. If nicotine does promote peripheral PPAR actions, or if brain PPARα regulates peripheral lipid metabolism likewise, this could further this explanation.

Alternatively, it is possible that nicotine interferes with glucose storage immediately following self-administration, during the dark phase in the current study. As such, there would be more reliance on fat, rather than glycogen, as an energy source during the light phase, when we detected differences in RER. There are some data demonstrating that nicotine results in insulin resistance (Eliasson et al. 1996; Liu et al. 2003; Wu et al. 2015), which would support this idea; although it has also been reported that nicotine increases insulin sensitivity (Xu et al. 2012). Another possibility is that RER is decreased by increased cholinergic tone caused by nAChR resensitization between self-administration sessions. Regardless of the mechanism, these data make clear that nicotine increases fat utilization after nicotine clearance.

In the current experiment, nicotine intake was low compared to previously published levels of self-administration at this dose over a similar time course. There are several parameters in the self-administration procedure that may explain these low levels of nicotine intake. First, rats were allowed to respond on a lever for infusion of nicotine without previous training for lever responding. Secondly, the 1-h/day sessions occurred in the final hour of the light cycle. Nicotine self-administration procedures typically occur well into the dark, active phase. Third, self-administration procedures typically use food restriction to increase levels of behavior (Rupprecht et al. 2015). In the current experiments, rats were fed ad libitum. The self-administration procedure used a compound visual stimulus, which is expected to be mildly reinforcing (Caggiula et al. 2002), which may explain the responding in the saline group. Furthermore, due to the low schedule of reinforcement and high nicotine dose used in the present experiment, enhancement of responding for the stimulus by nicotine may not be expected. The similar level of activity at the lever during self-administration between groups offers control of energy expenditure in the operant chamber, indicating that differential activity in the self-administration session likely does not contribute to differences in weight gain between groups. Nicotine self-administration in 1-h daily sessions allows for the study of the impact of nicotine on body weight regulation without the confound of the development of dependence and may better model the human condition, as smokers and non-smokers have similar daily caloric intake (Rupprecht et al. 2016).

Data from smokers on the impact of smoking and nicotine are varied. Administration of nicotine to abstinent smokers via nasal spray results in increased resting metabolic rate (Perkins et al. 1989). The current results differ from those seen in human smokers and demonstrate that expenditure shifts to fats as a fuel substrate precede nicotine-induced body weight changes. Smoking cigarettes can increase basal metabolic rate (Roth et al. 1944), although increases in energy expenditure without increases in basal metabolic rate have also been reported (Audrain et al. 1991; Perkins et al. 1986). Inhalation of smoke from very low nicotine content cigarettes can result in small increases in basal metabolic rate, indicating that the non-nicotine constituents in cigarettes or smoke inhalation can impact metabolism

(Perkins 1992; Perkins et al. 1989). However, data from rodent self-administration suggest that the combination of nicotine and non-nicotine constituents in cigarette smoke act to regulate body weight similarly to nicotine alone (Rupprecht et al. 2016), indicating that the impact of cigarette smoke on basal metabolism is likely due to behavioral action of inhalation and not additional psychoactive smoke chemicals.

There is a large body of work showing chronic experimenter-administered (Bellinger et al. 2010; Grebenstein et al. 2013; Wellman et al. 2005) and extended access to self-administered (Bunney et al. 2016; O'Dell et al. 2007; O'Dell et al. 2014) nicotine suppresses food intake, and some evidence that this occurs via reductions in meal size. One study demonstrated that chronic nicotine injections suppress food intake without lasting changes in respiratory exchange ratio or energy expenditure (Bellinger et al. 2010). Therefore, it is possible that in procedures that cause nicotine-induced suppression of food intake, RER shifts back toward carbohydrate utilization in defense of weight set point, and that these specific responses may be dependent upon route, dose, and contingency of administration. In the current data, self-administered nicotine significantly increased meal frequency with non-significant reductions in average meal size. Daily nicotine consumption in the current experiment was low, in contrast with previous work studying the impact of nicotine when self-administered over 23 h (Bunney et al. 2016; O'Dell et al. 2014). Therefore, high levels of nicotine intake regardless of administration route may be sufficient to suppress food intake. Nonetheless, the current data provide further evidence that when nicotine is self-administered in 1-h daily sessions, weight gain suppression occurs independent of changes in cumulative chow intake (Rupprecht et al. 2016), though the possibility exists that subtle changes in meal patterning, as detected on day 2 here, contribute to body weight regulation by nicotine.

Nicotine has been previously shown to suppress water intake (Clarke and Kumar 1984; Levin et al. 1987). Decreased fluid intake may contribute to rapid weight loss caused by nicotine consumption. However, the current data suggest that over time, tolerance to the hypodipsic effects of nicotine develop, suggesting that negative water balance likely does not contribute to continued weight loss by nicotine across many days. Further, there was no difference in water weight between groups at the end of the experiment, whereas there was a specific reduction in body fat gained. This is in contrast to existing data demonstrating that water intake suppression by nicotine is long lasting, though these effects resulted from high daily nicotine exposure (up to 10 mg/kg/day nicotine) (Clarke and Kumar 1984).

The results of the current experiment demonstrate that self-administered nicotine in male rats suppresses body weight, potentially via increased fat oxidation, without changes in activity, energy expenditure, or feeding behavior. Nicotine has been previously reported to increase thermogenesis and slow gastric emptying (de Morentin et al. 2012; Perkins et al. 1996; Scott et al. 1992; Seoane-Collazo et al. 2014). The design of the current experiments cannot rule out the possibility that other parameters not included in our experimental design may contribute to the effect of self-administered nicotine on energy balance. Nonetheless, results from this experiment demonstrate that increased relative utilization of fat as a fuel substrate may be key in nicotine-induced weight loss.

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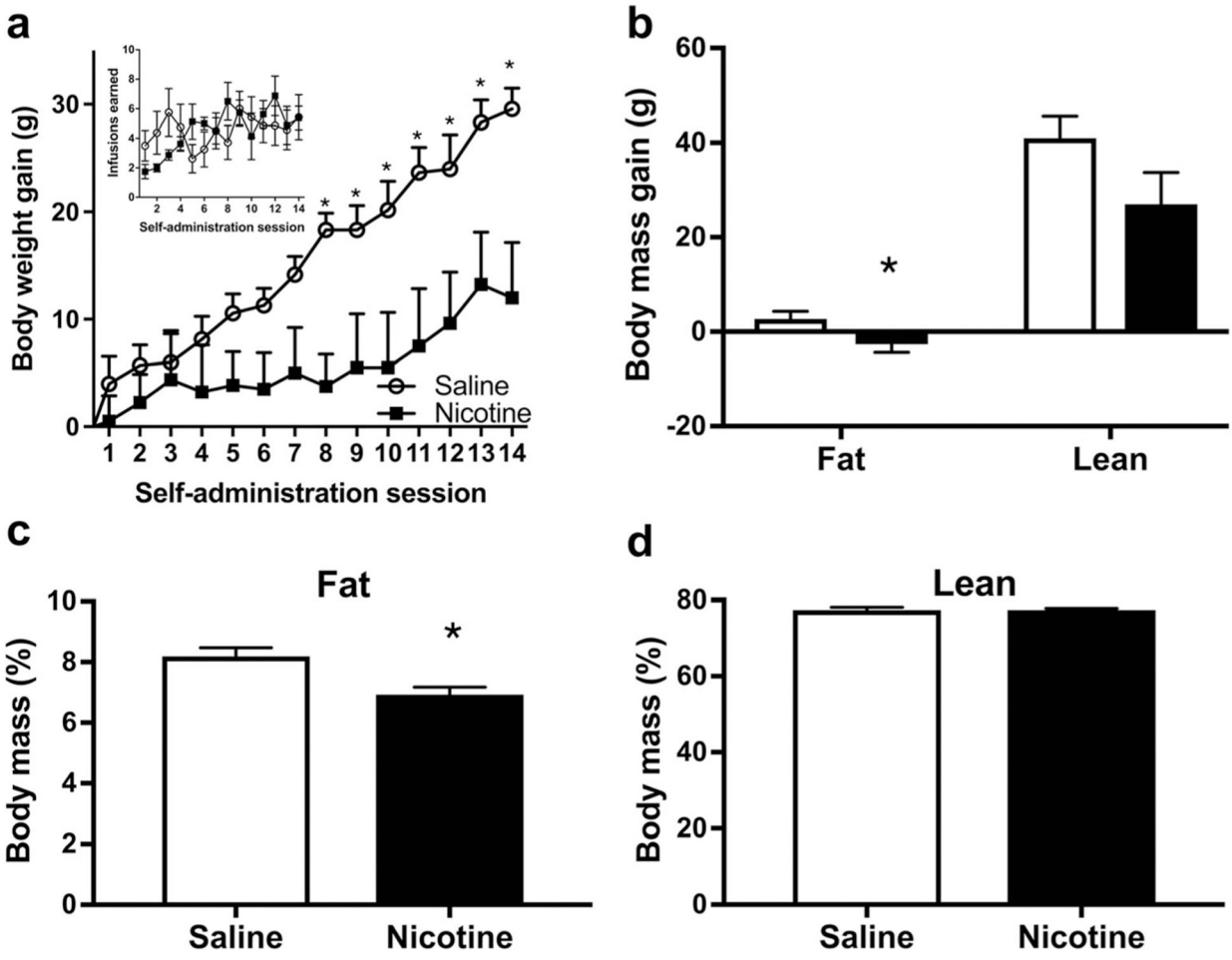

Fig. 1.

Self-administered nicotine significantly suppressed body weight gain (**a**), and fat mass, but not lean mass, gain (**b**). Nicotine reduced the percentage of fat mass (**c**) but not lean mass (**d**) compared to saline, over 14 days of self-administration. Infusions earned in 1-h daily sessions is graphed as an inset in panel **a**. The asterisk indicates $p < 0.05$ between drug groups

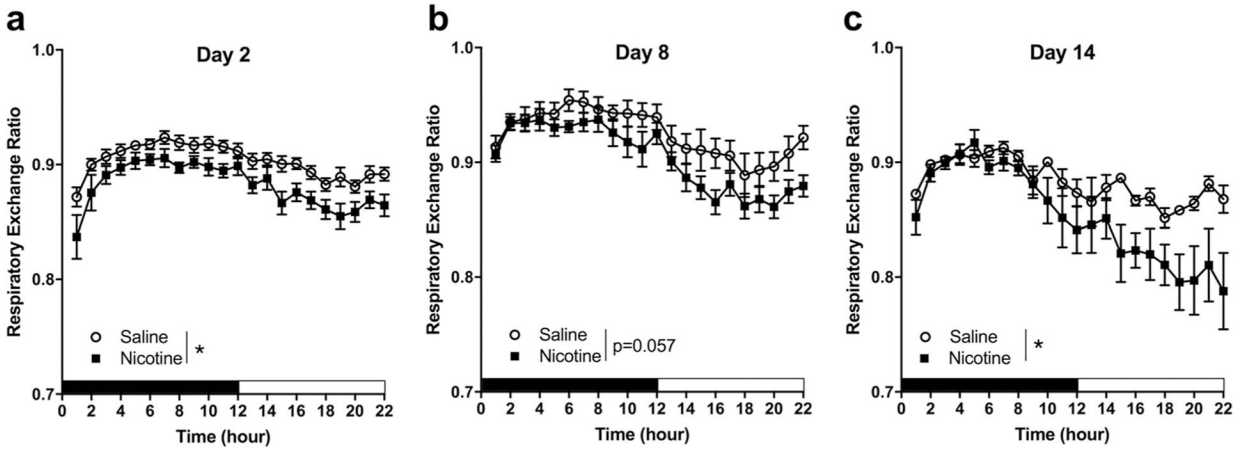

Fig. 2.

Self-administered nicotine reduced RER on Days 2 (**a**), 8 (**b**), and 14 (**c**). The dark bar indicates dark cycle, and the open bar indicates light cycle during each 22-h phase. Due to a technical error, $n = 8$ per group in (**a**) and (**b**), and $n = 4$ per group in (**c**). The asterisk indicates $p < 0.05$ between drug groups over 22 h

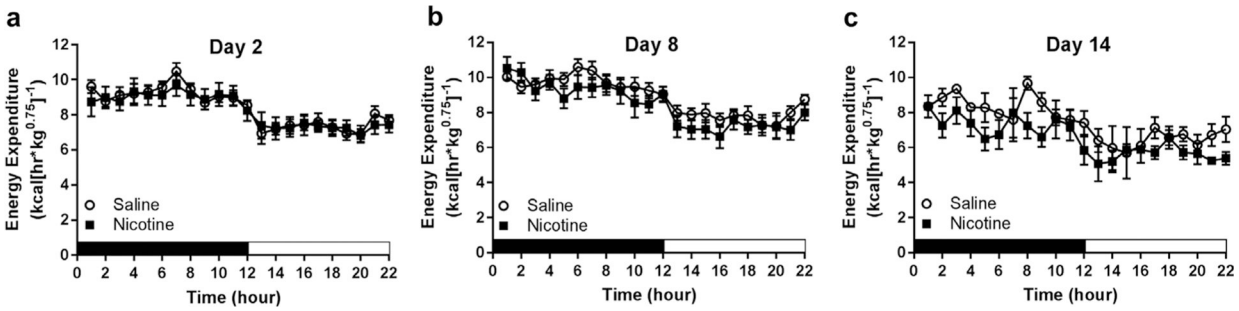

Fig. 3.

Self-administered nicotine did not affect energy expenditure (**a**–**c**). The dark bar indicates dark cycle, and the open bar indicates light cycle during each 22-h phase. Due to a technical error, $n = 8$ per group in (**a**) and (**b**), and $n = 4$ per group in (**c**)

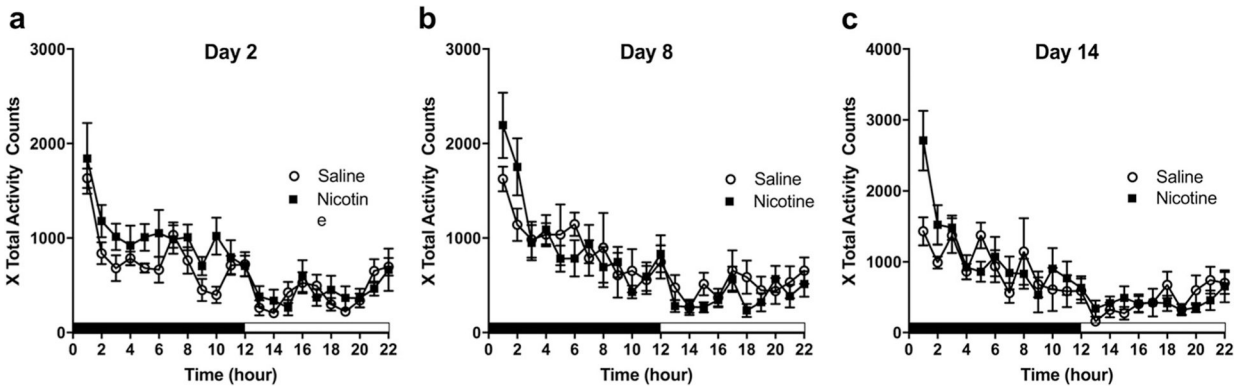

Fig. 4.

Self-administered nicotine did not alter the activity (**a**–**c**). The dark bar indicates dark cycle, and the open bar indicates light cycle during each 22-h phase

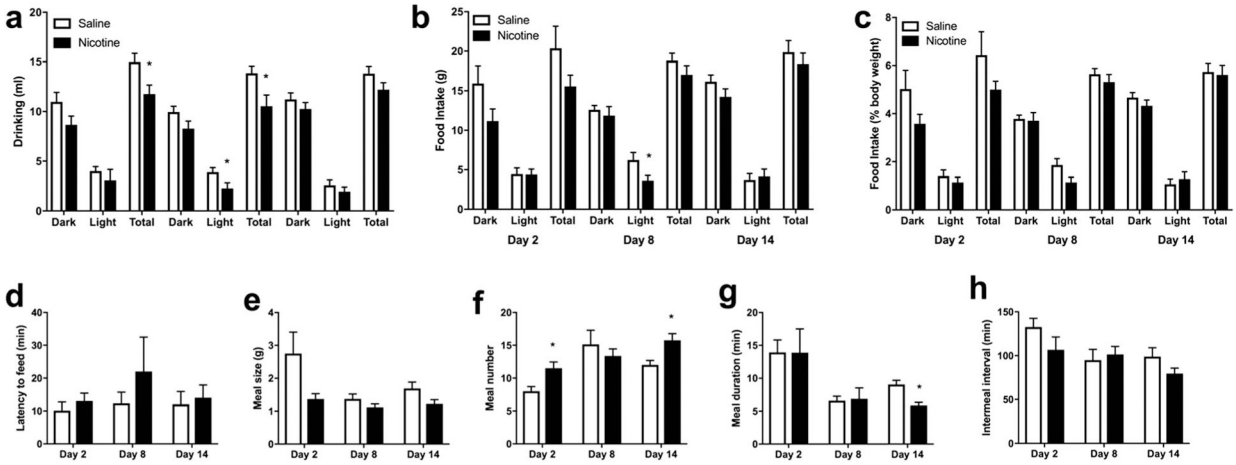

Fig. 5.

Self-administered nicotine at this dose did not significantly impact total food intake (**a**, **b**). Nicotine suppressed light cycle absolute food intake on Day 8 (Fig. 5a). Nicotine suppressed water intake on Days 2 and 8 (**c**). There was no impact of nicotine on latency to feed (**d**), meal size (**e**), meal duration (**g**), or intermeal interval (**h**); with the exception of decreased meal duration on Day 14. Self-administered nicotine significantly increased meal number on Days 2 and 14 (**f**). The asterisk indicates $p < 0.05$ between drug groups

Table 1

Meal pattern parameters during dark and light phase of the light cycles

	Day 2		Day 8		Day 14	
	Saline	**Nicotine**	**Saline**	**Nicotine**	**Saline**	**Nicotine**
Meal size (g)	2.9±0.8 2.2±0.4	1.4±0.2 1.1±0.2	1.4±0.2 1.3±0.2	1.1±0.1 1.1±0.1	1.7±0.2 1.3±0.2	1.2±0.1* 1.2±0.3
Meal number	6.0±0.7 2.2±0.2	7.7±0.9 3.7±0.5*	10.2±1.2 4.8±1.0	10.2±0.8 3.1±0.4	9.4±0.4 2.2±0.3	12.1±1.0* 3.6±0.3*
Meal duration (min)	33.7±18.3 16.0±9.2	9.93±1.1 20.1±9.5	6.83±0.5 6.21±1.3	11.6±2.9 6.41±2.0	9.10±0.8 8.33±1.2	6.41±0.6* 4.35±0.9*
Intermeal interval (min)	91.8±13.6 313.4±20.8	85.6±11.9 151.7±24.7*	62.1±4.9 170.7±38.3	68.1±6.4 235.5±50.3	60.1±6.6 273.7±53.5	54.1±5.2 164.5±14.7

The top line in each box is the average for the dark phase (highlighted in gray), and the bottom number is average for the light cycle

* $p < 0.05$ comparing saline and nicotine within each phase of the light cycle on that day

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