Published in final edited form as:

Psychopharmacology (Berl). 2016 December ; 233(23-24): 3953–3964. doi:10.1007/s00213-016-4426-3.

Characterizing the relationship between increases in the cost of nicotine and decreases in nicotine content in adult male rats: Implications for tobacco regulation

Tracy T. Smith¹, Laura E. Rupprecht², Alan F. Sved^{1,2,*}, and Eric C. Donny^{1,*}

¹Department of Psychology, University of Pittsburgh, 210 S. Bouquet Street, Pittsburgh, PA 15260

²Department of Neuroscience, University of Pittsburgh, A210 Langley Hall, Pittsburgh, PA 15260

Abstract

BACKGROUND—A large reduction in the nicotine content of cigarettes may benefit public health by reducing the rate and the prevalence of smoking. A behavioral economics framework suggests that a decrease in nicotine content may be considered an increase in the unit price of nicotine (unit price = reinforcer cost / reinforcer magnitude). Increasing the price of cigarettes (i.e., increasing reinforcer cost) would be considered an equivalent change in unit price to reducing nicotine content (i.e., reducing reinforcer magnitude).

OBJECTIVES—The goal of the present experiments was to characterize the relationship between increases in nicotine cost and decreases in nicotine dose.

MATERIALS AND METHODS—A rat self-administration model was used to assess this relationship across three experiments, with an emphasis on very low nicotine doses to model a potential nicotine reduction policy. Cost was manipulated via changes in the number of responses required to earn an infusion.

RESULTS—Results show that increases in the cost of nicotine and decreases in nicotine content were not equivalent manipulations. Nicotine consumption was more sensitive to nicotine dose than to nicotine cost. Nicotine consumption was also not equivalent across a variety of cost and dose combinations forming a single unit price.

CONCLUSIONS—Results of the present studies suggest that nicotine reduction is likely to have a large impact on nicotine exposure from cigarettes.

Keywords

Nicotine reduction; Behavioral economics; Unit Price; Nicotine; Tobacco Regulation; Self-Administration

Corresponding Author: Tracy T. Smith, Ph.D., Department of Psychology, University of Pittsburgh, 4120 Sennott Square, 210 S. Bouquet Street, Pittsburgh, Pennsylvania, 15260, Telephone: (412) 624-8525; tracysmith@pitt.edu.

*These authors contributed equally and serve as co-senior authors.

Portions of these data were presented at the annual meeting of the Society for Nicotine and Tobacco Research, Philadelphia PA, February 25-28, 2015. These experiments served as the basis for the first author's dissertation in partial fulfillment of her doctoral degree. In addition to Drs. Sved and Donny, Dr. Kenneth Perkins, Dr. Saul Shiffman, and Dr. Mary Torregrossa served on the dissertation committee and their input was greatly appreciated.

Introduction

In 2009, the Food and Drug Administration was given the authority to regulate the content of nicotine in cigarettes, and recent research suggests that a large reduction in nicotine content may result in lower rates of smoking, lower levels of nicotine dependence, and an increase in quit attempts (Donny et al. 2015). A behavioral economics framework may be useful for researchers and policy makers interested in nicotine reduction (Donny et al. 2012; Smith et al. 2014). Within the framework of behavioral economics, changes in the consumption of a reinforcer occur as a function of the unit price of that reinforcer, and unit price can be manipulated through changes in reinforcer cost and reinforcer magnitude (unit price = reinforcer cost / reinforcer magnitude). Because nicotine is the primary reinforcing constituent in cigarettes, a reduction in nicotine content may be considered a reduction in reinforcer magnitude and an increase in the unit price of cigarettes. Viewing nicotine reduction as an increase in unit price allows for the application of existing literature regarding how changes in unit price affect reinforcer consumption to be applied to nicotine reduction (Smith et al. 2014). Decreases in nicotine content may be functionally equivalent to an increase in the cost of cigarettes because both manipulations increase the unit price of nicotine. Understanding the relationship between increases in nicotine cost and decreases in nicotine content will have important implications for a potential nicotine reduction policy.

Characterizing the relationship between increasing cigarette cost and decreasing nicotine content could allow existing literature examining how escalating cost changes cigarette consumption to be leveraged to better understand the likely outcomes of nicotine reduction. For example, when cigarette taxes are increased, the decrease in cigarette consumption is proportionally less than the increase in price (i.e., it is inelastic) (Chaloupka et al. 2012). When nicotine consumption is inelastic, monetary expenditure increases when cigarette cost is increased. If the price of cigarettes were increased enough, the proportional change in consumption would presumably be more than the increase in price (i.e., elastic). The unit price model would suggest that changes in nicotine consumption as a function of small changes in nicotine content are also likely to be inelastic, meaning that small decreases in nicotine content would result in increases in smoking behavior, and a large decrease may be necessary to decrease smoking behavior. Furthermore, because cost and reinforcer magnitude both contribute to unit price, the threshold nicotine content for maintaining smoking behavior should depend on the cost of cigarettes. Finally, if sensitivity to nicotine content and sensitivity to nicotine cost are highly correlated, research on cigarette taxation could be used to make predictions about individual differences in response to nicotine reduction.

To date, no research has used a behavioral economics analysis to examine changes in nicotine consumption when the nicotine content within cigarettes is directly manipulated, although there is one report showing that a unit price model can characterize changes in nicotine consumption when nicotine *yield* is manipulated (DeGrandpre et al. 1992). Previous research has generally supported the assumption that increases in reinforcer cost and decreases in reinforcer magnitude are comparable manipulations of unit price (Bickel et al. 1990; Carroll et al. 1991; Collier et al. 1986; DeGrandpre et al. 1993; Foster and Hackenberg 2004; Hursh et al. 1988; Woolverton and English 1997), but other reports have

suggested the assumption has limitations (English et al. 1995; Nader et al. 1993; Sumpter et al. 2004; Woolverton and English 1997). Most relevant to the current research question, DeGrandpre et al. (1993) showed that the unit price model effectively characterized changes in cigarette consumption when cost was manipulated through changes in effort and reinforcer magnitude was manipulated through the number of cigarette puffs.

There is evidence to suggest that low reinforcer magnitudes—even those still high enough to maintain responding—may constitute an exception to the unit price model (i.e., the low-dose exception). Bickel et al. (1990) and DeGrandpre et al. (1993) applied the unit price model to data from many previously published studies using a variety of reinforcers and each found one example in which very low drug doses did not maintain consumption levels as high as would be predicted from the unit price model (Bickel et al. 1990; DeGrandpre et al. 1993). The possibility of a low-dose exception was also noted in one experimental report. Bickel et al. (1991) used the unit price model to characterize changes in cigarette puff consumption and observed that for one participant in particular, unit prices created using only one cigarette puff produced lower consumption than other combinations of the same unit price that utilized higher reinforcer magnitudes. A low-dose exception to the unit price model is especially important for the application of behavioral economics to a potential nicotine reduction policy because it suggests that a very low nicotine content cigarette, like those that would exist in a post-regulation marketplace, may produce nicotine intake levels even lower than would be predicted from a unit price approach.

The aim of these studies was to characterize the relationship between increases in the cost of nicotine and decreases in nicotine content. We chose to investigate this research question using a rodent self-administration paradigm, in which rats receive intravenous infusions of nicotine contingent on their own responding, because nicotine delivery and nicotine consumption can be precisely measured, whereas in human smokers nicotine delivery depends on how smokers use their cigarettes. Cost is manipulated using the number of responses that are required to earn an infusion of nicotine (i.e., Fixed Ratio, FR). Nicotine self-administration has been used successfully to characterize changes in consumption when nicotine dose is reduced (Grebstein et al. 2013; Grebstein et al. 2015). Our analyses focused on whether nicotine consumption was likely to change more, less, or similarly when unit price is manipulated through decreases in nicotine dose as when it is manipulated through increases in nicotine cost. A strict behavioral economics framework would suggest that the two manipulations should be equivalent, but the low-dose exception would predict that the relationship will fail to be maintained when very low doses are used.

Methods

Subjects

Male Sprague-Dawley rats (Harlan-Farms, IN) weighing between 200 and 225 g upon arrival were used as subjects (N=86). Rats are estimated to have been P49-P56 upon arrival (estimated from growth curves provided by Harlan-Farms (ENVIGO 2008)). Three experiments were conducted, and Experiments 1 and 3 each involved two separate cohorts that completed the experiment at separate times. Results did not differ as a function of cohort. Rats were housed individually in tub cages on a ventilated rack with an automatic

watering system. Temperature in the colony room was kept between 20 and 23 degrees Celsius. Rats were kept on a reverse light-dark 12:12 hour schedule (lights on 7:00PM), and all self-administration sessions occurred during the dark phase. Rats received ad libitum chow for the first seven days while habituating to individual home cages.

Procedures

Surgery—At least eight days after arrival, rats were implanted with jugular catheters. Procedures for jugular catheterization were as previously described (Smith et al. 2013). Rats were allowed at least five days of recovery following surgery. For the first five days following surgery, each rat had its cannula flushed once daily with 1 ml of a sterile saline solution containing heparin (3 U), an antibiotic, and streptokinase (833.3 U) to maintain catheter patency and prevent infection. The antibiotic changed depending on drug availability was either timentin (6.67 mg), cefazolin (10 mg), or gentamicin (1 mg). After this initial post-surgery time period, the flushing solution contained only the heparin and the antibiotic.

General Self-Administration Procedures—Standard self-administration experimental chambers (ENV-008 CT; Med-Associates) were configured as previously described (Smith et al. 2013), and included two nose poke holes below two stimulus lights on one wall of the chamber. Rats were given the opportunity to respond via nosepokes for i.v. infusions. The side of the active nosepoke hole (left vs. right) was counterbalanced across rats. Because reinforcers are frequently accompanied by environmental stimuli which may come to act as conditioned stimuli or conditioned reinforcers, an initially neutral cue light stimulus was paired with each nicotine infusion. Active pokes resulted in a simultaneous onset of an intravenous infusion, a 3-s cue light presentation and time-out period according to the reinforcement schedule in effect. Active nosepokes during time out and inactive nosepokes were recorded, but had no consequence. Sessions lasted at least two hours and were conducted seven days per week. Rats received 20 g of chow per day delivered in the home cage after each session. Each time out extended the length of the session by 3 s; this procedure ensures that each rat had two hours of “time-in” to respond, regardless of the number of infusions earned. All rats began acquisition on an FR2 (two responses required to earn each infusion) using 60 µg/kg/infusion nicotine, and, with the exception of the first cohort in Experiment 1 (see below), the FR schedule required to earn an infusion gradually increased across sessions to reach a training condition (FR10, 60 µg/kg/infusion) prior to beginning the experiment. Acquisition procedures differed slightly between cohorts of rats and experiments (e.g., the number of responses required to earn an infusion (FR) was increased across sessions and the number of sessions at each FR varied between cohorts or experiments), but the unit price procedure was the same. No pre-training with a food reinforcer was used. Catheter patency was tested (5 mg/kg intravenous methohexital) at the end of each experiment, and at least once during each experiment, and data for each rat are included through the last unit-price combination followed by a passed patency test.

Nicotine hydrogen tartrate salt (Sigma, St. Louis, MO) was dissolved in 0.9% saline (doses expressed as free base). All solutions were sterilized by being passed through a 0.22 µm filter. In Experiment 1, nicotine was delivered using a 5-ml syringe in a volume of 0.1 ml/kg/

infusion in approximately 1 s. During Experiments 2 and 3 when low nicotine doses were used, rats sometimes earned enough infusions in a single session to empty the drug syringe. For these experiments, drug was delivered using a 10-ml syringe in a volume of 0.05 ml/kg/infusion in approximately 0.5 s. This change was made when it became necessary during the unit price procedure of Experiment 2.

Training Condition—In the first cohort of Experiment 1, rats began the experiment following an FR2 schedule of reinforcement in acquisition, and self-administration behavior was very low in the beginning of the experiment (first two unit-price combinations), likely as a result of large changes in FR requirement, which functioned as extinction when rats never made enough responses to experience the contingency. A training condition was established consisting of an FR10 for 60 µg/kg/infusion nicotine. A single session at the training condition was inserted between each unit-price combination to re-establish behavior that may have extinguished, and the first two combinations were repeated at the end of the Experiment (data are shown from these two replications only). Rats in all other studies reached this training condition before beginning the unit price procedure and experienced the training condition between each unit-price combination.

Experiment 1: Evaluating changes in consumption using above-threshold nicotine doses—The aim of Experiment 1 was to assess whether increases in FR (cost) and decreases in the dose of nicotine change behavior equivalently when doses are in the range expected to maintain behavior. Rats experienced six unit prices, and each rat experienced each unit price twice, creating 12 total combinations (Table 1). Six combinations all used the same dose of nicotine, but the number of responses required to earn an infusion (FR, cost) increased across unit prices (i.e., ratio escalation). The other six combinations all required the same number of responses to earn an infusion, but the dose of nicotine decreased across unit prices (i.e., dose reduction). Nicotine doses in this experiment were chosen to be in a range expected to maintain self-administration behavior (Smith et al. 2013). Rats experienced four sessions at each unit-price combination, and each rat experienced the combinations in a random order.

Experiment 2: Evaluating changes in consumption using below-threshold nicotine doses—The aim of Experiment 2 was to extend the results of Experiment 1 using a second dose-range that included doses below the hypothesized threshold for maintaining self-administration behavior (Smith et al. 2013). Previous research has suggested that very low doses may be an exception to the assumption that increases in cost and decreases in reinforcer magnitude are equivalent manipulations (Bickel et al. 1991; DeGrandpre et al. 1993; Hursh and Winger 1995). If nicotine dose is reduced below this threshold, consumption may drop drastically even in instances where a unit price approach predicts that consumption would be maintained (Bickel et al. 1991). If a nicotine reduction policy is enacted, the reduced nicotine content will be one that is hypothesized to be below the threshold for maintaining smoking behavior (or maintaining nicotine dependence), so the relationship between nicotine cost and very low nicotine doses is particularly important to explore.

The unit price manipulation was similar to Experiment 1, except that doses 10 times lower than those in Experiment 1 were used for the dose-reduction combinations, and rats responded on an FR1 for these combinations (Table 1). Nicotine doses in this experiment were chosen such that the majority of doses are not expected to maintain self-administration behavior ($<7.5 \mu\text{g/kg/infusion}$) (Smith et al. 2013).

Experiment 3: Evaluating changes in consumption across a single unit price

—The aim of Experiment 3 was to assess whether consumption was equivalent at a single unit price regardless of the FR/dose combination used to create that unit price. A unit price of 0.533 was chosen because it was low enough to maintain behavior in Experiment 1 and high enough to create combinations that used low FRs and low doses. The unit price procedure was similar to the one used in Experiments 1 and 2, except that the combinations used create a single unit price (Table 2). One additional combination involved rats responding for saline plus the cue; this was added to test whether nicotine contributed to responding at the lowest FR/dose combination or responding was entirely cue maintained. Due to a technical error, rats only experienced three sessions on their seventh unit-price combination, but because rats experience combinations in a random order, this impacts only a small number of data points at each combination.

Data Analysis—The primary outcome was average consumption over the last two sessions at each unit-price combination ($\mu\text{g/kg}$). For Experiments 1 and 2, rats were excluded if they failed to earn an infusion at any ratio-escalation combinations (Experiment 1: 4 of 32 rats, Experiment 2: 1 of 32 rats). For Experiment 3, rats were excluded if they failed to earn at least two infusions at baseline (average of last two sessions before unit price procedure; 5 of 23 rats). In both situations, a test of cost sensitivity would be inappropriate. In Experiment 3 when rats only experienced three sessions at the seventh combination, the second and third sessions were averaged for data analysis. These data points are consistent with remaining data points at each combination. In Experiments 1 and 2, analyses focused on comparing: 1) consumption for the two combinations at each unit price, 2) how the two manipulations change consumption across the range of unit prices that maintain consumption, and 3) how the two manipulations change consumption after reaching unit prices that do not maintain consumption. For comparing consumption at each unit price, omnibus repeated-measures ANOVAs were followed by paired-samples t-tests. For follow-up tests, a Bonferroni correction was used to control type-1 error ($\alpha=0.008$). Effect sizes are included for all comparisons (Partial η^2 (ANOVA), Cohen's d (t-tests)). Because of the theoretical importance of hypothesized equivalence, when no significant differences were found for consumption or for free parameters, Two One-Sided Tests of equivalence were used, with the margin of equivalence (δ) set at 25% of the overall mean. These analyses are included in the supplementary material. Twenty-five percent of the mean was chosen because it was smaller than the standard deviation in all cases and seemed to best characterize the data, but a different margin of equivalence would necessarily change which differences meet significance. Type 1 error rate was set at 0.05.

For the second objective, evaluating behavior changes across the range of unit prices that maintain behavior, a demand curve analysis was employed. Demand curves are used within

behavioral economics to characterize changes in reinforcer consumption by plotting reinforcer consumption as a function of unit price (see Supplementary Figure 1). Demand curves have been shown to conform well to an exponential equation (Hursh and Silberberg 2008):

$$\log Q = \log Q_0 + k (e^{-\alpha(Q_0 C)} - 1) \quad 1$$

in which Q is consumption at a given unit price, C , and k is a scaling parameter. Q_0 and α are free parameters; Q_0 estimates consumption if the reinforcer were free (graphically the y-intercept), and α estimates the rate at which consumption changes as a function of unit price (graphically the rate of change in the slope). α might be thought of as sensitivity to unit price (i.e., elasticity), and has been described as a measure of the essential value of a reinforcer.

The last two sessions at each unit-price combination were used to calculate consumption (total nicotine infused per session in $\mu\text{g/kg}$). Two demand curves were created for each subject: one for the dose-reduction and one for the ratio-escalation, and Equation 1 was fitted to each demand curve using a GraphPad Prism template available from the Institutes for Behavior Resources (<http://www.ibrinc.org/index.php?id=181>). $k=3.2$ for all demand curves in Experiment 1 and Experiment 2. For each demand curve, data points were excluded if consumption fell below 10% of baseline or to 0. Q_0 and α scores more than three standard deviations from the mean were excluded. Scores from cost escalation were correlated with scores from dose reduction (Pearson correlation).

For the third objective, breakpoint (BP, highest unit price maintaining consumption at or above 10% of baseline) was compared between the two manipulations using a Wilcoxon Signed Ranked Test for ordinal data. To report effect size, the Z statistic was divided by the square root of the number of observations (r statistic). Visual inspection of individual demand curves suggested that when BP was reached for ratio-escalation curves, the subsequent change in consumption is often drastic, while the change in consumption for dose-reduction curves was more gradual. However, the change in consumption immediately following breakpoint could not be compared because rats often maintained behavior across the full range of dose-reduction combinations tested. Thus, the maximum instance of elasticity was compared between the two manipulations. For each data point, the proportional change in consumption given the proportional change in unit price was calculated (proportional decrease = $1 - (\% \text{ decrease in consumption} / \% \text{ increase in unit price})$), and the lowest value was compared between the two manipulations. Negative values indicate a larger percentage change in consumption than the percentage change in unit price.

Data analysis for Experiment 3 focused on testing whether consumption was equivalent across the seven unit-price combinations. Planned comparisons tested whether each combination was different from the highest and lowest dose combination. An independent samples t-test compared the number of infusions earned at the lowest dose combination to the number of infusions earned on the saline combination.

Results

Experiment 1: Evaluating changes in consumption using above-threshold nicotine doses

Average consumption at each unit price for both manipulations is shown in Figure 1A. The number of rats at each data point is variable due to catheter failure ($n=27-32$). A 2 X 6 repeated-measures ANOVA revealed a significant effect of unit price ($F(5, 125) = 94.66, p < 0.05$, Partial $\eta^2=0.79$), but no effect of manipulation ($p > .05$, Partial $\eta^2=0.03$), or interaction ($p > 0.05$, Partial $\eta^2=0.04$). Paired samples t -tests conducted at each of the six unit prices failed to reveal any significant differences in consumption between manipulations of nicotine cost and manipulations of nicotine dose ($ps > 0.008$; 0.133: $d = 0.18$; 0.267: $d = 0.04$; 0.4: $d = 0.32$; 0.533: $d = 0.22$; 0.8: $d = 0.35$; 1.33: $d = 0.196$). To assess whether the two manipulations may have differed in the degree to which they produced stable behavior in the four sessions that were allotted for each combination, a 2 X 6 repeated-measures ANOVA was used to analyze the difference in consumption between the third and fourth session at each of the 12 unit prices. The effects of unit price (Partial $\eta^2=0.03$), manipulation (Partial $\eta^2=0.00$), and the interaction (Partial $\eta^2=0.03$) were not significant ($p > 0.05$ for all).

A demand curve analysis was employed to assess whether manipulations of FR and dose change consumption similarly across the range of unit prices that maintain consumption. Values more than three standard deviations from the mean were excluded (Q_0 : 2 values, α : 1 value), and only data points where behavior was maintained were included (defined as consumption at or above 10% of baseline). Four rats had two or fewer data points on at least one of the two curves, and were not included in the demand analysis ($n=28$ for demand analysis). Curve fits were good for both ratio and dose fits, but R^2 values were significantly better for dose curves than for ratio curves ($t(27) = 2.78, p < 0.01, d = 0.52$). Ratio and dose Q_0 values were not significantly different from each other ($p > 0.05, d = 0.07$) (Figure 1B). α values for the dose manipulation were significantly greater than α values for the ratio manipulation ($t(26) = 3.41, p = 0.002, d = 0.66$), suggesting that consumption is more sensitive to dose manipulations across the range of unit prices that maintain behavior (Figure 1C). Q_0 scores determined in each rat based on cost escalation and dose reduction were also highly correlated ($r = 0.50, p = 0.009$), but the correlation of α scores did not meet significance ($r = 0.30, p > 0.05$), suggesting that sensitivity to FR is a poor predictor of sensitivity to nicotine dose.

BP was significantly higher for the dose procedure than for the ratio procedure ($Z = 3.62, p < 0.001, r = 0.50$) (Figure 1D). This analysis was only conducted for rats that completed the entire procedure ($n=26$). Sixteen rats had a higher dose BP than ratio BP, 10 rats had the same BP for both procedures, and 0 rats had a higher ratio BP than a dose BP. Visual inspection of individual demand curves suggested that the ratio escalation curves tended to decrease drastically after reaching a BP, while dose reduction curves showed a more gradual change across unit prices. A paired samples t -test confirmed the ratio escalation procedure produced a larger maximum instance of elasticity than the dose reduction procedure ($n=26, t(25) = 4.79, p < 0.001, d = 0.96$) (Figure 1E).

Experiment 2: Evaluating changes in consumption using below-threshold nicotine doses

Average consumption at each unit price for both manipulations is shown in Figure 2A. The number of rats at each data point is variable due to catheter failure ($n=28-31$). A 2 X 6 repeated-measures ANOVA revealed a significant effect of unit price ($F(5, 130) = 76.06, p < 0.001$, Partial $\eta^2=0.75$), a significant effect of manipulation ($F(1, 26) = 32.21, p < 0.001$, Partial $\eta^2=0.55$), and a significant interaction ($F(5, 130)=10.17, p < 0.001$, Partial $\eta^2=0.28$). Paired samples t-tests confirmed that consumption was significantly different between manipulations of nicotine cost and manipulations of nicotine dose at the three lowest unit prices ($n=28-31$, 0.133: $t(27) = 7.16, p < 0.001, d=1.35$); 0.267: $t(29) = 3.92, p = 0.001, d=0.71$; $t(30) = 3.13, p = 0.004, d=0.56$). At the three higher unit prices, consumption for the two combinations failed to meet criteria for a significant difference ($p > 0.008$; 0.533: $d=0.29$; 0.8: $d=0.05$; 1.33: $d=0.20$). To assess whether the two manipulations may have differed in the degree to which they produced stable behavior in the four sessions allotted at each combination, a 2 X 6 repeated-measures ANOVA was used to analyze the difference in consumption between the third and fourth session at each of the 12 unit prices. There was a significant effect of unit price on stability ($F(5,130)=2.30, p < 0.05$, Partial $\eta^2=0.08$), but no effect of manipulation ($p > 0.05$, Partial $\eta^2=0.00$), and no interaction ($p > 0.05$, Partial $\eta^2=0.01$).

As in Experiment 1, a demand analysis was employed to test whether the two manipulations changed behavior differently across the range of unit prices that maintained behavior. Only data points where behavior was maintained were included (defined as consumption at or above 10% of baseline). Rats that had two or fewer data points on at least one of the curves were excluded ($n=18$ for demand analysis). Fits were good for both ratio and dose fits, and R^2 values were not significantly different between curves ($p > 0.05, d=0.07$). Q_0 was higher for ratio-escalation than dose reduction, and α was lower for ratio-escalation than dose-reduction ($Q_0: t(17) = 4.08, p = 0.001, d=1.04$; $\alpha: t(18) = 6.92, p < 0.001, d=1.68$) (Figures 2B and 2C). Parameters from ratio-escalation and dose-reduction curves were not significantly correlated with each other ($Q_0: r=0.26, p > 0.05$; $\alpha: r=0.45, p > 0.05$), suggesting that an individual's response to one manipulation is a poor predictor of their response to the other manipulation.

BP was not significantly different between the two manipulations ($p=0.182, r=0.26$) (Figure 2D). This analysis was only conducted for rats that completed the entire procedure ($n=26$). However, the BP for dose was higher than the breakpoint for ratio for 14 rats, the same for both manipulations for 8 rats, and higher for ratio than for dose for 4 rats. As in Experiment 1, the maximum decrease was larger for the ratio-escalation manipulation than for the dose-reduction manipulation ($n=26, t(25) = 4.52, p < 0.001, d=0.90$) (Figure 2E).

Experiment 3: Evaluating changes in consumption across a single unit price

Figure 3A shows consumption across the seven unit-price combinations (saline excluded because consumption cannot be plotted) ($n=22-23$). Qualitatively, there appears to be an inverted-U shape to the graph, such that consumption increases across the first few combinations, is high for the middle combinations, and then is lower at the highest dose combination. Paired samples t-tests using FR1/1.875 $\mu\text{g/kg/infusion}$ as the reference group

revealed that consumption was significantly greater at FR2/3.75, FR3/5.625, FR4/7.5, and FR12/22.5 combinations (FR2/3.75: $t(23) = 3.99$, $p = 0.001$, $d = 0.89$; FR3/5.625: $t(23) = 5.36$, $p < 0.001$, $d = 1.19$; FR4/7.5: $t(22) = 3.77$, $p = 0.001$, $d = 0.79$; FR12/22.5: $t(23) = 4.89$, $p < 0.001$, $d = 1.20$). Consumption at the other two combinations did not meet criteria for a significant difference ($ps > 0.008$; FR24/45: $d = 0.34$; FR32/60: $d = 0.12$). Paired samples *t*-tests using FR32/60 as the reference group revealed that consumption was significantly greater at the FR12/22.5 combination (FR12/22.5: $t(23) = 2.73$, $p = 0.012$, $d = 0.56$), but did not meet criteria for a significant difference at the other combinations ($ps > 0.008$; FR1/1.875: $d = \text{same as above}$; FR2/3.75: $d = 0.29$; FR3/5.625: $d = 0.44$; FR4/7.5: $d = 0.32$; FR24/45: $d = 0.54$).

Figure 3B shows the average number of infusions earned at each of the eight combinations. A paired-samples *t*-test confirmed that rats earned significantly more infusions at the FR1/1.875 $\mu\text{g/kg/infusion}$ combination than at the FR1/saline combination ($t(21) = 3.91$, $p = 0.001$, $d = 0.96$). Differences between other combinations were not tested because the FR varies across combinations, making other differences difficult to interpret.

Discussion

The present investigation showed that increasing the cost of nicotine and decreasing nicotine dose will change nicotine consumption differently. There were five main findings: 1) At low unit prices that maintain consumption, decreases in nicotine consumption were larger when nicotine dose was decreased than when nicotine cost was increased. 2) Analyses of breakpoints and maximum instances of elasticity suggest that manipulations of cost produce lower breakpoints followed by larger changes in consumption than manipulations of dose. 3) Sensitivity to nicotine cost and sensitivity to nicotine dose were not significantly correlated, suggesting that individual sensitivity to cigarette taxation is likely to be a poor predictor of sensitivity to a reduction in nicotine content; 4) In one experiment, nicotine consumption was not equivalent when tested across seven combinations of a single unit price; 5) There was a large degree of inter-subject variability in sensitivity to both manipulations, breakpoint, and consumption at any given unit price.

The present analyses used nicotine consumption as the primary outcome because reinforcer consumption is the primary outcome in a behavioral economics framework. However, smoke exposure is the most relevant outcome from a public health perspective, and it is important to note that the relationship between nicotine consumption and smoke exposure is different for increases in cigarette cost and decreases in nicotine content. In the present self-administration paradigm, nicotine infusions might be thought of as analogous to smoke exposure (Smith et al. 2014). However, when unit price is increased through decreases in the nicotine content of cigarettes, cumulative smoke exposure will not track with the changes in nicotine consumption. If the proportional decrease in nicotine consumption is smaller than the proportional increase in unit price (i.e., consumption is inelastic), smoke exposure is increasing (as are nicotine infusions). Likewise, if the proportional decrease in nicotine consumption is larger than the proportional increase in unit price (i.e., consumption is elastic), smoke exposure is decreasing. When unit price is increased through an increase in cigarette cost, changes in nicotine consumption will track with changes in smoke exposure,

but total dollars spent on smoking would not. The change in dollars spent on cigarettes would depend on the elasticity of nicotine consumption.

Results from these experiments have important implications for nicotine reduction. Increasing the cost of cigarettes is commonly considered to be one of the most effective tobacco control interventions, and these data show that nicotine consumption is even more sensitive to decreases in nicotine content than to increases in the cost of nicotine. Researchers have hypothesized that a large reduction in nicotine intake may lead to a reduction or elimination of nicotine dependence (Benowitz and Henningfield 1994; Benowitz and Henningfield 2013), and these data suggest that a reduction in nicotine content will be highly effective at reducing nicotine intake. Prior research on cigarette taxation suggests that for every 10% increase in the price of cigarettes, there is a 4% reduction in cigarette consumption (elasticity is 0.4) (Chaloupka and Warner 1999). Because nicotine consumption is more sensitive to nicotine content than to the cost of nicotine, the elasticity of nicotine consumption is likely to be higher than 0.4 when nicotine content is decreased. The individual data shown in the present paper reflected a large degree of variability among subjects on all the reported measures (sensitivity to cost, breakpoint, maximum elasticity, and consumption at a single unit price). It is likely that there would be much more variability in a population of human smokers who differ on a wide range of historical and environmental factors. Future experiments should consider including females and adolescents, as the present studies used adult male rats.

Imbedded in the unit price model is the assumption that the threshold nicotine content is likely to be moderated by the price of cigarettes. This is important to consider given that most clinical trials provide cigarettes for no monetary cost, and any nonmonetary cost (effort to travel and participate in the study) is difficult to quantify. The results of Experiment 3 suggest that very low doses are likely to suppress consumption more than higher doses and costs that create the same unit price. Thus, while cost may moderate the threshold nicotine content for maintaining behavior, low costs are unlikely to abolish the impact of very low nicotine contents on nicotine consumption. Experiment 3 also showed that very high costs suppressed consumption below what would be expected given the unit price. Thus, the greatest suppression of nicotine consumption is likely to come from very low nicotine content cigarettes that are combined with very high costs.

In many ways, behavioral economics provides a useful framework for understanding the impact of reinforcer cost and reinforcer magnitude—nicotine consumption decreased as a function of increases in nicotine cost or decreases in nicotine dose, and these changes were well characterized by demand curves. However, the results of the present study suggest some limitations for the unit price approach, which posits that increases in the cost of a reinforcer and decreases in the magnitude of a reinforcer should be equivalent manipulations. Although researchers have previously noted that low doses might be an exception to the unit price model, the doses used in Experiment 1 are within a relatively standard dose range, so it is unlikely that a low-dose exception is entirely responsible for this finding. One explanation for the increased sensitivity to dose across unit prices that maintain consumption is that the pharmacological effect of several small doses of nicotine may not be equivalent to one large dose of nicotine, even if they total the same total drug consumption. There is substantial

evidence that the rate of drug delivery may be a critical factor in producing any given pharmacological effect, and especially in functioning as a primary reinforcer for many drugs of abuse (Abreu et al. 2001; Balster and Schuster 1973; Comer et al. 2009; Marsch et al. 2001; Nelson et al. 2006; Panlilio et al. 1998; Sorge and Clarke 2009; Wakasa et al. 1995; Wing and Shoaib 2013). Decreased breakpoints and higher instances of elasticity for manipulations of cost may be related to differences in cue delivery, as the cue likely takes on value through its pairing with nicotine. In the procedure used here, rats continue to receive frequent cue delivery when nicotine dose is decreased but cue delivery becomes more infrequent when FR is increased. Responding for the cue is also likely impacted by reinforcement enhancement, a phenomenon whereby nicotine noncontingently increases the value of reinforcers (Caggiula et al. 2009; Donny et al. 2003; Rupprecht et al. 2015). Although the inequity in cue delivery complicates the results, the present procedure in which the cue is delivered along with each infusion most closely models reinforcer delivery in the natural environment, where reinforcers are delivered in the context of other stimuli (Conklin and Tiffany 2002). Of course, it is impossible to perfectly mimic the environmental stimuli that accompany smoking. The complex conditioning that takes place for cigarette smokers may contribute to less elastic demand for nicotine in the real world.

These data have some limitations. Regarding the policy implications of the study, there are important differences between a rat self-administration paradigm and human smokers experiencing an increase in the monetary cost of cigarettes or a reduction in the nicotine content of cigarettes. As already discussed, smokers are able to modify their nicotine intake in more ways than rats self-administering intravenous nicotine. Humans are also able to defend nicotine intake when the unit price of cigarettes is increased by switching to another tobacco product with a lower unit price. Furthermore, tobacco products differ from each other and from nicotine self-administration in the rate at which they deliver nicotine, and the rate at which a reinforcer is delivered may impact sensitivity to dose. Tobacco products also contain many non-nicotine cigarette smoke constituents (Rodgman and Perfetti 2013), and it is possible that these constituents may contribute to reinforcement value. Rats received four sessions at each unit-price combination. There were no significant differences between the two manipulations in the degree of stability, but it is possible that the use of a formal criterion for stability before changing unit-price combinations would have changed the results. Furthermore, self-administration sessions were limited to two hours of time-in responding and infusions were paired with a short time-out, and it is possible that the results may have differed if rats had been given unlimited access to nicotine.

The present study characterized the relationship between increases in nicotine cost and decreases in nicotine dose. Increases in nicotine cost and decreases in nicotine dose were not equivalent manipulations, and sensitivity to one manipulation was a poor predictor of sensitivity to the other manipulation. The lack of equivalence between manipulations places some limits on the utility of existing data regarding the impact of cost on nicotine consumption to formulation of a nicotine reduction policy. The relationship between cost and dose characterized in this report has important implications for a potential nicotine reduction policy. The results suggest that nicotine consumption is likely to be more sensitive to decreases in nicotine content than to increases in cigarette cost. Nicotine intake has been hypothesized as critical in dependence on combustible cigarettes (Benowitz and

Henningfield 1994; Benowitz and Henningfield 2013), so the high degree of sensitivity to decreases in nicotine content is encouraging. Furthermore, a strict unit price model would predict that if the price of cigarettes is made low enough, nicotine consumption could be maintained even if nicotine content is greatly reduced. However, previous literature has also pointed to the possibility of an exception to the unit price model for low nicotine doses. The results of Experiments 2 and 3 suggest are in line with that hypothesis; if nicotine content is low enough, a very low cost will not increase consumption to the level that would be predicted from a unit price approach. Overall, the results suggest that nicotine reduction is likely to be a highly effective method for reducing nicotine intake.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

Thank you to Samuel Gutherz, Emily Pitzer, Elizabeth Shupe, E. Corina Andriescu, Kayla Convry, Samantha Cwalina, Dora Danko, Mackenzie Meixner, Jessica Pelland, Hangil Seo, Nicole Silva, and Marisa Wallas for assistance in conducting experimental sessions. Research reported in this publication was supported by the National Institute on Drug Abuse and FDA Center for Tobacco Products (CTP) (U54 DA031659 awarded to E.C.D.) The funding source had no other role other than financial support. The content is solely the responsibility of the authors and does not necessarily represent the official views of the NIH or the Food and Drug Administration. Funding for Tracy Smith was provided by the National Institute on Drug Abuse (F31 DA037643) and the National Cancer Institute (T32 CA186783).

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Figure 1.

Data from Experiment 1. Significant differences indicated by *. A) Average consumption (+SEM). B) and C) Free parameter values from best fitting function of Equation 1. D) BP was defined as the highest unit price at which consumption was maintained at or above 10% of baseline (average of last two training condition sessions prior to start of the unit price manipulation). E) Maximum instance of elasticity for ratio-escalation and dose-reduction curves in Experiment 1 (n=26). For each data point, the proportional change in consumption given the proportional change in unit price was calculated (see data analysis section), and the lowest value for each curve was compared. Negative values indicate a larger percentage change in consumption than the percentage change in unit price.

Figure 2.

Data from Experiment 2. Significant differences indicated by *. A) Average consumption (+SEM). B) and C) Free parameter values from best fitting function of Equation 1. D) BP was defined as the highest unit price at which consumption was maintained at or above 10% of baseline (average of last two training condition sessions prior to start of the unit price manipulation). E) Maximum instance of elasticity for ratio-escalation and dose-reduction curves in Experiment 1 (n=26). For each data point, the proportional change in consumption given the proportional change in unit price was calculated, and the lowest value for each curve was compared. Negative values indicate a larger percentage change in consumption than the percentage change in unit price.

Figure 3.

A) Consumption across the seven unit-price combinations (saline excluded because consumption cannot be plotted) (n=22-23). Significant difference from FR1/1.875 indicated by *. Significant difference from both the FR1/1.875 group and the FR32/60 group indicated by **. B) Infusions earned at each combination. Significant difference between FR1/1.875 and FR1/SAL indicated with *.

Table 1

FR/Dose combinations used in Experiments 1 and 2.

	Unit Price: FR/Nicotine Dose (µg/kg/infusion)												
	0.133		0.267		0.4		0.533		0.8		1.33		
	FR	Dose	FR	Dose	FR	Dose	FR	Dose	FR	Dose	FR	Dose	Experiment
FR Escalation	8	60	16	60	24	60	32	60	48	60	80	60	1, 2
Dose Reduction	10	75	10	37.5	10	25	10	18.75	10	12.5	10	7.5	1
Dose Reduction	1	7.5	1	3.75	1	2.5	1	1.875	1	1.25	1	0.75	2

Table 2

FR/Dose combinations used in Experiment 3.

Unit Price=0.553	
FR	µg/kg/infusion
1	1.875
2	3.75
3	5.625
4	7.5
12	22.5
24	45
32	60

Note: Rats experienced one additional combination in which completing an FR1 schedule resulted in an infusion of saline along with the normal cue conditions.