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ORIGINAL INVESTIGATION

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Differential effects of nicotine on alcohol consumption in men and women

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Abstract *Rationale:* Nicotine and alcohol are frequently co-used, suggesting that use of one drug may facilitate use of the other. Furthermore, because men and women differ in their responses to both drugs, it is possible that men and women also differ in their responses to the combination of nicotine and alcohol. *Objective:* This experiment was designed to investigate the effects of nicotine on consumption and subjective and physiological effects of alcohol in healthy male and female social drinkers. *Materials and methods:* Healthy light smoking, social drinkers (22 men and 12 women) participated in a three-session, double-blind within-subject study. They were pretreated with transdermal nicotine (7 or 14 mg) or placebo, followed two h later by an alcoholic beverage, and subsequent opportunities to "purchase" and consume more of the same drink. Outcome measures included the number of alcoholic beverages consumed and subjective and physiological effects. *Results:* Nicotine increased alcohol consumption in men, whereas it decreased alcohol consumption in women. These effects were even more pronounced after excluding participants reporting nausea after nicotine administration. Nicotine alone increased subjective arousal in men but decreased positive mood in women. Nicotine increased the sedative-like effects of alcohol in both sexes. *Conclusions:* These findings indicate that both the subjective effects of nicotine and the effects of nicotine on alcohol consumption differ markedly in men and women. The findings extend existing data on sex differences in the effects of either nicotine or cigarette smoking on alcohol consumption, and support the idea that the pharmacological effects of nicotine may differ in men and women.

Keywords Nicotine · Ethanol · Reinforcement · Smoking · Drug-interaction · Choice · Transdermal · Sex differences · Women

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Introduction

Nicotine and alcohol are often used together. Smoking tobacco is common in settings where alcohol is consumed (Siegel and Skeer 2003), and individuals who habitually use one substance are likely also to use the other (Zacny 1990). For example, 80–90% of smokers regularly drink alcohol, compared to 66% of the general population, and smokers tend to be heavier drinkers than non-smokers (Friedman et al. 1974; Strine et al. 2005). Conversely, 80% of alcoholics smoke, compared to only 23% smokers in the general population (Miller and Gold 1998; NCHS and CDC 2004). Recently, Dierker et al. (2006) reported a high proximal association between smoking and drinking among 225 first-year-college students, using weekly follow-back diaries over 7 months. Their results confirm that occasional users of both drugs are much more likely to smoke when they drink, and to drink when they smoke.

The reasons for the high prevalence of co-use of tobacco and alcohol are not fully understood. The co-use may reflect preexisting risk factors in certain individuals, or it may reflect environmental factors that facilitate the use of both drugs. Alternatively, co-use could also result from a pharmacological interaction between nicotine and alcohol, such that use of one drug facilitates use of the other. That is, alcohol may facilitate smoking, or nicotine may facilitate drinking. Indeed, there is experimental evidence that ethanol increases the reinforcing properties of tobacco smoking and nicotine (i.e., Griffiths et al. 1976; Mintz et al. 1985; Mitchell et al. 1995; Rose et al. 2004), and there is

limited evidence that nicotine may increase the reinforcing value of ethanol (Barrett et al. 2006; Perkins et al. 2000; Potthoff et al. 1983; Smith et al. 1999).

Studies with both non-humans and humans support the idea that nicotine increases consumption of alcohol. Potthoff et al. (1983) found that rats implanted with chronic slow nicotine release devices consumed more ethanol than control animals. This intake was not due to increased calorie seeking; several other abused drugs failed to increase ethanol intake. Other studies have shown that nicotine increases ethanol consumption in both ethanol-preferring and normal strains of rats, and after subchronic or acute administration of nicotine (Blomqvist et al. 1996; Le et al. 2000; Smith et al. 1999). Interestingly, male alcohol-preferring (Prats) also self-administer both nicotine and sucrose more readily than non-preferring (NP) rats, although the P and NP animals do not differ in cocaine self-administration (Le et al. 2006). In humans, Perkins et al. (2000) reported that male smokers consumed less alcohol after abstaining from smoking overnight, compared to normal smoking, and that alcohol produced more sedative effects after smoking abstinence. These findings are consistent with the idea that nicotine enhances the reinforcing effects of ethanol, but the study lacked a placebo control, and acute withdrawal could also have played a role in reduced alcohol consumption.

Kouri et al. (2004) recently reported that transdermal nicotine (21 mg) increased participants' reports of feeling the effects of ethanol (0.4 and 0.7 g/kg), feeling drunk and feeling euphoric. Nicotine also increased the desire to drink and smoke in these moderate, non-dependent male smokers. This pattern of subjective responses suggested that nicotine might have also increased alcohol consumption if the participants had been given the opportunity to drink. Barrett et al. (2006) found that nicotinized, but not denicotinized, cigarettes increased motivation among male, non-dependent smokers to consume alcohol (compared to water), using a progressive ratio schedule. Finally, the nicotinic antagonist, mecamylamine, dampens the subjective and perhaps the reinforcing effects of alcohol (Blomqvist et al. 2002; Chi and de Wit 2003). Thus, evidence in both laboratory animals and humans suggest that nicotine enhances the reinforcing effects of alcohol.

One important limitation of the two recent studies on the effects of nicotine on responses to alcohol (Barrett et al. 2006; Kouri et al. 2004) is that they were conducted using only men. There is evidence that there are sex differences in responses to nicotine (Perkins et al. 2002) as well as to the nicotinic antagonist mecamylamine (Chi and de Wit 2003; Young et al. 2005). Perkins et al. (2002) found that the pharmacological effects of nicotine play a more important role in smoking behavior among men, whereas, women are more reactive to sensory smoking cues. Perkins (1999) also found that women were less sensitive to changes in dose of a nicotine nasal spray. More recently, Chaudhri et al. (2005) have also reported sex differences in the reinforcing effects of nicotine in rats. Chi and de Wit (2003) found that mecamylamine attenuated the positive subjective effects of alcohol and self-reported desire to drink more in men than in women (but see also Blomqvist et al. 2002). These findings suggest that the effects of nicotine on alcohol responses or consumption may differ in men and women.

In the present study, 34 social-drinking light smokers ("chippers") participated in three sessions in which they were pretreated with placebo or nicotine (7 or 14 mg) patches. Participants consumed one required 'priming' dose of alcohol (0.2 g/kg; 2.75 h after nicotine), and then had opportunities to consume up to eight additional doses of alcohol over the next 2 h (0.1 g/kg each). We used a sensitive procedure for examining changes in alcohol value, which used individualized drink values and systematically varied drink prices (Young et al. 2005). We hypothesized that nicotine would increase the euphorigenic effects of the required dose of alcohol, and increase the number of drinks consumed. Based on the Perkins et al. (2002) findings that men are more sensitive to the pharmacological effects of nicotine, we further expected that this effect would be more pronounced in males than in females.

Materials and methods

Participant recruitment

Twenty-two male and 12 female social drinkers, aged 21 to 41, who smoked between one and ten cigarettes per day, participated. Light smokers were recruited to reduce the influence of nicotine withdrawal on placebo sessions. Participants were recruited from the university and surrounding communities through posters, newspaper advertisements, and word-of-mouth referrals. Initial eligibility was ascertained during a telephone interview screening process. Potential participants underwent further screening by completing a psychiatric symptom checklist (SCL-90; Derogatis 1983), the Michigan Alcoholism Screening Test (MAST; Selzer 1971), and a detailed health and drug-use questionnaire.

Screening included a semi-structured psychiatric screening interview based on the Structured Clinical Interview for DSM-IV Disorders (SCID; First et al. 1996), an electrocardiogram, and a physical examination. Inclusion criteria were: (1) consuming four or more alcoholic drinks per week, and two or more on one occasion, (2) regularly smoking one to ten cigarettes per day, (3) having a high school diploma or equivalent, (4) having a body mass index value between 19 and 26 kg/m^2. Exclusion criteria included any current medical condition requiring medication, history of or current Axis I psychiatric diagnoses (DSM-IV-TR; APA 2000), history of or current substance-use disorder, lack of fluency in English, cardiovascular disease, high or low blood pressure, or abnormal electrocardiogram. Women were excluded if they were pregnant, planning to become pregnant, breast-feeding, or had severe premenstrual symptoms.

Subjects signed informed consent before participating.

For blinding purposes, they were told that they might receive one or more of the following drugs: stimulant, sedative, antihistamine, beta-blocker, alcohol, or placebo.

Participants were instructed not to consume any drugs other than their usual amounts of caffeine and nicotine for 24 h prior to and 12 h after each of the study sessions, and to fast beginning at noon on session days. These procedures were approved by the Institutional Review Board at the University of Chicago.

Design

The study used a double-blind, within-subjects, placebo-controlled design. Each subject participated in three 6.5-h experimental sessions, separated by at least 72 h. During the sessions, participants received a patch containing either placebo or nicotine (7 or 14 mg; Nicoderm CQ; GlaxoSmithKline). Two hours and 45 min after the patch was administered, participants consumed a required, priming dose of alcohol (0.2 g/kg) over 5 min, and 10 min later completed self-report questionnaires. This time course was selected to correspond with peak plasma levels of nicotine after patch administration (Gorsline et al. 1992). Thirty minutes later, a 2-h drink choice period began, during which participants had opportunities to purchase and consume eight additional, optional 0.1-g/kg alcoholic beverages, one every 15 min. The price of the beverages varied across the opportunities, as described below. The primary dependent measure was the number of beverages each subject consumed during the 2-h choice procedure. Secondary measures included self-report measures of mood states, temperature, blood alcohol level, and cardiovascular measurements of blood pressure and heart rate.

Laboratory environment

The study was conducted in a recreational laboratory environment in the Human Behavioral Pharmacology Laboratory in the Department of Psychiatry at the University of Chicago Hospital. The environment resembled a living room, with upholstered chairs and sofas, incandescent lighting, decorated walls, tables with magazines, board games, and video entertainment units. Participants were tested in small groups of two to four individuals. Women were tested without regard to menstrual cycle phase because menstrual cycle phase does not strongly influence responses to either nicotine or alcohol Terner and de Wit (2006). During times when participants were not participating in tasks or completing questionnaires, they were allowed to relax, read magazines, play games, watch videos, and interact with other group members, but were not allowed to study or work.

Session procedures

For each experimental session, participants arrived at the laboratory at 1:30 P.M. (i.e., at −30 min or 30 min before patch administration). First, they provided breath and urine samples to verify compliance with drug abstinence instructions. Participants then relaxed for 10 min to stabilize subjective and physiological measures, and at 1:40 p.m. (−20 min) they completed baseline self-report questionnaires (see below), and temperature, heart rate, and blood pressure were measured. At 2:00 P.M. (0 min), a research assistant who was blind to the conditions placed a patch containing placebo or nicotine (7 or 14 mg). For the next 120 min participants relaxed to allow for drug absorption, and completed subjective ratings at 60 and 120 min. These ratings were used to assess the direct effects of the nicotine. At 4:45 p.m. (165 min), participants consumed the required alcoholic beverage (0.2 g/kg) within 5 min. Ten minutes later they completed questionnaires which were used to assess the combined effects of alcohol and nicotine.

At 5:00 P.M. (180 min), the 2-h choice procedure began during which participants could "buy" single drinks (0.1 g/kg ethanol) every 15 min for 2 h. Participants bought the drinks using tokens of varying, and individualized, value (see below). At 7:05 P.M. (305 min), immediately after the drinking period, subjective, behavioral, and physiological measures were taken. At 8:00 P.M. (360 min), before leaving the laboratory, participants completed a final questionnaire reporting how much they liked or disliked, overall, what they consumed. After completing all three sessions, participants were debriefed and paid for their participation. They were transported home provided that their BAL was below 0.04 dl/l.

Drink valuation and token procedure

During an orientation session before the first session, each subject completed a brief computerized questionnaire to estimate how much he or she valued an alcoholic drink. The questionnaire, consisting of systematic choices of money vs a drink, provided an equivalent monetary value for a standard alcoholic beverage (a can of beer, a glass of wine, one shot of liquor, etc), i.e., a value at which the subject was equally likely to choose the drink or the money. This personal drink value was used to set the 'cost' of optional drinks in the subsequent testing sessions.

At the beginning of each testing session, participants received 36 tokens, each worth 1/8 of the subject's estimated personal drink value for a standard drink. During the choice phase, participants were offered eight optional drinks, each containing 0.1 g/kg ethanol, about half a standard alcoholic drink. Therefore, each optional drink should have been worth about four tokens. Participants were told that they could "buy" drinks with tokens every 15 min over the next 2 h, and that any tokens left unspent would be redeemed for cash at the end of the session. Participants made their choices of beverage (or money) privately to reduce the possible influence of the group on beverage choices.

For each choice, the experimenter escorted the subject to another room and informed him of the price of the next drink. On four of the drink options, drinks were priced at four tokens, on two options they were "cheap" (two tokens) and on another two they were "expensive" (eight tokens). The cost of the drink was varied across trials to test for

potential effects of nicotine on cost/benefit considerations in drink choices, to test the sensitivity of our procedure (choice should be related to price), and to deter participants from planning drink decisions before purchase opportunities. Drink prices were presented in one of two orders over the eight drink options: four, two, eight, four, four, eight, two, and four, or four, eight, two, four, four, two, eight, and four tokens. These orders were alternated across sessions to further prevent participants from anticipating upcoming drink prices.

Drug preparation

Nicoderm CQ (GlaxoSmithKline, Research Triangle Park, NC, USA) patches containing 7 or 14 mg of nicotine were used. Placebo patches were the same in size and color and contained a small amount of capsaicin (0.075%) analgesic cream to match the tingling sensation of nicotine on the skin. Active and placebo patches were covered with medical adhesive tape to blind the participants and the research assistant.

Ethanol (Everclear 95%) was mixed with pulp-free, Minute Maid brand orange juice to a concentration of 16% ethanol. The doses were 0.2 g/kg (required dose) and 0.1 g/kg (optional dose). Ethanol doses administered to women were 10% lower to account for sex differences in body composition (Breslin et al. 1997). The beverages were served cold in styrofoam cups.

Dependent measures

The primary dependent measure was the number of beverages consumed. Beverage choices were examined in relation to nicotine dose, price, and sex. Secondary measures included self-report measures of drug effects, including the Stimulant and Sedative scales of the Biphasic Alcohol Effects Scale (BAES; Martin et al. 1993), the Drug Effects Questionnaire (DEQ; Johanson and Uhlenhuth 1980), the Addiction Research Center Inventory (ARCI; Martin et al. 1971), the Profile of Mood States (POMS; McNair et al. 1971), and the Visual Analogue Scale (VAS; Folstein and Luria 1973). Physiological measures included blood pressure, heart rate, temperature, and blood alcohol concentration. These measures were used to assess the effects of nicotine (pre-beverage), and the interaction between nicotine and alcohol (post-beverage).

Subjective drug effects

The Biphasic Alcohol Effects Scale (BAES; Martin et al. 1993) is a 14-item self-report adjective rating scale that is sensitive to the stimulant and sedative effects produced by ethanol. Participants indicate the extent to which they feel each of the 14 adjectives on a 10-point scale from "not at all" (0) to "extremely" (10).

The Drug Effects Questionnaire (DEQ; Johanson and Uhlenhuth 1980) consists of four questions concerning current drug effects. Participants indicate on 100-mm lines whether they: 1) are currently feeling any drug effects (from "none" to "a lot"), 2) like the effects they feel (from "not at all" to "very much"), 3) are high (from "not at all" to "very"), and 4) want more of the drug (from "not at all" to "very much").

The Addiction Research Center Inventory (ARCI; Martin et al. 1971) is a 49-item true–false questionnaire sensitive to the effects of five drug classes. This version has five empirically derived scales: Amphetamine (A) and Benzedrine Groups (BG), which are indices of stimulant-like effects; the Morphine–Benzedrine Group (MBG), which is a measure of euphoria; the Pentobarbital–Chlorpromazine–Alcohol Group (PCAG), which is an index of sedation; and Lysergic Acid Diethylamide (LSD), which is a measure of dysphoric and somatic symptoms.

The Profile of Mood States (POMS; McNair et al. 1971) consists of a 72-item self-report, multiple choice, adjective-rating system. Participants indicate the extent to which they are feeling each of the 72 adjectives on a five-point scale from "not at all" (0) to "extremely" (4) that best relates to how much they are feeling that particular adjective. The answers to these questions are then organized into eight-factor-analyzed scales: "friendliness", "anxiety", "depression", "fatigue", "anger", "elation", "confusion", and "vigor", and two composite scales, "arousal" and "positive mood".

The Visual Analogue Scale (VAS; Folstein and Luria 1973) consists of eight adjectives used to describe current drug effects. Participants mark on 100-mm lines whether they feel "stimulated", "high", "sleepy", "anxious", "elated", "nauseated", "sedated", and "hungry".

Physiological measures

Heart rate and blood pressure were measured using a Dinamap vital signs monitor Model 1846 (Criticon, Tampa, FL, USA). Temperature was measured orally by a digital IVAC TEMP-PLUS II thermometer (Alaris Medical Systems, San Diego, CA, USA). Breath alcohol level was measured by using digital Alco Sensor (Intoximeters, St. Louis, MO, USA).

Data analysis

The primary outcome measure was the number of alcoholic beverages chosen during the 2-h choice period. These choice data were analyzed using repeated measures ANOVA with dose of nicotine as a within-subject factor and sex as a between-subject factor. In separate analyses, drink price (two, four, or eight tokens) was also entered into the analysis with both dose and drink price as within-subject factors and sex as a between-subject factor. Because a substantial number of participants reported feeling nauseous after nicotine, the choice data were

analyzed separately for those individuals who did not report more than a 10% increase in nausea on the VAS scale at either dose of nicotine. Nine men and five women reported feeling nauseous, mostly after the 14-mg dose. Fisher-protected least significant difference (LSD) was used for all post hoc analyses.

Subjective, physiological, and behavioral measures were examined to assess the direct effects of nicotine and of the interactions between nicotine and alcohol. To assess the effects of nicotine, we utilized measures obtained before and 120 min after administration of the patch (placebo, 7 and 14 mg nicotine). After verifying that there were no spurious pre-patch differences across the nicotine conditions, we calculated change from baseline (i.e., pre-patch to 120 min) scores for each measure. These change scores were analyzed using two-way repeated measures (ANO VAs; dose, sex) for each outcome measure. To assess the interaction between nicotine and alcohol, we compared participants' ratings after they consumed the required beverage (i.e., before the choice phase) in the three nicotine pretreatment conditions (two-factor ANOVA; dose, sex). The last measure of subjective effects was not included in the analysis because participants differed in the amount of alcohol consumed.

Results

Participant demographics

One subject tested positive for cocaine and was dropped from the study. The demographic characteristics of the remaining participants in the study are summarized in Table 1. Most participants were in their mid-20s, they consumed on average one to two drinks per day and smoked about two to three cigarettes per day. Expired carbon monoxide readings averaged across sessions ranged from 1.33 to 12 ppm (mean±SD 2.9±3.2). Male participants were significantly older and heavier than females, and a higher proportion of the men reported having tried hallucinogens. Female participants consumed more caffeinated beverages.

Determination of alcohol value

The monetary values judged to be equivalent to a standard drink, as determined during the orientation session, varied among males from $0.20 to $2.44 (mean±SD $0.97±$0.15) and among females from $0.50 to $2.96 (mean±SD $1.47± $0.25). The mean monetary values did not significantly differ in men and women, and the individual monetary values were not related to the number of drinks participants chose in the choice phase of the study.

Table 1 Demographic characteristics of all participants, including those who did and did not experience nausea

	Males (n=21)	Females (n=12)
Age (years: mean±SD)	27.6±5.1	22.9±2.0*
Weight	165.4±17.3	136.7±21.0*
BMI (kg/m^2: mean±SD)	23.5±2.0	22.7±3.1
Race/Ethnicity (n)[a]		
Caucasian	14	7
African-American	5	4
Asian/Indian	1	1
Hispanic	2	1
Education (n)		
Some college	10	7
College degree	7	3
Advanced degree	4	2
Current drug use (mean±SD)		
Alcohol (drinks/week)	12.2±10.6	7.5±3.90
Cigarettes (cigs/week)	18.9±19.1	13.8±12.3
Caffeine (cups/day)	1.3±0.8	3.2±3.1*
Lifetime drug use (n; ever used)		
Stimulants	13	5
Sedatives	4	1
Hallucinogens	18	6
Opiates	9	2
Inhalants	4	1

[a]One male identified himself as Caucasian and Hispanic, and one female identified herself as Black and Hispanic
*=p<0.01

Effects of nicotine on alcohol choice

Nicotine had differential effects on alcohol consumption in men and women. In all participants (n=33), nicotine tended to increase alcohol consumption in men but tended to decrease in women [dose by gender interaction; $F(2, 62)$= 2.982, p=0.058; Fig. 1a]. However, nicotine produced nausea and vomiting in some participants (see below), which could have influenced alcohol choice. Therefore, we also examined choice among participants who did not report significant nausea, defined as less than a 10% increase on ratings of nausea at either dose of nicotine. Using this criterion, we analyzed the alcohol consumption data for 12 men and 7 women. In this analysis, nicotine produced opposing effects on alcohol consumption in men and women [dose by gender interaction; $F(2, 34)$=4.966, p=0.013; Fig. 1b]. LSD tests revealed that nicotine (14 mg) significantly increased alcohol consumption in men relative to placebo and relative to women after nicotine (7 and 14 mg). In contrast, nicotine (14 mg) decreased alcohol consumption in women relative to placebo.

Interactions between choice and price

Alcohol choice was also examined in relation to the price (in tokens) of each drink, using only those individuals in whom nicotine did not produce nausea. Overall, alcohol

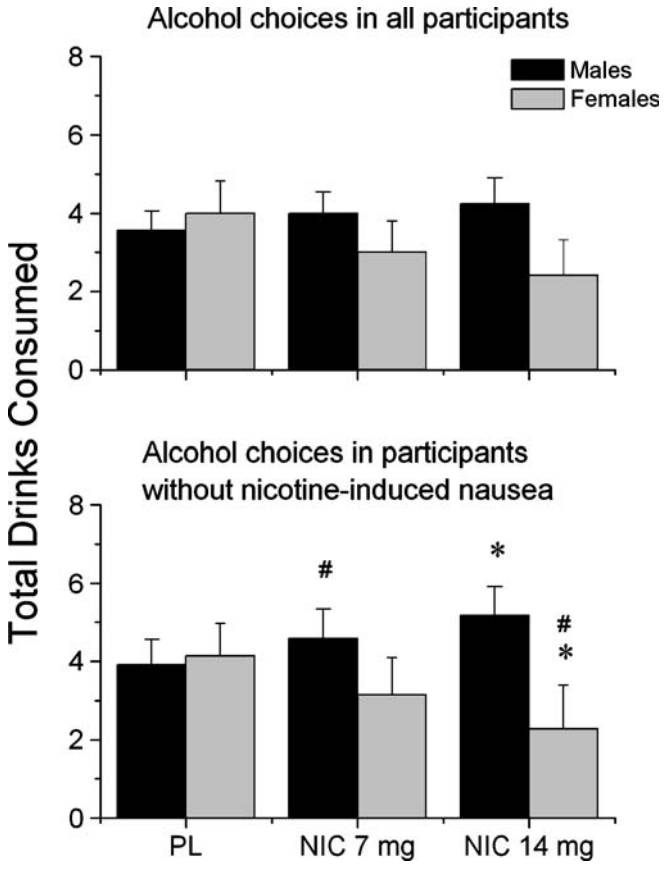

Fig. 1 Mean±SEM percent of available drinks chosen after placebo (PL), 7 mg and 14 mg nicotine (NIC). *Upper panel* shows effects of nicotine on all participants (n=21 males, 12 females). *Lower panel* shows only the participants who were not made nauseous by nicotine administration (n=12 males, 7 females). Note mean number of drinks chosen rather than percent available chosen was compared for statistical analysis. *indicates significant difference from placebo. # Indicates significant difference between men and women

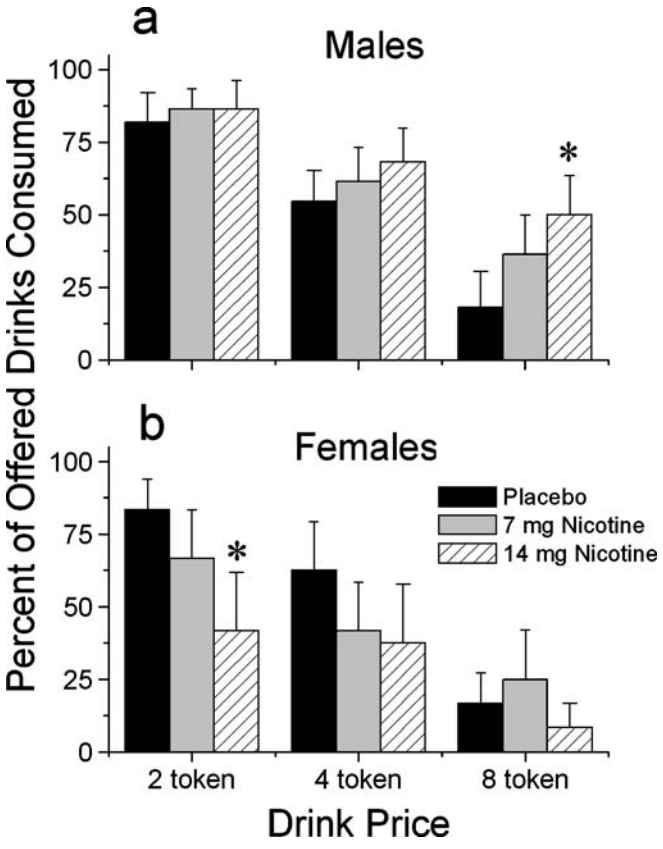

Fig. 2 Mean±SEM percent of available drinks chosen at the two-token ("cheap"), four-token (self-rated value), and eight-token ("expensive") choice conditions after placebo, 7 mg, and 14 mg nicotine in only those participants not made nauseous by nicotine administration. Males (n=12) are shown in the *upper panel* (**a**) and females (n=7) are shown in the *lower panel* (**b**). In both sexes, choice was inversely related to price. Note mean number of drinks chosen rather than percent available chosen compared for statistical analysis. *indicates significant difference between placebo and 14 mg nicotine

choices were inversely related to price [F(2, 34)=27.411, p<0.001]. Participants, on average, chose drinks 74.2% of the time when drinks were priced at two tokens, 53.8% of the time at four tokens, and 27.5% of the time at eight tokens. This orderly relationship indicated that our pricing procedure (Young et al. 2005) is valid and confirms the sensitivity of the procedure to interventions. Nicotine did not differentially affect alcohol choice depending on the price (i.e., no price-by-dose or price-by-dose-by-gender interaction). However, inspection of the means shown in Fig. 2 suggested that there were differential effects of nicotine on price in men and women. LSD analysis revealed that nicotine (14 mg) significantly increased drink choices at the eight-token price in men, whereas, it significantly decreased choices at the two-token price in women.

Effects of nicotine alone

In the full group of 33 participants, nicotine (14 mg) markedly increased VAS ratings of nausea (mean±SD placebo 0.029±0.08, nicotine 7 mg 0.032±0.09, and nicotine 14 mg 0.156±0.26). Three women vomited after

Table 2 Effects of nicotine

	Placebo	7 mg nicotine	14 mg nicotine
DEQ-like	0.001±0.023	0.029±0.021	−0.085±0.046*
VAS high	0.064±0.020	0.031±0.034	0.088±0.039*
POMS anxiety	0.211±0.302	0.000±0.478	1.737±0.841*
Systolic blood pressure (mm/Hg)	−6.263±1.871	1.842±2.321*	−2.842±2.766

Mean (±SEM) ratings of drug liking, feeling high, anxiety and systolic blood pressure in participants who did not report increases in nausea after nicotine. Values represent mean change from pre- to 120 min post-patch. Possible values for DEQ and VAS change scores range from −1.0 to 1.0. Possible values for POMS change scores range from −4.0 to 4.0. Significant main effects (ANOVA) were obtained on each measure

*Significant (p<0.05) difference from placebo, based on LSD test

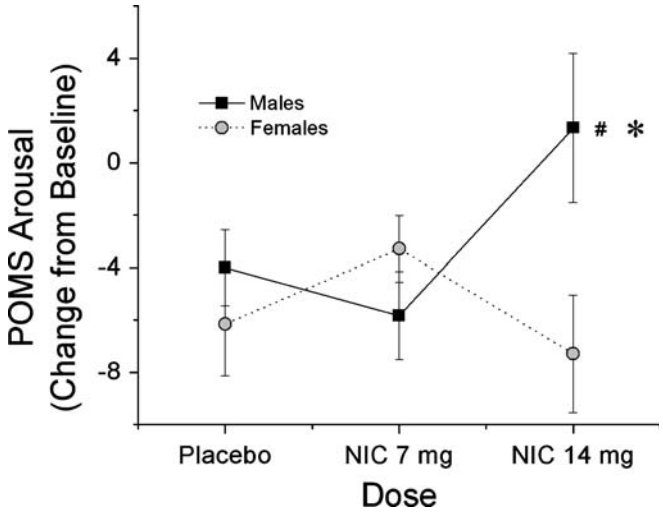

Fig. 3 Mean±SEM POMS ratings of "Arousal" in men (n=12) and women (n=7) not made nauseous by nicotine administration. * indicates significant difference from placebo. # indicates significant difference between men and women

receiving the 14-mg patch. Reports of nausea were not related to habitual smoking, weight, BMI, sex, or race.

The direct effects of nicotine were further examined using only those participants who reported no nausea at either dose. Table 2 depicts significant main effects of nicotine in these participants (12 men, 7 women). Nicotine (14 mg) significantly decreased DEQ ratings of "Liking" the drug effect [F(2, 34)=4.84, p=0.014] and increased ratings of "High" (VAS) [F(2, 34)=4.35, p=0.021], and "Anxiety" (POMS) [F(2, 34)=3.69, p=0.035]. Nicotine (7 mg) significantly increased systolic blood pressure [F(2, 34)=3.35, p=0.047], but nicotine did not affect diastolic blood pressure, heart rate, or temperature. The only significant differences between men and women were on "Arousal" and "Positive Mood" (POMS). Nicotine (14 mg) increased "Arousal" in men and not women [F(2, 34)= 3.44, p=0.044; Fig. 3]. LSD tests revealed that after nicotine (14 mg), ratings of "Arousal" were significantly greater compared to placebo and compared to women after 14 mg nicotine. In contrast, nicotine decreased "Positive Mood" ratings in women but not men [F(2, 34)=7.24, p=0.014; Fig. 4]. LSD tests revealed women had significantly higher ratings of "Positive Mood" than men at placebo and 7 mg nicotine, and women had significantly lower ratings of "Positive Mood" at 14 mg nicotine relative to placebo.

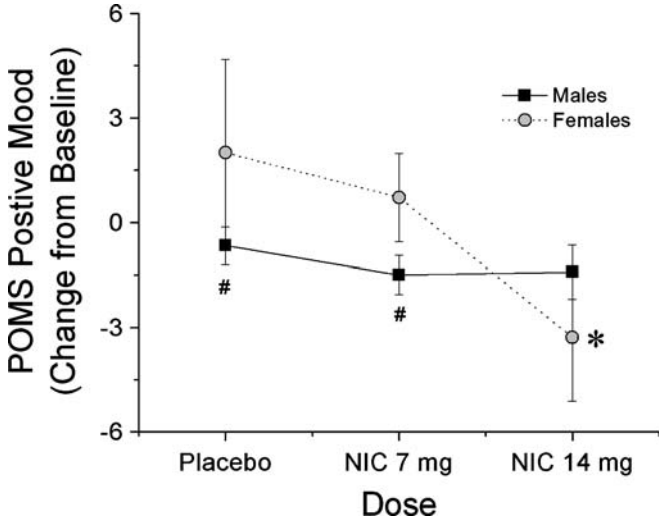

Fig. 4 Mean±SEM POMS ratings of "Positive mood" in men (n=12) and women (n=7) not made nauseous by nicotine administration. *indicates significant difference from placebo. # indicates significant difference between men and women

Effects of nicotine on responses to low dose of ethanol

To determine the effects of nicotine pretreatment on responses to alcohol, change scores were calculated using measures obtained immediately before and after the required alcohol beverage. Nicotine (14 mg) increased ratings of ARCI PCAG [F(2, 34)=4.37, p=0.020], indicating an increase post-alcohol on ratings of sedation. This effect was apparent in both men and women. Nicotine did not change responses to alcohol (0.2 g/kg) on other measures, and it did not alter blood alcohol levels. Regardless of nicotine pretreatment or sex, alcohol appeared to increase heart rate and ratings of "want more" (i.e., scores increased from pre- to post-alcohol in all three patch conditions in both men and women).

Discussion

In this paper, we report several interesting findings on the effects of transdermal nicotine on alcohol consumption in men and women. First, nicotine had differential effects on alcohol consumption in men and women. In men, nicotine (14 mg) increased alcohol consumption, whereas, in women this dose of nicotine decreased alcohol consumption. These effects of nicotine on alcohol choice became more apparent when the data from individuals who experienced nausea were removed from the analysis. Second, the sex differences in the effects of nicotine were especially apparent when the "cost" of the alcohol was varied. In men, nicotine most clearly increased alcohol consumption when the drinks were 'expensive', i.e., when participants were required to pay twice the estimated worth of the drink. In contrast, nicotine most clearly decreased alcohol consumption in women when the cost was low. Third, nicotine alone increased ratings of "arousal" in men, whereas, it decreased ratings of "positive mood" in women.

This study used a recently developed procedure to assess the effects of nicotine on alcohol consumption (Young et al. 2005), in which the equivalent monetary value of a standard drink was individually determined for each participant. This approach addressed the problem that the value of a drink varies across individuals: a fixed amount might have been too high for some participants and too low for others. The sensitivity of this measure was further enhanced by allowing participants to choose between

alcohol and alternative rewards of varying values. The alternative rewards were tokens, exchangeable for money, which varied from half (two tokens) to double (eight tokens) the subject's individualized value for a standard drink. As expected, participants chose alcohol more often when the alternative reward was small, showing that they were sensitive to changes in the experimental contingencies. Interestingly, there were relationships between the effects of nicotine and the value of the alternative reward, which differed in men and women. Whereas in men nicotine increased the choice of the "expensive" eight-token drinks, the drug decreased the consumption of the "cheap" two-token drinks in women. These findings further indicate that different factors control alcohol consumption in men and women.

Our findings are consistent with several past reports on the effects of nicotinic manipulations on alcohol consumption in both humans and laboratory animals (Barrett et al. 2006; Perkins et al. 2000; Potthoff et al. 1983; Smith et al. 1999). Perkins et al. (2000) reported that male, but not female, smokers consumed less alcohol after overnight abstinence from smoking. This is consistent with the idea that nicotine increases alcohol consumption in men. However, there were many methodological differences between Perkins et al. (2000) and the present studies, including the manner of administering nicotine (smoked vs transdermal and acute withdrawal vs acute administration). The present results are also consistent with the finding of Barrett et al. (2006) that light smoking men consumed more alcohol after smoking nicotine-containing, but not denicotinized, cigarettes. However, our study also included women and showed that the effects of nicotine on alcohol consumption may be sex-specific. Our results are also consistent with preclinical studies in which both acute and chronic administration of nicotine increased alcohol consumption (Blomqvist et al. 1996; Le et al. 2000; Potthoff et al. 1983; Smith et al. 1999). Sex differences were not examined in these animal studies, although the effects of nicotine alone are known to differ in male and female rats (Pogun 2001).

This study also provided information on the direct effects of nicotine on mood and physiological state, and these effects may shed light on the changes in alcohol consumption. First, nicotine (14 mg) produced subjective ratings of nausea in about 42% of this light smoking sample, at about equal rates in men and women. This effect is consistent with previous studies in which nicotine was administered to 'chippers' (Kalman 2002). Second, nicotine produced differential effects on mood in men and women. Men reported increased ratings of arousal, and women reported decreased ratings of positive mood. Interestingly, these mood effects in men and women may have influenced participants' choice of alcohol in the latter part of the session. That is, feeling stimulated (in men) may increase alcohol preference and perhaps may reduce the inhibitory influence of the cost of a drink. In contrast, the decreases in ratings of positive mood may have dampened preference for alcohol in women.

We also found that nicotine increased the acute sedative-like effects of alcohol in both men and women. Because this interaction was not sex-specific, it cannot simply account for the observed changes in alcohol consumption. However, this interaction can be compared to other recent reports on nicotine–alcohol interactions (Kouri et al. 2004; Perkins et al. 2000). In the Perkins et al. (2000) study, moderate smokers experienced less sedation from alcohol after normal smoking compared to overnight smoking abstinence, which is not consistent with our findings. However, Kouri et al. (2004) found, as we did, that nicotine (21 mg) increased the sedative-like effects of alcohol (0.4 and 0.7 g/kg) in moderate smokers. In that study, nicotine also increased reports of euphoria and "feeling drunk." We did not measure 'feeling drunk' in an effort to maintain the drug blinding. The enhancement of alcohol-induced euphoria in the Kouri et al. study may be related to the higher doses of nicotine and alcohol used, level of participants' smoking, or time after drinking when subjective effects were measured.

There are at least two possible explanations for the interaction between nicotine and alcohol consumption. First, nicotine appears to enhance the incentive properties of both unconditioned and conditioned reinforcers, perhaps through its effects on dopamine (Donny et al. 2003; Olausson et al. 2004; Rice and Cragg 2004; Zhang and Sulzer 2004). In rats, nicotine increased responses to both an unconditioned visual reinforcer (Donny et al. 2003) and a conditioned auditory reinforcer (Olausson et al. 2004). Thus, at least in men, nicotine appeared to enhance the reinforcing effects of alcohol in this study. Second, it is possible that the nicotine-induced changes in mood states altered the motivation to drink. This possibility could be examined in future studies where mood states are varied through non-pharmacological means.

It is possible that these different effects on men and women may not have resulted from a direct effect of gender, but were related to other sex differences such as body composition. However, neither body weight nor BMI were correlated with nicotine-induced nausea, or with mood changes after nicotine. Men were significantly older than women and there were some differences in prior drug use. Additionally, it is possible that different social factors influence alcohol consumption in men and women. Perhaps, women feel less comfortable consuming alcohol in the laboratory environment while experiencing the subjective effects of unknown drug. Whatever the underlying mechanisms, this is an interesting example of differential effects of a psychoactive drug in men and women, and supports the recognized need for more research on sex differences in the effects of drugs of abuse [(Roth et al. 2004; Terner and de Wit (2006)].

The study had both strengths and limitations. The strengths were the inclusion of men and women, the use of two doses of nicotine, the use of transdermal nicotine to isolate the pharmacological from conditioned effects of nicotine, and the use of a sensitive measure of alcohol consumption. The limitations relate primarily to the subject sample. First, this study used a small sample size, and

many subjects were excluded from the data analysis due to nausea. In addition, these results, obtained with light smokers, may not be generalizable to the broader population of smokers. Our rationale for recruiting light smokers was to minimize the influence of tolerance and dependence, albeit at the cost of the high incidence of nicotine-induced nausea. Similarly, this study used light social drinkers, and it is not known whether other effects would be observed with heavier habitual drinkers. Finally, in our study design we were only able to examine the effects of nicotine on responses to alcohol for a short period of time (i.e., soon after the first required drink). The effects of nicotine later in the time–effect curve of alcohol may yield different results.

This study demonstrates that nicotine, in the absence of sensory cues associated with smoking, has differential effects on alcohol consumption in men and women. Specifically, nicotine increased alcohol consumption in men and decreased it in women. This finding in men is consistent with earlier reports of nicotine-induced increases in alcohol consumption in both men and laboratory animals. However, the decreased consumption in women is a novel finding. The present study also suggested that nicotine has differential effects on the subjective responses to alcohol in men and women. These interesting findings lay the groundwork for future studies investigating the mechanisms underlying these effects.

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