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Effects of Dose, Gender, and Level of Physical Activity on Acute Metabolic Response to Nicotine

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PERKINS, K. A., L. H. EPSTEIN, J. E. SEXTON, R. L. STILLER AND R. G. JACOB. *Effects of dose, gender, and level of physical activity on acute metabolic response to nicotine*. PHARMACOL BIOCHEM BEHAV **40**(2) 203–208, 1991.—The acute thermogenic effect of nicotine was examined in cigarette smokers under conditions of rest and two levels of low-intensity physical activity comparable to that normally engaged in by sedentary adults. Male and female smokers (n = 10 each) each received 0 (placebo), 7.5, 15, or 30 μg/kg nicotine via measured-dose nasal spray once every 30 min for 90 min, with each dose presented on a separate occasion. After each dose presentation, subjects engaged in 10 min of rest or low-intensity activity at 30 or 60 watts (W) using a bicycle ergometer. For males, results indicated that expenditure attributable to nicotine was more than twice as large during 60-W activity compared with rest, while that during 30-W activity was intermediate. For females, expenditure attributable to nicotine was generally similar to that of males during rest and 30-W activity but was significantly lower during 60-W activity, indicating an apparent "inverted-U" relationship with activity intensity. The enhanced effect of nicotine was specific to energy expenditure, since heart rate showed dose-dependent changes that were generally similar regardless of activity level. These findings confirm a mediating influence of physical activity level on the acute metabolic effect of nicotine, especially in males, and may have implications for explaining individual differences in body weight changes due to tobacco smoking and cessation.

Energy expenditure Nicotine Smokers Gender Physical activity

CIGARETTE smoking is commonly associated with lower body weight (1, 17, 25), an effect which may be important in reinforcing smoking behavior (31). There is a large body of evidence that nicotine is the constituent of tobacco smoke responsible for this relationship [e.g., (10,12)]. Nevertheless, smoking and nicotine do not appear to decrease caloric intake in smokers (1, 23, 27) or increase physical activity (1,19), indicating that a thermogenic effect of nicotine may explain the lower body weights of smokers (22,24).

In several studies of males (26, 29, 30), we have consistently found that doses of nicotine approximating the intake of most smokers from a single cigarette produce a 5–7% increase in resting metabolic rate (RMR). Importantly, however, the magnitude of this effect varies greatly depending on the prevailing conditions present during nicotine intake. When compared with its effect at rest in the fasting state, nicotine's effect during low-intensity physical activity may be more than doubled [12% of RMR, (26)], while the effect following meal consumption may be sharply reduced [2% of RMR, (30)]. Given the greater frequency of smoking during casual activity (20) or following a meal (9), compared with fasting rest, these latter results may better approximate the amount of excess expenditure due to nicotine intake by free-living smokers.

Despite these results, a number of questions remain regarding nicotine's acute metabolic effects. First, the enhancement of nicotine's effect during low-intensity physical activity deserves further exploration, since adults spend a majority of their waking hours engaged in such activity (2,7). Although the intensity of activity employed in our previous study (26) approximated that of typical daily tasks of sedentary adult smokers, several hours per day may also be spent in tasks requiring greater exertion (2). It is unclear whether the enhanced metabolic effects of nicotine observed during light activity would be maintained, exacerbated, or suppressed at more strenuous levels of activity. Second, little is known about possible gender differences in these effects, a potentially important factor since smoking appears to exert a greater effect on body weight among females compared with males (38). Some animal research has suggested differences in other effects of nicotine as a function of gender [e.g., (12)]. However, to our knowledge, no study, animal or human, has directly compared the metabolic effects of nicotine in males vs. females. Finally, the dose-response nature of nicotine's metabolic effects is unclear. We previously found a nonlinear effect of dose on RMR, despite linear effects of dose on plasma nicotine and heart rate (29). If such a relationship is confirmed, there may be little difference in the acute metabolic

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consequences of tobacco smoking among smokers who typically absorb different amounts of nicotine per cigarette, although frequency of smoking may still be important.

The present study examined the acute metabolic effects of several nicotine doses in male and female smokers across rest and several relatively low intensities of physical activity simulating the intensity of typical casual activities of sedentary adults. As in our previous research (26, 29, 30), a measured-dose nasal spray procedure was used to standardize nicotine dosing between and within subjects. Heart rate (HR) response was also examined to compare the metabolic effects of nicotine with another effect known to be sensitive to dose (5,28).

METHOD

Subjects

Subjects were 10 male and 10 female smokers who smoked at least 15 cigs/day for 1 year. Males and females were similar in mean age (24.5 vs. 21.3 years, respectively) and smoking history (22.6 cigs/day for 5.7 years vs. 19.4 cigs/day for 2.9 years, respectively). Males and females were not matched in any way so that representative samples of each could be obtained. Thus males weighed more than females (69.6 vs. 60.5 kg), as expected, but there were no differences between genders when body weight was expressed relative to ideal weight for height and gender [3% vs. 0% over ideal for males and females, respectively (21)].

Assessment of Metabolic Rate and Heart Rate

Assessment of metabolic rate involved placement of a Speak-Easy II respiratory mask (Respironics Inc., Monroeville, PA) on the subject's face for collection of expired air O_2 and CO_2 into a 5-1 mixing chamber. Volume of inspired air was measured by Rayfield RAM-9200 spirometer (Rayfield Industries, Waitsfield, VT), while concentrations of O_2 and CO_2 were sampled from the mixing chamber at the rate of 500 ml/min by Beckman OM11 and LB2 analyzers. Volume and gas concentrations were fed continuously into an Apple IIe computer from which energy expenditure (kcal/min), oxygen consumption (VO_2), and respiratory exchange ratio (RER) were calculated from standard metabolic equations using data acquisition software developed by Rayfield Industries.

Heart rate was recorded continuously in beats per min (BPM) and obtained by counting the R-waves from a Grass polygraph displaying the EKG trace.

Nicotine/Placebo Dosing

Nicotine (7.5, 15, and 30 μg/kg) and placebo (0) were presented by a nasal spray pump procedure which produces reliable, dose-dependent increases in plasma nicotine (28,29). The range of nicotine doses (7.5–30 μg/kg, or 0.5–2.0 mg for average subject) was similar to the range of nicotine intake of most smokers from smoking a single cigarette (36). Each dose presentation consisted of 1.14 ml of 0.9% sodium chloride solution, together with the designated amount of nicotine, and peppermint flavoring oil (Lorann Oils, Lansing, MI), which was used to mask the taste and smell of nicotine. This method has been described previously (28,29).

Standardization of Physical Activity Intensity

Level of activity was standardized by having subjects pedal a Schwinn Biodyne bicycle ergometer modified to allow easy pedaling while remaining seated in a comfortable armchair, as described previously (26). During "rest," subjects remained at quiet rest with minimal movement [1 MET (i.e., 1 × RMR, approx. 1.0 kcal/min of energy expenditure)]. For the two levels of low-intensity activity, the ergometer power outputs were set so that subjects would expend energy at the target levels of 2.5 METS [30 watts (W) approx. 2.6 kcal/min] and 4.0 METS (60 W; approx. 4.2 kcal/min). These levels correspond to the energy expended during most of the common tasks performed by adults and are estimated to comprise about 10 out of 16 waking hours of the day (2). Subjects' performance was constantly monitored by an experimenter blind to dosing condition.

Procedure

Each subject participated in 4 morning sessions, one for each dose. Order of doses across sessions was counterbalanced between subjects, and the experimenter was kept blind to subject's dose order. All subjects arrived at the lab at 0800 after abstaining overnight from smoking, caffeine, food, and physical exertion. Overnight (12 h) smoking abstinence was confirmed by expired air carbon monoxide (CO) reading of $\leq$13 ppm. Subjects remained seated throughout each session in a comfortable armchair within a sound-attenuated experiment room. Silver-silver chloride electrodes were attached for HR measurement, followed by placement of the respiratory mask over the nose and mouth for metabolic assessment.

After a 10-min habituation period and a subsequent 15-min rest period to obtain RMR and resting HR, subjects engaged in a 5-min baseline activity period at one of the power outputs (30 W or 60 W) in order to determine expenditure prior to nicotine intake. Following a recovery rest, subjects engaged in a second 5-min baseline activity period at the other power output. Order of presentation of the power outputs was counter-balanced between subjects. A similar recovery rest followed this second baseline activity period. Then, subjects remained at rest for an additional 15 min to ensure complete return of RMR to baseline prior to dosing.

Subsequently, subjects were presented with placebo or one of the nicotine doses before engaging in one of the three intensities of activity (rest, 30 W, 60 W) for 10 min. Following this "trial," subjects rested quietly for nearly 20 min ("recovery") to allow plasma nicotine levels to decline prior to the next trial, involving presentation of the same dose and one of the other two activity intensities. In previous research (29), we have found that an interdose interval of 20 min is sufficiently long to prevent accumulation of plasma nicotine across four dose presentations, indicating that the 30-min intervals of the present study are also adequate. A third trial of nicotine/placebo presentation followed by activity or rest and recovery completed the session. Order of rest/activity intensities within the session was counterbalanced between subjects.

Statistical Analyses

Analysis of variance (ANOVA) was initially employed to: 1) determine any session or gender effects on dependent measures during the baseline rest or activity periods before dosing, and 2) verify the distinction in expenditure among the rest and two levels of low-intensity activity. As noted below, the results of these initial analyses revealed significant or nearly significant differences between males and females in energy expenditure, VO_2, RER, and HR during baseline periods (see the Results section), which made an overall analysis of covariance (ANCOVA) inappropriate (15). (This gender difference most likely was due in part to differences in lean body mass or perhaps aerobic fitness. As noted above, we did not match males and females on any

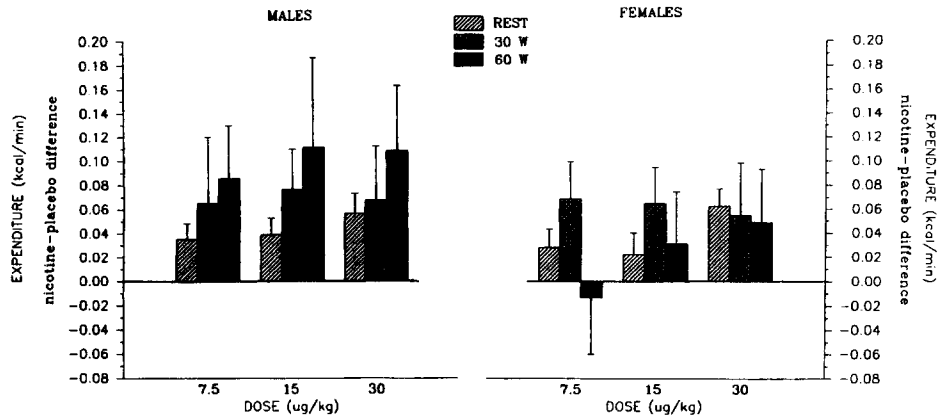

FIG. 1. Change from baseline (rest or activity) in energy expenditure attributable to nicotine (7.5, 15, and 30 μg/kg) in male and female smokers during rest, 30-W activity, and 60-W activity.

characteristic in order to obtain representative samples of each. Nevertheless, expenditure corrected for body weight or lean body mass was still significantly different between males and females during baseline activity.) Therefore, for all dependent measures, the effects of nicotine during activity trials were determined by separate ANCOVAs for males and females. Baseline rest or activity values served as covariates, and activity intensity (rest, 30 W, 60 W) and dose (0, 7.5, 15, 30 μg/kg) were within-subjects variables. Follow-up comparisons were conducted by Fisher's least significant difference *t*-test (15).

RESULTS

Energy Expenditure

Baseline differences. Energy expenditure was distinctly different among the baseline rest and two activity periods, $F(2,36) = 4051.62$, $p<0.0001$, as expected. There were no effects of session, $F(3,54) = 1.14$, n.s., or activity × session interaction, $F(6,108)<1$, confirming the effectiveness of counterbalancing the order of doses and activity intensities. However, there was a nearly significant effect of gender on baseline expenditure, $F(1,18) = 4.00$, $p<0.07$, as expenditure was lower for females than males during baseline rest (mean ± S.E.M. = 0.94 ± 0.01 vs. 1.08 ± 0.04 kcal/min, respectively), 30-W activity (2.55 ± 0.03 vs. 2.73 ± 0.07 kcal/min), and 60-W activity (4.23 ± 0.05 vs. 4.28 ± 0.08 kcal/min). Significant or nearly significant gender differences were also seen for baseline VO_2, $F(1,18) = 3.77$, $p<0.10$, and RER, $F(1,18) = 5.62$, $p<0.05$, as well as HR (described below). Therefore, despite the standardization of absolute intensity of activity designed to elicit similar absolute expenditure across subjects regardless of body weight, responses of females prior to nicotine dosing were still different from those of males. Because of these differences, analyses were conducted separately for males and females.

Nicotine effects. For males, energy expenditure was significantly increased by dose, $F(3,26) = 4.96$, $p<0.01$, and there was a significant interaction of dose × activity level, $F(6,53) = 10.71$, $p<0.001$, as the thermogenic effect of nicotine was enhanced during activity compared with rest. As shown in Fig. 1, this enhancement appeared to be linearly related to activity intensity; expenditure attributable to nicotine (i.e., difference from placebo) during 60-W activity was at least double that during rest, with expenditure due to nicotine during 30-W activity intermediate between 60-W activity and rest. Follow-up comparisons confirmed that the increased expenditure due to nicotine during 60-W activity was significantly greater than that during rest, $t(18) = 3.34$, $p<0.01$. However, this increase was only marginally greater than that during 30-W activity, $t(18) = 1.86$, $p<0.10$, and there was no reliable difference between 30-W activity and rest, $t(18) = 1.49$, n.s. Detailed examination of the effects of each dose revealed that expenditure due to the 15 μg/kg dose was significantly enhanced during 60 W activity compared with rest, $t(18) = 2.29$, $p<0.05$, but other comparisons were not significant.

For females, energy expenditure was only marginally increased by dose, $F(3,26) = 2.41$, $p<0.10$, but there was a significant dose × activity interaction, $F(6,53) = 11.59$, $p<0.001$. In contrast with males, the metabolic effects of nicotine in females appeared to be related to activity intensity in an "inverted-U," rather than linear, fashion (see Fig. 1). Consistent with this notion, follow-up comparisons indicated that the increase in expenditure due to nicotine during 60-W activity was significantly less than that during 30-W activity, $t(18) = 2.29$, $p<0.05$, while there was no significant difference between 60-W activity and rest, $t(18)<1$, or between 30-W activity and rest, $t(18) = 1.43$, n.s. In detailed comparisons, the effect due to the 7.5 μg/kg dose was significantly less during 60 W activity compared with 30-W activity, $t(18) = 2.36$, $p<0.05$, but there were no other significant differences. Despite the apparently different pattern of results for females compared with males, there was actually very little difference between them in expenditure due to nicotine during rest (0.044 vs. 0.037 kcal/min for males and females, respectively, averaged across doses) or 30-W activity (0.070 vs. 0.063 kcal/min). As shown in Fig. 1, only during the 60-W activity were the effects of nicotine different between males and females (0.102 vs. 0.022 kcal/min).

To determine whether the gender difference in body weight or lean body mass may have contributed to the observed difference in metabolic effect of nicotine during 60-W activity between males and females, the results for energy expenditure were reanalyzed twice, after correcting for body weight and for lean body mass (LBM). The results of each reanalysis were virtually identical with the results reported above for absolute expenditure, uncorrected for body weight. Thus the similarity between males and females in expenditure attributable to nicotine during rest and 30-W activity and the difference between them in expenditure during 60-W activity remained after correcting for gender differences in LBM (58.0 vs. 49.0 kg of LBM for males vs. females). For males vs. females, respectively, ex-

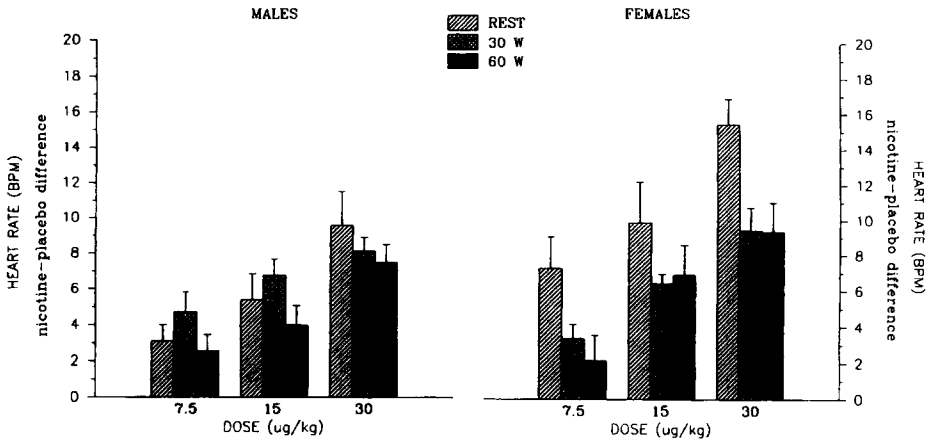

FIG. 2. Change from baseline (rest or activity) in heart rate attributable to nicotine in male and female smokers during rest, 30-W activity, and 60-W activity.

penditure due to nicotine was 0.045 vs. 0.045 kcal/kg of LBM/hour during rest, 0.072 vs. 0.077 kcal/kg of LBM/hour during 30 W activity, and 0.106 vs. 0.027 kcal/kg of LBM/hour during 60-W activity.

Similar to results for energy expenditure, the increase in VO_2 due to nicotine dose was significant for males, $F(3,26)=4.73$, $p<0.01$, but only marginally significant for females, $F(3,26)=2.58$, $p<0.10$. There was no significant effect of nicotine dose on RER for either males or females, $F(3,26)<1$ for both, as RER declined from baseline during the rest and activity trials across all doses.

Heart Rate

In addition to gender differences in baseline energy expenditure, HR was significantly higher in females compared with males, $F(1,18)=8.27$, $p<0.01$, during baseline rest (mean ± S.E.M. = 66.2 ± 1.3 vs. 60.4 ± 2.9 BPM, respectively), and the baseline activity periods at 30 W (91.0 ± 1.2 vs. 82.3 ± 3.0 BPM) and 60 W (109.7 ± 2.0 vs. 96.3 ± 3.6 BPM). For males, HR was significantly increased from baseline (rest or activity) by dose, $F(3,26)=40.88$, $p<0.001$, but not activity intensity, $F(2,17)<1$, as shown in Fig. 2. Therefore, the enhancement of nicotine's metabolic effect during activity was not observed with nicotine's effect on HR. In general, similar results were seen for females, as HR was significantly increased by dose, $F(3,26)=89.39$, $p<0.001$, but not activity, $F(2,17)=1.53$, n.s., also shown in Fig. 2. However, there was a significant dose × activity interaction effect, $F(6,53)=13.08$, $p<0.001$, in which females exhibited a larger HR response to nicotine during rest compared with 30-W activity, $t(18)=2.04$, $p<0.06$, or 60-W activity, $t(18)=2.16$, $p<0.05$. Notably, this pattern contrasts sharply with the pattern of results observed for energy expenditure (see Fig. 1).

DISCUSSION

The magnitude of the acute metabolic effect of nicotine was found in this study to be significantly influenced by intensity of physical activity. For males, across doses, nicotine's effect during 60-W activity was at least double the effect at rest, with the effect during 30-W activity intermediate. For females, however, the effect of nicotine during 60-W activity tended to be similar to that during rest but significantly less than nicotine's effect at 30-W activity, suggesting an "inverted-U" relationship of activity intensity with the thermogenic effect of nicotine. On the other hand, the metabolic responses of males and females to nicotine during rest and 30-W activity were virtually identical (Fig. 1), suggesting that any gender difference in metabolic effects of nicotine is confined to activity involving more strenuous exertion (i.e., at least 60-W intensity). Because of the relative infrequency of this intensity level of activity among sedentary smokers (19), this particular gender difference in response to nicotine may have little impact on energy balance. Indeed, the finding from this study of equal or reduced metabolic effects of nicotine in females appears to offer little help in explaining the greater effect of smoking on lowering body weight in females vs. males (38), and gender differences in nicotine effects on caloric intake may be more important (12, 13, 23).

It appears clear from this and several other recent studies that the metabolic effect of nicotine (or smoking) at rest, the condition arranged in most previous studies (24), provides only limited information concerning the potential influence of nicotine on energy expenditure in free-living humans. When the conditions under which nicotine is typically consumed are simulated, the magnitude of the acute metabolic effect of nicotine is often increased. Consistent with the findings from this and our previous study of activity (26), results from Hofstetter et al. (14) also suggest an enhanced effect of smoking during low-intensity physical activity. Tobacco smoking vs. no smoking prior to treadmill walking produced an increase equal to 10% of RMR in male and female smokers, larger than results of typical studies of effects of smoking in resting subjects (24). In addition, their subjects showed a 10% increase in total 24-h expenditure due to smoking, compared with not smoking, while engaged in spontaneous sedentary activity in an indirect calorimetry chamber. Furthermore, similar to the present study, another recent study found an apparently enhanced effect of caffeine on oxygen consumption during fairly strenuous exercise in males despite no enhancement of HR response (8), suggesting that activity-induced enhancement of metabolism may generalize across other commonly consumed drugs with thermogenic effects. Given the greater frequency of smoking during casual physical activity compared with quiet rest, greater attention to the metabolic effects of smoking under these conditions is needed. Thus it would seem that Roth et al.'s (34) observation from nearly a half century ago aptly describes the current state of this research: "Although most smoking occurs while a person is sitting or walking,

it appears from the literature that little work has been done under these conditions (p. 765)."

In this study, closer examination of metabolic effects of nicotine at rest, collapsed across males and females, revealed a dose-response relationship that appeared nonlinear at the lower end of the range, virtually identical to our previous study with male smokers (29). In the present study, the increases attributable to 7.5 and 15 μg/kg nicotine during rest (i.e., difference from placebo) were 0.032 and 0.031 kcal/min, respectively (vs. 0.059 kcal/min for 30 μg/kg). In our previous study (29), the increase for both the 7.5 and 15 μg/kg doses was 0.034 kcal/min. In both studies, this nonlinearity of metabolic response contrasted with linear increases in HR across doses. Therefore, across the lower end of the range of nicotine intake among regular smokers there may be little difference in the acute metabolic effects of tobacco smoking. Notably, Astrup et al. have reported a similar nonlinear metabolic effect of caffeine at the lower range of doses (3), as well as evidence for a synergistic metabolic effect between caffeine and ephedrine (4).

Additional research is needed to identify specific mechanisms responsible for the enhanced metabolic effect of nicotine during activity. Activity-induced changes in nicotine disposition may be important. However, given the very acute nature of the activity of the present study (i.e., 10 min in duration) and the typical half-life of approx. 2 h for nicotine in the body (5), alteration in nicotine disposition may be a less likely explanation. In addition, HR change was related to nicotine in a linear dose-dependent fashion regardless of activity intensity (i.e., additive with activity), while metabolic change was more closely dependent on activity intensity rather than nicotine dose. Thus, whatever the explanation for enhanced metabolic effects of nicotine during activity, it most likely is specific to metabolism and does not involve general changes with widespread effects. On the other hand, the enhanced metabolic effect of nicotine during activity appears to increase with duration of activity (26). Therefore, this extended enhancement of nicotine's metabolic effect during continuous, uninterrupted activity could be at least partially explained by changes in the disposition of nicotine (37) or the actions of catecholamines, especially norepinephrine (18, 32, 35). Interestingly, cocaine intake during physical activity has been found to produce enhanced (i.e., greater than additive) effects on plasma norepinephrine and epinephrine in rats (6).

Replication of the apparent gender difference in metabolic effects of nicotine during more strenuous activity (i.e., 60 W) is also needed. It is possible that a direct comparison between genders is somewhat misleading because of the different relative intensities of the activity trials between males and females due to differences in body weight or perhaps physical fitness (2). Thus a similar lack of metabolic influence of nicotine may be observed in males at even higher intensities of activity. Nevertheless, gender differences in response to nicotine have been noted in the literature. For example, Grunberg et al. (12) found that nicotine's appetite-suppressing effect may be greater in female compared with male rats. Gender differences in the disposition of nicotine have also been observed in humans (5) and rats (33). Conceivably, our findings may also be explained by gender differences in effects of nicotine on substrates responsible for its metabolic effect during activity, such as catecholamine release and resulting changes in insulin (11), glucose, or free fatty acid mobilization (16). However, we are unaware of research directly bearing on this possibility.

Since the enhanced metabolic effects of nicotine during activity would be removed following smoking cessation, these findings may provide a means by which to help explain the large individual differences in weight gain after cessation (17,38). Smokers who smoke mostly while busy with daily tasks would be likely to weigh less while still smoking and to gain more weight after stopping smoking, compared with smokers who smoke mostly at rest or after meals (30), holding constant caloric intake and overall physical activity. As noted, these implications may be more relevant for male than for female smokers, who demonstrated no enhancement of nicotine's effect during 60-W activity in the present study. Interestingly, recent results from Williamson et al. (38) tend to support this notion and the possible gender difference observed in this study. They found that engaging in recreational physical activity while still a smoker was directly related to amount of subsequent weight gain after smoking cessation in men but inversely related to weight gain in women. This gender difference in the relationship between habitual activity while a smoker and subsequent weight gain after quitting could be partly explained by removal of the metabolic effect of nicotine during moderate activity (i.e., 60 W), which as shown here may be substantially enhanced in males but reduced in females. Since nicotine replacement therapy (i.e., nicotine gum) attenuates weight gain after smoking cessation (10), it would be important to determine if a similar metabolic enhancement occurs when nicotine is consumed via this and other means during physical activity. Greater understanding of these effects could improve prediction and control of weight gain after cessation of nicotine intake, perhaps decreasing the likelihood of smoking relapse (17).

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