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Nicotine Effects during Physical Activity

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1. INTRODUCTION

Nicotine is one of the most widely used drugs in the world and is the critical ingredient that promotes tobacco use and dependence [1]. Although health risks due to nicotine *per se* are believed to be modest, tobacco consumption substantially increases health risks. Tobacco smoking is responsible for approximately three million deaths annually worldwide, a toll that is rising [2].

Nicotine elicits an array of subjective (mood), behavioural, and physiological effects in humans, and many are implicated in the onset and maintenance of tobacco dependence [1]. The vast majority of laboratory studies examining these effects in humans have done so under standardized conditions, with subjects free of recent drug or food consumption and maintained in a quiescent, restful state. This procedure can allow for cleaner examination of the effects of nicotine in isolation. However, results of these studies may not be very relevant to understanding the effects of nicotine in the natural environment since nicotine consumption via tobacco smoking usually occurs in conjunction with many other influences. Perhaps chief among these influences is light physical activity. Most adults perform various common tasks throughout the course of the day, such as office work, house work, walking, driving, and so on. Light activity of this kind comprises most of one's waking hours [3,4]. Thus, a clear understanding of nicotine's effects in the natural environment may not be possible without examining nicotine in conjunction with light activity [5].

This paper will review the modulating influence of light physical activity on selected subjective, metabolic, and cardiovascular effects of nicotine in humans, with emphasis on studies from the author's laboratory.

2. GENERAL PROCEDURES

2.1. Standardization of Activity

In each study, physical activity was standardized by having subjects pedal a cycle ergometer modified to allow easy pedalling while remaining seated behind it in a comfortable armchair. The activity level used in most studies was that producing a power output of 30 Watts, or 2.5 METs (2.5 times the energy expenditure at rest). To help subjects maintain

ergometer pedalling at 60 rev/min, a metronome and/or cycle ergometer speed sensor and feedback indicator were employed [6]. Subjects were also closely monitored to ensure compliance with instructions.

The activity level used was quite modest and much less intense than aerobic exercise, producing a heart rate increase of only about 20 beats/min (versus 80-100 beats/min increase during aerobic activity). This low intensity was employed because smokers are less likely than nonsmokers to engage in more intense activity (e.g. exercise) and, in any case, are very unlikely to do so while smoking. Therefore, examining effects of higher-intensity activity would have little relevance to naturalistic conditions.

2.2. Nicotine Dosing

Nicotine and placebo were administered in each study using a measured-dose nasal spray delivery procedure developed in our laboratory [6,7]. Doses were usually 15 or 20 μg/kg, comparable to the nicotine yield of a typical cigarette (approx. 1 mg). Doses were generally administered every 20 or 30 minutes for 60-120 minutes, to simulate intermittent cigarette smoking typically observed in the natural environment. This nasal spray procedure has several important advantages over tobacco smoking in examining nicotine effects in humans, primarily better control over nicotine dose administration. Dosing is extremely difficult with smoking because of variable puffing behaviour [8], which can be further altered depending on the situation, including physical activity, alcohol use, or psychological stress. Other advantages include the ability to correct nicotine doses for subject's body weight (as in animal studies) and to isolate effects due to nicotine as opposed to the thousands of other compounds in tobacco smoke. This method administers nicotine to the brain within minutes, slower than tobacco smoke inhalation but much more rapid than other common nicotine delivery systems such as gum or patch. It remains to be seen whether effects observed with nicotine nasal spray are completely generalizable to effects of tobacco smoking, but some research suggests close comparability of effects [9].

2.3. Other Common Procedures

Subjects in each study were young healthy smokers who smoked at least 15 cigarettes/day for at least one year. Each was given a full physical examination, interview, and urine drug screen to rule out presence of medical or psychiatric problems that would preclude their participation. Subjects were paid for their participation. Experimental sessions were conducted in the morning, following overnight abstinence from smoking, caffeine, and food. Each study usually involved a within-subjects design, in which each subject served as his or her own control and received all conditions being studied. Order of conditions across sessions was counter-balanced between subjects.

3. SUBJECTIVE EFFECTS

3.1. Subjective Arousal

Nicotine has been shown to produce mild "stimulant" subjective effects (e.g. increased vigour and arousal) under quiet, restful conditions. It is not clear that these effects are typically experienced by smokers in the natural environment, who are often engaged in various activities. We [10] examined the subjective effects of 20 μg/kg nicotine vs. placebo in male

and female smokers under conditions simulating light physical activity (described above) versus rest. Effects of 5 mg/kg caffeine (comparable to 3 cups of coffee) vs. decaffeinated coffee were also examined for comparison. Conditions were presented in separate sessions in a completely within-subjects design. Subjective "arousal" was significantly increased by nicotine alone under rest conditions (Fig. 1), as typically observed, but *completely attenuated* under activity. This attenuating effect of activity was found with both arousal measures (arousal portion of Stress-Arousal Check List [SACL], shown, and the Profile of Mood States [POMS] arousal scale) as well as the POMS vigour scale. Notably, there was no significant attenuating effect of activity on the arousing effects of caffeine, demonstrating pharmacological specificity of this influence. These results indicate that some subjective effects often attributable to nicotine intake may be less prominent when individuals smoke while engaged in casual activity. An increase in intensity of smoking (and amount of nicotine intake) may therefore be necessary in order to overcome this attenuating effect of activity.

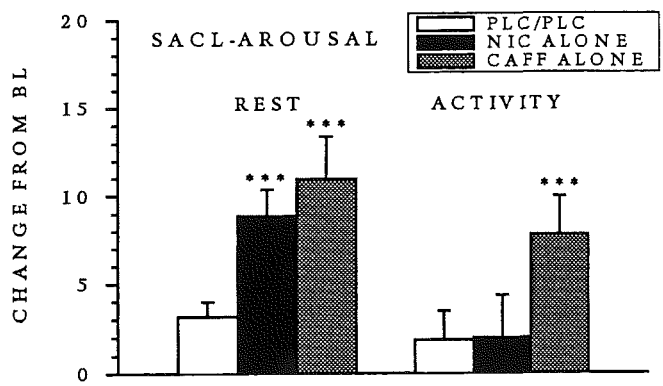

Fig. 1. Mean ± SE change from baseline (BL) rest or activity in SACL-Arousal self-report following drug intake during quiet rest and light physical activity (N=19).
*** P <0.001 for difference from placebo.

3.2. Perceived Exertion

Just as activity may attenuate some subjective effects of nicotine, nicotine may alter perception of physiological responses during exertion. For example, smoking and nicotine intake may reduce perception of muscle tension during exertion and attenuate pain sensitivity [see 11]. Because of these actions, nicotine may also alter perceived exertion during physical activity. Attenuation of perceived exertion, as well as muscle tension and pain sensitivity, could clearly contribute to reinforcement of tobacco smoking behaviour.

We examined the effect of intermittent administration of 0, 7.5, 15, and 30 μg/kg nicotine by nasal spray on ratings of perceived exertion (RPE, range = 6-20, "very very light" to "very very hard", resp.) during light (30 Watts) and moderate (60 Watts) physical activity by using a cycle ergometer [11]. (As stated previously, more strenuous work-rates were not employed since smokers are less likely than nonsmokers to engage in high-intensity exercise and, in any case, are very unlikely to do so during or immediately after smoking.) On each of four sessions, corresponding to the four nicotine doses, male and female smokers (n=10 each) pedalled at each of the two work-rates for 10 min, with a 20-min recovery period between the activity periods. Work-rates were assigned in counter-balanced order between subjects. Mean RPE was 8.7 at 30 Watts and 12.3 at 60 Watts, confirming the modest but different exertion

levels produced by the work-rates. In contrast with the attenuating effect of activity on the "arousing" effects of nicotine, above, nicotine had no significant effect in altering RPE during either work-rate. This lack of effect on RPE was observed despite clear dose-dependent increases in heart rate and systolic and diastolic blood pressure due to nicotine during activity.

In summary, the relationship between nicotine and activity on subjective ratings may be asymmetrical; light physical activity may attenuate the subjective arousal effects of nicotine but nicotine may have no effect on perceived exertion during light physical activity. It remains to be seen if RPE at higher-intensity activity is also unaffected by nicotine. Furthermore, smokers often have higher RPEs than nonsmokers at the same work-rate, even after controlling for possible differences in aerobic fitness [7]. This suggests that tobacco smoking (but probably not nicotine) may have chronic effects on increasing perceived exertion.

4. METABOLIC EFFECTS

There has been considerable interest in the effects of nicotine on energy expenditure, particularly because of the inverse relationship between smoking status and body weight [12]. For smoking to influence body weight, it would have to reduce food intake, increase energy expenditure, or both. Much of the weight-lowering effect of smoking is due to a reduction in eating, but some of it is also due to acutely increased energy expenditure (i.e. metabolic rate). There appears to be little chronic effect of smoking on resting energy expenditure (REE). Rather, each instance of smoking or nicotine intake causes a brief increase in expenditure of about 5-7% at rest for approximately 30 min after intake [12]. Although this effect is brief, most smokers consume nicotine once every 30-60 min in the absence of imposed restrictions, indicating that a regular pattern of smoking acutely increases energy expenditure for most of the day.

Although statistically significant, the magnitude of this acute increase in REE due to nicotine at rest is insufficient to account for much of the difference in body weight due to smoking. Importantly, there is clear evidence that the effect of nicotine on energy expenditure is substantially *enhanced* when consumed in conjunction with light physical activity [12]. This offers an explanation for how the metabolic effects of nicotine can, in fact, account for much more of the weight-reducing influence of smoking, since most smokers experience the effects of nicotine while performing various sedentary activities.

In our first study of nicotine's metabolic effects during light activity [7], male smokers (n=20) and nonsmokers (n=10) participated in two sessions, light activity (by cycle ergometry) or rest. Half of the smokers were administered 15 μg/kg nicotine every 20 min for 60 min on both days, while the other half were administered placebo. All nonsmokers received placebo on both days. The increase in REE attributable to nicotine was approximately 5%, consistent with other studies. However, the magnitude of this metabolic effect during light activity was more than doubled (Fig. 2), so that the increase attributable to nicotine during activity equalled 12% of REE. Such an effect of nicotine intake during casual activity in the natural environment could explain much of the change in energy balance due to smoking not accounted for by the change in eating. There was no difference between the groups of smokers and nonsmokers receiving placebo, indicating no chronic effect of smoking status on REE.

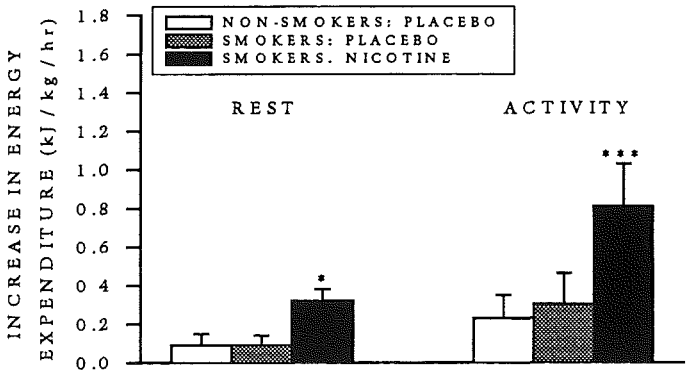

Fig. 2. Mean ± SE change from baseline rest or activity in energy expenditure following nicotine or placebo during quiet rest and light activity (N=10 each group).
* P <0.05 for difference from baseline.
*** P <0.001 for difference from baseline.

We have since replicated the enhanced metabolic effect of nicotine during light activity in two additional studies. In one [13], male and female smokers were administered 0, 7.5, 15, and 30 μg/kg nicotine, with one dose on a separate day. During each session, subjects rested quietly, pedalled at 30 Watts, and then at 60 Watts, with the order of conditions counter-balanced between subjects. Results showed that energy expenditure attributable to nicotine was enhanced in men in linear fashion with increasing work-rate (i.e. largest at 60 W, which was greater than the effect at 30 W, which was greater than the effect at rest). Although there was slight enhancement in women at 30 W, there was no enhancement of nicotine's effects at 60 W, indicating a curvilinear relationship of work-rate with enhancement of nicotine's metabolic effect.

In the second replication [6], male and female smokers participated in 8 sessions, involving administration of 15 μg/kg nicotine vs. placebo, 5 mg/kg caffeine vs. de-caffeinated coffee, and engagement in quiet rest vs. light activity (30 W), in a 2 (nicotine) x 2 (caffeine) x 2 (activity) design. Nicotine and caffeine each increased energy expenditure, and the effects of the two drugs combined were additive. As previously observed, there was significant enhancement of energy expenditure attributable to nicotine alone in men during light activity compared with rest. Expenditure attributable to caffeine alone and to nicotine combined with caffeine was also enhanced in men during activity compared with rest. However, in women, there was no activity-induced enhancement of the metabolic effects of nicotine, caffeine, or the two combined. Plasma nicotine levels were increased 10% by activity, suggesting that activity may slow clearance of nicotine from the body. Nevertheless, this altered kinetics of nicotine by activity was far too small to explain the substantial metabolic enhancement. Moreover, there was no significant alteration in caffeine kinetics by activity, despite the similarly enhanced metabolic effect.

Finally, we also examined individual differences in magnitude of acute metabolic response to 15 μg/kg nicotine at rest in 38 young male smokers [14]. Regression analyses indicated that this response was significantly related to aerobic fitness ($r = 0.58$) and typical physical activity (assessed by Leisure-Time Activity Survey, $r = 0.44$), as well as duration of smoking history ($r = 0.43$). Percent body fat was only marginally related to response ($r = -0.23$), and body weight was not related at all. Therefore, male smokers higher in fitness and with higher typical activity levels are likely to experience greater metabolic response to nicotine. Combined with the enhancing effect of engaging in activity following nicotine intake in men, this individual

difference suggests that smoking can produce substantial energy expenditure in more fit and active male smokers, perhaps accounting for some of the variability in weight change due to changes in smoking [12].

To summarize, in three studies, we found that the acute metabolic effects of nicotine were enhanced during light activity compared with rest in male smokers. This enhancement was generally not observed in women. Similar enhancement of metabolic effects due to tobacco smoking during light activity vs. rest in male smokers [15] has been found, indicating that this enhancement generalizes to nicotine intake by smoking. The sex difference in the influence of activity on metabolic effects of nicotine is puzzling since the difference in body weight due to smoking is greater in women than in men [16]. A smaller metabolic effect of nicotine in women despite a larger body weight difference due to smoking indicates that smoking must alter food intake to a much greater degree in women versus men [16]. The comparable activity-induced enhancement of REE following caffeine as well as nicotine shows that this enhancing effect of activity may occur with any thermogenic drug. Mechanisms to explain activity-induced enhancement of metabolic effects of nicotine are not clear, but altered drug kinetics is very unlikely. More probable is the notion that activity and nicotine (as well as caffeine and other thermogenic drugs) combine to produce greater than additive increases in catecholamines, particularly noradrenaline, which promotes energy expenditure [12]. Notably, animal studies have demonstrated activity-induced enhancement in catecholamine release following exposure to other drugs [17].

5. CARDIOVASCULAR EFFECTS

Although research has shown enhancement of metabolic effects of nicotine when combined with physical activity, there has been a consistent demonstration of a *lack* of enhanced cardiovascular effects of nicotine during activity. In each of the metabolic studies noted above, we simultaneously examined cardiovascular responses (heart rate [HR], systolic [SBP] and diastolic [DBP] blood pressure). Nicotine produced linear dose-dependent increases in each of these responses at rest as well as during light physical activity, which itself increases HR and SBP [6,7,13]. For example, in a study of nicotine and caffeine effects [6], we found that, relative to placebo, nicotine significantly increased HR, SBP, and DBP to virtually the same extent during quiet rest as during light activity. Similar additivity of cardiovascular actions was observed for caffeine during activity. Moreover, this additive cardiovascular effect of nicotine and activity was observed in women as well as men, in sharp contrast to the sex differences in metabolic results. Cardiovascular effects of nicotine and caffeine at rest were also additive, consistent with their additive metabolic effects. These results are consistent with the additive cardiovascular effects of nicotine combined with other influences, such as meal consumption [18] or psychological stress [19].

It is perhaps useful to examine the magnitude of the cardiovascular versus metabolic effects of nicotine, relative to effects due to light physical activity, in order to gauge the "metabolic appropriateness" of nicotine's cardiovascular effects. Increased cardiovascular responses due to physical activity are required in order to meet the increase in metabolic need (e.g. increased blood flow to muscles). Greater cardiovascular increases beyond that necessary to meet metabolic need may signify a pathogenic process. We have found [6] that the HR increase due to 20 μg/kg nicotine (+8 beats/min) is about 40% as large as that due to 30 Watts light

activity (+20 beats/min). Nicotine's influence on SBP is also slightly less than half that due to light activity. However, the metabolic effect of nicotine at rest (approximately 0.2 kJ/kg/h) is only about 4% as large as that due to light activity (5 kJ/kg/h), or about one-tenth the relative magnitude of its cardiovascular effects. This suggests that the cardiovascular increases due to nicotine are not metabolically justified.

6. CONCLUSIONS

This research demonstrates that, when discussing nicotine's effects during physical activity, it is essential to clarify which response domain (subjective, metabolic, cardiovascular) is the focus of discussion. We have found that activity can attenuate subjective arousal effects of nicotine, enhance acute metabolic effects of nicotine (in men), and have additive cardiovascular effects with nicotine. Nicotine also appears to have no effect on perceived exertion during light activity. This "response-specificity" of the influence of activity on nicotine also suggests that different mechanisms are probably responsible for the different types of responses. At the very least, these effects show very different dose-response relationships with that mechanism (e.g. catecholamines could have different dose-dependent influences on subjective vs. metabolic vs. cardiovascular responses). Future research should focus on identifying the precise mechanisms responsible for activity's influence on these different effects of nicotine. It would also be useful to determine whether similar effects are observed at more intense levels of activity, such as aerobic exercise.

7. ACKNOWLEDGMENTS

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Discussion: Nicotine effects during physical activity

J.P. Clarys:

I was a little bit surprised to hear that gum is slower in the delivery of nicotine while it is known that chewing those type of nicotine gums creates immediate dizziness and, in some cases, long-term dizziness. Is that not contradictory?

K.A. Perkins:

As in smoking, the intensity with which you chew the gum determines the delivery of nicotine. So I suppose within several minutes of vigorous chewing, you could get enough nicotine to begin to have those subjective effects. But using it people are normally instructed -fairly repeated chewing and then parking it between the cheek and gum for a while, then chewing- results in the rise in plasma nicotine I showed.

G. Atkinson:

There is evidence to suggest that nicotine absorption through the transdermal route is speeded up by exercise itself. Do you think this could have occurred with the nasal spray route, and if so, might it explain the increased thermogenic effects?

K.A. Perkins:

We have looked at plasma levels and actually have seen a very slight, but significant effect on plasma levels during activity such that they are higher. But it is on the order of about 10% which is not huge vs the more than doubling of the thermogenic effect. So I tend to discount that as the primary mechanism for that effect. There is some work in man showing that the effects of caffeine and cocaine on catecholamines are greatly enhanced during activity vs rest, that it is a more than additive effect. Unfortunately we have not measured catecholamines, but I think that there is probably a greater than additive effect on catecholamine increase due to nicotine and to the physical activity. But you are right. The kinetic effect really needed to be ruled out first, and we think that we have done that.

M. Orme:

I liked your model to try to get away from the problem of interindividual variation. I wonder whether any more could be explained by variations in the metabolic conversion of nicotine to cotinine. Some individuals may have more cotinine than others and this could explain the difference particularly as cotinine has pharmacological activity.

K.A. Perkins:

There is certainly a wide variability in the kinetics of nicotine, and in the production of cotinine. There are very rare individuals in which there is no C-oxidation at all and they have virtually no cotinine whatsoever, whereas typically you have 10 times the level of cotinine compared with nicotine in regular smokers. But beyond that, I really cannot address the individual differences.

P.M. Clarkson:

Athletes by and large do not smoke. However, there is one group of athletes for whom smoking is the norm and that is classical ballet dancers. These dancers do smoke to maintain weight, primarily. You present one mechanism on how weight maintenance would occur. If you would ask the dancers, they believe that smoking suppresses appetite.

K.A. Perkins:

It appears that in women the thermogenic effect of nicotine is much less marked. Therefore, not only does that not explain the greater effect on weight in women, it actually argues against it. So by the process of elimination, it has to be more on the appetite side that smoking impacts. We have done some work and there is other work to suggest that in fact smoking does have a greater effect on food intake in women than in men.

T. Reilly:

Nicotine is a stimulant and yet, it is used by many high performers to relax. I think you refer to this as your paradox, the nicotine paradox. By definition, a paradox is an apparent contradiction or conflict but there are a number of theories floating around. Which one do you think is the preferable one?

K.A. Perkins:

Nicotine paradox is not my term. It is from a review paper in the early 70s. I have just pointed out that nicotine seems to have these differential, opposing effects. I think that the best explanation is that if you have a high baseline degree of arousal, anxiety, etc. nicotine can decrease those levels. This is similar to the rate-dependent effects of drugs from behavioral pharmacology. If you already have a low baseline-level of arousal, etc., nicotine can produce an increase. It is often called a stimulant, but I think that is based on, first of all, the cardiovascular effects, which seem to occur regardless of the baseline state. If you are active and your heart rate is high, nicotine will not be additive with that.

D.A. Cowan:

My question is one of ethics. We need research funding, sport needs money. Should we associate sport with tobacco sponsorship? Should we have research funding based on tobacco sponsorship? I would like to hear your views.

K.A. Perkins:

That certainly is an issue in the United States. I think the evidence is pretty clear that, at least until the present time, there has been quite a bit of censorship on the part of the tobacco industry in terms of how and whether the results are published. There has been control over their own scientists' work and there has been control over external scientists' work, in terms, particularly, of who gets funded. I would not say that this is necessarily what everybody believes but that is my view on it, at least.

T. Reilly:

I think there are quite a few stories which would extend that. In the U.K., for example, to save the tobacco industry tax ten years ago, the Health Promotion Research Trust was set up, which was fuelled by money from the tobacco industry. That created a whole series of

questions for the people who were seeking funding, because essentially when funding is low, many people will seek grant aid from whoever it is available.

B. Ekblom:

The Karolinska Institute had an offer from the tobacco industry but this was turned down on the basis that the Institute did not want to be linked to the tobacco industry. I think they had got it right, although there was a lot of money involved.