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Nicotine Discrimination in Men and Women

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PERKINS, K. A. *Nicotine discrimination in men and women.* PHARMACOL BIOCHEM BEHAV **64**(2) 295–299, 1999.—Nicotine is the primary compound that maintains tobacco smoking behavior, and nicotine reinforcement may be related to its discriminative stimulus effects. Nicotine in novel form, isolated from tobacco smoke, is often reinforcing in men but not in women, and clinical trials with nicotine replacement via gum or patch have often shown less efficacy in women vs. men trying to quit smoking. We hypothesize that this sex difference in nicotine reinforcement or clinical efficacy may be related to reduced intensity of nicotine's discriminative stimulus effects in women. Using formal drug discrimination procedures, we have found in several studies that discrimination responding across nasal spray nicotine doses tends to be flatter for women than men (i.e., sex × dose interaction), suggesting reduced sensitivity to changes in dose. Results from the field of psychophysiology, involving detection of physiological changes, are generally consistent with our findings, and suggest that the environmental context accompanying physiological change is important in understanding this sex difference. The implications of this sex difference for smoking cessation treatment and future research directions are presented. © 1999 Elsevier Science Inc.

Nicotine Sex differences Drug discrimination Drug dependence Interoceptive stimulus effects

THERE is consistent evidence that women do not benefit as much from use of nicotine replacement in smoking cessation treatment. As discussed elsewhere in detail (10), women have slightly or significantly poorer outcome in nearly every clinical outcome study of nicotine replacement that presented outcome separately for men and women. In some of these studies, nicotine replacement was no better than placebo in women [e.g. (8)]. In no study did women have a significantly better outcome than men. Thus, although it is generally effective in fostering smoking abstinence, nicotine replacement appears to be less helpful to women smokers. Because treatment now focuses very heavily on nicotine replacement medication [e.g. (6)], a sex difference in efficacy of nicotine replacement suggests that this standard treatment approach may not be adequate for many women smokers, and that alternative approaches are needed.

A clear explanation for this sex difference in efficacy of nicotine replacement is not yet apparent because of the minimal attention paid to comparing nicotine effects between males and females (13,22). However, some research suggests that nicotine may be less reinforcing, positively or negatively, in women than in men (10,13). For example, we found that nasal spray self-administration among those quitting smoking was significantly greater in those receiving nicotine vs. placebo, showing that nicotine per se is reinforcing, but only among men and not women (16). Men randomly assigned to nicotine spary self-administered it twice as much as men assigned to placebo spray, while women assigned to either spray self-administered at the same rate as men assigned to placebo. There was no sex difference in placebo use, so it was unlikely that women were simply less comfortable using a nasal spray. Consistent with this finding, Killen et al. (8) found less 2 mg of nicotine gum use in women vs. men instructed to use it on a fixed schedule. Also clearly relevant is a study by Hatsukami et al. (4), reporting less withdrawal relief in women vs. men given 2 mg of nicotine gum during a quit attempt, despite equal gum use.

Similarly, when pretreated with nicotine or placebo nasal spray, men smokers readily compensate by reducing their smoking behavior concomitant with increasing nicotine pretreatment dose, while this compensation in smoking behavior is significantly less among women smokers (18). Among studies employing other routes of nicotine pretreatment (gum, patch, etc.), it is worth noting that most of those finding a significant decline in smoking behavior after pretreatment examined only male smokers, while studies not finding a significant decline generally included women smokers [see (10)]. These observations suggest that women are less sensitive to nicotine dose manipulations or find nicotine intake a less reinforcing consequence of smoking behavior compared to men.

There are few other studies examining human self-administration of nicotine in novel forms (i.e., isolated from tobacco), and so sex differences in nicotine reinforcement cannot be conclusively determined based on existing research. However, it is interesting to point out that only males were included in the classic research on IV nicotine self-administration in humans by Henningfield and Goldberg (5), and that virtually all published research on IV nicotine self-administration in animals involves only males [see (13)].

The primary focus of this article is to present research findings that suggest that reduced nicotine reinforcement (positive or negative) in women may be due, at least in part, to

their attenuated sensitivity to nicotine's discriminative stimulus effects.

NICOTINE DOSING AND DRUG DISCRIMINATION PROCEDURES

We have conducted a number of studies examining nicotine discrimination in men and women. To examine individual differences in the magnitude of drug response, it is essential that the drug dose be controlled (9). However, controlling the nicotine dose is difficult when administered by its usual method, tobacco smoking, because of a wide variability in puffing behavior (23). There are also several thousand other compounds in tobacco smoke, so the independent stimulus effects of nicotine as opposed to these other compounds cannot be easily ascertained in studies using tobacco smoking as the nicotine delivery method (7).

To solve this problem, we have employed a measured-dose nasal spray nicotine delivery system in our studies. This method delivers nicotine almost as rapidly as smoking, but in a more controlled fashion (14). This method also allows for correction of doses for subject body weight, which is important in examining sex differences because men and women differ in weight.

Each of our nicotine discrimination studies used the same general procedures, which were based on those developed by other researchers examining human discrimination of other drugs (1), and will be described briefly here.

Subjects participate after overnight abstinence from smoking and caffeine consumption. Discrimination training (learning to reliably discriminate between nicotine and placebo, referred to as spray "A" or spray "B") is achieved in one 3-h session because of the rapid action of nasal spray nicotine. Those successfully learning the discrimination (at least 80% correct identification) proceed to additional sessions involving, first, a test of maintenance of training dose discrimination and then a test of generalization of this discrimination across a range of nicotine doses usually administered in random order. The quantitative task of generalization responding consists of distributing 10 "chances" (poker chips) between two sides of a box, with one side labeled "A" and the other "B," based on how similar the dose they just received is to sprays "A" and "B." They are also told they will receive $.25 U.S. per "correct" chip placement, but are not given feedback on responding. (All receive the maximum monetary amount, $2.50/trial, after the end of the study, because there is actually no truly correct response for some trials.) Nicotine-appropriate responding is defined as the proportion of chances distributed on the side with the same letter code as the nicotine training dose (quantitative measure of discrimination).

Using this procedure, we found that (a) smokers can reliably discriminate nicotine vs. placebo nasal spray doses as well as among nicotine doses (12); (b) discrimination behavior is significantly influenced by the initial training doses used (11), as found in rats (28); (c) discrimination behavior is attenuated at higher doses in smokers vs. nonsmokers, suggesting chronic tolerance (19); and (d) pretreatment with nicotine attenuates subsequent nicotine discrimination responding in smokers, suggesting acute tolerance (15). Moreover, we have recently shown that nicotine discrimination is attenuated by central and peripheral nicotinic blockade with mecamylamine but not by peripheral blockade alone with trimethaphan, indicating that central effects of nicotine are essential to nasal spray nicotine discrimination (20).

SEX DIFFERENCES IN NICOTINE DISCRIMINATION

In several studies of nicotine discrimination, we have observed differential sensitivity of discrimination responding across generalization doses between men and women. In an early study not involving formal drug discrimination training, we gave male and female smokers a different dose of nicotine by nasal spray (0, 5, 10, or 20 μg/kg, in counterbalanced order) on 4 separate days [see (9)]. They were asked to place a check mark next to "nicotine" or "no nicotine" on a form, depending on whether or not they thought the spray they received contained nicotine. As shown in Fig. 1A, male smokers were able to differentiate placebo from the three active nicotine doses and from chance. For females, however, there were no differences between any doses in identification as "nicotine," and there were no differences between any doses and 50% nicotine identification (i.e., chance responding).

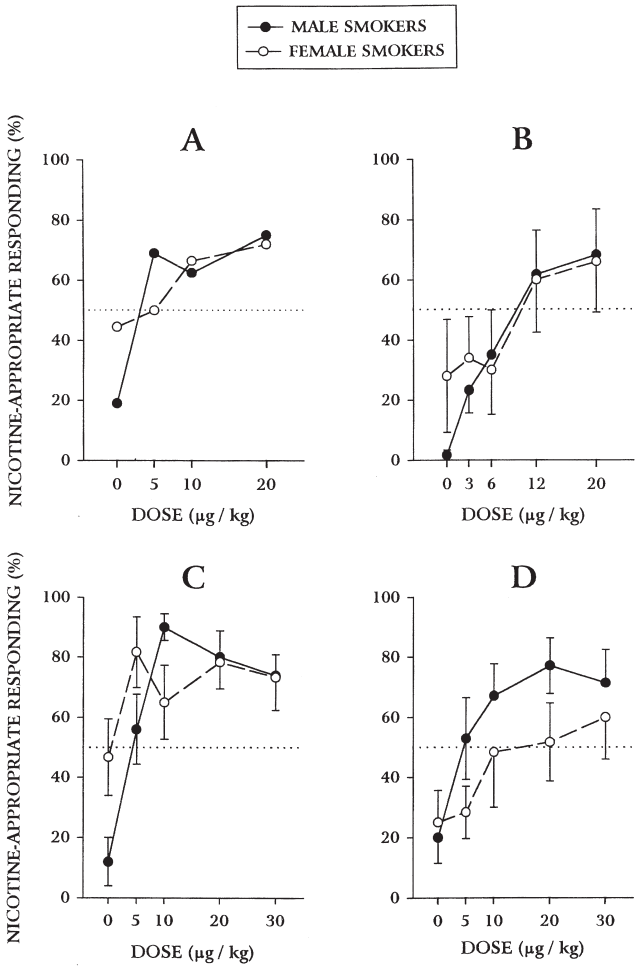

FIG. 1. Discrimination behavior (mean±SE nicotine-appropriate responding) across nicotine generalization doses administered by nasal spray in men and women smokers from different studies. Subjects were those who were: (A) untrained and asked to identify spray as containing "nicotine" or "no nicotine" [the proportion identifying as "nicotine" was taken as a quantal measure of discrimination; from (9)]; (B) initially trained to discriminate 20 μg/kg nicotine from placebo [adapted from (19)], or (C,D) initially trained to discriminate either 10 or 30 μg/kg nicotine, respectively, from placebo [adapted from (11)].

A subsequent, formal nicotine discrimination study did not find a sex difference in discrimination of 0 vs. 12 μg/kg nicotine by nasal spray, although the subjective responses associated with discrimination differed between men and women (12). However, a second study did find sex differences in nicotine-appropriate responding in women vs. men smokers formally trained to discriminate 0 vs. 20 μg/kg nicotine, as shown in Fig. 1B (19). The interaction of sex × generalization dose was significant. Moreover, women smokers reported significantly less "confidence" in the accuracy of their discrimination behavior during initial training (mean rating of 52±12 vs. 88±3 for men on a scale of 0—"not at all confident," to 100—"extremely confident"). We also examined nicotine self-administration on a separate day during this study using a "choice" procedure in which subjects were required to self-administer a specific number of sprays but were able to choose between the two training dose spray bottles. Nicotine choice was less than half as much in women vs. men smokers (10.8±3.8 vs. 23.0±6.2) nicotine sprays, respectively), very similar to our clinical study of outpatient nicotine spray use noted earlier (16).

A third study (11) replicated this flattened dose–response curve across generalization doses ranging from 0 to 30 μg/kg nicotine in women smokers initially trained to discriminate placebo from either 10 or 30 μg/kg (Fig. 1C and D, respectively; the main hypothesis concerned the role of training dose in nicotine discrimination). As in the prior study of untrained subjects, women in the 10 μg/kg training dose group were not as able as men to maintain discrimination of placebo from nicotine, although there was no sex difference in generalization responding at the highest nicotine doses (Fig. 1C). In contrast, among those in the 30 μg/kg training dose group, there was no sex difference at the lower generalization doses, but women emitted less nicotine-appropriate responding as generalization dose increased (Fig. 1D).

Combined with the self-administration results, these laboratory findings are consistent with the notion that women may find nicotine less reinforcing because they are less able to discriminate its interoceptive stimulus effects. A slightly different explanation is that women may be less sensitive to all effects of nicotine, not just its interoceptive effects. This does not appear to be the case, as we have found mostly no differences between men and women in their other subjective, performance, or cardiovascular responses to nicotine [e.g., (17)]. So, it is unlikely that there is a general hyporesponsivity to nicotine in women across all response domains.

NONNICOTINE EFFECTS OF SMOKING

Nevertheless, these results lead to an obvious question: if nicotine is less reinforcing in women, then why is the prevalence of smoking in the U.S. currently about the same for women and men? Because women smoke about as much as men, they must find something else about smoking, besides nicotine, more rewarding than do men. Although nicotine is the primary constituent of tobacco that reinforces smoking behavior, there is evidence that other, sensory, aspects of smoking may also be reinforcing, perhaps in a secondary manner [i.e., through conditioning; (26)].

To attempt to address this notion, we gave men and women a range of nicotine doses by controlled tobacco smoking (i.e., timing and duration of puffing behavior was determined by computerized instructions) or by nasal spray (21). We then superimposed the dose–response curves using plasma nicotine levels to compare nicotine administration methods (spray or smoking). If effects of smoking were due merely to nicotine per se, these dose–response curves should not differ between smoking vs. nasal spray methods, but should overlap. For most subjective effects and for heart rate, the plasma nicotine dose–response curves, in fact, did not differ between smoking or nasal spray, for both men and women. However, for certain positive subjective effects, men and women differed in the pattern of responding as a function of method of nicotine administration. Men responded little on pleasurable subjective effects of "comfortable" and "relaxed," whether they received nicotine by nasal spray or by smoking. Yet, while women responded similarly to men following nicotine by nasal spray, they reported substantial increases in both of these pleasurable effects following nicotine by tobacco smoking. Therefore, nicotine intake via smoking produced greater positive subjective effects in women than comparable nicotine intake by nasal spray, while men responded to nicotine similarly, regardless of method.

There is little other evidence to address this possibility, so it would still be speculative to state that nonnicotine smoking stimuli are more reinforcing in women vs. men. However, as noted previously, in our studies of nicotine discrimination women were more likely than men to emit nicotine-appropriate responding following placebo nasal spray. This suggests that women appeared to be more greatly influenced by the similar sensory effects of the placebo and nicotine sprays (which are designed to be similar) than by the distinct interoceptive effects of nicotine spray. Thus, women may focus more on sensory effects of drug consumption than do men, and less on the direct pharmacological effects.

Perhaps the most important implication of a greater influence of sensory effects on smoking behavior in women is that this may be evidence of greater conditioned reinforcement of smoking in women vs. men smokers (13). Greater influence of nonnicotine effects on smoking behavior of women could perhaps explain their apparently reduced reinforcement from nicotine administered in novel forms, as outlined previously. Similarly, the absence of these conditioned sensory stimuli may have a greater impact on women smokers in altering the typical complex of discriminative stimuli presented during cigarette smoking (26), disrupting their discrimination of the interoceptive stimulus effects of nicotine.

OTHER RESEARCH CONSISTENT WITH A SEX DIFFERENCE IN NICOTINE DISCRIMINATION

Research from a different field of study, psychophysiology, is also relevant to the discussion of sex differences in nicotine discrimination, and appears to be consistent with our observations (25). There has been significant interest within this field in identifying individual differences in accuracy of perception of physiological changes (which may produce interoceptive stimuli). It is believed that those who are less able to perceive adverse physiological changes (e.g., elevated heart rate), particularly during situations such as stress, may "push" themselves physically to an extent that is unhealthy. A typical procedure from this research is to instruct subjects at quiet rest to discriminate between a light signal flashing in synchrony with their own heart rate or essentially at random.

As reviewed by Roberts and Pennebaker (25), few reliable individual differences have been identified except one—sex; women are consistently less accurate than men in detecting physiological changes. This sex difference has been observed for detection of a variety of physiological indices, including blood pressure and blood glucose, as well as stomach contrac-

tions and respiratory resistance [see (25)]. Moreover, women do not improve their discrimination performance with feedback on their accuracy.

An important element influencing accuracy of responding is the presence or absence of an environmental context that may be associated with physiological changes. For example, when a situational context for the changes is provided (e.g., engaging in brief physical exercise, placing a hand in cold water, viewing a frightening movie), the ability of women to detect those physiological (interoceptive) changes improves to the point where they are not different from men. Notably, field studies in the natural environment (i.e., in the presence of a context) using ambulatory physiological monitoring generally do not find sex differences in perception of physiological changes; all subjects improve compared to responses in a sterile lab setting [i.e., in the absence of a context; (25)].

These observations may be quite relevant to sex differences in discrimination of nicotine with and without the presence of smoking stimuli. Nicotine administration by novel means, such as by gum, patch, or nasal spray, essentially involves intake of nicotine separated from the exteroceptive cues (or context) typically associated with it when smoking. These include the sight and smell of cigarette smoke and environmental situations routinely associated with smoking. Thus, poorer ability to detect interoceptive stimuli in the absence of an environmental context may explain why women are less able to discriminate nicotine administered by unfamiliar methods, such as in nicotine replacement therapy. However, the fact that women improve their detection of physiological changes when placed in a situational context suggests that they would also improve their ability to discriminate nicotine if it was administered via smoking; the familiar exteroceptive stimuli accompanying smoking may provide a clearer context for the interoceptive effects of nicotine.

CONCLUSIONS

Several studies have shown that women smokers are less sensitive than men smokers to nicotine's discriminative stimulus effects. Reduced sensitivity to these effects may explain why women appear to find nicotine per se less reinforcing (16), nicotine intake a less reinforcing consequence of tobacco smoking (18), and nicotine replacement less efficacious in reducing withdrawal after cessation (4), relative to men.

Because nicotine replacement is the most common method of treatment for smoking cessation (6), reduced sensitivity of women to nicotine's interoceptive effects suggests that this approach may be less appropriate for women than men. One alternative strategy may be to increase the nicotine replacement dosage to overcome this reduced sensitivity. This approach is supported by our results generally indicating less of a sex difference in discrimination at higher nicotine doses (see Fig. 1A–C), and by the observation that 4 mg gum attenuated withdrawal equally between men and women while 2 mg gum was less effective in women than men (4). However, significantly poor smoking cessation outcome in women vs. men has been observed with the largest dose nicotine patch generally in use (21 mg) (29). Moreover, other treatment strategies may be more appropriate for women, such as use of nonnicotine medications or of other products or counseling that specifically address conditioned reinforcement from exteroceptive (e.g., smoke stimuli) or other, nonnicotine elements of smoking behavior.

A number of future research directions are warranted to clarify this sex difference in nicotine discrimination. An obvious potential explanation for this difference may be hormonal levels in women vs. men, such as greater progesterone and estrogen in women (30). Manipulation of these hormonal levels, such as during different phases of the menstrual cycle, may correspondingly alter nicotine discrimination behavior in women [e.g. (24)]. It would also be important to determine the generalizability of this sex difference in discrimination to other drugs. If, as suggested by Roberts and Pennebaker (25), the key factor is interoceptive vs. exteroceptive stimuli from drug exposure administered in a novel form (i.e., absence of environmental context for interoceptive stimuli), then similarly reduced discrimination should be observed in women administered other drugs of abuse via novel methods. A third direction for future research is to determine the generalizability of this sex difference across species. Sex differences in discrimination of some drugs, including nicotine (27), have been reported in animals, but little systematic research has been conducted to characterize these differences or examine their potential mechanisms, except perhaps for morphine [e.g., (2)]. Observation of a similar sex difference between humans and other species would suggest that it is due to a fairly profound biological difference between males and females. On the other hand, failure to observe similar sex differences in other species could suggest that differences between men and women may result from cultural or social factors specific to humans. Finally, it would be important to examine the possible influence of procedural changes on sex differences in nicotine discrimination. For example, the apparent sex difference in morphine discrimination among rats may actually be due to response biases resulting from the reinforcement schedules used, rather than due to true differences in drug sensitivity between males and females (3). Thus, the sex differences in nicotine discrimination we have observed may be more or less robust with changes in instructions, reinforcement contingencies, route of nicotine administration, or other study procedures.

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