Nicotine discrimination in male and female smokers

Kenneth A. Perkins¹, Amy DiMarco¹, James E. Grobe¹, Annette Scierka², Richard L. Stiller²

¹Department of Psychiatry, University of Pittsburgh School of Medicine, Pittsburgh, PA 15213, USA
²Department of Anesthesiology, University of Pittsburgh School of Medicine, Pittsburgh, PA 15213, USA

Received: 27 December 1993 / Final version: 18 March 1994

Abstract. Discriminative stimulus effects of nicotine were evaluated in humans using formal behavioral drug discrimination procedures. Male and female smokers (n=9 each) were trained on day 1 to reliably discriminate 0 versus 12 μg/kg nicotine administered by measured-dose nasal spray. All subjects were able to reach criterion performance (at least 80% correct). Generalization of responding across nicotine doses of 0, 2, 4, 8, and 12 μg/kg (approximately 0–0.8 mg for typical subject) was then examined on day 2. Nicotine-appropriate responding was linearly related to dose, and subjects were able to distinguish the smallest dose (2 μg/kg) from placebo. Although there were no differences between males and females in behavioral discrimination, subjective effects were correlated with nicotine discrimination in females but not in males. These findings indicate that humans are able to discriminate among low doses of nicotine per se, that males and females may differ in the stimuli used to discriminate nicotine, and that drug discrimination procedures may be more sensitive than traditional subjective effects measures in distinguishing among low doses of nicotine.

Key words: Nicotine – Drug discrimination – Subjective effects – Smokers – Gender differences

Interoceptive stimulus effects of a drug may be critical in determining its reinforcing efficacy (Jasinski and Henningfield 1989). Thus, a key to understanding nicotine reinforcement in humans may be its relatively subtle but important subjective effects (Henningfield et al. 1985; USDHHS 1988; Perkins et al. 1993). Subjective effects of nicotine, although long apparent (e.g. Johnston 1942), have been difficult to quantify and classify because of their apparent complexity. At various times in the history of its study, nicotine has been classified as a “stimulant” or a “sedative” (USDHHS 1988). It is now known that nicotine may have many different subjective effects, including both “stimulant” and “sedative” effects, depending on a host of factors such as dose, time interval since administration, environmental context of administration, the specific dependent variable being measured, subject’s prior drug history, etc. (e.g., Mangan and Golding 1984; USDHHS 1988; Perkins, in press).

Because they are not independently observable, subjective effects of nicotine and other drugs have typically been assessed with various standardized or individually-tailored self-report measures (i.e. paper-and-pencil questionnaires and, more recently, computerized batteries; Preston and Bigelow 1991). One problem with these measures is that subjects are required to use experimenter-defined descriptors which may vary in familiarity and meaning across subjects, a particular obstacle for those from different cultures or across different generations (Fischman and Foltin 1991). Lack of sensitivity of self-report measures at low drug doses may also be a problem (e.g. Lamb et al. 1991). For these and other reasons, these measures may not provide a complete description of the interoceptive stimulus effects of nicotine.

Another, perhaps more reliable, method of assessing these effects is the drug discrimination procedure, which relies on observable behavioral responses to determine whether a drug’s stimulus effects have been perceived by the subject (Preston and Bigelow 1991). Research has shown that animals can discriminate nicotine from saline and among different doses of nicotine, and that mecamylamine, a nicotinic cholinergic blocker, can block nicotine’s discriminative stimulus effects (e.g., Yanagita et al. 1983; Stolerman 1987; Craft and Howard 1988; Rosecrans 1989). Examining the discriminative stimulus effects of nicotine in humans may be very useful in comparison with subjective (or with physiological or other behavioral) effects to help determine on what basis humans are able to perceive nicotine (Preston and Bigelow 1991).
Although there has been a recent increase in human drug discrimination research with a number of drugs, there has been very little research on human discrimination of nicotine (Kamien et al. 1993). One reason for the lack of studies may be the difficulty in presenting to human subjects measured bolus doses of nicotine, since nicotine dosing is imprecise via tobacco smoking (Pomerleau et al. 1989). Other methods of presenting nicotine doses (e.g. gum, patch) are also somewhat imprecise and lack the rapid uptake of nicotine common to tobacco smoking (Benowitz et al. 1990), a difference in pharmacokinetics which may produce very different subjective (and discriminative stimulus) effects (Henningfield and Keenan 1993).

To our knowledge, only one study, using tobacco smoking, has purported specifically to investigate discriminative stimulus effects of nicotine in humans using formal drug discrimination procedures. Kallman et al. (1982) found that smokers were able to accurately discriminate between a 1.3 mg (nicotine yield) and a 0.14 mg cigarette following training exposures to each, but they could not subsequently learn to discriminate between 0.69 and 0.28 mg yield cigarettes. However, it is very difficult to make conclusions about nicotine discrimination in humans based on these results for several reasons. First, in both of these tests, subjects were instructed to smoke the cigarettes “as they normally do”, which could have allowed for substantial variability in actual nicotine intake by subjects from each cigarette (USDHHS 1988). Thus, failure to discriminate the 0.69 versus 0.28 mg cigarettes may not have been due to a stimulus effect difference that was sub-threshold, but may instead have been caused by changes in smoking topography which resulted in similar nicotine dosing from the two cigarettes (i.e. subjects may have altered topography to increase nicotine extraction from 0.28 mg cigarette). Second, the subjective effects reportedly used by subjects to make the discrimination between cigarettes appeared to be primarily peripheral in nature and not even necessarily due to nicotine. The most common effect used by subjects was “harshness in throat”, although some subjects did report using “dizziness” (a central effect of nicotine) to discriminate cigarettes. Other peripheral effects used were “taste” and “fullness in lungs”, leaving open the possibility that this discrimination was based on some of the 3800 compounds in tobacco smoke other than nicotine (National Research Council 1986; Rose and Levin 1991). Therefore, although it appeared that smokers were able reliably to discriminate between 1.3 and 0.14 mg cigarettes, this study did not determine that this discrimination was based on differential intake of nicotine per se (Stolerman 1987). Moreover, this study did not test generalization of these effects to other nicotine doses, perhaps because of the methodological limitations of dosing via smoking, noted previously. Other research indirectly supports the notion that nicotine from tobacco smoking or other means may be discriminable by humans (e.g. Henningfield and Goldberg 1983; Rose 1984; Rose et al. 1989; Hughes et al. 1990; Perkins et al., in press), but no other studies have specifically investigated human discrimination of nicotine per se using formal drug discrimination procedures.

Finally, to our knowledge, there have been no specific comparisons of the discriminative stimulus effects of any drug, including nicotine, as a function of subject gender in either humans or animals. We have recently observed that female smokers appear to be less able than male smokers to correctly identify by self-report the presence versus absence of nicotine in nasal spray (Perkins, in press). We have also found that female smokers may not compensate for nicotine pre-loading with “down-regulation” of smoking behavior to the same extent as males (Perkins et al. 1992), suggesting possibly reduced sensitivity of females to nicotine dose. Somewhat similarly, other research has suggested reduced therapeutic efficacy of nicotine replacement for smoking cessation in female versus male smokers (Jackson et al. 1986; Sachs et al. 1992). Given the possibility of other differences in tobacco use between male and female smokers (Grunberg et al. 1991), it would be important to ascertain any potential gender-based variability in the discriminative stimulus effects of nicotine in humans.

In sum, despite a burgeoning literature on effects of nicotine in humans, it still appears to be the case that, as Stolerman (1987) concluded, “it is not even clear that nicotine can function as a discriminative stimulus in formal drug discrimination experiments in human subjects” (p. 448). The present study was designed formally to examine whether humans can indeed discriminate varying doses of nicotine per se presented by measured-dose nasal spray, and to investigate possible gender differences in the discriminative stimulus effects of nicotine.

Materials and methods

Subjects. Subjects were male and female smokers (n=9 each) who smoked at least 15 cigarettes/day for at least 1 year and did not currently use any other tobacco products. All subjects were examined by physician to rule out current or past significant medical or psychiatric problems, and urine drug screens were obtained to exclude subjects with substance abuse problems. Males and females were comparable in terms of mean±SEM age (22.2 ± 1.0 versus 23.0 ± 0.9 years, respectively), smoking frequency (17.7 ± 1.0 versus 19.2 ± 1.0 cigarettes/day), number of years smoking regularly (4.1 ± 0.9 versus 3.2 ± 0.7 years), nicotine content of preferred brand (0.9 ± 0.1 versus 0.8 ± 0.1 mg), and in Fagerstrom (1978) Tolerance Questionnaire score (5.0 ± 0.6 versus 5.1 ± 0.6), a commonly used measure of nicotine dependence.

Nicotine dosing method. Our basic nicotine dosing procedure has been described previously and shown to produce rapid and reliable dose-dependent boosts in plasma nicotine (Perkins et al. 1986, in press), as well as comparability in subjective effects with those of nicotine intake via controlled tobacco smoking (Perkins et al. 1994). Each dose was presented via measured-dose nasal spray pump bottle and consisted of 0.9% saline solution (1.4 ml) containing the designated amount of nicotine and 0.1% oil of peppermint to mask the taste and smell of nicotine. Capsaicin (pepper extract) was added to the solution to mask the acute irritation (<60 s) often caused by nicotine delivered nasally. Placebo consisted of saline, capsaicin, and oil of peppermint. [To equalize irritation across training (0.12 µg/kg) and testing doses (0.2, 4, 8, and 12 µg/kg), 60 µl capsaicin was added to 0, 2, and 4 µg/kg, while 30 µl capsaicin was added to 8 and 12 µg/kg.] Solutions were sterile and non-pyrogenic.