Euphoriant effects of nicotine in smokers

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Abstract. Two studies were conducted to replicate and extend previous demonstrations of smoking-induced, dose-related reports of euphoria, and to confirm this relationship using measures of plasma nicotine. In experiment 1, overnight-deprived subjects, in three different sessions, smoked ultralow-, high-nicotine, and usual-brand cigarettes. In experiment 2, ultralow-, medium-, and high-nicotine cigarettes were used, and plasma nicotine was measured. In both studies, subjects were asked to depress a button during euphoric sensations. Number of sensations for the ultralow-nicotine cigarette was significantly lower than for the high-nicotine cigarette in the first study, and than for both the medium- and high-nicotine conditions in the second; a significant linear trend was observed for number of sensations as a function of plasma nicotine level in the second study. For the high-nicotine cigarette, 19 of 22 subjects experienced at least one sensation (mean around three), starting around 2.5 min after lighting up. Together, these studies support the existence of a dose-response relationship for nicotine-induced euphoric sensations; suggest that they are more pronounced following overnight abstinence than following minimal deprivation, and in more dependent smokers; and characterize in detail the temporal features of these sensations.

Key words: Cigarette smoking – Dose-related – Euphoriant effects – Nicotine

Though early conceptualizations of “addiction” stressed the development of tolerance and the emergence of characteristic symptomatology upon withdrawal, most theorists now accept a broader definition of addiction that encompasses the pleasurable effects of a drug as well. The extent to which such sensations are associated with nicotine use, however, and to which they contribute to smoking behavior, are not well understood. The relative acceptability of nicotine in the past, compared with drugs like cocaine or amphetamines, is to some degree attributable to its failure to produce “highs” of sufficient magnitude to disrupt ongoing activity. In a study of around 1000 people seeking treatment for drug dependence, Kozlowski et al. (1989) found that cigarettes were rated as less pleasurable than alcohol or other drugs. In animals, the range of conditions under which nicotine demonstrates reinforcing stimulus properties is much more restricted than those for psychomotor stimulant, opiate, and sedative-hypnotic drugs (Dougherty et al. 1981).

On the other hand, nicotine has repeatedly been shown to produce EEG changes suggestive of cortical activation in both animals and humans, whether delivered intravenously, via smoking, or via nicotine gum (see USDHHS 1988); the response is partially prevented by the nicotinic cholinergic antagonist mecamylamine (Pickworth et al. 1988), and tolerance develops rapidly (Hubbard and Gohd 1975). A series of studies carried out at the Addiction Research Center of the National Institute on Drug Abuse indicated that intravenous nicotine injections produced dose-related decreases in alpha EEG activity, with multiple short episodes of euphoria appearing within 30 s of the injection (Jasinski et al. 1984). Nicotine, whether administered via smoking or intravenously, has been shown to produce dose-related increases in scores on drug liking and euphoria, brief in duration, fairly rapid in onset (for smoking, occurring within a minute after completion of a cigarette), and showing the development of acute tolerance (Henningfield 1984; Henningfield et al. 1987): intravenous infusion produces a “rush” similar, though shorter in duration, to that produced by cocaine or morphine (Henningfield and Jasinski 1983; Henningfield et al. 1986). Liking scores are attenuated by mecamylamine in a dose-related manner (Henningfield 1983).

This paper reports the results of two studies designed 1) to replicate previous reports that smoking and nicotine administration produce dose-related euphoria by asking subjects to depress a button when they experi-
enced euphoric sensations, and to confirm this relationship using direct measures of plasma nicotine; 2) to tease out the effects of nondrug factors by comparing a usual-brand cigarette with a research cigarette; 3) to examine the effects of abstinence versus minimal deprivation upon these sensations; 4) to assess the possible role of degree of dependence; and 5) to characterize the temporal features of such sensations. The apparatus used, a simplified version of a device used by Lukas and colleagues to investigate the euphoriant effects of intravenous nicotine, alcohol, and other drugs (Lukas et al. 1986), was intended to maximize our ability to capture evanescent effects by providing a continuous opportunity for subject-initiated reporting rather than periodic investigator-initiated querying. Experiment 1 was a preliminary study designed to verify the existence of the phenomenon under investigation and to determine which variables were likely to be of greatest interest. Subjects in this study smoked an ultralow-nicotine research cigarette (the control condition) in one session, a high-nicotine research cigarette in another session, and a usual-brand cigarette in a third (to assess the contribution of “familiarity” or other non-nicotine factors to the phenomenon, as well as to establish that it was part of the experiential repertoire of smokers under habitual smoking conditions). Both the first cigarette of the day and a second cigarette, half an hour later, were assessed. Based on the results of this study, a follow-up study was conducted in which blood samples were collected in order to determine actual nicotine intake and to attempt to relate nicotine levels to euphoria more systematically. Cigarettes of three distinct strengths (ultralow-, medium-, and high-nicotine) were used in an effort to establish a parametric dose-response relationship. Because the first cigarette of the day produced the most pronounced effects in the initial study, only that cigarette was tested in the second study.

Materials and methods

Subjects

Subjects for experiment 1 were ten male smokers recruited from the local community. Inclusion and exclusion criteria were as follows: age 20-40 years; smoked at least 5 years; Fagerstrom Tolerance Questionnaire (FTQ, a measure of nicotine dependence with possible scores ranging from 0 to 11; Fagerstrom 1978) at least 5; usual brand of cigarettes nonmenthol and having a nicotine yield of \( \geq 0.5 \) mg; no history of high blood pressure or cardiovascular problems; and not on any medications. Subjects for experiment 2 were 12 male smokers selected using the same inclusion and exclusion criteria except that minimum number of years smoked was 3 rather than 5 and nicotine yield of the subject’s usual-brand cigarette was not restricted.

Apparatus

During experimental sessions, subjects were seated in an easy chair in a room equipped with a one-way mirror. Heart-rate was monitored and recorded using a Grass Polygraph (Model 7B). All experimental sequences were controlled by an IBM AT computer. Standardized instructions were delivered via an Amiga computer equipped with a voice synthesizer; the Amiga was also used to present visual analogue scales, to which the subject responded using a mouse. No subject-experimenter interaction took place once a session began. During experiment 2, which involved blood sampling, an indwelling 18-gauge catheter was inserted in a left forearm vein and attached to a 1 m length of infusion-exfusion tubing that ran through a channel in the wall to allow unobtrusive withdrawal in the adjacent room; the line was heparinized, and samples were collected in tubes impregnated with EDTA to prevent clotting. They were kept on ice during the session, then centrifuged at 4°C, and kept frozen at -80°C. Samples were assayed for nicotine and cotinine using HPLC (Harisharan et al. 1988).

Standardized unfiltered high-nicotine (2.4 mg), medium-nicotine (1.3 mg) and ultralow-nicotine research cigarettes (0.2 mg) used in these studies were manufactured by the Tobacco and Health Research Institute, University of Kentucky (2R1, 1A3, and 3A1, respectively). (The ultralow-nicotine cigarette was intended as a control condition and expected to produce minimal nicotine intake; the rationale was to help maintain subject blindness and to avoid the possible “psychoactive” effects of non-nicotine substitutes.) Puff number and duration were measured using a gauge pressure transducer (LX 160-46; National Semiconductor); pressure changes produced by inhaling through a modified cigarette holder were transmitted to the pressure sensor via flexible plastic tubing, where they were converted to digital electric signals. Euphoric sensations were reported by the subject’s pressing, for the duration of the sensation, a push-button with output to the AT, which computed time of onset and duration of each button press.

Procedure

Experiment 1. Subjects were screened by telephone. If they appeared to meet eligibility requirements and wished to participate in the study after hearing it described, they were scheduled for three 1-h sessions separated by at least 1 day.

Subjects were requested to arrive at the lab at 8:00 a.m., without having smoked or ingested caffeine after midnight, and having eaten a standard breakfast (across the three sessions). Before the first session, the apparatus was demonstrated and a written informed consent document was obtained. Subjects were giving the following instructions for reporting euphoric effects: “People sometimes report experiencing pleasurable sensations when they smoke that might be described as a rush, a buzz, or a high. Not everybody experiences these, and not all cigarettes produce these sensations. We are currently testing different blends of tobacco to determine how likely they are to produce these sensations. If you happen to experience any of these pleasurable sensations while smoking today, please depress the button and hold it down for the duration of the sensation.” Electrodes were placed for collection of EKG data.

At the start of the session, the subject was asked to smoke a cigarette, using the cigarette holder designed to record topography, and to depress the button to report a buzz as described above. For the next half hour, the subject was permitted to read a magazine. The subject then smoked a second cigarette identical to the first one, following the same procedure as for the first cigarette. Subjects were exposed to three sessions, separated by at least 1 day. The first two, counterbalanced to control for order effects, involved a high-nicotine research cigarette on one day and an ultralow-nicotine research cigarette on the other. During the third session – always the last, to avoid possible contamination of our assessment of strictly dose-related effects by interspersing a condition in which nondrug factors might influence the dependent measure – the subject smoked his usual-brand cigarettes. Sessions 1 and 2 were run double-blind; session 3 was not. Subjects were paid $45 upon completion of the three sessions.