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A laboratory study of hydromorphone and cyclazocine on smoking behavior in residential polydrug users

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Abstract

The effects of cyclazocine and hydromorphone on spontaneous and laboratory cigarette smoking were compared in a double-blind, placebo-controlled, crossover study. Participants (seven men, one woman) received oral doses of placebo, cyclazocine (0.2, 0.4, and 0.8 mg) and hydromorphone (5 and 15 mg) in a randomized order on experimental days. Spontaneous smoking was recorded during two intervals on the experimental days: a 3-h period 5–8 h after drug administration (Interval 1), and the rest of the day (Interval 2). Measures of smoking topography and subjective and physiologic effects of a single cigarette were obtained on the experimental days. Neither hydromorphone nor cyclazocine significantly changed spontaneous smoking when compared to the placebo condition; however, compared to hydromorphone (5 mg), cyclazocine (0.4 and 0.8 mg) decreased spontaneous smoking during Interval 1. Hydromorphone (5 and 15 mg) and cyclazocine (0.4 and 0.8 mg) diminished smoking-induced increases in heart rate. Compared to the placebo condition, cyclazocine (0.2 and 0.4 mg) reduced exhaled carbon monoxide (CO) boost, a measure of smoke exposure. Further studies of the effects of kappa opioid agonists on smoking behavior may lead to a better understanding of the role of opiates in smoking behavior.

Keywords: Cyclazocine; Hydromorphone; Smoking; Polydrug use; Kappa opioid agonist

1. Introduction

Mounting evidence from preclinical and clinical studies suggests that interactions between nicotine and elements of the endogenous opioid system could mediate the effects of nicotine and cigarette smoking. (review: Pomerleau, 1998; Pomerleau and Rosecrans, 1989). However, studies on exogenous opiate administration on human cigarette smoking have yielded mixed results. In general, mu opioid antagonists decrease spontaneous smoking and smoking behavior (Gorelick et al., 1989; Karras and Kane, 1980; King and Meyer, 2000; Brauer et al., 1999), whereas mu opioid agonists are usually associated with increased smoking (Sutherland et al., 1995; Chait and Griffiths, 1984).

Although past smoking research has centered on the role of mu opioid endogenous ligands, exogenous agonists and antagonists, it has long been recognized that there are other endogenous opioid ligands and families of opiate binding sites that are distinct from the mu opioid system (Holaday, 1985)—one is the kappa opioid system. Kappa opiate agonists diminish the increased levels of dopamine in the nucleus accumbens typically seen after cocaine, amphetamine, and nicotine administration (Di Chiara and Imperato, 1988a; Maisonneuve et al., 1994). Hahn et al. (2000) reported that three specific kappa opioid agonists (U50,488, U69,593, and CI977) blocked nicotine-induced locomotor stimulation in the rat and intracerebroventricular injections of a specific kappa antagonist prevented this effect of U69,593.

On the basis of animal experiments, a test of the interaction of a kappa drug on human smoking behavior seemed warranted. The present study was conducted as part of a two-phase experiment. In the first phase (Single Dose Phase), the acute effects of hydromorphone, a selective mu agonist, were compared to those of cyclazocine, a kappa agonist/mu partial agonist (Archer et al., 1996). In the second phase (Interaction Phase), the effects of daily cyclazocine on intranasal cocaine were examined (Preston et al., 2004).

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2. Methods

2.1. Participants

To be eligible to participate, volunteers were required to be current users of opioids and cocaine. Eight volunteers (seven men) who were regular smokers agreed to participate. Their average age was 34.4 years (range = 31–39 years) and their weight averaged 73.4 kg (range = 50–86 kg). Participants smoked an average of 19.9 years (range = 13–23 years) and reported smoking an average of 14.4 cigarettes per day on admission (range = 4–30 cigarettes per day). Most of the participants began smoking in their teenage years; average age of onset was 13.8 years (range = 8–19 years). Their average score on a test for nicotine dependence was 3.6 (range = 0–8); scores above 6 indicate a high level of tobacco dependence (Heatherton et al., 1991). Participation in the study was voluntary and compensation was provided. All participants signed a written informed consent statement that had been approved by the NIDA Institutional Review Board.

2.2. Experimental design

The complete research study was conducted in two experimental phases, but only data from the Single Dose Phase are described in this report. In the Single Dose Phase, oral doses of hydromorphone (5 and 15 mg/75 kg), cyclazocine (0.2, 0.4, and 0.8 mg/75 kg) or identically appearing placebo capsules were administered on experimental days separated by at least 72 h. The order of presentation was randomized.

2.3. Experimental drugs

Cyclazocine is a kappa opiate agonist and mu partial agonist (Archer et al., 1996) that was evaluated as an analgesic and a treatment for heroin dependence (Martin et al., 1966; Resnick et al., 1970). Hydromorphone is an orally active mu opiate agonist that has no activity at kappa opioid receptors and is an FDA-approved analgesic used routinely as a prototypic mu opiate agonist in pharmacological studies (Preston and Bigelow, 2000). The duration of action of hydromorphone is about 4–6 h and the onset of analgesia can occur as early as 30 min (Sarhill et al., 2001).

2.4. Procedures

Participants resided in the NIDA IRP clinical research unit for the duration of the study (approximately 30 days). Over their entire residence, the participants maintained a smoking logbook that recorded the time of day when spontaneous smoking occurred. Experimental smoking topography data from a single cigarette (their own brand) were collected 5 h after administration of experimental drugs. The time point for the collection of the experimental smoking data was dictated by the study timeline, subject comfort, and logistics. There were significant increases in a 100-mm visual analog scale (VAS) measuring "any drug effect" 4 h after the 15-mg dose of hydromorphone (score = 33.8) and 0.8 mg cyclazocine (score = 38.1) compared to placebo (score = 3.7), suggesting that experimental smoking data were collected during a time of perceptible drug effect.

2.5. Dependent measures

2.5.1. Spontaneous smoking

Spontaneous smoking was analyzed from the smoking log on days when participants received experimental drugs. Participants were not allowed to smoke from 1 h before until 4 h after the administration of the test drugs. Cigarette consumption was measured during two time periods: first 3 h after ad lib smoking was allowed (Interval 1) and for the remainder of the day (Interval 2).

2.5.2. Experimental smoking

At the beginning of Interval 1, participants smoked a single cigarette through a topography mouthpiece of the CReSS smoking topography unit (Plowshare Technologies, Baltimore, MD) in a well-ventilated smoking chamber. Before and after smoking, blood pressure and heart rate were measured with an automated cardiovascular monitor (Datascope, Paramus, NJ), and exhaled carbon monoxide (CO) was measured in parts per million (ppm; Vitalograph, Lenexa, KS). Subjective measures of cigarette craving were indexed using a short form of the Questionnaire on Smoking Urges (Cox et al., 2001) before smoking. After smoking, participants rated cigarette "strength," "harshness," "taste," "satisfaction," "good effects," "bad effects," and "draw level" on a VAS and answered a single question on degree of cigarette liking that was scored with a four-point Likert Scale.

2.5.3. Smoking topography

Topography measures were obtained from the CReSS System. Participants smoked a single cigarette through a plastic mouthpiece connected to an analog/digital converter by a plastic tube. The topography system calculated and stored data on each individual puff for the following parameters: puff volume, puff duration, interpuff interval, and maximum puff velocity. Data from the first puff and puff volumes under 12 ml were excluded from the calculation. Data from all other puffs of the cigarette were averaged to obtain one value for each puff parameter (Buchhalter and Eissenberg, 2000; Lee et al., 2003). The experimenter recorded puffs per cigarette and time to smoke.

2.6. Data analyses

Data were analyzed using analysis of variance (ANOVA) methods (Winer et al., 1991). The main factor was drug condition (six levels: placebo, hydromorphone 5 and 15 mg, cyclazocine 0.2, 0.4, and 0.8 mg). For some dependent

variables (e.g., heart rate), change scores were analyzed. When the ANOVA indicated a significant effect on drug condition, post hoc analyses (paired *t* tests, Tukey's HSD) were used to identify the significant contrasts.

3. Results

3.1. Spontaneous smoking

Overall, there was a significant difference among the experimental conditions on spontaneous smoking during Interval 1 [$F(5,35) = 2.69$; $P < .05$]. Post hoc analyses indicated that neither cyclazocine nor hydromorphone had significant effects on spontaneous smoking compared to placebo, although the increased consumption after the low dose of hydromorphone approached significance ($P < .10$). Cigarette consumption after the higher doses of cyclazocine (0.4 and 0.8 mg) was significantly reduced compared to consumption after the low dose of hydromorphone. There were no significant differences in cigarette consumption during Interval 2.

3.2. Smoking topography

On the placebo day, the mean (± S.E.M.) puff volume, puff duration, interpuff interval, and puff velocity were 50.2 ± 2.1 ml, 1.2 ± 0.05 s, 23.8 ± 4.2 s, and 56.5 ± 2.7 ml/s, respectively. Neither cyclazocine nor hydromorphone changed smoking topography measures significantly.

3.3. Cardiovascular measures

Changes in systolic and diastolic blood pressure before and after smoking were computed, and the change scores were compared across experimental drugs. There were no significant differences in smoking-induced changes in diastolic and systolic blood pressure. However, a trend for changes in heart rate was observed [$F(5,35) = 2.38$, $P = .059$]. As shown in Fig. 1 (upper panel), smoking-induced increases in heart rate were reduced by both doses of hydromorphone and the two higher doses of cyclazocine (0.4 and 0.8 mg). After cyclazocine (0.2 mg), smoking increased heart rate by 12.5 beats/min.

3.4. Exhaled CO

Changes in exhaled CO before and after smoking were computed and compared across experimental drugs (Fig. 1, lower panel). The ANOVA indicated a significant difference among conditions [$F(5,35) = 2.63$; $P < .05$]. Post hoc tests indicated that the smoking-induced increase in exhaled CO was lower in experimental sessions in which cyclazocine was

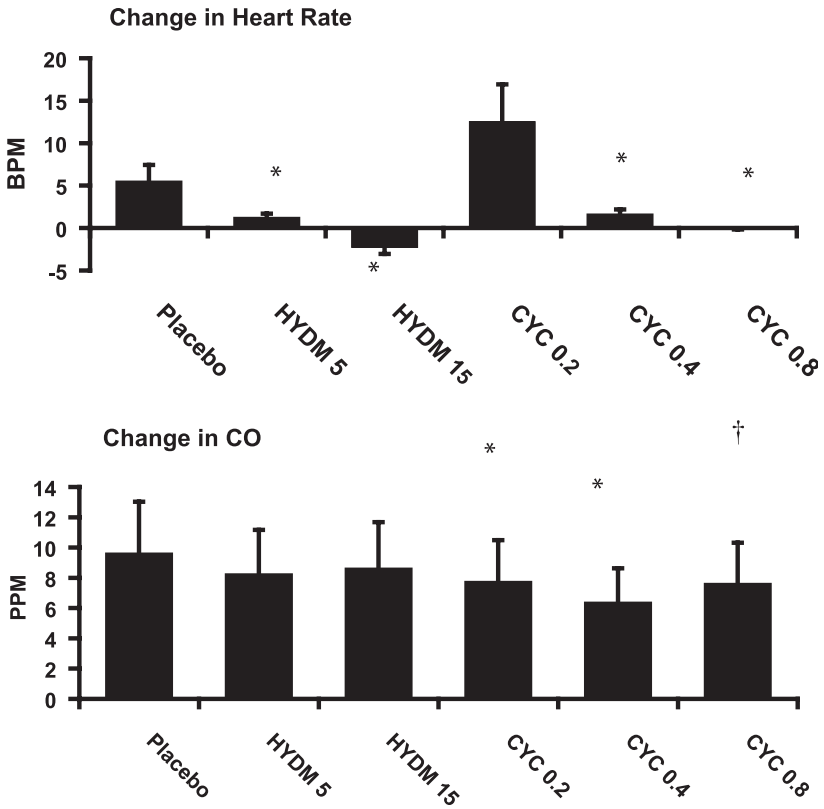

Fig. 1. Upper panel shows mean changes in heart rate (± S.E.M.) after smoking a single cigarette 4 h after the administration of the experimental drugs. Lower panel shows mean changes (± S.E.M.) in exhaled CO after smoking a single cigarette. * Value differs from placebo ($P < .05$; paired *t* test). † Value differs from placebo ($P < .10$).

administered compared to placebo. Exhaled CO was significantly ($P < .05$) lower after cyclazocine (0.2 and 0.4 mg) as compared to placebo administration. After cyclazocine (0.8 mg), there was a trend ($P < .10$) for lower exhaled CO.

3.5. Subjective measures

None of the drug conditions changed the scores of the Questionnaire on Smoking Urges (Cox et al., 1999), and there were no significant differences between the experimental drugs on the seven VAS scales that indexed cigarette liking. However, cyclazocine (0.2, 0.4, and 0.8 mg) tended to decrease liking scores on a four-point Likert Scale: 2.1, 2.0, and 1.6, respectively, compared to placebo (score = 2.4).

4. Discussion

Maisonneuve and Glick (1999) demonstrated that cyclazocine decreased nicotine self-administration in rats, but there have been no studies of the effects of kappa agonists on human smoking. Kappa opiate agonists decrease the release of dopamine in the nucleus accumbens induced by administration of stimulants (cocaine and nicotine) and mu opiate agonists (morphine; Maisonneuve et al., 1994; Glick et al., 1995). Because the rewarding effects of drugs appear related to the immediate release of dopamine (Di Chiara, 2000; Di Chiara and Imperato, 1988b), we determined if the kappa agonist action of cyclazocine diminished the effect and appeal of cigarette smoking.

Similar to the results of other clinical studies, the mu agonist hydromorphone produced modest and nonsignificant effects on measures of smoking behavior. For example, hydromorphone did not systemically change evaluations of "liking" and exhaled CO. Furthermore, hydromorphone increased spontaneous smoking (compared to placebo) in the first few hours after drug administration (Interval 1). In contrast, cyclazocine diminished some of the effects of cigarette smoking. For example, exhaled CO boost, a measure of smoke exposure, was significantly decreased after cyclazocine (0.2 and 0.4 mg), and cyclazocine caused significant reductions (compared to hydromorphone) in spontaneous smoking during Interval 1. Cyclazocine caused a nonsignificant reduction in liking for the experimentally smoked cigarette compared to the placebo day. These results suggest that the kappa agonist diminished smoking, whereas the mu agonist tended to increase smoking. These results are consistent with studies showing that methadone, a mu agonist, increased cigarette smoking (Chait and Griffiths, 1984; Schmitz et al., 1994). Furthermore, opiate antagonists diminish smoking behavior (Karras and Kane, 1980; Gorelick et al., 1989). Opiate antagonists act more effectively and potently to block mu than kappa opiate receptors (Pickworth and Sharpe, 1979; Martin et al., 1976), suggesting that antagonism of mu opiate receptors is responsible for the reduction in smoking behavior. Cyclazocine is a mixed opiate agonist–antagonist (Archer et al., 1996), acting as a mu partial agonist and a full agonist at the kappa receptor. The putative opposing actions of cyclazocine at mu and kappa receptor sites may account for its modest effects. That is, cyclazocine's activity as a mu partial agonist may increase smoking behavior and concomitantly oppose its kappa-mediated decrease in smoking.

Some limitations of this test-of-concept study should be acknowledged. The participants were recruited because they had a history of both opiate and cocaine abuse, and not on the basis of their cigarette smoking. They smoked fewer cigarettes per day (mean = 14.4) and were less tobacco dependent (FTND = 3.6) than smokers ordinarily enrolled in clinical trials of smoking cessation products (Hurt et al., 1997; Jorenby et al., 1999). Furthermore, the design of the study differed from a typical clinical trial because it was conducted in a small residential sample of polydrug users who expressed no interest in smoking cessation. Multiple statistical comparisons between the experimental drugs and placebo were made. Such comparisons are justified for this test-of-concept study; however, repeated statistical assessments may unduly raise the probability of finding a significant effect when there is none (Type I error). There is also a possibility that an actual effect would be missed (Type II error) because there were so few participants in the study that only very large effects would be detected.

Cyclazocine had attributes that made it appealing to use in this test-of-concept study, such as oral effectiveness, acceptable safety profile, and a suitable duration of action. The results of this initial study suggest that cyclazocine has modest effects to reduce the appeal and effect of cigarette smoking. More studies are needed to define the role of kappa agonists on smoking behavior. A study using a pure kappa agonist would be an important advance. Such studies would have the practical importance of evaluating a new class of drugs for smoking cessation and the theoretical relevance to understand opioid mechanisms in smoking behavior.

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