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Cigarette Smokers Self-Administer Intravenous Nicotine

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HENNINGFIELD, J. E., K. MIYASATO AND D. R. JASINSKI. *Cigarette smokers self-administer intravenous nicotine.* PHARMACOL BIOCHEM BEHAV 19(5) 887–890, 1983.—Human volunteers who smoked cigarettes were given the opportunity to press a lever that resulted in intravenous injections of saline or nicotine. Nicotine injections were taken in orderly patterns that were related to unit dose, whereas patterns of saline injections varied widely. Furthermore, the volunteers reported that nicotine produced subjective effects similar to those produced by administration of abused drugs such as morphine or cocaine.

Nicotine Human studies Cigarette smokers Drug abuse Self-administration

AMONG substances of compulsive use, tobacco is considered unique in that the pharmacologic activity of the psychoactive constituent, nicotine, has not been experimentally determined to be integral to ingestion. For many other substances of compulsive use, such as opium and coca, the pharmacologic activity of the substance is known to be integral to the behavior of self-ingestion. With regard to opium and coca, for instance, the derivatives, morphine and cocaine, respectively, are self-ingested and produce alterations in mood and feeling, including euphoria. One hypothesis is that the mechanisms underlying cigarette smoking are identical to those underlying opium and coca leaf use [5]. Recent findings that intravenous nicotine is self-administered by animals in drug self-administration paradigms are consistent with this hypothesis [1]. Findings from human studies of tobacco smoking and nicotine pharmacology suggest that such a hypothesis is plausible [3,4] but have left unanswered a critical question. That is, would cigarette smokers self-administer intravenous nicotine in place of cigarettes. To address this issue, the drug self-administration methodology, commonly used with animals, was adapted to a human paradigm [1].

METHOD

Six male cigarette smokers (mean age=36) resided on a residential research ward. Four subjects (SK, KU, PE, LA) had histories of abuse of a variety of drugs including opioids, stimulants and sedatives. Except during experimental sessions, subjects were free to smoke their usual brand of cigarettes but they were not given access to illicit or therapeutically used drugs. To measure smoking behavior, three subjects (BE, KO, LA) smoked their cigarettes using pocket held puff monitors [6]; each cigarette was individually dispensed and lit by the staff.

Subjects participated in three-hour experimental sessions which were scheduled one to three days apart. Prior to a session a catheter was inserted into a forearm vein and patency maintained with a gravity fed dextrose solution (12 ml per hr). Subjects were comfortably seated with access to an operant test panel equipped with two levers and attendant stimulus lights. A radio and reading material were also available. Cigarette smoking was not permitted for one hour prior to and during sessions. Lever pressing on one lever produced no injection although responses were recorded. Ten presses on the other lever activated an automatic syringe pump that delivered a 1-ml injection of nicotine or saline, given over ten seconds. A stimulus light and an auditory signal accompanied injections. For one minute following each injection, all stimulus lights were extinguished and neither lever was functional.

Immediately following each session, three structured questionnaires were administered to evaluate possible subjective effects produced by nicotine injections. The first was a short form (40 items) of the Addiction Research Center Inventory (ARCI) which contains empirically derived scales sensitive to the effects of several classes of psychoactive drugs [7]. The second was the Single Dose Questionnaire which contains a scale of drug liking and a drug identification list with the names of 12 commonly used drugs [7]. The third was a tobacco oriented questionnaire which contains scales for rating desire to smoke cigarettes and the strength of the prior dose of drug or cigarette.

Subjects were informed that participation in the study required only that they remain seated in the test room and not smoke cigarettes. They were told that pressing the levers

might result in the injection of nicotine but they were neither required nor encouraged to press the levers. Research staff and subjects were not informed as to the drug dose during any session (double-blind).

Safety measures included the following: (a) vital signs were collected before and after sessions, (b) the apparatus was inactivated for one minute following injections, (c) the number of injections available during successive 30-minute intervals was limited, (d) there was constant visual monitoring of the subject and his electrocardiogram by a trained nurse, and (e) both the nurse and the subject were free to abort the session at any time.

Subjects KU, SK, and PE were presented with either saline or one of three dose levels of nicotine (0.75, 1.5 and 3.0 mg per injection). Doses are expressed as the free base of nicotine hydrogen tartrate, which was placed in a sterile solution with bacteriostatic saline. These four conditions were presented in random order across sessions and once to each subject. Subjects BE and LA were presented with saline for seven consecutive sessions and then nicotine for seven sessions (1.5 mg per injection); this sequence was reversed for subject KO.

RESULTS AND DISCUSSION

All subjects pressed both levers within the first 30 minutes of the first test session. Subsequently, lever pressing occurred primarily on the lever which produced delivery of nicotine or saline, rather than on the other lever.

Figure 1 shows the pattern of nicotine deliveries to each subject at the 1.5 mg dose level. Nicotine deliveries occurred at regular intervals in patterns resembling those of humans smoking cigarettes and animals self-injecting psychomotor stimulants under analogous experimental conditions [2]. In contrast to the orderly patterns of nicotine self-administration, patterns of saline self-administration varied widely from subject to subject and were not replicable when subjects (BE, KO, LA) were repeatedly tested with saline. Figure 1 also shows that, across subjects, number of nicotine injections was an inverse function of unit dose (μg per kg).

Cumulative records of lever pressing from a subject presented with three dose levels of nicotine and saline are shown in Fig. 2. These records illustrate the pattern of lever pressing shared by all subjects which were intermittent cycles of rapid bursts of responding that ended when drug delivery began. Such patterns of fixed-ratio schedule lever pressing behavior are similar to those observed in studies with animals and humans using more commonly studied reinforcers such as food or money [2]. The figure also shows that number of deliveries was inversely related to amount of drug per delivery. For subject PE, number of deliveries were 25 at saline, 49 at 0.75 mg, 20 at 1.5 mg, and 10 at 3.0 mg nicotine per injection. In the third subject tested under such a procedure (SK), number of deliveries were 22 at saline, 5 at 0.75 mg, 8 at 1.5 mg, and 5 at 3.0 mg nicotine per injection. The cumulative records also illustrate the typical pattern of saline-maintained responding in which injections were obtained at a high rate at the start of the session, while during the rest of the session, injections were erratically spaced.

The two subjects without histories of illicit drug use (KO, BE) were presented with the 1.5 mg nicotine dose for seven sessions. Figure 3 shows that these subjects initially took only a few injections per session; however, subsequent sessions were accompanied by increasing numbers of injections. In contrast, when saline was presented for seven sessions, number of deliveries for KO decreased from a mean of 11.7 during the first three sessions to 4.7 during the last three sessions (range=4 to 15); for BE, number of saline deliveries varied widely across sessions with no trend and averaged 21.4 (range=3 to 31). For the third subject tested according to this procedure, saline deliveries decreased from a mean of 26.3 during the first three sessions to 14.0 during the last three sessions (range from all saline sessions=7 to 37), whereas nicotine deliveries were stable across all seven sessions (mean=22.9, range=13 to 29).

Immediately following each session, subjects completed structured questionnaires to assess alterations in subjective states accompanying injections. Since all subjects had been presented with both the 1.5 mg per injection dose and saline,

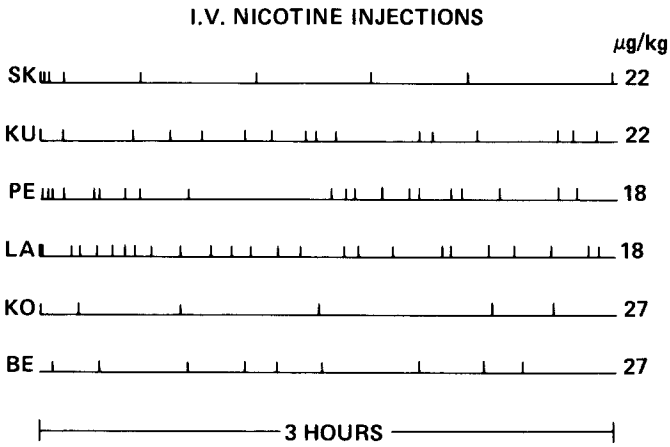

FIG. 1. Pattern of nicotine deliveries (vertical marks) obtained during the session in which the 1.5 mg per injection dose was available for subjects SK, KU and PE, and from a representative session at the 1.5 mg dose for subjects BE, KO and LA. The unit dose for each subject, expressed as μg nicotine per kg body weight, is indicated on the right side of each record. Number of injections per session, as shown in the figure, were inversely related to this expression of unit dose ($r=-0.91$).

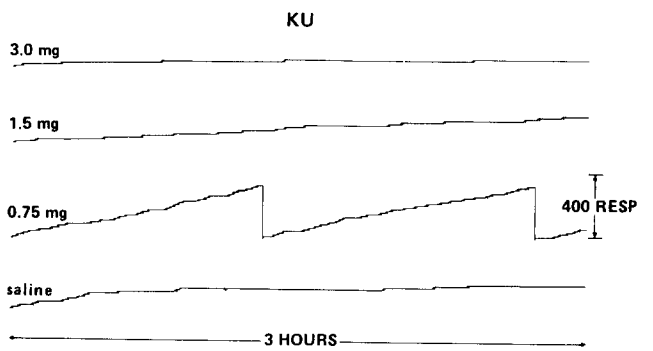

FIG. 2. Cumulative records from subject KU show patterns of lever pressing and injections during sessions. Responses are indicated by vertical increments and injections are indicated by the diagonal slash marks. The original records were retraced by an artist for clarity of presentation.

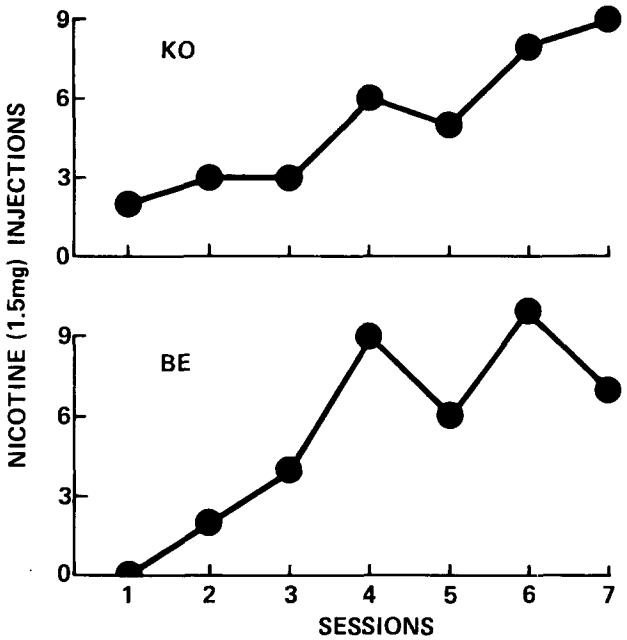

FIG. 3. For the two subjects without histories of drug dependence, number of nicotine deliveries per session are shown across the seven consecutive sessions in which 1.5 mg of nicotine per injection was available.

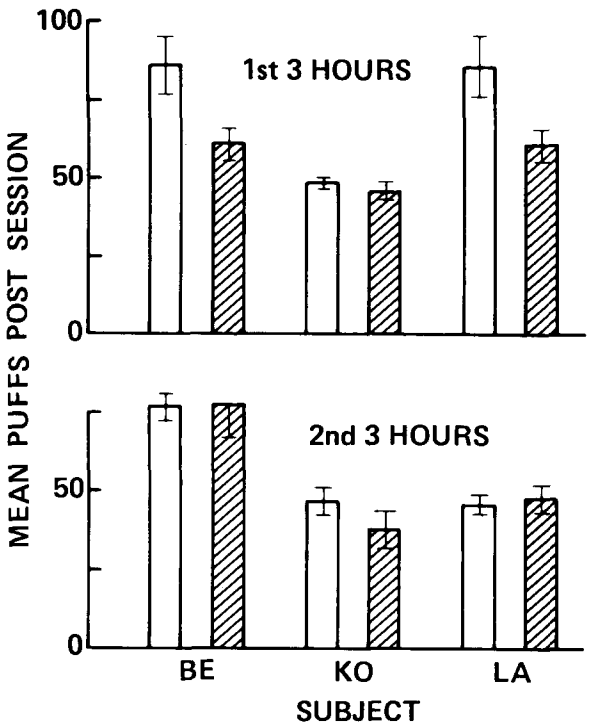

FIG. 4. Mean puffs taken during the three hours following sessions in which either nicotine (striped bars) or saline (open bars) were available for the three subjects who were tested at 7 sessions under each condition. Data shown are from periods of ad lib smoking following the last four sessions under each condition. The upper frame shows data from the first three hour block of time following sessions and the lower frame shows data from the second three hour block. Vertical lines indicate standard errors of the mean.

these data were grouped for analysis. On 5-point ordinal rating scales, nicotine significantly elevated "drug strength" and "drug liking" ($p<0.05$). In the three subjects who were tested at three dose levels, ratings of drug dose strength and drug liking were directly related to injection dose levels ($r>0.70$, for both measures).

Previous research has shown that persons with histories of drug dependence can identify drugs given to them. In the present study, the previously validated Single Dose Questionnaire [7], which contains a list of the street names of 10 commonly used drugs, was given following sessions. All four subjects with histories of drug dependence (including cocaine abuse) identified the nicotine injections as cocaine. Other research has shown that abused drugs function as euphoriants as defined by elevations in scores on the Morphine Benzedrine Group (MBG) scale of the Addiction Research Center Inventory [7]. In the present study, MBG scale scores were significantly elevated following sessions in which nicotine was self-administered ($p<0.05$). Scores on other scales of the ARCI were unchanged by nicotine self-administration.

Nicotine also produced dysphoric effects which became more intense with repeated injections over the course of a session, and were reported to limit the number of nicotine injections taken. These varied across subjects and included burning sensations produced by the injection in the arm of catheter placement (4 subjects); momentary shortness of breath accompanied by a feeling of fear (2 subjects); coughing (all 3 subjects tested at 3.0 mg). Additionally, three subjects reported nausea but continued to self-administer nicotine during those sessions and in subsequent sessions. The phenomena in which drug self-administration continues to occur following drug-induced sickness has been observed with human opiate abusers, as well as with animals which self-administer intravenous nicotine ([7] S. R. Goldberg, personal communication). Despite the occasional dysphoric effects of nicotine, no subjects withdrew themselves from the study, nor were any sessions terminated by the nurse observer. Furthermore, pre- and post-session evaluation of basic vital signs revealed the occurrence of no significant adverse physiological effects resulting from either the procedure or the drug.

The possible involvement of nicotine in cigarette smoking was evaluated by self-reported ratings of "desire to smoke," which were determined immediately following sessions, and by post session measurement of smoking behavior. A decreased desire to smoke was observed in only two subjects (KU, LA) following nicotine self-administration. However, in the three subjects whose smoking behavior was studied (BE, KO, LA), the number of cigarettes smoked and puffs taken were decreased following nicotine self-administration (puffs, $p<0.05$; cigarettes, $p<0.10$; data from last four sessions under each condition). Figure 4 shows that the effect was transient, being most pronounced during the first three-hour block of time following the sessions, with no difference in smoking rates produced by nicotine during the third three-hour block of time following sessions.

Our findings are that tobacco deprived cigarette smokers

self-administer nicotine, and that nicotine has euphoriant properties similar to morphine and cocaine. Saline was also self-administered but differed from nicotine in its behavioral effects in the following ways: saline deliveries did not produce subjective effects measured by the psychometric instruments; saline deliveries occurred in patterns that were highly variable, when compared to nicotine; saline injections decreased across sessions while nicotine deliveries were constant in subjects who were repeatedly tested with saline and nicotine. The apparent lack of orderliness of the saline self-administration data in the present study prevent any conclusions as to what variables controlled this behavior.

Taken together, the present findings indicate that nicotine produces certain effects in common with prototypic dependence producing drugs, and suggests that patterns of nicotine self-administration share commonalities with intravenous self-administration of more thoroughly studied drugs of abuse [2]. Furthermore, nicotine administration reduces subsequent cigarette smoking behavior. Therefore, we conclude that nicotine functions as an integral part of the behavioral process of compulsive tobacco use. Thus, these findings are consistent with others [5] which support the hypothesis that common mechanisms underly dependence to tobacco and other substances of abuse.

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