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Preferences for Tastes Paired With a Nicotine Antagonist in Rats Chronically Treated With Nicotine

R. F. MUCHA[1]

Institute for Medical Psychology and Behavioral Neurobiology, University of Tübingen, Gartenstr, 29, D-72740, Tübingen, Germany; Department of Pharmacology, University of Toronto; and Addiction Research Foundation of Ontario, Canada

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MUCHA, R. F. *Preferences for tastes paired with a nicotine antagonist in rats chronically treated with nicotine.* PHARMACOL BIOCHEM BEHAV **56**(2) 175–179, 1997.—The present report addressed the hypothesis that withdrawal from chronic nicotine treatment activates the same motivational processes as withdrawal from chronic opiate treatment. Conditioning produced by the nicotine antagonist mecamylamine in nicotine-treated animals was studied and compared to the well-known potentiation by opiate treatment of the aversive conditioning produced by the opiate antagonist naloxone. A sensitive two-flavor, three-trial, taste conditioning procedure was used and it was found that chronic treatment using Alzet minipumps for 1 month with nicotine (8 or 16 mg/kg/day) potentiated the ability of mecamylamine to produce taste conditioning. Thus, in nicotine-placebo control animals, only 1.0 mg/kg mecamylamine (s.c.) produced significant conditioning, whereas in nicotine-treated animals 0.5 and 1.0 mg/kg mecamylamine was effective. However, in contrast to chronic opiate treatment, which increases the aversive effect of an opiate antagonist (as confirmed here using treatment for one month with 0.25 mg/kg/day fentanyl and taste conditioning with 0.1 mg/kg naloxone, s.c.), the nicotine treatment changed the valence of the mecamylamine conditioning. The nicotine-naive animals avoided the mecamylamine-paired flavor, whereas the nicotine-exposed subjects preferred it. These findings indicated that there may be important differences between nicotine and opiate withdrawal. Not all effects of nicotine withdrawal in models of addiction can be assumed to be negatively motivating. **Copyright © 1997 Elsevier Science Inc.**

Nicotine Opiate Withdrawal discomfort Mecamylamine Naloxone Taste Conditioned aversion Conditioned preference

ABSTENTION from smoking is associated with intense craving for nicotine in chronic nicotine users and this is thought to be due in part to discomfort evoked by withdrawal signs. In recent years, evidence has accumulated suggesting that chronic treatment with nicotine has adaptive consequences similar to those of opiate treatment (8). However, it is not clear to what extent this similarity is to be found in the mechanisms of opiate and nicotine-produced adaptive processes or simply in the similarities in the test procedures that have been used to test these two drugs. To the extent that chronic nicotine treatment produces adaptive effects in a manner similar to chronic opiate exposure, one would expect that withdrawal from chronic exposure to nicotine should also produce aversive effects.

There are ample data showing that the discontinuation or reduction of chronic nicotine exposure (i.e., nicotine withdrawal) produces observable behavioral effects or withdrawal signs, but their mechanisms and the meaning of the signs for motivating behavior are not yet known. If one takes the observations in the opiate literature as a means to understand nicotines' effects, then it is clear that the long-term presence of opiates in the body gives rise to the homeostatic readjustments important for the motivational effects of withdrawal. The aversive effects of spontaneous and antagonist-precipitated opiate withdrawal can then be seen with a variety of methods of opiate treatment, which include implantation of morphine-containing pellets or opiate-delivering osmotic pumps (15). However, any motivational effects of nicotine withdrawal can

[1]Correspondence should be addressed to: Dr. Ron Mucha, Institute for Medical Psychology and Behavioral Neurobiology, University of Tübingen, Gartenstr, 29, D-72740, Tübingen, Germany.

only be inferred from studies that were not designed to study nicotine withdrawal independent of other behavioral processes. There is evidence from humans, for example, that the nicotine antagonist mecamylamine increases smoking behavior and it has also been reported that withdrawal from nicotine produces behavioral deficits in animals. Thus, mecamylamine produced in smokers increased puffing and number of cigarettes smoked (22), as well as increased expired carbon monoxide (18) and nicotine in blood (19). In addition, Corrigall et al. (4) showed in nicotine-injected rats that substitution of saline for the nicotine resulted in decreased pressing for food. However, the particular test situations used in these studies do not allow a conclusion that the effects of the discontinuation or reduction of the nicotine activity are actually aversive. Thus, the increase in smoking by mecamylamine in smokers may be an attempt by the subjects to achieve interoceptive discriminative cues that have come to be associated with their smoking. Also a disruption of lever pressing is not produced selectively by aversive events. Azrin and Hake, for example, showed that a positive secondary reinforcer disrupts a baseline of barpressing in the rat (2).

Accordingly, an important argument for the presence of an aversive state upon withdrawal from chronic nicotine exposure appears in recent reports of an opiate-like withdrawal syndrome seen with nicotine withdrawal. This is seen for spontaneous (12) and mecamylamine-precipitated nicotine withdrawal (13). However, various data in the literature on the motivational effects of drug withdrawal would suggest that the mere presence of similar signs of nicotine and opiate withdrawal does not allow a conclusion that the motivational effect of nicotine withdrawal is similar to that of opiate withdrawal. Indeed, recent analyses indicate that not all signs of opiate withdrawal signs have a linear relationship with the aversive effect of opiate withdrawal (14). Similar observations have been made for spontaneous benzodiazepine withdrawal (5), for quasi-withdrawal phenomena (17) and for psychostimulant withdrawal (16). All these studies took advantage of recently developed methods to test directly for withdrawal-produced motivation, using procedures based on preference conditioning (15). The evidence indicates that withdrawal is not a unitary process and that there is more than one mechanism producing different withdrawal phenomena. Indeed, motivational effects drug withdrawal seem to arise in forebrain structures whereas the nonmotivational signs may stem from lower structures of the brain (20).

It would follow, therefore, that direct motivational tests may be the only way to examine unequivocally whether and to what extent withdrawal from nicotine is aversive, as is seen for opiate withdrawal. Villanueva and colleagues (23) showed with a one-flavor taste conditioning procedure that nicotine withdrawal had no motivational effect. Moreover, while startle responses are believed to be potentiated by aversive events (11), it was seen that nicotine withdrawal reduces startle, suggesting that nicotine withdrawal could be positively motivating (1). This would mean that common assumptions about nicotine withdrawal could be incomplete. To our knowledge nicotine withdrawal has never been examined using procedures that are sensitive to both aversive and appetitive effects of drug withdrawal.

The objective of the present study was to test directly the motivating effects of withdrawal from chronic exposure to nicotine. We used a two-flavor taste conditioning procedure in which only one flavor is paired with drug withdrawal produced by the drug's antagonist. The method was originally developed for the study of opiate withdrawal motivation (15). Thus, in the untreated subject, a moderate dose of the opiate antagonist naloxone produces only a small taste aversion which is potentiated significantly when the same dose is used in opiate-treated animals. Mecamylamine produces a small taste aversion in untreated rats (21; Mana, Werk and Mucha, unpublished findings) and it was hypothesized that a significantly stronger taste aversion to the mecamylamine-paired flavor should be seen in nicotine-treated animals. Subcutaneously implanted osmotic minipumps were used to treat chronically with nicotine as recommended by Grunberg et al. (7). A treatment period of several weeks was chosen on the basis of the work of Corrigall et al. (4) who showed that animals were still showing changes in tolerance between 3 and 7 wk after the start of treatment. To help interpret the present results with nicotine, we tested rats treated for one month with an opiate for naloxone-produced taste aversion.

METHOD

Subject and Subject Preparation

The subjects were experimentally naive, 200–220 g adult, male Sprague–Dawley rats purchased from Charles River Ltd. and housed throughout the study in groups of six. The subjects were first trained on two consecutive days to drink under conditions of mild water deprivation (overnight) in single rat test cages (see Ref. 15). At body weights of 240–260 gm, the subjects were surgically prepared under halothane anesthesia with an osmotic pump or placebo (see Ref. 17). Exactly 14 days later, the rats were reanesthetised, the old pump was removed and a fresh pump was implanted. The pumps remained in situ until completion of the study.

Drugs and Test Solutions

The nicotine was delivered with Alzet 2ml2 osmotic pumps and fentanyl, with Alzet 2002 pumps. The estimated delivery rates of the two types of pump were 4.73 ml/h and 0.49 ml/h respectively. The nicotine delivering pumps were filled with nicotine bitartrate (Sigma Chemical Co) which was prepared with distilled water and adjusted to neutral pH. The fentanyl pumps were prepared with distilled water and fentanyl citrate (Janssen Pharmaceuticals). The solutions were prepared to deliver at the time of each implantation doses (expressed as free base) of 8 mg/kg/day or 16 mg/kg/day nicotine and 0.25 mg/kg/day fentanyl. Animals given placebo treatment were prepared with placebo pumps. In the fentanyl controls this consisted of pieces of teflon matched to the size of the pump. The nicotine controls were prepared with fresh saline-filled 2ml2 Alzet pumps for half of the animals and for the other half cleaned pumps that had been used previously to deliver saline.

Testing for taste conditioning was carried out using injections of 0.5 or 1.0 mg/kg mecamylamine (HCl, Sigma Chemical Co.) or 0.1 mg/kg naloxone (HCl, kindly donated by duPont de Nemours). The solutions were prepared with saline and injected IP in a volume of 1 ml/kg; doses were expressed as the free base. For the preference test, two flavored solutions were used. They consisted of 9.4 mM monosodium glutamate mixed with 92.7 NaCl and 0.71 mM sodium saccharin mixed with 1.13 mM citric acid, respectively (Sigma Chemical Co). These concentrations had been previously determined to minimize any preference in non-trained animals, as described previously (15).

Taste Conditioning

The taste conditioning was carried out using a 3-trial, unbiased, two-flavor taste conditioning procedure (15). The rats

received three pairings of a drug administration with one flavor and three identical pairings of drug vehicle with the other flavor. On a typical training trial, the water-deprived rat (overnight) was offered 4 ml of one of the flavors in its test cage, injected 10 min later with the appropriate experimental drug preparation or placebo and then returned to the home cage. Two trials were given each day, one in the morning and one in the afternoon, with no less than 4 h between trials. The rats were then given unlimited access to water at the end of the day between 18:00 and 19:00 h. Individual rats were used to determine only one data point on the taste test. In accordance with the principles of differential conditioning, subject assignment to particular conditions of treatment was random and the order of drug or vehicle exposure and sequence was balanced across the animals of each group; the pairing of particular flavor-drug combinations was also "counterbalanced". Testing was carried out the day after completion of the training; the pumps were not removed from the rats and the rats were not water deprived. The animals were placed individually into their test cage which was fitted with two drinking tubes containing 100 ml of each of the two flavored solutions and ad libitum food. The volume in ml consumed over 24 hr was measured for each flavored solution.

General Procedures, Designs, and Analyses

All rats were initially prepared with placebo- or drug-delivering pumps; 2 wk later the pumps were removed and reimplanted. Other than gentling five days a week, the rats received no other special treatment. On day 24 of treatment (10th day with the second pump) the rats were started on the taste conditioning. They were given two pairings with one of the flavors on each of three consecutive days and were tested on the 4th day, thereby completing the study on the 14th day of the second implant.

Of the seven groups of eight rats each, one group served as the fentanyl-treatment group and another as its placebo control. These rats were conditioned with 0.1 mg/kg naloxone as the training drug. The other five groups were used to study the effects of nicotine treatment on mecamylamine-produced taste conditioning. Two groups were treated with 8 mg/kg/day nicotine and trained with 0.5 and 1.0 mg/kg mecamylamine, respectively. Two groups were given the nicotine placebo-control treatment and conditioned using 0.5 and 1.0 mg/kg mecamylamine, respectively. The final group was treated with 16 mg/kg/day nicotine and trained on the taste procedure with 1.0 mg/kg mecamylamine.

For the statistical analysis of the taste conditioning the volumes consumed of the two solutions on the test day were used to compute a preference score for each rat. This score consisted of the difference between the volume consumed of the drug-and vehicle-paired flavor on the test day, expressed as percent of total fluid intake; however, before statistical analysis the data were subjected to an arcsin transformation (15). Analyses of variance (ANOVA) were used to evaluate the data according to the following designs: First, a two-way ANOVA with 2 levels of mecamylamine dose (0.5 vs 1.0 mg/kg) and nicotine treatment (8 mg/kg/day vs placebo) was used. Second, the data of all the rats that received the taste testing with 1.0 mg/kg mecamylamine were analysed using a simple oneway ANOVA with 3 levels of nicotine treatment (placebo, 8 mg/kg/day and 16 mg/kg/day). Finally, the data of the fentanyl-treated animals and their respective controls were evaluated with a separate oneway ANOVA. Post-hoc tests for mean differences were carried out using the Tukey HSD and

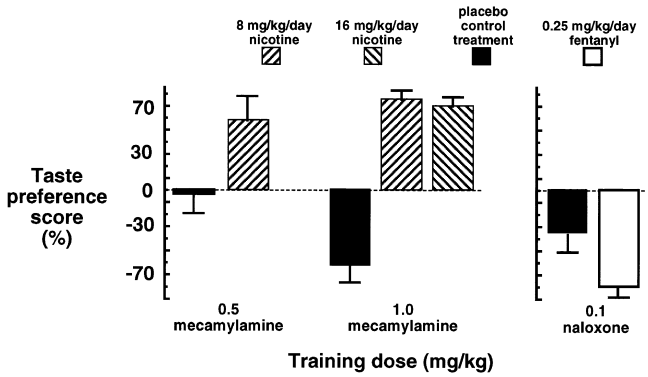

FIG. 1. Mean taste preference scores of seven groups of rats continuously infused for one month with a drug or given a placebo treatment and then trained on a taste conditioning procedure using the drugs' antagonist as the reinforcer. An increase in the score reflects an increase in the preference for the antagonist-paired flavor. Left panel: Data of rats treated with one of two doses of nicotine or placebo and trained with one of two doses of mecamylamine. Right panel: Data for rats treated with fentanyl or placebo and trained with naloxone. Data for each point in the Figure were derived from 6–8 rats (see Results).

Dunnett's test with a familywise error rate (9). In accordance with standard practice in the preference conditioning literature tests were also carried out to determine whether an individual dose produced conditioning. Thus, the flavor consumption of a group was analysed with Wilcoxon paired-ranks test, using the volumes of the two fluids consumed as the data. Also, the total volume of fluid consumed by the different groups and their body weights at the time of training were evaluated using ANOVA. All values presented here were expressed as mean ± SEM and the accepted level of significance was $p < 0.05$, two-tailed.

RESULTS

All animals completed the study in good health except for 4, all of which were in the nicotine treatment conditions; this difference between the control and nicotine groups was not significant ($\chi^2 = 1.4$). One animal was dropped from each of the 8 mg/kg/day groups and 2 from the 16 mg/kg/day group: three had lost their pumps, and one stopped eating. None of the data from these animals were included in the analyses. All remaining animals gained weight during the treatment, although there were significant differences among the weights on the first day of training, as indicated by an ANOVA of the data of the five different treatment conditions (fentanyl, fentanyl placebo control, 8 and 16 mg/kg/day nicotine and nicotine placebo control, $[F(4, 47) = 17.7, p < .001]$. Individual mean comparisons (all Tukey "HSD" tests, $p < 0.5$) indicated that weights of the fentanyl group (352.5 ± 5.2 gm, $n = 8$) and the fentanyl placebo (367.5 ± 7.4 gm, $n = 8$) and nicotine placebo groups (360.6 ± 5.7 gm, $n = 16$) differed significantly from those of the 8 mg/kg/day (319.7 ± 7.3 gm, $n = 14$) and the 16 mg/kg/day groups (291.5 ± 12.3 gm, $n = 6$).

The ANOVA of the data on the taste preference scores in the animals treated with 8 mg/kg/day nicotine revealed a significant effect of treatment $[F(1, 26) = 42.9, p < .001]$ and treatment-by-mecamylamine dose $[F(1, 26) = 7.4, p < .02]$. This effect was explained as a change from no effect or an aversion in the placebo control animals to a preference in the

nicotine-treated animals (see Fig. 1, left panel). For example, there was little preference for any particular flavor when conditioning in the placebo control animals was carried out with 0.5 mg/kg mecamylamine. However, there was a signifciantly higher preference for the drug-paired flavor when this mecamylamine dose was used in animals treated with nicotine (Tukey "HSD" test, $p < .05$).

Consideration of only the data from the three groups of animals trained with 1.0 mg/kg mecamylamine indicated that the drug-paired flavor was significantly avoided in the placebo-control group and signifcantly preferred by animals treated with 8 and 16 mg/kg nicotine (all Wilcoxon tests, $p < .05$). These differences were confirmed by a one way ANOVA of the preference scores [$F(1, 18) = 60.5, p < .001$] . Moreover, individual mean comparisons indicated that the mean for the placebo-control groups was significantly lower than those of the two nicotine-treated groups (both Dunnett's test, $p < .05$).

From Fig. 1 (right panel) it is also seen that naloxone acted as an unconditioned stimulus in both the placebo controls and the fentanyl-treated animals (both Wilcoxon tests, $p < .05$). The effect of the fentanyl treatment was to increase the aversion produced by naloxone in the placebo control animals [$F(1, 14) = 7.4, p < .02$].

Analysis of the total volume of water consumed on the taste test indicated no significant differences among the groups [$F(6, 45) = 1.9$]. The average overall volume of fluid consumed over the 24 h test was 85.9 ± 2.9 mls ($n = 52$).

DISCUSSION

The present results indicated that conditioned taste preferences are produced by pairing flavors with the nicotine antagonist, mecamylamine, in animals infused continuously for one month with nicotine. This contrasts with a mecamylamine-produced conditioned taste aversion seen in nicotine-naive, placebo-control animals. This also contrasts with data reported here that continuous infusion for one month with the morphine analog fentanyl potentiates the aversive conditioning produced by 0.1 mg/kg of the opiate antagonist, naloxone. The conditioned taste preference produced by the mecamylamine is probably not specific to a narrow set of test conditions, since it was seen with two mecamylamine doses and was produced with two nicotine treatment conditions.

Chronic nicotine treatment is believed to lead to adaptive changes that are similar to those produced by opiates (see Introduction). Nicotine produces a variety of effects normally seen with opiates, including tolerance, self-administration, discriminative effects and withdrawal signs (see Refs. 3, 8). Of particular clinical importance is the fact that smokers have withdrawal symptoms described as aversive (see Introduction) and it has been suggested that the mechanisms of these withdrawal signs may be similar to those of the well-known effects of opiate withdrawal (12). Chronic opiate treatment potentiates conditioned aversions produced by naloxone (eg., taste aversions), and these are believed to model opiate withdrawal dysphoria (15). Therefore, the present data indicate important differences in the way that chronic treatment with nicotine or opiates influence conditioning produced by their respective antagonists.

A full explanation of the conditioned preference effects of the mecamylamine in nicotine-treated animals is not possible. Whereas naloxone is a competitive antagonist at opioid receptors (10), mecamylamine is a noncompetitive inhibitor of nicotine activity (13). Mecamylamine does reduce a number of effects produced by nicotine, including nicotine-produced discriminative effects, nicotine self-admininstration and nicotine-produced decreases in food and water (3). Moreover, mecamylamine precipitates a nicotine withdrawal syndrome in animals chronically infused with nicotine (13). Accordingly, it is indeed likely that mecamylamine acted in the present study to reduce the effect of nicotine in our nicotine-infused animals and therefore resulted in some withdrawal. Moreover, the procedure used here involves preference conditioning, a direct test for motivational effects. Taken together the data would suggest that nicotine withdrawal in animals chronically infused with nicotine may be positively motivating. This means that opiate and nicotine treatment influence differently the motivating effects of their respective antagonists, and any hypothesis that opiate and nicotine withdrawal have similar motivational consequences may require some clarification.

Consistent with the present findings are various reports in the literature based on other models of the motivational effects of nicotine and drug withdrawal. Using a different taste conditioning procedure (Parker and Radow model), it was reported that discontinuation of chronic nicotine injections failed to show evidence of a conditioned aversion (23). With the Parker and Radow model we also found that amphetamine treatment failed to show any aversive effects, effects which were easily demonstrated after the discontinuation of opiate treatment (16). It is also seen that rats show a preference for a flavor that was paired with the recovery from a high dose of apomorphine (7). To the extent that nicotine itself is aversive at higher doses (21), it is possible that the infusion doses used here reached aversive levels by the time the mecamylamine was tested and that the discontinuation or reduction of the chronic nicotine treatment resulted in a behavioral effect because of a reduction of this uncomfortable state. The present data add, therefore, to the argument that discontinuation or reduction of chronic drug treatment does not necessarily mean that the subject is in an aversive state, as is usually the case when chronic opiate treatment is discontinued or reduced. Moreover, they even indicate that a behavioral effect of withdrawal may have positive consequences. If is further seen here that to actually gather information on this issue, it is necessary to test directly for the motivational effects.

Finally, some note should be made about caution in generalizing the present data to other nicotine-withdrawal test situations in animals and in human smokers. This is one of the first studies of the direct motivational effects of nicotine withdrawal using a procedure sensitive to both negative and positive motivational effects and it may require replication with other motivational tests, such as the place preference procedure. Similarly, any possibility that mecamylamine administration in smokers produces increased smoking behavior due nicotine withdrawal phenomena (see Introduction), is not inconsistent with the present data: The present study deals with the effect of continuous drug exposure produced by chronic infusion, this is a situation that is not directly comparable to the nicotine exposure produced by the self-administration seen in a smoker. Finally, mecamylamine's positive motivational effects in nicotine-treated animals should not be considered at odds with findings that mecamylamine precipitates a withdrawal syndrome in naive-and nicotine-treated animals (13). First of all, the nicotine doses used here were at least two times greater than those used in the Malin et al. studies; it should be noted, however, that the potentiation of the aversive effects of precipitated opiate withdrawal is seen over a wide range treatment doses (see 15 for Refs.). More importantly, from the literature on withdrawal from opiates and other drugs, it is clear that the commonly measured signs of with-

drawal are neither sufficient nor necessary indicators of the motivational effects of withdrawal (see Introduction).

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