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Influencing Cigarette Smoking with Nicotine Antagonists*

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Abstract. Antagonists of nicotine have been used in an attempt to resolve the continuing controversy about the role of nicotine as the primary reinforcer in cigarette smoking. Mecamylamine, an antagonist which readily penetrates to the central nervous system, increased the rate of cigarette smoking by about 30% in laboratory tests; this was accompanied by reduced blood pressure, impaired performance of a digit symbol substitution test, improved hand steadiness, and by dysphoria. The increased smoking may be regarded as self-titration with nicotine, an interpretation which receives some support from results obtained with pentolinium, an antagonist with predominantly peripheral actions. In the doses used, pentolinium did not affect smoking rate, blood pressure, or hand steadiness, but it impaired digit symbol performance and induced dysphoria. The different results with mecamylamine and pentolinium support previous evidence that the action of nicotine in the central nervous system has a small but clearly demonstrable role as a primary reinforcer of the smoking habit.

Key words: Tobacco — Smoking — Nicotine — Mecamylamine — Pentolinium.

Introduction

The diverse ways in which man uses tobacco may be described empirically as examples of nicotine self-administration. Such a definition implies that nicotine is the primary reinforcer which maintains cigarette smoking, but this has not been clearly demonstrated. Jarvik (1970, and in press) has emphasized that much of the evidence is circumstantial or inconclusive, and has also discussed limitations of alternative theories based on concepts such as oral gratification, pulmonary eroticism, satisfaction of manipulative tendencies, or visual and olfactory stimulation from fire and smoke. In such theories, little or no importance is attached to effects of nicotine in the body and brain (Larson and Silvette, 1968; Report, 1964).

A major difficulty with the nicotine hypothesis has been the rather slight consequences of supplying smokers with tobacco of low nicotine content; reports of withdrawal phenomena have not been confirmed and

* A preliminary account of this work has appeared previously (Jarvik, in press).

the smoking habit is not extinguished within 6 weeks (Finnegan, Larson and Haag, 1945; Goldfarb and Stolerman, unpublished data). "Cigarettes" made from lettuce leaves do not contain nicotine and are rated as highly unsatisfactory by most smokers, but this may be related to smell and taste; adding nicotine does not remedy this (Goldfarb, Jarvik and Glick, 1970; Agué, 1972). In some circumstances, smokers have been found to adjust their behavior so that they seem to obtain approximately the same amounts of nicotine from different types of cigarettes (Ashton and Watson, 1970; Frith, 1971). However, this is not always apparent (Goldfarb and Jarvik, in press), and it is difficult to be sure that such experiments demonstrate nicotine-seeking behavior; similar results would be expected if smokers avoid unusually large doses of nicotine. The generally milder, less irritating smoke from lower nicotine cigarettes may also contribute to the observed effects.

Pharmacological antagonists have, therefore, been used in an attempt to examine the possible consequences of reducing the nicotinic potency of cigarettes without affecting their taste. Experiments with an animal model of smoking provided a further incentive for using antagonists of nicotine; mecamylamine, a secondary amine which readily penetrates the blood-brain barrier, reversed monkeys' preferences for cigarette smoke over air (Glick, Jarvik and Nakamura, 1970). Hexamethonium, a quaternary antagonist with predominantly peripheral effects, was much less active in this test. Described below are analogous studies in man, with the antagonists mecamylamine and pentolinium.

Methods

Subjects

The subjects were paid volunteers, aged 18—35 years, who usually smoked 20 or more cigarettes a day. They were told that a drug which might affect the way people smoke was being studied and that currently, any effects which it might have on physical and mental performance were being examined. Questionnaires and interviews were used to exclude individuals taking other medication, or whose medical history suggested that it was not advisable for them to participate. Cigarettes smoked by the selected subjects delivered (nominally) 1.0—1.5 mg nicotine (Federal Trade Commission Report, 1971). All subjects were asked not to take drugs for non-medical reasons for 3 days before participating and for purposes of comparison, some non-smokers were tested in a supplementary experiment.

Drugs

Capsules containing graded doses of mecamylamine hydrochloride or pentolinium tartrate were prepared. These drugs were chosen as representatives of the secondary and quaternary compounds with ganglion-blocking properties; mecamylamine readily penetrates to the brain (Goodman and Gilman, 1970). The doses used were: mecamylamine 7.5—22.5 mg in 5 mg increments; pentolinium 100 and

150 mg. Smokers were tested with all doses; non-smokers with mecamylamine (12.5 and 22.5 mg) only. All subjects received lactose placebos as well as the drugs.

Procedure

The experiments began at 11 a.m. Up to six subjects participated on any one occasion and they were instructed not to smoke until they were given permission to do so. The subjects then swallowed the capsules and immediately performed a practice run on the short test battery described below. After having lunch and returning to the laboratory, the subjects repeated the test battery three times at 45-min intervals, beginning 90 min after taking the capsules. It was announced that smoking was permitted during this period, which lasted for about 2 h. The experimenters made notations on charts every time subjects lit cigarettes, and every time cigarettes were puffed. One experimenter could conveniently record the smoking behavior of three subjects and, usually, the same subjects were tested together under drug and placebo conditions. The procedures were similar when non-smokers were tested, and to maintain conditions as constant as possible, the experimenters made dummy notations on the charts normally used to record smoking behavior.

The study was conducted on a double-blind basis, with subjects serving as their own controls and receiving drug and placebo treatments 1 week apart. The order of treatments was balanced at each dose (with the one exception noted below), and the doses were progressively increased as the experiments proceeded. Statistical analyses were performed as described by Winer (1962) for repeated measures on groups of unequal size. The results for mecamylamine (22.5 mg) were excluded from the main analyses because this dose was given only to subjects previously tested under placebo and a lower dose. Although this precaution unbalanced the experimental design, it was considered necessary in view of the large individual differences in response to this drug (Paton, 1959; Goodman and Gilman, 1970).

The Test Battery

The following procedures were carried out repeatedly during each experimental session: measurements of blood pressure and pulse rate; digit symbol substitution test; hand steadiness test; assessment of subjective state. The purposes of the tests were 1. to divert attention from the measurement of smoking and 2. to facilitate assessment of anti-nicotinic effects of the drugs. Subjects worked in pairs, alternately performing the tests and recording each other's results (Dickens, Lader and Steinberg, 1965). The time required to complete the tests was about 15 min, and subjects had knowledge of results (except for blood pressure and pulse measurements). The details were as follows:

Systolic and diastolic pressures, in both sitting and standing positions, were recorded by an experimenter using a sphygmomanometer. In the digit symbol substitution test (Wechsler, 1944; Mirsky and Kornetsky, 1964) subjects were instructed to write symbols corresponding to a list of 75 digits, using a key which was available at all times. Hand steadiness was estimated with a stylus-in-hole apparatus (Frankenhaeuser, Myrsten, Waszak, Neri and Post, 1968); subjects tried to hold a stylus of 1 mm diameter in a hole in a metal plate without contacting the sides. Three 30-sec tests with progressively smaller holes were given, with 30-sec rest periods. The number and duration of contacts were recorded automatically. Subjective state was assessed with check lists of 25 adjectives describing various feelings and sensations, a procedure modified from Nowlis and Nowlis (1956) and Dickens *et al.* (1965).

Results

Smoking Behavior

Doses of mecamylamine from 7.5—17.5 mg increased, by about 30%, the mean numbers of cigarettes smoked in the 2 h sessions (Table 1). The overall drug vs. placebo difference was highly significant ($F = 10.70$, df 1,29, $P < 0.01$) and there were no substantial differences between doses ($F = 1.03$, df 2,29). A larger dose (22.5 mg) was tested in six subjects; again, more cigarettes were smoked after the drug than after placebo (5.0 as compared with 3.8). The incidence of adverse reactions, including dizziness and impaired vision, precluded further testing at this dose.

The number of times that subjects puffed on their cigarettes increased after mecamylamine, in proportion to the numbers of cigarettes smoked. As one would expect, the two measures were highly correlated, with $r = 0.79$ after placebo and $r = 0.83$ after mecamylamine (df 30, $P < 0.001$ in both cases). Pentolinium did not affect smoking consistently; the larger dose tended to reduce the number of cigarettes smoked, but neither dose affected the number of puffs. No sign of an increased rate of smoking was apparent with either index.

At the end of each session, subjects were asked to assess, on ten-point scales, the satisfaction that they derived from smoking during the experiment, and the apparent strength of their cigarettes. The drugs did not influence these ratings consistently, although reduced satisfaction ($P < 0.05$) was reported with mecamylamine in a dose of 12.5 mg only.

Blood Pressure

The most consistent results were obtained with systolic pressures in seated subjects; to provide an index of drug action, the means of the

Table 1. Mean numbers of cigarettes smoked, and puffs on cigarettes, during 2 h sessions after administration of drugs. Mecamylamine increased the rate of smoking whereas pentolinium, if anything, reduced it

Drug treatment	*n*	Cigarettes after drug	Cigarettes after placebo	Puffs after drug	Puffs after placebo
Mecamylamine 7.5 mg	8	4.4*	3.4	38.1	30.4
Mecamylamine 12.5 mg	14	4.8*	3.2	36.9*	26.1
Mecamylamine 17.5 mg	10	3.8	3.4	36.6	32.8
Means	32	4.3**	3.4	37.2*	29.7
Pentolinium 100 mg	10	3.6	3.8	32.9	35.4
Pentolinium 150 mg	10	3.3*	4.3	36.6	39.5
Means	20	3.4	4.0	34.8	37.5

* $P < 0.05$. — ** $P < 0.01$.

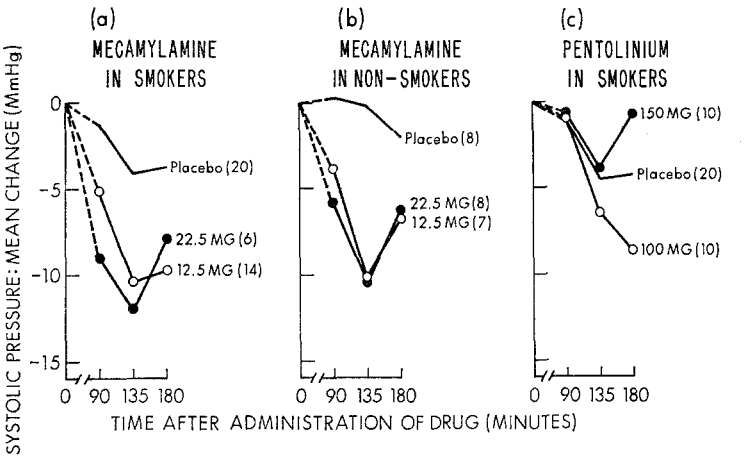

Fig. 1. Changes in systolic blood pressures of seated subjects after administration of ganglion-blocking drugs. Mecamylamine lowered the mean pressure of smokers and non-smokers, but pentolinium had no significant effects in the doses used. Signs of recovery were apparent 180 min after mecamylamine was taken. Figures in brackets indicate the numbers of subjects in each group

readings taken at 90, 135 and 180 min after administering the drugs were calculated. Doses of mecamylamine from 7.5—17.5 mg reduced the mean systolic blood pressure of smokers by about 10 mm of mercury, as compared with the results after placebo capsules ($F = 5.17$, df 1,29, $P < 0.05$), but there were no significant differences between doses. Even with 22.5 mg, the mean effect was not bigger, but periods of severe hypotension occurred in individuals. There did not seem to be a correlation between hypotensive efficacy and the amount of smoking.

The results with non-smokers were similar; there was a significant fall in systolic pressure ($F = 7.68$, df 1,14, $P < 0.05$), but no sign of a dose-related effect. Representative results are shown in Fig. 1 (a) and (b). Mecamylamine also increased the mean pulse rate of non-smokers from 81.0 to 85.4 ($F = 4.71$, df 1,14, $P < 0.05$), but it did not affect this measure in smokers. In the doses used, pentolinium did not bring about consistent changes in blood pressure (Fig. 1 c) or pulse rate of smokers.

Digit Symbol Substitution Test

Both mecamylamine and pentolinium slightly increased the time required for completion of this test (Table 2). Accuracy was unaffected and the results were similar in smokers and non-smokers. The largest dose of mecamylamine (22.5 mg) had a bigger effect and 95.0 sec were needed for completion of the test, as compared with 75.2 sec for a different group

Table 2. Mean times required to complete digit symbol substitution tests after administration of drugs to six groups of subjects. Each score is the average for the three tests carried out at different times after the drugs were taken. Both mecamylamine and pentolinium impaired performance

Drug treatment	*n*	Time after drug (sec)	Time after placebo (sec)
Mecamylamine 7.5 mg	8	82.9*	77.6
Mecamylamine 12.5 mg	14	85.6	83.0
Mecamylamine 17.5 mg	10	84.2	78.4
Means	32	84.2**	79.7
Pentolinium 100 mg	10	96.3*	85.2
Pentolinium 150 mg	10	95.5	90.3
Means	20	95.9*	87.8

Significant differences from placebo scores:
* $P < 0.05$. — ** $P < 0.01$.

of placebo subjects that had had the same amount of practice ($t = 2.59$, df 10, $P < 0.05$).

Hand Steadiness

The correlation between the number of contacts and the total time of contact of stylus with hole decreased progressively with task difficulty ($r = 0.93$, 0.85, and 0.68 for holes with diameters of 3.0, 2.5, and 2.0 mm respectively, $n = 60$). The scores were log-transformed throughout to stabilize variances, and the results obtained with the 3.0 mm hole were selected for further analysis because these had yielded the highest correlation between time and frequency measures.

Mecamylamine (7.5—17.5 mg) improved hand steadiness in smokers ($F = 4.40$, df 1,27, $P < 0.05$) and the effect was clearest with a dose of 12.5 mg. In non-smokers, this dose tended to impair steadiness, but improvement would have been more difficult to detect because non-smokers tended to be steadier than smokers under placebo conditions. Pentolinium had no significant effects in smokers (Fig. 2), and was not tested in non-smokers.

Subjective Reports

Both mecamylamine and pentolinium brought about consistent changes in the reports of subjective feelings and sensations. The 25 adjectives on the check list were classified into two categories, "desirable" and "undesirable", in accordance with previous practice (Dickens *et al.*, 1965). The numbers of adjectives checked were calculated for each

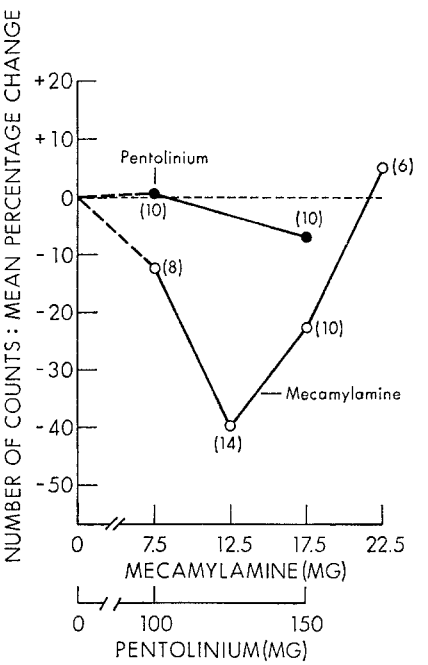

Fig. 2. Hand steadiness of smokers measured with a stylus-in-hole apparatus, and expressed as differences between percentage changes from starting baselines after drug and placebo administration. Mecamylamine improved steadiness over a limited dose range, whereas pentolinium had no significant effects at the doses used. Changes in steadiness after placebos were negligible and are represented by the dashed line. The figures in brackets indicate the numbers of subjects in each group

category, summed across the three times that the check list was completed after drug or placebo. Mecamylamine and pentolinium reduced the total number of "desirable" self-reports and increased the total number of "undesirable" self-reports. For example, drugged subjects rated themselves as being less efficient, less sociable, and less alert, and as more tense, mentally slow and drowsy. Profiles of the responses to mecamylamine are shown in Fig. 3, with the five adjectives least frequently checked omitted, for clarity. The results with pentolinium were similar but more variable, possibly because the number of subjects was smaller.

To construct dose response curves, a "dysphoria index" was calculated for each subject, as the percentage of the total number of self-reports which were in the "undesirable" category. This index provided a single measure encompassing both the reduced number of "desirable",

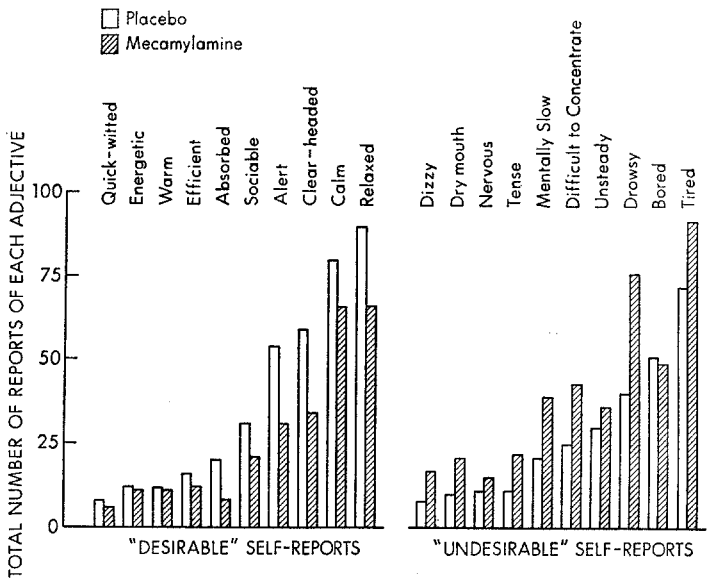

Fig. 3. Profiles of subjective state; each histogram shows the total number of times that subjects ($n = 54$) checked individual adjectives during the period 90 to 180 min after mecamylamine or placebo capsules. The results for a range of doses (7.5—22.5 mg) have been pooled and it can be seen that the drug had consistent effects; it reduced the frequency of "desirable" and increased that of "undesirable" self-reports. Dose response relations are shown in Fig. 4

and the increased number of "undesirable" self-reports. All 25 adjectives on the check list were included and the scores so obtained were subjected to the arc-sin transformation before statistical tests were applied. Fig. 4 shows the dose-response relations for mecamylamine and pentolinium. Mecamylamine increased the dysphoria index in a dose-related manner ($F = 15.16$, df 1,49, $P < 0.001$); the results in smokers and non-smokers did not differ significantly and have been pooled. The dysphoria index was also higher after pentolinium than after placebo, and it seemed that doses of 100—150 mg of pentolinium were approximately equivalent to 7.5—17.5 mg of mecamylamine, on this basis.

Discussion

Mecamylamine, in a range of doses, increased the rate of cigarette smoking during laboratory tests, a finding which may be regarded as evidence for self-titration with nicotine. To support the validity of this interpretation, we shall argue 1. that the doses of mecamylamine were

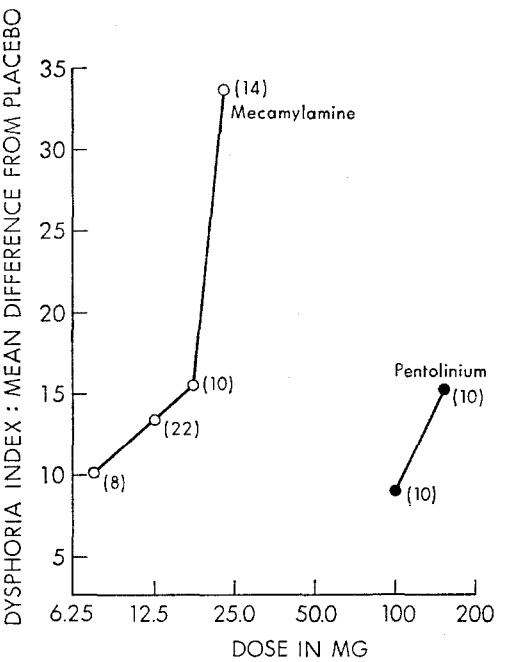

Fig. 4. Dose-related increases in a dysphoria index after administering mecamylamine or pentolinium. The index was calculated for each subject as the percentage of the total number of self-reports which were classified as "undesirable", and the curves show the mean drug-placebo difference for each group of subjects. The figures in brackets indicate the numbers of subjects in the groups

adequate to block nicotine absorbed by smoking and 2. that other effects of mecamylamine probably did not account for the results.

The doses of mecamylamine were similar to those used clinically for treating hypertension (Goodman and Gilman, 1970) and the demonstrated changes in the mean pulse rate and blood pressure testify to the adequacy of dosage by these criteria. The dose of mecamylamine needed to block nicotine is much smaller than that which impairs ganglionic transmission in animals (Wong and Long, 1968) and, therefore, the rather small decreases in mean blood pressure in our experiments with normotensive subjects do not necessarily indicate that inadequate doses were used. However, it is difficult to be sure that mecamylamine completely blocked all the actions of nicotine.

The results with the digit symbol substitution test and the check lists of subjective feelings and sensations also indicate that active doses of mecamylamine were given, but the most direct evidence for antagonism

of nicotine came from the hand steadiness test. Nicotine absorbed from cigarette smoke was previously found to impair performance on the stylus-in-hole test (Edwards, 1948; Frankenhaeuser *et al.*, 1968) and an improved performance would, therefore, be expected after administering an antagonist of nicotine to smokers. We demonstrated this, but the dose required was critical; mecamylamine itself has been reported to induce tremor at high doses (Paton, 1959; Goodman and Gilman, 1970).

Thus, mecamylamine had significant effects on all four components of the test battery, but only the subjective reports were clearly dose-related. The lack of dose-response relations with the objective tests may be attributed to variable absorption, errors in measurements or other uncontrolled sources of variance. Animal experiments provide additional evidence that mecamylamine can be a highly effective antagonist of nicotine in the central and peripheral nervous systems (e.g. Stone, Meckelnburg and Torchiana, 1958; Morrison, Goodyear and Sellers, 1969).

It is also conceivable that mecamylamine, while effectively blocking nicotine, may have increased smoking by a different mechanism. For example, dysphoria may have functioned as a mild stressor. This seems improbable because pentolinium also produced dysphoria, but did not increase smoking. However, the value of pentolinium as a control was limited by uncertainties about dosage; although both the digit symbol substitution test and the dysphoria index were affected by pentolinium, there was no change in the mean blood pressure. Larger doses (180 to 200 mg) elicited unpredictable bouts of severe hypotension and blurred vision, which were consistent with the expected variation in absorption (Freis and Wilson, 1956; Smirk and McQueen, 1957). A further complication is that active amounts of quaternary agents may pass the blood-brain barrier (Izquierdo and Izquierdo, 1971; Asghar and Roth, 1971). It may not, therefore, be correct to assume that peripheral actions are the sole source of any possible sedative effects of hexamethonium (Paton and Steinberg, 1956), or of our essentially similar findings with pentolinium. These problems notwithstanding, the results suggest that mecamylamine increased smoking and improved hand steadiness by central actions, but slowed digit symbol performance and produced dysphoria by peripheral mechanisms.

The increased smoking after taking mecamylamine parallels that sometimes seen with cigarettes delivering reduced amounts of nicotine (Ashton and Watson, 1970, Frith, 1971). In contrast, administering nicotine in capsules or by intravenous infusion lowers the smoking rate (Lucchesi, Schuster and Emley, 1967; Jarvik, Glick and Nakamura, 1970). Thus, several different manipulations associated with nicotine delivery have mutually consistent effects predictable from the hypothesis

that nicotine is a primary reinforcer of smoking. The weight which can be attached to this body of evidence is limited by the small size of the observed changes in smoking rate. For example, mecamylamine boosted smoking by about 30%; it is difficult to be sure that this was accompanied by changed plasma levels of nicotine until direct measurements are made. The different results with monkeys (Glick *et al.*, 1970) may be a function of dose and time course effects, the much longer history of smoking in our human subjects, or other limitations of the animal model. The monkeys were given mecamylamine repeatedly, but the human volunteers received single doses only; chronic studies in man have been difficult to complete, due to adverse reactions to the drug.

Our experiments, and those done previously (for review, see Jarvik, 1970), support the view that nicotine plays a small but demonstrable role as a primary reinforcer maintaining the smoking habit. In experiments with rats and monkeys, a reinforcing action of nicotine alone, in the absence of smoke, has been reported (Deneau and Inoki, 1967; Clark, 1969). Other alkaloids in tobacco were much less active in pharmacological tests (Clark, Rand and Vanov, 1965). What other forms of reinforcement may be involved? Perhaps part of the reward of smoking arises from taste and other localized sensations which the act produces in the oro-pharyngeal and respiratory tracts (Larson and Silvette, 1968). Learned associations between tastes and subsequent actions of ingested substances are formed very easily (Revusky and Garcia, 1970); we speculate that the taste and smell of tobacco smoke can serve as secondary (conditioned) reinforcers due to their previous, repeated association with effects of nicotine, the presumptive primary reinforcer.

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