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Evidence for a Behavioral Deficit During Withdrawal From Chronic Nicotine Treatment[1]

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CORRIGALL, W. A., S. HERLING AND K. M. COEN. *Evidence for a behavioral deficit during withdrawal from chronic nicotine treatment.* PHARMACOL BIOCHEM BEHAV **33**(3) 559–562, 1989.—Rats that had been trained to respond for food on a fixed-interval 3-minute schedule were treated once daily with nicotine (2 mg/kg) for 50 days. Animals developed marked tolerance to the depressant effect of nicotine as measured by the decreased effect of the treatment dose on response rates over days. Substitution of saline for nicotine during chronic treatment resulted in response rates which were significantly less than pretreatment values. In addition, following cessation of chronic treatment, response rates were initially suppressed below pretreatment rates; by the third day of withdrawal, response rates had returned to baseline levels. It is proposed that the response deficit observed during nicotine absence represents one behavioral component of a nicotine withdrawal syndrome.

Nicotine Withdrawal Chronic Tolerance Physical dependence Behavioral dependence

A variety of studies have demonstrated that nicotine treatment produces tolerance [e.g., reviews in (1,10)]. For example, acute tolerance can be demonstrated after a single pretreatment with nicotine (12). In addition, chronic treatment with the drug leads to the development of tolerance to its depressant effects, as measured with locomotor activity tests (2, 4, 13) and operant behavior (3, 6, 9). In contrast, less is known about the period following chronic nicotine treatment. Part of the reason for this is the absence of an overt withdrawal syndrome such as can occur in opioid abstinence. Although animal studies have shown that there are changes in food consumption following termination of chronic treatment (6), and that rats maintained on daily nicotine show deficits in avoidance behavior during withdrawal (7), other evidence of a nicotine withdrawal syndrome in animals has not been reported. In fact, several studies have specifically noted the absence of any indices of withdrawal (4,13). While the situation with respect to human smoking behavior suggests that tobacco withdrawal is a highly variable phenomenon, it is apparent that withdrawal symptoms are most evident in subjects who have had high intake of tobacco products (1). In addition, human studies have shown that tobacco abstinence results in performance deficits which can be ameliorated by nicotine (10).

Therefore, the objective of the present study was to examine whether animals administered a high dose of nicotine chronically would show behavioral alterations following cessation of drug treatment. To test this we have examined responding maintained by delivery of food on a fixed-interval schedule (5).

METHOD

Subjects were eight male Long-Evans rats (Charles River; Lachine, Quebec), 240–290 g in weight, and drug naive at the time they began these experiments. For the duration of the study, animals were maintained in a reversed light-dark cycle on a controlled feeding schedule (receiving approximately 4 standard lab chow pellets each day several hours after their operant sessions). Water was continuously available.

Animals were trained to respond for single 45-mg food pellets in a 3-min fixed-interval schedule (FI-3 min). Because we wanted to assess the effects of nicotine treatment and withdrawal over a protracted period of time, daily sessions consisted of 4 components of 20-min duration, each separated by 20-min periods in which food was not available. A maximum of 5 food pellets were available in each 20-min fixed-interval component. Injections, initially of saline, were given 20 min before the first FI component of each session. The operant schedule thus allows determination of response rates over 4 times postinjection, namely, 20–40, 60–80, 100–120 and 140–160 minutes. Animals were habituated to having operant sessions on some days and not on others; when

[1]The views expressed in this publication are those of the authors and do not necessarily reflect those of the Addiction Research Foundation.

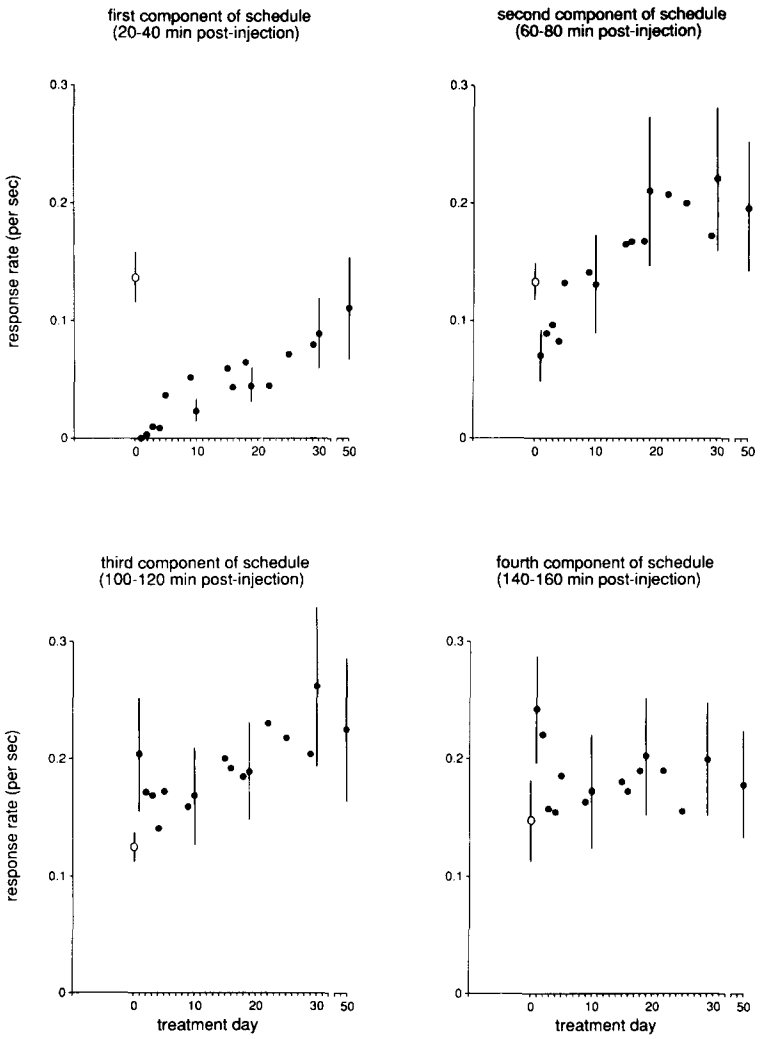

FIG. 1. Response rates in each of the four fixed-interval (FI) components of the operant sessions prior to, and during, chronic treatment with 2 mg/kg nicotine. Points are mean rates for the sample of 8 subjects; error bars show ± 1 standard error of the mean (SEM). The points shown on day 0 (open circles) are the control values (i.e., pretreatment with saline) obtained on the day immediately prior to the start of chronic treatment with nicotine.

response rates were stable under these conditions, chronic treatment was begun.

Chronic treatment was carried out for a period of 50 days. During this time animals received a single daily subcutaneous injection of 2 mg/kg nicotine bitartrate (dose calculated as the base). On some of the treatment days the animals were permitted to respond for food on the FI-3 min schedule, beginning 20 minutes after the injection, as was done for saline pretreatments. Specifically, nicotine injections were followed by food sessions on treatment days 1, 2, 3, 4, 5, 9, 10, 15, 16, 18, 19, 22, 25, 29, 30 and 50. On the other treatment days, the nicotine was administered at approximately the same time of the day, but in the home cages. During withdrawal, saline injections were followed by food sessions on days 1, 3, 6, 7, 8, 9, 10 and 13 in order to maintain the regimen of intermittent food sessions used during chronic treatment. The choice as to which days would include a food session and which would not was arbitrarily made.

To assess single-day withdrawal from nicotine early in treatment, saline was substituted for nicotine on day 20; the chronic nicotine treatment for that day was administered after the session. To assess withdrawal after 50 days of chronic treatment, animals were given daily saline injections.

Response rates in the last operant session prior to the beginning of nicotine treatment were used as pretreatment control values. Data presented in the figures are mean values of response rates for the sample of 8 subjects. Statistical analyses were done with *t*-tests.

RESULTS

The effects of nicotine treatment on response rates maintained by food are shown in Fig. 1. On day 1, responding was suppressed completely in the first component of the schedule (20–40 min after nicotine injection) and suppressed by approximately 40% in the second component (60–80 min after nicotine). However, at longer times postinjection, particularly in the third component of the

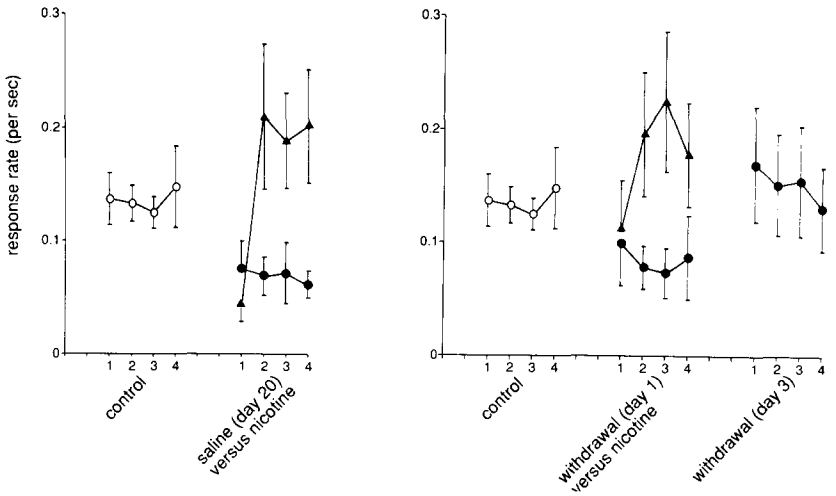

FIG. 2. Left-hand graph: Response rates (mean ± SEM) across the four components of the schedule during saline treatment prior to chronic nicotine (open circles) and during saline treatment in lieu of nicotine on day 20 (filled circles). For comparison, response rates under nicotine from the previous day (day 19) are also shown (filled triangles). The numbers on the abscissa refer to the components of the food schedule. Right-hand graph: Response rates during prechronic saline (open circles) and on the first and third days of nicotine withdrawal after 50 days of treatment (filled circles). For comparison, response rates under nicotine on the last day of chronic treatment (day 50) are also shown (filled triangles).

session, the stimulant effect of nicotine was apparent. Over the course of repeated daily injections with 2 mg/kg nicotine, marked tolerance developed to the depressant effect of the drug. In contrast, changes in the stimulant effect of nicotine during chronic treatment, as seen in the third component of the schedule, were of smaller magnitude and were in the direction of sensitization rather than tolerance.

The consequences of substituting saline for nicotine on day 20 are shown in Fig. 2 (left-hand side). During the session following saline injection, animals' response rates across the four FI components were consistently suppressed by almost 50% relative to pretreatment values, and these differences were statistically significant [first FI component, $t(7)=4.74$, $p<0.005$; second FI component, $t(7)=6.19$, $p=0.001$; third FI component, $t(7)=3.98$, $p<0.01$; fourth FI component, $t(7)=3.29$, $p<0.05$]. Notice also, that in comparison to the nicotine treatment of the previous day, response rates during saline substitution were much lower, except during component 1 of the schedule (where prominent rate-suppressant effects of nicotine still occur).

On the first day after chronic treatment ended (Fig. 2, right-hand side), response rates were suppressed by essentially the same amount as on day 20, and rates in 3 of the 4 components were significantly different from the pretreatment control [first FI, $t(7)=2.33$, $p=0.05$; second FI, $t(7)=4.37$, $p<0.005$; third FI, $t(7)=5.72$, $p=0.001$; fourth FI, $t(7)=1.11$, n.s.]. However, on the third and subsequent days of drug withdrawal, response rates were clearly not different from pretreatment values.

DISCUSSION

Acute administration of nicotine is known to produce behavioral suppression after high doses, and excitation after low doses or at long times after high doses [e.g., (5,14)]. In this study, the biphasic effects of acutely administered nicotine (e.g., treatment day 1) on the response rates for food-maintained operant behavior are consistent with these known effects. During chronic treatment with nicotine, obvious and marked tolerance developed to the rate-decreasing effects of the drug, a finding consistent with other studies using locomotor activity tests and operant responding [e.g., (2, 4, 6, 9, 12, 13)]. Tolerance to the stimulant effects of the drug did not develop; rather, the prominent stimulant effects evident in the third component increased over time, also in essential concordance with the research cited above.

The purpose of the present experiment was to examine the effects of nicotine withdrawal. This was done by substituting saline for nicotine on a single day during chronic treatment, and after 50 days of chronic treatment. Treatment with saline on day 20 resulted in response rates that were significantly below pretreatment values in all four FI components. Similarly, at the end of the chronic treatment period, response rates were markedly reduced on the first nicotine-free day. These response rate deficits appear to reflect an inability of the animals to function at pretreatment levels in the absence of the drug, and as such may represent a nicotine behavioral dependence syndrome. Similar findings have recently been reported for cocaine (15). However, with cocaine, response rate changes lasted for several days and included complete response cessation. In that study, cocaine was delivered continuously at high doses for 24 hours each day via intravenous catheters. In the present study, single daily injections were used. These methodological differences, along with differences between the two drugs themselves, may account for the differing degrees of response suppression observed during drug withdrawal in the two studies.

The suppression observed at day 20 during saline substitution was comparable to the suppression on the first day of withdrawal after 50 days of nicotine treatment. However, at these two times, the degree of tolerance to nicotine was clearly different; at day 20 the animals had not developed the same degree of tolerance that they had by day 50. Consequently it appears that the animals had developed the maximal behavioral dependence well before tolerance was maximal.

The present findings cannot be interpreted as being due to a reduction in feeding during the operant sessions, since in spite of the decreased response rate, animals typically obtained the scheduled 5 food pellets in each FI component, and consistently ate all

of the pellets that they obtained. Therefore, the response rate suppression during withdrawal of nicotine appears to reflect a true response deficit as opposed to appetitive alterations. In any event, withdrawal would be expected to produce, if anything, no change or an increase in consumption, rather than a decrease (7).

An alternative explanation which might be entertained is that the response deficit seen following withdrawal of nicotine is the expression of a conditioned drug effect. In our study, nicotine was not paired exclusively with the operant environment, but the environment during chronic treatment was consistently paired with nicotine. It is possible, therefore, that exposure to the operant chambers could come to elicit a conditioned response. However, if the conditioned response were drug-opposite, counteracting the depressant effects of nicotine (as might be expected since tolerance develops clearly to the depressant effects of the drug), it is difficult to understand why there would not be response rates greater than control values produced during saline substitution. Furthermore, the short duration of the response deficit argues against a conditioning hypothesis, since one would expect extinction of the conditioned response to occur over a longer time than one or two trials.

Yet another explanation for the behavioral suppression is that nicotine administered prior to the operant sessions produced state-dependent learning, so that in the absence of nicotine responding was attenuated. However, nicotine was followed by food-reinforced operant sessions on only 16 of the 50 treatment days, and only 11 nicotine-food session pairings had occurred prior to saline substitution on day 20. Other nicotine treatments were not followed by food sessions. There appears to be minimal opportunity, therefore, for the production of state-dependent learning.

There have been few reports of a nicotine abstinence syndrome in animals. Indeed, with locomotor activity tests, dependence has been reported to be minimal or absent (4,13). Nicotine withdrawal in rodents does lead to increased consumption of food (7) unless only bland, low calorie foods are available. In addition, animals show deficits in avoidance behavior when tested after chronic treatment (8), an observation that has been attributed to nicotine's ability to relieve stress. In contrast, the task used in the present study was not related to relief of stress, yet performance deficits were observed following nicotine withdrawal. This seems to be similar to the situation in humans in which tobacco abstinence has been associated with performance deficits (10).

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