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# (−)-Nornicotine Partially Substitutes for (+)-Amphetamine in a Drug Discrimination Paradigm in Rats

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BARDO, M. T., R. A. BEVINS, J. E. KLEBAUR, P. A. CROOKS AND L. P. DWOSKIN. *(−)-Nornicotine partially substitutes for (+)-amphetamine in a drug discrimination paradigm in rats.* PHARMACOL BIOCHEM BEHAV **58**(4)1083–1087, 1997—Rats were trained in a two-lever food-reinforced operant task to discriminate (+)-amphetamine (1 mg/kg) from saline. After discrimination training stabilized, test doses of (+)-amphetamine (0.0625–2.0 mg/kg), (−)-nicotine (0.1–1.0 mg/kg), or (−)-nornicotine (1–10 mg/kg) were assessed for their ability to substitute for the (+)-amphetamine training dose during brief test sessions in which food reinforcement was withheld. As expected, as the test dose of (+)-amphetamine increased, there was a dose-related increase in drug-appropriate responding, with both 1 and 2 mg/kg test doses substituting fully for the (+)-amphetamine training dose. Both (−)-nicotine and (−)-nornicotine showed partial substitution (approximately 50% drug-appropriate responding) for the (+)-amphetamine training dose, with (−)-nicotine being more potent than (−)-nornicotine. Rate suppressant effects prevented the assessment of higher doses of (−)-nicotine or (−)-nornicotine. Thus, while (−)-nicotine and (−)-nornicotine share similar discriminative stimulus properties, the mechanism that mediates this effect appears to differ, at least in part, from that activated by (+)-amphetamine. © 1997 Elsevier Science Inc.

Drug discrimination Amphetamine Nicotine Nornicotine Drug cue Discriminative stimulus Rat

IT is widely recognized that nicotine plays a major role in the maintenance of tobacco smoking behavior. Similar to other types of stimulant drugs such as amphetamine, evidence indicates that dopaminergic systems in the brain mediate, at least in part, the ability of nicotine to produce reinforcement (7, 8,27), locomotor sensitization (5), and discriminative stimulus effects (21,25). Because both nicotine and amphetamine release dopamine (10,20), this common action may explain why these drugs produce discriminative stimulus effects that partially substitute for each other (4,16,29). However, full substitution between nicotine and amphetamine discriminative stimulus effects is generally not obtained. The lack of full substitution may result because the discriminative stimulus effect of nicotine, in contrast to amphetamine, involves a significant cholinergic component (15,30).

In addition to nicotine, other active alkaloids in tobacco may contribute to the stimulant-like behavioral effects of smoking tobacco. Nornicotine is an alkaloid in tobacco that is detectable in the urine of human smokers (34). In addition to being a constituent of tobacco, nornicotine is a minor nicotine metabolite formed from the oxidative *N*-demethylation of nicotine (2). When rats are injected peripherally with (−)-nicotine, the natural enantiomer of nicotine found in tobacco, significant levels of nornicotine are detected in brain 4 h later (9).

Evidence suggests that nornicotine may have behavioral effects similar to other stimulant drugs. For example, in one study using dogs, both (−)-nicotine and (±)-nornicotine altered responding under two different food-maintained operant schedules in a manner similar to cocaine (24). More recently, repeated treatments of either enantiomer of nicotine or nornicotine have been shown to produce stimulant-like behavioral sensitization (11,28). In these studies, (−)-nornicotine was less potent than (−)-nicotine.

Aside from its effects on operant responding and locomotor activity, however, it is unclear if nornicotine produces either discriminative stimulus or reinforcing effects like other stimulants. The present study, therefore, used a drug discrimination paradigm in rats to examine the ability of (−)-nornico-

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tine to substitute for (+)-amphetamine, thus providing evidence regarding shared discriminative stimulus properties.

## METHODS

### *Animals*

Nine male Sprague–Dawley rats were obtained from Harlan Industries (Indianapolis, IN) and were caged individually with free access to water in the home cage. Food access was restricted to maintain body weights at approximately 80% of free-feeding weight. Prior to the start of the experiment, all rats received a single injection of (+)-amphetamine (1 mg/kg, IP) as part of an unrelated experiment.

### *Apparatus*

Six operant chambers (ENV-001, Med Associates, St Albans, VT) enclosed in a sound attenuating environment were used. Located in the bottom center of the front panel in each chamber was a 5 × 4.2-cm opening to a recessed food tray. Two metal response levers were located on the front panel, one on each side of the food tray. The center of each lever was mounted 7.3 cm from the grid floor. A 28-V cue light, 3 cm in diameter, was centered 6 cm above each lever. A personal computer, interfaced to the chamber with Med Associates equipment, controlled the experimental sessions and collected data.

### *Procedure*

*(+)-Amphetamine discrimination training.* The general procedures utilized to establish (+)-amphetamine discrimination were similar to those outlined previously (13). Briefly, rats were first given access to food pellets (45 mg sucrose pellet, Noyes Co., Lancaster, NH) dispensed at various intervals into the food tray with both levels present; a response on either lever during this initial phase resulted in food delivery. One lever was then removed and the rat was shaped to depress the other lever for food reinforcement. Following this, rats received 15-min daily sessions in which the lever (left or right) available for food reinforcement was alternated daily. Across these daily sessions, the fixed ratio (FR) requirement to obtain food was gradually increased from an FR1 to an FR25. The start of each session was signaled by the onset of both cue lights mounted above the levers. The termination of each session was signaled by the offset of these lights. This training phase was continued until the rat earned 20 reinforcers on an FR25 schedule for 2 days.

(+)-Amphetamine discrimination training was conducted Monday through Friday. For this training, both levers were mounted in the chamber. (+)-Amphetamine (A; 1 mg/kg) or saline (S), was injected IP 15 min prior to the start of each session, with the order of daily injections being either AASS or SSAA. The left lever was designated as the drug-correct lever for four rats, while the right lever was drug-correct for five rats. On Monday, Wednesday, and Friday, injection-appropriate responding was food reinforced on an FR25 schedule for the entire 15-min session. However, 2-min extinction periods were instituted at the beginning of sessions on Tuesday and Thursday (one drug and one saline test per week) to assess the control of (+)-amphetamine (or saline) over responding. During this brief extinction period the distribution of responding was monitored, but lever pressing did not result in food reinforcement. During the remaining 13 min of these sessions, contingent reinforcement for injection-appropriate responding was reinstated. This phase of training was continued until: 1) the rat completed the first FR25 on the correct level for 10 consecutive sessions; and 2) the rat completed 80% or more responses on the injection-appropriate lever during four consecutive extinction periods.

*(+)-Amphetamine, (−)-nicotine, and (−)-nornicotine substitution tests.* The substitution phase of the study was identical to the previously described (+)-amphetamine discrimination phase, except for the Friday session, which was decreased to a 4-min extinction session with no food available. This session was used to assess the ability of (+)-amphetamine (0.0625, 0.125, 0.25, 0.5. 1.0, or 2.0 mg/kg), (−)-nicotine (0, 0.1, 0.3, 1.0, or 3.0 mg/kg) and (−)-nornicotine (0, 1, 3, or 10 mg/kg) to substitute for the (+)-amphetamine training dose. Each dose was administered on two different Friday sessions according to a randomized block design. All rats were first administered each (+)-amphetamine dose (two determinations per dose) 15 min prior to the substitution test session. Subsequently, rats were tested with each (−)-nicotine dose (two determinations per dose), followed by each (−)-nornicotine dose (one to three determinations per dose). (−)-Nicotine and (−)-nornicotine test doses were given either 15 min (four rats) or 45 min (five rats) prior to the beginning of the session. For each determination of drug-appropriate responding, rats were required to perform 15 or more responses during the 4-min extinction session. In all cases, substitution testing was conducted only if the rat responded with 80% or better injection-appropriate responding during the 2-min extinction periods on Tuesday and Thursday prior to the respective Friday session. Rats that did not meet this criterion remained in the home cage on Friday and were fed their daily allotment of food.

### *Drugs*

(+)-Amphetamine sulfate and (−)-nicotine bitartrate were purchased from Sigma Chemical Co. (St. Louis, MO) and Research Biochemicals Inc. (Natick, MA), respectively. (−)-Nornicotine diperchlorate was synthesized according to unpublished methods (Crooks et al., unpublished). (−)-Nornicotine was prepared as the perchlorate salt from the resolution of racemic norcotinine into its enantiomers, followed by borane-THF reduction of the enantiomerically pure (−)-norcotinine to (−)-nornicotine. All drugs were dissolved in saline and injected IP in a volume of 1 ml/kg. Dosages were based on the salt form of each drug.

## RESULTS

Figure 1 illustrates the dose–effect curves for percent drug-appropriate lever pressing and total number of lever presses when (+)-amphetamine, (−)-nicotine, or (−)-nornicotine was given 15 min prior to the substitution test session. As expected, as the test dose of (+)-amphetamine increased, a graded increase in drug-appropriate lever pressing was observed, $F(5,35) = 113.16$, $p < 0.001$. The highest doses of amphetamine (1 and 2 mg/kg) tested produced greater than 80% drug-appropriate responding, indicating that these doses substituted fully for the training dose of (+)-amphetamine (1 mg/kg). A significant dose-related decrease in total number of lever presses was also observed during the (+)-amphetamine substitution test session, $F(5,35) = 13.22$, $p < 0.001$.

As shown in Fig. 1, when administered 15 min prior to the substitution test session, dose-related increases in drug-appropriate lever pressing were also evident with either (−)-nicotine, $F(3,9) = 9.60$, $p < 0.01$, or (−)-nornicotine $F(2,6) = 3.48$ $p < 0.05$. Approximately 50% drug-appropriate responding was engendered by (−)-nicotine (1 mg/kg) or (−)-nornicotine (3 mg/kg), indicating partial substitution. Across the dose

ranges examined, the total number of lever presses were decreased on substitution tests with (−)-nicotine, $F(3,9) = 17.36$, $p < 0.001$, and (−)-nornicotine, $F(2,6) = 12.20$, $p < 0.01$. At higher doses of (−)-nicotine and (−)-nornicotine, rats failed to meet the criterion of 15 or more responses during the 4-min extinction session, thus precluding determination of percent drug-appropriate responding (data not shown).

To reduce the rate suppressant effects of (−)-nicotine and (−)-nornicotine, the same doses were administered 45 min prior to the substitution session (see Fig. 2). Similar to the results obtained after 15 min, dose-related increases in drug-appropriate lever pressing were evident on substitution sessions after administration of (−)-nicotine, $F(4,12) \pm 3.87$, $p < 0.05$, or (−)-nornicotine, $F(3,6) = 4.15$, $p < 0.05$. The maximum amount of drug-appropriate responding was obtained at 1 mg/kg (−)-nicotine or 10 mg/kg (−)-nornicotine. These doses engendered approximately 50% drug-appropriate responding, indicating partial substitution was obtained. A significant decrease in total number of lever presses was also observed on substitution tests with (−)-nicotine, $F(4,12) = 2.75$, $p < 0.05$, and (−)-nornicotine, $F(3,6) = 10.22$, $p < 0.01$.

To further characterize the partial substitution effects evident in Fig. 1 and 2, data collected across the 4-min extinction sessions were also examined in individual rats (data not shown). When administered 15 min prior to the substitution test, one rat reached 84% drug-appropriate responding (i.e., full substitution) when tested with 1 mg/kg (−)-nicotine; however, drug-appropriate responses for all other rats ranged between 27–58% for (−)-nicotine (1 mg/kg) and between 23–57% for (−)-nornicotine (3 mg/kg). When administered 45 min prior to the substitution test, drug-appropriate responses for all rats ranged between 31–59% for (−)-nicotine (1 mg/kg) and between 33–61% for (−)-nornicotine (10 mg/kg), thus showing partial substitution.

It may be argued that the only meaningful data collected during the extinction phase is limited to the distribution of responses that complete the FR requirement established during training (1). Therefore, we also examined the data from individual rats up to the point at which the FR25 schedule was completed on the drug lever during the 4-min extinction session (data not shown). When administered 15 min prior to the substitution test, this measure revealed that one rat had 4% drug-appropriate responding (i.e., no substitution) when tested with 1 mg/kg (−)-nicotine and another rat had 18% drug-appropriate responding (i.e., no substitution) when tested with 3 mg/kg (−)-nornicotine; however, drug-appropriate responses for all other rats ranged between 30–77% for (−)-nicotine (1 mg/kg) and between 23–48% for (−)-nornicotine (3 mg/kg). When administered 45 min prior to the substitution test, one rat had 17% drug-appropriate responding (i.e., no substitution) when tested with 1 mg/kg (−)-nicotine and another rat had 7% drug-appropriate responding (i.e., no substitution) when tested with 10 mg/kg (−)-nornicotine; however, drug-appropriate responses for all other rats ranged between 41–73% for (−)-nicotine (1 mg/kg) and between 37–68% for (−)-nornicotine (10 mg/kg). Thus, individual data indicated that partial substitution was obtained among the majority of rats.

## DISCUSSION

Previous work has shown that (−)-nornicotine substitutes fully for (−)-nicotine in a drug discrimination paradigm in rats (14). The present study demonstrates that (−)-nornicotine also has a behavioral profile similar to (−)-nicotine when tested for its ability to substitute for (+)-amphetamine as a discriminative stimulus. Because both (−)-nicotine and (−)-nornicotine partially substituted for (+)-amphetamine in the drug discrimination paradigm, both of these drugs may possess, at least to some extent, stimulant-like discriminative stimulus effects. Although (−)-nornicotine was less potent

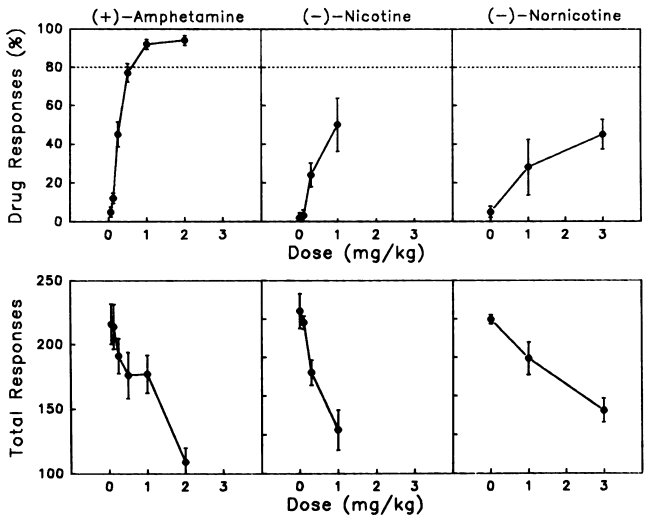


FIG. 1. Mean percent of drug-appropriate responses (top panels) and total responses (bottom panels) when (+)-amphetamine, (−)-nicotine, or (−)-nornicotine were administered 15 min prior to the substitution test session.

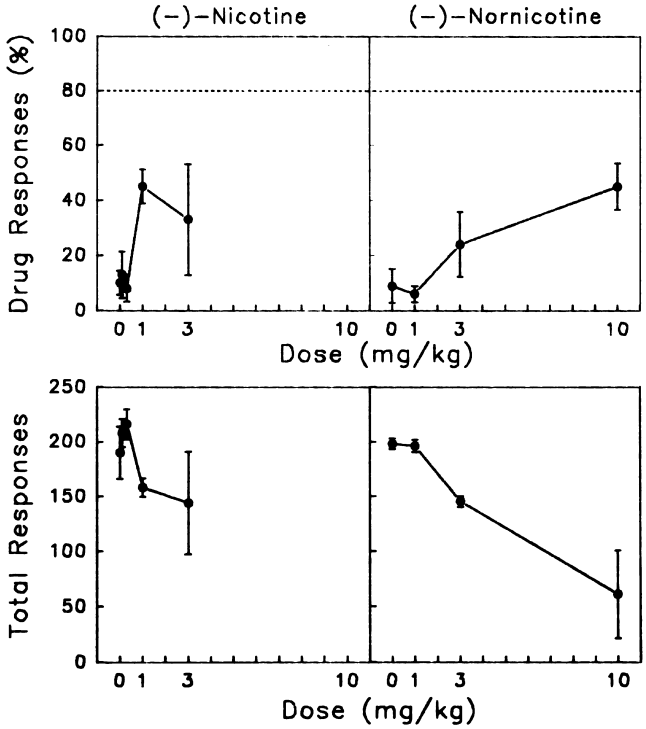


FIG. 2. Mean percent of drug-appropriate responses (top panels) and total responses (bottom panels) when (−)-nicotine or (−)-nornicotine were administered 45 min prior to the substitution test session.

than (−)-nicotine in its ability to partially substitute for (+)-amphetamine, (−)-nornicotine had a similar maximal stimulus substitution efficacy compared to (−)-nicotine. The observed difference in potency is in good agreement with other studies comparing (−)-nicotine and (−)-nornicotine effects on locomotor activity and schedule-controlled operant responding (11,23).

With regard to drug discrimination studies in general, several factors may explain why a test drug produces partial, rather than full, substitution for the training drug. With opiate drugs, for example, partial agonists may produce partial substitution when tested against full agonists (33). This explanation assumes that partial and full agonists compete for a single population of receptors, and that partial agonists have a lower maximal stimulus substitution efficacy than full agonists at the receptor population. However, because (−)-nicotine and (−)-nornicotine do not compete directly with amphetamine for any receptor population, this explanation does not apply to the partial substitution observed in the present report.

Alternatively, instances of partial substitution may also reflect an averaging artifact that occurs when group data do not adequately represent individual data. That is, if some individual rats at a particular dose show full substitution (better than 80% drug-appropriate responding), whereas other rats show no substitution (less than 20% drug-appropriate responding), combining the data would yield a group average indicative of partial substitution (approximately 50% drug-appropriate responding). Contrary to this explanation, however, examination of responding in individual rats during the 4-min extinction session revealed that the majority of rats showed partial substitution with (−)-nicotine and (−)-nornicotine across the dose ranges examined. Partial substitution was also evident when individual data were limited to the time interval of the extinction session in which the FR25 requirement on the drug lever was completed. This latter finding is important because lever choice after completion of the FR requirement may be altered due to the withholding of reinforcement (1). Thus, the group data showing partial substitution were representative of the effect observed among individuals.

Another potential explanation for obtaining partial substitution is that rate-suppressant effects may prevent the expression of full substitution. In the present study, both (−)-nicotine and (−)-nornicotine had clear rate-suppressant effects, perhaps due the activation of locomotor behavior that is incompatible with lever pressing (5,11,28). At 15 min after injection of the highest doses of (−)-nicotine and (−)-nornicotine tested, the rate-suppressant effects precluded the assessment of drug-appropriate responding. At 45 min after injection, however, response rates were sufficient to define drug-appropriate responding across all doses of (−)-nicotine and (−)-nornicotine tested. Even in this latter condition, when substantial responding was obtained, drug-appropriate responding did not exceed approximately 50% with either (−)-nicotine or (−)-nornicotine. Moreover, it is important to note that (+)-amphetamine had rate suppressant effects similar to (−)-nicotine and (−)-nornicotine. Despite this rate suppression, (+)-amphetamine produced full substitution during the extinction session. Thus, it seems unlikely that nonspecific rate suppression effects account for the partial substitution obtained with (−)-nicotine and (−)-nornicotine.

The more likely explanation for the partial substitution evident in the present study is that the mechanisms that underlie the discriminative stimulus effects of (−)-nicotine and (−)-nornicotine do not overlap completely with the mechanisms that underlie the discriminative stimulus effect of (−)-amphetamine. Evidence indicates that enhanced dopamine release is responsible, at least in part, for the discriminative stimulus effects of (+)-amphetamine (3,31) and (−)-nicotine (21). However, differential effects of these drugs at dopaminergic somatodendritic (ventral tegmental area) and terminal (nucleus accumbens) brain regions may underlie the differential discriminative stimulus effects obtained. That is, while (+)-amphetamine releases dopamine directly at the presynaptic terminal, (−)-nicotine-induced dopamine release in vivo may be regulated by nicotinic receptors primarily in the ventral tegmental area (19). Concomitant with this neurochemical dissociation, (+)-amphetamine–induced locomotor behavior involves primarily the nucleus accumbens, whereas (−)-nicotine seems to increase locomotor behavior primarily via an action in the ventral tegmental area (17,22). Further, although both (+)-amphetamine and (−)-nicotine produce locomotor sensitization with repeated treatments, cross-sensitization between (+)-amphetamine and (−)-nicotine has not been observed (32), suggesting different mechanisms of action. Perhaps differential actions on dopaminergic systems are responsible for the failure of either (−)-nicotine or (−)-nornicotine to substitution fully for (+)-amphetamine in the present report.

Alternatively, the differential actions of (+)-amphetamine, (−)-nicotine, and (−)-nornicotine on nondopaminergic systems may explain the partial substitution obtained in the present report. In contrast to (+)-amphetamine, the discriminative stimulus effect of nicotine appears to involve a significant cholinergic component rather than a dopaminergic component (6,15,30). Consistent with this, studies using intracranial drug microinjection techniques have demonstrated that the discriminative stimulus effect of amphetamine involves the nucleus accumbens (18), whereas the discriminative stimulus effect of nicotine involves the hippocampus (26). Further, while $H_1$ histamine antagonists substitute fully for (+)-amphetamine in a drug discrimination paradigm (12), histamine receptors may not be involved in the discriminative stimulus effects of (−)-nicotine or (−)-nornicotine. Thus, differential activation of cholinergic or histaminergic systems may interfere with the ability of (−)-nicotine or (−)-nornicotine to produce a dopamine-mediated discriminative stimulus effect similar to that produced by (+)-amphetamine.

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