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BRIEF COMMUNICATION

Dopamine Mechanisms Play at Best a Small Role in the Nicotine Discriminative Stimulus

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CORRIGALL, W. A. AND K. M. COEN. *Dopamine mechanisms play at best a small role in the nicotine discriminative stimulus.* PHARMACOL BIOCHEM BEHAV **48**(3) 817–820; 1994.—The ability of D_1 and D_2 dopamine antagonists to reduce the subjective effects of nicotine was examined in rats trained to discriminate nicotine (0.3 mg/kg, base) from saline. Each of SCH 23390 (a D_1 antagonist) and spiperone (a D_2 antagonist) reduced responding on the drug-appropriate lever, and produced a reduction in overall response rates. The nicotine cue was also tested for generalization to the dopamine reuptake blocker GBR 12909. Doses of GBR 12909 that produced complete responding on the drug-appropriate lever in cocaine-trained animals led to only minimal selection of the nicotine-appropriate lever in nicotine-trained animals; as with the dopamine antagonists, response rates after GBR 12909 were markedly reduced in nicotine-trained, but not in cocaine-trained, rats. These data suggest that dopaminergic mechanisms play, at best, a small role in the discriminative stimulus properties of nicotine.

Nicotine discrimination Dopamine reuptake GBR 12909 Dopamine antagonists SCH 23390 Spiperone

NUMEROUS studies have implicated dopaminergic mechanisms in the effects of nicotine at the neurochemical and behavioral levels [e.g., (1,3,10,12,13)]. In particular, we have recently established that the reinforcing effects of nicotine have a dopaminergic substrate (4,6), likely the ascending mesolimbic dopamine system (8) of the midbrain. It appears that nicotine targets this system by acting through nicotinic cholinergic receptors at, or in the vicinity of, the ventral tegmental area (7). This is a different mechanism than that of cocaine, which also targets the mesolimbic dopamine system, but does so at the level of the dopamine synaptic field in the nucleus accumbens [e.g., (14,16,17,22)].

Closely allied to the reinforcing effects of drugs are their subjective effects, in animals measured with drug discrimination methodology. Dopaminergic mechanisms have been shown to be important in the discriminative stimulus properties of cocaine [e.g., (2,23)] and have also been implicated in the discriminative stimulus properties of nicotine. Depletion of central dopamine produced by intraventricular infusion of the neurotoxin 6-hydroxydopamine has a small effect on the nicotine cue (18). Reavill and Stolerman (15) have reported that the dopamine antagonists haloperidol and SCH 23390 attenuate the nicotine discriminative stimulus, but reduce response rates also. In this same study, a decrease in response rate also accompanied a modest generalization to the D_1 agonist SKF 38393. The dopamine release inhibitor CGS 10746B has been shown to reduce the nicotine discriminative stimulus, but effects on response rate were not reported (19). Although these studies are few in number, they do point to the same conclusion, that is, that the nicotine cue can be reduced by reducing dopamine's action, and increased by mimicking it. One purpose of the present study was to reexamine the ability of selective dopamine receptor antagonists to reduce the nicotine discriminative stimulus. The original study of dopamine antagonists undertaken by Reavill and Stolerman (15) used a nicotine training dose of 0.1 mg/kg. If the subjective effects of nicotine are dopamine dependent, the magnitude of the training dose of nicotine may influence the outcome of dopamine manipulations. We have, therefore, employed a higher, midrange dose of nicotine in this study, although still a dose in the range normally used in nicotine discrimination [e.g., (20)].

One mechanism through which nicotine could elevate synaptic dopamine is by inhibition of dopamine reuptake pro-

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cesses (11). If dopamine contributes to the nicotine cue by this mechanism, one would expect that the nicotine cue would generalize to dopamine reuptake inhibitors. To test this hypothesis was the second purpose of this study.

METHOD

Subjects were drug-naive, male, Long-Evans rats (Charles River, Lachine, Quebec). Animals were housed in a reversed light–dark cycle colony room (lights off between 0700 and 1900 h). Prior to the start of experimental procedures, animals had ad lib access to food and water, and weighed approximately 300 g. Discrimination training and testing was carried out as previously described (5). In brief, animals were deprived of food for a short period (24 h), and trained to press a lever on a continuous reinforcement (CRF) schedule for food pellets (45 mg). Schedule requirements were then progressively increased to fixed ratio 10 (FR10) for each 45 mg food pellet, and discrimination training was begun. Two separate groups of animals were used in these experiments, one trained to discriminate nicotine (0.3 mg/kg SC, bitartrate salt, dose expressed as the base) from saline and a second trained to discriminate cocaine (10 mg/kg IP, hydrochloride salt, dose as the base) from saline. Each weekday animals received an injection of either the training drug or saline. Injection times were 20 min prior to the start of the operant session for nicotine, and 15 min for cocaine. These parameters represent doses and treatment times within the range used previously for nicotine and cocaine drug discrimination studies (9,20,21). The day-to-day choice of drug or saline during training was varied according to one of two predetermined sequences: either DSSDS SDSDD SDDSS DSDSD or SDDSS DSDSD DSDDS SDSDS, where S represents an injection of saline and D represents a injection of the training dose of drug. Schedule requirements were such that responding on the incorrect lever reset the response requirement on the correct one. Session duration was 15 min. To eliminate possible olfactory cues, consecutive subjects running in the same chamber received opposite training injections on some days and the same injections on others. Training continued for approximately 8 weeks until, over a 2-week period, no more than two incorrect responses occurred before the delivery of the first food pellet in the session, and at least 90% of the total responses in the session were made on the correct lever.

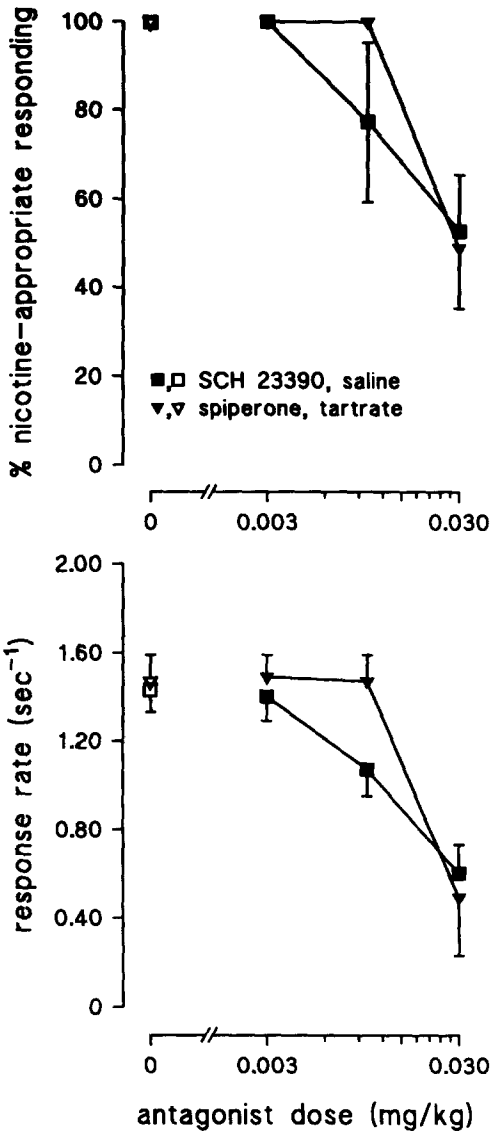

FIG. 1. Effects of the dopamine antagonists SCH 23390 or spiperone on nicotine discrimination (upper panel) and response rates (lower panel) at the nicotine training dose of 0.3 mg/kg. Data here and in Fig. 2 is presented as the mean ± SEM. Sample size is six at each data point. SCH 23390 was injected 30 min prior to nicotine; spiperone was injected 60 min before nicotine.

Test days occurred on Tuesdays and Fridays, subject to maintenance of criterion training performance on intervening days. On test days, both levers were active and every FR10 on either lever resulted in delivery of a food pellet. Tests drugs included nicotine bitartrate (Sigma Chemical Co., St. Louis, MO), the D_1 antagonist SCH 23390 hydrochloride, the D_2 antagonist spiperone, and the dopamine reuptake inhibitor GBR 12909 hydrochloride (the latter three drugs from RBI, Natick, MA). Animals were generally tested once with each dose of a given compound, except for testing of the nicotine-trained subjects with GBR 12909, in which two different pretreatment times were examined. SCH 23390 was prepared in saline, spiperone was dissolved in 0.1 ml of 0.1 N tartaric acid and made up to the required volume in saline, and GBR 12909 was dissolved in distilled water. Nicotine was dissolved in saline and the pH adjusted to 7.0 ± 0.1. In all cases, the appropriate vehicle was tested at the zero-dose point. All doses refer to the base.

The following tests were carried out in nicotine-trained animals: a) a nicotine dose–effect curve; b) tests of generalization of the nicotine cue to GBR 12909 injected either 5 or 60 min presession (9,23); c) tests of SCH 23390 or spiperone injected 30 or 60 min, respectively, prior to the training dose of nicotine (6,23). In cocaine-trained animals, generalization to GBR 12909 was tested using a presession injection time of 60 min (9).

Data are presented as the means of percent responding on the drug-appropriate lever, and of response rates; error bars show standard errors of the mean (SEM).

RESULTS AND DISCUSSION

The effects of treatment with D_1 and D_2 selective antagonists on nicotine discrimination trained at 0.3 mg/kg are shown in Fig. 1. SCH 23390 and spiperone were used as D_1 and D_2 antagonists, respectively, because we had previously demonstrated that these compounds could attenuate nicotine self-administration. In the present study, both antagonists

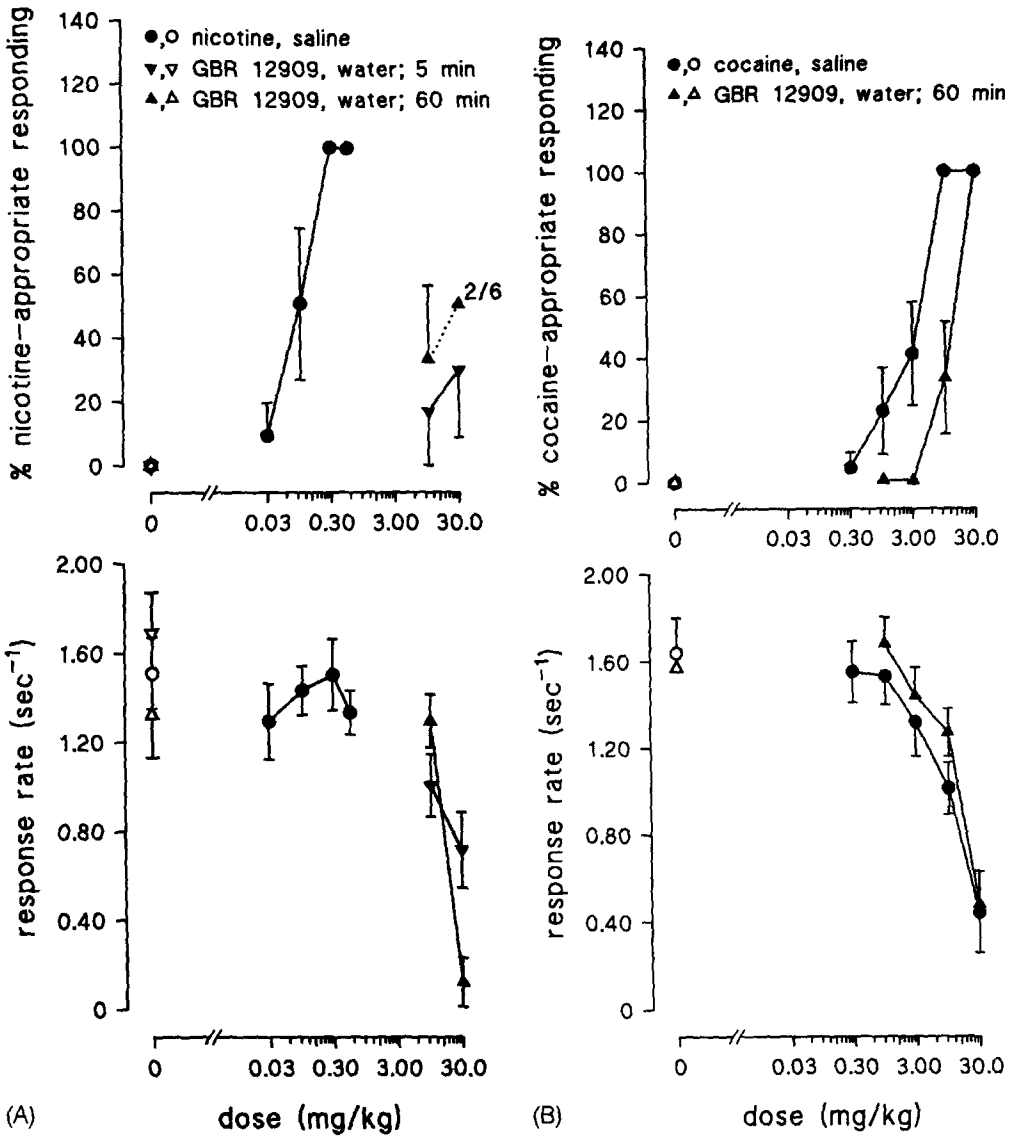

FIG. 2. (A) Comparison of a range of doses of nicotine and GBR 12909 on selection of the nicotine-appropriate lever and associated operant response rates (n = 6 at each point, except at the 30 mg/kg dose of GBR 12909 tested at 60 min, at which four animals did not respond). The error bar is not shown because it is large and represents only two subjects. (B) Comparison of cocaine and GBR 12909 in cocaine-trained animals (n = 9 at each data point).

produced a partial decrease in selection of the drug-appropriate lever, and in each case there was a similar reduction in response rate. Such effects on response rate are consistent with previous research with these antagonists that has shown that they can have marked effects on response rates of food-maintained behavior (5). As a result of these rate alterations, it is not possible to exclude nonspecific factors from these effects. However, because percent scores were used to measure responding on the drug-appropriate lever, one might expect discrimination to be independent of overall rate, at least over a reasonable range. Therefore it is possible that these dopamine antagonists do have a small specific effect on the nicotine cue. On the other hand, the fact that there appears to be little difference in the effects of dopamine antagonists on the nicotine cue trained at different nicotine doses, 0.1 mg/kg in the study of Reavill and Stolerman (15) compared to 0.3 mg/kg in the present study, lends support to the interpretation that the antagonist effects are nonspecific.

Although dopamine mechanisms have been shown to be important in cocaine discrimination, experiments have suggested that more than a single receptor subtype may be involved [e.g., (2,23)]. Based on dopamine antagonist data alone, therefore, one might conclude that nicotine's discriminative stimulus properties depend on several dopamine receptor subtypes, and are not evident after treatment with an antagonist selective only for one.

A second purpose of this study was to examine whether the dopamine reuptake inhibitor GBR 12909 could produce a nicotine-like cue. Animals trained to discriminate nicotine were tested either 5 min or 60 min after IP administration of

GBR 12909. These times were chosen because they represent the range at which GBR 12909 has been shown to engender drug-appropriate responding in cocaine-trained animals. As shown in Fig. 2A, there was minimal generalization of the nicotine cue to GBR 12909 at either time point. With the longer preinjection time, there appeared to be more behavioral suppression, manifest in a greater decrease in response rates. Indeed, after the longer preinjection time only two of the six subjects responded at all after 30 mg/kg GBR 12909. As a positive control for these experiments, we also tested GBR 12909 in rats trained to discriminate 10 mg/kg cocaine from saline. In contrast to nicotine-trained animals, cocaine-trained subjects generalized completely to GBR 12909 at a dose of 30 mg/kg, and partially at lower doses [Fig. 2B; see also (23)]. In addition, response rates after either cocaine or GBR 12909 in cocaine-trained rats were comparable, perhaps suggesting that the mechanisms of tolerance to the rate-decreasing effects of cocaine are shared by GBR 12909, but that crosstolerance between the rate-altering effects of nicotine and those of GBR 12909 does not occur. The absence of generalization of the nicotine cue to GBR 12909 may be more compelling evidence that dopamine mechanisms are not critical in nicotine discrimination than is the dopamine antagonist data. Certainly increasing synaptic concentrations of dopamine by reuptake blockade does not produce generalization to the nicotine cue.

Overall, these data suggest that dopaminergic mechanisms play, at best, a small role in the discriminative stimulus properties of nicotine at a training dose of 0.3 mg/kg. Previously we have concluded that dopaminergic mechanisms are important in nicotine reinforcement. The latter conclusion was based initially on the effects on dopamine antagonists on nicotine self-administration (6). In that research, too, we faced the issue of whether the effects of the antagonists were specific or nonspecific, and resolved it by examining averaged cumulative records that showed that the dopamine antagonist effects occurred temporally after the animals had sampled nicotine, suggesting that they result from an action on mechanisms directly implicated in nicotine reinforcement. Because drug discrimination represents an initial choice behavior, one cannot use the same approach. However, in more recent self-administration research we have shown that the involvement of particular dopamine cells in nicotine reinforcement is likely, because nicotinic antagonists microinjected into the A10 region of the brain will block self-administration (7). Were one to make assumptions about the particular dopamine pathway(s) that might subserve nicotine's discriminative stimulus effect, the same type of approach might profitably be used to investigate the role of dopaminergic cells in nicotine reinforcement without the confounding effects that seem so frequently to attend direct dopamine manipulations.

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