ELSEVIER

European Journal of Pharmacology 294 (1995) 281–288

ejp

Cross-generalization between a cocaine cue and two antihistamines

David V. Gauvin *, Kathy L. Carl, Richard J. Briscoe, Mary Vallett, Frank A. Holloway

Psychobiology Laboratories, Department of Psychiatry and Behavioral Sciences, University of Oklahoma Health Sciences Center, Research Building, 302R, P.O. Box 26901, Oklahoma City, OK 73190-3000, USA

Received 9 February 1995; revised 15 August 1995; accepted 25 August 1995

Abstract

Rats were trained to discriminate between 10 mg/kg cocaine and saline injections under a fixed ratio 10 schedule of food-motivated lever press responding. Once stimulus control was achieved, reinforced test sessions were conducted to assess the degree of generalization of a wide range of cocaine doses and the cross-generalization between the cocaine training stimulus and two over-the-counter antihistaminic drugs, diphenhydramine and doxylamine, when administered with saline or in drug combinations. Cocaine produced a dose-dependent generalization to the 10 mg/kg training stimulus. Cocaine also produced mild rate-increasing effects at low test doses and response rate suppression at higher doses. Both diphenhydramine and doxylamine produced a partial generalization to the 10 mg/kg cocaine training stimulus. Drug mixtures produced complete cross-generalization with the training cue.

Keywords: Drug discrimination; Cocaine; Diphenhydramine; Doxylamine

1. Introduction

In 1989 this laboratory reported the dose-dependent cross-generalization of over-the-counter phenylethylamines to the discriminative stimulus effects of a 10 mg/kg cocaine training cue (Gauvin et al., 1989b). Ephedrine, phenylpropanolamine, and caffeine administered in a triple combination produced complete generalization to the training dose of cocaine. In a further set of ancillary studies we have utilized these three over-the-counter stimulants as discriminative training stimuli when administered singly and in binary and ternary combinations. Surprisingly, a number of these training stimuli produced complete cross-generalization with various doses of cocaine test injections (Gauvin et al., 1993b).

The purpose of the present study was to further extend the analysis of the cross-generalization profiles between the discriminative stimulus effects of a 10 mg/kg cocaine training cue and other over-the-counter compounds. Two of the older antihistamines, doxylamine and diphenhydramine, were selected for testing because of their widespread use with limited reports of abuse. Additionally, these two specific antihistamines produce multiple behavioral and physiological effects in both humans and animals and have been hypothesized to interact with similar neuronal mechanisms to those of cocaine (see below).

Doxylamine (2-[α-(2-dimethylaminoethoxy)-α-methylbenzyl]-pyridine) succinate is one of the older antihistaminic drugs (Brown and Werner, 1948; Sperber et al., 1949; Sjöqvist and Lasagna, 1967) and is the active ingredient in a number of sleep-aids in the United States (Unisom Nightime Sleep Aid, Vicks Nyquil, etc., Dowd, 1992). Diphenhydramine (β-dimethylaminoethyl benzhydryl ether hydrochloride) has been approved for human use for almost 5 decades and is typically found in sleep-aids (Nytol, Sominex), topical anti-itch/analgesic ointments (Benadryl anti-itch cream, Caladryl) and cold and allergy medications (Benadryl elixir, Benadryl decongestant).

The specific mechanism(s) for the central nervous system action of antihistaminics is unknown (Speeg et al., 1981; Schwartz et al., 1991). While the most commonly used antihistaminics have high affinity for both the histamine H_1 and H_2 (central and peripheral) receptors (Green, 1994), at high concentrations they are local anesthetics. Interestingly, many histamine H_1

* Corresponding author. Dept. PSBS, Research Bldg., 302R, P.O. Box 26901, Oklahoma City, OK 73190-3000, USA. Tel.: (405) 271-2011; fax: (405) 271-2356.

SSDI 0014-2999(95)00550-1

receptor antagonists block muscarinic (acetylcholine), benzodiazepine, β-adrenoceptors, 5-HT, norepinephrine, and dopamine receptors (Prell and Green, 1986; Schwartz et al., 1991) and have been linked to the release of endogenous or synaptic histamine in both in vivo and in vitro assays (Arunlakshana, 1953). This histamine release by antihistamines is mostly associated with excitatory responses such as increases in neuronal firing rates and depolarization, facilitation of signal transduction, and reduced K^+ conductance (Green, 1994). Additionally, there is no similarity between the regional distribution of the type 1 histamine receptor and regional distribution of histamine, its metabolites, the enzymes that synthesize and metabolize histamine, nor histaminergic nerve endings (Green, 1994). These diverse actions of the antihistaminics have led to paradoxical findings in both clinical and laboratory settings.

The older antihistamines can both stimulate and depress the central nervous system in humans and animals. Central nervous system stimulation, defined as restlessness, nervousness, and inability to sleep, has occurred in humans after the administration of conventional doses of the older H_1 histamine antagonists (Garrison, 1990). Doxylamine has been found to perform better than 100 mg of secobarbital in inducing sleep in humans (Sjöqvist and Lasagna, 1967), but it can also produce a complex syndrome of excitatory electro-encephalographic (EEG) changes and with escalating doses can produce EEG paroxysms and eventually tonic-clonic seizures (Douglas, 1985). Similarly, administration of doxylamine in animals has produced sedation and excitation, predominantly neurogenic in origin involving motor, sensory, and autonomic nervous systems (Gruhzit and Fisken, 1947). The alternate antihistamine in this study, diphenhydramine, also has been reported to produce both excitation and sedation in both humans (Douglas, 1985; Garrison, 1990; Dowd, 1992) and animals (Schwartz et al., 1991; Prell and Green, 1986). Independent of overdose, the factors involved in the expression of either stimulation or sedation within the conventional dose range are not known at present, but the bidirectional nature of the behavioral effects of the antihistamines is common to both humans and animals and clearly does not reflect a species-specific differential response to these compounds.

Neuronal histamine has been reported to be enriched in the hypothalamic area, from which fibers containing the amine project to the forebrain including the striatum (Garbarg et al., 1974, 1976). Additionally, antihistamines have demonstrated monoaminergic uptake blockade by direct interactions with the re-uptake membrane pumps of noradrenaline and dopamine (Carlsson and Lindquist, 1969). Striatal neuronal sites and aminergic uptake blockade are often implicated in cocaine's behavioral effects (Cooper et al., 1991). The excitatory behavioral effects produced by the antihistamines in both humans and animals, their role in activation of forebrain and striatal pathways, and their direct blockade of aminergic uptake mechanisms led us to explore the similarities between cocaine and these two over-the-counter antihistaminics. We utilized the drug discrimination task because the experimental subject relies on the unobservable subjective effects of drug injections to solve the discrimination task. These same subjective effects have been implicated in a drugs' abuse liability (Overton, 1987) and the degree of cross-generalization between drugs has been hypothesized to accurately reflect the degree of subjective similarity between them (Harland et al., 1989; Holloway and Gauvin, 1989).

2. Materials and methods

2.1. Animals

Twelve male Sprague Dawley rats (300–325 g) were purchased from Sasco (Omaha, NE, USA), allowed to acclimate to the laboratory colony room for one week, and then reduced to 85% of their free-feeding weights. Each rat was allowed to gain 10 g per month body weight throughout the study to allow for normal growth.

2.2. Procedure

The drug discrimination procedure used in the present experiment has been previously used in this laboratory (Gauvin et al., 1993a,b,c; Holloway, 1993) and is described in greater detail elsewhere (Gauvin et al., 1993c). Briefly, rats were trained in standard operant chambers equipped with two response levers, stimulus lamps, houselight, and automated pellet dispenser. Behavioral contingencies and data collection were achieved by Commodore-64C microcomputer systems (American Neuroscience Research Foundation, Yukon, OK, USA) interfaced (Rayfield Electronics, Waitsfield, VT, USA) with the operant chambers (Lafayette Instruments, Lafayette, IN, USA). Animals were trained to press a lever for food reinforcer deliveries on either of the two levers in 10-min experimental sessions. The correct lever to obtain food was determined by the 10 mg/kg cocaine hydrochloride or saline injection administered (intraperitoneally) 15 min prior to the session. The number of responses required for reinforcement was gradually increased to a fixed ratio 10 schedule. Rats were trained 5 days per week. Training continued until each rat met the criteria of emitting fewer than 20 responses prior to the delivery of the first reinforcer and of emitting greater than 90% of the total session responses on the drug stimulus-ap-

propriate lever for 4 consecutive days. Each rat was then required to meet these criteria for four consecutive sessions in a double alternation sequence (i.e., cocaine–cocaine–saline–saline).

2.3. Test sessions

After discriminative control was established, test sessions were conducted. Test sessions were identical to training sessions, except (1) a novel drug or dose was administered, and (2) ten consecutive responses on either lever produced food. Training and test sessions were alternated throughout the week (i.e., cocaine train, saline train, test, cocaine train, test, saline train, etc.). If a rat did not meet the performance criteria for stimulus control during a training session, further testing was postponed until one successful cocaine- and saline-training day was achieved. Each test condition was tested only once in each of ten trained rats. As an injection control for drug mixture tests, each cocaine, saline, diphenhydramine, and doxylamine test was preceded by two injections administered on alternate sides of the peritoneal area (i.e., saline plus cocaine, saline plus saline, etc.). The tests were administered in a specific drug order, but within a specific drug test cycle the doses were administered in random order. The order of drug tests was as follows: (1) cocaine, (2) diphenhydramine, (3) doxylamine, (4) 10 mg/kg diphenhydramine plus various doses of doxylamine, (5) 10 mg/kg doxylamine plus various doses of diphenhydramine, (6) 17.8 mg/kg diphenhydramine plus various doses of doxylamine, and (7) 56 mg/kg doxylamine plus various doses of diphenhydramine.

2.4. Drugs

All drugs were prepared daily and stored in light-attenuating bottles. Cocaine hydrochloride, diphenhydramine hydrochloride, and doxylamine (succinate salt) were purchased from Sigma Chemical Co. (St. Louis, MO, USA). Each drug was weighed, expressed as the salt, and dissolved in normal sterile saline and administered in a 1 ml/kg volume. An equivalent volume of saline was administered on saline training days. All injections were administered i.p. Objective signs of physiological and/or behavioral toxicity were conducted during each test session via the chamber viewing windows. During drug interaction tests the specific doses of doxylamine and diphenhydramine were selected from the limited range of doses producing partial generalization and doses which we predicted would not produce lethality or long-term toxicity. Doses of drugs larger than those presented here were not administered in accordance with the new NIH guidelines governing research on animal subjects, which has established the conservative practice of restricting both the number and dose of drugs administered to the rats to those which adequately address the question-at-hand.

2.5. Data analysis

The data are presented as the group mean percentage of the total session responses emitted on the cocaine-appropriate lever. A test condition was considered to produce 'complete generalization' (i.e., discriminative effects similar to those of the 10 mg/kg cocaine training stimulus) if at least 90% of the total session responses were emitted on the cocaine-appropriate lever. The average response rates after drug injections are expressed in responses per second. Such response rates provide a second measure of behavioral effects of the drug which appears to be independent of the distribution of response choice on the two levers.

All data were analyzed using a repeated-measures (dose × time) mixed-factor analysis of variance with a posteriori tests for individual dose and time comparisons using Duncan's new multiple range test (CSS:Statistica, Tulsa, OK, USA). Additional estimates of the effects of the antihistamine mixtures from those of the same drugs when administered singly were made using the strategy provided by Mariathasan and Stolerman (1992) and first proposed by Mackintosh (1974). The predicted response choice measure to mixture tests was calculated from the response choice measure engendered by each drug element as follows: $R_M = (R_A + R_B) - (R_A \times R_B)$, where R_M is the predicted probability of cocaine-appropriate responding engendered by antihistamine mixture tests, R_A is the response probability of cocaine-appropriate responding engendered by one drug element (i.e., diphenhydramine) and R_B is the response probability of cocaine-appropriate responding engendered by the other drug element (i.e., doxylamine). This predicted probability was expressed as a percentage of total test session responses. Individual t-tests were conducted to make statistical comparisons between predicted and actual response choice values during these mixture test sessions.

3. Results

Stimulus control by the two training stimuli was achieved in an average of 40 training sessions (1.71 S.E., range 37–53 days). Fig. 1 demonstrates that test sessions conducted with various doses of cocaine (0.32–32 mg/kg) produced a dose-dependent increase in the percentage of total sessions responses emitted on the cocaine-appropriate lever (upper graphic: $F(9,45) = 17.28$, $P = 10^{-7}$) and a biphasic effect on the group mean rates of lever-press responding (bottom

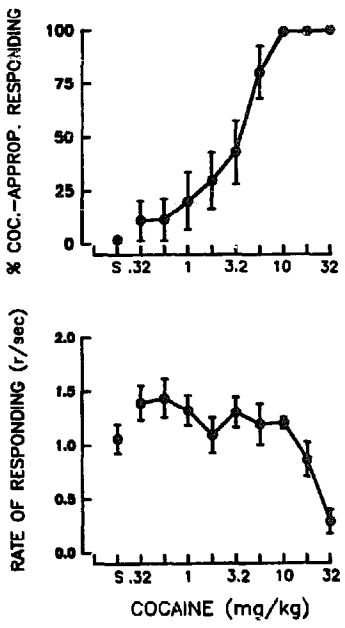

Fig. 1. Cocaine dose-effect functions. Mean (S.E.) percentage of total session responses emitted on the cocaine-appropriate lever (top graphic) and the mean (S.E.) rates of responding, expressed in r/s, (bottom graphic) are displayed as a function of cocaine test dose. Rats were trained to discriminate between 10 mg/kg cocaine and saline in a two-choice food-motivated drug discrimination task under a fixed ratio 10 schedule of reinforcement. Ten minute reinforced test sessions were conducted with a wide range of cocaine doses (0.32–32 mg/kg). Data from the saline test session is displayed above the 'S' on the abscissa. Each point represents the mean of 10 rats.

graphic: $F(9,81) = 8.81$, $P = 10^{-7}$). Low doses of cocaine produced significant rate-increasing effects when compared to saline control rates at both the 0.32 and 0.56 mg/kg test doses (Duncan's test: $P < 0.05$). Higher cocaine test doses produced a dose-dependent decrease in the rates-of-responding.

Fig. 2 shows the results from diphenhydramine + saline and diphenhydramine + doxylamine test sessions. Diphenhydramine in combination with saline (closed circles) produced a dose-dependent increase in cocaine-appropriate responding ($F(4,32) = 5.47$, $P = 0.001$) up to a peak level of 78% at the 17.8 mg/kg test dose; a level of responding characteristically referred to as 'partial generalization' (Holloway and Gauvin, 1989). Relatedly, diphenhydramine produced a dose-dependent decrease in the group mean rates-of-responding ($F(5,40) = 8.39$, $P < 0.001$). The results of test sessions conducted with mixtures of diphenhydramine in combination with 10 mg/kg (filled triangles) or 56 mg/kg doxylamine (open circles) are also shown in Fig. 2. Both drug mixtures produced significant dose-dependent generalization to the 10 mg/kg cocaine training stimulus ($F(3,12) = 9.37$, $P = 0.002$: diphenhydramine plus 10 mg/kg doxylamine; $F(2,20) = 12.4$, $P = 0.003$: diphenhydramine plus 56 mg/kg doxylamine). Whereas the combination of 10 mg/kg doxylamine plus 32 mg/kg diphenhydramine produced complete generalization to the cocaine training stimulus (100 ± 0 cocaine-appropriate responding), the 10 mg/kg diphenhydramine plus 56 mg/kg doxylamine combination engendered a peak of only 82% (± 16) cocaine-appropriate responding. Both drug mixtures produced dose-dependent rate suppression ($F(3,21) = 19.3$, $P < 10^{-5}$: diphenhydramine plus 10 mg/kg doxylamine; $F(3,24) = 18.6$, $P < 10^{-5}$: diphenhydramine plus 56 mg/kg doxylamine).

Fig. 3 shows the results of tests conducted with doxylamine in combination with saline (closed circles), 10 mg/kg diphenhydramine (closed triangles), and 17.8 mg/kg diphenhydramine (open circles). In contrast to diphenhydramine, doxylamine in combination with saline did not produce a dose-dependent increase in cocaine-appropriate responding ($F(3,21) = 2.46$, $P = 0.09$, n.s.), but did engender a peak level of 47% drug lever responding at a doxylamine test dose of 56 mg/kg; again, characteristically referred to as 'partial generalization'. Doxylamine was less potent than diphenhydramine in producing significant response rate suppression ($F(3,21) = 5.03$, $P = 0.009$). Both mixtures produced significant dose-dependent generalization to the 10 mg/kg cocaine training stimulus ($F(4,20) = 13.29$, $P = 0.004$: doxylamine plus 10 mg/kg diphenhydramine; $F(2,18) = 14.6$, $P < 0.001$: doxylamine plus

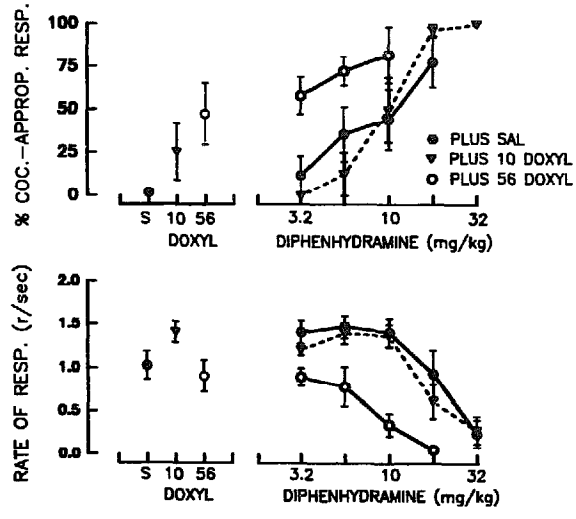

Fig. 2. Cross-generalization functions to the 10 mg/kg cocaine training stimulus for diphenhydramine administered in combination with saline (closed circles), 10 mg/kg doxylamine (closed triangles), or 56 mg/kg doxylamine (open circles). Top graphic: Mean (S.E.) percentage of total session responses emitted on the cocaine-appropriate lever during 10 min reinforced test sessions. Bottom graphic: Mean (S.E.) rates-of-responding, expressed in r/s, are plotted as a function of diphenhydramine test dose. Each point represents the mean of 8 or 9 rats. 32 mg/kg diphenhydramine produced response rate suppression to a degree that the response-choice measure could not be assessed (i.e., less than 2 reinforcer deliveries). Data from saline, 10 mg/kg doxylamine, and 56 mg/kg doxylamine test sessions are displayed above the 'S', '10' and '56' on the left-hand side of the abscissa.

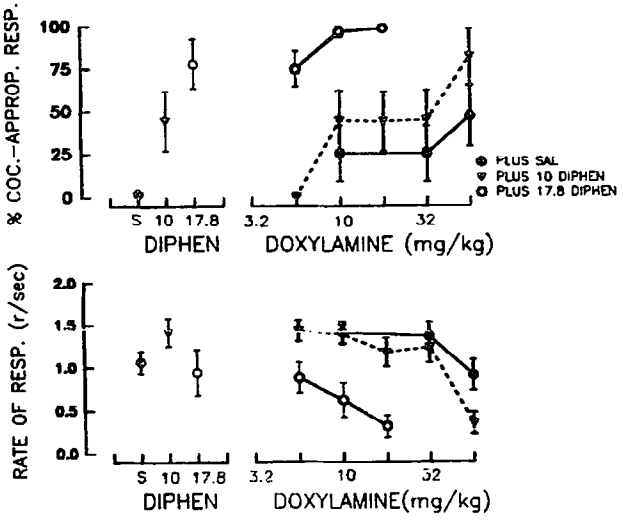

Fig. 3. Cross-generalization functions to the 10 mg/kg cocaine training stimulus for doxylamine administered in combination with saline (closed circles), 10 mg/kg diphenhydramine (closed triangles), or 17.8 mg/kg diphenhydramine (open circles). Data from saline, 10 mg/kg diphenhydramine, and 17.8 mg/kg diphenhydramine test sessions are displayed above the 'S', '10' and '17.8' on the left-hand side of the abscissa. Details as described in Fig. 2.

17.8 mg/kg diphenhydramine). The combination of 17.8 mg/kg diphenhydramine plus 17.8 mg/kg doxylamine produced complete generalization to the cocaine training stimulus (100 + 0 cocaine-appropriate responding). As described above for Fig. 2, the 10 mg/kg diphenhydramine plus 56 mg/kg doxylamine combination engendered a peak of only 82% cocaine-appropriate responding. Both doxylamine plus diphenhydramine combinations produced dose-dependent rate suppression ($F(4,32) = 13.29$, $P < 10^{-5}$: doxylamine plus 10 mg/kg diphenhydramine; $F(2,24) = 14.8$, $P < 0.001$: doxylamine plus 17.8 mg/kg diphenhydramine).

The predicted responses to 10 mg/kg diphenhydramine plus 56 mg/kg doxylamine, 17.8 mg/kg diphenhydramine plus 10 mg/kg doxylamine, 10 mg/kg doxylamine plus 32 mg/kg diphenhydramine mixtures were calculated from the response to the corresponding doses of the component drug elements (see Section 2.5). The predicted responses for the discriminative effects of the mixtures were very similar to those of the actual dose-effect. The differences between the actual and predicted values were not statistically different (10 mg/kg diphenhydramine + 56 mg/kg doxylamine: $t(7) = 0.32$, n.s.; 17.8 mg/kg diphenhydramine + 10 mg/kg doxylamine: $t(7) = 0.56$, n.s.; and 10 mg/kg doxylamine + 32 mg/kg diphenhydramine: $t(7) = 1.5$, n.s.).

4. Discussion

The present study is similar to our two previous reports demonstrating a significant degree of subjective similarity between the discriminative stimulus properties of over-the-counter compounds and the controlled stimulant – cocaine (Gauvin et al., 1989a, 1993b). Both diphenhydramine and doxylamine, common antihistaminics, produced qualitative dose-dependent partial generalization to the 10 mg/kg cocaine cue in rats. When these two over-the-counter compounds were tested in three increasingly incremented mixtures of 10, 17.8, and 32 mg/kg diphenhydramine in combination with 10, 32, and 56 mg/kg doxylamine, respectively, the actual percentage of total session responses emitted on the cocaine-appropriate lever were not significantly different than that predicted from simple effect additivity (cf. Woolverton, 1987).

We find the cross-generalization between the cocaine training cue and the two antihistaminics perplexing and significant because: (1) While cocaine is classified as a psychomotor stimulant, both diphenhydramine and doxylamine are the active ingredients in over-the-counter sleep-aids. In the present study both cocaine and antihistamine combinations produce cocaine-appropriate responding – an objective measure typically used to characterize similar receptor mechanisms. (2) The induction of behavioral excitation has been reported previously in both humans and animals with these over-the-counter antihistamines (see Introduction), the specific dose(s) which engendered maximal levels of cocaine-appropriate responding by each drug administered singly and in combinations produced behavioral signs of excitation during the pretreatment interval and during a short period after the test session. These signs included spontaneous jumping and circling and head dipping stereotypies. (3) While high doses of antihistaminics are local anesthetics, the more typical local anesthetics, lidocaine and procaine, previously have failed to produce any drug-appropriate responding in rats trained to discriminate between cocaine and saline (Colpaert et al., 1979). And, (4) while the drug discrimination task typically has been classified as a pharmacologically specific behavioral assay (Overton, 1987; Young and Sannerud, 1989), the cocaine training stimulus has limited anti-histaminergic activity.

The discriminative stimulus properties of the over-the-counter antihistaminics as training stimuli have been reported previously using animal subjects (Overton, 1978; Winter, 1985; White, 1985). In animals trained to discriminate an antihistamine from saline there is complete cross-generalization to most other antihistamines and partial generalization to the rest. White and Rumbold (1988) have summarized these findings from animal drug discrimination studies and have concluded that the preponderance of data suggests that the discriminative stimulus effects of the antihistamines are based on the histamine H_1 receptor antagonist properties of the drugs and that these his-

tamine H_1 receptor antagonists may share common properties but there may also be differences which prevent complete generalization. Within these animal studies, however, none have reported cross-generalization tests with cocaine.

In a reciprocal set of studies designed to assess the similarities between controlled stimulants and the antihistaminics, Evans and Johanson (1989) have trained pigeons and rhesus monkeys to discriminate the presence and absence of *d*-amphetamine and tested cross-generalization with some antihistamines. All three trained pigeons cross-generalized the 2.0 mg/kg amphetamine stimulus to diphenhydramine test stimuli (10 mg/kg or less); and all three trained monkeys failed to emit any amphetamine-appropriate responding during diphenhydramine test sessions. Evans et al. (1991) also have trained one group of pigeons to discriminate the presence and absence of another over-the-counter antihistamine, chlorpheniramine (Chlor-Trimeton) and another group to discriminate the presence and absence of the controlled antihistamine, promethazine (Phenergan). Diphenhydramine failed to produced complete cross-generalization in all subjects trained to discriminate the over-the-counter antihistamine, chlorpheniramine. However, diphenhydramine did engender at least 80% drug-appropriate responding in pigeons trained to discriminate the controlled compound promethazine. Doxylamine cross-generalization tests were not conducted. Tests conducted with *d*-amphetamine produced complete generalization in two pigeons, partial generalization in one pigeon, and no generalization in the final pigeon trained to discriminate between saline and the over-the-counter compound chlorpheniramine. Amphetamine engendered complete generalization in only one of four trained pigeons in the promethazine group. Evans et al. (1991) concluded that these effects were probably due to 'nonspecific' effects of the antihistamines; however, there are little, if any, 'specific' effects to the antihistamines (see below).

While doxylamine is one of the oldest antihistamines, it has not been systematically studied in the recent published reports; however, in recent reviews the subjective effects of doxylamine have been reported to produce both excitation and sedation in clinical populations (Dowd, 1992; Douglas, 1985; Garrison, 1990; Higgins et al., 1968). On the other hand, the subjective effects of diphenhydramine have been recently assessed in human subjects. In a brief abstract, Mumford and Griffiths (1993) have reported that diphenhydramine, relative to placebo, produced increases in scores on subject's liking of the drug, desire to take the drug again, and monetary value of the drug. Interestingly, the same subjects reported increases in ratings of 'dysphoria' within the same dose range of diphenhydramine which produced the increases in 'liking' scales. Preston et al. (1992) assessed the subjective effects of diphenhydramine in contrast to lorazepam and methocarbamol. The authors were unable to clearly differentiate among the test compounds of various measures of positive mood effects. However, diphenhydramine produced fewer increases in measures of positive mood and more adverse 'side-effects'. Further, diphenhydramine produced performance impairments that varied across measures and produced an overall profile of sedative subjective effects. It should not be surprising that human sedative/hypnotic abusers, with a long history of attending to or cueing into the sedative-hypnotic drug dimension, would characterize diphenhydramine as a sedative. Other human self-report data from patients not in a laboratory setting but receiving therapeutic doses of diphenhydramine have characterized the subjective effects as both sedative-like or stimulant-like (Dowd, 1992; Douglas, 1985; Garrison, 1990; Higgins et al., 1968). Based on the work by Helson (1966) we have previously suggested that an individual's 'frame of reference' would determine the subjective effects of drug administration (Gauvin et al., 1989a). Therefore, it would be interesting to investigate the differential mood responses to antihistamine administration in stimulant or cocaine abusers.

Clearly, the neuropharmacological mechanisms by which cocaine and the two antihistamines used in the present study produce similar subjective effects are not known at this time, but all three compounds do produce similar responses in a number of the same neurotransmitter systems implicated in cocaine's subjective effects, including norepinephrine, dopamine, and serotonin (see Introduction). The cross-generalization between the antihistaminics and cocaine may also be due to the transitory endogenous release and potentiation of histamine by antihistamine administration (Green, 1994). This conclusion is similar to previous reports of potentiation of agonist activity by co-administration of an antagonist (Stephenson and Ginsborg, 1969) in both the dopamine (Gudelsky and Moore, 1977; Janssen, 1967; Von Voigtlander and Moore, 1973; Kehr, 1976; Lidsky and Banerjee, 1993) and opioid systems (Gauvin and Young, 1989a,b) and may be related to the negative efficacy of the antagonist itself (cf. Kenakin, 1993,1994). We have previously shown simple effect and dose additivity between a cocaine training stimulus and the adenosine receptor antagonist, caffeine (Harland et al., 1989). Since histamine and adenosine coexist in the same neurons (Green, 1994; Linden, 1994), the cross-generalization between the antihistaminics and the cocaine training dose may be due to activation of similar adenosinergic mechanisms.

Interestingly, both Levine (1983) and Gerald (1981) have used the class of antihistamines as exemplars to explain the lack of selectivity and specificity of drugs. All drugs are capable of producing more than one

effect (Gerald, 1981). The antihistamines are nonspecific drugs – not because they produce many effects, but because the effects they produce are the consequence of more than one mechanism of action (Levine, 1983). As described above, Green (1994) has concluded that there is no similarity between the regional distribution of the histamine H_1 receptor and regional distribution of histamine, its metabolites, the enzymes that synthesize and metabolize histamine, nor histaminergic nerve endings. Therefore, the exact mechanisms by which the histamine H_1 receptor antagonists engendered cocaine-appropriate responding in the present study, most probably do not reflect specific actions at a single receptor site but rather the consequence of a number of different actions initiated by more than one mechanism (cf. Levine, 1983; Gerald, 1981; Green, 1994).

The drug discrimination task has been used as a preclinical screening assay for the abuse liability of drugs. Overton (1971) has claimed that rats would make drug-appropriate choices during substitution tests *if and only if* they were tested under the influence of drugs that pharmacologically resemble the training dose of the training drug. Since that report a number of laboratories have applied the drug discrimination procedure as a method for the investigation of a variety of psychopharmacological and neuropharmacological questions, including studies of the effects of drugs that underlie drug abuse (cf. Overton, 1987). The present study demonstrated subjective similarity between antihistaminics and the 10 mg/kg cocaine training stimulus in a preclinical screening assay for abuse liability. While the self-administration of diphenhydramine has been previously reported in squirrel monkeys (Bergman and Spealman, 1986), when compared to the millions of dollars in yearly sales, these compounds have typically shown minimal abuse liability in humans. The antihistaminics tested in the current study do not share equivalent binding characteristics at the most common mechanism attributed to the abuse liability of cocaine (dopamine re-uptake blockade; cf. Brown and Vernikos, 1980 or Carlsson and Lindquist, 1969), and do not structurally resemble cocaine. It should be noted that diphenhydramine has demonstrated activity through 5-HT receptor mechanisms (Brown and Vernikos, 1980 or Carlsson and Lindquist, 1969), which have been recently implicated in the behavioral effects of cocaine (cf. Cunningham and Lakoski, 1990; Cunningham et al., 1992). The antihistaminergic-induced activity in the serotonin system may explain the cross-generalization profiles in the present study and the self-adminstration of diphenhydramine in the Bergman and Spealman (1986) study.

Therapeutically, the antihistaminics have been typically used for sleep induction while to our knowledge the use/abuse of cocaine has never been reported to induce sleep. Further research will elucidate the subjective commonalities between the over-the-counter antihistaminics and cocaine.

Acknowledgements

The authors would like to thank Ms. Lynn Montgomery for her excellent administrative assistance. This research project was supported by a NIDA grant (No. DA04444-06) to F.A.H. and D.V.G. and NIAAA training grant (No. 5T32 AA07222) to F.A.H.

References

Arunlakshana, O., 1953, Histamine release by antihistamines, J. Physiol. 119, 47P.

Bergman, J. and R.D. Spealman, 1986, Some behavioral effects of histamine H_1 antagonists in squirrel monkeys, J. Pharmacol. Exp. Ther. 239, 104.

Brown, B.B. and H.W. Werner, 1948, The pharmacological properties of 2-[α-methylbenzyl]-pyridine succinate, a new antihistaminic agent, J. Lab. Clin. Med. 33, 325.

Brown, P.A. and J. Vernikos, 1980, Antihistamine effects on synaptosomal uptake of serotonin, norepinephrine and dopamine, Eur. J. Pharmacol. 65, 89.

Carlsson, A. and M. Lindquist, 1969, Central and peripheral monoaminergic membrane-pump blockade by some addictive analgesics and antihistamines, J. Pharm. Pharmacol. 21, 460.

Colpaert, F.C., C.J.E. Niemegeers and P.A.J. Janssen, 1979, Discriminative stimulus properties of cocaine: neuropharmacological characteristics as derived from stimulus generalization experiments, Pharmacol. Biochem. Behav. 10, 535.

Cooper, J.R., F.E. Bloom and R.H. Roth, 1991, The Biochemical Basis of Neuropharmacology (Oxford University Press, New York).

Cunningham, K.A. and J.M. Lakoski, 1990, The interaction of cocaine with serotonin dorsal raphe neurons, Neuropsychopharmacology 3, 41.

Cunningham, K.A., J.M. Paris and N.E. Goeders, 1992, Serotonin neurotransmission in cocaine sensitization, Ann. NY Acad. Sci. 654, 117.

Douglas, D.W., 1985, Histamine and 5-hydroxytryptamine (serotonin) and their antagonists, in: The Pharmacological Basis of Therapeutics, eds. A.G. Gilman, L.S. Goodman, T.W. Rall and F. Murad (Macmillan Publishing, New York) p. 605.

Dowd, A.L., 1992, Physicians' Desk Reference for Nonprescription Drugs, 13th edn. (Medical Economics Data, Montvale, NJ).

Evans, S.M. and C.E. Johanson, 1989, Discriminative stimulus properties of histamine H_1-antagonists in animals trained to discriminate *d*-amphetamine or pentobarbital, J. Pharmacol. Exp. Ther. 250, 779.

Evans, S.M., J.P. Zacny, W.L. Woolverton and C.E. Johanson, 1991, The discriminative stimulus effects of histamine H_1-antagonist in pigeons, Behav. Pharmacol. 2, 447.

Garbarg, M., G. Barbin, J. Feger and J.C. Schwartz, 1974, Histaminergic pathway in rat brain evidenced by lesions of the medial forebrain bundle, Science 186, 833.

Garbarg, M., G. Barbin, S. Bischoff, H. Pollard and J.C. Schwartz, 1976, Dual localization of histamine in an ascending neuronal pathway and in non-neuronal cells evidenced by lesions in the lateral hypothalamic area, Brain Res. 106, 333.

Garrison, J.C., 1990, Histamine, bradykinin, 5-hydroxytryptamine,

and their antagonists, in: The Pharmacological Basis of Therapeutics, eds. A.G. Gilman, T.W. Rall, A.S. Nies and P. Taylor (Pergamon Press, New York) p. 575.

Gauvin, D.V. and F.A. Holloway, 1993, The discriminative stimulus properties of an ethanol-nicotine mixture in rats, J. Psychopharmacol. 7, 52.

Gauvin, D.V. and A.M. Young, 1989a, Evidence for perceptual masking of the discriminative morphine stimulus, Psychopharmacology 98, 212.

Gauvin, D.V. and A.M. Young, 1989b, Perceptual masking of drug stimuli, Drug Dev. Res. 16, 151.

Gauvin, D.V., R.D. Harland and F.A. Holloway, 1989a, Drug discrimination procedures: a method to analyze adaptation level of affective states, Drug Dev. Res. 16, 183.

Gauvin, D.V., R.D. Harland, R.C. Michaelis and F.A. Holloway, 1989b, Caffeine-phenylethylamine combinations mimic the cocaine discriminative cue, Life Sci. 44, 67.

Gauvin, D.V., K.L. Goulden and F.A. Holloway, 1993a, State-dependent stimulus control: cueing attributes of ethanol 'hangover' in rats, Alcohol. Clin. Exp. Res. 17, 1210.

Gauvin, D.V., K.R. Moore, B.D. Youngblood and F.A. Holloway, 1993b, The discriminative stimulus properties of legal, over-the-counter stimulants administered singly and in binary and ternary combinations, Psychopharmacology 110, 309.

Gauvin, D.V., J.M. Peirce and F.A. Holloway, 1993d, Perceptual masking of the chlordiazepoxide discriminative cue by both caffeine and buspirone, Pharmacol. Biochem. Behav. 47, 153.

Gerald, M.C., 1981, Pharmacology: An Introduction to Drugs (Prentice-Hall, Englewood Cliffs, NJ).

Green, J.P., 1994, Histamine. in: Basic Neurochemistry, eds. G.J. Siegel, B.W. Agranoff, R.W. Albers and P.B. Molinoff (Raven Press, New York) p. 309.

Gruhzit, O.M. and R.A. Fisken, 1947, A toxicological study of two histamine antagonists of the benzhydryl alkamine ether group, J. Pharmacol. Exp. Ther. 89, 227.

Gudelsky, G.M. and K.E. Moore, 1977, A comparison of the effects of haloperidol on dopamine turnover in the striatum, olfactory tubercle and median emminence, J. Pharmacol. Exp. Ther. 202, 149.

Harland, R.D., D.V. Gauvin, R.C. Michaelis, J.M. Carney, T.W. Seale and F.A. Holloway, 1989, Behavioral interaction between cocaine and caffeine: a drug-discrimination analysis in rats, Pharmacol. Biochem. Behav. 32, 1017.

Helson H., 1966, Adaptation-Level Theory: An Experimental and Systematic Approach to Behavior (Harper and Row, New York).

Higgins, E.A., A.W. Davis, V. Fiorica, P.F. Iampietro, J.A. Vaughan and G.E. Funkhauser, 1968, Effects of two antihistamine-containing compounds upon performance at three altitudes, Aviation Medical Report AM68-15 (Federal Aviation Administration, Washington, DC).

Holloway, F.A. and D.V. Gauvin, 1989, Comments on method and theory in drug discrimination: a potpourri of problems, perplexities, and possibilities, Drug Dev. Res. 16, 195.

Janssen, P.A.J., 1967, The pharmacology of haloperidol, Int. J. Neuropsychiatry 3, S10.

Kehr, W.V., 1976, Wechselwirkung von Dopaminrezeptoragonisten und -antagonisten hinsichtlich Dopaminsynthese und -metabolismus, Arzneim.-Forsch. 26, 1086.

Kenakin, T., 1993, Pharmacologic Analysis of Drug-Receptor Interaction, 2nd edn. (Raven Press, New York).

Kenakin, T., 1994, On the definition of efficacy, Trends Pharmacol. Sci. 15, 408.

Levine, R.R., 1983, Pharmacology: Drug Actions and Reactions (Little, Brown and Co., Boston, MA).

Lidsky, T.I. and S.P. Banerjee, 1993, Acute administration of haloperidol enhances dopaminergic transmission, J. Pharmacol. Exp. Ther. 265, 1193.

Linden, J., 1994, Purinergic Systems, in: Basic Neurochemistry, eds. G.J. Siegel, B.W. Agranoff, R.W. Albers and P.B. Molinoff (Raven Press, New York) p. 401.

Mackintosh, N.J., 1974, The Psychology of Animal Learning (Academic Press, London).

Mariathasan, E.A. and I.P. Stolerman, 1992, Drug discrimination studies in rats with caffeine and phenylpropanolamine administered separately and as mixtures, Psychopharmacology 109, 99.

Mumford, G.K. and R.R. Griffiths, 1993, Subjective and reinforcing effects of diphenhydramine and lorazepam, in: Problems of Drug Dependence 1992: Proceeding of the 54th Annual Scientific Meeting of the College on Problems of Drug Dependence, ed. L.S. Harris (NIDA Research Monograph No. 132 [ADM 93-3505]) (U.S. Government Printing Office, Washington, DC) p. 30.

Overton, D.A., 1971, Discriminative control of behavior by drug states, in: Stimulus Properties of Drugs, eds. T. Thompson and R. Pickens (Appleton-Century-Crofts, New York) p. 87.

Overton, D.A., 1978, Discriminable effects of antihistamine drugs, Arch. Int. Pharmacodyn. Ther. 232, 221.

Overton, D.A., 1987, Application and limitations of the drug discrimination method for the study of drug abuse, in: Methods of Assessing the Reinforcing Properties of Abused Drugs, ed. M.A. Bozarth (Springer, New York, Berlin, Heidelberg, London, Paris, Tokyo) p. 291.

Prell, G.D. and J.P. Green, 1986, Histamine as a neuroregulator, in: Annual Review of Neuroscience, Vol. 9, eds. W.M. Cowan, E.M. Shooter, C.F. Stevens and R.F. Thompson (Annual Reviews, Palo Alto, CA) p. 209.

Preston, K.L., B. Wolf, J.J. Guarino and R.R. Griffiths, 1992, Subjective and behavioral effects of diphenhydramine, lorazepam and methocarbamol: evaluation of abuse liability, J. Pharmacol. Exp. Ther. 262, 707.

Schwartz, J.C., J.M. Arrang, M. Garbarg, H. Pollard and M. Ruat, 1991, Histaminergic transmission in the mammalian brain, Physiol. Rev. 71, 1.

Sjöqvist, F. and L. Lasagna, 1967, The hypnotic efficacy of doxylamine, Clin. Pharmacol. Ther. 8, 48.

Speeg, K.V., S. Wang, G.R. Avant, R. Parker and S. Schenker, 1981, In vitro antagonism of benzodiazepine binding to cerebral receptors by H_1 and H_2 antihistamines, J. Lab. Clin. Med. 97, 112.

Sperber, N., D. Papa, E. Schwenk and M. Sherlock, 1949, Pyridyl-substituted alkamine ethers as antihistaminic agents, J. Am. Chem. Soc. 71, 887.

Stephenson, R.P. and B.L. Ginsborg, 1969, Potentiation by an antagonist, Nature 222, 790.

Von Voigtlander, P.F. and K.E. Moore, 1973, In vivo release of H_3-dopamine from the brain during the administration of haloperidol, Res. Commun. Chem. Pathol. Pharmacol. 5, 223.

White, J.M., 1985, The discriminative stimulus properties of mepyramine, Life Sci. 37, 1145.

White, J.M. and G.R. Rumbold, 1988, Behavioral effects of histamine and its antagonists: a review, Psychopharmacology 94, 1.

Winter, J.C., 1985, Sedation and the stimulus properties of antihistamines, Pharmacol. Biochem. Behav. 22, 15.

Woolverton, W.L., 1987, Analysis of drug interactions in behavioral pharmacology, in: Advances in Behavioral Pharmacology, Vol. 6, eds. T. Thompson, P.B. Dews and J.E. Barrett (Lawrence Erlbaum, Hillsdale, NJ) p. 275.

Young, A.M. and C.A. Sannerud, 1989, Tolerance to drug discriminative stimuli, in: Psychoactive Drugs: Tolerance and Sensitization, eds. A.J. Goudie and M.W. Emmett- Oglesby (Humana Press, New Jersey) p. 221.