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Discrimination of cocaethylene in rats trained to discriminate between its components

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Abstract

Two groups of eight male Normalized/National Institutes of Health (N/Nih) rats were used in a food-motivated, 2-lever drug discrimination task with one group being trained to discriminate between 10 mg/kg cocaine vs. 1 g/kg ethanol, whereas the second group was trained to discriminate the metabolic product of these two agents, i.e., cocaethylene (10 mg/kg) vs. its saline vehicle. All drugs were administered intraperitoneally and training/testing was conducted 15 min post-injection. Once both groups of animals attained criterion performance, they were each tested in sessions, interspersed with maintenance sessions, with numerous doses of both cocaine and cocaethylene; this resulted in a typical dose–response relationship in each group but indicated that the cocaine-ethanol trained animals were more sensitive to the lower doses of cocaine (as indicated by a decreased ED_{50} value, i.e., 1.74 mg/kg) when compared to previously trained cocaine-saline animals (ED_{50} 4.22 mg/kg) and, that in both groups, cocaine was significantly more potent than was cocaethylene. Although numerous laboratories have trained drug vs. drug in the drug discrimination paradigm, this is the first study to train animals to discriminate between two drugs which, although having different discriminative properties, form a third psychoactive compound when co-administered. The sensitivity of drug–drug testing vs. drug-saline testing is discussed, as well as the use of these two agents in human abuse.

Keywords: Stimulus properties of drugs; Cocaine; Ethanol; Cocaethylene drug–drug discrimination; (Dose–response); (Rat)

1. Introduction

The coadministration of the two drugs of abuse, cocaine and ethanol, appears to be increasingly popular in that over half of all chronic cocaine users simultaneously report consuming alcoholic beverages (Grant and Harford, 1990). Anecdotal reports suggest that the alcoholic beverage allows for a heightened cocaine euphorigenic experience and avoids the aversive side effects associated with the rapid decline in cocaine blood/brain levels; this is supported by controlled studies in human volunteers that demonstrate the combination produces an enhanced feeling of euphoria which lasts longer than cocaine alone (McCance-Katz et al., 1993). When an alcoholic beverage (ethanol) is ingested at the same time that cocaine is administered, the human liver carboxylesterase enzymes produce a unique third substance (Rafla and Epstein, 1979). This represents the only known example of the body producing a novel psychoactive drug exclusively during the administration of two other drugs of abuse, i.e., the alcohol-derived cocaine metabolite is produced only when alcohol is consumed in that it is not a natural alkaloid of coca, nor is it found in the normal catabolism of cocaine. This substance is known by various names, the most popular of which is cocaethylene (Dean et al., 1992). Cocaethylene has a pharmacological profile similar to that of cocaine in that it blocks presynaptic dopamine transport that, in turn, results in increased synaptic levels and enhanced post-synaptic stimulation. It has been shown to be equipotent in its dopamine transporter site affinity in both rat (Hearn et al., 1991) and human (Jatlow et al., 1991) brain tissue, as well as in its ability to inhibit dopamine reuptake into rat striatal synaptosomes (McCance-Katz et al., 1993).

Behavioral studies in animals, likewise, indicate similarities in the effects of cocaine and cocaethylene in that both compounds produce increased locomotor activity in the rat and both can function as reinforcers in self-administration experiments in rhesus monkeys (Jatlow et al., 1991). In addition, many laboratories have shown cocaine capable of producing conditioned place preference (see Hoffman, 1989), and at least one laboratory (Schechter, 1995a) has shown cocaethylene capable of producing this effect. Lastly, and perhaps most important to this work, at least three laboratories (Katz et al., 1992; Schechter, 1995b;

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Woodward et al., 1991) have been the sites of experiments in which rats were trained to discriminate the interoceptive stimulus cues produced by cocaine and were, subsequently, shown to generalize their discriminative performance when administered cocaethylene. Thus, the interoceptive cues produced by cocaine appear to be similar to those produced by cocaethylene. This generalization has been shown to be symmetrical in that the cueing stimuli in rats trained to discriminate cocaethylene generalize to cocaine (Schechter, 1995c).

The extensive utilization of the behavioral paradigm utilizing the stimulus properties of drugs has allowed for increasing adoption of it as a specific in vivo assay of centrally active drugs (Stolerman et al., 1989). In effect, the vast majority of these studies involve training a drug vs. a non-drug condition where the differentiated discriminative stimulus cues function to signal the presence or absence of the drug, respectively. In contrast, fewer studies have investigated the drug–drug procedure in which animals are trained to discriminate between the interoceptive cues produced by two different drugs allowing for a generalization gradient to be established for both drugs (Seiden and Dystra, 1977; Swedberg and Järbe, 1986). As early as 1979, it was suggested (Barry and Krimmer, 1979) that the strength or distinctiveness of the drug-produced interoceptive cue not only depends on the dose of the drug used, but on the characteristic of the drug and, thus, two drugs at equivalent potencies may differ in distinctiveness from the drug-nondrug condition. Thus, the drug–drug condition would be more distinctive, differentiating and, thereby, discriminable than either of the two drug-saline conditions. More recent work (Swedberg and Järbe, 1985) has, indeed, evidenced that relative stimulus control in drug–drug experiments is a more specific measurement of discriminative stimulus control than it is in drug-saline experiments. The purpose of the present study was to train rats to discriminate between the two components that are required to exist simultaneously in the body, i.e., cocaine and ethanol, to produce cocaethylene, and at the same time, train other animals to discriminate the consequent metabolite cocaethylene from saline; discriminative sensitivities could then be compared with previously published results employing rats trained to discriminate cocaine from its saline vehicle (Schechter, 1995b). The interesting feature of this drug–drug test resides in the fact that the drug combination itself produces a third compound and generalization testing to that third substance, cocaethylene, in both groups of animals was planned.

2. Materials and methods

2.1. Subjects

Sixteen male rats of the N/Nih descent were obtained from the Small Animal Section of the National Center for Research Resources of the National Institutes of Health. After a week of quarantine, they were placed into individual wire cages in a facility with an ambient temperature of 20–22°C and maintained on a 12/12 light/dark cycle with lights on at 06:00 h. Behavioral training/testing was conducted in a room separate from the animal colony. Water was available ad libitum in their home cages and daily rationing of approximately 18 g of commercial rat chow allowed maintenance of their body weights at approximately 90% of that determined by free-feeding control rats of the same age and sex. This procedure was in place to facilitate motivation of operant performance for food reward. Half of the animals were randomly assigned to the drug (10 mg/kg cocaethylene) vs. saline (vehicle), whereas half were designated to be trained to the drug–drug condition, i.e., 10 mg/kg cocaine vs. 1 g/kg ethanol.

2.2. Apparatus

Ten standard rat operant chambers (Lafayette Instrument Corp., Lafayette, IN, USA) were the experimental space; each contained two levers situated 7 cm apart and 7 cm above a metal grid floor. Equidistant between the levers was placed a food receptacle into which a 45 mg (Noyes, Lancaster, NH, USA) food pellet was delivered. Each operant chamber was enclosed in a sound-attenuated enclosure with an exhaust fan and a 9 W house light. Solid-state programming equipment (Med Associates, St. Albans, VT, USA) was located in an adjacent room and was used to control and record the discrimination sessions.

2.3. Training to lever-press

The food-restricted rats assigned to the ethanol-cocaine group were administered 1 ml/kg saline (0.9% NaCl in distilled water) by intraperitoneal (i.p.) injection 15 min prior to being placed into the apparatus and trained to press one of the two levers at which time one press produced one food pellet (fixed-ratio 1 (FR1)). For half of each group of animals, this lever was designated to be the left lever and for the other half of the rats, it was the right lever. It was that lever that, on the subsequent day, was designated the ‘cocaine-appropriate’ lever and 15 min after the i.p. administration of an equal volume (1 ml/kg) allowing for 10 mg/kg cocaine (hydrochloride; as salt), the animals were required to press that lever on the FR1 schedule. This procedure was continued with the animals’ schedule of reinforcement gradually incremented to a fixed-ratio 10 (FR10) requirement over 10 consecutive days. On the subsequent day, the animals were injected with 1 g/kg ethanol (10%, w/v) and were required to press the opposite lever 15 min after injection in order to receive food reinforcement on the FR1 schedule. This requirement was incremented over the next 6 days until

each animal was pressing the second lever after ethanol on an FR10 schedule.

In the cocaethylene-saline trained animals, the same procedure was employed except that saline was administered from the outset and the FR1 to FR10 schedule was incremented over 10 days on the designated vehicle-correct lever. Subsequently, the rats were required to press the opposite lever (left for half, right for the other half) 15 min after the i.p. administration of 10 mg/kg cocaethylene. The FR1 schedule, after cocaethylene on the opposite lever, was incremented over 7 days until an FR10 was well-established.

2.4. Discrimination training

Once the rats were pressing both levers according to the drug (or saline vehicle) administered and the animals were reinforced on the FR10 schedule, discrimination training commenced. This training began 15 min after the daily administration of either ethanol or cocaine in the drug–drug animals and at the same post-injection time after either cocaethylene or saline in the drug-saline animals. The schedule of administration was, in the first group, D_1–D_2–D_2–D_1–D_1; D_2–D_1–D_1–D_2–D_2, where $D_1 = 10$ mg/kg cocaine; $D_2 = 1$ g/kg ethanol, and for the drug-saline animals the schedule was D–S–S–D–D; S–D–D–S–S, where D = 10 mg/kg cocaethylene and S = 0.9% saline vehicle. The first lever upon which 10 responses were accumulated at the beginning of each session was considered the 'selected lever' for that daily session. At the time of the 10th response, presses on both the selected and unselected lever were recorded. However, the session was continued, regardless of the correctness of the selected lever, until 400 responses were made on the correct lever for that session and, therefore, until 40 reinforcements (on the FR10 schedule) were received. Presses on the incorrect lever produced no programmed consequences. Animals were required to select the correct lever appropriate for the substance injected on that day in 8 of 10 consecutive training sessions. This 8/10 performance criterion was required twice before subsequent dose–response testing commenced.

2.5. Dose–response tests

Of the eight cocaine-ethanol rats, two died of unknown causes but the six surviving rats in this group attained the discriminative performance criterion, as did the eight cocaethylene-saline trained rats. Once this training criterion was reached, the administration regimen was limited to every other day to maintain discrimination. Thus, on every second day, either 1 g/kg ethanol or 10 mg/kg cocaine was tested in the drug–drug animals, whereas 10 mg/kg cocaethylene or saline was administered and tested in the drug-saline animals. If any animal was seen to fall below the 8 correct of 10 consecutive sessions criterion during these maintenance-day tests, the data on their dose–response responding were to be precluded from the results. This, however, did not occur. On maintenance days, the rats were given reinforcements on the FR10 schedule for either 10 min or after 400 responses on the injection-appropriate lever, whichever came first. In the cocaine-ethanol trained rats, intervening days were used to test doses of cocaine different than the 10 mg/kg used in training, various doses of cocaethylene, a single dose of ethanol and saline. Each test dose was administered twice; once following an ethanol maintenance session and once following a cocaine maintenance session. This counterbalancing procedure was used to control for any possible residual influences from the previous day's maintenance session.

Likewise, the 10 mg/kg cocaethylene-trained rats were administered various doses of cocaine or cocaethylene 15 min prior to testing. Each dose followed either a 10 mg/kg cocaethylene maintenance day or a saline maintenance day. In all cases on test days, the animal was immediately removed upon making 10 responses on either of the two levers, without receiving reinforcement. This intended to preclude reinforcement, albeit training, at a different dose or drug state than used in initial training.

2.6. Measurement and data analysis

The data collected in the drug discrimination sessions were expressed as a quantal measurement which indicates the percentage of rats in each group that chose the drug-appropriate lever as their selected lever, i.e., the lever first accumulating 10 presses. This was either the ethanol-lever after ethanol or the cocaine-lever after cocaine in the drug–drug animals, in contrast to the cocaethylene-correct lever or saline-correct lever in the drug-saline animals. When a novel drug was seen to produce 80% quantal responses on the lever trained with any drug, this novel drug was assessed to generalize to, or substitute for, the drug used in training. For the drug–drug animal, it was necessary to choose one of the two drugs to allow for this calculation and, therefore, the quantal measurement was determined by the number of rats selecting the cocaine-appropriate lever. A computer-generated formulation of the Litchfield-Wilcoxon procedure (Tallarida and Murray, 1986), which employs probits vs. log-dose effects, was used to generate ED_{50} values, with 95% confidence limits, from quantal responses in the cocaethylene-saline rats with various doses of both cocaethylene and cocaine, whereas this analysis was applied to the cocaine-ethanol rats after the same two dose–response experiments. In addition, the ED_{50} values could be compared to animals trained to discriminate 10 mg/kg cocaine from its vehicle and later tested for generalization to cocaethylene as previously reported (Schechter, 1995b).

3. Results

Both the drug–drug (cocaine-ethanol) and drug–vehicle (cocaethylene-saline) animals reached criterion performance by the 8th week of training, thus, after 20 sessions under one condition and 20 sessions under the other 'state' (Fig. 1). These rats were, subsequently, tested with 1.25, 2.5, 5 and 10 mg/kg cocaine, as well as 5, 10 and 15 mg/kg cocaethylene. Table 1A indicates that animals trained to 10 mg/kg cocaine vs. 1 g/kg ethanol chose the cocaine-appropriate lever on 96.7% of the maintenance sessions during the dose–response experiments and chose the same lever on 5.6% of all cases after administration of 1000 mg/kg ethanol ('TD' in Table 1A). Thus, 94.4% of all sessions after ethanol resulted in the first 10 responses accumulating on the ethanol-appropriate lever. When lower doses of cocaine were administered to the cocaine-ethanol trained animals on two occasions each, the quantal measurement, i.e., percent cocaine lever selection, decreased with the lowest (1.25 mg/kg) cocaine doses tested producing 41.7% of responses on that lever. Application of the Litchfield-Wilcoxon analysis to these cocaine data allows for calculation of an ED_{50} value (95% confidence limits) of 1.74 (0.96–3.14) mg/kg. When 15 mg/kg cocaethylene was administered to cocaine-ethanol trained animals, there was a complete generalization with 100% of the selected lever in two trials being the cocaine-appropriate lever. Decreasing doses of cocaethylene at 10 and 5 mg/kg produced decreasing quantal discrimination performance and allowed for an ED_{50} value of 5.93 (4.30–8.15) mg/kg. Lastly, the administration of saline, a third state in the drug—drug trained animals, produced 41.7% of responses on the cocaine lever, slightly less than what might be considered random responding, i.e., 50% on each of the two levers.

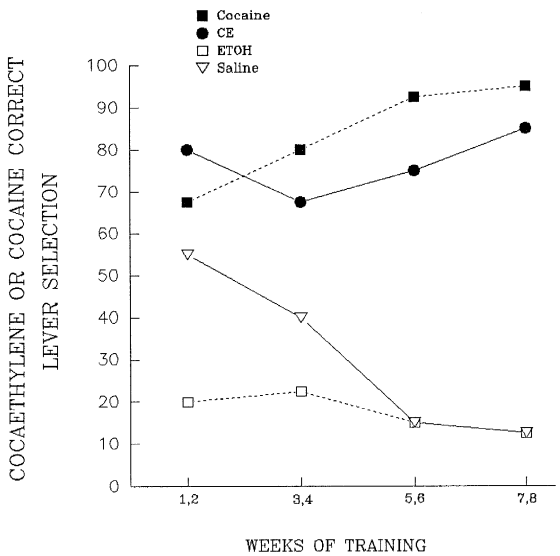

Fig. 1. Learning curve for rats trained to discriminate 10 mg/kg cocaine (closed squares) vs. 1 g/kg (10%, w/v) ethanol (open squares), as well as rats trained to discriminate between 10 mg/kg cocaethylene (CE; closed circles) vs. its saline vehicle (open inverted triangles). Ordinate: Percentage of rats selecting the cocaethylene-correct lever (cocaethylene-saline trained) or the cocaine-appropriate lever (cocaine-ethanol trained). Abscissa: Weeks of training after lever-press training on both levers was established (see Section 2). Each 2-week period contained 5 sessions in one state and 5 in the other state according to a pseudo-random schedule.

Table 1
Dose–response effect to 1.25–10 mg/kg cocaine and 5–15 mg/kg cocaethylene in rats trained to discriminate: (A) 10 mg/kg cocaine from 1 g/kg ethanol ($n = 6$) or (B) 10 mg/kg cocaethylene from saline ($n = 8$)

	Dose (mg/kg)	A. Cocaine-ethanol trained (Percent cocaine-lever selection)	B. Cocaethylene-saline trained (Percent cocaethylene-lever selection)
Tested with:			
Cocaine	10 [a]	96.7	87.5
	5	83.3	81.3
	2.5	58.3	56.3
	1.25	41.7	18.8
Cocaethylene	15	100.0	93.3
	10 [b]	75.0	81.3
	5	41.7	41.7
	0 (saline; TD)		9.4
Saline	–	41.7	
Ethanol	1000 (TD)	5.6	

TD, training dose.
[a] TD for cocaine-ethanol trained rats.
[b] TD for cocaethylene-saline trained rats.

When the cocaethylene-saline trained rats were tested with various doses of cocaine (Table 1B), a similar decrease in quantal discriminative performance occurred with decreasing doses. Both 5 and 10 mg/kg cocaine produced what might be adjudged to be generalization at or above the 80% level. The dose–response relationship allowed for a calculation of an ED_{50} value equal to 2.54 (1.70–3.80) mg/kg in the eight animals. In addition, the lower half of Table 1B indicates that the training dose of 10 mg/kg of cocaethylene produced 81.3% of responding on the cocaethylene-correct lever, whereas saline maintenance session tests ('TD' in Table 1B) allowed for 9.4% of responding on this lever (or 90.6% responding on the saline-appropriate lever). Likewise, the varying dose of cocathylene, with administration/testing of one higher and one lower dose than used in training, produced a 'typical' dose–response relationship in the cocaethylene-saline trained animals.

The ED_{50} values for the cocaine-ethanol (Table 1A) and the cocaethylene-saline (Table 1B) trained animals are compared to previously trained cocaine-saline rats (Jatlow et al., 1991) and presented in Table 2. Application of potency ratio analysis (Tallarida and Murray, 1986) indicates that the cocaine-ethanol trained animals had a signifi-

Table 2
ED_{50} values (95% CL) for (A) cocaine-ethanol ($n = 6$), (B) cocaethylene-saline ($n = 8$) or (C) cocaine-saline trained ($n = 10$) rats tested with either cocaine or cocaethylene

	Rats trained to:		
	A. Cocaine-ethanol	B. Cocaethylene-saline	C. Cocaine-saline [a]
Tested with:			
Cocaine	1.74 [b]	2.54	4.22
	(0.96–3.14)	(1.70–3.80)	(3.20–5.51)
Cocaethylene	5.93 [b]	6.50	13.26
	(4.30–8.15)	(5.03–8.41)	(10.23–17.31)
Cocaethylene/cocaine	3.41	2.56	3.14

[a] Results from Schechter, 1995b: TD, 10 mg/kg cocaine. [b] Significantly lower ($P < 0.05$) than ED_{50} value for cocaine in cocaine-saline trained rats.

cantly lower ($P < 0.05$) ED_{50} value with cocaine than did the cocaine-saline trained rats and that in all three groups of animals, the cocaethylene/cocaine ratio ranged from approximately 2.6 to 3.4 times suggesting that cocaine was significantly ($P < 0.05$) more potent in all groups than was cocaethylene.

4. Discussion

Psychoactive drugs can produce interoceptive stimuli in a behavioral paradigm known as stimulus discrimination learning that permits differential responding; this observation has been increasingly adopted as a specific in vivo assay to test centrally active drugs (Stolerman et al., 1989). The vast majority of these drug discrimination studies employ rats by training them to discriminate between a drug state and the state produced by the vehicle used to dissolve the drug, the non-drug condition. Thus, discriminative stimuli signal the presence or absence of the drug, respectively. Once the rats are trained to discriminate between the drug and non-drug state, experiments can be conducted to indicate comparisons between the stimulus properties of the trained- and the novel-drug state. If a novel drug is tested and seen to produce 80% or more of the responses upon the lever trained under the influence of the original drug, it is said to substitute for the trained drug; this is also known as generalization to, or transfer from, the trained drug to the test drug condition. Another comparison can be made when animals are trained to discriminate between two drugs. In this situation, it is not the presence or absence of the drug that is tested, but rather the effects that allow the animal to make a differential response to the first drug by pressing one of two levers vs. some effect inherent in the interoceptive cueing properties of the second drug that differ from the first drug that allows the animal to make an equal, but opposite, discriminative response when administered the second drug. The specific drug stimuli complexes, thereby, are attended to by the rats in order to make differential responses.

Interestingly, ethanol has generally been conceded to be the first drug employed in training animals to discriminate between the drug state and the non-drug state (Conger, 1951). Ethanol was also the first drug reported to be used to train animals drug vs. drug. This occurred in 1973 (Krimmer and Barry, 1973) when rats were trained to discriminate between 1 g/kg ethanol and 10 mg/kg pentobarbital. This study was of interest in light of the fact that both ethanol and pentobarbital are considered central nervous system depressants and, therefore, there must be a singular mechanistic/neurochemical action of each of ethanol and pentobarbital to which a rat can attend so as to differentiate an interoceptive cue to allow it to choose between the two distinct responses. In other work, the discrimination between a drug and a second drug has been more easily understood as drugs that are considered stimulants, in one case pentylenetetrazol, can be trained with drugs considered to be depressant such as chlordiazepoxide (Gauvin et al., 1989); amphetamine vs. pentobarbital (Schechter, 1981) is another example.

Another interesting mode of training involves administering two drugs in a mixture and training them on one lever vs. their vehicle. This type of study allows for the multiple discriminative stimuli inherent in the two drugs to be tested vs. saline and has been used to investigate these separate interoceptive cues by decreasing doses of one or the other of the two drugs used in the training mixture, or by testing the one drug by itself. This is well shown with amphetamine + pentobarbitone, morphine + nicotine, pentazocine + tripelennamine and caffeine + phenylpropanolamine used in a mixture and trained on one lever with saline trained on the second lever (Stolerman et al., 1991). In each and every case, approximately 60% of the responses were made on the lever trained with a mixture when each of the two components of that mixture was tried individually. This would indicate, as it did to the authors (Stolerman et al., 1991), that mixtures are more discriminable when two drugs are present then they are when each drug is tested. The most parsimonious explanation for this resides in the possibility that the two drugs in the mixture are each allowing for a distinct interoceptive

cueing stimulus to which the animals are attending when tested with one of the two drugs of the mixture. Less than all of these stimuli are present and there is, therefore, a decrement to the ability to discriminate by the absence of the stimuli normally present in the mixture presented by administering only one of the two drugs. In reality, a mixture of isomeric compounds is trained when a drug such as *d,l*-amphetamine is employed in that the *d*-amphetamine isomer has a different discriminative potency than does the *l*-amphetamine isomer (Schechter, 1978).

In the present experimentation, a quite different array of discriminative stimulus properties were made available to the animals in that the two drugs used to allow for differential responding, i.e., cocaine vs. ethanol, can actually (in mixture) produce a third compound, cocaethylene. This laboratory has been the site of research that indicated that there is a symmetrical generalization between cocaine and cocaethylene (Schechter, 1995b). In contrast, rats trained to ethanol vs. saline do not generalize to cocaethylene. In addition, animals trained to cocaethylene vs. saline generalize to cocaine but not to ethanol by itself (Schechter, 1995c). When lower doses then used in training of cocaine or ethanol are co-administered, the cocaethylene-trained animals identify the mixture as cocaethylene, Thus, the formation of cocaethylene by co-administration of ethanol + cocaine allows for the rapid formation of cocaethylene. This rapidity of cocaethylene formation has been shown to be 2.5 min in mice (Boyer and Petersen, 1992) and less than 15 min in rats (Dean et al., 1992). Cocaethylene has also been found to be detectable within 30 min when cocaine and ethanol are administered in human volunteers (McCance-Katz et al., 1993).

In the present experimentation, cocaine was invariably shown to be more potent in each of the animal groups in that the ED_{50} values for cocaine were significantly lower than the ED_{50} values for cocaethylene (Table 2 indicating non-overlap of 95% confidence limits). In addition, when cocaine is administered to animals trained to discriminate between cocaine and ethanol, it produced a significantly more potent effect as indicated by a significantly lower ED_{50} value than when it was trained vs. saline. This finding evidences the suggestion that the strength or distinctiveness of the drug-produced interoceptive cue is different and, in fact, more discriminable in a drug–drug training condition than it is in the drug–saline training condition (Barry and Krimmer, 1979; Swedberg and Järbe, 1985).

Another important observation was made in the cocaine vs. ethanol (drug–drug) trained animals. The administration of saline which, in effect, is a third state, produced close to random responding of 41.7%. This would indicate that the doses used in training of 10 mg/kg cocaine vs. 1 g/kg ethanol had a relatively equal strength in producing the discriminative cueing properties in these animals, with only a slight bias towards cocaine. The administration of three doses of cocaethylene to cocaine-trained animals showed generalization to cocaine. This had previously been shown to occur in animals trained to discriminate between cocaine and saline (Schechter, 1995b) and this study supplements the two previous studies employing either cocaethylene or cocaine vs. saline vehicle to demonstrate generalization between these two drugs.

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References

Barry III, H. and E.C. Krimmer, 1979, Differential stimulus attributes of chlordiazepoxide and pentobarbital, Neuropharmacology 18, 991.

Boyer, C.S. and D.R. Petersen, 1992, Enzymatic basis for the transesterification of cocaine in the presence of ethanol: evidence for the participation of microsomal carboxyl-esterases, J. Pharmacol. Exp. Ther. 260, 939.

Conger, J.J., 1951, The effect of alcohol on conflict behavior in the albino rat, Q. J. Stud. Alcohol 12, 1.

Dean, R.A., E.T. Harper, N. Dumaual, D.A. Stoeckel and W.F. Bosron, 1992, Effects of ethanol on cocaine metabolism: formation of cocaethylene and norcocaethylene, Toxicol. Appl. Pharmacol. 117, 1.

Gauvin, D.V., R.D. Harland, J.R. Criado, R.C. Michaelis and F.A. Holloway, 1989, The discriminative stimulus properties of ethanol and acute ethanol withdrawal states in rats, Drug Alcohol. Depend. 24, 103.

Grant, B.F. and T.C. Harford, 1990, Concurrent and simultaneous use of alcohol with cocaine: results of national survey, Drug Alcohol. Depend. 25, 97.

Hearn, W.L., D.D. Flynn, G.W. Hime, S. Rose, J.C. Cofina, E. Mantero-Atienza, C.F. Wetli and D.C. Mash, 1991, Cocaethylene: a unique cocaine metabolite displays high affinity for the dopamine transporter, J. Neurochem. 56, 698.

Hoffman, D.C., 1989, The use of place conditioning in studying the neuropharmacology of drug reinforcement, Brain Res. Bull. 23, 373.

Jatlow, P., J.D. Elsworth, C.W. Bradberry, G. Winger, J.R. Taylor, R. Russell and R.H. Roth, 1991, Cocaethylene: a neuropharmacologically active metabolite associated with concurrent cocaine-ethanol ingestion, Life Sci. 48, 1787.

Katz, J.L., P. Terry and J.M. Witkin, 1992, Comparative behavioral pharmacology and toxicology of cocaine and its ethanol-derived metabolite cocaine ethyl-ester (cocaethylene), Life Sci. 50, 1351.

Krimmer, E.C. and H. Barry III, 1973, Differential stimulus characteristics of alcohol and pentobarbital in rats, Proc. Am. Psychol. Assoc. 8, 1005.

McCance-Katz, E.F., L.H. Price, C.J. McDougle, T.R. Kosten, J.E. Black and P.I. Jatlow, 1993, Concurrent cocaine-ethanol ingestion in humans: pharmacology, physiology, behavior and the role of cocaethylene, Psychopharmacology 111, 39.

Rafla, P.K. and H.L. Epstein, 1979, Identification of cocaine in human urine in the presence of ethyl alcohol, J. Anal. Toxicol. 3, 59.

Schechter, M.D., 1978, Stimulus properties of *d*-amphetamine as compared to *l*-amphetamine, Eur. J. Pharmacol. 47, 461.

Schechter, M.D., 1981, Rapid acquisition of a two-drug discrimination: time of day effect on saline state, Pharmacol. Biochem. Behav. 14, 269.

Schechter, M.D., 1995a, Cocaethylene produces conditioned place preference in rats, Pharmacol. Biochem. Behav. 51, 549.

Schechter, M.D., 1995b, Discriminative effects of cocaethylene in rats trained to discriminate cocaine or ethanol, Life Sci. 55, 1030.

Schechter, M.D., 1995c, Cocaethylene produces discriminative stimulus properties in the rat: effect of cocaine and ethanol coadministration, Pharmacol. Biochem. Behav. 51, 285.

Seiden, L.S. and L.A. Dystra, 1977, Psychopharmacology: A Behavioral and Biochemical Approach (Van Nostrand Reinhold, New York, NY) p. 397.

Stolerman, I.P., F. Rasuland and P.J. Shine, 1989, Trends in drug discrimination research analyzed with cross-indexed bibliography, 1984–1987, Psychopharmacology 98, 1.

Stolerman, I.P., E.A. Mariathasan and H.S. Garcha, 1991, Discriminative stimulus effects of drug mixtures in rats, in: Drug Discrimination: Applications to Drug Abuse Research, eds. R.A. Glennon, T.U.C. Järbe and J. Frankenheim (National Institute on Drug Abuse Research Monograph No. 116, US Dept. of Health and Human Services, Washington, DC) p. 277.

Swedberg, M.D.B. and T.U.C. Järbe, 1985, Drug discrimination procedures: roles of relative stimulus control in two-drug cases, Psychopharmacology 86, 444.

Swedberg, M.D.B. and T.U.C. Järbe, 1986, Drug discrimination procedures: differential characteristics of the drug A vs. drug B and the drug A vs. drug B vs. no drug cases, Psychopharmacology 90, 341.

Tallarida, R.J. and R.B. Murray, 1986, Manual of Pharmacologic Calculations with Computer Programs, 2nd edn. (Springer, New York, NY).

Woodward, J.J., R. Mansbach, F.I. Carroll and R.L. Balster, 1991, Cocaethylene inhibits dopamine uptake and produces cocaine-like actions in drug discrimination studies, Eur. J. Pharmacol. 197, 235.