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Perceptual Masking of the Chlordiazepoxide Discriminative Cue by Both Caffeine and Buspirone

DAVID V. GAUVIN,[1] JESSICA M. PEIRCE AND FRANK A. HOLLOWAY

Department of Psychiatry & Behavioral Sciences, University of Oklahoma Health Sciences Center, Oklahoma City, OK 73190

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GAUVIN, D. V., J. M. PEIRCE AND F. A. HOLLOWAY. *Perceptual masking of the chlordiazepoxide discriminative cue by both caffeine and buspirone.* PHARMACOL BIOCHEM BEHAV 47(1) 153–159, 1994.—Twelve male Sprague-Dawley rats were trained to discriminate between the interoceptive stimulus attributes of 5 mg/kg chlordiazepoxide (CDP) and saline in a two-lever operant task under a fixed-ratio 10 (FR-10) schedule of food reinforcement. Caffeine, buspirone, and Ro 15-1788 failed to engender complete generalization when tested in combination with saline. In drug interaction test sessions caffeine (56 mg/kg) blocked the discriminative stimulus properties of the training dose of CDP *and* shifted the CDP discriminative dose–response function to the right. This rightward shift in CDP discriminative function was paralleled by a concomitant downward shift in the rate-of-responding dose–response function. Drug interaction test sessions conducted with 3.2 mg/kg of buspirone in combination with various doses of CDP engendered a downward shift in both the discriminative and rate-of-responding dose–response functions. Because 3.2 mg/kg buspirone in combination with the training dose of CDP resulted in complete response rate suppression, additional combination tests were conducted with 3 mg/kg CDP, a dose which reliably engendered >90% CDP-appropriate responding, and various doses of buspirone. Similar to the CDP–caffeine interactions, buspirone blocked the cueing properties of 3 mg/kg CDP with a parallel reduction in response rates. Interaction test sessions conducted with Ro 15-1788 and CDP resulted in rightward shifts in *both* the discriminative and rate functions of CDP. We suggest that the interactions between CDP and both caffeine and buspirone resulted from the perceptual masking of the interoceptive (subjective) effects of CDP, whereas the interaction between Ro 15-1788 and CDP reflect pharmacological antagonism.

Drug discrimination Masking Chlordiazepoxide Caffeine Buspirone

IN 1989 Gauvin and Young (19,20,21) provided evidence suggesting that the discriminative stimulus attibutes of morphine could be blocked by the coadministration of amphetamine. This specific drug combination is commonly referred to as a "speedball," and these authors suggested that this infra-(effect-)additive interaction was best characterized as perceptual masking of the morphine discriminative (reference) stimulus by amphetamine (the masker) (cf. 21). We decided to further investigate the masking effect using a common benzodiazepine, chlordiazepoxide, as the reference stimulus.

Chlordiazepoxide is a water-soluble benzodiazepine chiefly prescribed in the treatment of anxiety. It has been repeatedly suggested that the benzodiazepines exert their anxiolytic effects through the GABA/chloride ionophore complex (14), but it is also generally accepted that all drugs have multiple effects. Therefore, it is not surprising to find reports that the benzodiazepines may have additional effects through the noradrenergic (50,51,55) and serotonergic (57) pathways.

Caffeine is a trimethylated xanthine. Its central nervous system (CNS) effects have been attributed to 1) an increase in norepinephrine excretion; 2) sensitization of central catecholamine postsynaptic receptors, including dopamine; 3) possible alteration of cyclic AMP and cyclic GMP; 4) modification of calcium's neuromodulating effects; 5) possible alterations in acetylcholine and serotonin turnover and receptor binding; and 6) inhibition of the CNS effects of adenosine or other endogenous purines and possible competitive antagonism of naturally occurring benzodiazepine receptors (46). Numerous reports have demonstrated the anxiogenic effects of caffeine (4,5,10,11,18,28,30,31,52,54). A number of other published reports have demonstrated infra-additive (antagonistic) interactions between other behavioral effects of caffeine and benzodiazepines (3,15,33,34,35,42,43,44,59,61,62).

[1] Requests for reprints should be addressed to David V. Gauvin, University of Oklahoma Health Sciences Center, Research Building, 302R, P.O. Box 26901, Oklahoma City, OK 73190-3000.

The putative anxiolytic, buspirone, is a lipophilic dibasic heterocyclic (49) believed to be a selective 5-HT_{1A} receptor agonist (9,13). Early in its development, buspirone was believed to be a possible antipsychotic agent because it displayed properties associated with dopaminergic antagonism (22,47), while α_2 adrenergic antagonism by buspirone has also been demonstrated (23,50,51). In spite of buspirone's putative anxiolytic effects an increasing number of reports demonstrate just the reverse: robust anxiogenic responses in both humans and animals administered the drug (1,2,12,17,29,32,36,37, 40,45,48,53). Interestingly, behavior indices of anxiety such as nervousness, jitteriness, and insomnia were statistically significant (at the $P < .01$ level) in both the German and United States preclinical trials of buspirone (16,39,58).

The purpose of the present study was to investigate the interaction between chlordiazepoxide, an anxiolytic agent reported to act through a selective transduction mechanism at the GABA/chloride ionophore complex, and two other drugs which have been repeatedly reported to produce an anxiogenic subjective profile, caffeine and buspirone, reported to act through multiple transduction sites. We have previously shown mutual antagonism of the discriminative attributes of both CDP and pentylenetetrazole in rats using a three-choice saline–CDP–pentylenetetrazole drug discrimination task (18). With respect to the current study, we predicted that the discriminative stimulus attributes of chlordiazepoxide, which are most probably based on its anxiolytic affective component (18), would be blocked or masked by two other anxiogenic agents, caffeine and buspirone, without reference to specific GABA/chloride channel mediation.

METHODS

Subjects

Twelve male Sprague–Dawley rats weighing 300–325 g were purchased from Dominion Laboratory (Omaha). Rats were individually housed in stainless-steel suspended cages and initially given ad lib access to food and water. Each rat was allowed a one-week acclimation period to their new environment prior to being placed on a food-deprivation schedule to reduce their body weights to 85% of their free feeding weights. The rats' body weights were initially maintained by restricted access to food, supplemental to that earned in the experimental session. The rats were allowed to gain 10 g per month to allow for normal growth and development. The animal colony room was maintained on a 12-h light/dark cycle (lights on at 0600), 20–22°C, and relative humidity of 60%.

Apparatus

Experimental sessions were conducted in four standard rat operant chambers (Lafayette Instruments, Lafayette, IN) equipped with two response levers, two stimulus lamps, a house lamp, and a pellet dispenser, housed within sound-attenuating cubicles equipped with exhaust fans to mask extraneous external noise. Experimental contingencies and data collection were controlled by a set of Commodore 64C microcomputer systems interfaced with the operant chambers (American Neuroscience Research Foundation, Yukon, OK).

Initial Training

Subjects were trained to the location and operation of the pellet dispenser and to operate both levers by the method of successive approximations. The illumination of the stimulus and house lamps signalled the beginning of the experimental sessions. Initially, each response on either lever was reinforced (one 45 mg food pellet, P.J. Noyes Inc., Lancaster, NH). Once each rat was trained to press the lever for food, it received either a saline (SAL) or 5-mg/kg chlordiazepoxide (CDP) injection IP 15 min prior to the session. The appropriate lever to obtain food was determined by the discriminative stimulus injection administered. Sessions ended after 100 food deliveries or 10 min, whichever occurred first. The number of responses required for reinforcement was gradually increased across successive sessions until 10 consecutive responses (fixed-ratio 10 [FR10]) were required. Once the contingencies for reinforcement were raised above FR1, responses on the inappropriate lever reset the ratio requirement on the appropriate lever. Training sessions were conducted five to seven days per week under a random injection schedule. Drug discrimination 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 >90% of the total session responses on the stimulus-appropriate lever for four consecutive days. Each rat was then required to meet these criteria for four consecutive sessions in a double alternation sequence (i.e., CDP-CDP-SAL-SAL).

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) 10 consecutive responses on either lever produced food. Training and test sessions alternated throughout the week (i.e., CDP train, SAL train, test, SAL train, test, CDP 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 CDP- and SAL-training day was achieved (i.e, one successful CDP-training day and one successful SAL-training day). Each test condition was tested only once in each of 10 trained rats. Drug tests were administered in a pseudorandomized fashion.

Drugs

All drugs were prepared daily and stored in light-attenuating bottles. Chlordiazepoxide hydrochloride, buspirone hydrochloride, and caffeine (anhydrous base) was purchased from Sigma Chemical Co. (St. Louis). Ro 15-1788/001 (Flumazenil, Lot# E123968) was generously donated by Dr. Peter Sorter, Hoffman-LaRoche Inc. (Nutley, NJ) and dissolved in saline with two drops of Tween-80. The bottle containing the Ro 15-1788 solution was suspended in a water-filled Cole-Parmer sonicator (Model 8850) until time of injection. Chlordiazepoxide and buspirone were weighed, expressed as the salt, and dissolved in normal sterile saline. Caffeine was expressed as the base, dissolved in normal saline, and gently warmed in a metabolic shaking water bath (45°C) to insure solubility. Equivalent volumes of saline were administered on saline-training days (1 ml/kg). All injections were administered IP. Caffeine was administered at various time points prior to the test sessions as detailed in the Results section. Chlordiazepoxide, buspirone, and Ro 15-1788 were administered 15 min prior to test sessions. Drug interaction tests were conducted with the specific doses of 56 mg/kg caffeine and 3.2 mg/kg buspirone because these same doses engendered >90% pentylenetetrazole-appropriate responding when tested in our previous three-choice drug discrimination task

using 5 mg/kg CDP, saline, and 15 mg/kg pentylenetetrazole [(18), buspirone data unpublished observations].

Data Analysis

The data are presented as the group mean percentage of the total session responses emitted on the CDP-appropriate lever. We assume this metric monotonically maps the degree of similarity between test and training drugs. As we have previously suggested, partial generalization to a training drug stimulus reflects an accurate assessment of the relative qualitative and/or quantitative similarities between the test drug and the training drug (24,25). A test condition was considered to produce "complete generalization" (i.e., discriminative effects similar to those of the training dose of CDP) if at least 90% of the total session responses were emitted on the CDP-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 or drug-associated state which appears to be independent of the distribution of response choice on the two levers. Group average ED_{50}s were estimated by linear regression analyses of individual data. 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 (26).

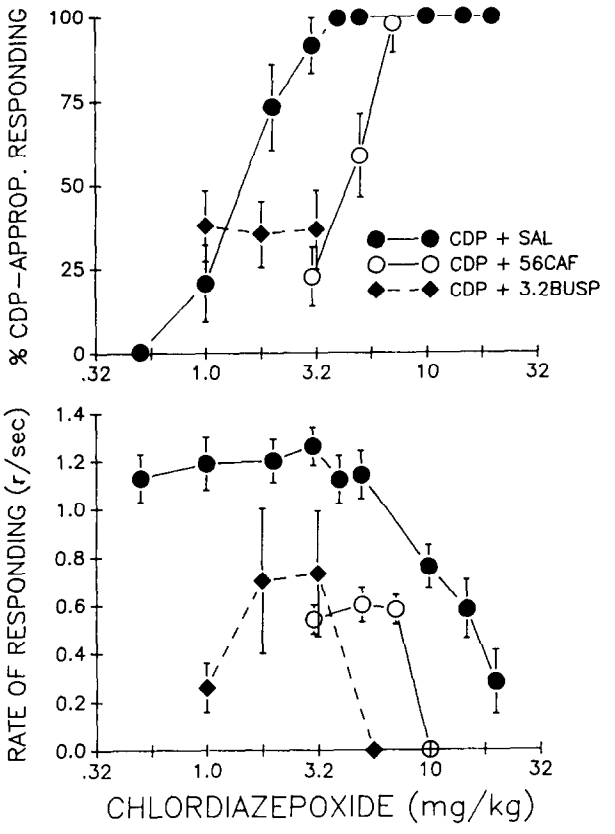

FIG. 1. Dose-related effects of CDP in 12 rats trained to discriminate between 5 mg/kg CDP and saline (●). The group mean (±SE) percentage of total session responses emitted on the CDP-appropriate lever during 10 min reinforced test sessions are shown in the top panel. The group mean (±SE) rate-of-responding expressed in responses per second are shown in the bottom panel. The blockade of the stimulus attributes of CDP by both caffeine (○) and buspirone (♦) are also plotted. Caffeine pretreatments (N = 10) shifted the CDP response choice function (○; top panel) to the right *and* the CDP response rate function downward (bottom panel). Concomitant administration of buspirone and CDP (N = 8) shifted both the response choice and rate functions downward.

TABLE 1

CAFFEINE + SALINE DOSE-RESPONSE

Caffeine Dose (mg/kg)	% CDP-Appropriate Responding	Rates-of-Responding
3.2	0	1.22 ± 0.13
10	0.17 ± 0.07	1.23 ± 0.11
17.8	0.34 ± 0.32	0.77 ± 0.11
32	0	0.72 ± 0.1
56	29.4 ± 2.1	0.65 ± 0.1

RESULTS

All animals met the training criteria for stimulus control by 5 mg/kg CDP and saline within a range of 24 to 42 training sessions. The CDP stimulus generalization function is depicted in Fig. 1 (described below). Tables 1 and 2 show the data from test sessions conducted with caffeine administered with saline or CDP, respectively, in 10 trained rats. Table 1 shows that caffeine administered 45 min prior to test sessions engendered partial generalization between 56 mg/kg caffeine and the training dose of CDP (Duncan's test: 56 mg/kg vs. SAL and 56 mg/kg vs. 5 mg/kg CDP; $P < .05$). Although rates of responding at the 56 mg/kg caffeine dose appeared to be at a high enough rate to warrant testing higher doses, previous work in this laboratory has repeatedly demonstrated that a one-eighth common log unit increment upward in the caffeine dose (~75 mg/kg) produces behavioral toxicity in this strain of rats, defined as severe rhinitis, lacrimation, and "head-bobbing" stereotypies, which totally disrupted operant performance. Similar behavioral indicators of toxicity were not present prior to, during, or after test sessions conducted with the 56 mg/kg caffeine dose. Therefore, higher caffeine doses were not tested. Table 2 shows the time-response functions resulting from fixing the test drug combination at 5 mg/kg CDP *plus* 56 mg/kg caffeine. CDP was always administered 15 min prior to the test sessions, and caffeine was administered at the various (listed) pretreatment time intervals. The largest decrement in the percentage of total session responses emitted on the CDP-appropriate lever was engendered at a

TABLE 2

CAFFEINE MASKING TIME-RESPONSE FUNCTION—5 mg/kg CDP (15 MIN PRETREATMENT) PLUS 56 mg/kg CAF (VARYING TIME PRETREATMENT)

56 mg/kg CAF Pretreatment Times	CDP-Appropriate Responding	Rate-of-Responding
15	74.9 ± 12.5	0.72 ± 0.07
30	69.5 ± 12.4	0.44 ± 0.06
45	58.8 ± 12.4	0.63 ± 0.07
60	83.6 ± 7.7	0.60 ± 0.07
75	81.6 ± 10.7	0.53 ± 0.06
90	88.6 ± 9.7	0.61 ± 0.10
120	85.2 ± 9.0	0.54 ± 0.10

TABLE 3

BUSPIRONE DOSE-RESPONSE FUNCTION

Buspirone Dose (mg/kg)	% CDP-Appropriate Responding	Rate-of-Responding
1.0	0.05 ± 0.03	1.0 ± 0.11
3.2	32.3 ± 12.6	0.28 ± 0.10
10	(< 10 responses)	0

caffeine pretreatment interval of 45 min. Rates of responding were relatively stable across the full testing time period. Therefore, the caffeine pretreatment interval of 45 min was selected for the completion of the CDP plus caffeine interaction test sessions (see below and Fig. 1).

Tables 3 and 4 show the data from test sessions conducted with buspirone in combination with saline or CDP, respectively. Buspirone failed to completely generalize with the 5 mg/kg CDP training stimulus within a narrow test dose range (1.0 to 10 mg/kg) that completely suppressed rates-of-responding (Table 3). Test sessions with the training dose of CDP in combination with even smaller doses of buspirone resulted in total rate suppression (0.32 and 0.56 mg/kg, data not shown). Therefore, additional buspirone interaction tests were conducted by selecting a lower dose of CDP (3 mg/kg) which, when administered with saline, repeatedly engendered >90% CDP-appropriate responding. Combining 3 mg/kg CDP with various doses of buspirone produced a biphasic shift in both the percentage of total session responses emitted on the CDP-appropriate lever and the rate-of-responding (Table 4). Paradoxically, the combination of 3.2 mg/kg buspirone with 3 mg/kg CDP resulted in the greatest reduction in the response choice measure and the lowest decrease in the response rate measure. Interestingly, when tested in combination with saline, the 3.2 mg/kg buspirone dose engendered partial generalization (20% < CDP-appropriate responding < 80%) with the 5 mg/kg CDP training stimulus (Table 3).

Figure 1 presents the data from test sessions conducted with various doses of CDP in combination with saline, 56 mg/kg caffeine, or 3.2 mg/kg buspirone. CDP engendered a dose-dependent graded increase in the percentage of total session responses emitted on the CDP-appropriate lever and a concomitant biphasic change in the rats' rate-of-responding. The ED_{50} or threshold dose for the percentage of total session responses emitted on the CDP-appropriate lever was 1.46

TABLE 4

BUSPIRONE MASKING OF 3 mg/kg CDP–3 mg/kg CDP (15 MIN PRETREATMENT) PLUS VARIOUS DOSES OF BUSPIRONE (15 MIN PRETREATMENT)

Buspirone Dose (mg/kg)	%CDP-Appropriate Responding	Rate-of-Responding
0 (saline)	91.5 ± 8.2	1.26 ± 0.08
1.0	83.9 ± 10.0	0.57 ± 0.12
1.8	68.3 ± 14.7	0.50 ± 0.14
3.2	36.7 ± 11.7	0.73 ± 0.26
5.6	57.0 ± 11.3	0.20 ± 0.16
10	(< 10 responses)	0.10 ± 0.1
17.8	(< 10 responses)	0

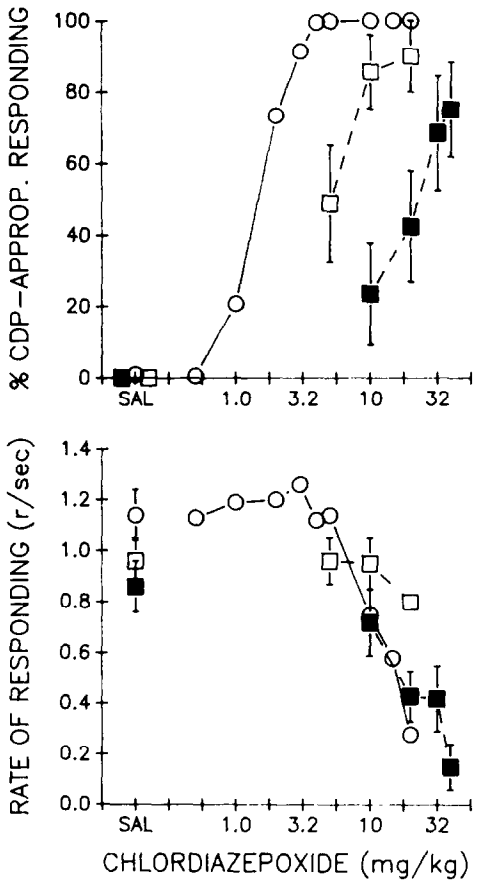

FIG. 2. The pharmacological antagonistic effects of 3.2 mg/kg (□) and 10 mg/kg (■) Ro 15-1788 on the behavioral effects of CDP (○). In contrast to the behavioral effects of caffeine–CDP and buspirone–CDP interactions, Ro 15-1788 shifted both the response choice and response rate functions to the right. Both test doses of Ro 15-1788 failed to engender significant CDP-appropriate responding when tested in combination with saline; □ and ■ above SAL on the abscissae. Details as described in Fig. 1; each point represents the mean of 10 subjects.

(±0.10) mg/kg and 17.1 (±0.22) mg/kg for the CDP-associated response rate suppression. Figure 1 also demonstrates the perceptual blockade of the CDP training stimulus, administered 15 min prior to the test sessions, by the drug masking stimulus, 56 mg/kg caffeine, administered 45 min prior to the test sessions (i.e., 30 min prior to CDP injection). The addition of 56 mg/kg caffeine resulted in approximately a one-half log unit shift to the right in the CDP dose-response generalization function, which corresponded to an approximate 2.5-fold increase in the ED_{50}. In contrast to the rightward shifts in the stimulus generalization function, the rate-of-responding dose-response function demonstrated a downward shift to the left.

Drug interaction test sessions were also conducted after the concomitant administration of CDP and 3.2 mg/kg buspirone (Fig. 1). Both the discriminative and rate-of-responding dose-response functions were shifted downward. However, as can be seen in Table 3, buspirone, when administered in combination with saline, produced a significant response-rate decrement within a narrow dose range (one-half log unit dose incre-

ment), which might explain why the blockade of the CDP training stimulus by 3.2 mg/kg buspirone could not be surmounted by increasing the test dose of CDP. It should be noted that the mean percentage of total session responses emitted on the CDP-appropriate lever during buspirone–CDP interaction test sessions did not significantly differ from the mean percentage engendered by test sessions conducted with 3.2 mg/kg buspirone in combination with saline.

Figure 2 shows the data resulting from drug antagonism studies conducted with CDP in combination with 3.2 and 10 mg/kg Ro 15-1788. In contrast to the behavioral indices of perceptual masking of the CDP stimulus by caffeine and buspirone, both doses of the pharmacological antagonist Ro 15-1788 shifted the CDP dose–response functions for the response choice *and* response rate measures to the right.

DISCUSSION

The results of the present study demonstrate that the discriminative stimulus properties of CDP can be blocked by concomitant administration of 1) caffeine, 2) buspirone, and 3) Ro 15-1788. The blockade of CDP by caffeine and buspirone was restricted to the perceptual response measure only—that is, to the mean percentage of total session responses emitted on the CDP-appropriate lever. The caffeine–CDP interaction tests demonstrated a surmountable blockade of the CDP stimulus by caffeine. In contrast, buspirone–CDP interaction tests demonstrated that the mean percentage of total session responses emitted on the CDP-appropriate lever did not differ from the mean percentage engendered by 3.2 mg/kg buspirone when adminstered with saline. We believe that the discriminative attributes of CDP are primarily based on the anxiolytic dimensional aspects of the drug (18). Caffeine and buspirone have been shown to increase the self-report of anxiety symptoms in humans (see the introductory section) and, analogously, have engendered anxiogenic-like responses in animals within behavioral assays believed to be sensitive to the interoceptive or subjective effects of drug states (cf. 1,2). The data from the present study support our view that the anxiolytic attributes of CDP were masked by the anxiogenic attributes of both caffeine and buspirone. In contrast to these latter interactions within the subjective domain of CDP, caffeine and buspirone shifted the rate-of-responding dose–response functions downward and to the left.

Browne and colleagues have previously reported blockade of the discriminative stimulus attributes of 1) 3.2 mg/kg PCP by N^6-cyclohexyladenosine, L-phenylisopropyladenosine, D-phenylisopropyladenosine, haloperidol, diazepam, vasopressin, doxapram, and naloxone (8); 2) 3.2 mg/kg THC by clonidine and physostigmine (7); and 3) 3.2 mg/kg yohimbine by diazepam, clonazepam, flurazepam, chlordiazepoxide, meprobamate, phenobarbital, alprazolam, prazosin, and haloperidol (6). Negus et al. (38) have also reported blockade of the discriminative stimulus attributes of the kappa opioid agonist U50,488 by three mu opioid agonists (morphine, fentanyl, and buprenorphine) *and* the blockade of the discriminative stimulus attributes of morphine by the kappa opioid agonist bremazocine. Additionally, Gauvin and Young (19,20,21) have contrasted the blockade of the discriminative stimulus properties of morphine by both amphetamine and naltrexone. All of these studies have reported data similar to those of the present interactions between CDP and the anxiogenic compounds caffeine and buspirone in two respects: 1) blockade of the discriminative stimulus attibutes of one drug by another pharmacological agent outside the training drug receptor class, and (2) when reported, a coinciding diminution of response rates. We suggest that the results of the present CDP–caffeine and CDP–buspirone interactions, and those of the other studies (cited above), may reflect a similar interactive phenomenon referred to in the exteroceptive stimulus literature as "perceptual masking" (27,63).

The concept of perceptual masking was first introduced by Wegel and Lane (60), who quantitatively demonstrated the masking of pure tones by pure tones in the auditory system (41,56). The definition of "masking" is strictly operational and does not imply any specific physiological process (63). The masking effect is operationally defined as an attenuation, decrement, or occlusion of the stimulus properties of the training drug (reference stimulus) by the coadministration of another drug (masker) which is not the pharmacological antagonist of the training drug stimulus. With respect to masking phenomena from other sensory systems, the reduction or attenuation in the reference stimulus does not necessarily require the total blockade of that stimulus by the masker stimulus. The partial blockade of the discriminative stimulus properties of CDP in the present study supports the sensory interpretation of drug discrimination in that drugs producing similar sensory effects may mask one another more effectively than drugs that produce markedly dissimilar effects. In the present study, 3.2 mg/kg buspirone engendered the largest increase in the percentage of total session responses that were emitted on the CDP-appropriate lever and produced the largest decrement in the response-choice measure when administered in combination with 5 mg/kg CDP.

The interactive effects between CDP and the hypothesized anxiogenic compounds caffeine and buspirone, which we refer to as perceptual masking, differ from the demonstrated antagonistic interaction between CDP and the pharmacological benzodiazepine antagonist Ro 15-1788. Ro 15-1788 produced a blockade of both dependent measures of CDP-associated effects.

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