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Blockade of Latent Inhibition Following Pharmacological Increase or Decrease of $GABA_A$ Transmission

LAURENT LACROIX, SIMONA SPINELLI, LAUS M. BROERSEN[1] AND JORAM FELDON

Behavioural Neurobiology Laboratory, The Swiss Federal Institute of Technology Zurich, Schorenstrasse 16, 8603 Schwerzenbach, Switzerland

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LACROIX, L., S. SPINELLI, L. M. BROERSEN AND J. FELDON. *Blockade of latent inhibition following pharmacological increase and decrease of $GABA_A$ transmission*. PHARMACOL BIOCHEM BEHAV **66**(4) 893–901, 2000.—The latent inhibition (LI) phenomenon refers to the retardation in learning of an association between a stimulus and a consequence if that stimulus had been previously experienced without consequence. An earlier study demonstrated that the benzodiazepine receptor agonist chlordiazepoxide (CDP), when administered before the phase of preexposure to the to-be-conditioned stimulus, impaired animals' ability to develop LI. The present study was designed to investigate the effect of the anxiogenic drugs pentylenetetrazole (PTZ) and the benzodiazepine partial inverse agonist Ro15-4513 on LI. Both anxiogenics, in contrast to CDP, are known for their GABA inhibitory action. The effects produced by the combined administration of a GABAergic function facilitator and inhibitor (CDP/PTZ and CDP/Ro15-4513) were also investigated. Both anxiogenic drugs led to an attenuation of LI, and, similarly to CDP, this attenuation was exclusively due to their administration prior to the preexposure stage of the experiment. However, this effect was abolished when anxiolytic and anxiogenic drugs were administered together, suggesting a pharmacological rather than behavioral summation of effects. These data also demonstrate the bidirectional GABAergic modulation of the LI phenomenon: both increased and decreased $GABA_A$ receptor activation led to reduced LI, thereby suggesting that an optimal receptor activation level is necessary for the normal establishment of LI. © 2000 Elsevier Science Inc.

Latent inhibition Attention $GABA_A$ receptors Ro15-4513 Pentylenetetrazole Chlordiazepoxide Rat

THE latent inhibition (LI) phenomenon has been described as the retardation of an association between a stimulus and reinforcement, if that stimulus has been previously repeatedly experienced without consequences (47). It is considered as an index of the capacity of organisms to ignore irrelevant stimuli, and has been demonstrated in a variety of mammalian species, including humans, in classical and instrumental conditioning procedures (44,45).

Investigations on cognitive deficits in schizophrenia have established that LI is disrupted in some subsets of schizophrenic patients [(2,18,25,27,68); but see (65)], as well as in normal humans either with high scores on questionnaires measuring schizotypy or treated with the psychotomimetic dopamine releaser amphetamine (3,14,26,46,67). Similar deficits as reported for schizophrenic patients were observed in rats treated with amphetamine [(62,74–77); for review, see (23)], and amphetamine-induced deficits were reversed by neuroleptic drugs (62,70,78). The similarities between LI data in humans and rats following pharmacological manipulations converged to support the contention that disruption of LI in rats can be used to model the failure of schizophrenics to ignore irrelevant stimuli (21,22,48,59,62,72,73). Although extensive drug studies in rats have stressed the importance of the mesolimbic dopaminergic system in modulating LI, one study has demonstrated that the benzodiazepine (BZD) receptor agonist chlordiazepoxide (CDP) impaired animals'

[1]Present address: Graduate School Neurosciences Amsterdam, Netherlands Institute for Brain Research, Meibergdreef 33, 1105 AZ Amsterdam-ZO, The Netherlands.

Requests for reprints should be addressed to J. Feldon, Behavioural Neurobiology Laboratory, The Swiss Federal Institute of Technology Zurich, Schorenstrasse 16, Postfach, CH-8603, Schwerzenbach, Switzerland.

ability to develop LI (20). CDP disrupted LI when administered prior to the preexposure stage of the experiment. This result seemed to indicate that CDP was involved in the disruption of the acquisition of LI, in line with studies that have associated CDP with a deficit in attentional processes (51).

Because the effects of BZD agonists are considered to be a consequence of their facilitation of GABAergic function (40,64), the role played by CDP in LI contributed to the hypothesis that a GABAergic mechanism was involved in the establishment of LI (23). Interestingly, dysfunction of the GABAergic system has been associated with psychoses, including schizophrenia (5,53,66). Evidence supporting the hypothesis of GABA receptor-mediated hyperactivity as an important component of schizophrenic symptoms is indirect. Increased GABAergic activity, either directly via a $GABA_A$ agonist, such as muscimol, or indirectly via inhibition of enzymes essential for the metabolism of GABA, can produce psychotomimetic effects (5,54,58,66,71). Likewise, BZD agonists at the BZD site of the $GABA_A$ receptor complex produce schizophrenic symptoms, whereas partial inverse agonists reduce schizophrenic symptoms, supporting the view that hyperactivity of GABAergic pathways may be responsible for symptoms associated with this disorder (28,63).

Against this background, the present study was undertaken to extend our knowledge of the GABAergic influence on LI. More specifically, an attempt was made to further characterize GABAergic modulation of LI by examining the effect on LI of compounds that inhibit GABAergic function. As an initial step, we investigated the effect of the anxiogenic drug pentylenetetrazole (PTZ). In contrast to CDP, PTZ is known to be a picrotoxin-like noncompetitive GABA antagonist that inhibits GABAergic function by reducing the function of the GABA-coupled chloride channel (1,12,50,57). PTZ, also known as metrazole, has been used in the treatment of schizophrenia and affective psychoses (38,52). Based on the effects of CDP on LI, and the opposite pharmacological effects displayed by CDP and PTZ on GABAergic function, a possible enhancement of LI was expected after PTZ administration.

In Experiment 1, we examined the effect of PTZ on LI in a dose–response study using three different subconvulsive doses with administration prior to the preexposure stage, the time at which CDP must be administered so as to have an effect on LI (20). Because PTZ showed an effect on LI only at the highest dose, in Experiment 2 this dose was used to delineate the effects of PTZ in each of the critical stages of the LI paradigm, namely, preexposure and conditioning. Thus, PTZ, at a dose of 20 mg/kg, was administered in a factorial crossover design. Contrary to our expectation, PTZ administration led to a similar effect as CDP, i.e., (a) PTZ affected LI only when administered in the preexposure stage of the experiment, and (b) PTZ blocked LI. On the basis of these results, in all subsequent experiments, drug was administered in the preexposure stage only. Moreover, to see whether the drugs would show additive or interactive effects, in Experiment 3 we examined the effect of CDP and PTZ in a coadministration design.

BZD receptors are known to exert a bidirectional modulation of the $GABA_A$ receptor complex. Thus, upon binding to BZD receptors, inverse agonists have opposite functional effects to those of classical agonists and thus decrease the action of $GABA_A$ at GABA receptors. The fact that both agonists and inverse agonists are blocked by BZD receptor antagonists (i.e., compounds with no or negligible intrinsic activity, such as flumazenil) indicates that they act through the same receptor (33). Therefore, to further assess the role played by the BZD receptors in LI, we also examined the effect of the imidazobenzodiazepine partial inverse agonist Ro15-4513. The use of a partial inverse agonist was based on the particular property of this novel ligand to mimic the profile of action of full inverse agonists but with reduced unwanted side effects (17,29,30,69). In contrast to CDP, Ro15-4513 negatively modulates the effects of GABA on chloride conductance by decreasing the time that ion channels spend in the open configuration (40,64). Thus, Ro15-4513 was expected to show effects similar to those observed with PTZ. As for PTZ, a dose–response study based on data from the literature was carried out in Experiment 4 to determine at which dose Ro15-4513 affected LI (8,36). Subsequently, the most effective dose was used in Experiment 5 to assess the effects on LI of the concomitant administration of CDP and Ro15-4513.

METHOD

Animals

Male Wistar rats (Zur:WIST(HanIbm), Institute of Toxicology, Schwerzenbach, Switzerland) were approximately 3 months old at the start of the experiment. Throughout the experiment the animals were individually housed in Macrolon type III cages (48 × 27 × 20 cm) under conditions of controlled temperature (21 ± 1°C) and humidity (55 ± 5%) on a 12-h light/12-h dark schedule (lights on 1900–0700 h). Food (Nafag 9431, Eberle Nafag AG, Gossau, CH) was available ad lib in the home cages throughout the experiment. All the experiments were carried out in accordance with the Swiss federal regulations for animal experimentation.

Drugs

Pentylenetetrazole (PTZ) (Sigma, Switzerland) was dissolved in 0.9% saline (VEH1) and administered subcutaneously 10 min prior to the start of the sessions. Depending on the experimental design (see below), the following subconvulsant doses were used: 5 mg/kg (PTZ5), 10 mg/kg (PTZ10), or 20 mg/kg (PTZ20). HCl-chlordiazepoxide (CDP) (RBI, USA) was dissolved in 0.9% saline and administered intraperitoneally 20 min prior to the start of the session at a 5 mg/kg dose. Ro15-4513 (Hoffmann–LaRoche Pharm., Switzerland) was prepared as an emulsion in 0.3% Tween 80 vehicle saline solution (VEH2) (Sigma) and administered intraperitoneally 15 min prior to the start of the session. Depending on the experimental design the following doses were used: 3 mg/kg/2 ml (RO3), 6 mg/kg/2 ml (RO6), or 9 mg/kg/2 ml (RO9).

Drug solutions were freshly prepared before each daily administration and thoroughly mixed before every injection.

Apparatus and Procedure

The LI apparatus consisted of four Coulbourn Instruments test cages (Model E10-10), each set in a ventilated sound-attenuating Coulbourn Instruments isolation cubicle (Model E10-20). A drinking bottle with a tube opening of 3-mm diameter could be inserted into the chamber through a 3 × 4-cm hole located in the center of the right wall of the chamber, 1.5 cm above the grid floor. Licks were detected by a Coulbourn Instruments infrared optical lickometer (Model E24-01). Activity in the chambers was detected by an infrared activity monitor (model E24-61) mounted on the ceiling. It was operated in the "movement unit" mode, in which a 10-ms pulse is produced each time the monitor detects a change in the animal's infrared heat pattern. This results in a series of

pulses ("activity counts") at a frequency proportional to the amount of movement made by the animal. Scrambled shocks (US) were delivered through the cage floor from a Coulbourn Instruments shocker (Model E13-14) and scanner (Model E13-13). The preexposed, to-be-conditioned stimulus (CS) was generated from a 28-V, 40-mA house light located on the right wall of the chamber 26 cm above the grid floor. The experiment was conducted in a dark chamber.

Prior to the beginning of the experiments, rats were handled for 6 days for about 2 min each day, and were simultaneously placed on a 23-h water restriction schedule, which continued throughout the LI experiment. Water in the test apparatus was given in addition to the daily ration given during 1 h in the home cages.

LI was assessed using a CER procedure consisting of baseline, preexposure, conditioning, rebaseline, and test stages. An on-baseline procedure was used (allowing the rats to drink during the preexposure and conditioning stages). Rats were run in squads of four.

Baseline lick training. On each of 5 days, each rat was placed into the experimental chamber in darkness and allowed to drink from the water bottle for 20 min. The rat was then returned to its home cage and allowed access to water for 60 min, at least 30 min following the end of the session.

Preexposure. Each rat was placed in the experimental chamber. The CS was a 5-s steady houselight. Preexposed (PE) animals received 40 presentations of the CS with a fixed interstimulus interval (ISI) of 25 s. The nonpreexposed (NPE) animals were confined to the chamber for the same duration without receiving the CS.

Conditioning. Each rat received two CS-shock pairings, 5 and 10 min after the start of the session. Light parameters were identical to those used in preexposure. The 1-s, 0.5-mA shock immediately followed light termination. After the last pairing, rats were left in the experimental chamber for an additional 5 min.

Rebaseline. Each animal was given a drinking session as in baseline.

Test. Each animal was placed into the chamber with the houselight off and allowed to drink from the bottle. The light (CS) was presented to each of the four rats after it completed 275 licks, and lasted for 15 min.

Preexposure, conditioning, rebaseline, and test sessions were given 24 h apart.

Data Analysis

The total number of activity counts and total number of licks were recorded after drug administration during the preexposure stage in all experiments. The same measures were also recorded after drug administration during the conditioning stage in Experiment 2. During the test the time to complete licks 251–275 or the A-period (25 licks prior to CS) and the time required to complete licks 276–300 or the B-period (25 licks after CS onset) were recorded.

LI was assessed by a suppression ratio (SR) calculated as follows: A-period / (A-period + B-period). A higher SR reflects a lower suppression of drinking. LI consists of lower suppression of drinking in the PE compared with the NPE rats.

Data were analyzed using analysis of variance (ANOVA). Further analyses of significant main effects were conducted using Fisher's PLSD post hoc tests. Contrast analysis of the mean comparisons in the analysis of variance (61) was applied to assess the difference between the PE and NPE condition (LI phenomenon) within a drug administration group. Statistical significance was set at a probability level of $p < 0.05$ for all tests.

Experimental Design

Eighty naive rats participated in all LI experiments except for Experiment 5, which included 120 rats.

In Experiment 1, rats were allocated to eight groups in a 2×4 factorial design consisting of the main factors preexposure (NPE, PE) and drug administration in preexposure (VEH1, PTZ5, PTZ10, or PTZ20).

In Experiment 2, rats were allocated to eight groups in a $2 \times 2 \times 2$ factorial design consisting of the main factors preexposure (NPE, PE), drug administration in the preexposure stage (VEH1, PTZ20) and drug administration in the conditioning stage (VEH1, PTZ20). Drugs were administered in a factorial crossover design, i.e., groups that were drug treated (PTZ20) or vehicle treated (VEH1) during the preexposure stage were subdivided during the conditioning stage into two subgroups, one subgroup receiving the same treatment (PTZ20-PTZ20 or VEH1-VEH1) and the other being submitted to the alternate condition (PTZ20-VEH1 or VEH1-PTZ20).

In Experiment 3, rats were allocated to eight groups in a $2 \times 2 \times 2$ factorial design consisting of the main factors preexposure (NPE, PE), CDP drug administration in preexposure (VEH1, CDP), and PTZ drug administration in preexposure (VEH1, PTZ20).

In Experiment 4, rats were allocated to eight groups in a 2×4 factorial design consisting of the main factors preexposure (NPE, PE) and drug administration in preexposure (VEH2, RO3, RO6, or RO9).

In Experiment 5, rats were allocated to eight groups in a $2 \times 2 \times 2$ factorial design consisting of the main factors preexposure (NPE, PE), CDP drug administration in preexposure (VEH2, CDP), and Ro15-4513 drug administration in preexposure (VEH2, RO6).

RESULTS

Experiment 1: Effects of 5.0, 10.0, and 20.0 mg/kg PTZ Administered in the Preexposure Stage on LI

Activity during the preexposure session. Subjects treated with 20 mg/kg PTZ were less active (328 ± 62) than those treated with 10 mg/kg PTZ (631 ± 78), 5 mg/kg PTZ (918 ± 106), or vehicle (822 ± 86) during the preexposure session. This was supported by the significant main effect of drug, $F(3, 72) = 10.38$, $p < 0.001$. Further post hoc analysis indicated that the subjects given the 20-mg/kg dose were less active than all the other groups ($p < 0.01$). The subjects given the 10-mg/kg dose were less active than those given the 5-mg/kg dose ($p < 0.05$), which did not differ from the vehicle group. In addition, preexposed subjects were more active (786 ± 72) than the nonpreexposed subjects (564 ± 60). This was supported by the significant effect of preexposure, $F(1, 72) = 7.55$, $p < 0.01$. No interaction between the factors of preexposure and PTZ dose could be detected.

Licking during the preexposure session: total licks. There were no significant main effects or interactions. The overall mean was 1683 ± 63 licks.

Test session: time to complete 25 licks prior to stimulus presentation. None of the groups differed in the time to complete 25 licks prior to the presentation of the stimulus (A-period). The overall mean was 5 ± 0.5 s.

Test session: suppression ratios. Figure 1 presents the suppression ratios of the PE and NPE groups in each of the four drug conditions (VEH1, PTZ5, PTZ10, and PTZ20). LI was evident for all groups except for the group receiving the 20-mg PTZ dose. The 4×2 ANOVA revealed only a signifi-

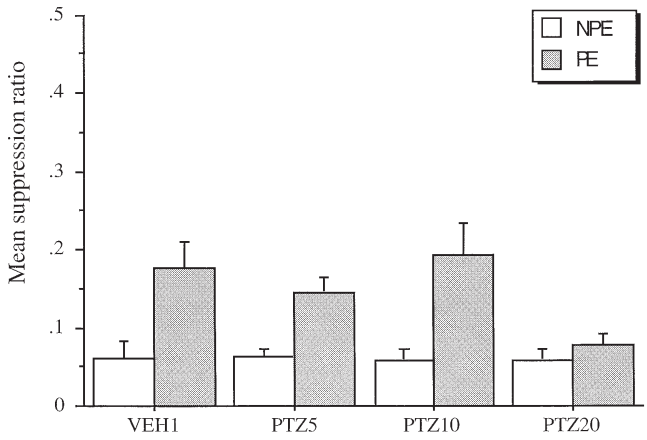

FIG. 1. Suppression ratios (mean ± SEM) of the preexposed (PE) and nonpreexposed (NPE) groups under four drug doses of pentylenetetrazole administered only during the preexposure stage of the experiment: saline (VEH1), 5.0 (PTZ5), 10.0 (PTZ10), and 20.0 mg/kg (PTZ20).

cant effect of preexposure, $F(1, 72) = 24.62$, $p < 0.001$. A separate 2 × 2 ANOVA comparing the vehicle-treated subjects with subjects receiving 20 mg PTZ revealed a significant drug × preexposure interaction, $F(1, 36) = 4.2$, $p < 0.05$, indicating a significant reduction of LI in the PTZ20 group compared with the VEH1 group.

Experiment 2: Effects of 20 mg/kg PTZ Administered in the Preexposure and/or Conditioning Stage on LI

Activity during the preexposure session. PTZ20-treated animals were less active (346 ± 31) than vehicle-treated animals (731 ± 38) during the preexposure session. This was supported by the significant main effect of drug, $F(1, 60) = 67.95$, $p < 0.001$. In addition, PE subjects were more active (604 ± 52) than the NPE subjects (472 ± 43). This was supported by the significant main effect of preexposure, $F(1, 60) = 7.97$, $p < 0.007$. No interaction between the factors of drug and preexposure could be detected.

Licking during the preexposure session: total licks. PTZ20-treated animals drank less (853 ± 89 licks) than the vehicle-treated animals (1401 ± 85 licks). This was supported by the significant main effect of drug, $F(1, 60) = 19.16$, $p < 0.001$.

Activity during the conditioning session. Animals treated with PTZ20 in the conditioning stage were less active (312 ± 33) than animals treated with vehicle in the conditioning stage (556 ± 27). This was supported by the significant main effect of drug in conditioning, $F(1, 56) = 37.54$, $p < 0.001$. In contrast, animals treated with PTZ during the preexposure stage were more active (489 ± 32) during conditioning than those treated with vehicle during preexposure (387 ± 47). This was supported by the significant main effect of drug in preexposure, $F(1, 56) = 6.07$, $p < 0.02$. The latter result, however, was primarily due to the fact that the reduction in activity seen in animals injected with PTZ in the conditioning stage, compared to animals injected with vehicle in the conditioning stage, was much smaller in the animals that had experienced PTZ20 already during preexposure (PTZ20-PTZ20 = 408 ± 41, PTZ20-VEH1 = 570 ± 42) than in those animals that had experienced vehicle during preexposure (VEH1-PTZ20 = 229 ± 30, VEH1-VEH1 = 546 ± 39). This was supported by the significant interaction of drug in preexposure × drug in conditioning, $F(1, 56) = 4.07$, $p < 0.05$.

Licking during the conditioning session: total licks. As with activity, animals treated with PTZ20 during conditioning drank less (437 ± 54 licks) than animals treated with vehicle during conditioning (776 ± 64 licks). This was supported by the significant main effect of drug in conditioning, $F(1, 56) = 15.75$, $p < 0.001$. Furthermore, animals that were treated with PTZ20 during the preexposure stage drank more (700 ± 61 licks) during conditioning than animals treated with vehicle during preexposure (525 ± 69 licks). This was supported by the significant main effect of drug in preexposure, $F(1, 56) = 4.19$, $p < 0.05$.

Test session: time to complete 25 licks prior to stimulus presentation. The eight groups did not differ in the time they required to complete 25 licks just prior to the presentation of the stimulus (A-period). The overall mean was 13 ± 3 s.

Test session: suppression ratios. Figure 2 depicts the suppression ratios of the PE and NPE groups in each of the four drug conditions: vehicle in preexposure and conditioning (VEH1-VEH1), PTZ20 in preexposure and vehicle in conditioning (PTZ20-VEH1), vehicle in preexposure and PTZ20 in conditioning (VEH1-PTZ20), and PTZ in both preexposure and conditioning (PTZ20-PTZ20). LI was evident only in groups injected with vehicle in the preexposure stage. The groups injected with PTZ20 in the preexposure stage demonstrated no LI at all. Drug in the conditioning stage had no effect whatsoever. These results were supported by the significant main effect of preexposure, $F(1, 56) = 13.11$, $p < 0.001$, by the significant main effect of drug in preexposure, $F(1, 56) = 5.24$, $p < 0.03$, as well as by the significant interaction of drug in preexposure × preexposure, $F(1, 56) = 8.71$, $p < 0.005$. No other main effects or interactions were significant.

Experiment 3: Effects of 5 mg/kg CDP and/or 20 mg/kg PTZ Administered in the Preexposure Stage on LI

Activity during the preexposure session. Activity counts were significantly reduced both by CDP (562 ± 72) and by PTZ20 (439 ± 51) compared with VEH1 (1074 ± 71). The coadministration of CDP and PTZ20 attenuated both reductions (776 ±

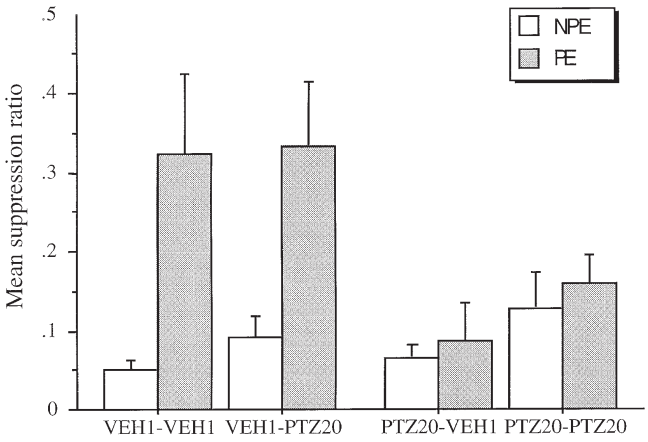

FIG. 2. Suppression ratios (mean ± SEM) of the preexposed (PE) and nonpreexposed (NPE) groups treated with 20.0 mg/kg pentylenetetrazole in preexposure and conditioning in a factorial crossover design yielding four drug conditions: saline-saline (VEH1-VEH1), saline-PTZ (VEH1-PTZ20), PTZ-saline (PTZ20-VEH1), and PTZ-PTZ (PTZ20-PTZ20).

73), although the difference between CDP + PTZ20 and VEH1 was still significant ($p < 0.01$). These results were supported by the significant main effect of PTZ20, $F(1, 72) = 9.47$, $p < 0.01$, as well as the significant interaction of CDP × PTZ20, $F(1, 72) = 40.10$, $p < 0.001$, and the contrast analysis on the interaction of CDP × PTZ20, which revealed significant differences between the VEH1-treated group and the PTZ20 ($p < 0.001$), CDP ($p < 0.001$), and CDP + PTZ20 ($p < 0.003$)-treated groups.

Licking during the preexposure session: total licks. CDP and PTZ20 affected the total number of licks during the preexposure session in opposite directions. CDP increased the number of licks (2155 ± 103), whereas PTZ20 reduced the number of licks (1304 ± 129) relative to VEH1 (1670 ± 75). CDP antagonised the effects of PTZ20, as the coadministration resulted in an increased number of licks (2029 ± 123). These results were supported by the significant main effect of CDP, $F(1, 72) = 29.38$, $p < 0.001$, and of PTZ20, $F(1, 72) = 4.92$, $p < 0.05$.

Test session: time to complete 25 licks prior to stimulus presentation. None of the groups differed in the times to complete 25 licks prior to the presentation of the stimulus (A-period). The overall mean was 7 ± 1 s.

Test session: suppression ratios. Figure 3 presents the suppression ratios of the PE and NPE groups in each of the four drug conditions: VEH1 + VEH1, VEH1 + PTZ20, CDP + VEH1, and CDP + PTZ20. It can be seen that LI was evident only for the VEH1 + VEH1 and CDP + PTZ20 groups. There was no LI at all in the CDP + VEH1 and VEH1 + PTZ20 groups. This was supported by the significant main effect of preexposure, $F(1, 72) = 12.45$, $p < 0.001$, the significant interaction of preexposure × CDP × PTZ20, $F(1, 72) = 3.95$, $p < 0.05$, and the contrast analysis on the preexposure effect for each of the groups VEH1 + VEH1 ($p < 0.05$), VEH1 + PTZ20 ($p = 0.27$), CDP + VEH1 ($p = 0.65$), and CDP + PTZ20 ($p < 0.01$).

Experiment 4: Effects of 3.0, 6.0, and 9.0 mg/kg Ro15-4513 Administered in the Preexposure Stage on LI

Activity during the preexposure session. Activity counts were significantly reduced by all doses of Ro15-4513 to about the same level (3 mg/kg, 447 ± 56; 6 mg/kg, 364 ± 54, and 9 mg/kg, 423 ± 68) compared with VEH2 (808 ± 91). This was supported by the significant main effect of drug, $F(3, 72) = 8.86$, $p < 0.001$.

Licking during the preexposure session: total licks. Ro15-4513 decreased significantly the total number of licks during the preexposure session at 3 mg/kg (1713 ± 99), 6 mg/kg (1474 ± 89), and 9 mg/kg (1469 ± 90) compared with VEH2 (2043 ± 113). These results were supported by the significant main effect of drug, $F(3, 72) = 7.42$, $p < 0.001$.

Test session: time to complete 25 licks prior to stimulus presentation. None of the groups differed in the time to complete 25 licks prior to the presentation of the stimulus (A-period). The overall mean was 6 ± 0.7 s.

Test session: suppression ratios. Figure 4 presents the suppression ratios of the PE and NPE groups in each of the four drug conditions: VEH2, RO3, RO6, and RO9. It can be seen that LI was evident only for the VEH2 and RO9 groups. No LI was seen for the RO3 and RO6 groups. This was supported by the significant main effect of preexposure, $F(1, 72) = 8.4$, $p < 0.005$, and the contrast analysis on the preexposure effect for each of the groups VEH2 ($p < 0.01$), RO3 ($p = 0.32$), RO6 ($p = 0.98$), and RO9 ($p < 0.01$).

Experiment 5: Effects of 5 mg/kg CDP and/or 6.0 mg/kg Ro15-4513 Administered in the Preexposure Stage on LI

Activity during the preexposure session. Activity counts were significantly reduced by Ro15-4513 (479 ± 48), CDP (479 ± 61), and by CDP-Ro15-4513 (411 ± 37) relative to VEH2 (822 ± 65). This was supported by the significant main effect of CDP injection, $F(1, 112) = 14.26$, $p < 0.001$, Ro15-4513 injection, $F(1, 112) = 15.56$, $p < 0.001$, and the interaction CDP × Ro15-4513 injection, $F(1, 112) = 6.67$, $p < 0.01$.

Licking during the preexposure session: total licks. Ro15-4513 and CDP affected the drinking behavior during the preexposure session in an opposite manner. Ro15-4513 decreased significantly the total number of licks during the preexposure (1554 ± 80) while CDP increased it (2795 ± 138) compared with VEH2 (2046 ± 78). Interestingly, as with PTZ, the Ro15-4513 effects were antagonized when the drugs were coadmin-

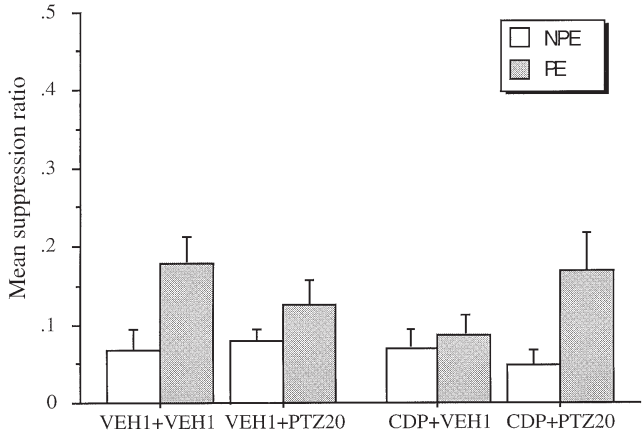

FIG. 3. Suppression ratios (mean ± SEM) of the preexposed (PE) and nonpreexposed (NPE) groups treated during preexposure with saline (VEH1 + VEH1), 20.0 mg/kg pentylenetetrazole (VEH1 + PTZ20), 5.0 mg/kg CDP (CDP + VEH1), and 5.0 mg/kg CDP combined with 20.0 mg/kg pentylenetetrazole (CDP + PTZ20).

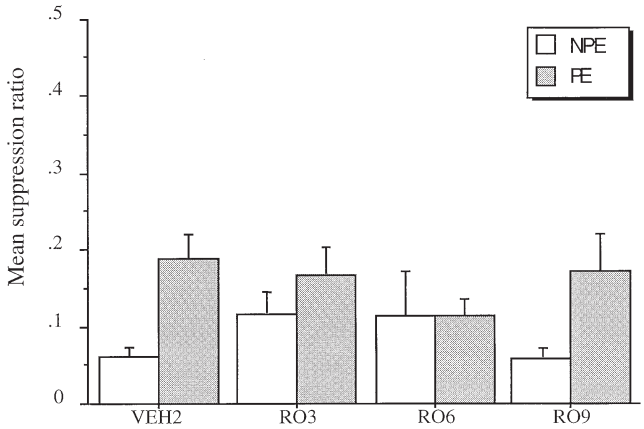

FIG. 4. Suppression ratios (mean ± SEM) of the preexposed (PE) and nonpreexposed (NPE) groups under four drug doses of Ro15-4513 administered only during the preexposure stage of the experiment: 0.3% Tween 80 saline vehicle (VEH2), 3.0 (RO3), 6.0 (RO6), and 9.0 mg/kg (RO9).

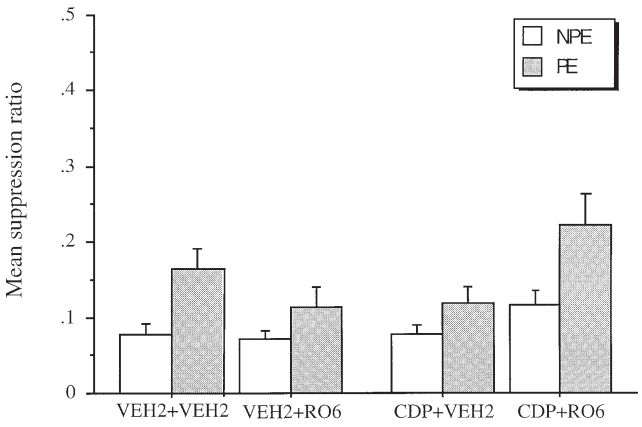

FIG. 5. Suppression ratios (mean ± SEM) of the preexposed (PE) and nonpreexposed (NPE) groups treated during preexposure with 0.3% Tween 80 saline vehicle (VEH2 + VEH2), 6.0 mg/kg Ro15-4513 (VEH2 + RO6), 5.0 mg/kg CDP (CDP + VEH2), and 5.0 mg/kg CDP combined with 6.0 mg/kg Ro15-4513 (CDP + RO6).

istered, i.e., CDP + Ro15-4513 (1896 ± 99). These results were supported by the significant main effect of CDP injection, $F(1, 112) = 27.46$, $p < 0.001$, Ro15-4513 injection, $F(1, 112) = 45.11$, $p < 0.001$, and the interaction CDP × Ro15-4513 injection, $F(1, 112) = 3.9$, $p < 0.05$.

Test session: time to complete 25 licks prior to stimulus presentation. None of the groups differed in the time to complete 25 licks prior to the presentation of the stimulus (A-period). The overall mean was 5 ± 0.3 s.

Test session: suppression ratios. Figure 5 presents the suppression ratios of the PE and NPE groups in each of the four drug conditions: VEH2 + VEH2, VEH2 + RO6, CDP + VEH2, and CDP + RO6. It can be seen that no LI was present for the RO6 and CDP groups, whereas LI was evident for both VEH2 + VEH2 and CDP + RO6 groups. This was supported by the significant main effect of preexposure, $F(1, 112) = 16.79$, $p < 0.001$, the significant interaction of RO6 × CDP, $F(1, 112) = 8.38$, $p < 0.01$, and the near significant interaction of preexposure × RO6 × CDP, $F(1, 112) = 2.63$, $p < 0.10$, as well as by contrast analysis on the preexposure effect for each of the groups VEH2 + VEH2 ($p < 0.05$), VEH2 + RO6 ($p = 0.21$), CDP + VEH2 ($p = 0.23$), and CDP + RO6 ($p < 0.01$).

DISCUSSION

The present study was carried out to examine the effect of GABA-BZD receptor ligands on LI using the GABA function facilitator CDP and the GABA function inhibitors PTZ and Ro15-4513. CDP disrupted LI when administered during the preexposure stage of the procedure, as previously reported by Feldon and Weiner (20). Surprisingly, the administration of PTZ or Ro15-4513 also disrupted LI when administered in the preexposure stage. However, the concomitant administration of CDP with either PTZ or Ro15-4513 led to normal LI, suggesting that all these drugs act at the same receptor complex to achieve their effects on LI.

In this study, the effects of each drug on ambulation and drinking are consistent with prior reports. CDP, PTZ, and Ro15-4513 reduced ambulatory behavior. These results are in line with previous reports (9,11,19,37), although some controversies exist as to the effects of CDP on locomotion (41). According to the literature, benzodiazepine agonists increase water intake, whereas drugs that inhibit GABAergic function by acting at the benzodiazepine receptor or at the chloride channel levels, reduce water consumption (10,11,13,19,49). In line with these documented effects, in this study CDP markedly increased water intake, whereas PTZ and Ro15-4513 decreased drinking behavior. However, although PTZ and Ro15-4513 produced identical effects when administered alone, they produced different effects when administered concomitantly with CDP. CDP still increased the amount of water intake when coadministered with PTZ, but not when coadministered with Ro15-4513. The different effects of PTZ and Ro15-4513, when coadministered with CDP, may reflect their actions at different GABA-BZD binding sites, inasmuch as PTZ acts at the picrotoxin site of the GABA chloride channel, and Ro15-4513 binds at the benzodiazepine site.

Apart from their behavioral effects on ambulation and drinking, which confirmed their effectiveness, all drugs also affected the acquisition of LI. CDP disrupted LI, supporting and extending Feldon and Weiner's findings to an "on baseline" CER procedure (i.e., in which the rats are allowed to drink during preexposure and conditioning), as did both PTZ and Ro15-4513. This outcome seems to indicate that both an increase and a decrease of GABAergic function are deleterious to the establishment of LI. In addition, the fact that concomitant administration of CDP with PTZ prevented the LI-disruptive effect of each drug confirmed the previously reported functional antagonism of these two compounds (6,7). Normal LI was also obtained when CDP and Ro15-4513 were coadministered, as was expected given their opposite pharmacological actions at the BZD receptors. Taken together, these results suggest that in this study LI was disrupted in both cases through an identical pharmacological mechanism involving GABA-BZD receptors, and, more generally, they provide evidence for a GABAergic modulation of LI.

The fact that GABA-BZD receptor ligands affect LI exclusively during preexposure contrasts with dopaminergic drugs, which influence LI when administered during the conditioning stage [for discussion, see (23,24)]. Whereas haloperidol enhances the animal's ability to continue to respond to a stimulus as irrelevant when it is followed by reinforcement, amphetamine disrupts this ability. Both the blockade of dopaminergic transmission by haloperidol and the enhancement of dopaminergic transmission by amphetamine have an effect on LI that is restricted to the conditioning stage. The disruption of LI through drug administration in conditioning (e.g., amphetamine) is considered to result from an overactivation of sensory processes, allowing the preexposed CS to enter more readily into association with the US (23). These effects of dopaminergic drugs indicate that they do not affect the animal's ability to learn to ignore irrelevant stimuli, but rather the subsequent expression of this learning.

In contrast, an impact only in preexposure implies that the drugs affect the acquisition of the CS-no event contingency. The capacity of drugs to selectively affect LI when administered during the preexposure stage has been demonstrated with serotonergic drugs. For example, Killcross et al. (39), using a procedure known to be insufficient to produce LI in control animals, showed enhanced LI only after administration of the 5-HT_{1A} antagonist WAY 100635 only prior to preexposure. Furthermore, Hitchcock et al. (31) demonstrated that the 5-$HT_{2A/C}$ agonist 1-(2,5-dimethoxy-4-iodophenyl)-2-aminopropane (DOI), which has hallucinogenic properties in humans, disrupted LI when administered only at the preexposure stage. This effect was prevented by haloperidol, cloza-

pine, risperidone, and the selective 5-HT_{2A} antagonist MDL 100,907. The cholinergic system has also been implicated in the acquisition of LI by Rochford et al. (60), who suggested that the stimulation of nicotine receptors during preexposure leads to enhancement of LI. In the same study, nicotine or nicotinic agonists also enhanced LI when administered only in conditioning, which is inconsistent with a previous report showing that nicotine disrupts LI when administered in conditioning (35). However, the effects of the stimulation of nicotine receptors on LI have been shown to depend on CS preexposure parameters, with long and short stimulus duration enhancing and disrupting LI, respectively (60).

Although our results support the notion that the serotonergic, cholinergic, and GABAergic systems are implicated in the acquisition of LI, their profiles of action appeared to be different. Activation and inhibition of the serotonergic system disrupted and enhanced LI, respectively, whereas activation of the cholinergic system disrupted or enhanced LI, depending on CS preexposure parameters, and both facilitation and inhibition of the GABAergic system impaired LI using identical parameters. The disruption of the acquisition of LI can be interpreted as a result of interference with stimulus processing leading to an impaired capability to detect the significance of the information in the environment. Interestingly, the alteration of information processing and/or decision making has been considered to be a general feature of the behavioral effect of BZD (13,16,42,43,56). Indeed, BZD agonists, including CDP, have been shown to impair attentional processes (32,51). Recent studies have also suggested that BZD inverse agonists affect attentional abilities. For example, McGaughy and Sarter (51) reported impairment of animals' ability to discriminate between visual signals and nonsignal events after administration of either CDP or the BZD partial inverse agonist RU 33965 in an operant task measuring attention or vigilance. Although both drugs induced attentional deficits, the nature of these deficits was different. The deficit induced by CDP was related to hypoattention, i.e., the failure to attend and select stimuli, whereas the deficit induced by RU 33965 was related to hyperattention, i.e., the inability to ignore irrelevant stimuli. Against this background, the similar disruption of LI by CDP, PTZ, and Ro15-4513 may be explained by suggesting that CDP, by facilitating GABAergic function, induced hypoattention, whereas PTZ and Ro15-4513, by inhibiting GABAergic function, induced hyperattention. Thus, both hypo- and hyperattention during the acquisition of the CS-no event contingency in the preexposure stage would result in the disruption of LI.

In terms of mechanisms implicated in the disruption of LI, a key role has been attributed to the mesolimbic dopaminergic system, and the hippocampus (73). Given the effects of dopaminergic agents on LI, it has been proposed that the mesolimbic dopaminergic system does not participate in learning the stimulus-no event contingency in the preexposure stage but is activated in conditioning when the nonreinforced stimulus is followed by reinforcement. The hippocampus is considered to play a role in stimulus associability by determining the mismatch between old and new predictions arising from a target stimulus. Thus, a possible neural substrate for pharmacological agents operating in the preexposure stage is the hippocampus. Against this background, it is interesting to note that in vivo microdialysis studies have demonstrated that BZD ligands modulate ACh release in cortical areas, including the hippocampus. Infusion of BZD agonists (e.g., CDP) within the basal forebrain decreases cortical ACh, whereas infusion of BZD inverse agonists induces increased cortical ACh (32,34,55). Thus, our results may stem from a bidirectional modulation of cortical cholinergic activity by GABA-BZD receptor ligands, resulting in the disruption of LI as a function of attentional deficits.

Whatever the mechanism involved, because LI appears to model some of the symptoms of schizophrenia, the present results of a GABAergic modulation of LI may have implications regarding the GABA hypothesis of schizophrenia (4,15,53). Accordingly, our results provide evidence that both GABAergic stimulation and GABAergic inhibition play an important role in the symptomatology of schizophrenia. Therefore these results justify further investigation of the function of the GABA-BZD modulation of LI and the role of the GABAergic function in the pathophysiology of this disorder.

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