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Baclofen Alters Ethanol-Stimulated Activity but not Conditioned Place Preference or Taste Aversion in Mice

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CHESTER, J. A. AND C. L. CUNNINGHAM. *Baclofen alters ethanol-stimulated activity but not conditioned place preference or taste aversion in mice.* PHARMACOL BIOCHEM BEHAV **63**(2) 325–331, 1999.—The present experiments examined the effects of the $GABA_B$ receptor agonist, baclofen, on the acquisition of ethanol-induced conditioned place preference (CPP) and conditioned taste aversion (CTA) in male DBA/2J mice. Mice in the CPP experiment received four pairings of ethanol (2 g/kg) with a distinctive floor stimulus for a 5-min conditioning session (CS+ sessions). On intervening days (CS− sessions), mice received saline injections paired with a different floor type. On CS+ days, mice also received one of four doses of baclofen (0.0, 2.5, 5.0, or 7.5 mg/kg) 15 min before an injection of ethanol. For the preference test, all mice received saline injections, and were placed on a half-grid and half-hole floor for a 60-min session. Baclofen dose dependently reduced ethanol-stimulated activity, but did not alter the magnitude of ethanol-induced CPP at any dose. For the CTA experiment, mice were adapted to a 2-h per day water restriction regimen followed by five conditioning trials every 48 h. During conditioning trials, subjects received an injection of saline or baclofen (2.0 and 6.0 mg/kg) 15 min before injection of 2 g/kg ethanol or saline following 1-h access to a saccharin solution. Baclofen did not alter the magnitude of ethanol-induced CTA at any dose. In addition, baclofen alone did not produce a CTA. Overall, these studies show that activation of $GABA_B$ receptors with baclofen reduces ethanol-induced locomotor activation, but does not alter ethanol's rewarding or aversive effects in the CPP and CTA paradigms in DBA/2J mice. © 1999 Elsevier Science Inc.

Alcohol DBA/2J Reward Aversion GABA Locomotor activity Place conditioning Taste conditioning

ATTEMPTS to elucidate the neurochemical substrates involved in ethanol's motivational effects have focused on several neurotransmitter systems, including dopamine, serotonin, opioid, glutamate, and gamma-aminobutyric acid (GABA) [for reviews see (21,22,48)]. GABA is the primary inhibitory neurotransmitter in the brain, which exerts its actions primarily via two distinct receptor subtypes, $GABA_A$ and $GABA_B$. Several lines of evidence indicate that ethanol exerts many of its pharmacological and behavioral effects through an interaction with the GABA receptor system [for reviews see (29,34,49)]. However, relatively few studies have examined the role of GABA receptor subtypes in the motivational effects of ethanol. Of these studies, ethanol drinking and self-administration tasks have been the most commonly used procedures to examine the effect of GABA manipulations on ethanol's motivational properties.

Much of the evidence implicating the GABA receptor system in ethanol's motivational effects comes from studies showing that $GABA_A$ receptor antagonists (3,38) and benzodiazepine partial inverse agonists (1,5,23–25,33,43,54) consistently reduce ethanol self-administration in rats. However, several studies have also reported a decrease in ethanol self-administration with administration of the nonselective GABA agonists gamma-butyrolactone (19), AOAA, a GABA decarboxylase inhibitor (15), and calcium-acetyl-homotaurine (2). In addition, the specific $GABA_A$ antagonist, bicuculline, attenuated the decrease in ethanol intake observed with calcium-acetyl-homotaurine, suggesting that the $GABA_A$ receptor

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is involved in mediating the effect of calcium-acetyl-homotaurine on ethanol intake.

The few studies that have examined a role for the $GABA_B$ receptor in modulating ethanol self-administration have provided inconsistent results. In one study, the selective $GABA_B$ agonist, baclofen, increased ethanol intake, but also increased total fluid intake, suggesting the effect of baclofen was not selective for ethanol's motivational effects (46). In another study, baclofen decreased ethanol intake without altering total fluid intake (15). The discrepancy between these two studies is possibly due to different doses of baclofen or different procedures used to measure ethanol self-administration. For example, in one study, baclofen was administered daily during an acquisition phase of self-administration (46), while in the other study, rats were first selected that were ethanol-preferring before examining the effect of daily baclofen administration on the maintenance of ethanol self-administration (15). More recently, it has been shown that direct injections of baclofen into the dorsal raphe nucleus had no effect on ethanol or water consumption (50). Thus, the role of $GABA_B$ receptors in modulating ethanol self-administration remains unclear.

A potential problem in interpreting self-administration studies is that GABAergic manipulations may be affecting mechanisms involved in consummatory behavior rather that affecting a mechanism modulating ethanol's motivational properties. Indeed, baclofen (18,37) and $GABA_A$/benzodiazepine receptor agonists have been shown to stimulate feeding in nondeprived rats (7), while benzodiazepine receptor antagonists reduce food consumption (7). In addition, ethanol self-administration may be influenced by both rewarding and aversive effects of ethanol, which may be mediated by independent neural mechanisms. Thus, changes in self-administration behavior following pharmacological manipulations may be due to an increase or decrease in ethanol's rewarding or aversive properties. This may account for the discrepancies in the self-administration studies, where a reduction in ethanol self-administration was observed with both GABA agonists and antagonists.

The present experiments use the place and taste conditioning paradigms to examine the effects of the $GABA_B$ receptor agonist, baclofen, on the rewarding and aversive properties of ethanol. One advantage of the place and taste conditioning procedures relative to the oral self-administration paradigm is that they avoid interpretive problems regarding possible nonspecific effects of an agonist or antagonist on consummatory behavior, because pharmacological agents are not administered during expression of place or taste conditioning. Another advantage of these paradigms is that they can be used to separately measure both rewarding and aversive effects of ethanol. In this regard, they are also useful for assessing the effects of drugs that may increase or decrease the magnitude of place or taste conditioning, and these drugs can be assessed independently for their own motivational properties as a measure of control.

The purpose of the current studies was to investigate the role of the $GABA_B$ receptor in modulating the acquisition of ethanol-induced conditioned place preference (CPP) and conditioned taste aversion (CTA) in DBA/2J mice. Based on self-administration studies (15,46), it was hypothesized that $GABA_B$ receptor activation modulates ethanol's motivational effects. The present experiments examined the effect of various doses of baclofen on ethanol's rewarding and aversive effects in the CPP and CTA paradigms. Because the existing self-administration data are contradictory, a clear directional prediction for baclofen's effect on ethanol-induced CPP and CTA could not be made.

METHOD

Subjects

Subjects in both experiments were adult male inbred mice (DBA/2J) obtained from the Jackson Laboratory (Bar Harbor, ME) at 6 weeks of age. For the place conditioning study, mice were housed in polycarbonate cages (27.9 × 9.5 × 12.7 cm) in groups of four. For the taste conditioning study, mice were housed individually in hanging stainless steel cages (12 × 18 × 18 cm) with wire mesh fronts and bottoms. Animals were allowed to acclimate to the colony room for 12–14 days before training. During place conditioning, animals were allowed free access to food and water. During taste conditioning, lab chow was continuously available; however, daily access to fluids was restricted according to the procedure described below. Ambient temperature was maintained at 21 ± 1°C. Experimental procedures were conducted during the light phase of a 12:12 light:dark cycle (lights on at 0700 h).

Apparatus

Twelve identical acrylic and aluminum boxes (30 × 15 × 15 cm) were separately enclosed in ventilated, light, and sound-attenuating chambers (Coulbourn Model E10-20). Six sets of infrared light sources and photodetectors were mounted opposite each other at 5-cm intervals along the length of each box, 2.2 cm above the floor. Occlusion of the infrared light beams was used to measure general activity and location of the animal (left or right) within the box. Total activity counts were recorded every minute by computer (10 ms resolution). The floor of each box consisted of interchangeable halves of one of two distinct textures. "Grid" floors consisted of 2.3-mm stainless steel rods mounted 6.4 mm apart in acrylic rails. "Hole" floors consisted of perforated 16-gauge stainless steel with 6.4-mm round holes on 9.5-mm staggered centers. This combination of floor textures was selected on the basis of previous studies showing that drug-naive DBA/2J mice spend approximately equal time on each floor type during drug-free preference tests (9,12,13). The floors and the inside of the boxes were wiped with a damp sponge and the litter paper beneath the floors was changed between animals.

The taste-conditioning experiment was conducted in the home cages. Water and saccharin solutions were presented at room temperature in 25-ml graduated glass cylinders fitted with stainless steel drinking spouts inserted through the front of the cage. Consumption was measured to the nearest 0.1 ml, and was corrected for evaporation and spillage by subtracting the mean fluid loss measured in two drinking tubes placed on empty cages for an equal amount of time.

Drugs

Ethanol (20% v/v) was prepared from a 95% stock solution using saline as the vehicle. Ethanol was administered intraperitoneally (IP), and the dose was varied by manipulating injection volume. Baclofen (Sigma Chemical Co., St. Louis, MO) was dissolved in saline and administered IP in an injection volume of 10 ml/kg.

Procedure

Place conditioning. The place-conditioning study involved one habituation session, eight conditioning sessions, and one

test session. A 2-day weekend break occurred between the first four and last four conditioning sessions. For the habituation session, mice received an injection of saline immediately before being placed in the conditioning box for 5 min on a smooth paper floor. The purpose of the habituation session was to reduce the stress associated with the novelty of experimental procedures and exposure to the apparatus. Mice were not exposed to the distinctive floor textures to avoid latent inhibition.

For conditioning, mice were randomly assigned to one of four baclofen dose groups: 0.0 (saline), 2.5. 5.0, and 7.5 mg/kg (n = 24/dose group). Within each of the four dose groups, mice were randomly assigned to one of two conditioning subgroups (G+ or G−) and exposed to a Pavlovian differential conditioning procedure. On alternating days, mice in the G+ group received an injection of ethanol (2 g/kg; 12.5 ml/kg) immediately before a 5 min session on the grid floor (CS+ sessions). On intervening days, these mice received saline immediately before exposure to the hole floor (CS− sessions). Conversely, mice in the G− group received ethanol paired with the hole floor and saline paired with the grid floor. During conditioning trials, all mice had access to both sides of the apparatus on a homogeneous floor type. All mice received two IP injections before each conditioning session. During CS+ sessions, G+ subjects received an injection of saline, 2.5, 5.0, or 7.5 mg/kg baclofen 15 min before an injection of ethanol and were placed on the grid floor for a 5-min session. During CS− sessions, these mice received two saline injections 15 min apart before a 5-min session on the hole floor. Conversely, G− subjects received saline/ethanol (0.0 mg/kg group) or baclofen/ethanol paired with the hole floor and saline paired with the grid floor. These doses of baclofen were chosen because they are within the range known to alter ethanol's behavioral effects (8,32). Conditioning groups were matched for overall exposure to CS type (grid or hole) and drug treatment, and the order of drug exposure was counterbalanced within groups. Thus, this procedure provides control over exposure to both the CS (floor type) and the US (ethanol) in both G+ and G− subgroups, with subgroups differing only in the specific floor–ethanol pairing (10). The dose of ethanol (2 g/kg) was chosen because it has previously been shown in mice to produce a strong preference for the paired tactile stimuli [e.g., (6,14)]. The 5-min session duration was chosen based on previous studies showing that it produced a stronger conditioned place preference with ethanol in DBA/2J mice than did longer session durations (14).

For the 60-min test session, all mice received two injections of saline 15 min apart to match the cues during conditioning days. The floor of each box was half grid and half hole with left/right position counterbalanced within groups.

Taste conditioning. Subjects were adapted to a water-restriction schedule (2-h water per day) over a 7-day period. At 48-h intervals over the next 10 days, all mice received 1-h access to a solution of saccharin (0.15% w/v sodium saccharin in tap water).

Mice were randomly assigned to one of five drug treatment groups (n = 12/group): saline/saline (S/S), baclofen (2.0 mg/kg)/saline [B(2.0)/S], saline/ethanol (S/E), baclofen (2.0 mg/kg)/ethanol [B(2.0)/E], and baclofen (6.0 mg/kg)/ethanol [B(6.0)/E]. Due to constraints on the number of experimental groups that could be tested, we chose to examine only the lower dose of baclofen (2.0 mg/kg) with saline. Immediately after 1-h access to saccharin, mice received injections of saline or baclofen 15 min before injections of saline or ethanol (2.5 g/kg). All mice also received 30-min access to tap water 5 h after each saccharin access period to prevent dehydration. Two-hour access to tap water was given during intervening days.

RESULTS

Place Conditioning

Data were analyzed by analysis of variance (ANOVA) with the alpha level set at 0.05.

Conditioning. Figure 1 shows mean activity counts per minute during conditioning trials 1–4 averaged across each baclofen dose group. Ethanol produced significant locomotor activation in the 0.0 mg/kg group during CS+ sessions relative to saline on CS− sessions. Baclofen produced a dose-dependent reduction in ethanol-stimulated locomotor activity during CS+ sessions. As previously observed with DBA/2J mice [e.g., (6)], activity counts were higher on the last CS+ session compared to the first CS+ session in all baclofen dose groups, suggesting the development of sensitization to ethanol's locomotor-stimulant effects.

Two-way ANOVAs (dose × trials) were separately conducted for CS+ and CS− session data. The CS+ ANOVA revealed a significant effect of dose, $F(3, 92) = 29.9$, $p < 0.001$, and trials, $F(3, 276) = 12.4$, $p < 0.001$, but no interaction was found ($F < 1$). The effect of trials indicates that ethanol-induced locomotor sensitization occurred across the four conditioning trials. The lack of interaction signifies that baclofen did not alter the development of sensitization at any dose. Follow-up comparisons of drug treatment groups showed significant differences between all baclofen dose groups (ps ≤ 0.01), except between 0.0 and 2.5 mg/kg (p = 0.09). The CS− ANOVA showed a significant effect of trials, $F(3, 273) = 9.6$, $p < 0.001$, indicating habituation to experimental procedures occurred across the four trials. No effect of dose or interaction was found.

Preference testing. Preliminary analyses indicated that differences among dose groups did not vary as a function of time. Therefore, the data shown in Fig. 2 are collapsed over the 60-min test session to simplify presentation of the results. Figure 2 shows the mean (±SEM) seconds per minute spent on the grid floor by both conditioning subgroups in the four baclofen dose groups during the preference test. G+ subgroups in each drug treatment group spent significantly more time on the grid floor relative to G− subgroups, indicating the development of ethanol-induced CPP for the grid floor. Baclofen appeared to have little effect on the magnitude of preference.

Overall analysis of the data (baclofen dose × conditioning group ANOVA) yielded a significant effect of conditioning group, $F(1, 88) = 81.1$, $p < 0.001$, indicating a conditioned place preference for the ethanol-paired floor. No significant effect of baclofen dose or interaction was found. Thus, these data indicate that baclofen did not alter the acquisition of ethanol-induced CPP at any dose.

Mean (±SEM) activity counts per min during the 60-min test were 33.6 ± 1.6, 31.2 ± 1.4, 31.0 ± 1.4, and 30.0 ± 1.3, for the 0.0, 2.5, 5.0, and 7.5 mg/kg baclofen groups, respectively. No significant differences in test activity levels were found, $F(3, 92) = 1.1$, $p = 0.4$.

Taste Conditioning

Mean (±SEM) consumption of saccharin on trial 1 (before conditioning) for each drug treatment group was 2.92 ± 0.16, 2.91 ± 0.14, 2.82 ± 0.14, 2.87 ± 0.16, and 3.03 ± 0.12 for S/S, B(2.0)/S, S/E, B(2.0)/E, and B(6.0)/E, respectively. One-way

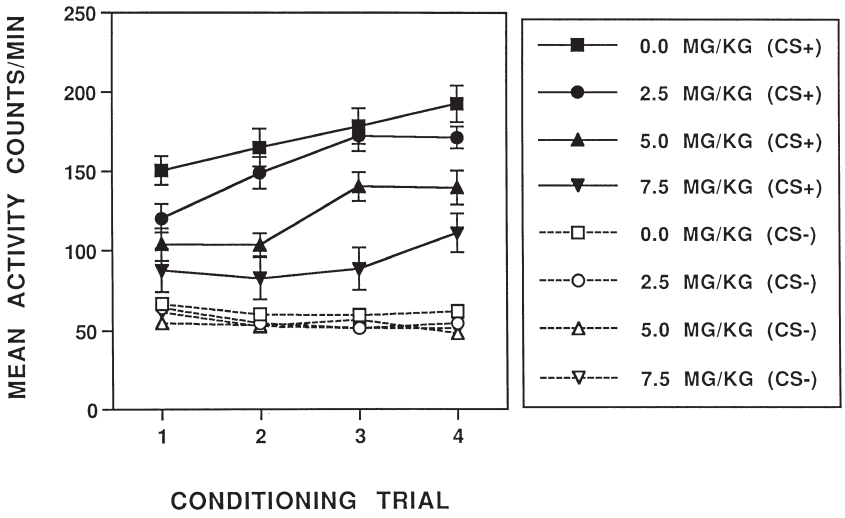

FIG. 1. Mean (±SEM) activity counts per min following ethanol (CS+ sessions) and saline (CS− sessions) for each baclofen dose group (n = 24/group) during conditioning trials 1–4. On CS+ days, mice received saline (0.0 mg/kg) or baclofen (2.5, 5.0, or 7.5 mg/kg) 15 min before 2 g/kg ethanol. All mice received saline/saline injections on CS− days. Data are shown collapsed across the 5-min conditioning sessions.

ANOVA of trial 1 intakes indicated no significant difference between groups in preconditioning consumption of saccharin (p = 0.9). Nevertheless, to offset minor initial differences in saccharin intake and facilitate presentation of the data, difference scores were calculated for each subject by subtracting the milliliters of saccharin consumed on trial 1 from the amount consumed on subsequent conditioning trials. Figure 3 shows mean difference scores for each drug treatment group across conditioning trials 2–6.

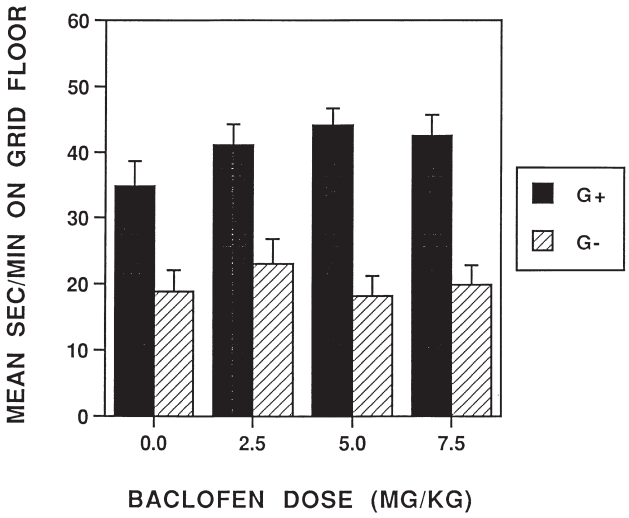

FIG. 2. Mean (+SEM) seconds per min spent on the grid floor by conditioning subgroups (G+ and G−; n = 12/subgroup) of each baclofen dose group during the preference test. During conditioning, mice in the G+ subgroups received saline or baclofen (2.5, 5.0, 7.5 mg/kg) 15 min before ethanol (2 g/kg) paired with the grid floor and saline injections paired with the hole floor. Conversely, mice in the G− subgroups received saline/ethanol (0.0 mg/kg group) or baclofen/ethanol paired with the hole floor and saline paired with the grid floor. Data are shown collapsed across the 60-min test session.

Ethanol-saccharin pairings produced reductions in saccharin intake across trials, indicating the development of CTA in the S/E group. Two-way ANOVA of S/S and S/E groups (drug treatment × trials) showed significant effects of drug treatment, $F(1, 22) = 27.1, p < 0.001$, trials, $F(4, 88) = 20.6, p < 0.001$, and interaction, $F(4, 88) = 15.1, p < 0.001$, signifying the development of ethanol-induced CTA across trials in the S/E group. All ethanol-treated groups (S/E, B(2.0)/E, B(6.0)/E) showed a similar magnitude of CTA across trials, suggesting no effect of baclofen pretreatment (2.0 or 6.0 mg/kg) on ethanol-induced CTA. This conclusion was supported by two-way ANOVA of ethanol-treated groups (drug treatment × trials), which showed a significant effect of trials, $F(4, 132) = 85.6, p < 0.001$, but no effect of drug treatment or interaction. A separate two-way ANOVA of S/S and B(2.0)/S groups yielded a marginally significant effect of trials, $F(4, 88) = 2.5$, $p = 0.05$, but no effect of drug treatment or interaction (Fs < 1). This analysis indicates that administration of baclofen alone (2.0 mg/kg) did not produce a CTA.

DISCUSSION

The present experiments examined a role for the $GABA_B$ receptor in modulating ethanol's rewarding and aversive effects in the CPP and CTA paradigms. The results of the place-conditioning study showed that the acquisition of ethanol-induced CPP was not altered by baclofen, the selective $GABA_B$ agonist. The taste-conditioning study showed that baclofen did not alter the acquisition of ethanol-induced CTA. In addition, administration of baclofen alone (2.0 mg/kg) did not produce a CTA. This finding is consistent with a previous study showing that baclofen does not produce a CTA in rats (17). Overall, these results do not support the hypothesis that the $GABA_B$ receptor is involved in modulating ethanol's motivational effects in the CPP and CTA paradigms.

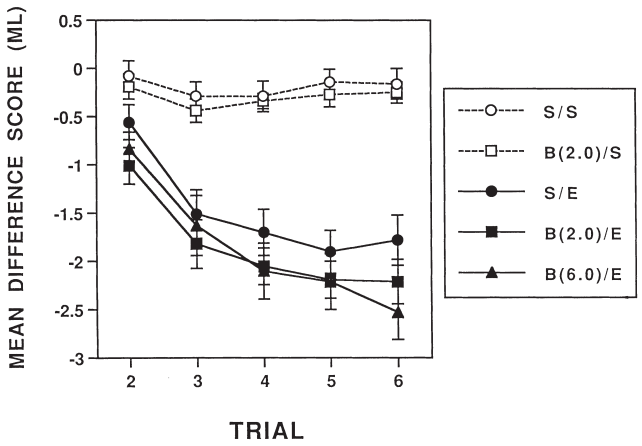

FIG. 3. Mean (±SEM) difference scores (ml) during taste conditioning trials 2–6 for each drug treatment group (n = 12/group). During conditioning, mice received 1-h access to saccharin followed by injections of saline or baclofen (2.0 or 6.0 mg/kg) 15 min before injections of saline or ethanol (2.5 g/kg). Group abbreviations in legend refer to drug treatment on conditioning trial days: S/S (saline/saline), B(2.0)/S [baclofen (2.0 mg/kg)/saline], S/E (saline/ethanol), B(2.0)/E [baclofen (2.0 mg/kg)/ethanol], and B(6.0)/E [baclofen (6.0 mg/kg)/ethanol]. Difference scores were calculated by subtracting the ml of saccharin consumed on trial 1 from the amount consumed on subsequent conditioning trials.

The finding that baclofen dose dependently reduced ethanol-stimulated activity in the CPP experiment is consistent with previous studies (8,22,44). It is possible that this effect of baclofen is due to a reduction in ethanol-stimulated dopamine release. Baclofen has been shown to decrease the activity of dopamine neurons (20,31,36) and decrease extracellular dopamine levels in the VTA (27) and nucleus accumbens (55). In addition, baclofen has also been shown to reduce the motor-stimulant effect of other drugs known to act through an increase in dopamine levels, such as cocaine or amphetamine (26,30). Consistent with previous studies [e.g., (6,9,40)], these data also suggest a dissociation between ethanol's rewarding and locomotor effects, because baclofen dose dependently decreased ethanol-stimulated activity, but did not alter the magnitude of ethanol-induced CPP. Activity data from the CPP experiment also showed that baclofen did not alter the development of sensitization to ethanol's stimulant effects. This finding is inconsistent with a recent study showing that baclofen in a similar dose range blocks locomotor sensitization to 2 g/kg ethanol in DBA/2J mice (4). The reason for this discrepancy is unknown, but may be due to differences in experimental procedures. For example, in the present study, ethanol was administered every 48 h, whereas ethanol was administered on a 24-h daily schedule in the other study (4). Also, mice in the other study did not receive intermittent saline (CS−) injections in the activity chamber.

The present experiments are the first to examine a role for the $GABA_B$ receptor in modulating ethanol's motivational effects in the CPP and CTA learning paradigms. A few studies have examined the effects of $GABA_B$ receptor activation in modulating ethanol's motivational properties in the self-administration paradigm (15,46,50). However, these studies were contradictory because baclofen was shown to both reduce established ethanol consumption (15) and facilitate the acquisition of voluntary ethanol consumption (46). Moreover, in the latter study, baclofen also increased total fluid intake, suggesting that the facilitatory effect of baclofen was not specific to ethanol consumption. The discrepancy between these studies may be due to different doses of baclofen used or procedural differences in the self-administration paradigm. Regardless, the present data do not support self-administration studies that suggest baclofen alters ethanol's motivational effects. However, the present results are consistent with a recent study that showed no effect on ethanol or water intake when baclofen was administered directly into the dorsal raphe nucleus (50), an area where activation of $GABA_A$ receptors has been shown to increase ethanol self-administration (51). Taken together, the results of previous self-administration studies and the present experiments suggest that the neural mechanisms modulating ethanol's motivational effects in the self-administration paradigm may be different from those modulating ethanol's motivational effects in the CPP and CTA paradigms.

The present results suggest that $GABA_B$ receptors are not involved in modulating ethanol-induced CPP and CTA. However, we have recently shown that ethanol-induced CPP is increased in DBA/2J mice with administration of the $GABA_A$ antagonists, picrotoxin and bicuculline. In addition, picrotoxin dose dependently enhanced ethanol-induced CTA (Chester and Cunningham, in press). Thus, these studies suggest that $GABA_A$ receptor blockade may increase ethanol's rewarding and aversive effects in these paradigms. The finding that $GABA_A$, but not $GABA_B$ receptors modulate ethanol's motivational properties in these paradigms may be due to their different mechanisms of action in the brain. Although activation of both subtypes produce neuronal inhibition, $GABA_A$ receptors mediate fast synaptic transmission through activation of chloride ion channels (53), whereas $GABA_B$ receptors are responsible for slow synaptic transmission through G-protein coupled mechanisms (35). It may be that fast synaptic transmission through $GABA_A$ receptor activation in reward-related pathways is important for modulating ethanol's motivational effects in the CPP and CTA paradigms.

In contrast to the present results, $GABA_B$ receptors have been shown to play an important role in modulating the rewarding effects of other drugs of abuse, such as cocaine and morphine. For example, baclofen has been reported to attenuate cocaine self-administration (41,42,45) and morphine-induced CPP in rats (52). It has been suggested this effect of baclofen is due to an effect of $GABA_B$ receptor-mediated inhibition of dopamine neurons (27,36). It has been hypothesized that dopamine also plays a primary role in the motivational effects of ethanol (16,28). However, the present results suggest that ethanol's motivational effects in the CPP and CTA paradigms may not be sensitive to baclofen-induced changes in dopamine transmission. This suggestion is consistent with studies that showed no effect of the dopamine antagonist, haloperidol, on the acquisition (40) or expression (11) of ethanol-induced CPP. However, another study did report a reduction in ethanol-induced CTA with administration of haloperidol and the selective D_2 receptor antagonist, eticlopride (39).

There are several possible reasons for the difference between baclofen's effect in previous self-administration studies and the present results. For example, it is possible that subject vs. experimenter control over ethanol exposure is an important factor in determining baclofen's effect in the self-administration paradigm. Thus, baclofen may specifically interact with a neural pathway important for modulating oral ethanol self-administration, and this pathway may be distinct from the

pathways modulating ethanol-induced CPP and CTA. In addition, baclofen's effect on ethanol self-administration may be unique to rats. Alternatively, the reported effects of baclofen in the self-administration studies may have been due to a nonspecific effect of baclofen on consummatory behavior (18,37), rather than a selective effect on ethanol's motivational effects. It is also possible that baclofen produced a change in ethanol self-administration by altering the taste or orosensory properties of ethanol. For example, it has recently been shown with taste reactivity tests that $GABA_A$/benzodiazepine agonists increase the palatability of ethanol (47). Clearly, more studies are needed to determine the effect of baclofen on ethanol self-administration behavior. Nevertheless, the results of the present experiments suggest that $GABA_B$ receptor activation does not modulate ethanol's rewarding or aversive effects in DBA/2J mice in the CPP and CTA paradigms.

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