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The Effects of $GABA_B$ Ligands on Alcohol Withdrawal in Mice

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HUMENIUK, R. E., J. M. WHITE AND J. ONG. *The effects of $GABA_B$ ligands on alcohol withdrawal in mice.* PHARMACOL BIOCHEM BEHAV **49**(3) 561-566, 1994.—Recent research suggests that the $GABA_B$ receptor may mediate some of the acute effects of alcohol, but little is known of its involvement in alcohol withdrawal. Mice made dependent on alcohol exhibited tremor and tail arch when consumption ceased. Diazepam dose-dependently attenuated both tremor and tail arch, whereas baclofen had no effect on either of these two withdrawal symptoms. However, baclofen dose-dependently induced convulsant behaviour in the withdrawing mice, and this was significantly attenuated by the $GABA_B$ antagonists phaclofen (50 mg/kg) and CGP 35348 (300 mg/kg), but not BPBA (50 mg/kg). Phaclofen, BPBA, and CGP 35348, when administered alone and in combination with a single dose of baclofen, did have an effect on tremor, although the magnitude was small in comparison to that seen with diazepam. It appears that the $GABA_B$ receptor may play a role in mediating convulsions during alcohol withdrawal, and that in this system baclofen is proconvulsant.

Alcohol withdrawal Tremor Convulsions $GABA_B$ receptor Baclofen Phaclofen BPBA CGP 35348 Diazepam

IT IS WELL established that long-term use of high doses of alcohol induces physical dependence, which manifests itself upon discontinuation of use. The characteristic symptoms of withdrawal include tremor, sweating, insomnia, anxiety, and seizures, and can be observed in both humans (35) and laboratory animals (15,34). However, recent research has indicated that dependence does not only develop after months of virtual continual intoxication, but can occur within the time course of a single drinking episode. Accordingly, there is a continuum of dependence, with lower-level dependence occurring with consumption of lower quantities of alcohol (18). This research clearly implies that alcohol dependence is relevent to a larger population than previously thought.

Much emphasis has been placed on elucidating the mechanisms underlying alcohol intoxication and dependence. Various neurotransmitter receptor systems have been implicated in the effects of alcohol on the central nervous system, including excitatory amino acid receptors such as *N*-methyl-D-aspartate (NMDA) receptors (27). Changes in neuronal dihydropyridine-sensitive calcium channels also appear to play a role (28,43), and attention has also been directed towards the involvement of the classical inhibitory neurotransmitter gamma-aminobutyric acid (GABA).

The actions of GABA are mediated through two distinct receptors. The bicuculline-sensitive $GABA_A$ receptor is an hetero-oligomeric complex that contains a multiplicity of interacting sites for benzodiazepines, barbiturates, and steroids, coupled to an integral chloride channel. There is much evidence that $GABA_A$ receptors play a role in both the intoxicating (10) and withdrawal effects of alcohol (5). Moreover, benzodiazepines reduce at least some alcohol withdrawal symptoms (9).

Much less is known about the $GABA_B$ receptor due to the slow development of selective ligands. The $GABA_B$ receptor is bicuculline insensitive and is activated by baclofen, which is an agonist for the site (4). Recently developed $GABA_B$ receptor antagonists include phaclofen, beta-phenyl-beta-alanine (BPBA), also referred to as 3-amino-3-phenylproprionic acid, and CGP 35348 [3-aminopropyl(diethoxymethyl)phosphinic acid] (17,23). The role of $GABA_B$ receptors in mediating the effects of alcohol is not yet known. Baclofen has been shown to attenuate the acute locomotor stimulatory effects of ethanol in mice (7,21). Moreover, it has also been reported that some of the $GABA_B$ antagonists, such as phaclofen, BPBA, and 2-hydroxysaclofen, attenuate some of the acute behavioural effects of alcohol (1,21). There is also evidence to indi-

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cate that peripheral $GABA_B$ receptors in the mouse vas deferens are desensitized by chronic alcohol treatment, which may account for some of the peripheral symptoms observed in alcohol dependence and withdrawal (38). Additionally, baclofen has been shown to reduce aggression and tremor, but not seizures, in rats withdrawing from alcohol (11).

The aims of this study were to investigate the modulatory effects of $GABA_B$ ligands on alcohol withdrawal. The severity, variability, and frequency of withdrawal symptoms are reliant upon a number of factors including the species and strain of animal used, the method of administration of alcohol, and the concentration and time over which alcohol is delivered. Swiss-Webster mice that received alcohol through inhalation displayed lethargy, tremor, tail arch, startle to noise, convulsions on handling, spontaneous convulsions, and death during withdrawal, with particular symptoms manifested at different times during the withdrawal syndrome (16). TO mice that were administered alcohol through inhalation displayed tremor and convulsions during withdrawal (29). These signs appeared to peak mainly 3.5-6.5 h after cessation from alcohol inhalation. In studies of C57BL/6 mice fed alcohol in a liquid diet according to a number of different schedules, hypothermia, tremor, and seizures were most intense 4-8 h after cessation of alcohol drinking (34).

To be able to detect both increases and decreases in withdrawal intensity, a model of dependence was developed that resulted in reliable manifestation of tremor, but infrequent convulsions. The withdrawal rating scales used were based on our own observations, and previous studies (29). Several measures of withdrawal were assessed (hypothermia, tremor, tail arch, and convulsions) because different symptoms may be mediated via separate neurochemical systems (12). These withdrawal symptoms were most severe 5-6.5 h after cessation of alcohol consumption. Preliminary studies had also shown that withdrawal severity was stable over this time.

A dose-response curve was determined for the $GABA_B$ agonist baclofen. A single dose of baclofen was then coadministered with $GABA_B$ antagonists (phaclofen, BPBA, and CGP 35348) to test for $GABA_B$ specificity, and the antagonists were also administered alone. For comparison, a diazepam dose-response curve was established using our set of withdrawal measures.

METHOD

Young adult, female C57BL/6 mice, housed four per cage, were administered alcohol via a liquid diet over a period of 8 days. On day 1 they received the liquid diet only. On day 2 they received a 3% v/v alcohol mixture followed by a 5% mixture on day 3, and 6% for the remaining 5 days. The liquid diet was composed of 16% weight per total volume of a chocolate-flavoured, low-fat meal replacement formula (Nutratrim, Healthfoods International Ltd., NZ). On the morning of testing (day 8), the alcohol solution was replaced with water, and the mice were placed in separate cages. Testing occurred between 5 and 6.5 h after cessation of alcohol consumption. This is when symptoms were most intense and were also stable.

To minimise the number of animals and enable each animal to serve as its own control, cumulative dosing procedures were used (42). A complete dose-response curve was determined in each mouse by administering an initial dose of saline, followed by three increasing doses of the test drug, 30 min apart. Withdrawal severity was assessed during a 10-min period, once after the initial administration of saline, and 20 min after administration of each dose of the drug. Where two drugs were administered (baclofen and an antagonist), the antagonist was administered cumulatively as outlined above, and a single dose of baclofen (20 mg/kg) was delivered concurrently with the first dose of the antagonist. The cumulative doses of the drugs used were (±)baclofen at 5, 10, and 20 mg/kg; diazepam at 5, 10, and 20 mg/kg; phaclofen at 10, 30, and 50 mg/kg; BPBA at 10, 30, and 50 mg/kg; and CGP 35348 at 100, 200, and 300 mg/kg. Based on extensive experience of examining their behavioural effects, all of the $GABA_B$ ligands tested here are effective within the time course used (20,21).

The parameters of withdrawal assessed were degree of tremor, tail arch, convulsant behaviour, and hypothermia. Temperature was measured rectally using a small probe lubricated with sunflower oil and inserted 1-2 cm. These were recorded by a digital thermometer (HL Integrated Anritherm thermometer, Extech equipment). Tremor and convulsant behaviour were each rated on a scale from 0-8 as follows:

0: no tremor/convulsions observable
1-2: mild-severe tremor/convulsions when picked up by tail and spun 360°
3-4: mild-severe tremor/convulsions when picked up by tail
5-6: mild-severe tremor/convulsions when cage was moved
7-8: mild-severe tremor/convulsions occuring spontaneously and repeatedly

Tail-arch was assessed on a scale from 0-3 as follows:

0: no tail arch
1: tail elevated less than 30°
2: tail elevated between 30-60°
3: tail elevated greater than 60°

The drugs used in this study were (±)baclofen (Research Biochemicals Incorporated), diazepam (Roche), phaclofen (Research Biochemicals Incorporated), and BPBA (beta-phenyl-beta-alanine, gift from Rolf Prager, Flinders University, South Australia), CGP 35348 [3-aminopropyl(diethoxymethyl)phosphinic acid, Ciba-Geigy].

All drugs were dissolved in 0.9% physiological saline, excluding diazepam, which was made up in 50% DMSO. Drugs were administered IP in an injection volume of 10 ml/kg. Drug solutions were coded to ensure that the experimenter was unaware of the treatment each animal received. The doses of the drugs used were based on those of our earlier studies (20,21). Furthermore, when administered to nondependent animals, these drugs do not induce tremor, convulsions, or tail arch at the doses tested, but baclofen, BPBA, and diazepam do produce hypothermia.

The effect of each drug was compared with its own control using one-way ANOVA with replications, followed by Dunnett's tests. In the case of groups receiving two drugs, the effectiveness of various antagonists against baclofen-induced effects was compared using a one-way ANOVA followed by Dunnett's tests. Two-way ANOVAs were used to compare the effects of the antagonist when administered alone with the effects when the antagonist was administered with baclofen. Each group was comprised of 6-9 animals.

RESULTS

Alcohol withdrawal resulted in hypothermia, tremor, and tail arch, and was stable between 5 and 6.5 h (data not shown). The hypothermic response (which was an average drop of 6°C) was not reversed by any of the ligands tested (i.e., diazepam, baclofen, phaclofen, BPBA, or CGP 35348; data not shown).

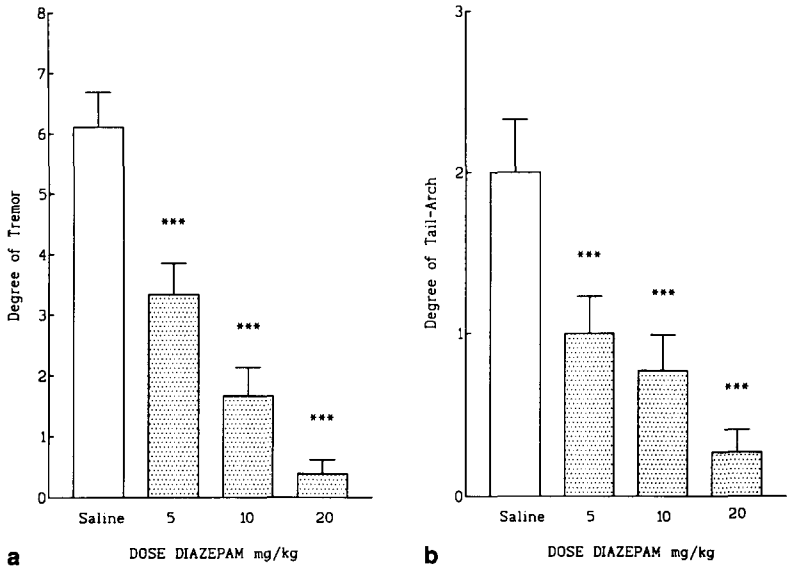

FIG. 1. Effects of diazepam on tremor and tail arch. Diazepam dose-dependently attenuated tremor and tail arch at doses 5, 10, and 20 mg/kg: ***$p < 0.005$ for all doses, compared with saline control. Results are expressed as mean ± SEM.

Diazepam (5, 10, and 20 mg/kg) dose-dependently attenuated tremor ($p < 0.005$ for all doses) (Fig. 1a). Similarly, Fig. 1b shows that diazepam dose-dependently decreased tail arch ($p < 0.005$ for all doses). In contrast, baclofen (5, 10, and 20 mg/kg) had no effect on tremor (Fig. 2a) or tail arch (Fig. 2b). However, baclofen dose-dependently induced significant convulsive behaviour at both 10 and 20 mg/kg ($p < 0.005$) (Fig. 2c).

The antagonists phaclofen (50 mg/kg), BPBA (50 mg/kg), and CGP 35348 (300 mg/kg) were combined with a single dose of baclofen (20 mg/kg) (Fig. 3). BPBA had little effect, but phaclofen significantly attenuated baclofen-induced convulsions ($p < 0.05$), whereas CGP 35348 completely blocked the response ($p < 0.005$). When administered alone, neither phaclofen, BPBA, nor CGP 35348 exerted any proconvulsant effects.

Phaclofen alone (10, 30, and 50 mg/kg) had no significant effect on tremor (Fig. 4a); however, a dose of 50 mg/kg significantly attenuated tail arch ($p < 0.05$) (Fig. 4d) compared with saline control. Phaclofen administered with a single dose of baclofen (20 mg/kg) did not significantly affect tremor (Fig. 4a), or tail arch (Fig. 4d).

BPBA alone produced a significant decrease in tremor at 50 mg/kg ($p < 0.05$) compared with saline control (Fig. 4b).

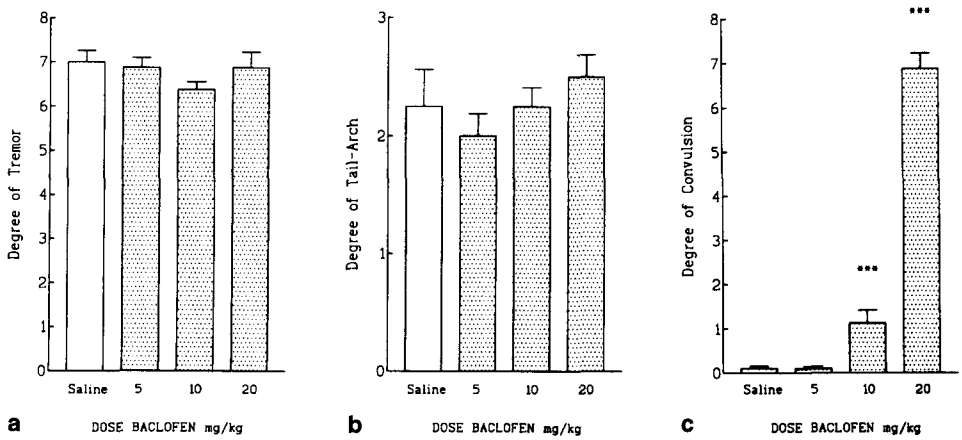

FIG. 2. Effects of baclofen on tremor, tail arch, and convulsion. Baclofen had no effect on tremor or tail arch, but induced significant dose-dependent convulsive behaviour at 10 and 20 mg/kg: ***$p < 0.005$ compared with saline control. Results are expressed as mean ± SEM.

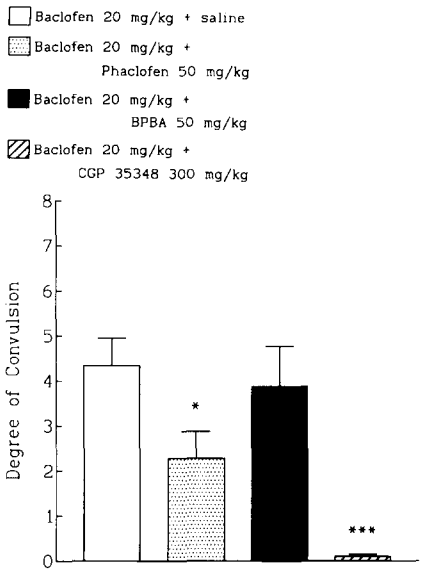

FIG. 3. Effects of phaclofen (50 mg/kg), BPBA (50 mg/kg), and CGP 35348 (300 mg/kg) against baclofen-induced convulsions (20 mg/kg). Phaclofen significantly attenuated convulsions compared with baclofen alone: $*p < 0.05$. BPBA had no significant effect and CGP 35348 significantly and completely blocked the response compared with baclofen alone: $***p < 0.005$. Results are expressed as mean ± SEM.

The same doses of BPBA did not significantly alter tail arch (Fig. 4e). When BPBA was administered concurrently with baclofen (20 mg/kg), tremor was significantly reduced at doses 10 and 30 mg/kg ($p < 0.01$, $p < 0.05$ respectively) (Fig. 4b), but there was no effect on tail arch (Fig. 4e).

CGP 35348 (100, 200, and 300 mg/kg) had no significant effect on tail arch, either alone or in combination with baclofen (20 mg/kg) (Fig. 4f). However, CGP 35348 alone significantly reduced tremor at 200 and 300 mg/kg compared with saline control ($p < 0.05$, $p < 0.01$, respectively). Moreover, in combination with baclofen (20 mg/kg), tremor was reduced at 200 and 300 mg/kg ($p < 0.01$) (Fig. 4c).

Results of two-way ANOVAs revealed that there were no significant interactive effects that would indicate modification of the effects of the antagonists (phaclofen, BPBA, and CGP 35348) by baclofen (Fig. 4).

DISCUSSION

The assessment developed for alcohol withdrawal in this study is similar to others used for mice (29), and included hypothermia (34), tremor, and tail arch (15). Tremor was characterised by whole-body spasm, with forelimb extension and facial grimace when held up by the tail. Hypothermia was insensitive to diazepam, indicating that it may be mediated by a different neurochemical mechanism, or may be a carryover from alcohol intoxication rather than a true withdrawal symptom. Other types of behaviour displayed spontaneously during withdrawal included apparent hallucinations, convulsive behaviour, back arch, vocalisations, hyperactivity, and hypoactivity, but none of these particular symptoms occurred at a frequency that justified measurement.

An earlier study with rats found that baclofen attenuates withdrawal-induced tremor (11). In contrast, we found that baclofen, when administered alone, did not reduce withdrawal tremor at any of the doses tested, nor did it attenuate tail arch. However, it is interesting to note that when 20 mg/kg of baclofen was coadministered with the antagonist CGP 35348 tremor was reduced dose dependently. Coadministration of baclofen with BPBA also produced significant attenuation at some doses, though this was not dose dependent. Moreover, when BPBA and CGP 35348 were administered alone, a dose-dependent reduction was also seen. Phaclofen alone had no effect. In contrast to the effects on tremor, the action of these three antagonists, both alone and in combination with baclofen, on tail arch was without effect, although the highest dose of phaclofen produced a significant decrease when administered alone. In summary, $GABA_B$ ligands BPBA and CGP 35348 appear to reduce alcohol withdrawal tremor, but the magnitude of the change is small when compared to the effect of diazepam. Moreover, there are no significant interactive effects between antagonists administered alone and in the presence of baclofen.

Interestingly, baclofen significantly induced dose-dependent convulsions in the withdrawing mice, characterised by whole body rolls and twists, head rolls, thrashing, and swimming type movements of fore and hind limbs. These doses of baclofen (10 and 20 mg/kg), when administered in the absence of alcohol withdrawal, did not induce convulsive behaviour, but did produce significant muscle relaxation. Furthermore, phaclofen attenuated the convulsions induced by baclofen, and CGP 35348 completely blocked the response. In contrast, BPBA had little effect. The comparative efficacy of phaclofen and CGP 35348 in blocking the effects of baclofen on alcohol-related responses is similar to the difference found in our earlier research (21). Some of our other studies have also shown BPBA to have poor antagonistic properties in vivo (20,21). The action of the antagonists indicates that the mechanism involved in this type of baclofen-induced convulsant behaviour is $GABA_B$ specific. The fact that convulsant behaviour, more than tremor or tail arch behaviour, appears to be $GABA_B$ mediated suggests that different mechanisms may be involved for these withdrawal symptoms.

There are other studies suggesting that the $GABA_B$ receptor is involved in seizure mediation. For example, research has shown that in lethargic (*lh/lh*) mice that exhibit spontaneous absence seizures, $GABA_B$ antagonists suppress these seizures, whereas baclofen exacerbates them (19). Interestingly, an increased number of $GABA_B$ receptors in this particular mouse strain has been shown (26). There are other studies to suggest that baclofen is proepileptic in both animals (6,8,30,32,40,41) and humans (2,36,39). Moreover, efforts have recently been directed towards testing $GABA_B$ antagonists for clinical use as potential antiabsence seizure therapy (24,31). Conversely, there is evidence showing that baclofen exerts an antiepileptic effect in some animal models of epilepsy (3,13,22). Thus, it appears that there is a complex relationship between $GABA_B$ receptors and seizures, and baclofen may augment some seizures and inhibit others (37). It is worth noting that the mechanism of action of other pro- and antiepileptic drugs is not always well understood, and efficacy is dependent upon a wide range of factors, including the type of seizure elicited (33).

One possible mechanism by which baclofen may elicit convulsions during alcohol withdrawal is through action at autoreceptors, or presynaptic inhibitory interneurons, thus inducing an overall disinhibitory state (6,32). Another possible mechanism of action is an interplay between low threshold calcium currents (T-currents) and $GABA_B$ receptors, where T-channels are deinactivated by $GABA_B$ receptor-mediated

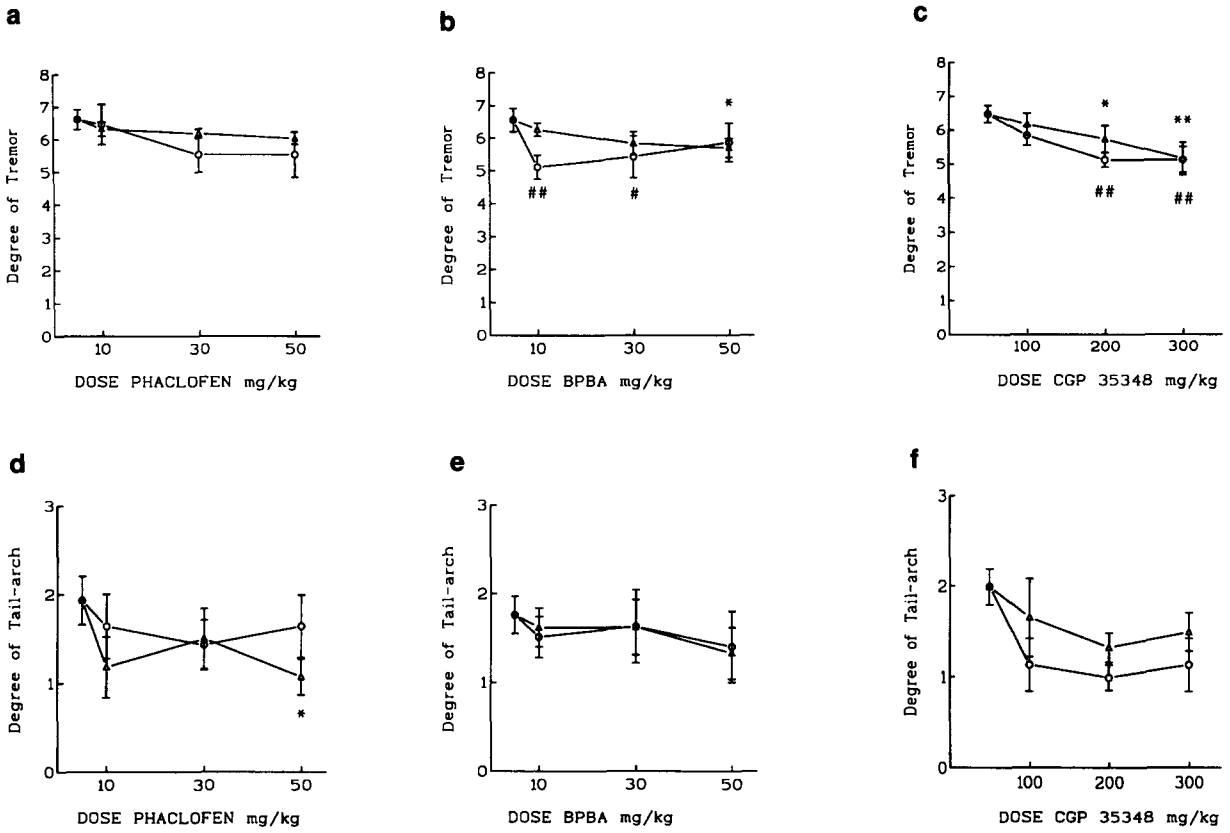

FIG. 4. Dose-response effects of the antagonists phaclofen, BPBA, and CGP 35348 alone (△), and in combination with baclofen 20 mg/kg (○), on tremor and tail arch where (●) represents saline control. Phaclofen alone, and in the presence of baclofen, had no significant effect on tremor. Phaclofen alone significantly attenuated tail arch at 50 mg/kg: $*p < 0.05$; however, it had no significant effect in conjunction with baclofen. BPBA reduced tremor when administered alone at 50 mg/kg: $*p < 0.05$, and also attenuated tremor in the presence of baclofen at 10 mg/kg: $\#\#p < 0.01$, and 30 mg/kg: $\#p < 0.05$. BPBA was without significant effect on tail arch, both in the absence and presence of baclofen. CGP 35348 attenuated tremor when administered alone at 200 mg/kg: $*p <$ 0.05 and 300 mg/kg: $**p < 0.01$, and also when coadministered with baclofen at 200 and 300 mg/kg: $\#\#p < 0.01$. CGP 35348 had no significant effect on tail arch both alone and in the presence of baclofen. No statistically significant interactive effects were observed for either tremor or tail arch with any of the antagonists when action alone was compared with effect in conjunction with baclofen.

hyperpolarisations, thus generating wave discharges (19). In the present study, the administration of alcohol may have led to the development of a predisposition to epileptiform convulsions, or a kindling-type effect, thus making the mice more sensitive to the proconvulsant effects of baclofen (8,14).

It appears then that baclofen exerts a proconvulsant effect in withdrawing mice and that the GABA$_B$ receptor may play a role in mediating this symptom of alcohol withdrawal. It has been suggested that baclofen reduces alcohol withdrawal tremor (11), and baclofen has also been shown to have a small ameliorating effect in opiate withdrawal (25). However, our investigations show that baclofen may be proconvulsant during alcohol withdrawal and, if there is some commonality across species, may be potentially dangerous in a clinical situation for those patients undergoing baclofen therapy and withdrawing from alcohol.

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