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Antiabsence Seizure Activity of Specific $GABA_B$ and γ-Hydroxybutyric Acid Receptor Antagonists

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SNEAD, O. C. III. *Antiabsence seizure activity of specific $GABA_B$ and γ-hydroxybutyric acid receptor antagonists.* PHARMACOL BIOCHEM BEHAV 53(1) 73–79, 1996.—γ-Hydroxybutyric acid (GHB) is a naturally occurring compound that has the ability to induce generalized absence seizures possibly by $GABA_B$-receptor-mediated mechanisms. The object of these experiments was to examine the effectiveness of a range of specific $GABA_B$-receptor agonists and antagonists of varying specificity, as well as the specific GHB-receptor antagonist NCS 382, in two experimental animal models of generalized absence seizures: one in which the seizures are induced by GHB and the other in which the seizures are induced by administration of low-dose (20-mg/kg) pentylenetetrazole. All specific $GABA_B$-receptor antagonists as well as the specific GHB-receptor antagonist produced blockade of experimental absence seizures in both models; pretreatment with $GABA_B$-receptor agonists resulted in generalized absence status epilepticus lasting for hours. These data confirm the concept that specific $GABA_B$-receptor antagonist activity confers antiabsence seizure activity, suggest that the same holds for specific GHB-receptor antagonists, and raise the possibility that both GHB- and $GABA_B$-antagonist drugs have the potential to be useful therapeutic agents in generalized absence seizures.

Absence γ-Hydroxybutyric acid γ-Butyrolactone $GABA_B$ Epilepsy Seizure Rat Pentylenetetrazole Petit mal EEG Baclofen Phaclofen Saclofen

PETIT MAL or generalized absence seizures differ clinically and experimentally from other seizure types (2). Absence seizures occur in children and have the classic electroencephalographic (EEG) abnormality of 3/s spike wave discharge, which is associated with behavioral arrest and occasional automatisms, but no aura or postictal state (19). Pharmacologically, absence seizures respond to ethosuximide, valproate, and trimethadione (26), and are worsened by phenytoin and carbamazepine (28). A peculiar characteristic of generalized absence seizures is that, unlike generalized convulsive seizures, enhancement of γ-aminobutyric acid (GABA)-mediated activity potentiates clinical (23) and all experimental forms of generalized absence seizure activity and may be sufficient to produce bilaterally synchronous spike wave discharges (SWD) under certain conditions (12).

γ-Hydroxybutyric acid (GHB) is a naturally occurring short-chain fatty acid that is synthesized from GABA (31). This compound has biologic significance for two reasons. First, GHB has many properties that suggest it may have a role as a neurotransmitter or neuromodulator (37). Second, GHB has the ability to induce generalized absence-like seizures in a number of species (30), as well as to exacerbate absence seizures in other experimental models of this disorder (10), apparently by a GHB-receptor-mediated mechanism (16). The GHB model of generalized absence seizures in rat meets all of the criteria alluded to earlier, including its exacerbation by both $GABA_A$ and $GABA_B$ agonists.

The hypothesis that $GABA_B$-receptor-mediated mechanisms might be operative in the pathogenesis of generalized absence seizures was formulated in response to two observations in the laboratory. First, the neurophysiologic substrate in thalamus for absence seizures (i.e., the low-threshold calcium potential) has been shown to be mediated by the $GABA_B$ receptor (9). Second, a specific $GABA_B$-receptor antagonist,

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CGP 35348, blocked the occurrence of SWD in four experimental models of generalized absence seizures in rats (13, 17,33), including the GHB model (33).

GHB has been proposed to act at the $GABA_B$-postsynaptic receptor to produce absence-like seizures (3). However, there is some evidence to argue against this hypothesis. GHB has little or no affinity for [^{3}H]$GABA_B$-receptor binding, nor do $GABA_B$ agonists and antagonists have any affinity for the [^{3}H]GHB-binding site (34). Moreover, [^{3}H]$GABA_B$- and [^{3}H]GHB-binding sites are common only to the superficial cortical laminae in brain and have a different ontogeny (36). Finally, the concentration of GHB required to mimic the postsynaptic effects of $GABA_B$ agonists in rat is 1-3 mM (38,39), whereas the concentration of GHB in brain required to produce absence-like seizures in rat is 240 μM (32).

The object of these experiments was to test the hypothesis that absence seizures are mediated by a GHB/$GABA_B$-receptor complex and further, that both GHB- and $GABA_B$-receptor activity are needed for the manifestation of experimental absence seizures. Thus, antagonism of this putative GHB/$GABA_B$-receptor complex, either by specific GHB-receptor or $GABA_B$-receptor antagonists, would be predicted to result in attenuation or blockade of experimental absence seizures.

METHODS

Animals

Male Sprague–Dawley rats (Charles River Labs, Charles River, DE), weighing 250–300 g, were used for all experiments involving adult animals. These animals were housed singly, with ad lib access to food and water, and water, and maintained on a 12 L : 12 D cycle. All animals were drug-naive.

Surgeries and Recordings

Permanent epidural electrodes, and where indicated, a cannula in the lateral ventricle, were implanted in control and drug-treated animals under halothane anesthesia to allow continuous recording of the electrocorticogram (ECoG). A total of 7 days were allowed for recovery before the commencement of experiments. All ECoG recordings were made with animals in the freely moving state in shielded, heated, clear Plexiglas containers so that the behavioral response to drug could be observed and correlated with any drug-induced ECoG event. The ECoG was recorded continuously for 60 min before the administration of any drug, and for 3 h after the administration of γ-butyrolactone (GBL) or pentylenetetrazole (PTZ).

Drugs

GBL and PTZ, phaclofen, and 2-OH-saclofen were obtained from Sigma Chemical Co. (St. Louis, MO). (−)Baclofen, (+)baclofen, and (+)baclofen were gifts from Dr. John Daley. NCS 382 was a gift from Prof. J. J. Bourguignon. 3-Amino-propylphosphinic acid was a gift from Dr. W. Kreutner (Schering Plough, NJ). Phaclofen, 2-OH saclofen, and 3-APPA were given intracerebroventricularly (ICV). All other drugs were given intraperitoneally (IP). GBL was given in a dose of 100 mg/kg as the pure drug. In previous work standardizing the GHB model of generalized seizures, GBL has been used to induce the absence-like seizure because GBL produces exactly the same progression of EEG and behavioral events in the rat as GHB (25,27), but with a more rapid onset of action and predictable dose response (1). GBL is converted rapidly and irreversibly to GHB after parenteral administration (14,15) and is biologically inactive (32).

PTZ was given in a dose of 20 mg/kg, IP. This dose produces EEG and behavioral changes more similar to those observed in human absence seizures than higher doses of PTZ, which result in clonic seizures and spike trains (11,22). PTZ, the baclofen isomers, and NCS 382 were each dissolved in normal saline to produce a dosage volume of 1 ml/kg. Each dose of 3-amino-propylphosphinic acid (3-APPA), phaclofen, and 2-OH-saclofen was dissolved in normal saline in a volume of 1 μl for ICV administration. All control animals received normal saline, IP, in a dose of 1 ml/kg instead of the $GABA_B$ agonists or GHB antagonist, or normal saline in a dose of 1 μl, ICV, instead of the $GABA_B$ agonist or antagonists.

Isomers of baclofen [(−), (+), or (±)] were given IP in doses ranging from 0.5–5 mg/kg 60 min before either PTZ or GBL. The specific $GABA_B$-receptor agonist 3-APPA (20) was given ICV in doses ranging from 10–75 μg. The specific $GABA_B$ antagonists 2-OH saclofen or phaclofen (4) were each given ICV in a dose range of 10–200 μg. All drugs given ICV were administered 5 min before either PTZ or GBL. The specific GHB receptor antagonist NCS 382 (21) was given IP in doses ranging from 100–500 mg/kg 60 min before either PTZ or GBL.

Following GHB or PTZ administration, the experimental absence seizures were quantitated as described subsequently. Paired, drug-naive controls were used in all experiments using saline in lieu of the specific $GABA_B$-receptor agonists. In separate experiments each specific $GABA_B$-receptor agonist and antagonist, as well as NSC 382, was given alone across the same dose range as in the GBL/PTZ studies to determine whether the drug produced any ECoG or behavioral changes.

Data Analysis

The experimental absence seizures induced by both GHB and PTZ were objectively quantitated by measuring the duration of the bilaterally synchronous spike wave discharge (SWD) induced by these compounds. Latency was defined as the time in minutes from the administration of PTZ or GBL to the onset of SWD as recorded on ECoG. GHB- and PTZ-induced SWD durations were compared in drug-treated animals vs. paired saline controls controls. Means and standard errors were calculated for all SWD data. The data were expressed in latency of SWD onset (minutes) and cumulated SWD duration (seconds) for 20-min periods (11). Data were subjected to analysis by two-way analysis of variance (ANOVA) with time treated as a repeated measure. There were six animals in each group for all experiments. In dose-response studies, ED_{50}'s were calculated for the $GABA_B$ agonists and antagonists and the GHB antagonists in the GHB model of absence seizures. This was done by dividing the cumulative SWD duration in animals administered the drug in question by the cumulative SWD duration in control animals. The resulting percent control cumulative SWD duration duration was plotted (y axis) vs. log dose of the drug in question (x axis). A linear regression analysis analysis of these data was used to calculate ED_{50} and ED_{100} data.

RESULTS

Effect of Baclofen Isomers and 3-APPA in Experimental Absence Seizures

In control experiments, systemic administration of 100 mg/kg GBL resulted in bilaterally synchronous SWD associ-

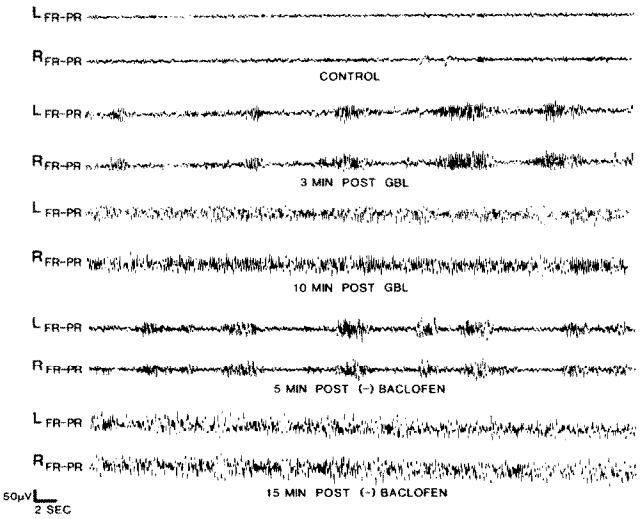

FIG. 1. Electrocorticogram of a rat that received either saline, 100 mg/kg GBL, or 5 mg/kg (−)baclofen, IP. Although both GBL and (−)baclofen administration resulted in SWD, there was a more striking behavioral concomitant in the GBL-treated animals with starring, behavioral arrest, and facial myoclonus.

ated with behavioral arrest, vibrissal twitching, and facial myoclonus, all within 4–5 min of administration (Fig. 1). The SWD had a frequency of 4–6 counts/s with an amplitude of 200–400 mV. Within 4 min of onset, the SWD became continuous. The response to PTZ was identical to that observed after GBL administration in terms of behavior and EEG findings, except that the SWD never became continuous in the PTZ-treated animals but occurred in bursts lasting 1–5 s.

(+) and (±)Baclofen and 3-APPA alone produced no discernable EEG or behavioral changes; however, (−)baclofen in the highest dose of 5 mg/kg produced bursts of bilaterally synchronous SWD associated with behavioral arrest, which appeared to be similar to that induced by both PTZ and GHB (Fig. 1). Latency from either GBL or PTZ administration to onset of SWD was not significantly changed by (−), (+), or (±)baclofen, or 3-APPA treatment. Also, the duration of SWD for GBL- or PTZ-induced absence was not significantly altered by (+)baclofen, the inactive $GABA_B$ agonist. In contrast, both of the active $GABA_B$ agonists, (−) and (±)baclofen, produced a highly significant ($p < 0.001$) prolongation of these durations (Fig. 2A and B). However the efficacy of the (−) and (±) isomers in this regard was different with an ED_{100} of 2.6 mg/kg and an ED_{50} of 1.2 mg/kg respectively; the racemic baclofen showed an ED_{100} of 5 mg/kg and ED_{50} of 3.6 mg/kg. ICV 3-APPA was also associated with a significant increase in SWD duration, but was not as effective in this regard as (−)baclofen (Fig. 3A and B). The ED_{100} of 3-APPA was 30 μg. Even maximal doses of 3-APPA did not exacerbate the SWD in either model to the extent of (−)baclofen. Animals pretreated with doses of (−)baclofen >3 mg/kg before the administration of either GBL or PTZ developed absence status epilepticus, which lasted 4–5 h.

Effect of 2-OH Saclofen and Phaclofen on Experimental Absence Seizures

Pretreatment with the $GABA_B$ antagonists 2-OH saclofen and phaclofen resulted in a significant decrease in the duration

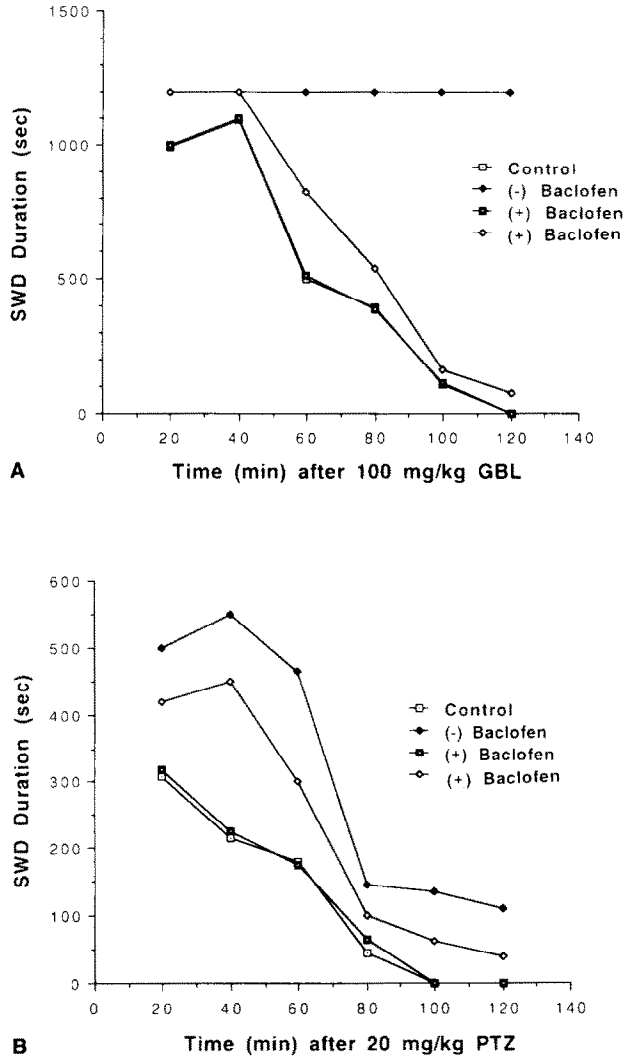

FIG. 2. (A) Mean SWD durations in groups of animals ($n = 6$ for each treatment group; SEM < 10%, and not shown) that received 3 mg/kg of either (−), (+), or (±) baclofen, IP, before 100 mg/kg GBL. The mean SWD durations at all time points until 320 min after GBL administration in the (−)baclofen-treated group were significantly increased ($p < 0.001$) compared with the means of the control groups for corresponding time points. Although the data shown are inclusive of 140 min following GBL administration, the continuous SWD continued uninterrupted in the (−)baclofen group for 240 min. The mean SWD durations at the 20-, 40-, 60-, and 80-min time points after GBL administration in the (±)baclofen-treated group were significantly increased ($p < 0.05$) compared with the means of the control groups for corresponding time points. The mean SWD durations in the (+)baclofen-treated animals were not significantly different from controls at all time points. (B) Mean SWD durations in groups of animals ($n = 6$ for each treatment group; SEM < 10%, and not shown) that received 3 mg/kg of either (−), (+), or (±)baclofen, IP, before 20 mg/kg PTZ. Both the (−) and (±)baclofen group showed mean SWD durations that were significantly increased ($p < 0.001$ and <0.03, respectively) at all time points compared with mean SWD durations at comparable time points in control animals. The mean SWD durations in the (+)baclofen-treated animals were not significantly different from controls.

of both GHB- (Fig. 4A) and PTZ-induced (Fig. 4B) absence seizures. Although the dose response curves for both phaclofen and 2-OH saclofen were steep, probably because of the ICV route of administration, phaclofen seemed to be more efficaceous than 2-OH saclofen in its ability to suppress experimental absence seizures in the models used. The minimum effective ICV dose of phaclofen that produced a significant decrease in SWD duration when compared with controls was 30 μg; that of 2-OH saclofen was 50 μg. The ED_{50} of phaclofen in terms was 50 μg, and that of 2-OH saclofen was 75 μg. Doses of 2-OH saclofen > 75 μg resulted in electrographic seizure activity with bursts of spikes, but with no behavioral correlates. Phaclofen alone produced no change in EEG or behavior from baseline. Latency from either GBL or PTZ administration to the onset of SWD was not significantly changed by either drug.

Effect of NCS 382 on Experimental Absence Seizures

NCS 382 pretreatment resulted in significant attenuation of SWD duration in both models of experimental absence seizures studied (Fig. 5A and B). The ED_{50} and ED_{100} of NCS 382 were 220 and 400 mg/kg, respectively. Latency from either GBL or PTZ administration to onset of SWD was not significantly changed by NCS 382.

DISCUSSION

The results of these experiments may be summarized as follows. First, all the of $GABA_B$ agonists used significantly exacerbated experimental absence seizures. The more specific the agonist, the greater was the potentiation with the inactive isomer (+)baclofen failing to alter significantly mean SWD durations in either absence model. The most potent $GABA_B$ agonist, (−)baclofen, appeared to induce absence-like seizures when given alone at high doses (Fig. 1). The relatively weak activity of 3-APPA in both absence models was surprising in view of the fact that this compound has been reported to be a potent agonist at presynaptic $GABA_B$ receptors associated with both excitatory and inhibitory synapses, and also to activate postsynaptic $GABA_B$ receptors (20). The regional distribution of 3-APPA after the ICV route of administration is unknown. The weak effect of this compound in the current studies might be due to limited diffusion after ICV administration.

Second, all of the $GABA_B$ antagonists used in this study attenuated or blocked experimental absence seizures with different ED_{50} values. Finally, the specific GHB antagonist used in these studies, NCS 382, attenuated seizures in both absence models.

GABAergic mechanisms have long been hypothesized to be involved in the pathogenesis of generalized absence seizures. Previous studies concerning the role of GABA in the neurophysiology and neuropharmacology of generalized absence seizures have been directed at $GABA_A$-mediated mechanisms (35). Although $GABA_A$ and $GABA_B$ agonists both prolong experimental absence seizure activity, only $GABA_B$ antagonists attenuate or block absence seizures (33). Additional evidence in support of a role for $GABA_B$-mediated mechanisms in the burst-firing of thalamocortical cells concerns data showing that the $GABA_B$ receptor mediates activation of the low-threshold calcium potential in the thalamus (9). Furthermore, IV administration of baclofen has been shown to increase rhythmic burst firing in thalamocortical cells of the ventrobasal complex (8), a finding commensurate with the current data.

Although there is strong evidence that postsynaptic

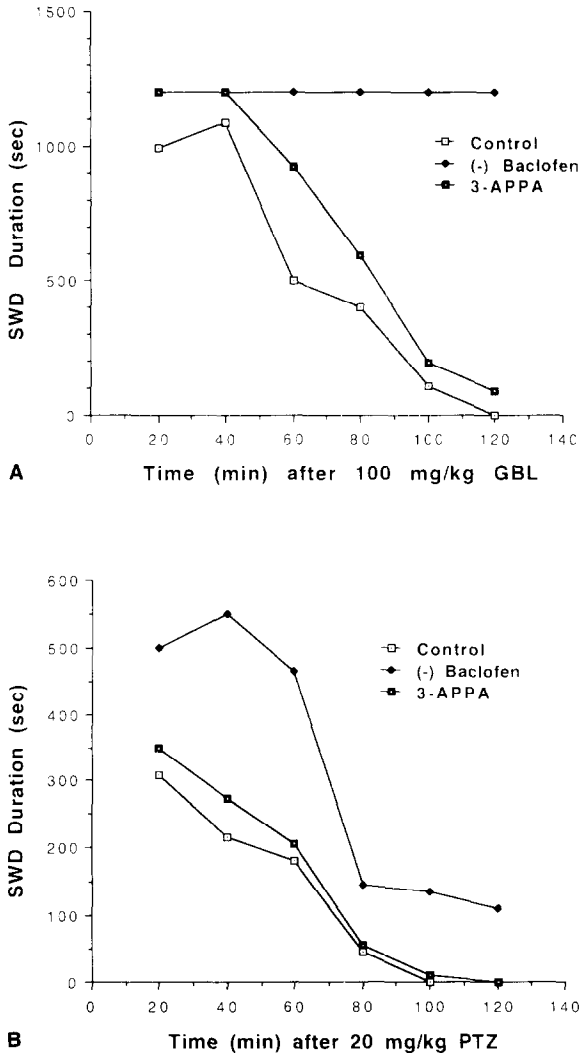

FIG. 3. (A) Mean SWD durations in groups of animals (n = 6 for each treatment group; SEM < 10%, and not shown) that received 3 mg/kg of either (−)baclofen, IP, or 25 μg 3-APPA, ICV, before 100 mg/kg GBL. The mean SWD durations at all time points after GBL administration in the (−)baclofen-treated group were significantly increased ($p < 0.001$) compared with the means of control animals for corresponding time points. The (−)baclofen data presented here are the same as those shown in Fig. 2A, and are presented for comparison purposes. The mean SWD durations at the 20-, 40-, 60-, and 80-min time points after GBL administration in the 3-APPA-treated group were significantly increased ($p < 0.05$) compared with the mean SWD durations of the control animals for corresponding time points. (B) Mean SWD durations in groups of animals (n = 6 for each treatment group; SEM < 10%, and not shown) that received 3 mg/kg of either (−)baclofen or 25 μg 3-APPA, ICV, before 20 mg/kg PTZ. The (−)baclofen-treated group showed significantly increased mean SWD durations ($p < 0.001$) at all time points compared with the same time points in control animals. The (−)baclofen data presented here are the same as those shown in Fig. 2B and are presented for comparison purposes. The mean SWD durations at the 20- and 40-min time points after PTZ administration were significantly increased ($p < 0.02$) in the 3-APPA-treated group compared with the mean SWD durations of control animals for corresponding time points.

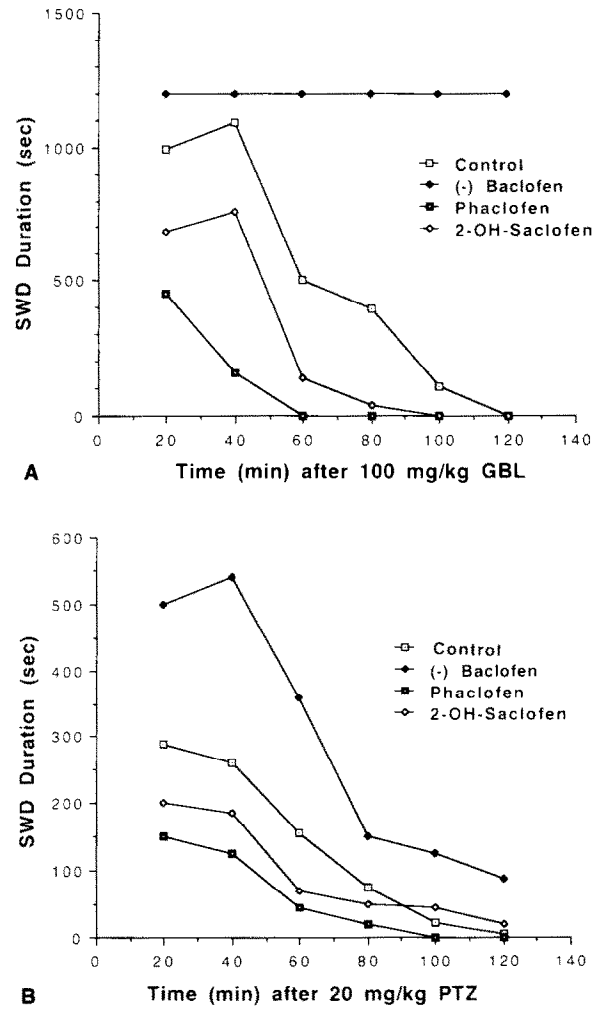

FIG. 4. (A) Mean SWD durations in groups of animals (n = 6 for each treatment group; SEM < 10%, and not shown) that received either 3 mg/kg (−)baclofen, IP; 75 μg 2 OH-saclofen, ICV; or 50 μg phaclofen, ICV, before 100 mg/kg GBL. (−)Baclofen resulted in a significant ($p < 0.001$) increase in mean SWD durations compared with control groups at all time points. The (−)baclofen data presented here are the same as those shown in Fig. 2A and are presented for comparison purposes. Phaclofen and 2-OH saclofen resulted in a significant reduction in mean SWD durations compared with control groups at 20, 40, 60, and 80 min following GBL administration. p for phaclofen at 20, 40, and 60 min following GBL administration was <0.001, and that for 2-OH-saclofen at the same time points was <0.05. (B) Mean SWD durations in groups of animals (n = 6 for each treatment group; SEM < 10%, and not shown) that received either 3 mg/kg (−)baclofen, IP; 75 μg 2 OH-saclofen, ICV; or 50 μg phaclofen, ICV, before 20 mg/kg PTZ. (−)Baclofen resulted in a signifcant ($p < 0.001$) increase in SWD duration at all time points compared with control groups. The (−)baclofen data presented here are the same as those shown in Fig. 2B and are presented for comparison purposes. 2-OH saclofen and phaclofen pretreatment resulted in a significant ($p < 0.05$ and 0.01, respectively) reduction in mean SWD durations at 20, 40, and 60 min following PTZ administration compared with mean SWD durations in control animals at those time points. Phaclofen pretreatment resulted in a significant ($p < 0.05$) reduction in mean SWD durations at 80 and 100 min following PTZ administration compared with control animals at those time points, but 2-OH-saclofen-treated animals showed no significant alteration in mean SWD durations at 80 and 100 min following PTZ administration compared with control animals.

$GABA_B$-receptor-mediated inhibitory postsynaptic potentials are important to the generation of absence-like rhythms in thalamic and cortical neurons (9,18), presynaptic $GABA_B$ receptors located on both GABAergic and glutamatergic nerve terminals (5,24) also control excitation and inhibition within thalamocortical circuitry via control of neurotransmitter release (6), and in this way may also have a role in absence seizures. Recent electrophysiologic and biochemical studies provide convincing evidence for the heterogeneity of presynaptic $GABA_B$ receptors located on GABAergic and glutamatergic nerve terminals based on specific $GABA_B$ receptor-antagonist sensitivity (5–7). Phaclofen antagonizes (−)baclofen-induced inhibition of GABA release without affecting (−)baclofen-induced inhibition of glutamate release.

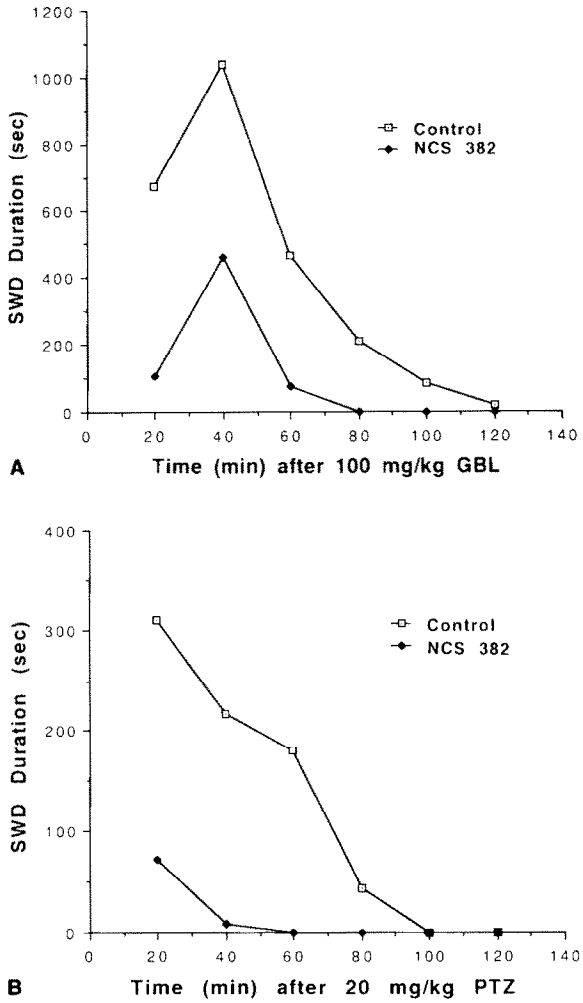

FIG. 5. (A) Mean SWD durations in groups of animals (n = 6 for each treatment group; SEM < 10%, and not shown) that received 300 mg/kg NCS 382, IP, before 100 mg/kg GBL. The NCS 382-treated group showed mean SWD durations that were significantly decreased ($p < 0.03$) at 20, 40, 60, 80, and 100 min following GBL administration compared with mean SWD durations in control animals at comparable time points. (B) SWD duration in groups of animals (n = 6 for each treatment group; SEM < 10%, and not shown) that received 300 mg/kg NCS 382, IP, before 20 mg/kg PTZ. The NCS 382-treated group showed mean SWD durations that were significantly decreased ($p < 0.02$) at 20, 40, 60, and 80 min following PTZ administration compared with control animals at those time points.

However, CGP 35348, a more potent $GABA_B$ antagonist than phaclofen in binding studies, but a fairly weak antiabsence compound, specifically blocks the effect of (−)baclofen on glutamate release with little effect on (−)baclofen-induced changes in release of GABA (5). The varying potencies of the $GABA_B$-receptor antagonists in the current studies are difficult to compare, because both drugs were given ICV. However, phaclofen did appear to be more effective than 2-OH saclofen in supressing experimentally induced generalized absence seizures in terms of ED_{50} values.

The antiabsence seizure activity of the specific GHB receptor antagonist NCS 382 is consistent with data showing that this compound also has antiabsence activity in a genetic rat model of absence seizures (21). Taken in conjunction with published data (13,17,33) and the current experiments showing that $GABA_B$ antagonists also possess antiabsence seizure activity, these data suggest that both GHB- and $GABA_B$-receptor sites may be involved in the pathogenesis of generalized absence seizures. Indeed, one might conclude that antiabsence activity is a defining feature of both GHB- and $GABA_B$-receptor antagonists.

In summary, the current experiments lend credence to the hypothesis that generalized absence seizures are mediated by a GHB/$GABA_B$-receptor complex and that both GHB and $GABA_B$ components of this putative complex may be involved in the genesis of absence seizures. Moreover, the data raise the possibility that $GABA_B$ and GHB antagonists may have clinical therapeutic potential in generalized absence seizures.

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