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Strychnine-insensitive glycine site antagonists attenuate a cardiac arrest-induced movement disorder

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Abstract

Male Sprague-Dawley rats underwent experimentally induced cardiac arrest and resuscitation, subsequently exhibiting involuntary jerking movements (myoclonus) with salient features similar to the human form of the disorder. The novel strychnine-insensitive glycine site antagonists ACEA-1011 (5-chloro-7-trifluoromethyl-1,2,3,4-tetrahydroquinoxaline-2,3,-dione) and ACEA-1021 (5-nitro-6,7-dichloro-quinoxalinedione) significantly attenuated the myoclonus in cardiac-arrested rats. (+)-HA-966, (±)-HA-966 (3-amino-1-hydroxy-2-pyrrolidinone), and felbamate (2-phenyl-1,3-propanediol dicarbamate) were also effective. Although the drugs vary in their selectivity for strychnine-insensitive glycine sites, they all possess antagonist activity at these sites. Vehicle injections (saline, dimethyl sulfoxide, water) were without effect and no obvious side effects were observed with any of the ligands tested in this study. Since hyperexcitability in the central nervous system is thought to underlie myoclonus, the attenuation of excitatory amino acid neurotransmission through antagonism of strychnine-insensitive glycine sites provides a logical mechanism of action for the antimyoclonic effects observed herein.

Keywords: Myoclonus; Hypoxia; NMDA (*N*-methyl-D-aspartate); Ischemia; HA-966; ACEA-1011; ACEA-1021; Glycine

1. Introduction

Activation of strychnine-insensitive glycine sites on the NMDA receptor allosterically modulates excitatory amino acid neurotransmission (cf. Thomson, 1989). Antagonists at these sites often elicit similar functional effects as competitive and non-competitive NMDA receptor antagonists (Anthony and Nevins, 1993; Koek and Colpaert, 1990; Morris et al., 1986; Watanabe et al., 1992). Because strychnine-insensitive glycine site antagonists provide a means for indirectly attenuating excitatory amino acid neurotransmission, they are of considerable interest in terms of their potential clinical relevance for treating disease states in which neural overactivity is involved.

One such disorder is myoclonus, which is characterized by sudden, brief, shock-like involuntary movements caused by active muscular contractions or inhibitions (Fahn, 1986). The involuntary jerking movements that are characteristic of myoclonus can occur spontaneously, or be induced by action or other stimuli such as noises, light flashes or touch (Fahn, 1986). Myoclonus can be precipitated by many pathological conditions affecting the central nervous system, including cardiac arrest (Fahn, 1979). Myoclonus resulting from cardiac arrest is considered a type of post-hypoxic myoclonus (Fahn, 1979) and in humans, its presence after resuscitation from cardiac arrest is predictive of poor recovery or increased possibility of death (Wijdicks et al., 1994). Although ischemia and other factors may contribute to myoclonus following a cardiac arrest, for the sake of consistency with the clinical literature, we will continue to refer to the disorder as post-hypoxic myoclonus.

Until recently, no realistic animal model was available to study post-hypoxic myoclonus. We recently described an animal model of cardiac arrest-induced post-hypoxic myoclonus with salient features that are similar to the human equivalent of the disorder (Truong et al., 1994). The etiology and pharmacology associated with the involuntary muscle jerks in these cardiac-arrested rats are consistent with post-hypoxic myoclonus, and appear to be distinguishable

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from seizures and startle responses (Truong et al., 1994).

In this paper, we tested the ability of (±)-HA-966, (+)-HA-966 (3-amino-1-hydroxy-2-pyrrolidinone), ACEA-1011 (5-chloro-7-trifluoromethyl-1,2,3,4-tetrahydroquinoxaline-2,3-dione) and ACEA-1021 (5-nitro-6,7-dichloro-quinoxalinedione) to attenuate audiogenic myoclonus in these cardiac-arrested rats. All four compounds possess preferential affinity for strychnine-insensitive glycine sites, although (±)-HA-966 is also known to have γ-aminobutyric acid (GABAergic) actions (Foster and Kemp, 1989; Lufty et al., 1994; Singh et al., 1990a; Woodward et al., 1993). In addition, various concentrations of the novel anticonvulsant felbamate (2-phenyl-1,3-propanediol dicarbamate) were tested (Bourgeois et al., 1993; Faught et al., 1993; Leppik et al., 1991; Sachdeo et al., 1992; Theodore et al., 1991). Although the mechanism of action of felbamate is still debated, it is to our knowledge the only clinically available compound that is thought to act, at least in part, as a strychnine-insensitive glycine site antagonist (McCabe et al., 1993).

2. Materials and methods

2.1. Cardiac arrest procedure

Male Sprague-Dawley rats (Zivic Miller, Zelinople, PA, USA; 200–250 g) underwent cardiac arrest and resuscitation as described in detail elsewhere (Truong et al., 1994). All procedures followed those approved by the University of California Irvine Institutional Animal Care and Use Committee. Briefly, rats were fasted for 12–24 h prior to surgery. The animals were then anesthetized, tracheotomized, and attached to a ventilator and polygraph. Body temperature was maintained at 38.5°C using a servo-feedback circuit. A femoral vein and artery were cannulated for the delivery of drugs and monitoring of blood pressure, respectively. Rats were paralyzed with succinylcholine to facilitate the cardiac arrest, which was induced with transthoracic intracardiac injections of KCl and cessation of ventilation. Resuscitation began 8 min subsequent to the arrest. The animals were then weaned from the ventilator, extubated, and allowed to recover for at least 4 days prior to behavioral testing.

2.2. Drugs

(±)-HA-966 and (+)-HA-966 were obtained from Research Biochemicals International (Natick, MA, USA) and prepared in saline. ACEA-1011 and ACEA-1021 were kindly provided by Dr. Eckard Weber (Department of Pharmacology, University of California Irvine, Irvine, CA, USA) and dissolved in dimethyl sulfoxide (DMSO). Felbamate was obtained from Carter Wallace (Cranbury, NJ, USA) and administered as a suspension in water. All of the drugs were prepared on the day of behavioral testing.

2.3. Behavioral testing

Although the cardiac-arrested rats exhibited spontaneous myoclonus, audiogenic myoclonus was chosen as the behavioral endpoint because it persists for a longer period of time (Truong et al., 1994), and the time-locked nature of the response to auditory stimuli facilitates the quantification of the severity of the abnormal movements. Using previously described procedures, the cardiac-arrested rats were evaluated for audiogenic myoclonus after allowing them to recover for at least 4 days after resuscitation (Truong et al., 1994).

Briefly, the rats were exposed to a train of 45 acoustic stimuli (95 dB, 40 ms, 1 Hz clicks generated by a metronome) and the muscle jerks to each click were scored as follows: 0 – no reaction; 1 – ear twitch; 2 – ear and head jerk; 3 – ear, head, and shoulder jerk; 4 – whole body jerk; and 5 – whole body jerk of such severity that it caused a jump. The sum of the scores for the 45 clicks yielded the total score for each rat. Thus, the maximum score was 225 and the minimum was 0; in practice, the minimum score was rarely below 45. In our initial report, the average score for a normal, non-cardiac-arrested rat was 73 ± 16 while the average score for a cardiac-arrested rat was significantly higher at 157 ± 13 (Truong et al., 1994). Therefore, using this scoring system, a 50% reduction in the myoclonus score of a cardiac-arrested rat approximated a normal response. The scoring system was implemented in this manner because it was possible that a drug might incapacitate a cardiac-arrested rat to the point where it was incapable of responding, thus yielding a score that was significantly lower than a normal rat.

The baseline (time 0) score for each rat was determined prior to drug administration. Following this determination, a drug or control vehicle was administered and the rat was retested 30, 60, 90 and 120 min later. The following drugs and concentrations were tested in cardiac-arrested rats: ACEA-1011 (50, 25, and 10 mg/kg, $n = 13$; i.p.), ACEA-1021 (50 and 25 mg/kg, $n = 10$; i.p.), felbamate (1000 and 500 mg/kg, $n = 12$; p.o.), (±)-HA-966 (10 and 5 mg/kg, $n = 10$; i.p.), (+)-HA-966 (10 mg/kg, $n = 3$; i.p.), saline ($n = 7$; i.p.), DMSO ($n = 6$; i.p.), and water ($n = 6$; p.o.). Rats were tested a maximum of 8 times, with at least 48 h intervening between each drug administration.

As an additional control, normal rats underwent the same testing procedures as the cardiac-arrested animals to rule out the possibility that the changes elicited by the strychnine-insensitive glycine site antagonists were due to alterations in auditory perception (e.g. the

stimuli sounded softer) or the ability to respond to sounds. Normal animals with a baseline score of 73 or greater were used in this portion of the study. Since this cutoff (73) represents the mean score of normal animals previously reported (Truong et al., 1994), the animals used in this portion of the study represent normal rats exhibiting average or higher than average responses to the auditory stimuli. This criterion was set to facilitate the detection of drug-induced decreases in the responses of the animals. Normal animals were treated with (+)-HA-966 (10 mg/kg, $n = 6$), felbamate (1000 mg/kg, $n = 6$), or saline ($n = 6$).

2.4. Data analysis

The effect of the drug was represented as the percent change from the total score at time zero (baseline determination). Analysis of variance was used to compare effects between drugs and doses. Student's t-test was used for comparisons between two groups. For all of the statistics, a significance level of $P < 0.05$ was used.

3. Results

3.1. Cardiac-arrested rats

There were no significant differences between the changes in myoclonus scores produced by saline, water, and DMSO ($F(2,18) = 0.65$; n.s.; Fig. 1). Therefore, the various vehicles were combined into a single control group for the rest of the analyses. All of the other compounds tested in this study (ACEA-1011, ACEA-1021, (±)-HA-966, (+)-HA-966, felbamate) significantly reduced the myoclonus in cardiac-arrested rats.

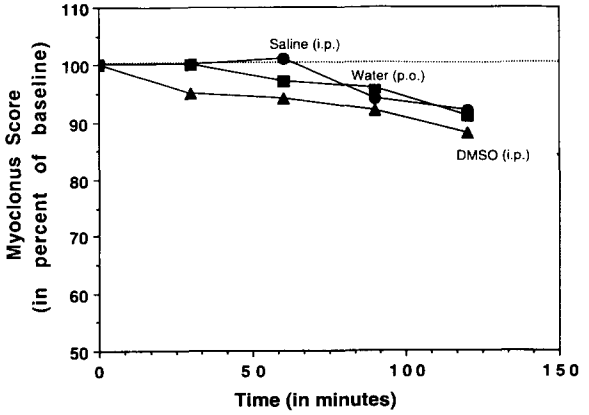

Fig. 1. Vehicle injections of saline, water, and DMSO had no significant effect on the severity of audiogenic myoclonus exhibited by cardiac-arrested rats ($F(2,18) = 0.65$; n.s.). 100% signifies no change from the baseline (pre-injection) myoclonus score. For the sake of clarity, no standard error bars are shown in the graph, but they ranged from 2–6%.

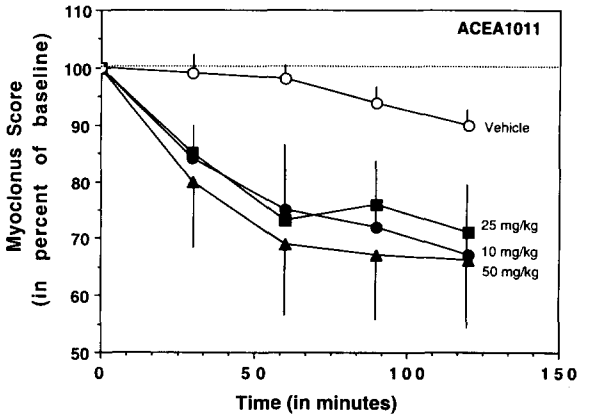

Fig. 2. Treatment of cardiac-arrested rats with the novel strychnine-insensitive glycine site antagonist ACEA-1011 (10, 25, and 50 mg/kg, i.p.) significantly attenuated audiogenic myoclonus ($P < 0.006$). 100% represents no change from the baseline (pre-injection) myoclonus score, while 50% approximates the response of a normal, non-cardiac arrested rat.

The novel strychnine-insensitive glycine site antagonists ACEA-1011 and ACEA-1021 attenuated myoclonus in a dose-dependent manner (ACEA-1011 $F(3,30) = 5.31$; $P < 0.006$ and ACEA-1021 $F(2,28) = 12.84$; $P < 0.001$; Figs. 2 and 3). An analysis of variance also revealed dose-dependent attenuation of the severity of the muscle jerks by (±)-HA-966 ($F(2,28) = 24.42$; $P < 0.001$; Fig. 4). Since the (+)-isomer of (±)-HA-966 is the active form, a single, high dose of (+)-HA-966 was also tested in the cardiac-arrested rats and found to significantly reduce the myoclonus in these animals ($t = 2.03$; $P < 0.05$). There was a significant difference between the extent of attenuation of myoclonus produced by equivalent doses of (±)-HA-966 and (+)-HA-966 ($t = 2.49$, $P < 0.05$; Fig. 5), with the racemic form producing a greater reduction in the severity of the muscle jerks. The novel anticonvulsant felbamate

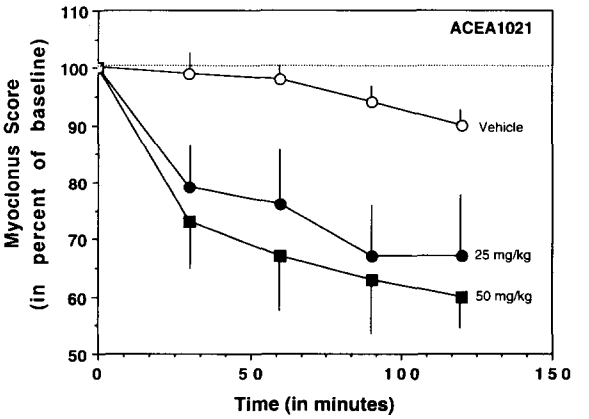

Fig. 3. Dose-dependent attenuation of myoclonus was produced by the novel strychnine-insensitive glycine site antagonist ACEA-1021 (25 and 50 mg/kg, i.p.; $P < 0.001$). 100% signifies no change from the baseline (pre-injection) myoclonus score, while 50% approximates the response of a normal, non-cardiac arrested rat.

likewise reduced the myoclonus in cardiac-arrested rats in a dose-related manner ($F(2,30) = 14.40$; $P < 0.001$; Fig. 6).

3.2. Normal rats

In contrast to the attenuation of the myoclonus in cardiac-arrested rats, the drugs failed to alter the auditory-induced responses in normal animals that were subjected to the same testing procedures as cardiac-arrested rats. An analysis of variance revealed no significant difference between the scores of normal rats

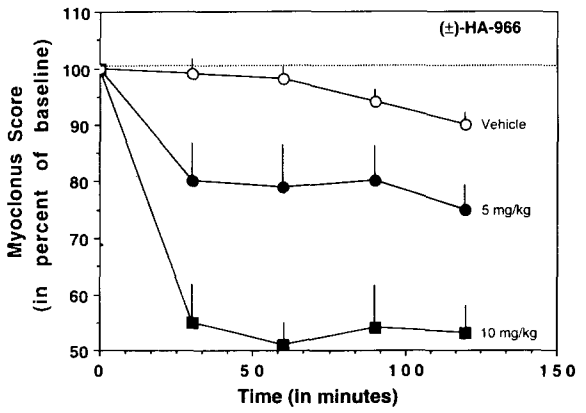

Fig. 4. Various doses (5 and 10 mg/kg, i.p.) of (±)-HA-966 were administered to cardiac-arrested rats. (±)-HA-966 dose-dependently attenuated the severity of myoclonus in cardiac-arrested rats ($P < 0.001$). 100% reflects no change from the baseline (pre-injection) myoclonus score of the cardiac-arrested rats, while 50% approximates the response of a normal, non-cardiac arrested rat.

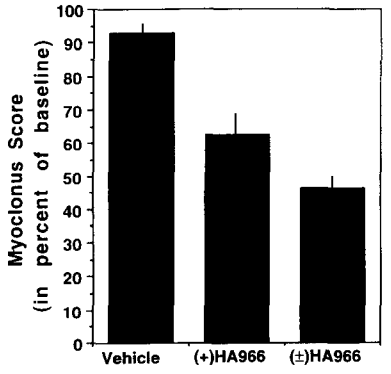

Fig. 5. The selective, strychnine-insensitive glycine site antagonist, (+)-HA-966 (10 mg/kg, i.p.), significantly reduced the severity of the myoclonus in the cardiac-arrested rats ($P < 0.05$). An equivalent dose (10 mg/kg, i.p.) of the racemic form of the drug, (±)-HA-966, produced an additional 26% attenuation in the myoclonus scores of the rats, a difference that is significantly greater than the effect produced by (+)-HA-966 alone ($P < 0.05$). The bars represent the mean ± S.E.M. of the peak change in myoclonus score during the 120 min testing session, with 100% signifying no change from the baseline (pre-injection) myoclonus score.

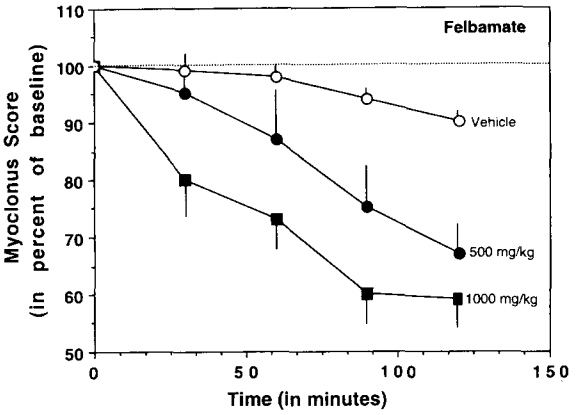

Fig. 6. The novel anticonvulsant felbamate also significantly reduced the myoclonus in cardiac-arrested rats in a dose-related manner (500 and 1000 mg/kg, p.o.; $P < 0.001$). 100% reflects no change from the baseline (pre-drug) myoclonus score, while 50% approximates the response of a normal, non-cardiac arrested rat.

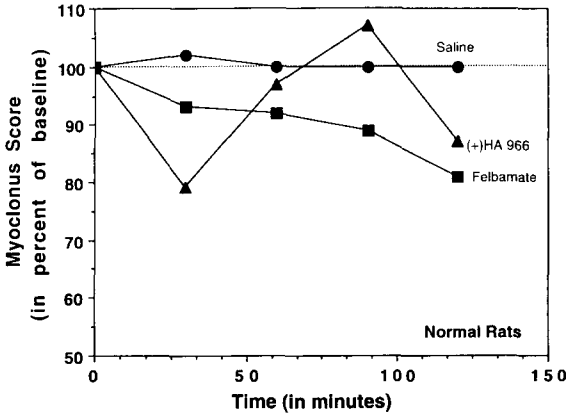

Fig. 7. Administration of felbamate (1000 mg/kg, p.o.) and (+)-HA-966 (10 mg/kg, i.p.) into normal rats did not produce a significant change in responses to auditory stimuli as compared to a vehicle injection of saline. The normal rats were exposed to the same stimuli in this portion of the study as the cardiac-arrested rats, suggesting that the attenuation in the mycolonus scores of cardiac-arrested rats could not be explained by possible changes in auditory perception or motor impairments that may have been caused by the drugs. For the sake of clarity, standard error bars are not shown in the graph, but they ranged from 3–18%.

treated with saline, (+)-HA-966, or felbamate ($F(2,15) = 3.39$; n.s.; Fig. 7).

4. Discussion

ACEA-1011, ACEA-1021, (+)-HA-966, (±)-HA-966, and felbamate significantly attenuated audiogenic myoclonus in the cardiac-arrested rats. In contrast, administration of various vehicles such as saline, water and DMSO was without effect. Although the drugs that were tested in this study vary in their selectivity for strychnine-insensitive glycine sites, they have all been

reported to act, at least in part, as antagonists at these sites (Foster and Kemp, 1989; Lufty et al., 1994; McCabe et al., 1993; Woodward et al., 1993). The data taken as a whole, together with the preferential selectivity of ACEA-1011, ACEA-1021, and (+)-HA-966 for strychnine-insensitive glycine sites (Lufty et al., 1994; Singh et al., 1990a; Woodward et al., 1993), strongly suggest the involvement of strychnine-insensitive glycine sites in the antimyoclonic effects observed herein. The more complicated mechanisms of (±)-HA-966 and felbamate are described in additional detail below.

(±)-HA-966 which has GABAergic effects in addition to its actions through strychnine-insensitive glycine sites, produced antimyoclonic effects in the cardiac-arrested rats. Although (±)-HA-966 exhibited greater antimyoclonic effects than the selective, (+)-isomer of the drug when equivalent doses were compared, the extent of the antimyoclonic effects of (+)-HA-966 (which presumably represent the actions mediated through strychnine-insensitive glycine sites), represented approximately 74% of the total antimyoclonic efficacy of (±)-HA-966. The additional 26% may be attributable to the GABAergic effects of the (−)-isomer (Singh et al., 1990a). Since myoclonus is associated with excessive activation of the central nervous system, the greater antimyoclonic efficacy of (±)-HA-966 as compared to the more selective (+)-HA-966 could be explained by the dual ability of (±)-HA-966 to (1) decrease excitation through antagonism of strychnine-insensitive glycine sites via the (+)-isomer, and (2) increase inhibition through GABAergic effects of the (−)-isomer. Since GABA antagonists and channel blockers induce myoclonus in animals (Patel and Slater, 1987; Tarsy et al., 1978; Vo et al., 1993), and drugs with GABA enhancing properties such as valproic acid and clonazepam have antimyoclonic effects in humans (Meldrum, 1986), it is likely that the GABAergic actions of (±)-HA-966 additively enhanced the antimyoclonic effects that were mediated through strychnine-insensitive glycine sites in this study.

The anticonvulsant and neuroprotective drug felbamate also reduced myoclonus in the cardiac-arrested rats. Although felbamate is thought to act, at least in part, through strychnine-insensitive glycine sites (McCabe et al., 1993), other mechanisms of action are also possible (e.g. indirect or non-specific actions at the NMDA receptor-associated ion channel, indirect GABA potentiating effects; White et al., 1992; Rho et al., 1994). Potential non-specific effects of felbamate are of particular concern because the doses used in the cardiac-arrested rats were higher than effective doses that have been reported in some anticonvulsant paradigms (Swinyard et al., 1986). However, since we have previously shown that the plasma concentrations of felbamate in the rats at the time of antimyoclonic activity were comparable to the top levels reported in humans during anticonvulsant trials (Truong et al., 1994), the doses, while high, are reasonable. The felbamate doses used for antimyoclonic effects are in fact more comparable to those used to obtain neuroprotective actions in vivo, an effect which also involves the modulation of excitatory amino acid activity (Wasterlain et al., 1992; Wasterlain et al., 1993). The need to use relatively high doses of felbamate in this study may therefore be related to the post-cardiac-arrested state of the rats. Although the precise mechanism for the antimyoclonic efficacy of felbamate is equivocal, it is noteworthy that felbamate acted in a dose-dependent manner in this study, suggesting the involvement of a receptor-mediated mechanism. Since felbamate is the only drug to our knowledge that is available clinically and is thought to act, at least in part, as a strychnine-insensitive glycine antagonist (McCabe et al., 1993), it was chosen for inclusion in this study because of its potential clinical relevance.

The ability of strychnine-insensitive glycine site antagonists to negatively modulate excitatory amino acid neurotransmission provides a logical mechanism of action for reducing myoclonus. Excessive excitation in the central nervous system is thought to contribute to myoclonus (Van Woert et al., 1986) and there is some evidence for the involvement of amino acids in the pathophysiology of the disorder (Chapman et al., 1991; Mathis and Ungerer, 1992; Pearce et al., 1991). It is thus conceivable that drugs that can reduce this effect have potential benefit for the treatment of the disorder.

Inasmuch as the drugs used in this study may have clinical relevance, it is noteworthy that they appear to have a high therapeutic index. In the present study, the drugs were able to attenuate audiogenic myoclonus in cardiac-arrested rats without exhibiting obvious side effects. Although adverse drug effects were not tested separately, the cardiac-arrested rats were carefully observed and monitored after drug administration because we were very concerned that the rats might be vulnerable to potential drug-induced adverse reactions. However, we did not notice any obvious side effects in the present study although we have in the past observed sedation and ataxia when other classes of antimyoclonic drugs were used (unpublished observations). It should be noted that other investigators have reported sedation or ataxia with (±)-HA-966, but these side effects were associated with higher doses than those required for the antimyoclonic effects in this study, and may be mediated through GABAergic actions of the (−)-isomer of the compound (Bonta et al., 1971; Dunn et al., 1992; Singh et al., 1990a,b). Other studies have in fact shown that (+)-HA-966 (i.e. the isomer that is more potent as a strychnine-insensitive glycine site antagonist), is devoid of numerous side

effects, including ataxia, within the dose range that produced antimyoclonic effects in our study and anxiolytic actions in another study (Dunn et al., 1992). The novel strychnine-insensitive glycine site antagonists, ACEA-1011 and ACEA-1021, have also been reported to have favorable therapeutic indices (Lufty et al., 1993, 1994), and in the clinic, felbamate is associated with low toxicity and a correspondingly high margin of safety (Faught et al., 1993; Leppik et al., 1991; Theodore et al., 1991). This pattern contrasts with the poor margin of safety and low efficacy of many competitive and non-competitive NMDA antagonists previously investigated by others (cf. Harris et al., 1992).

Although relatively little is known about the functional effects of strychnine-insensitive glycine site antagonists on auditory perception or motor control, the antimyoclonic effects observed in this study were probably not attributable to non-specific, debilitating effects of the drugs on these processes and systems. Normal (non-cardiac-arrested) rats that underwent the same behavioral testing as cardiac-arrested rats did not exhibit significant changes in their responses to the auditory stimuli after administration of the drugs, suggesting that the drugs did not impair the hearing of the rats per se, or the ability of the rats to respond to sounds.

Also, it should be noted that the present findings are not contradictory with previous reports of the potential role of glycine in myoclonus, which have tended to focus on the classical (inhibitory, strychnine-sensitive) glycine site. Strychnine, which is an antagonist at the classical glycine receptor, produces myoclonus in both humans and animals (Chung and Van Woert, 1984; Swanson et al., 1962) and deficiencies in the classical glycine receptor have been associated with genetic disorders with a myoclonic component in animals (Becker, 1990; Gundlach, 1990). Since glycine has inhibitory effects at its classical receptor, a deficiency, produced either genetically or through an antagonist, would result in the loss of inhibition. This disinhibition would then be expected to contribute to hyperexcitability in the nervous system, a state which is associated with myoclonus. Therefore, although glycine has different actions through separate sites: (1) inhibitory effects through the classical glycine receptor and (2) excitatory effects by modulating the NMDA receptor through the strychnine-insensitive glycine site, dysfunctions at either site can lead to the neuronal overactivity that is thought to contribute to myoclonus.

The antimyoclonic effects of strychnine-insensitive glycine site antagonists in cardiac-arrested rats, together with their anticonvulsant and anti-ischemic actions (Balster et al., 1993; McCabe et al., 1993; Vartanian and Taylor, 1991), suggest their potential utility for treating myoclonus, as well as other ischemia-related, seizure and movement disorders that are associated with excessive excitation in the central nervous system. The apparent high margin of safety of these compounds (Dunn et al., 1992; Lufty et al., 1993, 1994) is further encouraging because it suggests that strychnine-insensitive glycine site antagonists are particularly well-suited for use in vivo.

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