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Antimyoclonic effect of gabapentin in a posthypoxic animal model of myoclonus

Anumantha G. Kanthasamy, Toan Q. Vu, Richard J. Yun, Daniel D. Truong *

Parkinson and Movement Disorders Program, Department of Neurology, College of Medicine, University of California Irvine, Irvine, CA 92717, USA

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Abstract

The antimyoclonic property of the novel antiepileptic drug, gabapentin (1-(aminomethyl) cyclohexane acetic acid), was tested in cardiac arrest- and *p,p'*-DDT (1,1,1-trichloro-2,2-bis(*p*-chlorophenyl)ethane)-induced animal models of myoclonus. Gabapentin dose-dependently attenuated myoclonus in posthypoxic rats for more than 3 h. The drug was also found to be effective in controlling the early stages of seizures following the anoxic insult. In contrast, the drug was ineffective in controlling either myoclonus or seizures in *p,p'*-DDT-treated animals. These results suggest that gabapentin can be used as an effective therapeutic agent in an acute hypoxia/ischemia-induced neurological disorder. The data further indicate that distinct neurological mechanisms may be operating in the expression of myoclonus among posthypoxic and *p,p'*-DDT-induced animal models.

Keywords: GABA (γ-aminobutyric acid); Excitatory amino acid; Seizure; Ischemia; Neurological disorder; Drug screening; Antiepileptic

1. Introduction

The neurological disorder myoclonus is characterized by sudden, brief, shock-like involuntary contractions or inhibitions of a single and/or group of skeletal muscles (Fahn, 1986). The underlying biochemical mechanism(s) for this neurological disorder remain elusive, but imbalances in several neurotransmitter systems, predominantly serotonin (De Lean et al., 1976; Matsumoto et al., 1995b), γ-aminobutyric acid (GABA) (Nguyen et al., 1995; Patel and Slater, 1987; Snodgrass, 1990), monoamines (Artieda and Obeso, 1993; Mervaala et al., 1990) and glutamate (Chapman et al., 1991; Van Woert et al., 1986) have been documented. Nevertheless, the contribution of one or more of these neurotransmitters in the pathophysiology of myoclonus is enigmatic.

Animal models of myoclonus have been particularly useful in predicting novel therapeutic agents. Cardiac arrest and *p,p'*-DDT (1,1,1-trichloro-2,2-bis(*p*-chlorophenyl)ethane)-induced myoclonus are two animal models currently available to study the neurological basis of this disease (Hwang and Van Woert, 1978; Truong et al., 1989, 1994). These animal models exhibit neurological features that resemble myoclonus in humans. Among various antimyoclonic drugs, serotonergic agents and classical anticonvulsants have been shown to be the most effective in attenuating myoclonus in experimental animals and humans (Deahl and Trimble, 1991; De Lean et al., 1976; Truong et al., 1994). However, these drugs are unsuccessful in controlling severe forms of stimulus-sensitive posthypoxic myoclonus and seizures which can often be life-threatening (Krumholz et al., 1988; Wijdicks et al., 1994). Therefore, identification of new and improved antimyoclonic agents will facilitate better medical management of this neurological disorder.

Standard antiepileptic drugs which were developed empirically and have antimyoclonic properties unfortunately produce adverse neurotoxic effects, which is a limiting factor in their long-term tolerability. Gabapentin (1-(aminomethyl) cyclohexane acetic acid; Neurontin) is a new and novel antiepileptic drug that has higher efficacy and fewer side effects than conventional antiepileptic drugs. Although its precise mechanism of action remains elusive (Goa and Sorkin, 1993; Taylor, 1993), gabapentin has been found to be effective in maximal electroshock seizure and electrical kindling models (Bartoszyk et al., 1986; Bar-

* Corresponding author. 154 Med Surge I, Parkinson and Movement Disorders Program, Department of Neurology, University of California Irvine, Irvine, CA 92717, USA. Tel.: (714) 824-2571; fax: (714) 824-2938; e-mail: ddtruong@uci.edu.

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toszyk and Hamer, 1987). Recently, gabapentin has successfully been employed to treat both partial and generalized seizures in humans (Chadwick, 1993; Ramsay, 1994). In view of its potential clinical importance, and since some antiepileptic drugs have inherent antimyoclonic properties, it was decided to determine whether gabapentin has any such therapeutic potential in posthypoxic and *p,p'*-DDT-induced myoclonus models.

2. Materials and methods

2.1. Animals

Adult male Sprague-Dawley rats (200–225 g) were purchased from Zivic Miller Laboratory (Alison Park, PA, USA) and were housed two per cage in a temperature controlled room (23°C) with a 12 h/12 h light and dark cycle. Food and water were provided ad libitum. All experimental procedures were approved by the University of California Irvine Institutional Animal Care and Use Committee.

2.2. Animal models of myoclonus

Our previous cardiac arrest procedure using intracardiac injection of potassium chloride (Truong et al., 1994) was modified to a mechanical obstruction procedure to enhance the survival rate and facilitate the post-operative care of the animals. The rats were anesthetized with ketamine (100 mg/kg i.p.), and atropine (0.4 mg/kg i.p.) was administered to prevent respiratory secretion. Methoxyflurane was provided as supplemental anesthesia if necessary. The trachea was exposed to intube an 18 gauge catheter, which was then attached to the ventilator (settings: 425 ml/min NO_2, 175 ml/min O_2, 60 strokes/min, 5 cm H_2O positive end-expiratory pressure). The rats were placed on a heating pad, and EKG electrodes were attached. The body temperature was maintained at 37 ± 0.5°C with a rectal temperature probe controlled by a servo-feedback circuit. The left femoral artery and vein were catheterized (21 gauge) to monitor arterial blood pressure and for the administration of drugs, respectively. Cardiac arrest was initiated and maintained by obstructing the carotid artery with an occlusion device (L-shaped loop) and simultaneously compressing the chest using a modification of the procedure described by Kawai et al. (1992). Resuscitation began 7–10 min following the cardiac arrest by resuming ventilation (100 strokes/min, 100% O_2), manual thoracic compression, and intravenous injection of 10 μg/kg epinephrine and 4 mEq/kg sodium bicarbonate. After successful resuscitation, rats were weaned from the ventilator, the catheters removed, and the wounds sutured.

In the chemical-induced model, rats received 100 mg/kg of *p,p'*-DDT (in olive oil) through an orogastric feeding tube. In our hands, this dose of *p,p'*-DDT produced stimulus sensitive myoclonus in 90% of rats within 2 h of administration.

2.3. Behavioral testing

After at least 3 days of post-surgical recovery, the rats were tested for auditory stimulus-induced myoclonus as previously described (Truong et al., 1994; Matsumoto et al., 1995a). Rats were placed in clear Plexiglas cages (44×22 cm) at least 10 min prior to the behavioral testing and then they were presented with 45 clicks (95 dB, 0.75 Hz, 40 ms) of a metronome stimulus. The involuntary muscle jerks to each click were scored based on the following criteria: 0 – no jerks; 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 cumulative score of 45 clicks yielded the total myoclonus score for each animal. The baseline score was determined for each animal prior to injection of gabapentin (10–300 mg/kg i.p.) or an equivalent volume of saline. The score was determined at different time points over the 3 h testing session. In the case of the 10 mg/kg dose, the testing was conducted over an 8 h period.

In *p,p'*-DDT-treated rats, gabapentin was administered when the animals exhibited audiogenic myoclonus which was usually 2–3 h after the neurotoxin treatment, but before they displayed spontaneous myoclonus and seizures (Truong et al., 1989; Pranzatelli et al., 1994). Audiogenic seizures in posthypoxic rats were quantitated using the rating scale of Jobe et al. (1992), which assigns scores from 0 (no seizure) to 9 (generalized tonic-clonic seizure with complete hindlimb extension). The spontaneous myoclonus and seizure in *p,p'*-DDT-treated rats was calculated as a percentage of animals that exihibited these behaviors as compared to the saline-treated group.

2.4. Statistics

The data were expressed as means ± S.E.M. The significance of differences between treatments was determined using analysis of variance, and the significance was accepted at $P < 0.05$ or better.

3. Results

The onset of behavioral abnormalities in the posthypoxic model appeared to be time related. Rats exhibited audiogenic seizures within 12 h of 7–10 min of cardiac arrest. The intensity of these seizures appeared to reach a maximum between 18–26 h, then faded progressively and disappeared completely at around 48–60 h. The types of seizures exhibited by the rats included tonic, partial with wild running behavior, and generalized clonic-tonic with loss of consciousness. After 3 days of recovery following cardiac arrest, rats exhibited stimulus-sensitive myoclonus.

The myoclonus was very intense at 3–10 days, with the severity fading after this time.

3.1. Effect of gabapentin on stimulus-sensitive myoclonus in posthypoxic rats

The ability of gabapentin to reduce posthypoxic myoclonus was tested 4–8 days after surgery (Fig. 1). Gabapentin treatment produced a significant dose-dependent antimyoclonic effect ($P < 0.05$). Post-hoc tests revealed significant differences between the treatment groups at 15–60 min, suggesting that the dose-responsive portion of the effect was attributable to these early time points. At 300 mg/kg, the effect was very rapid whereas at lower doses a late onset of the action was observed. There was no significant difference between the extent of antimyoclonic effect between the treatment groups at the later time points (90–180 min). However, even at the lowest tested dose (10 mg/kg), gabapentin displayed a profound antimyoclonic effect starting from 120 min. In some animals ($n = 5$), the behavioral testing was monitored for longer time points at the 10 mg/kg dose level, and the maximum antimyoclonic effect persisted for 180–300 min, with the effect declining thereafter and almost completely disappearing 7–8 h post-injection. Furthermore, administration of 30 or 100 mg/kg of gabapentin to a group of normal rats ($n = 4$ in each group) did not alter the baseline behavioral score to the auditory stimuli used to induce myoclonus in posthypoxic rats (70–90; data not shown). In addition, at these dose levels gabapentin treatment did not produce any visible adverse behavioral effects except mild somnolence in both normal and posthypoxic rats.

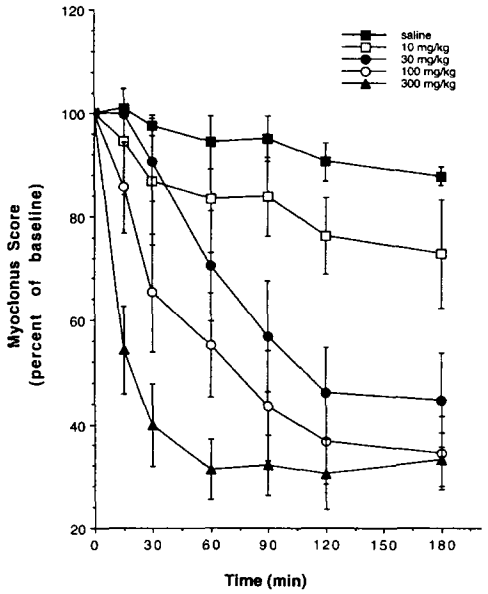

Fig. 1. Antimyoclonic effect of gabapentin in posthypoxia-induced myoclonus in rats. Rats were administered with either saline or gabapentin (10, 30, 100, or 300 mg/kg i.p.), and audiogenic myoclonus was monitored at different time points over a 3 h period. Data represent mean ± S.E.M. of 5–8 animals in each group. A significant difference from the saline-treated group ($P < 0.05$ or better) was noted at all the various time points except at 15 min for the 30 mg/kg dose, and 15–90 min for the 10 mg/kg dose.

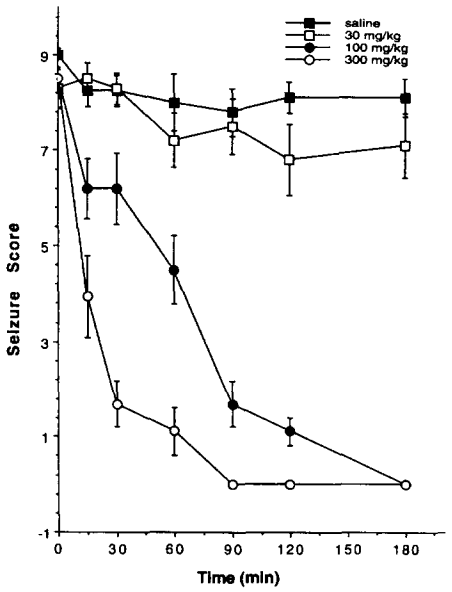

Fig. 2. Antiseizure effect of gabapentin in posthypoxia-induced myoclonus in rats. Rats were administered with either saline or gabapentin (30, 100 or 300 mg/kg i.p.), and audiogenic seizures were monitored at different time points over a 3 h period. Data represent mean ± S.E.M. of 4–6 animals in each group. A significant difference from the saline-treated group ($P < 0.05$ or better) was noted at the various time points at the 100 and 300 mg/kg doses.

3.2. Effect of gabapentin on audiogenic seizures in posthypoxic rats

Fig. 2 depicts the antiseizure activity of gabapentin on audiogenic seizures in posthypoxic rats. Administration of 30–300 mg/kg at 18–26 h after the cardiac arrest surgery significantly ($P < 0.05$) attenuated posthypoxic seizures. At the 30 mg/kg dose, the drug was not effective in controlling the audiogenic seizures whereas higher doses (100 and 300 mg/kg) elicited a rapid and prolonged antiepileptic action.

3.3. Effect of gabapentin on stimulus-sensitive myoclonus and spontaneous seizures in p,p'-DDT-treated rats

In order to ascertain whether gabapentin attenuates p,p'-DDT-induced myoclonus, the drug was tested in a p,p'-DDT model. None of the tested doses of gabapentin (30–300 mg) was effective in controlling myoclonus (Fig. 3). For the sake of clarity, only the effects of higher doses of gabapentin (100 and 300 mg) are depicted. In addition, gabapentin at 30–300 mg/kg was also tested to see whether it has antiepileptic effects on the p,p'-DDT-treated animals. p,p'-DDT induced seizures in 78–80% of gabapentin (30–300 mg/kg)-treated rats as compared to 82% in saline-treated animals, indicating the lack of signif-

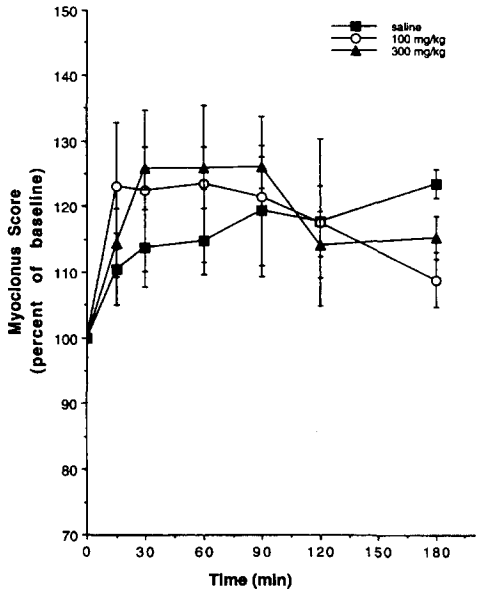

Fig. 3. Effect of gabapentin in p,p'DDT-induced myoclonus in rats. Rats were administered p,p'-DDT (100 mg/kg p.o.) and then they were treated 2 h later with either saline or gabapentin (30, 100 or 300 mg/kg i.p.). The audiogenic myoclonus was monitored at different time points over a 3 h period. Data represents mean ± S.E.M. of 4–5 animals in each group.

icant antiseizure effects of the drug in this chemical-induced animal model of myoclonus.

4. Discussion

The experimental results indicate that gabapentin, a new antiepileptic medication, can effectively attenuate posthypoxic myoclonus and seizures. In contrast, the drug was not effective in controlling p,p'-DDT-induced myoclonus and seizures. The animal models and methodological approaches employed in this study have previously been shown to be reliable for the identification of newer therapeutic agents for myoclonus (Matsumoto et al., 1995a; Truong et al., 1989, 1994). The dose and time-dependent effect of gabapentin reveals a specific pharmacological action in attenuating the posthypoxic form of this neurological disorder. Higher concentrations appear to act very rapidly in reducing myoclonus episodes, and are also very effective in reducing posthypoxic seizures. In addition, gabapentin treatment did not significantly alter the responses of normal rats to the auditory stimuli used to induce myoclonus in cardiac arrested rats, suggesting that the drug does not interfere with acoustic stimulated behavioral measurements. Taken together, this study strongly suggests that gabapentin possesses antimyoclonic properties that can effectively attenuate posthypoxic myoclonus. This result indicates that the drug may have clinical utility in controlling ischemia- and hypoxia-induced secondary neurological complications such as seizures and myoclonus.

Gabapentin is most effective when it is administered either orally or intraperitoneally. It is a stable, lipophilic, and neutral drug that easily crosses the blood-brain barrier and readily accesses the central nervous system (CNS) (Welty et al., 1993). Pharmacokinetic data indicate that the brain concentration of the drug readily reaches plasma levels within 1 h of administration (Welty et al., 1993). Despite some conflicting reports on the dose-response relationship of gabapentin in antiepileptic clinical trials (US Gabapentin Study Group), the majority of studies have documented the existence of a linear relationship (Sivenius et al., 1991; Goa and Sorkin, 1993). As enumerated in the present study, a dose-dependent effect was observed at 1 h, at a time point when the levels in the CNS attain plasma levels. At a later time point (3 h), the same maximum response was achievable at all the doses used in myoclonus testing. Furthermore, even at the 10 mg/kg dose, the antimyoclonic effect paralled the pharmacokinetic profile of the drug (Welty et al., 1993), confirming that the drug exhibits a specific antimyoclonic action. Since the drug does not undergo biotransformation in humans, its clinical potential for drug interaction appears to be minimal (Hooper et al., 1991). Gabapentin has a wide margin of safety between pharmacological and toxicological dosing, and is relatively free from sedative side effects (Browne, 1993). Thus, the favorable pharmacokinetic properties and safety profile lend credence to the clinical advantages of the drug over other conventional antiepileptic and antimyoclonic drugs.

The precise mechanism by which gabapentin exerts its antiepileptic action is unclear (Taylor, 1993). Although gabapentin is a structural analog of GABA, it does not directly interact with GABAergic systems (Rock et al., 1993). However, biochemical studies have indicated that gabapentin acts indirectly through GABAergic neurotransmission. It has been shown that therapeutically relevant concentrations of gabapentin enhance brain GABA levels in select brain areas by altering activities of metabolic enzymes such as glutamic acid decarboxylase and GABA-transaminase (Löscher et al., 1991; Taylor et al., 1992). The rapid onset of the antimyoclonic effects observed in the present study does not support the notion that changes in GABA metabolism are involved, at least in the early phase of the effect. However, increased GABA levels as a result of its metabolic effect may be recruited in the later phase of antimyoclonic activity. Furthermore, other GABAergic effects of gabapentin including an increase in stimulated release of GABA (Kocsis and Honmou, 1994; Honmou et al., 1995) have been reported. Taken together, it seems reasonable to speculate that a GABAergic component may be involved in the antimyoclonic property of gabapentin. This view is strengthened by the fact that hypofunctioning of GABAergic neurotransmission has been reported in other animal models of hypoxia/ischemia-in-

duced neurological disorder (Kawai et al., 1995; Shuaib et al., 1994).

In addition to the GABAergic mechanism, an alternative viable hypothesis exists which is based on interference by the drug on the L-amino acid transporter (Taylor, 1994). Recent studies involving the interaction of gabapentin with the L-amino acid transporter suggest that the drug may reduce glutamate excitation by blocking the uptake of other branched-chain amino acids. Also, one cannot rule out an excitatory-mediated mechanism in the posthypoxic model since it is a well-characterized biochemical change in hypoxic/ischemic CNS damage. Our recent study supports the involvement of an excitatory mechanism in myoclonus because strychnine-insensitive glycine antagonists reduced myoclonus in a posthypoxic animal model (Matsumoto et al., 1995a). It has also been reported that gabapentin (30–240 mg/kg i.p.) reduces excitatory amino acid-induced seizures in rats, indicating an antagonistic effect of the drug on neuronal excitation (Bartoszyk, 1983). Gabapentin has also been shown to interact with novel binding sites on neuronal membranes in areas with excitatory synapses (Hill et al., 1993). Considering the complex and diverse pathophysiology of myoclonus and the wide range of pharmacological actions of gabapentin, it is not surprising that multiple and overlapping pharmacological mechanisms may be operative in the antimyoclonic properties of the drug. Recent studies indicate that altered GABAergic and glutaminergic neurotransmission are critical components of audiogenic seizure initiation in experimental animals (Cordero et al., 1994; Faingold et al., 1994). Overall, it appears that alterations in 'excitation-inhibition homeostasis' may result in the expression of the neurological disorder, and that gabapentin somehow restores the homeostasis, thereby attenuating the myoclonus.

The inability of the drug to alter the *p,p'*-DDT-induced neurological syndrome suggests a dissimilar neurological mechanism in *p,p'*-DDT-treated animals, and emphasizes the need to use caution in extrapolating the biochemical and neurochemical findings in the chemical-induced model to posthypoxic myoclonus. Furthermore, this study indicates how different neural mechanisms can converge to manifest a neurological dysfunction such as myoclonus, and strengthens our earlier findings that the cardiac arrest-induced animal model of myoclonus may be a suitable model to study the neurological disorder.

In conclusion, this study demonstrates that gabapentin is a novel drug that possesses antimyoclonic and anti-seizure properties in a posthypoxic animal model of myoclonus, and that it may have therapeutic potential for treating neurological impairments associated with ischemic and hypoxic insults.

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