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Effect of gabapentin on sleep patterns disturbed by epilepsy

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ABSTRACT

For a long time, numerous sleep alterations induced by nocturnal epilepsy have been described. Such alterations include sleep fragmentation, decrement of sleep efficiency, increment of the wake time after sleep onset (WASO), increment of light sleep, and decrement of sleep depth. On the other hand, gabapentin (GBP), an antiepileptic drug analog of γ-aminobutyric acid (GABA) used as adjunctive and eventually, as a monotherapeutic treatment, induces a significant improvement in patients with both focal and secondarily generalized partial seizures. In experimental epilepsy models, this drug protects against pentylenetetrazol (PTZ)-induced convulsions. In consideration of such GBP properties, the aim of this work was to investigate its efficacy to protect against sleep disturbances provoked by convulsive seizures induced by the administration of PTZ.

Nine-hour (9-hour) polygraphic studies were carried out in chronically implanted male adult Wistar rats separated into 4 different groups of 6 individuals. Control recordings in each group were done after saline administration. One group received a SC Subcutaneous (SC) injection of 50 mg/kg of PTZ alone while the other three groups were injected with either 15, 30, or 60 mg/kg IP Intraperitoneal (IP) of GBP 30 min prior to PTZ (50 mg/kg SC) administration.

Animals displayed the whole range of electrophysiological and behavioral manifestations of the disease during the epileptic episodes induced by PTZ administration, and the states of vigilance were significantly altered. Insomnia occurred immediately after PTZ injection preceding the appearance of the first epileptic symptoms. Thus, both slow wave sleep (SWS) and rapid eye movement sleep (REM sleep) were completely inhibited during a relatively long period of time.

The disturbing effects of epilepsy on sleep decreased when animals were under GBP treatment. Improvement of sleep was dependent on the administered dose of this antiepileptic drug.

1. Introduction

The occurrence of epilepsy during sleep has been described by numerous authors through centuries [1]. Despite multiple attempts to control it, this neurological disease persists as a health issue of high relevance in our time.

Several sleep alterations induced by nocturnal epilepsy have been described. Such alterations include sleep fragmentation, decrement of sleep efficiency, lengthening of sleep latency, increment of the wake time after sleep onset (WASO), increment of light sleep (non-rapid eye movement (NREM) stages 1 and 2), and decrement of sleep depth (NREM stage 3 and rapid eye movement (REM) sleep). Patients having this type of epilepsy exhibit different diurnal symptoms such as excessive somnolence, attentional disturbances, as well as learning and memory deficiencies. These symptoms are originated by both sleep disturbances caused by epilepsy and antiepileptic pharmacotherapy.

Brain excitability varies throughout the sleep stages; this explains why certain types of epilepsy can be originated at a determined time of the sleep-waking cycle [2,3]. Nevertheless, the neurophysiological mechanisms involved in these brain excitability changes remain poorly understood. Different types of experimental animal models have been implemented in order to analyze the sleep disturbances induced by epileptic seizures [4,5]. In this context, it has been observed that the chemical model consisting of the administration of pentylenetetrazol (PTZ) induces generalized convulsive seizures by inhibiting γ-aminobutyric acid type A ($GABA_A$) receptors.

Seizures induced by PTZ, which show high similarity to generalized seizures in humans, are originated by activation of the reticular formation [6]. This model has been used as a test system for analyzing the effect of generalized seizures on sleep pattern organization and testing the efficiency of antiepileptic drugs [7].

On the other hand, gabapentin (GBP), an antiepileptic drug analog of γ-aminobutyric acid (GABA) that was designed as a GABA agonist, readily passes through the blood–brain barrier, but it has no affinity for the $GABA_A$-receptor complex. In clinical practice, the adjunctive and eventually monotherapeutic use of GBP induced a significant improvement in patients with both focal and secondarily generalized partial seizures [8]. In experimental epilepsy models, the drug protects against PTZ-induced tonic but not clonic convulsions [9].

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The precise pharmacological mechanism of GBP in humans remains unknown. However, its use has been widely expanded. It has been utilized for the treatment of several neurological disorders such as neuropathic pain and restless leg syndrome [10–13].

Gabapentin enhances slow wave sleep (SWS) in patients with primary insomnia. It also improves sleep quality by elevating sleep efficiency and decreasing spontaneous arousal. These findings suggest that GBP may be beneficial in the treatment of primary insomnia [14].

In consideration of the GBP properties described above, the aim of this work was to investigate the efficacy of GBP to protect against sleep disturbances provoked by convulsive seizures induced by the administration of PTZ.

2. Methods

The study was carried out in chronically implanted male adult Wistar rats. Keeping them under general anesthesia (sodium pentobarbital; 50 mg/kg Intraperitoneal (IP)), a pair of stainless steel electrodes was placed on the anterior (2 mm anterior to bregma, 2.5 mm lateral to the midline) and the posterior (5 mm posterior to bregma, 2.5 mm lateral to the midline) brain areas in order to monitor the cerebral electrical activity. Electrooculogram (EOG) was recorded by means of two steel electrodes placed on the external and internal canthi of the right eye. Electromyogram (EMG) was obtained with two stainless steel wires threaded into the nuchal muscles. The electrode leads were welded to a connector fixed on the skull with acrylic cement.

After a recovery period of at least seven days, rats with recording leads attached were placed separately in transparent Plexiglas boxes in order to observe their behavior across the experimental periods and correlate it to electrophysiological recordings. Animals had free access to food and water, and they were at an environmental temperature of 23 ± 2 °C, exposed to light for 12 h (07 to 19 h), and kept in the dark for 12 h (19 to 07 h). All animals were treated according to regulations specified by the Bioethical Committee and the Mexican Standard for the production, care and use of laboratory animals NOM-062-Z00-1999.

Animals were separated into 4 different groups of 6 individuals. Control recordings, in each group, were done after saline administration. In subsequent recordings, one group received an injection of 50 mg/kg (SC) of PTZ alone while each of the other three groups were injected with either 15, 30, or 60 mg/kg (IP) of GBP 30 min prior to PTZ administration at 50 mg/kg (SC) (Table 1). Gabapentin was obtained from Pfizer.

Polygraphic recordings were carried out during 9 continuous hours (from 10 to 19 h) throughout three consecutive days with a Model 7 Grass electroencephalograph at a paper speed of 3 mm/s with samples taken at other speeds. The first day was for control recording, the second day for the administration of substances, and the third one for recovering.

The states of vigilance were characterized by presenting a determined electroencephalogram EEG pattern (Fig. 1). During Wakefulness (W), electroencephalogram EEG displayed a low voltage fast activity pattern. When passing from W to SWS, the brain activity slowed down, and a high voltage slow waves pattern was installed; while during REM sleep, an EEG activity similar to that of W was observed.

Behavior was also different across the states of vigilance. During W, animals exhibited open eyes. They ate, drank, and performed grooming activities. During SWS, animals remained immobile with closed eyes. They displayed eye movement and muscular twitching during REM sleep.

Behavioral scoring of the Racine's scale was used to assess seizure intensity [15].

2.1. Data analysis

Polygraphic recordings were scored visually on the basis of one-second epochs, and the total time spent by animals in each state of vigilance per 9-hour periods was measured. Sleep scores were done by two experimenters. Additionally, average duration and frequency of the REM sleep phase were obtained.

Statistical analysis was performed by means of a mixed-design analysis of variance(ANOVA) model used both between and within-subject variables to determine significant differences among the effects induced by the drugs under investigation. Discrepancies with $p < 0.05$ were considered statistically significant.

3. Results

Under control conditions, animals exhibited the 3 different states of vigilance, identified as described in Methods.

3.1. Quantitative data

In control conditions, rats spent 232.6 ± 28.5 (Mean ± Standard deviation (SD)) min in W while they remained 264.8 ± 29.6 (Mean ± SD) min in SWS and 42.6 ± 11.56 (Mean ± SD) min in REM sleep during the 9-hour recording period. Total sleeping time corresponded to 56.93% of the 9-hour period; 7.89% was spent in REM sleep and 49.04% in SWS. The REM sleep phases occurred only after several minutes of SWS and were never observed immediately following W. Animals presented an average number of 32.3 REM sleep episodes across the 9-hour recording time.

3.2. Induction of seizures

All of the animals administered with PTZ presented generalized tonic–clonic seizures displaying a tonic phase with hind limb extension and a clonic phase with myoclonus of the anterior and posterior limbs. At the same time, there was synchronized bursting EEG activity and trains of EEG high voltage fluctuations coinciding with motor events (Fig. 2).

Sometimes, dissociation between EEG activity and behavior was observed. Animals were behaviorally awake while displaying an EEG activity constituted by high amplitude slow waves.

3.3. Latency to the myoclonic jerks and generalized tonic–clonic seizures

The administration of PTZ induced progressively installed motor alterations, including head nodding, masticator movements, and myoclonic twitches of the face and limbs. The first seizure parameter observed after administration of this drug was the myoclonic jerk, displayed 63 ± 4 s (Mean ± SD) after PTZ administration. It was characterized by body shakings and after 30 min, was followed by generalized seizures. In relation to behavioral characteristics, the animals reached the behavioral level 5 of the Racine scale.

Table 1
Experimental groups.

Group	Day 1 Control	Day 2 Drug administration	Day 3 Recovery
1	Saline solution	Pentylenetetrazol, 50 mg/kg (SC)	Postdrug administration recording
2	Saline solution	Gabapentin, 15 mg/kg (IP) + Pentylenetetrazol, 50 mg/kg (SC)	Postdrug administration recording
3	Saline solution	Gabapentin, 30 mg/kg (IP) + Pentylenetetrazol, 50 mg/kg (SC)	Postdrug administration recording
4	Saline solution	Gabapentin, 60 mg/kg (IP) + Pentylenetetrazol, 50 mg/kg (SC)	Postdrug administration recording

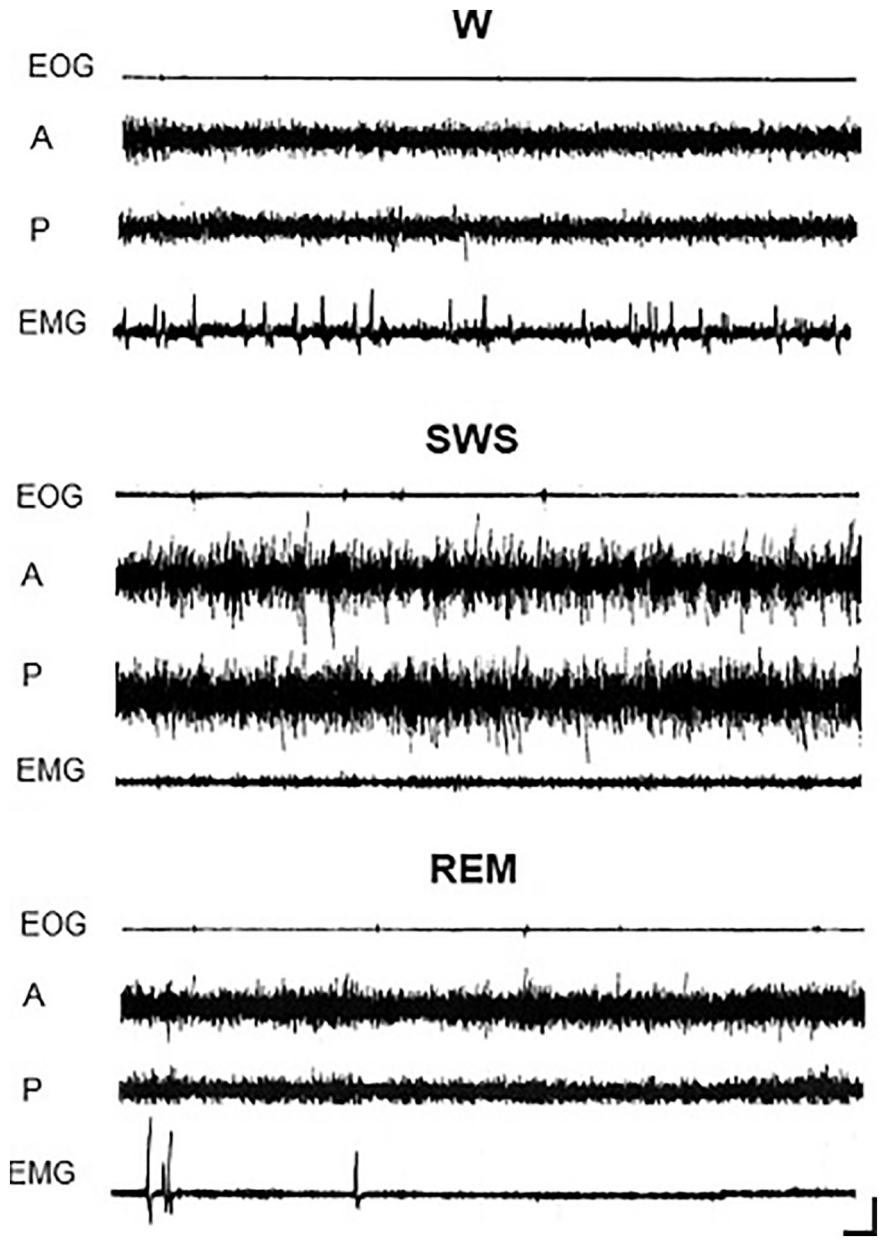

Fig. 1. States of vigilance during control conditions. EOG, Electrooculogram; A, Anterior cortex; P, Posterior cortex; EMG, Electromyogram. Cal. 5 s, 50 μv.

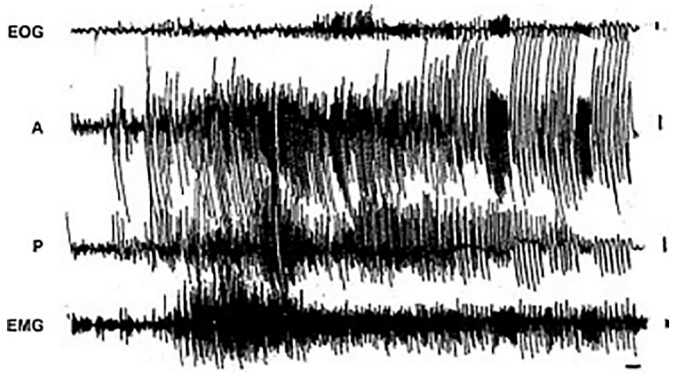

Fig. 2. Polygraphic recording during epilepsy induced by PTZ. EOG, Electrooculogram; A, Anterior cortex; P, Posterior cortex; EMG, Electromyogram. Cal. 5 s; 50 μv.

Following PTZ administration, time spent by animals in W increased from 232.6 ± 28.5 min (Mean ± SD) to 444.6 ± 41.9 (Mean ± SD) min. This increment was statistically significant ($p < 0.05$) compared with the values registered on the control and the recovery days. Levels of W similar to those registered for subjects under control conditions were observed during the subsequent recording day (Fig. 3). In contrast, both SWS and REM sleep were significantly reduced ($p < 0.05$) compared with those during the control and the recovery days. The decrement was more conspicuous for REM sleep. Slow wave sleep went from 264.8 ± 29.6 to 93.3 ± 41.7 (Mean ± SD) min and REM sleep from 42.6 ± 11.6 min to 2.1 ± 0.1 (Mean ± SD) min (Fig. 3).

When seizures stopped, the amount of time spent in both sleep phases remained under the registered value on the control day throughout the 9-hour recording period of PTZ administration. During the subsequent recording day (recovery day), both SWS and REM sleep showed

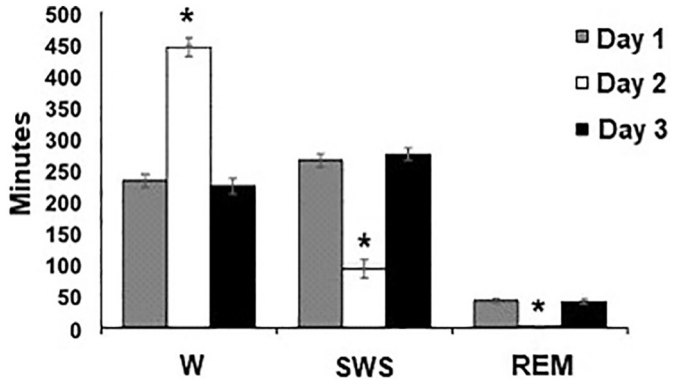

Fig. 3. Mean duration of the vigilance states under control conditions (Day 1) and after PTZ administration (Day 2). A significant increment in W (*$p < 0.05$) was observed on the day of PTZ administration concomitantly with a significant decrement both in SWS and REM sleep (*$p < 0.05$). Control levels of states of vigilance were recovered one day after PTZ administration (Day 3).

a trend of recovery as indicated by similar values to those of animals under control conditions (Fig. 3).

The average duration of REM sleep stages was 78 ± 21 (Mean ± SD) s under basal conditions. This average value did not show variations statistically significant on subsequent recordings following PTZ administration when REM sleep was occasionally present.

Total time spent by animals in each state of vigilance was recovered one day after PTZ administration, since a similar value to that of animals in basal conditions was observed. Increment compensatory of REM sleep was not observed.

3.4. Effects of GBP + PTZ

The administration of different doses of GBP exerted an inhibitory effect on convulsive seizures and sleep disturbances induced by PTZ injection.

Animals receiving a low dose of GBP (15 mg/kg) showed only slight variations in the amounts of W and SWS in comparison with those of animals under control conditions both on the PTZ administration day and on the following day (recovery day). In contrast, the amount of REM sleep significantly increased ($p < 0.05$) in comparison with that in rats under control levels (49.26 ± 3.4 min), on the day of drug administration (64.45 ± 5.6 min), and on the following one (recovery day) (Fig. 4). In relation to behavioral characteristics, the animals under the effect of GBP low dose reached the behavioral level 3 of the Racine scale.

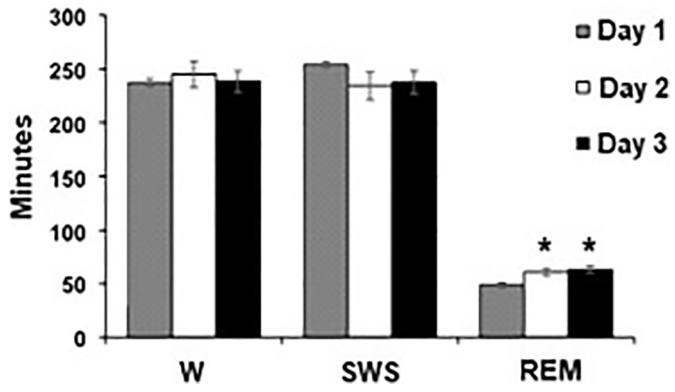

Fig. 4. Mean duration of the vigilance states under control conditions (Day 1) and after PTZ administration in gabapentin (15 mg/kg)-pretreated animals. Both W and SWS did not show significant changes across the three recording days. In contrast, REM sleep amount significantly increased (*$p < 0.05$) in comparison with control levels on the day of drug administration (Day 2) and the following day (Day 3).

When a 30 mg/kg dose of GBP was previously administered to animals treated with PTZ, W decreased significantly ($p < 0.05$) from 238.9 ± 27.2 to 192.8 ± 43.5 (Mean ± SD) min while SWS increased from 251.1 ± 23.4 to 278.0 ± 28.5 (Mean ± SD) min without reaching significant levels. At the same time, REM sleep showed a significant increment ($p < 0.05$) from 50.0 ± 5.1 to 69.2 ± 18.1 (Mean ± SD) min. Levels of the three states of vigilance remained without additional significant variations during the recovery day (Fig. 5). Convulsive behavior decreased to stage 1 of the Racine scale.

Under the higher dose of GBP (60 mg/kg), W diminished to minimal levels from 240.4 ± 28.4 to 181.4 ± 24.3 (Mean ± SD) min. In contrast, SWS increased from 251.3 ± 27.9 to 285.2 ± 22.6 (Mean ± SD), and REM sleep amounts also did from 48.3 ± 8.7 to 73.4 ± 12.3 (Mean ± SD) min. Similar levels for the three states of vigilance remained in the recovery day (Fig. 6).

Convulsive behavior displayed by animals reached the stage 1 according to the Racine scale.

As observed in dose–response curves, the effects exerted on the states of vigilance by PTZ administration were inhibited by GBP pretreatment. With increasing GBP dose administrated, the time spent in W decreased concomitantly (Fig. 7). While both SWS (Fig. 8) and REM sleep (Fig. 9) showed a tendency to increase.

3.5. REM sleep frequency

Under basal conditions, animals exhibited throughout the period recording an average amount of 32.8 ± 11.3 (Mean ± SD) REM sleep episodes. This value decreased to 3.8 ± 2.7 (Mean ± SD) episodes in the recording day after PTZ administration ($p < 0.05$, compared with the values of the control and the recovery day). Afterwards, an important recuperation was observed in GBP-pretreated animals on the subsequent recording day showing a value similar to that of animals under control conditions. The amount of these episodes was similar to that of control conditions without significant differences among the three different administrated doses: 25.3 ± 9.6, 28.9 ± 7.9, and 29.5 ± 16.2 (Mean ± SD) episodes respectively (Fig. 10).

4. Discussion

The animal model of generalized epilepsy implemented in this investigation displayed the whole range of electrophysiological and behavioral manifestations described previously by Racine [15] during the epileptic episodes induced by PTZ administration. These findings, confirmed by several authors [16–18], show that this model is a suitable option for experimental studies related to this type of epilepsy.

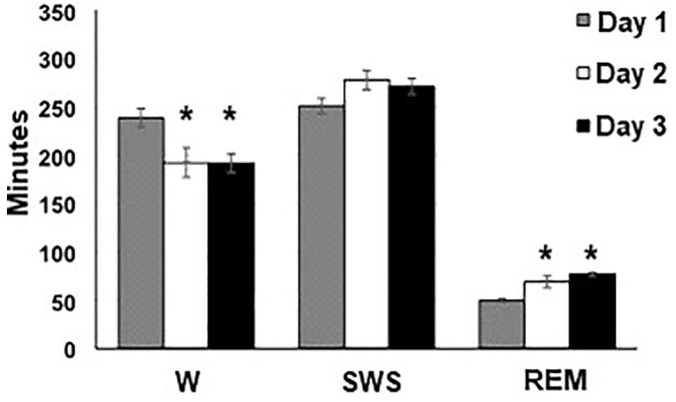

Fig. 5. Mean duration of the vigilance states under control conditions and after PTZ administration in gabapentin (30 mg/kg)-pretreated animals. A significant decrement (*$p < 0.05$) was observed in W during the days after drug administration (Day 2, Day 3) and a significant increase in REM sleep in those days while SWS did not show significant variations.

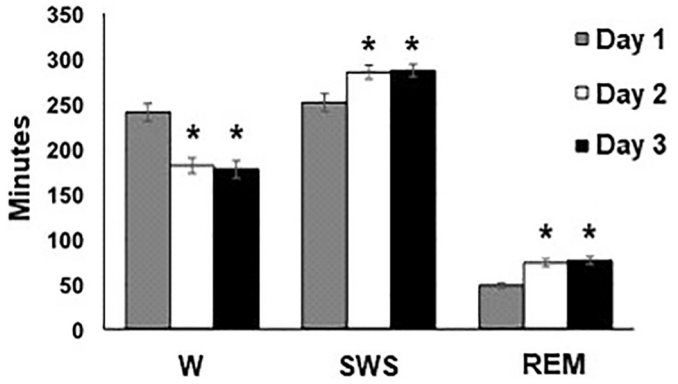

Fig. 6. Mean duration of the vigilance states under control conditions and after PTZ administration in gabapentin (60 mg/kg)-pretreated animals. Significant variations (*p < 0.05) were observed in the three states of vigilance. W decreased while SWS and REM sleep increased across the two days after drug administration (Day 2 and Day 3).

The convulsant effects of PTZ manifested 30 min after its administration induced the occurrence of spike–waves and polyspikes on the EEG and generalized seizures. These electroencephalographic manifestations have been associated with biochemical and histological alterations similar to those in humans with epilepsy [16,17].

It has been suggested that the pontine reticular formation participates in the generation and maintenance of generalized epileptic seizures [19–21]. In particular, the *Pontis caudalis nucleus* neurons mediated by N-methyl D-aspartate (NMDA) receptors are involved in the generation of behaviors related to seizure episodes [22]. Neurochemical studies have evidenced that PTZ binds to the picrotoxin site of the GABA receptor complex, disturbing the activity of GABA/Benzodiazepine (BDZ)-coupled chloride channel [23] and blocking GABA-mediated postsynaptic inhibition [24]. Additionally, it has been described that seizures provoked by PTZ are not mediated by benzodiazepine receptors [25].

The states of vigilance were significantly altered by the presence of generalized epilepsy induced by the administration of PTZ. Insomnia was immediately present after PTZ administration preceding the appearance of the first epileptic symptoms. Consequently, both SWS and REM sleep were completely inhibited during a relatively long period of time.

The inhibition of both sleep phases, particularly REM sleep, may be associated with repetition of complex partial attacks or secondary generalization of seizures.

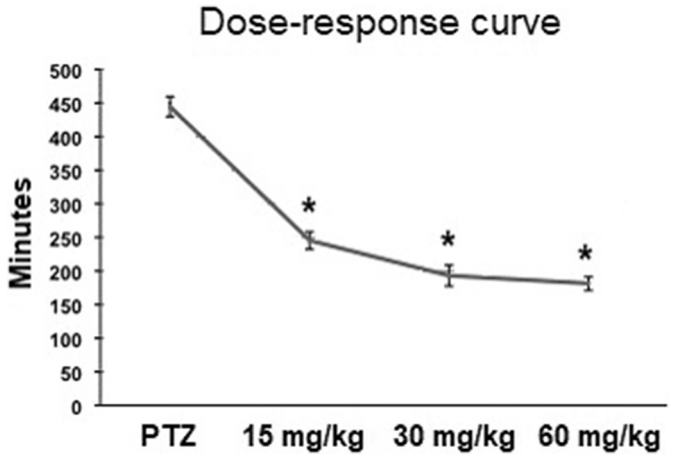

Fig. 7. Time spent in W by PTZ-treated animals under the effects of gabapentin. A significant decrement (*p < 0.05) in W was observed after gabapentin administration. Additionally, there is a gradual decrement related to drug dose, without reaching significant differences in relation to gabapentin administration dose.

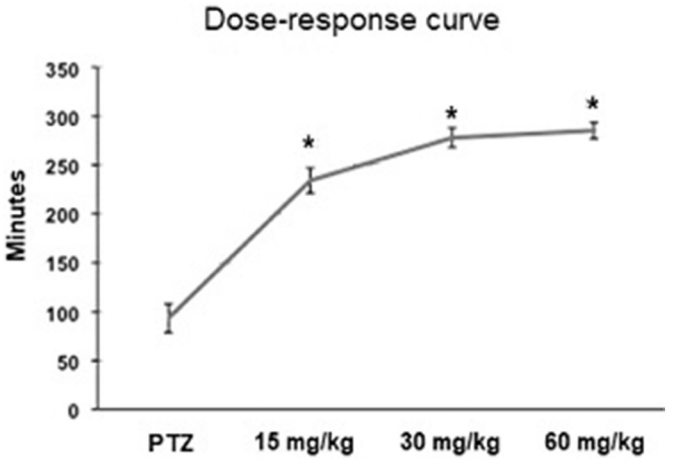

Fig. 8. Time spent in SWS by PTZ-treated animals under the effects of gabapentin. A significant increment (*p < 0.05) in SWS was observed after gabapentin administration. The additional increment related to gabapentin dose was not significant.

Pentylenetetrazol-induced epilepsy is related to reticular formation nuclei activation [26] that may be responsible for the significant increment of W. However, the mechanism by which this drug elicits its action is not yet well understood. Pellmar and Wilson [27] showed that PTZ mainly reduced the chloride channel conductance and to a minor extent, the sodium and potassium channels conductance. Similarly, Onozuka and Tsujitani [28] showed that PTZ causes neuronal bursting activity by altering the ionic conductance of sodium and potassium channels by changes in intracellular Ca^{2+}-related processes.

As previously described, there is a relationship between sleep, sleep deprivation, and epilepsy. However, the neurophysiological mechanisms for this relationship are not completely understood. It has been suggested that the relationship is reciprocal. In other words, both sleep and sleep deprivation have an excitatory effect on the genesis and propagation of the seizures [29]. This could explain the inhibition of both REM and SWS observed immediately after a single convulsive seizure.

The disturbing effects of epilepsy on sleep decreased when animals were under GBP treatment. Improvement of sleep depended on the administered dose of this antiepileptic drug. On day 2 of drug administration, the animals under low dose (15 mg/kg ip) reached the behavioral level 3 of the Racine scale while those under medium (30 mg/kg ip) and high (60 mg/kg ip) doses showed behavioral characteristics

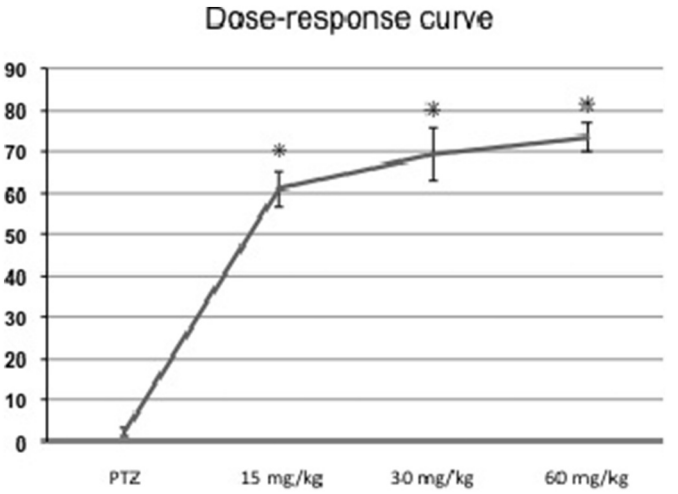

Fig. 9. Time spent in REM sleep by PTZ-treated animals under gabapentin effect. A significant increment in REM sleep is observed after gabapentin administration (*p < 0.05). The additional increment related to gabapentin dose was not significant.

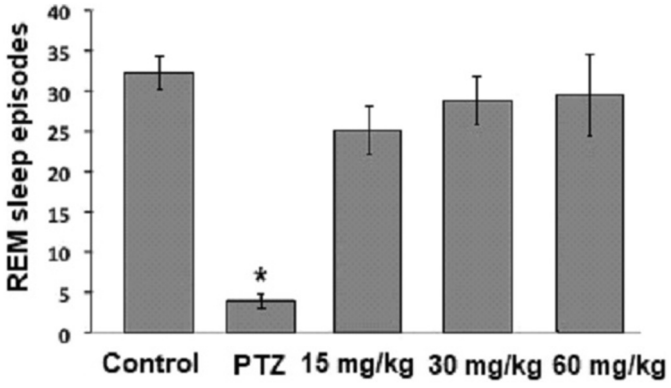

Fig. 10. Effect of administration of PTZ alone and gabapentin-pretreated animals on number of REM sleep episodes. A significant decrement in the amount of REM sleep episodes is observed by administration of PTZ alone ($p < 0.001$). In contrast, the amount of these episodes returned at control levels in the gabapentin pretreated.

corresponding to level 1. The behavioral levels displayed by GBP-treated animals were less intense than those without treatment. These findings suggest an inhibitory effect exerted by GBP on epileptic activity induced by PTZ. This effect may be exerted by activation of the chloride channels that induce postsynaptic inhibition by hyperpolarization due to an increment in extracellular GABA resulting from an increase in the glutamate decarboxylase. Likewise, GBP blocks the Ca^{++} transport to neuronal interior contributing to a reduction of neuronal excitability [30–32].

Both SWS and REM sleep were inhibited after PTZ administration since the time spent by animals in both sleep phases was reduced, remaining significantly lower than that of subjects under control conditions across the whole 9-hour recording period. The amount of sleep returned to baseline levels during the recovery day as described previously by Mexicano et al. [33]. In contrast, animals receiving PTZ after the administration of low (15 mg/kg ip) and medium (30 mg/kg ip) doses of GBP showed a decrement in epileptic activity, SWS amount was not affected while REM sleep showed an important increment. However, at a high dose of GBP (60 mg/kg ip), both SWS and REM sleep amounts increased significantly from 251.3 ± 27.9 to 285.2 ± 22.6 (Mean $\pm$ SD) and from 48.3 ± 8.7 to 73.4 ± 12.3 (Mean $\pm$ SD) min respectively.

These results suggest that the inhibition of epilepsy by GBP administration facilitates the triggering mechanisms of sleep in concordance to previous reports [4,34,35]. It is likely that facilitation of REM sleep induced by GBP results from "interference" of this drug on the $\alpha 2\delta 1$ subunit of voltage-gated P and N calcium channels, which modulate the acetylcholine activity that participates in REM sleep regulation [32,36–40].

Gabapentin is a drug that was developed based on the hypothesis that generating nonhydrolyzable analogs of GABA would lead to the development of an antiepileptic agent. While it is indeed a good anticonvulsant, its activity is not exerted on the GABAergic system but on the $\alpha 2\delta 1$ subunit.

The identification of the $\alpha 2\delta 1$ subunit as the receptor for this antiepileptic drug may be an important finding for sleep therapeutics in patients having nocturnal epilepsy.

Conflict of interest

There is no conflict of interest.

Acknowledgments

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