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Journal of Neurological Disorders & Stroke

Review Article

Effect of Epilepsy and Antiepileptic Treatment on Reference and Working Memory

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Abstract

Epilepsy is one of the most frequent neurological alterations affecting significantly the quality of life of the individuals who suffer it. Temporal Lobe Epilepsy (TLE) is one of the most severe types of epilepsies commonly presented in the world population. It is characterized by neuronal damage in regions of the limbic system, such as the amygdala and the hippocampus (mesial temporal lobe sclerosis). These lesions provoke alterations in cognitive processes, including learning and memory.

Since epilepsy is a highly prevalent disease in the world population, experimental models have been implemented to investigate its physiopathology and test the effectiveness of anticonvulsive drugs.

The Kainic Acid (KA) model to produce TLE in rats and phenobarbital (PB) as antiepileptic drug were used in this study. Four groups of rats trained on a spatial task were used and once they met the learning criteria, one group was administered with saline solution, the second group with PB, the third with KA, and the last group with PB+KA. Results indicate that the epileptic seizures induced by KA produced deficits on reference ($p<0.01$) and working memories ($p<0.001$). PB administered 30 minutes prior KA inhibited the development of *status epilepticus*, protected against alterations of reference memory and minimized those of working memory. These findings suggest that reference and working memories are a part of different functional systems.

Special Issue on

Epilepsy and Seizures

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Submitted: 06 February 2014

Accepted: 03 May 2014

Published: 10 May 2014

Keywords

- Epilepsy
- Antiepileptic treatment
- Epilepticus

INTRODUCTION

Epilepsy is one of the most frequent neurological diseases found in the world population. It has been estimated that about 50 million people in the world suffer this disease [1]. The World Health Organization (WHO) defines epilepsy as "a chronic affection of diverse etiologies, characterized by recurrent seizures resulting in excessive electrical discharges in a group of brain cells (epileptic seizures) independently of the clinic and para-clinic symptoms eventually associated". Different types of epilepsy exist; one of the most frequent is the Temporal Lobe Epilepsy (TLE) in which the epileptic seizures are originated in regions of the limbic system (amygdala, hippocampal formation, temporal cortex). The clinic manifestations of this type of epilepsy include affective and autonomous components, in addition to cognitive alterations. The TLE is partially complex and in some cases the conscience may be altered (*Commission on Classification and Terminology of the International League Against Epilepsy* [2]. This type of partial complex seizures may become secondarily generalized, producing tonic-clonic seizures or simply tonic or clonic seizures of the *grand mal* type. The epileptic seizures usually last from 3 to 30 minutes. When the seizures become recurrent in a period of more than 30 minutes, with or without loss of consciousness, they are called *status epilepticus*; however, there has been considerable rethinking about the precise duration that a seizure must last for it to be designated as such. *Status epilepticus* is an emergency medical situation due to its severe effects on the Central Nervous System (CNS) because it may produce progressive neuronal damage. In order to avoid this damage, pharmacological treatment is usually required.

The neuronal damage resulting from TLE is known as mesial temporal lobe sclerosis, which is characterized by neuronal loss and astrocytosis on the pyramidal cell layer in the regions of the hippocampal formation, parahippocampal cortex, entorhinal cortex, perirhinal cortex, and amygdala [3]. The degree of neuronal loss has been correlated to the intensity and severity of the seizures [4]. In addition to death and neuronal changes, as part of mesial temporal sclerosis, reduction in the amount of $GABA_A$, NMDA and kainate receptors in regions CA3 and CA1 of the hippocampus has been reported [5]. There is also sprouting of mossy fibers, astroglial activation and microglial responses [6], indicating reorganization of synaptic circuits [7].

Some patients suffering TLE show cognitive and psychiatric alterations such as amnesia, depression, irritability and anxiety [8-10]. Among the cognitive processes with major alterations in

patients with TLE are memory and learning [11,12] originated by neuronal damage in structures related to these processes, such as hippocampus and other regions of the temporal lobe. Intensity of memory alterations correlates with the degree of temporal mesial sclerosis in patients with TLE [13].

About 80% of epilepsies can be controlled by means of antiepileptic drugs. One of the drugs used as antiepileptic agent is phenobarbital (PB), which has shown to be adequate to control initial or secondary generalized seizures, as well as, partial seizures and the *status epilepticus* [14-16]. PB inhibits epileptic seizures via the $GABA_A$ receptor by increasing the inhibitory effect of the γ-amino butyric acid (GABA) and diminishing the glutamatergic and cholinergic excitation [17]. PB increases the efficacy of the $GABA_A$ receptor lengthening the opening of the chlorine (Cl^-) channels. The increased flow of (Cl^-) hyperpolarizes the postsynaptic neuron inhibiting the generation of epileptic activity [16]. At the same time, PB may inhibit at the presynaptic level, the liberation of the excitatory neurotransmitter [17].

PB is utilized in the control of generalized and partial seizures; it is also the first choice to treat the *status epilepticus* [18,19]. At high doses, this drug can cause diurnal somnolence, sedation and also cognitive problems, which include psychomotor processing speed, sustained attention, memory, and learning abilities [8], [9,20,21]. In animal models, it has been reported that this barbiturate produces deterioration in the consolidation of spatial memory [22].

The use of animal models allows a wide range of research possibilities including the search for etiologic clues, molecular targets, and biomarkers. Because epilepsy is a highly prevalent disease in the world population and given its severity and implications in the life quality of patients suffering it, animal experimental models have been implemented to investigate the physiopathology of epilepsy. These models have been fundamental in the study of the basic neuronal mechanisms implicated in the generation, propagation, and suppression of epileptic seizures, as well as, in assessing the effects of epilepsy on cognition and organism's behavior. These models have also been useful in evaluating anticonvulsive drugs and their collateral effects [5,23].

There are different types of experimental models. In physical models, convulsive activity is evoked through electric stimulation of the brain tissue, for example, *kindling* [24,25]. In chemical models, different convulsing compounds are used; some of them are GABAergic antagonistic or glutamatergic agonistics [26-28].

Administering of Kainic acid (KA), a glutamate analog, which acts on the CNS through the receptors of this neurotransmitter [27] is one of the chemical models of TLE. Systemic administration of KA in doses ranging from 8 to 12 mg/kg produce epileptic seizures, which can become *status epilepticus* inducing mesial temporal sclerosis similar to those caused by TLE in humans [5].

Status epilepticus and paroxistic discharges surging from the limbic system, induced by systemic administration of KA, cause progressive loss of neurons in various structures of the CNS, particularly on those of the limbic system. The most vulnerable structure to this type of damage is the hippocampus, where the pyramidal cells of the subfields CA3 and CA1 have a great amount of glutamate receptors making them highly sensible to KA. Furthermore, other structures are affected, such as the amygdala, parahippocampal region, piriform cortex, striatum, and the thalamic reticular nucleus [26-28].

Studies using the KA model show that epileptic rats exhibit alterations in learning and spatial memory (especially in short term memory), in addition to high anxiety levels [29-30]. When PB is administered prior to KA, it protects against memory deficit caused by this agent in the water maze [31]. Likewise, PB in doses of 40 mg/kg is efficient in protecting rats against seizures induced by KA [32,33].

LEARNING AND SPATIAL MEMORY

When we make contact with the world, we are committed with a spatial cognition, interacting with spaces and places around us, we build representations of the environment and our own space inside of it [34]. The knowledge of the space can be acquired in diverse ways: through direct exploration, maps, descriptions, or by a combination of them. These acquisition ways are interchangeable, although each one of them has its own complexity and variability.

The spatial routes of memory activate hippocampal structures in the brain [34-37]. It has been reported that the hippocampus integrates and uses "cognitive maps" that animals utilize to move around their environment [35].

Moreover, the hippocampus is essential in declarative memory, which not only implies declaring knowledge verbally but, it also involves facial and spatial memories, and other "declared" material to produce an image in the mind, without the need to express it verbally [38]. Therefore, animals such as rats have declarative memory, besides a spatial one, whose biological substrate corresponds mainly to regions of the medial temporal lobe and hippocampus [37,38]. Olton and Papas [39] proposed that the hippocampus is functionally essential for the working memory, demonstrating that a lesion in this region damages this type of memory, but not to the reference one.

Spatial memory can be displayed as short and long-term memory. Short-term memory is understood as the capacity to remember information after a brief time interval, while long-term memory is conceived as the capacity of remembering information after a long time interval. However, new explanatory models to classify memory have been proposed. In recent years, the concept of working memory has been explained as an integrative system to maintain and manipulate information during the execution of a complex task [40]. This type of memory is also referred as the situation in which the animal requires to retain the information from several essays carried out during a short time period [41]. Its function consists in recovering and manipulating the stored information [40,42].

In opinion of Olton [41], working memory is understood as a transitory storage, in which the information is processed in an active manner according to its changing characteristics, while reference memory indicates that all learning requires the association between two or more stimuli, or with their subsequent responses. Once the associations have been established, they become part of the reference memory as "the permanence of an

acquired psychological structure". Then, reference memory is the long-term retention of the information necessary to accomplish the accurate use of entering and recently acquired information [43]. The main difference between working and reference memories can be defined in terms of information stability. In working memory, the information depends on the contextual stimuli; therefore, it is unstable through time. In the case of reference memory, the organism must remember a number of rules which are the same for all the essays. Then, the reference memory is that whose contents are stable throughout time, while the working memory is that employed with the purpose of monitoring the variable characteristics of the experience, which along with the stable characteristics; determine the adequate response to a given situation [39].

Studies using the KA model have been conducted to evaluate alterations in learning and spatial memory due to neuronal damage caused by epileptic seizures. These studies show that rats administered with KA develop epileptic seizures in addition to alterations in learning and spatial memory, especially in short-term memory. The behavior of these experimental animals is also characterized by high levels of anxiety [29,30]. The deficits in this type of tasks are explained by lesions in the areas CA1 and CA3 of the hippocampus, which are crucial in spatial tasks [44,45]. Nevertheless, there are controversies in this model in relation to spatial learning troubles, since some authors report that rats with lesions in the regions CA1 and CA3 of the hippocampus induced by KA, reach the same learning levels as the control rats after a 10 day training [45]. This result suggests that lesions in the hippocampus can cause damage in learning acquisition speed; increasing learning latency in spatial tasks [45], but the capacity to codify spatial relationships is preserved. These findings are explained as the result of new dendritic sprouts of the mossy fibers in the hippocampal formation, produced by KA administration, although some of these aberrant sprouts can facilitate the occurrence of seizures which induce brain damage.

On the other hand, Handelmann and Olton [44] have reported that rats with hippocampal destruction caused by KA are able to adequately perform spatial tasks when they are trained prior the lesion, while the animals not previously trained show persisting deterioration of spatial learning. Other types of experimental epilepsy models also alter the execution of spatial tasks. For example, in the hippocampal *kindling* model, the spatial memory is altered up to 21 days after stimulation [31].

The use of mazes constitutes one of the most common methods employed in experiments carried out on rats to evaluate spatial memory processes. The radial maze, designed by Olton and Samuelson [46] is a behavioral procedure that allows evaluating spatial cognition, it possesses differential demands of both working and reference memories, in other words, it allows simultaneous but differential evaluation of both memory types in rats. It has been described that rats resolve this task with the use of extra-maze signals or clues as components of a spatial map. Such signals, allow them to distinguish a place in a well-known environment [47]. In this model, rewards are placed in the same arms of the radial maze in several sessions and the rat must learn the reward position, according to the spatial map built with the support of extra-maze signals or clues. Food is the most frequent "reward" utilized in hungry rats.

Due to the fact that the cerebral areas commonly damaged in TLE correspond to regions in the temporal medial lobe, which are also associated with learning and memory processes, this study aimed to evaluate the effect of FB on convulsive seizures and functional disturbances on reference and working memories caused by KA.

METHODS

Subjects

Twenty Wistar male rats weighing between 300 and 500 g were utilized in this experiment. The animals were kept in individual boxes at an average temperature of 20±2 ºC, in a light-darkness cycle of 12:12 hr, with *ad limitum* water supply, and 80% food deprived. The experimental procedures were conducted under the international guidelines seeking to avoid unnecessary suffering in the animals used.

Equipment

A nine arm wood radial maze (figure 1) with a central platform of 30 cm diameter and limited by a translucent acrylic wall of 3 cm height was utilized. The wall had doors which opened and closed towards each one of the nine arms allowing access. The arms were 10 cm wide and 60 cm long, and the closest part to the central platform had an acrylic wall of 12 cm height and 25 cm length. At the end of each arm, a feeder of 3 cm diameter and 1 cm height was located. The maze was placed 1 m above the floor level.

Procedure

Six extra-maze visuo-spatial signals were placed around the maze (figure 1). Pieces of rat food were used as rewards; these were placed in six of the nine arms, which were classified as arms "with reward" and "without reward". The arm distribution was as follows: two with reward, one without reward, two with reward, one without reward, two with reward, and one without reward. This order was kept constant throughout the whole experiment. The rewards were never replaced during the same session.

Exploration/recognition stage

In the first 10 sessions (one per day), all rats were given *ad*

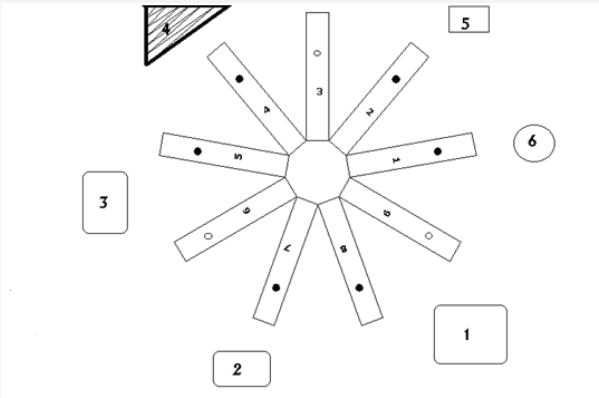


Figure 1 Nine arm radial maze showing the clues distribution. ● With reward; ○ without reward.

libitum access to food and water. In these sessions, the rats freely explored the maze with its doors open for 15 min. At this stage, none of the arms contained a reward.

Food deprivation stage

During the following nine days, the rats were deprived of 80% of their food and they were maintained under this condition until the end of the experiment. In this stage, the rats did not explore the maze.

Training stage in the nine-arm radial maze

The rats were placed in the central platform of the maze with closed doors, preventing access to the arms. After 10 sec, the doors were opened and rats could choose to go through any of the nine arms. Once a rat had visited an arm and returned to the central platform, the doors were closed for 10 sec. After this time, the doors were opened again and the rat could choose to go through another arm. Each visit of the rat to an arm was considered an essay. The session was finished after 15 min or once the rat had consumed the six rewards, whatever event occurred first. This stage was considered complete once the rats met the learning criterion, that is, they picked up the six rewards in a maximum of 7 essays; therefore duration was different for each rat.

Evaluation stage of reference and working memories

The animals were separated randomly in four groups, and the described procedure for previous sessions was then used. However, during the 10 sessions of this stage the probability of a correct response for the two memory types was evaluated.

The probability of a correct response for the two memories is the resulting quotient of the number of correct responses divided by the total number of responses. One correct response in reference memory consisted of visiting any of the arms that contained a "reward", while an error was made when an arm "without reward" was visited. A correct response in working memory was visiting any of the arms that still had a reward.

Drug administration

Once all the previous stages were completed the drugs were administered to the rats divided into four experimental groups.

A control group received saline solution, the second group PB (50 mg/kg, ip) synthetized by Armstrong Labs of México S. A. de C. V., the third group was administered KA (10 mg/kg, subcutaneously) from Sigma Aldrich, and the fourth PB 30 min prior KA administration in the doses previously cited.

Post-evaluation Stage of reference and working memories

This stage consisted in 10 sessions and was conducted 72 hr after substance administration using the same procedure as in the pre-evaluation stage.

Statistical analyses

One-way ANOVAs and post-hoc Tukey's HSD tests were used to compare the probability of correct responses of both working and reference memories, for the four groups of rats.

In order to compare the probability of a correct response between the Evaluation and Post-evaluation stages, the *t*-student test was employed. All analyses were conducted using the SPSS 11.0 software for Windows.

RESULTS

At the end of the exploration stage, all rats went through the maze without any difficulty. Likewise, in the training stage, all rats met the learning criteria between sessions 18 and 24 (graphs 1 and 2). At the beginning of the training stage, the rats either took the 15 min allowed for the session going through the maze and picking the six rewards, or, they were not able to pick up all of them into the mentioned time. While at the end of this stage, once the rats had learned the distribution pattern of the rewards, they picked up the six rewards approximately in two minutes, making few mistakes, that is, the rats increased their probability of a correct response in the two memory types: reference and working.

Evaluation stage

In the Evaluation stage, prior the administration of substances, the total of animals in the four groups picked up the six rewards in approximately two minutes, reason why these sessions had such duration. The average probability of a correct response in reference memory was similar in all the groups; in the control group was 0.84, in the group assigned to receive PB was 0.83, for the KA group 0.87, and for the group that was provided with both PB and KA was 0.86 (graph 3). The observed differences were not statistically significant in the execution of this type of memory for any of the four groups ($F = 2.785$, $p = 0.55$). Likewise, the average probability for a correct response in working memory did not show either significant differences among any of the groups ($F = 1.62$, $p = 0.2$). It was 0.98 for the control group, 0.97 for the PB group, 0.97 for the KA group and 0.99 for the PB+KA group (graph 4).

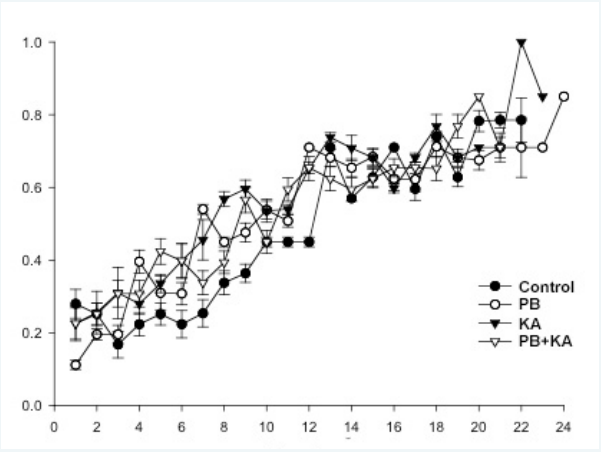
Drug administration

The control group of rats, administered with saline solution did not show any behavioral alterations. Rats treated with PB showed behavioral sleep between 20 and 30 min after drug administration, they remained immobile, lying down on the box floor with eyes closed. However, these rats were responsive to environmental stimuli. The behavioral immobility period lasted between 2 and 3 hr, then these animals showed low activity during a similar period. Approximately six hours after PB was administered, their behavior returned to normal levels.

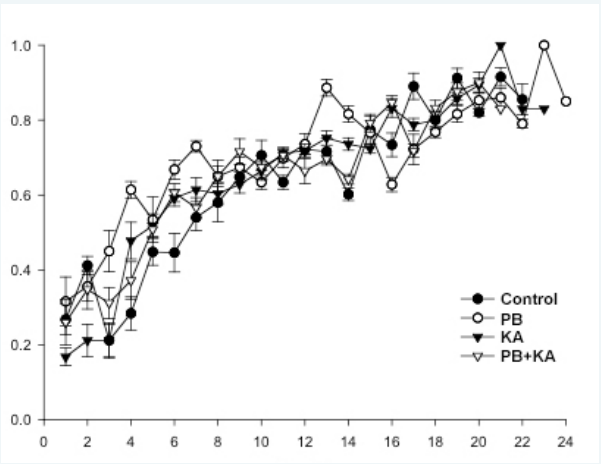
Rats treated with KA developed *status epilepticus,* exhibiting the behavioral characteristics previously described in the literature [26]. Approximately 20 min after KA treatment, theses rats showed catatonic posture, fixed sight with lack of response to environmental stimuli, loss of muscular tone in extremities and marked ataxia. The group, administered with PB 30 min prior KA, did not show any motor alterations. They were initially very active, but without seizures and after a few hours they laid down on the box floor going sometimes to sleep.

Post-evaluation

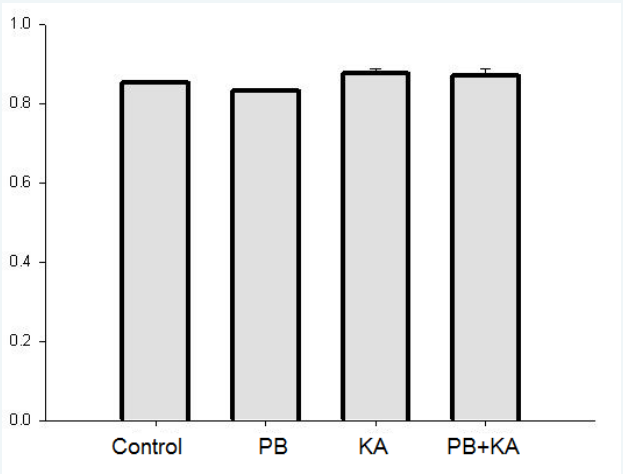
The rats in the control group conducted the task in a



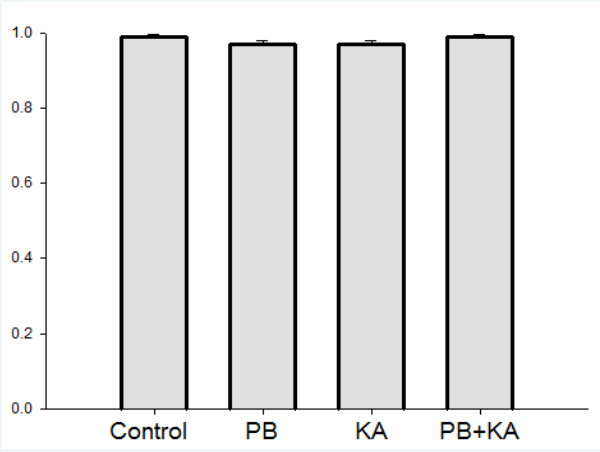
Graph 1 Acquisition curve of reference memory strategy for the four experimental groups, during the Training Stage. ± Standard Error. X: Sessions; Y: Probability of correct responses.



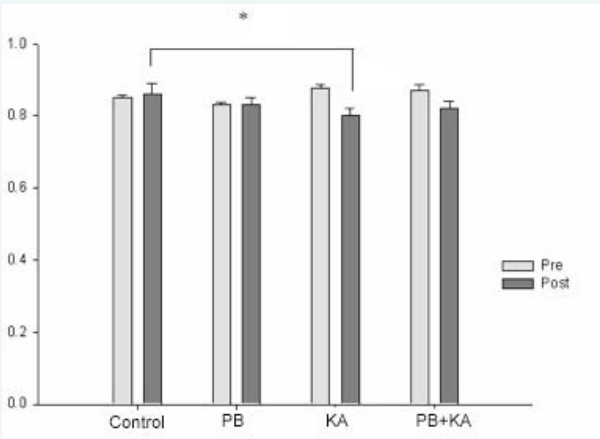
Graph 2 Acquisition curve of working memory strategy for the four experimental groups, during the Training Stage. ± Standard Error. X: Sessions; Y: Probability of correct responses.



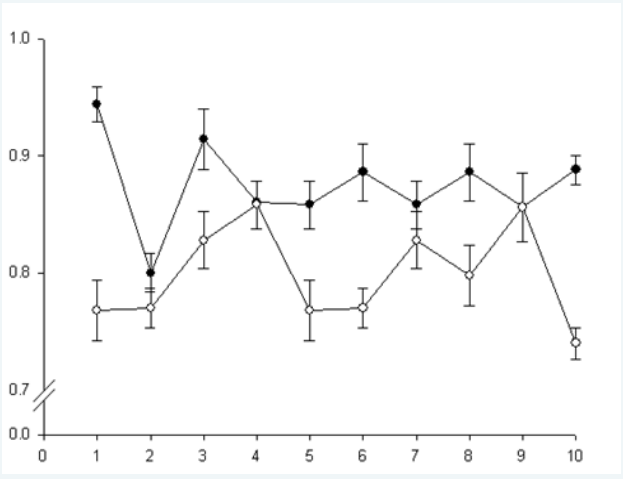
Graph 3 Average probability of correct responses in reference memory for the four experimental groups in the 10 sessions of the Evaluation Stage. ± Standard Error.



Graph 4 Average probability of correct responses in working memory for the four experimental groups in the 10 sessions of the Evaluation Stage. ± Standard Error.



Graph 5 Average probability of correct responses in reference memory for the four groups of rats in the 10 sessions of the evaluation (Pre) and Post-evaluation Stages. ± Standard Error.



Graph 6 Probability of correct responses in reference memory for the KA group exhibited during the 10 sessions of the Evaluation Stage (●) and the 10 sessions corresponding to the Post-Evaluation Stage (o). ± Standard Error. X: Session; Y: Probability of a correct response.

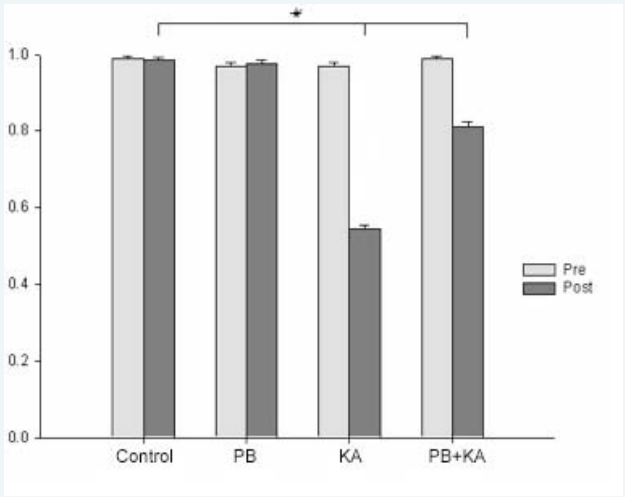
similar manner as they did in the evaluation stage. While the rats provided with KA took more time picking up all six rewards, when compared to their performance displayed prior KA administration in the Evaluation Stage, as well as, with the performance of the other three groups.

Average probability of a correct response for reference memory in the Post-Evaluation Stage showed minimal differences among the four groups: for the control group was 0.85, for the PB group was 0.83, for the KA group was 0.79, and for the PB+KA group was 0.81 (graph 5).

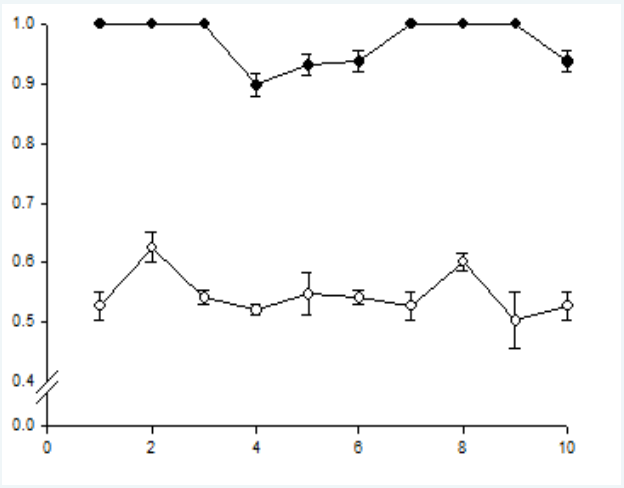
One-way ANOVA was conducted to compare the differences among the reference memory execution showed by the four experimental groups after drug administration. Control rats did not show significant differences when compared to the rats in groups PB and PB+KA ($p = 0.298$ and $p = 0.092$, respectively). The KA group of rats did not show differences in the execution of this type of memory when compared with rats in groups PB and PB+KA ($p = 0.233$ and $p = 0.569$), but it did when compared to control group ($F = 4.777$, $p<0.01$).

When reference memory execution of the Evaluation Stage was compared to that of the Post-evaluation Stage within the same group, only the group that received KA showed significant differences in the probability of correct responses ($t = 4.018$, $p<0.01$) (graph 6).

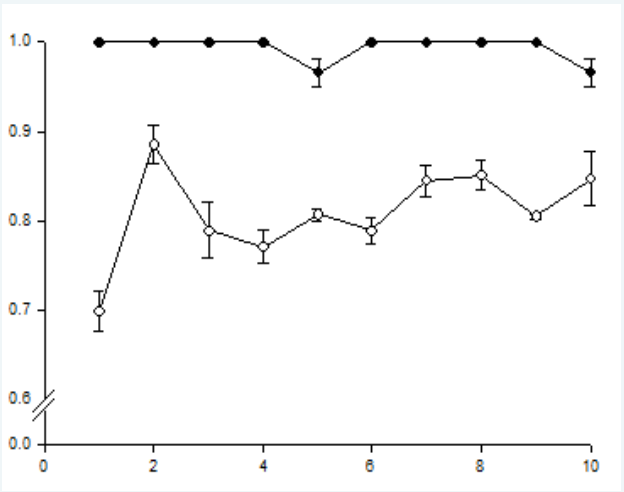
Of the four groups of rats only those that received KA and PB+KA exhibited a decrease statistically significant in the probability of a correct response in working memory. The average probability of a correct response in working memory of the control group was 0.98, that of the PB group was 0.97; while for the KA group was 0.54 ($p<0.001$) and for the PB+KA group was 0.80 ($p<0.001$) (graph 7,8 and 9). The difference between KA and PB+KA groups was also statistically significant indicating a protective effect of PB against memory deterioration induced by KA administration.



Graph 7 Average probability of correct responses in working memory for the four experimental groups in the 10 sessions at the Evaluation (Pre) and Post-Evaluation Stages. ± Standard Error *=p<0.001.



Graph 8 Average Probability of correct responses in working memory for the group of rats provided with KA during the 10 sessions of the Evaluation (●) and the 10 sessions of the Post-evaluation (o) Stages. ± Standard Error.



Graph 9 Average Probability of correct responses in working memory for the group of rats with PB+KA during the 10 sessions of the Evaluation Stage (●) and the 10 of the Post-evaluation Stage (o) . ± Standard Error.

DISCUSSION

According to WHO statistics (2012) [1] there is a significant number of people worldwide suffering of epilepsy becoming a public health problem. This situation has impulsed numerous research groups, to implement diverse methodologies in order to investigate the underlying physiopathological mechanisms involved in the different epilepsy types and to implement efficient therapeutic strategies

The experimental models have played a fundamental role in this quest. In the present work, the experimental model of TLE induced by KA was utilized. As previously described in the results section, the totality of the rats separated in four experimental groups acquired the strategies to use reference and working memories during the Training Stage, before drug administration.

These findings agree with those reported by other authors in similar experiments [46]. During this process, the rats used extra-maze signals as components of a spatial map, showing orientating behavior when they moved across the maze. Some of the rats, spun around their own axis in the central platform prior choosing an arm to visit.

After administering KA, the exploratory behavior was inhibited, since animals remained immobile inside the maze during a considerable time of the evaluation session, or, they ran disoriented through the maze, complicating the task execution. Furthermore, the animals were very reactive to environmental stimuli in addition to present motor activity alterations. This type of behavior has been observed in animals after lesions of the amygdala and hippocampal afferents induced by KA administration [29,39].

When the learning criterion, consisting of picking up the six rewards in a maximum of seven essays was met, it was considered that the rat had acquired the strategy needed for reference and working memories. Since learning causes changes in the organism's behavior [48], in this experimental study, we considered that such changes were expressed as the choice of an arm containing the reward.

After KA administration, the rats showed deficits in the two types of analyzed memories, with working memory presenting a more marked deterioration. Moreover, when PB+KA were administrated, the rats showed deficits in working memory but not in that of reference.

It was proposed that the hippocampus is the substrate for working memory [39], and that damage to this region results in selective deficits in working memory processes, with intact reference memory. This dissociation has been demonstrated successfully in animal hippocampal lesion studies using maze conditional discrimination tasks [49].

Since the hippocampus is severely damaged by epileptic seizures induced by KA administration [5,26-28], the deficit in working memory is higher than that in reference memory. Such observation indicates that the neurobiological substrate of the reference memory is different from that of working memory [39,50]; therefore, both types of memory showed differential reactivity against this drug. Studies with animals suggest that the cerebral temporal cortex participates in reference memory, which also is involved in the storage of long term memory [38].

The information required to be stored by prolonged periods is kept as reference memory; while working memory, characterized by its flexibility and constant updating, is not required to be stored for a long time [35], [36,37].

The PB administration inhibited the development of *status epilepticus* caused by KA, suppressing all the behavioral components of the limbic seizures.

According to some authors, inhibition of the *status epilepticus* could occur through blockage of propagation of the epileptic activity from the limbic system towards the motor cerebral areas and by the partial protection against neuronal damage exerted by PB [51]. These mechanisms would explain the affectation observed only in working memory but not in the reference one.

The rats administered only with KA showed epileptic seizures, which could be induced by mesial temporal sclerosis developed in the hippocampus, amygdala, parahippocampal cortex, and other cerebral structures [28], which are essential in acquisition and evocation of spatial information [37]. This neuronal damage alters several cognitive functions including the reference and working memories, suggesting the participation of the mentioned structures in the regulation of such functions [7,47].

In another study [44], reported that when only the CA3 pyramidal cell layer was destroyed by micro- injection of KA into the hippocampus, the rats previously trained executed spatial tasks without problem. In contrast, in our work, KA administration was systemic; this type of administration tends to cause neuronal death in a bigger number of areas, not only in hippocampal regions. For this reason, severe deficits were observed since acquisition of spatial strategies to conduct tasks in mazes requires the integrity not only of the hippocampus, but also, of other brain regions, such as, the amygdala, the piriform cortex, the striatum and the thalamic nuclei [26], [27,28].

In conclusion, using the experimental TLE model it was evidenced the possible existence of different neurobiological mechanisms participating independently in regulating reference and working memories. Additionally, it was shown that the degree of memory affectation may be reduced by the use of antiepileptic drugs.

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Cite this article

Ayala-Guerrero F, Reyes A, Mexicano G (2014) Effect of Epilepsy and Antiepileptic Treatment on Reference and Working Memory . J Neurol Disord Stroke 2(3): 1065.