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Vinpocetine inhibits the epileptic cortical activity and auditory alterations induced by pentylenetetrazole in the guinea pig in vivo

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Abstract

Here we investigate the effect of the neuroprotective drug, vinpocetine on the epileptic cortical activity, on the alterations of the later waves of brainstem auditory evoked potentials (BAEPs) and on the hearing decline induced by the convulsing agent, pentylenetetrazole (PTZ). Vinpocetine at doses from 2 to 10 mg/kg inhibits the tonic–clonic convulsions induced by PTZ (100 mg/kg). Vinpocetine injected at a dose of 2 mg/kg 4 h before PTZ completely prevents the characteristic electroencephalogram (EEG) changes induced by PTZ for the ictal and post-ictal periods. Vinpocetine also abolished the PTZ-induced changes in the amplitude and latency of the later waves of the BAEPs in response to pure tone burst monoaural stimuli (frequency 8 or 4 kHz intensity 100 dB), and the PTZ-induced increase in the BAEP threshold. These results show the antiepileptic potential of vinpocetine and indicate the capability of vinpocetine to prevent the changes in the BAEP waves associated with the hearing loss observed during generalized epilepsy.

Keywords: Antiepileptic drugs; Brainstem auditory evoked potentials; Cognitive functions; Epilepsy; Hearing; Superior olivary complex

1. Introduction

Brainstem auditory evoked potentials (BAEPs) are far field-evoked potentials that consist of several waves that occur within 10 ms post-stimulus. Determination of BAEPs threshold represents an objective measure of the hearing sensitivity. Because stimuli of progressively higher intensity (in dB) are needed for evoking BAEPs as the auditory sensitivity declines. BAEPs are also useful in the clinical diagnosis of retro-cochlear lesions (Hall, 1992; Malhotra, 1997; Pratt et al., 1998; Schmidt et al., 2001).

In the guinea pig Wada and Starr (1983a,b,c) demonstrate that each BAEP wave arises from a focal region of the auditory pathway. For instance, a change in amplitude or latency of P1, the first wave component of BAEPs in the guinea pig, is indicative of a cochlear nerve alteration, while changes in P3 and P4, that are the waves of BAEPs that express the activity of the medial and the lateral superior olivary nuclei, respectively, are indicative of retro-cochlear alterations.

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Recently we found that experimental epilepsy induced by two different convulsing agents in the guinea pig in vivo is accompanied by alterations in P3 and P4 and by hearing loss (Nekrassov and Sitges, 2003). In a previous study also in the guinea pig in vivo we have shown that the alterations in the P1 wave of BAEPs and the hearing loss induced by an antibiotic aminoglycoside were completely prevented by vinpocetine (Nekrassov and Sitges, 2000).

Vinpocetine (ethyl apovincamine-22-oate) was found to have a strong but possibly subtype selective blocking effect on sodium channels (Erdö et al., 1996; Zhou et al., 2003) that reduces brain presynaptic Na^+ channels permeability in vitro (Tretter and Adam-Vizi, 1998; Sitges and Nekrassov, 1998, 1999) and has shown to be a memory enhancer in animals and humans (Subhan and Hindmarch, 1985; Bhatti and Hindmarch, 1987; DeNoble, 1987). Other mechanisms including inhibition of phospholipase activity and blockage of other ion channels may contribute to the memory enhancing effect.

Considering that the mechanism of action of several classic antiepileptic drugs is the blockade of sodium channels (Lingamaneni and Hemmings, 2003) and that a great number of epileptic patients suffer from memory disturbances (Prevey et al., 1998; Jokeit and Ebner, 1999; Theodore et al., 1999; Meador, 2001), it was of interest to investigate the effect of vinpocetine on the epileptic cortical activity and on the alterations of the auditory pathway induced in an experimental animal model of epilepsy. For this purpose, in the present study the changes on the electroencephalogram (EEG), the BAEP wave components and the auditory threshold induced by pentylenetetrazole (PTZ) at a convulsing dose were tested in guinea pigs pre-treated with vinpocetine.

2. Methods

Experiments were performed in pigmented adult male guinea pigs initially weighing 349 ± 38 g. BAEP recordings were used to evaluate the hearing status of each animal and EEG recordings to evaluate changes in cortical excitability. For BAEP recordings, needle electrodes were placed subcutaneous at the ipsilateral left pinna (reference electrode), the contralateral pinna (ground electrode) and the vertex (active electrode). For EEG recordings, needle electrodes were placed subcutaneous over the left temporal area (active electrode) and over the left frontal area between the midline and the arched portion of the orbital crest (reference electrode). BAEP and EEG recordings were performed in a sound proof room with a Nihon-Kohden Neuropack IV Mini (MEB-5304K) system. Prior to each sequence of recordings, guinea pigs were anaesthetised by ketamine (50/10 mg/kg xylazine, i.p.) for restraining movement, stress and muscular activity. This anaesthetic was chosen because in the guinea pig it does not change the latency or the amplitude of the BAEP waves or the BAEP threshold within the time of the experiments (Nekrassov and Sitges, 2003).

Recordings were taken following the methods previously reported in Nekrassov and Sitges (2000, 2003). For the BAEP recordings monaural tone burst stimuli of 4 and 8 kHz were delivered by TDH 39 earphone located 1 cm from the left ear. The right ear was blocked with a special wax plug that substantially reduced the sound level at this ear. Four or 8 kHz alternating polarity tone bursts (20/s), with 2 ms duration and 0.5 ms rise–fall times were used for evoking the potentials. Responses were amplified and averaged (500 responses), displayed vertex positive up and saved to disk for off-line analyses. We first give the three trials (500 each) at the 8 kHz tone frequency followed by the three trials (500 each) at 4 kHz. Each trial takes 25 s as 20 stimuli are delivered per second. The interval between trials takes 5 s. The time interval between the two tone frequencies is about 15 s. The equipment averages the responses at each frequency automatically.

The Institutional Animal Use and Care Committee approved all experimental procedures.

2.1. Experimental animals

Eight guinea pigs were entered into the study. In a first set of experiments the animals were injected with vehicle 4 h before anaesthesia. For testing the effect of vinpocetine, a second set of experiments in which the same animals were injected with vinpocetine (2 mg/kg) 4 h before anaesthesia was done 10 days after the first set of experiments. Ten min after the injection of the anaesthetic solution three types of recordings, namely the BAEP recordings elicited

by a stimulus of high intensity (100 dB), the BAEP recordings for determination of the auditory threshold and the EEG recordings, were obtained in the animals pre-injected with vehicle and, 10 days after, in the same animals pre-injected with vinpocetine. Immediately after getting those recordings, the animals were injected (i.p.) with PTZ 100 mg/kg for obtaining a new series of recordings taken at specific times after PTZ injection. For instance, the EEG recordings for the ictal period were taken within the first 2 min after the injection of PTZ, and the BAEP recordings evoked by 100 dB or the EEG recordings for the post-ictal period were taken 10, 20, 30 and 50 min after the injection of PTZ. The recordings for determination of the BAEP thresholds were taken 30 and 50 min after PTZ. All the recordings were taken within 1 h after PTZ injection taking into account the start and duration time of the ictal and post-ictal periods induced by the convulsing agent.

A third set of recordings was taken 2 weeks after the second set of experiments for testing again the effect of PTZ alone.

PTZ was obtained from ICN Biochemicals, Inc. (Aurora, Ohio) and vinpocetine was a kind gift of Armstrong International (Laboratorios Armstrong de México, S.A. de C.V.). PTZ was dissolved in saline and vinpocetine in a saline acidified (with HCl) solution adjusted to pH 4 (with NaOH). Vehicle refers to the acidified saline used to dissolve vinpocetine.

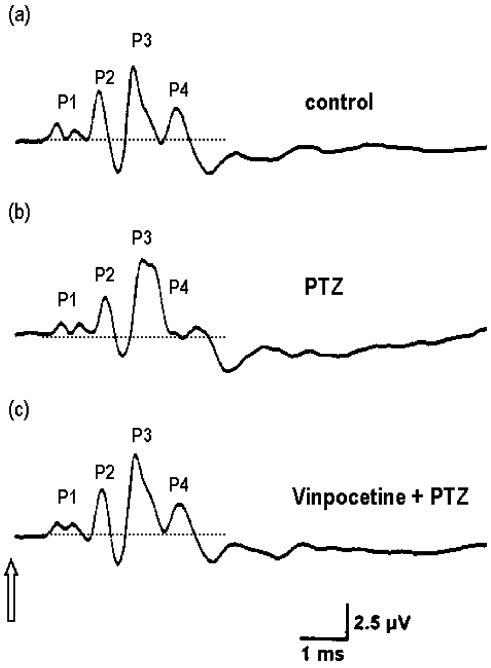

Fig. 1. Representative ABR recordings taken before (a) and 50 min after the injection of 100 mg/kg PTZ in the animal pre-injected with vehicle (b), or with 2 mg/kg vinpocetine (c) 4 h before PTZ. The recording before the injection of PTZ in the animal pre-injected with vinpocetine is not presented because is very similar to the control recording shown in (a). The arrow indicates the onset time of the monaural pure tone stimulus of high frequency (8 kHz) and high intensity (100 dB). Each trace represents the average of 500 responses.

2.2. Determination of BAEP wave parameters and BAEP threshold

The latency and amplitude of each wave component of the BAEP elicited by the stimulus of high intensity (100 dB) with pure tone frequencies of 4 or 8 kHz was measured in all the BAEP recordings obtained under the different experimental conditions at the specified times. The latency of each BAEP wave (in ms) refers to the time interval between the onset of the auditory stimulus and the positive peak of the wave. The onset of the stimulus is indicated by the vertical arrow at the bottom of the recordings on Fig. 1. The peak amplitude (in μV) of each wave of the BAEP is the difference between the positive peak of the wave and the reference baseline (trace between the stimulus and the appearance of the first BAEP wave on Fig. 1). Representative BAEP recordings elicited by the stimulus of high intensity (100 dB) at a tone frequency of 8 kHz obtained in an animal pre-injected with vehicle before the injection of PTZ, 50 min after the injection of PTZ, and 50 min after the injection of PTZ when the same animal was pre-injected with vinpocetine 10 days after are shown in Fig. 1.

BAEP recordings elicited by stimuli of progressively lower intensity (in dB) were used for determining the BAEP threshold. Threshold is defined as the lowest stimulus intensity (in dB) at which the P3 wave of the BAEP could still be recorded in three consecutive trials (each trial equals the average response to 500 stimuli). For obtaining the auditory threshold a tone burst response induced with an intensity of 100 dB normal hearing level (nHL) was initially recorded. Then thresholds were determined for each stimulus by reducing the intensity at 20 and 10 dB nHL intervals,

and then at 5 dB intervals down from a supra-threshold BAEP recording to identify the lowest level at which reproducible waves could be recognised. The sound threshold level was also objectively estimated. The amplitude of the P3 wave at the peak was plotted against the corresponding sound intensity in order to construct input–output curves at 20, 10 and 5 dB nHL steps for 4 and 8 kHz.

2.3. Statistics

Student's *t*-test (paired) was used for the evaluation of the differences between results obtained before and at the specified times after PTZ injection. The criterion for statistical significance for all measures was $P \leq 0.05$. All data are expressed as mean ± standard error of the mean.

3. Results

The effect of vinpocetine at increasing doses (range from 0.5 to 10 mg/kg) was first tested on the tonic–clonic convulsions induced by the injection of 100 mg/kg PTZ in non-anaesthetized animals. Since from the dose of 2 mg/kg, the anticonvulsing effect of vinpocetine was clearly observed, this dose was chosen to carry out the experiments in the anaesthetized animals.

3.1. Vinpocetine inhibits all the changes induced by PTZ on the EEG

All anaesthetized animals injected with PTZ developed motor generalized seizures. The onset of seizures accompanied by repetitive high amplitude spike-sharp wave activity in the EEG tracing appears suddenly within the first 2 min after PTZ injection (second trace in Fig. 2a). This dramatic change on the cortical activity elicited by PTZ in the anaesthetized guinea pigs during convulsions is followed by a typical pattern of cortical activity characterized by rhythmic spike bursts of high amplitude (traces below "Before" on Fig. 3a). The time of duration of this typical pattern of cortical activity, that is not accompanied by convulsions is referred as the post-ictal period.

The seizures and the changes on the cortical activity induced by PTZ for the ictal and post-ictal periods are completely prevented by vinpocetine (2 mg/kg). Characteristic EEG recordings under control conditions (i.e. before the injection of PTZ) are shown in the top traces on Figs. 2 and 3. Notice that before the injection of the convulsing agent, PTZ, no difference in the cortical activity of the animals pre-injected with vehicle and of the animals pre-injected with vinpocetine was observed (compare the top traces on Fig. 2a and b for example). In contrast, the changes induced by PTZ on the EEG after about 2 min (ictal period) in

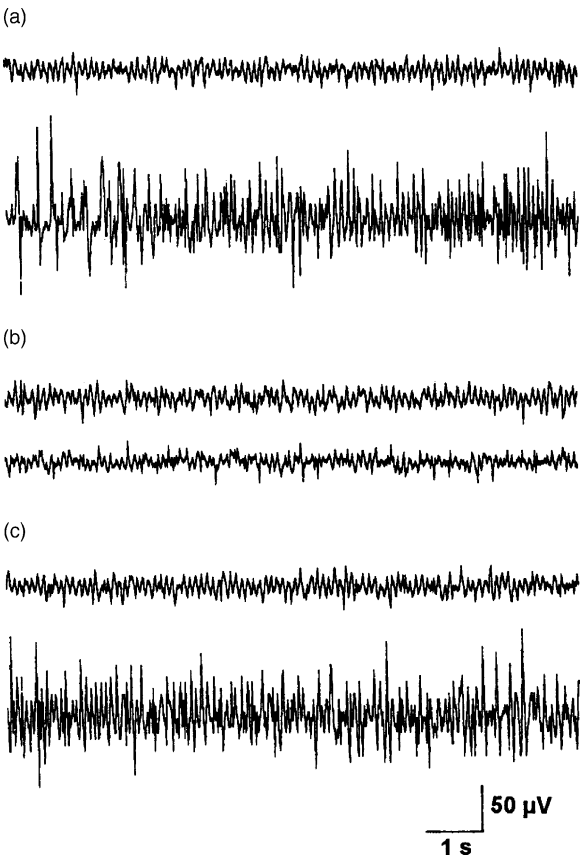

Fig. 2. Vinpocetine inhibits the changes on the EEG induced by PTZ for the ictal period. (a) EEG recordings taken in a representative animal pre-injected with vehicle before (first trace) and about 2 min after the injection of PTZ (second trace). (b) EEG recordings taken 10 days after in the same animal but pre-injected with 2 mg/kg vinpocetine before (first trace) and about 2 min after the injection of PTZ (second trace). (c) EEG recordings taken 2 weeks after the recordings with vinpocetine in the same animal, but pre-injected with vehicle before (first trace) and about 2 min after the injection of PTZ (second trace).

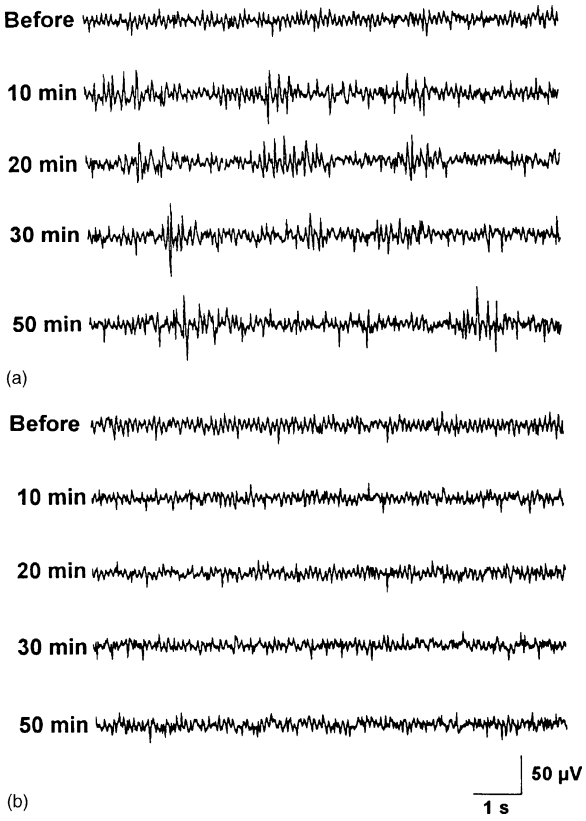

Fig. 3. Vinpocetine prevents from the changes on the cortical activity induced by PTZ for the post-ictal period. (a) EEG recordings taken in a representative animal injected with vehicle before (top trace) and at the indicated times after the injection of PTZ. (b) EEG recordings taken in the same representative animal injected with 2 mg/kg vinpocetine 10 days after before (top trace) and at the indicated times after the injection of PTZ.

the animals pre-injected with vehicle (second trace on Fig. 2a) are completely lost when PTZ is injected in the vinpocetine pre-treated animals (second trace on Fig. 2b).

The changes on the EEG induced by PTZ 10, 20, 30 and 50 min after its injection (post-ictal period) are shown below the control (top) recording on Fig. 3a. In the animals pre-injected with vinpocetine the cortical changes induced by PTZ for the post-ictal period are lost (see recordings from a representative animal below the top trace on Fig. 3b).

When the animals were injected again with PTZ in the absence of vinpocetine 2 weeks later, all the changes induced by PTZ in the first set of experiments (i.e. animals pre-injected with vehicle before PTZ) were observed again. An example of the EEG recordings taken before and about 2 min after the injection of PTZ in the same representative animal 2 weeks after is shown on the traces of Fig. 2c. The EEG changes induced by the third injection of PTZ for the post-ictal period are not shown on Fig. 3, but are very similar to those observed on Fig. 3a.

3.2. Vinpocetine inhibits the reduction in P4 wave peak amplitude induced by PTZ

The left column on Table 1 shows that the amplitude of P4 in response to the stimulus of 100 dB is progressively reduced by PTZ for 50 min at two tone frequencies (4 and 8 kHz). In the animals pre-injected with vinpocetine these reductions in P4 amplitude induced by PTZ at 8 and 4 kHz are lost.

Notice that vinpocetine alone does not change P4 amplitude, as before the injection of PTZ, the amplitudes of P4 in the animals pre-injected with vehicle (“Before” on left columns) and in the animals pre-injected with vinpocetine (“Before” on right columns) are not statistically different.

The amplitudes of the other first three waves of the BAEP, namely P1–P3, induced by 100 dB at both tone frequencies remain unchanged by PTZ either in the

Table 1
Vinpocetine overcome the PTZ-induced decrease in P4 amplitude[a]

	PTZ	Vinpocetine + PTZ
8 kHz		
Before	2.88 ± 0.1	2.69 ± 0.1
10 min	2.07 ± 0.4[b]	2.56 ± 0.1
20 min	1.99 ± 0.3[b]	2.71 ± 0.2
30 min	1.92 ± 0.3[b]	2.55 ± 0.2
50 min	1.51 ± 0.5[b]	2.56 ± 0.1
4 kHz		
Before	3.14 ± 0.1	2.82 ± 0.3
10 min	1.70 ± 0.5[b]	2.55 ± 0.3
20 min	2.12 ± 0.4[b]	2.52 ± 0.2
30 min	1.84 ± 0.4[b]	2.55 ± 0.2
50 min	2.11 ± 0.3[b]	2.52 ± 0.2

[a] Results are the average ± S.E.M. values (in μV) of data obtained from eight animals. ‘Before’ refers to the indicated P4 amplitude value before PTZ administration.
[b] Significant difference between P4 wave peak amplitude before and at the indicated time after PTZ injection.

animals pre-injected with vehicle or in the animals pre-injected with vinpocetine (data not shown).

3.3. Vinpocetine inhibits the increase induced by PTZ on BAEP waves latency

In agreement with our previous study (Nekrassov and Sitges, 2003), in the animals pre-injected with vehicle PTZ significantly increased the latency of P2–P4 wave components of the BAEP induced by 100 dB at 4 and 8 kHz. In contrast, in the animals pre-injected with vinpocetine the increase exerted by PTZ on the latency of those waves was lost (Fig. 4). PTZ does not change P1 latency.

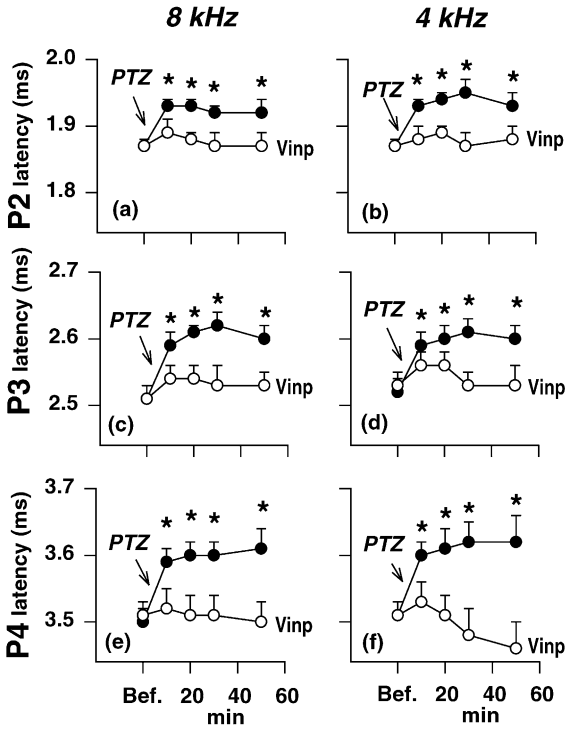

Fig. 4. Vinpocetine inhibits the increase in P2–P4 wave peak latencies induced by PTZ. The latencies of the wave components of the ABR induced by a stimulus intensity of 100 dB nHL at 8 kHz (left graphs) and 4 kHz (right graphs) tone frequencies were determined before the injection of 100 mg/kg PTZ (Bef.) and 10, 20, 30 and 50 min after the injection of PTZ in the animals pre-injected with vehicle (black circles) or with 2 mg/kg vinpocetine (empty circles). Results are the mean ± S.E.M. values of eight independent animals. (∗) Statistically significant difference between data obtained before and at the indicated time after the injection of PTZ.

Table 2
Vinpocetine inhibits the increase in the auditory threshold[a] induced by PTZ

	PTZ	Vinpocetine + PTZ
8 kHz		
Before	7.0 ± 1.2	6.0 ± 1.0
30 min	17 ± 2.0[b]	6.0 ± 1.0
50 min	21 ± 2.4[b]	6.0 ± 1.0
4 kHz		
Before	21 ± 1.0	20 ± 1.6
30 min	28 ± 2.0[b]	18 ± 1.2
50 min	29 ± 1.0[b]	18 ± 1.2

[a] Results are the average ± S.E.M. values (in dB) of data obtained from eight animals. 'Before' refers to the auditory threshold (see Section 2) before PTZ injection in vehicle (left columns) or vinpocetine (rigth columns) treated animals.

[b] Significant difference between the threshold obtained before and at the indicated time after PTZ injection in the animals pre-injected with vehicle (left columns) or with vinpocetine (rigth columns).

Vinpocetine alone does not change the latency of the BAEP waves, as before the injection of PTZ ("Bef." on Fig. 4) all the data points in the animals pre-injected with vehicle and in the animals pre-injected with vinpocetine are overlapped.

3.4. Vinpocetine inhibits the hearing loss induced by PTZ

The auditory thresholds for 8 and 4 kHz tone frequencies were tested in all animals before the injection of PTZ and then 30 and 50 min after the injection of PTZ in the animals pre-injected with the vehicle or in the animals pre-injected with vinpocetine. Table 2 shows that the marked increase on the auditory threshold induced by PTZ in the animals pre-injected with vehicle at the two tone frequencies tested is lost in the animals pre-injected with vinpocetine. Vinpocetine alone (i.e. before the injection of PTZ) does not change the BAEP threshold.

4. Discussion

The present work shows that vinpocetine is an effective inhibitor of the EEG changes, BAEP waves changes and hearing decline induced by PTZ in the guinea pig in vivo.

The positive effect of vinpocetine on seizure control is indicated by the complete cancellation of all the epileptic manifestations induced by PTZ, such as the convulsions and the EEG epileptic cortical activity for the ictal and post-ictal periods. However, the complete prevention exerted by vinpocetine from 2 mg/kg on the convulsions induced by PTZ in non-anaesthetized guinea pigs reported here, contrasts with a couple of previous studies in rats, in which the anticonvulsant capability of vinpocetine on the behavioural stages induced by PTZ-kindling was explored. For instance, in one study (Schmidt, 1990) a dose of vinpocetine 10 times higher than that used here was required to obtain a clear reduction of the behavioural manifestations of epilepsy, and in the other study no effect of 1 mg/kg vinpocetine on the severity of seizure stages was found (Becker and Grecksch, 1995). Probably the different experimental models of epilepsy used (kindling versus acute) or the taxonomic differences between rats and guinea pigs (Graur et al., 1991; Teskey et al., 1995) explain the higher potency and efficacy of vinpocetine found here.

In the guinea pig P3 and P4 are two BAEP waves of retro-cochlear origin that express the activity of the medial and lateral superior olivary nuclei, respectively (Wada and Starr, 1983a,b,c). Our finding that by eliminating the alterations in P3 and P4 induced by experimental epilepsy the hearing decline is also eliminated, further supports our previous conclusion that the hearing loss observed in animal models of generalized epilepsy is connected with the alterations in the activity of the generators of the BAEP waves localized in nuclei of the superior olive (Nekrassov and Sitges, 2003). The increased BAEP waves latencies and thresholds shown here in the acute PTZ animal model of epilepsy, along with the previously reported alterations in BAEP waves and elevated BAEP thresholds in epileptic patients (Rodin et al., 1982; Mervaala et al., 1986; Phillips et al., 1990; Soliman et al., 1993) suggests that epilepsy per se can cause hearing deficits, that may probably contribute to the deleterious cognition concomitant to epilepsy (Prevey et al., 1998; Meador, 2001).

Medication with antiepileptic drugs of either the "old and new generations" exerts a positive effect on seizure control (at least in about 70% of epileptic patients), but unfortunately is generally accompanied by serious adverse effects, among which cognition decline is particularly important (Vermeulen and Aldenkamp, 1995; Gates, 2000; Brunbech and Sabers, 2002; Schmidt, 2002). Considering the antiepileptic potential of vinpocetine along with its capacity to improve cognitive functions, it seems likely that vinpocetine could be a potential alternative for the treatment of epilepsies.

In previous works, changes in the auditory structures of the superior olivary complex have shown to accompany (Fisman, 1975) and even precede (Kohsaka et al., 1999; Kohsaka et al., 2001) the epileptic activity in patients. If we assume that the frequent disturbances of the superior olivary nuclei reduce hearing in epileptic patients with high chronicity, prevention of the alterations in the BAEP waves generated in the superior olivary nuclei might be an additional advantage for the treatment of epilepsies.

Another problem of the available antiepileptic drugs is that they fail to produce a perceptible impact on the progression of the illness (Hernandez, 1997; Temkin et al., 2001; Schmidt, 2002). In the present study the protective action of vinpocetine against the effects on EEG and BAEPs were tested in an acute model of epilepsy. Although, our previous findings that vinpocetine exerts a long term (more than half a year) beneficial action on the hearing loss, weight loss and mortality induced by amikacin in the guinea pig (Nekrassov and Sitges, 2000), might suggest that vinpocetine could also be beneficial for treating the progression of the illness.

In summary, the present data indicate that vinpocetine represents a promising alternative for the treatment of epilepsy.

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