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Acute and chronic effects of carbamazepine, phenytoin, valproate and vinpocetine on BAEP parameters and threshold in the guinea pig

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Abstract

Objective: To characterize the acute and chronic effects of the antiepileptic drugs (AEDs): carbamazepine (CBZ), phenytoin (PHT), valproic acid (VPA) and vinpocetine (VPC), at doses 20, 6, 30 and 2 mg/kg, respectively, on the latencies and amplitudes of the waves of brainstem auditory evoked potentials (BAEPs) elicited by a supra-threshold stimulus alongside BAEP threshold.
Methods: BAEPs elicited by a stimulus of high (100 dB nHL) intensity and BAEP thresholds were obtained at 4 and 8 kHz: before, after the start of treatment, and following 28 days of a daily injection of the AEDs.
Results: After the start of treatment BAEPs were unchanged. After the long term treatment, CBZ and PHT increased P3 and P4 wave peak latencies and reduced P4 amplitude. Chronic VPA did not modify BAEP waves, and chronic VPC reduced P3 and P4 latencies. P1 and P2 were unchanged. BAEP thresholds at 4 and 8 kHz were increased by CBZ, PHT and VPA, and decreased by VPC.
Conclusions: The chronic administration of several AEDs modifies BAEP waves of retro-cochlear origin.
Significance: Alterations in the generators of the later waves of BAEPs underlie, in most cases, the changes in hearing sensitivity produced by the long term treatment with AEDs at therapeutic relevant doses.

Keywords: AEDs; Brainstem auditory evoked potentials; 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. Several studies carried out in patients medicated with antiepileptic drugs (AEDs) commonly used for the treatment of epilepsy, such as carbamazepine (CBZ), phenytoin (PHT) or valproic acid (VPA), suggest that these drugs produce abnormalities in the waves of BAEPs and in some cases hearing deficits (Armon et al., 1990; Medaglini et al., 1988; Chan et al., 1990; Japaridze et al., 1993; Yuksel et al., 1995; Rysz and Gajkowski, 1996; De la Cruz and Bance, 1999; Verrotti et al., 2000; Wakamoto et al., 2004; Braun and Chaloupka, 2005).

Since epileptic patients are medicated for a long time, and frequently with more than one AED, systematic studies directed to investigate the effects of a specific AED on the waves of BAEPs in epileptic patients become complicated. Unfortunately, in the few studies in which the effects of AEDs on the waves of BAEPs were tested in animal models, AEDs were acutely administrated and at extremely high doses (Faingold and Stittsworth, 1981; Hirose et al., 1986, 1990). In those studies, 150 mg/kg CBZ acutely administrated increased the latency of all waves of BAEPs in the rat, and a toxic dose (40 mg/kg) of acute PHT abolished all waves of BAEPs in the rat and in the cat.

Interestingly, in the pentylenetetrazole (PTZ) and the 4-aminopyridine (4-AP) pharmacological animal models of epilepsy, increased latencies and decreased amplitudes of the later waves of BAEPs, P3 and P4, were also observed

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(Nekrassov and Sitges, 2003); and moreover, vinpocetine (VCP, ethyl apovincamine-22-oate), a nootropic drug with antiepileptic potential acutely administrated at a concentration of 2 mg/kg, which is sufficient to prevent convulsions in the above animal models of epilepsy, did not modify the waves of BAEPs but inhibited the alterations of the waves of BAEPs induced by the convulsing agents PTZ and 4-AP (Nekrassov and Sitges, 2004; Sitges and Nekrassov, 2004).

To our knowledge systematic studies on the long term effects of AEDs at relevant doses, namely non toxic doses similar to those used for the treatment of epileptic patients, on the waves of BAEPs in experimental animal models are missing. Therefore, the chronic effects of 2 mg/kg VPC, and of CBZ, PHT and VPA at moderate concentrations on the amplitude and latency of the waves of BAEPs elicited by a supra-threshold stimulus were investigated here in the guinea pig.

2. Methods

2.1. BAEP recordings

BAEP recordings were performed in a sound proof room using a Nihon-Kohden Neuropack IV Mini (MEB-5304K) system following the method that we have previously used in several studies (Nekrassov and Sitges, 2000, 2003, 2004; Sitges and Nekrassov, 2004). Briefly, needle electrodes were placed subcutaneously at the ipsilateral left pinna (reference electrode), the contralateral pinna (ground electrode), and the vertex (active electrode). Monaural stimuli of 8 and 4 kHz were delivered by a TDH 39 earphone located 1 cm from the left ear. The right ear was blocked with a special wax plug that reduces the sound level at this ear. In order to estimate the attenuating power of the plug to the stimulus of 100 dB nHL the amplitude of wave P3 with the plug and with both ears open was compared. At 8 kHz the ear plug reduced P3 amplitude in 37 ± 5 dB, and at 4 kHz in 32 ± 7 dB. Alternating polarity tone bursts (20/s) with 2 ms duration and 0.5 ms rise-fall times were used to evoke the potentials. Responses were digitally filtered (bandpass: 100–3000 Hz), amplified and averaged, displayed vertex positive up and saved on disk for off-line analyses. We first gave three consecutive trials (each trial equaling the average response to 500 stimuli) at the 8 kHz tone frequency followed by three trials at 4 kHz. Each trial took 25 s as 20 stimuli were delivered per second. The time interval between the two tone frequencies was about 15 s. The equipment averaged the responses at each frequency automatically. To obtain the BAEP thresholds, stimuli of progressively lower intensity (in dB normal hearing level, nHL), starting from a stimulus of supra-threshold intensity (100 dB), were delivered. Threshold was defined as the lowest stimulus intensity at which the P3 wave of the BAEP could still be recorded in the three consecutive trials. To identify the auditory threshold, stimulus intensity was progressively reduced by steps of 20, 10 and 5 dB. The inter-stimulus interval when reducing the intensity was not longer than 5 s.

The recordings obtained with the supra-threshold stimulus of 100 dB (nHL) at 4 and 8 kHz under the different experimental conditions were used to determine the effects of the AEDs on the latency and amplitude of the waves of BAEPs.

2.2. Experimental animals

The study started with 35 pigmented adult male guinea pigs. In order to evaluate their hearing status the BAEP threshold of each animal at 8 kHz was obtained. Five animals presented abnormally elevated BAEP thresholds (above 25 dB, at 8 kHz). These hypo-acoustic animals were removed from the study. The remaining 30 animals, initially weighing 266 ± 6 g, were included in the study. Prior to each sequence of recordings, the guinea pigs were anaesthetized with ketamine (50 mg/kg/10 mg/kg xylazine, i.p.) to prevent movement, stress and muscular activity. In the first set of recordings (taken before any treatment was started), each anaesthetized animal was implanted with a microchip for later identification. The animals were then divided in five groups of six animals per group, distributed in such a way as to obtain similar BAEP thresholds across the groups before treatment started. Groups were defined by the substance to be injected. The control group was injected with vehicle and the experimental groups with: CBZ (20 mg/kg), PHT (6 mg/kg), VPA (30 mg/kg) or VPC (2 mg/kg). One week after the control recordings were obtained, a second set of recordings was made about 2 h after the first injection according to the condition to be tested (vehicle or one of the AEDs). The animals were then injected daily for 28 days. On day 28, another set of recordings was obtained.

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

2.3. Drugs

All the AEDs tested were a kind gift of Psicofarma S.A. de C.V. (México). VPA (4.5% w/v) was dissolved in a solution containing 10% ethanol and 10% glycerin; PHT sodium salt (5% w/v) in a solution containing 10% ethanol, 40% propylene glycol and 0.1% NaOH;. CBZ (1.5% w/v) in a solution containing 20% ethanol and 60% propylene glycol; and VPC (0.3% w/v) in a solution containing 10% ethanol and 60% propylene glycol and citric acid (1.7% w/v). A solution containing 10% ethanol and 60% propylene glycol was used as the vehicle injected in control animals. The maximal volume of vehicle, or of solution containing the dissolved AED injected, never exceed 0.5 ml, even in the case of the heaviest animals at the end of the experimental series after the 28 days.

2.4. Statistics

The ANOVA test was used for the evaluation of the differences between control (before start of treatment) and