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Retinal function and histopathology in rabbits treated with Topiramate

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Short title: Topiramate effects in rabbit retina

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Abstract

Purpose: To evaluate retinal function and histopathology in rabbits treated orally with the anti-epileptic drug topiramate.

Methods: Six rabbits were treated with a daily oral dose of topiramate orally during a period of eight months. Six rabbits receiving water served as controls. Blood samples were analyzed for determination of topiramate serum levels in order to ensure successful drug exposition.

Standardized full-field electroretinograms (ERGs) were performed before treatment and then at 2, 3 and 8 months during the treatment period. After terminating treatment the rabbits were sacrificed and the morphology of the sectioned retina was studied.

Results: After eight months of treatment the full-field ERG demonstrated normal rod function in treated and control rabbits, but the light adapted 30 Hz flicker b-wave amplitude was significantly reduced in the treated rabbits. This was the case for both the light adapted (Wilcoxon signed ranks test, $p=0.046$) and the dark adapted (Wilcoxon signed ranks test, $p=0.028$) 30 Hz flicker response from the treated rabbits. Retinal immunohistology revealed a severe accumulation of GABA in amacrine cells and in the inner plexiform layer in 4 of 6 treated rabbits compared to the controls.

Conclusions: Topiramate, orally administrated to rabbits, may cause a significant reduction of the retinal function demonstrated by the reduced b-wave amplitude in the full-field ERG, as well as changes in immunohistology characterized by a severe accumulation of GABA in the inner retina. The retinal dysfunction and the morphological changes indicate that topiramate may damage the retina, similarly to vigabatrin (another anti-epileptic drug).

Keywords: Topiramate, electroretinogram, immunohistochemistry, drug toxicity, rabbit.

Introduction

Topiramate, an antiepileptic drug, is frequently used in the management of refractory epilepsy, not satisfactory controlled by traditional anticonvulsants. It is known to significantly increase human cerebral gamma-aminobutyrate (GABA) thereby increasing the threshold for seizure activity. Several different mechanisms of action are involved, such as blocking of sodium channels, enhancement of GABA-mediated chloride fluxes across the post-synaptic membrane, positive modulation of GABA-A receptors and a mild inhibition of carbonic anhydrase.^{1, 2} Another anti-epileptic drug that increases cerebral GABA-levels is vigabatrin (inhibits GABA-transaminase), which has been shown to cause severe, persistent visual field constriction.³⁻⁶ Several electrophysiological studies of patients treated with vigabatrin, have demonstrated reduced photopic amplitudes indicating actual dysfunction of an unspecified cell level in the retina.⁷⁻⁸ We have previously shown that the visual field defect (typically a bilateral nasal-inferior constriction) in patients treated with vigabatrin, is actually correlated with changes in the full-field electroretinogram (ERG) characterized by a reduced 30 Hz flicker response and a preserved scotopic response.⁹

Initially, complex epilepsy was the only indication for treatment with topiramate. Recently it has been suggested that topiramate may be useful in the treatment of obesity¹⁰⁻¹⁵, eating disorders¹⁶⁻²⁰, migraine²¹⁻³¹, bipolar disorders³²⁻³⁵, other psychiatric disorders³⁶⁻⁴², alcohol dependence⁴³⁻⁴⁷ and other addictive disorders⁴⁸. Also the drug is more frequently used in the management of childhood epilepsy⁴⁹⁻⁵¹.

The objective of the present study was to evaluate retinal function and morphology, in rabbits treated orally with topiramate during a period of 8 months, which in humans would correspond to a period of approximately 20 years.

Material and methods

Subjects and medication

Seven fully grown rabbits (body weight 4-5 kg) were treated with a daily oral dose of topiramate during a period of 8 months. Nine rabbits receiving water were included as controls and were examined according to the protocol used for the treated rabbits. All rabbits (treated subjects and controls) were seven months old on entry to the study. One treated rabbit and three controls died unexpectedly during the study, and were therefore excluded.

In previous studies a suspension of topiramate in aqueous 0.5 % sodium carboxymethyl-cellulose (CMC) has been dosed via gastric intubation in rabbits (Janssen-Cilag AB, Sollentuna, Sweden). Suspensions of topiramate, at concentrations of 1 and 75 mg/mL, in 0.5 % CMC have been shown to be stable for at least 5 weeks at 4°C and 25°C (Janssen-Cilag AB, Sollentuna, Sweden). A dose of 20 mg/kg/day in rabbits has been suggested to be equivalent to the human therapeutic dose of topiramate (Janssen-Cilag AB, Sollentuna, Sweden). Therefore, suspensions of topiramate tablets 50 mg/mL in 0.5 % CMC were prepared for 5 weeks at a time and the initial dosage of this preparation was 0.4 mL/kg /day (=20mg/kg/day), thus the rabbits (body weight 4-5 kg) received approximately 80-100mg topiramate on one occasion every day. The suspensions were stored in room temperature and given orally using a syringe.

Concentrations of topiramate in serum were measured on two occasions during the treatment period, in order to ensure successful drug exposition. Blood samples were collected from the ear-vein of the rabbits. The individual drug dose was adjusted depending on the presence or absence of drug side-effects (loss of appetite). This study was conducted by acceptance from the ethical committee for animal research at the University of Lund. The research procedures were in accordance with the ARVO statement for the use of animals in ophthalmic and vision research.

Electrophysiology

Standardized full-field electroretinography (ERG) (slightly modified for rabbit ERG⁵³) was assessed on three occasions prior to treatment and on three occasions during treatment (2 months, 3 months and eight months after initiating treatment). The ERGs were recorded with a Nicolet

analysis system (Nicolet Biomedical Instruments, Madison Wisconsin) as described previously.⁵²⁻
⁵³, The examinations were conducted according to the International Society for Clinical Electrophysiology of Vision (ISCEV) standards.⁵⁴ The right eye was tested after maximal pupil dilation with topical 1% cyclopentolate hydrochloride, and after at least 30 minutes of dark adaptation. A Burian-Allen bipolar ERG contact lens electrode was applied on the topically anesthetized cornea together with a sub-cutaneous ground electrode on the neck. Responses were obtained with a wide band filter (-3dB at 1Hz and 500 Hz), stimulating with single full field flashes (30 μ s) with dim blue light (Wratten filters #47, 47A and 47B), and with white light (integrated luminance 0.81cd-s/m²). Responses from 30 Hz flickering white light (integrated luminance 0.81cd-s/m²) averaged from 20 sweeps with no background illumination, and with background illumination (34 cd/m²) until two successive identical curves were obtained.⁵³ Oscillatory potentials were recorded from the dark adapted eye, with white light (integrated luminance 0.81cd-s/m²) and by applying an overall band pass filter from 100 Hz (low frequency filter - LFF) to 300 Hz (high frequency filter - HFF). The referred luminance of the different light stimuli has been measured from a photometer on the light reflected from the Ganzfeld sphere. At each stimulus intensity the recording were repeated to ensure reproducibility (ie until two successive identical curves were obtained), but no stimuli was repeated at intervals less than 0.5 s. All rabbits were sedated with Hypnorm 0.6 ml (fentanylcitrate 0.315 mg/ml and fluanisone 10 mg/ml, VetaPharma Ltd, Leeds, UK) during the examination.

Tissue preparation

The rabbits were euthanized by an intravenous overdose of barbiturates. The eyes were enucleated within one minute and fixed for 30 minutes in freshly prepared 4% phosphate buffered formaldehyde, generated from paraformaldehyde (Merck, Darmstadt, Germany) at pH 7.4 in 0.1

M Sörensen's phosphate buffer (primary and secondary NaHPO; Merck). The eyes were then transected at the *ora serrata*. The anterior segment, lens and vitreous body were discarded. The posterior segment were postfixed in the same fixative for 3,5 hours, at 4°C. The tissue was then rinsed and cryoprotected by transferring it stepwise through solutions of increasing concentrations of sucrose (10, 15 and 20%) in the Sörensen's buffer. The eyecups were then divided into two parts by a vertical incision from the superior to the inferior retinal margins comprising the optic disc. The two halves were embedded in Yazulla media (30% egg albumen and 3 % gelatine in water) and then sectioned (12µ) in the cryostat (-21°C) starting at the central part and moving towards the peripheral part of the eye. The sections were collected on chrome alum coated slides, air dried, and stored at -20°C until used.

Immunohistochemistry

The sections were thawed and washed in 0.1 M sodium phosphate buffered saline pH 7,2 (PBS) with 0.25% Triton X-100 (PBST). For diluting the primary and secondary antibodies, 1% bovine serum albumin was added in PBST. The sections from the eyes were then incubated in the primary antibodies vimentin, GFAP and GABA (targeting Müllercells, gliacells and GABA ergic cells, respectively), for 16-18 hrs, in 4°C. After rinsing, the slides were mounted in a custom made anti-fading mounting media. The slides were examined using immunofluorescence imaging and photographed by a digital camera (Nikon Eclipse 800).

Results

Medication

Because of loss of appetite, a known adverse effect of topiramate, we were forced to adjust the doses of the medication depending on how the individual rabbit tolerated the drug. In all treated rabbits serum topiramate levels were within the range of 3.24 – 15.87 µmol/L when treatment was tolerated, and low or undetectable (<2.8µmol/L) when the dose was reduced because of loss of

appetite. The drug tolerance in the treated rabbits varied considerably which is demonstrated by the range of topiramate serum concentrations. At first time point for measuring topiramate concentration (2,5 months of treatment) four rabbits had elevated concentrations, which were the same rabbits as those with histopathological changes (Table). Up to this timepoint all treated rabbits had the same dose of topiramate, which was later reduced because of side effects.

Electrophysiology

Five different full-field ERG responses (dark adapted and light adapted) from one of the rabbits (2A-041) are presented in Figure 1. The figure shows a selective reduction of the 30 Hz flicker response, both dark- and light adapted, in contrast to the rod response that remains unaffected.

Initially, before treatment the fullfield ERG results were similar in the six treated rabbits and in the six controls. After eight months of treatment the full-field ERG (last examination) demonstrated normal rod function in treated and control rabbits, but a significantly reduced light adapted 30 Hz flicker response in treated rabbits (Wilcoxon signed ranks test, $p=0.046$). Comparison in the treated group before and after treatment demonstrated a significant difference in the light adapted, and the dark adapted 30Hz flicker response and for P1, P2, P3 in the oscillatory potentials (Wilcoxon signed ranks test, $p=0.028$).

Full-field ERG b-wave amplitudes from all treated rabbits, resulting from stimulation with dim blue light single flash (selective rod response), white light single flash (total retinal response) and 30 Hz flicker white light dark and light adapted, before and after treatment, are presented in the Table. All treated rabbits demonstrated reduced 30 Hz flicker responses after treatment, which is also shown (for one rabbit) in Fig. 1. Also the oscillatory potential (OP) amplitudes were significantly reduced after treatment (Table). There was no difference in implicit time for the 30 Hz flicker white light stimulation, before and after treatment.

Histology of retina

GABA

The retinal sections presented (Fig 2) are from two controls and all treated rabbits. In four of the treated animals, significant pathology in immunostaining could be identified in the retinal sections. The immunoreactivity was enhanced in the amacrine cells. GABA-positive cellbodies appeared in the inner nuclear layer (INL) and among the ganglion cells (GGL). In the inner plexiform layer (IPL) the staining was strong, and no clear layering could be seen (Fig. 2). In the retina of the control animals and in two treated animals the amacrine cells in the INL were moderately immunoreactive, and a clear layering could be seen in the IPL.

GFAP and vimentin

The staining with GFAP and vimentin did not show any significant differences between treated rabbits and controls.

Discussion

Antiepileptics are given to a broad population as the worldwide annual incidence of epilepsy ranges from 24-53/100 000.⁵⁵ Adverse effects of antiepileptics are continuously being studied and reported, especially since vigabatrin, an carbanhydreaes blocker was found to cause severe and probably irreversible visual field defects.³⁻⁶

In comparison, topiramate has not as frequently been associated with visual field defects. In higher doses it is known to cause other visual disturbances such as acute angle closure glaucoma and diplopia/nystagmus.⁵⁶ So far 14 reports (up to september 2005) of non characteristic visual field defects have been submitted to the World Health Organisation (WHO) collaborating Centre for International Drug Monitoring, some of which have been determined to have a possible association with topiramate. In a recently published case report the authors describe a patient with an incongruent homonymous hemianopsia possibly caused by topiramate.⁵⁷ Another case was reported recently describing a patient with bilaterally constricted visual fields verified by a reduced multifocal electroretinogram indicating a diffuse retinal dysfunction possibly caused by

topiramate.⁵⁸ In the present study we have demonstrated alterations in the full-field ERG in topiramate treated rabbits similar to the previously reported alterations in retinal function and morphology caused by vigabatrin.⁵² These results indicate that topiramate may also have adverse effects on retinal function which in turn may cause visual field defects.

The pathogenesis behind this retinal dysfunction is still unknown. We have previously found glial cell pathology in vigabatrin treated rabbits.⁵² In the present study the histopathology results were similar showing in 4 of 6 treated rabbits a pathological immunohistology, mainly a severe accumulation of GABA in amacrine cells and in the inner plexiform layer. This was not seen in all treated rabbits, which may indicate that the reduced function precedes the immunohistochemical pathology. However, the four rabbits with histopathological changes in retinal sections, also had significantly elevated concentrations of topiramate in serum after 2 months of treatment.

Adverse effects in the retina are important to investigate because of a continuous widening of indications for treatment with topiramate, from complex epilepsy being the only indication only a few years ago, to currently testing treatment for several other diagnoses such as migraine, bipolar disorders, eating disorders and obesity¹⁰⁻⁴⁸. The results from this study indicate that some caution should be taken until further studies have revealed the toxicology pattern for this drug. Also patients should be aware of these ocular side effects, and a full-field ERG performed on every patient reporting visual disturbance.

We conclude that topiramate, orally administrated to rabbits, may cause a significantly reduced retinal function reflected by the diminished b-wave amplitude in the full-field ERG, which has previously not been reported. Retinal histopathology in treated rabbits correlated significantly with serum levels of topiramate, but not totally with the reduced retinal function. Further toxicological studies, including objective evaluation of retinal function, are needed as the indications for treatment with topiramate are numerous today.

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Legends:

Table

ERG data demonstrating responses (b-wave amplitudes) to five different stimulations before (upper) and after (lower) treatment with topiramate for all treated rabbits and mean values for the controls. The rabbits with positive histopathology (+) had elevated levels of topiramate in serum.

Figure 1

Full-field ERG from rabbit 2A-041 before and after treatment with topiramate (December 12th 2002 and November 19th, 2003). The ERG traces demonstrate that the responses to dim blue light (integrated luminance 0.81cd-s/m²) remains unaffected by topiramate while the b-wave amplitude to 30 Hz flickering white light (integrated luminance 0.81cd-s/m²) with no background illumination, and with background illumination (34 cd/m²) are significantly reduced by the drug. The 30 Hz flicker response in the rabbit ERG, before treatment, contains a 2nd small positive peak, which is a flash artefact

Figure 2

GABA immunoreactivity in two controls (top row) and in the retina from all treated animals. The GABA-activity was enhanced in the inner retina: in the amacrine cells (arrow head) in the displaced amacrine cells and in the ganglion cell (arrow), in four of six treated rabbits. Ph=photoreceptors, inner and outer segments INL=inner nuclear layer, ONL=outer nuclear layer, GGL=ganglion cell layer.

Table 1

Rabbit	<i>Dim blue light</i> Amplitude (μV)	<i>White light</i> Amplitude (μV)	<i>30 Hz flicker</i> Amplitude (μV)	<i>30 Hz flicker</i> Amplitude (μV)	Oscillatory potentials P1/ P2/ P3 Amplitude (μV)	Topiramate serum μmol/L	Histopathology
2A-040	121 76	139 92	25 7	20 5	22/27/23 15/ 14/ 13	<2.8	-
2A-032	40 74	89 98	16 6	16 6	19/ 29/ 20 11/ 15/ 12	12.23	+
2A-033	50 94	124 100	18 4	13 4	19/ 26/ 19 12/ 23/ 15	15.87	+
2A-041	68 96	158 115	31 10	29 8	26/ 43/ 19 8/ 13/ 20	5.69	+
2A-042	130 96	202 130	33 13	26 11	34/ 50/ 36 19/ 30/ 21	6.44	+
2A-094	91 56	188 125	24 6	20 5	26/ 36/ 29 14/ 18/ 15	<2.8	-
Six controls Mean\pm STD	94\pm45	161\pm68	20.1\pm7.1	15.5\pm7.1	24\pm11/ 31\pm15/ 24\pm12		

Before treatment

After treatment

Darkadapted

Blue light

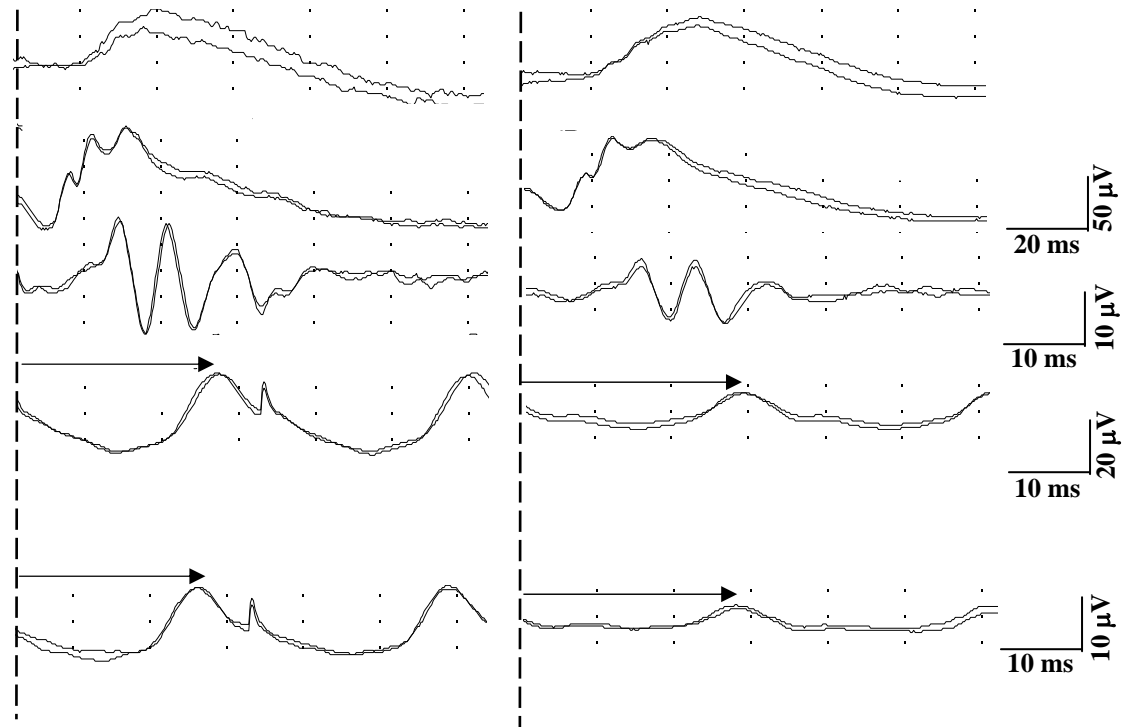
Combined response

Oscillatory potentials

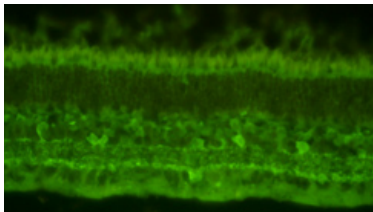
30 Hz flicker responses

Lightadapted

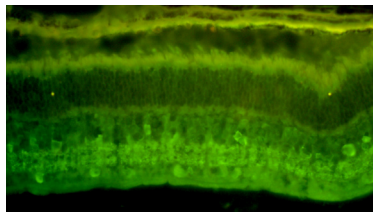
30 Hz flicker responses



Control

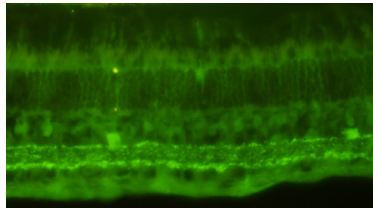


Control

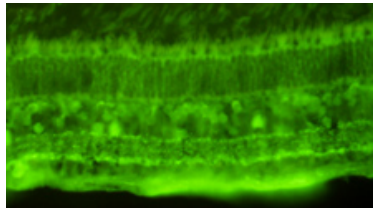


Ph
ONL
INL
GGL

2A-040

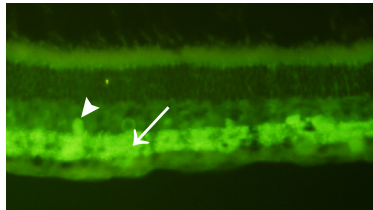


2A-094

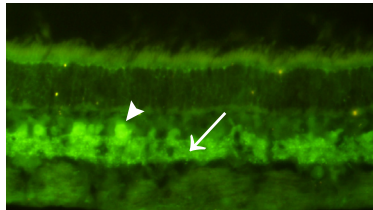


Ph
ONL
INL
GGL

2A-033

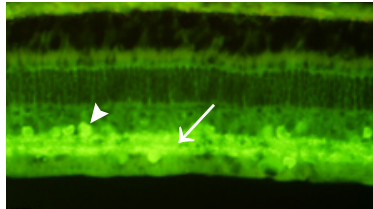


2A-041

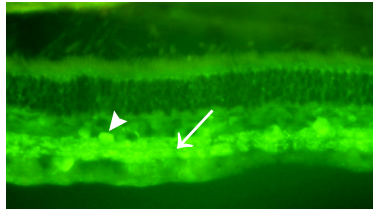


Ph
ONL
INL
GGL

2A-032



2A-042



Ph
ONL
INL
GGL