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Ultrastructural features of astrocytes in the cortex of the hippocampal gyrus and in the neocortex of the temporal lobe in an experimental model of febrile seizures and with the use of topiramate

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Abstract

The objective of the current study was ultrastructural assessment of astroglia in specimens of the hippocampal cortex and neocortex of the temporal lobe in our own experimental model of febrile seizures (FS) in rats, as well as the analysis of the influence of a structurally novel broad spectrum anticonvulsant, topiramate (TPM), upon these cells in the CNS regions studied. The current study was inspired by some interesting literature reports on the in vitro *investigation into the biological effects of TPM in primary cultures of rat cortical astrocytes and by the lack of data concerning astroglial morphology* in vivo *in an experimental model with this antiepileptic. In the FS group, the most pronounced changes in the study cell population referred to protoplasmic astroglia and were observed in approximately 3/4 of these cells. The abnormalities were similarly expressed in the two CNS regions studied, in terms of both quantity and quality. They were characterized by considerable swelling and degenerative changes, both in astrocytic perikarya and their processes. Changes were visible in the elements of the granular endoplasmic reticulum and mitochondria, which had a condensed configuration. In the group receiving topiramate directly after the induction of FS, submicroscopic changes in protoplasmic astrocytes were similarly expressed as in the FS group. However, in the group receiving the drug prior to the induction of FS its protective action was observed on the morphology of approximately 1/3 of the population of the protoplasmic astroglial cells. The remaining protoplasmic astrocytes still showed features of considerable or moderately pronounced injury. The beneficial effect of TPM on the ultrastructure of part of the population of the protoplasmic astroglia in the group in which the drug was applied prior to the induction of FS can be explained, among others, by a protective effect of the blood-brain barrier enhanced by the drug administration, as indicated by our earlier findings.*

Key words: *experimental febrile seizures, topiramate, protoplasmic astrocytes, hippocampal cortex, neocortex, ultrastructure.*

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Introduction

Hyperthermia-induced convulsions, i.e. febrile seizures (FS), with a worldwide incidence as high as 6.7% of children, are one of the most frequent reasons for seeking paediatric care. They are the most common form of seizures in childhood and have been associated with an increased risk of epilepsy later in life [12,13]. Some researchers claim that prolonged FS are a frequent cause of temporal lobe epilepsy, associated in about 2/3 of cases with the pathology defined as mesial temporal sclerosis, characterized mainly by specific hippocampal neuronal losses and gliosis [15,18,21,26].

The mechanisms underlying generation of febrile seizures are poorly understood. They have been suspected to have a genetic basis, and recently, mutations in GABAA receptor and medium channel genes have been identified that are associated with febrile seizures and generalized seizures with febrile seizures plus pedigrees (Kang 2006).

Recently, application of the new antiepileptic drug topiramate (TPM), a structurally novel broad spectrum anticonvulsant, has been considered, presumably with a very good effect, in the therapy of febrile seizures in children. Although this medication is widely used in patients as an antiepileptic agent with multiple targets in epilepsy, epileptic state and brain ischaemia [11,16,19], it has not yet been instituted in the clinical practice for the treatment of hyperthermic convulsions, still remaining at the stage of multidisciplinary experimental studies.

According to many authors, the mechanism of the anticonvulsant action of TPM is multidirectional and so far not fully known [9,12,23,25,28,31].

There are numerous studies on neuroprotective effects of the drug in various experimental models of neuronal damage, including epilepsy, epileptic state, global brain ischaemia, perinatal hypoxia-ischaemia, motor neuron diseases, and traumas of the facial nerve [1,7,8,14,17,22,23,29], apart from our morphological reports on febrile seizures [20,27].

Many researchers claim, mainly based on *in vitro* studies of cultured cortical astrocytes, that the effect of topiramate on glial cells, which are intimately involved in the normal functioning of neurons, plays a significant role in its anticonvulsive action, as in the case of most antiepileptic drugs [2,3,4,14,24,25]. Biochemically, the interaction with the excitatory neurotransmission, e.g. glutamate receptors, which play an essential role in the excitotoxic neuronal damage, is believed to be an important part of its anticonvulsant effect [25,30,31].

The current study was inspired by some interesting literature reports on the *in vitro* investigation into the biological effects of topiramate in primary cultures of rat cortical astrocytes, i.e. in primary astrocytes cultured separately or together with neurons [2-5,24,25,30] and by the lack of data concerning astroglial morphology *in vivo* in an experimental model with this antiepileptic.

We have not found similar *in vivo* study reports, apart from our earlier histological investigations associated with morphometric analysis regarding pyramidal neurons, performed on rat ammonal cortex in an experimental model of febrile seizures and after administration of topiramate [27], or ultrastructural analysis of the blood-brain barrier (BBB) components of this region of the CNS in an analogous experimental model [20],

Thus, the aim of the current study was the electron-microscopic assessment of astroglial cells in specimens of the hippocampal cortex and neocortex of the temporal lobe in our experimental model of febrile seizures in rats and the influence of topiramate upon these cells in the CNS regions studied.

Material and Methods

The study was performed on 18 young male Wistar rats aged 22-30 days. The animals were divided into four groups – three experimental and one control (five rats in each experimental group and three in the control). The degree of brain maturity in such animals corresponds to that of 1- or 2-year-old children.

The rats used for our experiment were pre-selected according to the standard pharmacological screening test.

The FS group consisted of rats with induced febrile seizures. Hyperthermic stress was induced by placing animals in a water bath filled with 45°C warm water. Water temperature was maintained at the same level. The rats were put into water for 4 minutes until convulsions appeared and then moved to a separate container lined with lignin. The animals, except for control rats, were placed in the water bath for four consecutive days.

In the FS + TPM group, topiramate (Topamax, f. Jaansen-Cilag; 80/kg b.m. dissolved in 2 ml normal saline) was administered with an intragastric tube,

immediately after each convulsion episode (every animal received the drug four times altogether).

In the TPM + FS group, topiramate was administered in the same way and at the same dose, prior to the induction of febrile seizures, i.e. 90 minutes before the animals were placed in the water bath.

Control animals and the FS group received only normal saline. The dose of topiramate was chosen according to literature references [7,29].

A detailed description of the methodology was presented in our previous papers [20,27].

Preparation for electron microscopy

Seventy-two hours after the last convulsion episode, the rats were anesthetized with Nembutal (25 mg/kg b.w., i.p.) and transcardially perfused with fixative solution of 2% paraformaldehyde and 2.5% glutaraldehyde in 0.1 M cacodylate buffer pH 7.4. After removal of the brains, hippocampal and temporal lobe samples were taken and fixed in the same solution for 24 h at 20°C. Post-fixation was completed with 1% osmium tetroxide. After dehydration in ethanol and propylene oxide, small specimens (1 mm^3) of the gyrus hippocampal cortex and the neocortex of the temporal lobe were processed routinely for embedding in Epon 812. Semithin sections were stained with methylene blue and examined in the light microscope. Ultrathin sections were double stained with uranyl acetate and lead citrate and examined with a transmission electron microscope (Opton 900 PC, Zeiss, Oberkochen, Germany). The material obtained from the gyrus hippocampal cortex and neocortex of the temporal lobe in the control group was processed using the same techniques as for experimental groups.

Results

FS group

The animals with induced febrile seizures presented essential ultrastructural changes in the cells of astroglia, mainly in protoplasmic astrocytes, of the hippocampal cortex and neocortex of the temporal lobe. They were similarly pronounced, both in quantitative and qualitative terms, in the two CNS regions studied. After these seizures, the vast majority, i.e. about 3/4 of the protoplasmic astrocytes, exhibited considerable swelling and degenerative changes, including degradation. This referred to astrocytic perikarya and their processes, both perivascular, as we reported earlier [20], and lying loosely in the neuropil of the brain regions studied. The remaining protoplasmic astrocytes revealed slight or moderate swelling.

The cytoplasm of distinctly swollen protoplasmic astrocytes displayed markedly reduced electron density (Figs. 1-4). It was frequently characterized by electron lucency, being almost completely empty, with dispersed residual cellular organelles (Fig. 3).

The cellular nuclei of such astrocytes were considerably enlarged, translucent, with a small amount of heterochromatin irregularly located under the nuclear envelope (Figs. 1-3).

Among the residual cellular organelles there were fragments of granular endoplasmic reticulum (GER), chaotically scattered ribosomes that sometimes formed tiny clusters and pleomorphic mitochondria (Figs. 1-3). Occasionally, vacuolar structures of varied size and shape, originating due to dilation of the smooth endoplasmic reticulum, empty (Fig. 3) or filled with delicate microfibrillar material, as well as structurally differentiated lysosomes, were visible (Fig. 4). Quite often abnormal residual organelles were grouped in the perinuclear region (Figs. 2, 4).

The altered astrocytes contained a decreased number of gliofilaments (Fig. 2) or these filaments were even completely lost.

Sometimes, however, markedly damaged remnant endoplasmic organelles were seen in the neighbourhood of relatively well preserved organelles.

GER pattern was one of the endoplasmic abnormalities. Frequently, GER elements were elongated, "stretched" and torn, with a segmentally reduced number of ribosomal granules. They seemed to form single reticular structures (Fig. 1); occasionally they were markedly shortened and dilated (Fig. 3).

However, the most pronounced mitochondrial changes were characterized by increased electron density of the matrix (Figs. 1, 2), sometimes with accompanying blurring of the normal internal structure of these organelles and their shrinkage, which morphologically corresponds to the mitochondria having a condensed configuration [6,10].

Most damaged astrocytic cells showed features of decomposition.

Altered astrocytic perikarya of protoplasmic astrocytes could often be found adhered to the pyramidal neurons in the regions studied, frequently showing intensified degenerative changes, usually

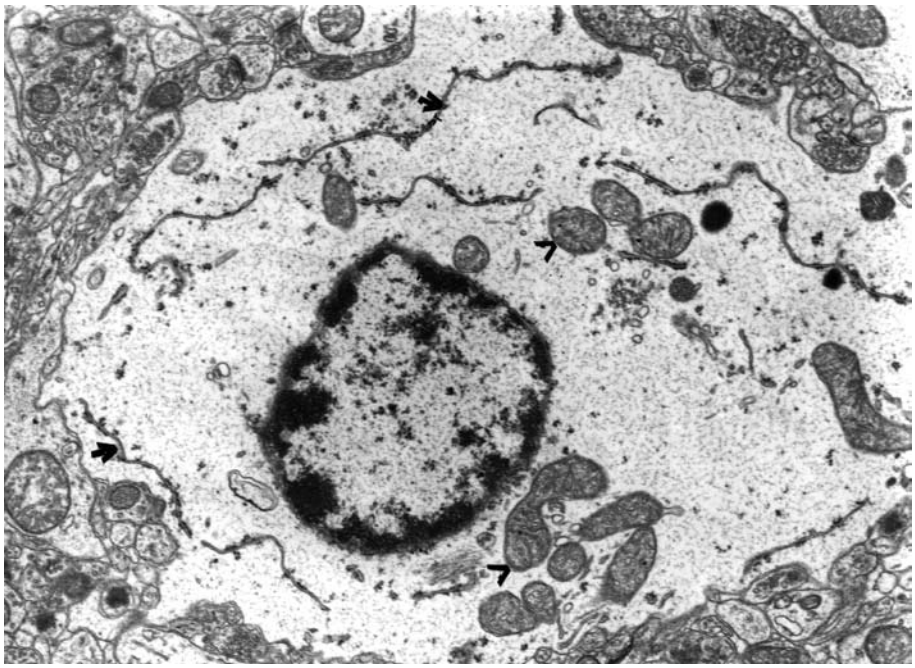

Fig. 1. Picture of a swollen protoplasmic astrocyte surrounded by neuropil elements. The cellular nucleus is translucent, with a small amount of heterochromatin irregularly concentrated under the nuclear envelope. Cell cytoplasm shows a considerable decrease in electron density. Fragments of granular endoplasmic reticulum (->) are markedly elongated ("stretched"), torn in places, as if forming single elements of the reticulum, showing features of segmental degranulation. Mitochondria (>) having slightly increased electron density of the matrix are slightly shrunken. Hippocampal cortex. FS group. Original magn. × 7000.

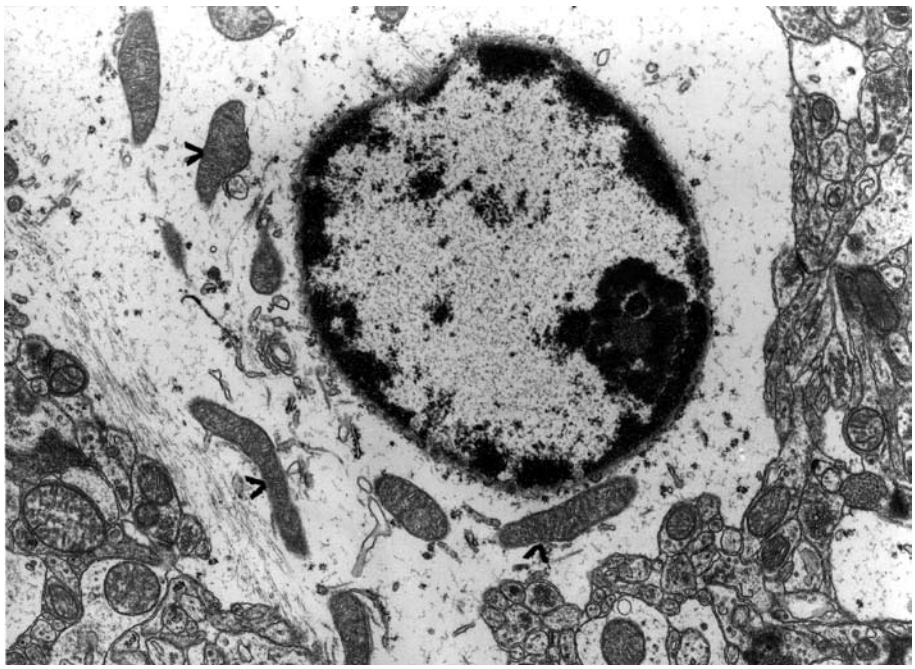

Fig. 2. Fragment of a swollen protoplasmic astrocyte contains a reduced number of endoplasmic organelles grouped mainly in the perinuclear region. Pleomorphic mitochondria, some shrunken, with a condensed configuration (>); the residue cell gliofilaments seen on the periphery. Hippocampal cortex. FS group. Original magn. × 7000.

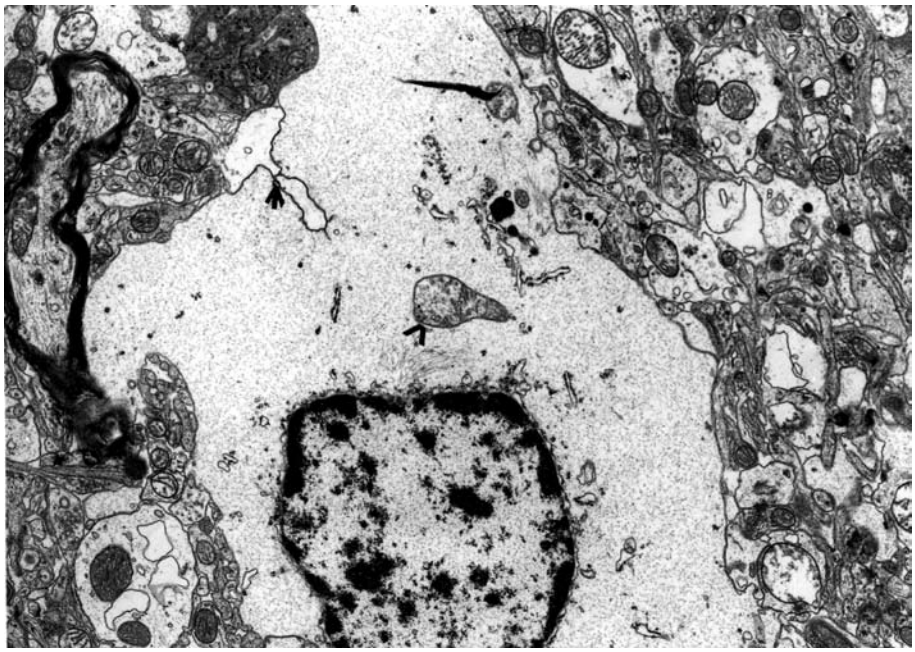

Fig. 3. Fragment of a pronouncedly swollen protoplasmic astrocyte – a cell of almost empty electron-lucent cytoplasm containing only a few remnant organelles. Among them, focally swollen mitochondria (>), irregular in shape, empty vacuolar structure (->) and markedly shortened granular endoplasmic reticular channels. Enclosing elements of neuropil are substantially altered. Neocortex. FS group. Original magn. × 4400.

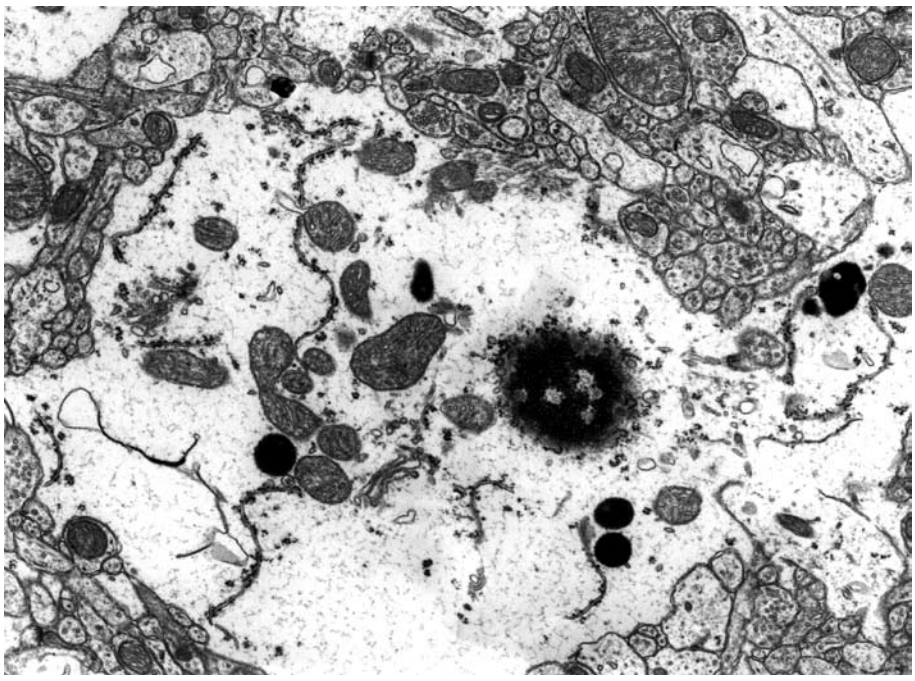

Fig. 4. Fragment of a markedly swollen disintegrating perikaryon of the protoplasmic astrocyte enclosed by altered neuropil elements; the electron-lucent cell cytoplasm shows fine, structurally differentiated lysosomes. FS group. Neocortex. Original magn. × 7000.

in the form of shrunken "dark neurons", as reported previously [20].

A detailed ultrastructural assessment of neuronal changes observed both in the ammonal cortex and in the neocortex of the temporal lobe in an experimental model of febrile seizures in rats is in preparation.

It should be noted that in our previous study, in the same group of animals with febrile seizures, ultrastructural indices showed considerable damage to the BBB of the hippocampal cortex [20].

FS + TPM group

The electron microscopic picture of the protoplasmic astrocytes of the hippocampal cortex and neocortex of the temporal lobe in the animals which after experimentally induced febrile seizures received topiramate showed changes quantitatively and qualitatively similar to those observed in the FS group (Figs. 5, 6).

TPM + FS group

In the animals receiving topiramate prior to febrile seizures, topiramate was found to exert a beneficial effect on the ultrastructural picture of about 1/3 of the protoplasmic astrocytes of the hippocampal cortex and neocortex of the temporal lobe. Such astrocytes, both of perikarya and their processes, showed relatively slight abnormalities compared to the control group (Figs. 7, 8), or were normal.

Another 1/3 of the protoplasmic astroglial cells revealed moderately pronounced swelling. The remaining 1/3 of the cells examined still showed submicroscopic abnormalities corresponding to advanced changes observed in the FS group.

Interesting in this group was a marked beneficial effect of topiramate on the electron-microscopic picture of the BBB components observed in more than half of the microcirculatory capillaries of the CNS regions examined, which was revealed in our earlier study [20]. Also neuronal abnormalities, including

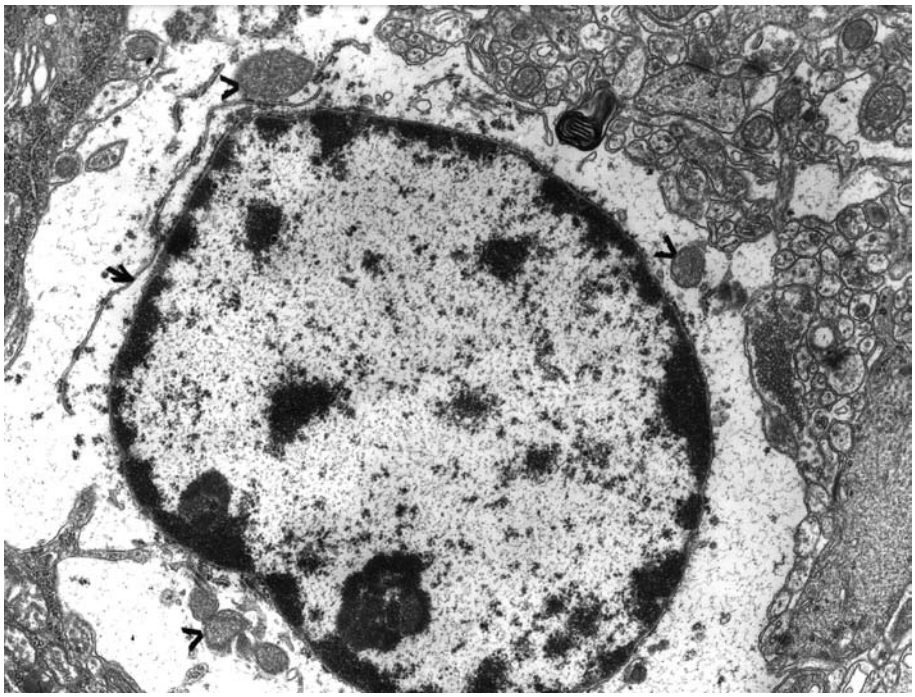

Fig. 5. Fragment of a markedly swollen perikaryon of protoplasmic astrocyte enclosed by neuropil elements. Residual organelles are situated in the vicinity of a substantially swollen cell nucleus containing a very small amount of heterochromatin irregularly located near the nuclear envelope. Visible is a single, markedly elongated ("stretched") element of granular endoplasmic reticulum (->) with features of marked degranulation and tiny dark mitochondria (>) Hippocampal cortex. FS + TPM group. Original magn. × 7000.

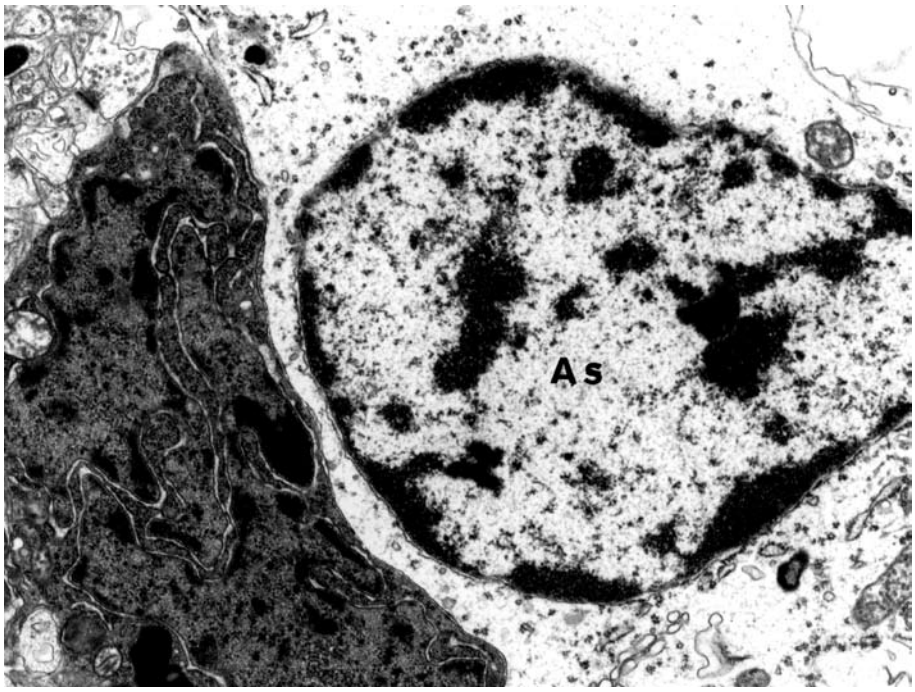

Fig. 6. Fragment of a considerably swollen protoplasmic astrocyte adhering to a shrunken dark neuron. Relatively numerous ribosomes are visible among residual endoplasmic organelles of the astrocyte. Neocortex. FS + TPM group. Original magn. × 7000.

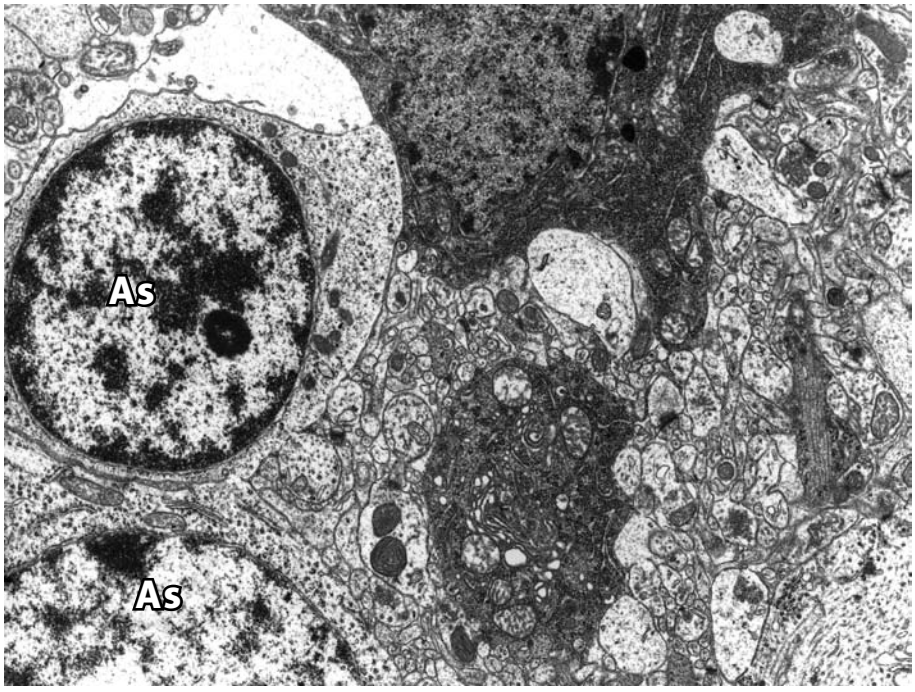

Fig. 7. Well preserved protoplasmic astrocytes (As) in the close vicinity of damaged neurons; the upper astrocyte adheres to a shrunken perikaryon of the nerve cell. Hippocampal cortex. TPM + FS group. Original magn. × 4400.

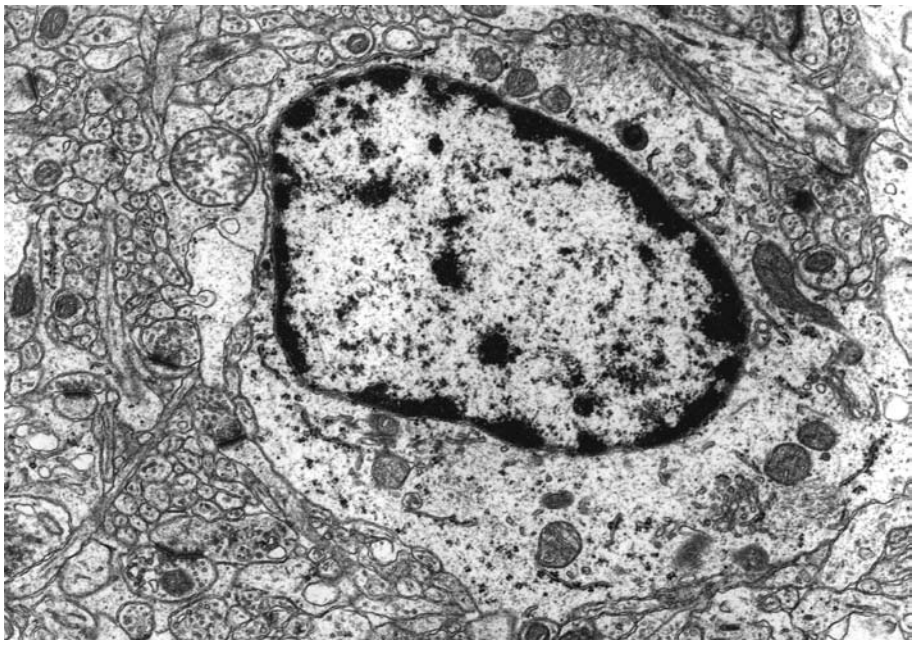

Fig. 8. Picture of a well preserved protoplasmic astrocyte enclosed by neuropil elements. Whereas the cell nucleus shows features of swelling, the endoplasmic organelles are relatively well preserved. Neocortex. TPM + FS group. Original magn. × 7000.

shrunken dark pyramidal neurons, were much less common than in the FS group, which will be presented in our future report.

Discussion

In the animals with induced febrile seizures, i.e. in the FS group, the most pronounced ultrastructural alterations affected approximately 3/4 of the population of the protoplasmic astroglia of the hippocampal cortex and neocortex of the temporal lobe. They were manifested by considerable swelling and degenerative changes, including degradation, both in the astrocytic perikarya and their processes. Damage to GER elements (elongation, "stretching", segmental degranulation) and mitochondria (condensed configuration) was the major manifestation. These abnormalities were accompanied by distinct damage to structural elements of the blood-brain barrier of the hippocampal cortex, mainly as a substantial increase in BBB permeability with remarkable involvement of perivascular astroglial processes [20].

The general pattern of the most pronounced ultrastructural changes within organelles, especially in the mitochondria and GER of the protoplasmic astrocytes in the FS group, displays disorders in some intercellular biochemical events, such as inhibition of oxidative phosphorylation or abnormal protein synthesis.

The morphological changes in astrocytes, especially those affecting mitochondria and GER, as well as BBB damage in the FS group observed in our study, resembled the alterations reported by Dydyk and Pluta [6] in the motor and sensory cortex of the brain in the course of experimental hyperthermia in rabbits. Condensation of mitochondria as a pathomorphological phenomenon indicates low-energetic status of these organelles and according to some authors suggests substantial conformation of matrix proteins [10].

In the FS + TPM group (antiepileptic administered after induction of febrile seizures), submicroscopic changes affecting protoplasmic astrocytes in the CNS regions studied were similarly expressed as in the FS group.

However, in the TPM + FS group (antiepileptic administered prior to febrile seizures), topiramate had a beneficial effect on approximately 1/3 of the protoplasmic astroglial cells. About 1/3 of the remaining protoplasmic astrocytes still showed features

of marked or moderate damage, which may reflect the morphological condition of neurons indicating distinct protective properties of the astroglial cells towards neurons and suggesting that they are the first line of defence against damaging factors. This has been confirmed by *in vitro* studies on primary rat astrocyte cultures incubated with topiramate [2-5,24,25,30].

In a study concerning newborn rat astroglial cells and neurons in primary cortical cultures, incubated with glutamic acid and a few antiepileptic drugs, such as topiramate, valproic acid, phenytoin and N-acetylcysteine, Angehagen et al. [2] observed the highest survival rate of neurons in the case of topiramate application. However, the cells of astroglia in this culture remained injured, which the authors explain by a likely glial buffering effect that could protect neurons. In their subsequent study, Angehagen et al. [3] observed a protective effect of topiramate against glutamate- and kainate-induced neurotoxicity in primary neuronal-astroglial cultures. The same authors [4] also demonstrated that in cultured cortical astrocytes, topiramate (1-100 mum) significantly reduced the phosphorylation level of GluR1 subunits. Furthermore, their results indicated that topiramate binds to AMPA receptors in the dephosphorylated state and thereby exerts an allosteric modulatory effect on the ion channel [4].

Cardile et al. [5] studied the *in vitro* effects of the anticonvulsant drugs gabapentin and topiramate on the production of reactive oxygen species and nitric oxide, the activity of glutamine synthetase and cell viability in primary cultures of rat cortical astrocytes. They noted a slight effect of gabapentin on biochemical processes/metabolic activities occurring in the cells examined, whereas topiramate was observed to induce even greater stressor effects on these cells.

Similarly, Pavone and Cardile [24], who studied the effect of numerous antiepileptic drugs in different concentrations on metabolic activities of rat astrocyte cultures, noticed that topiramate, like carbamazepine and oxcarbazepine, induces stress on these cells at all concentrations. They suggested that these drugs could be worse tolerated by cortical astrocytes, as compared to other antiepileptics studied, i.e. gabapentin, lamotrigine, tiagabine and levetiracetam.

Poulsen et al. [25] and Swanson et al. [30] in their interesting pharmacological studies demonstrated that in prolonged exposure to topiramate astrocytes co-cultured with neurons expressed glutamate transporters GLAST and GLT-1, responsible for the inactivation of glutamate as a neurotransmitter.

In our *in vivo* study, topiramate was found to have a beneficial effect on the structural status of approximately 1/3 of the population of protoplasmic astroglial cells of the hippocampal cortex and neocortex of the temporal lobe prior to febrile seizures, which may be explained, among others, by a protective action of cerebral cortex microcirculation, enhanced by drug administration, on this cell population. In our earlier study, prophylactic administration of topiramate in the TPM + FS group prevented substantial damage to structural elements of the BBB, mainly to the endothelial lining of the CNS regions studied in over half of the capillaries [20]. This may reflect the morphological picture of the cells assessed and the fact that approximately 30% of them were saved, although some other explanations may also be possible.

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