Acta Neuropathol (Berl) (1986) 69:54–65

Acta Neuropathologica

Effect of an Extract of Ginkgo Biloba on Triethyltin-induced Cerebral Edema

M. Otani[1], S. S. Chatterjee[2], B. Gabard[2] and G. W. Kreutzberg[1]

[1] Dept. of Neuromorphology, Max Planck Institute of Psychiatry, Am Klopferspitz 18A, D-8033 Planegg-Martinsried, Federal Republic of Germany
[2] Dept. of Pharmacology, Dr. Willmar Schwabe Arzneimittel, Karlsruhe, Federal Republic of Germany

Summary. The effect of an extract of Ginkgo biloba was studied on cerebral edema in rats intoxicated with triethyltin chloride (TET). Brains of TET-treated rats showed elevated water and sodium levels and a significant increase in the sodium/potassium ratio. Animals treated with TET plus the extract did not show water and electrolyte changes. The course of intoxication and treatment was studied light- and electron-microscopically. A severe edema with extensive vacuolization was seen in the cerebral and cerebellar white matter. Morphometric measurements revealed a significant decrease in these manifestations of the cytotoxic edema when the animals were treated with an extract of Ginkgo biloba. Thus, we conclude that this extract has a protective effect on the development of a cytotoxic edema in the white matter of the brain.

Key words: Cerebral edema – Triethyltin intoxication – Myelin – Electrolyte analysis – Morphometry – Treatment of brain edema – Ginkgo biloba

Introduction

Safe management of cerebral edema is still one of the unsolved problems in neurology and neurosurgery. Although its pathophysiology is well understood the possibilities for pharmacological treatment are limited. It would therefore be of obvious clinical interest to discover new pharmacologic principles for influencing cerebral edema. Intoxication with triethyltin (TET) is known to cause a cytotoxic edema in the white matter of the CNS (Aleu et al. 1963). This provides a useful model to study experimentally the development of cerebral edema and the effect drugs can exert upon it. Such studies have been carried out to investigate the effects of hypertonic urea (Levy et al. 1965) or corticosteroids (Taylor et al. 1965; Studer et al. 1973). We report here the effect of an extract of Ginkgo biloba (EGB) on the development of cytotoxic edema in the white matter of TET-intoxicated rats. This standardized extract contains a number of flavonoids together with some Ginkgo biloba specific flavone glycoside esters and terpenes (Bilobalide and Ginkolides A, B, and C). It is used clinically in various European countries for the treatment of peripheral and cerebral ischemic diseases but not in edema (for a review see Chatterjee and Trunzler 1981). Recently, some biochemical and behavioral studies describing the effect of EGB on TET-intoxicated animals have been reported (Gabard and Chatterjee 1980; Chatterjee and Gabard 1984; Karcher et al. 1984).

Offprint requests to: Prof. G. W. Kreutzberg, MD (address see above)

Material and Methods

The standardized extract of Ginkgo biloba was supplied by Dr. Willmar Schwabe, Arzneimittel (Karlsruhe, FRG) and was the same as that used in the commercial preparation, Tebonine®.

Male Sprague-Dawley rats (n = 23), weighing between 200 and 300 g, were used. They were kept on a standard diet (Altromine) and tap water ad libitum before the start of the experiment. The animals were divided into three groups and subjected to the following treatments.

Control rats (group 1) were supplied further with normal drinking water. TET-intoxicated rats (group 2) were given drinking water containing triethyltin chloride (TET = 0.002%) ad libitum during 14 days. TET-plus EGB-treated rats (group 3) were given water containing TET (0.002%) and simultaneously given 10 ml/kg water containing 100 mg/kg EGB once a day, 5 days per week during 14 days. In addition, control rats and TET-intoxicated rats were given 10 ml/kg normal water once a day over the same time period.

The rats were weighed every day and were killed on day 15. Some of the animals (n = 14) were used for measuring electrolytes and water content and were killed by decapitation. The brains were rapidly removed and the two hemispheres

Table 1. Water and electrolyte contents of the brains. As compared with the water content of the samples from control rats, the water content from TET-intoxicated rats is elevated by 3.6%, whereas the water content from TET-plus EGB-treated rats is virtually unchanged. Similarly, the sodium content and the sodium-potassium ratio from TET-intoxicated rats are elevated by 75% and 50%, respectively, whereas these contents from TET- plus EGB-treated rats are unchanged. The potassium content is not significantly different from that of control rats in any of TET-intoxicated rats and TET- plus EGB-treated rats

Group	Water content (%)	Na (mmol/kg · dry)	K (mmol/kg · dry)	Na/K
Control	78.30 ± 0.12	182.9 ± 19.2	378.9 ± 22.8	0.48 ± 0.05
TET	81.08 ± 0.31	319.8 ± 32.7	443.0 ± 10.9	0.72 ± 0.06
TET + EGB	78.57 ± 0.20	179.3 ± 26.2	411.9 ± 9.8	0.44 ± 0.07

separated. One hemisphere was used for analysis of sodium and potassium contents by means of flame photometry. The other hemisphere was used for determination of the water content after drying to constant weight (12 h, 90° C).

The remaining animals from each group ($n = 9$) were taken for the morphological studies. The animals were killed by intracardiac perfusion of cacodylate-buffered 2% glutaraldehyde and 4% formaldehyde. The perfused brains were removed, and immersion fixation in the same solution was continued.

The brains were then separated by a sagittal midline section, and one hemisphere was used for light microscopy and morphometry, while the other was used for electron microscopy. For electron microscopy, samples of frontal cortex, corpus callosum (A 30), commissura anterior (A 30), and striatum were osmicated, dehydrated, and embedded in Epon. During the dehydration sequence uranyl acetate staining was applied for 25 min in 70% ethanol. Ultrathin sections were poststained with Reynold's lead citrate. Electron micrographs were taken with a Zeiss EM-10A. Paraffin sections 8 and 12 μm thick for light microscopy were stained with Nissl and Spielmeyer's myelin stain, respectively.

Morphometry

The TET-induced edema is characterized by an extensive vacuolization of the cerebral white matter. The degree of vacuolization can be measured in histological sections by utilizing a computerized texture analysis system (Leitz TAS). The system recognizes the "holes" in the sections and performs automatic planimetry calculating the percentage area of vacuoles vs. tissue. Since lumina of the brain vessels cannot be discriminated, they are included in the vacuole measurement. In the untreated control animals the values measured for vacuoles thus represent the brain vasculature. We selected the samples to perform the measurements in the same areas in all animals. These were the corpus callosum, cingulum, commissura anterior, frontal cortex, commissura fornicis, capsula interna, caudatus putamen, hippocampus, thalamus, hypothalamus, amygdaloid nucleus, optic tract, crus cerebri, corticospinal tract, spinal tract of the trigeminal nerve, cerebellar white matter, and cerebellar cortex. Each myelin-stained section was measured more than five times in each rat. As the standard deviations (SD) were large in corpus callosum, cingulum, and commissura anterior, measurements were made in different preparations at the same distance from the interaural line.

Results

Electrolyte Analyses

The water and electrolyte contents of the brains are shown in Table 1. As compared to the water content of the samples from control rats, the water content from TET-intoxicated rats was elevated by 2%, whereas the water content from TET-plus EGB-treated rats was virtually unchanged. Similarly, the sodium content and the sodium-potassium ratio from TET-intoxicated rats were elevated by 45%, whereas these values from TET-plus EGB-treated rats were unchanged. The potassium content of TET-intoxicated rats and TET-plus EGB-treated rats was not significantly different from that of control rats.

Light Microscopy

TET-intoxicated rats showed marked vacuolization of the myelinated areas in comparison with normal rat brain (Figs. 1–3). Variable degrees of sponginess of the myelinated areas were seen in the tissues of TET-intoxicated rats (Fig. 4). In particular, the corpus callosum (Fig. 5) and cerebellar white matter (Fig. 6) of TET-intoxicated rats showed marked confluent vacuolization. In light microscopy of TET-plus EGB-treated rats, vacuoles in the myelinated areas were present to a much lesser degree (Fig. 7) as compared to those of TET-intoxicated rats. Vacuoles in corpus callosum (Fig. 8) and in cerebellar white matter (Fig. 9) were separated by relatively well-preserved myelin.

Morphometry

The edematous changes in the TET-intoxicated rats appeared most strikingly in the capsula interna, cerebellar white matter, optic tract, crus cerebri, corticospinal tract, spinal tract of the trigeminal nerve (Table 2). The rats receiving TET plus EGB demonstrated considerably less vacuolization in all myelinated areas but still more than in the controls. Figures of about 1% or less measured in the controls represent the blood vessels as mentioned in Material and Methods. In the corpus callosum, cingulum and commissura anterior, various degrees of edema were shown, especially in TET-intoxicated rats (Fig. 10). In those white matter areas, more severe edema was generally found in anterior parts as compared to posterior parts. The edema found in those tissues was

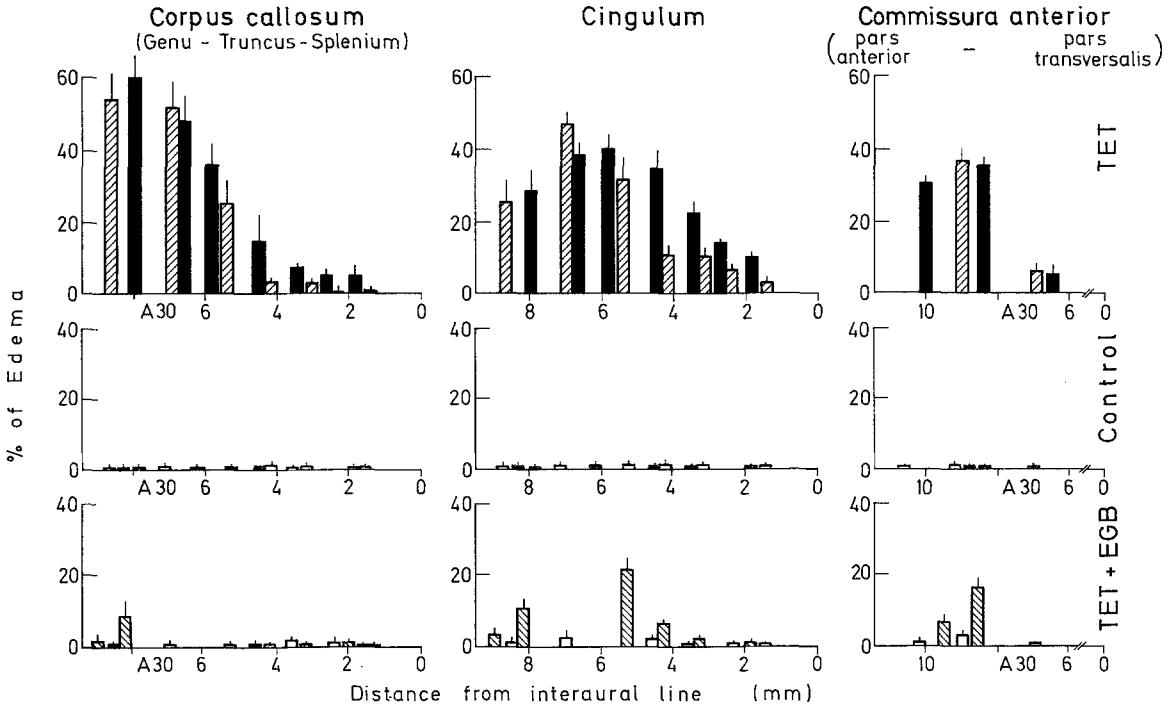


Fig. 1. Two TET-intoxicated (▨ ■), two control (□ ■) and two TET- plus EGB-treated (□ ▧) rats were analyzed for the area of edema in corpus callosum, cingulum, and commissura anterior. Histograms show the percentage of edema in the tissue (*ordinate*) in relation to the distance from the interaural line (*abscissa*) in frontal sections of rat brain. Each *column* represents the average of five measurements ($n = 5$) ± SD

Table 2. Effects of TET and EGB on the percentage of area of edema in control, TET-intoxicated, and TET- plus EGB-treated rat brain tissues

Tissue	Control (%)		TET (%)		TET + EGB (%)	
Corpus callosum (Genu-Truncus-Splenium)	0.9 ± 0.6	0.5 ± 0.3	24.7 ± 22.3	22.1 ± 25.3	1.1 ± 0.6	1.7 ± 1.7
Corpus callosum (Radiatio)	1.1 ± 0.6	0.8 ± 0.5	45.7 ± 10.4	46.7 ± 11.8	4.6 ± 1.7	18.1 ± 9.8
Cingulum	1.5 ± 0.5	0.8 ± 0.7	32.9 ± 15.1	21.7 ± 18.0	2.6 ± 3.2	5.9 ± 3.7
Commissura anterior (pars anterior)	1.2 ± 0.3	0.8 ± 0.4	32.9 ± 2.7	36.5 ± 2.6	2.2 ± 1.0	11.2 ± 5.4
Cortex	0.5 ± 0.3	0.1 ± 0.1	0.4 ± 0.2	0.1 ± 0.1	0.1 ± 0.1	0.1 ± 0.1
Commissura fornicis (dorsalis)	0.8 ± 0.5	0.2 ± 0.2	50.7 ± 8.6	35.8 ± 9.4	2.7 ± 2.3	10.3 ± 6.7
Capsula interna	0.6 ± 0.9	0.6 ± 0.4	60.2 ± 6.5	62.2 ± 4.2	12.8 ± 3.9	30.2 ± 8.8
Caudatus putamen	0.8 ± 0.3	0.9 ± 0.8	13.0 ± 3.8	18.1 ± 10.0	0.8 ± 0.5	2.5 ± 1.8
Hippocampus	0.3 ± 0.2	0.2 ± 0.2	0.6 ± 0.1	0.2 ± 0.1	0.2 ± 0.1	0.3 ± 0.2
Thalamus	0.2 ± 0.2	0.3 ± 0.2	3.2 ± 0.8	1.1 ± 0.7	0.8 ± 0.6	0.2 ± 0.2
Hypothalamus	0.4 ± 0.3	0.2 ± 0.1	0.3 ± 0.1	0.1 ± 0.1	0.2 ± 0.1	0.1 ± 0.1
Amygdaloid nucleus	0.2 ± 0.1	0.1 ± 0.0	0.4 ± 0.1	0.2 ± 0.1	0.1 ± 0.0	0.2 ± 0.1
Optic tract	0.1 ± 0.1	0.3 ± 0.2	69.8 ± 2.3	61.5 ± 4.4	13.9 ± 1.4	24.8 ± 6.8
Crus cerebri	0.4 ± 0.1	0.2 ± 0.1	71.4 ± 3.0	54.7 ± 3.9	23.3 ± 6.6	35.6 ± 1.9
Corticospinal tract	0.1 ± 0.1	0.3 ± 0.1	63.4 ± 3.2	68.9 ± 1.7	10.4 ± 1.7	24.4 ± 4.7
Spinal tract of the trigeminal nerve	0.3 ± 0.1	0.4 ± 0.3	57.2 ± 2.8	52.8 ± 3.5	3.2 ± 0.7	13.8 ± 4.5
Cerebellar white matter	0.6 ± 0.4	0.1 ± 0.1	52.5 ± 16.6	53.9 ± 12.6	6.4 ± 2.6	27.1 ± 5.3
Cerebellar cortex	0.3 ± 0.2	0.2 ± 0.2	0.4 ± 0.4	0.2 ± 0.1	0.3 ± 0.3	0.4 ± 0.1

Two control, two TET-intoxicated, and two TET- plus EGB-treated rats were analyzed for the area of edema in brain tissues. Each number represents the average of more than five measurements ($n \geqq 5$) ± SD

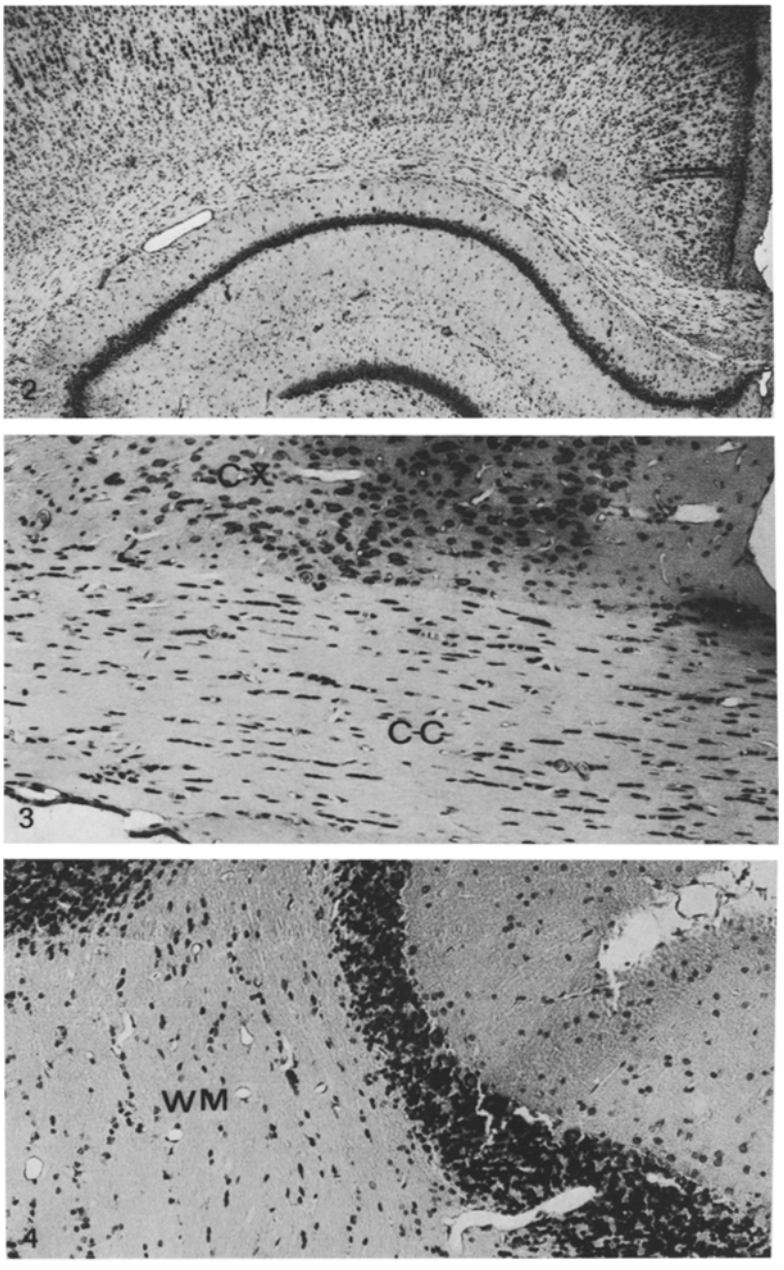


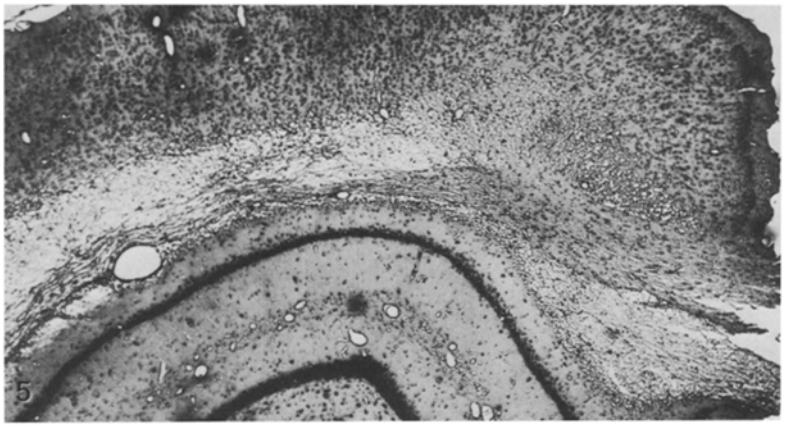
Fig. 2–4. Nissl stain of the areas where measurements were made, untreated controls: **Fig. 2.** Parts of the cerebral hemisphere including the hippocampus, ×30. **Fig. 3.** Deep layers of the cerebral cortex (*CX*) and the corpus callosum (*CC*), ×120. **Fig. 4.** Cerebellar cortex and white matter (*WM*), ×120

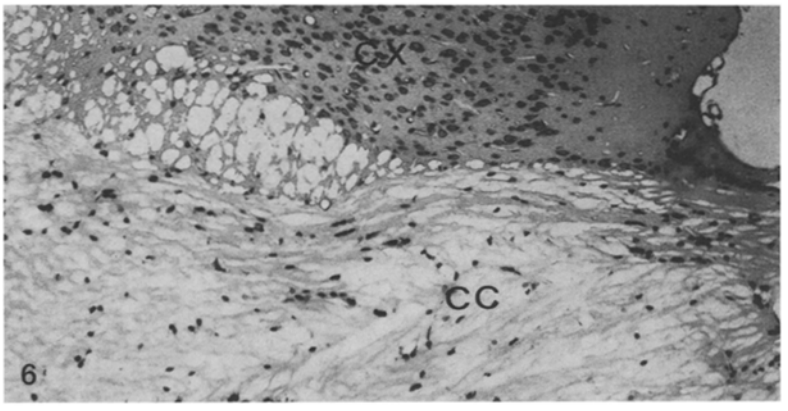
also quantitatively less severe when treated with EGB in addition to TET. However, the percentages of the areas of edema in TET-plus EGB-treated rats were still larger than in the controls.

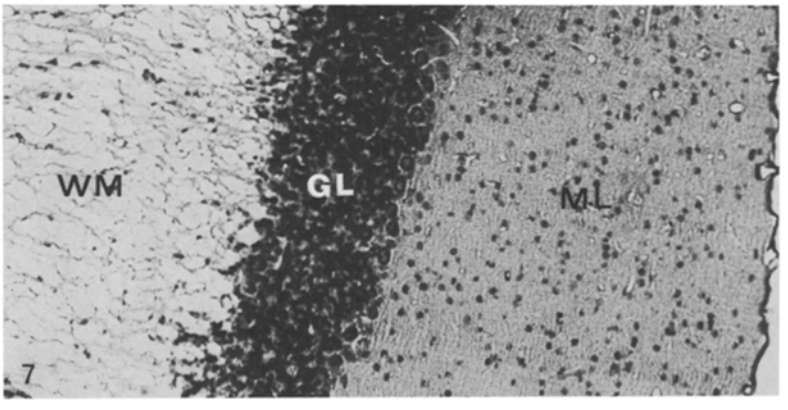
Electron Microscopy

Electron microscopy confirms the light-microscopic findings described above. In normal rats the myelin sheaths were compact (Fig. 11), whereas intramyelin vacuoles formed by splitting and distension of myelin lamellae were seen in the brains of both TET-intoxicated rats and TET-plus EGB-treated rats. This splitting of myelin sheaths at the intraperiod line (Fig. 12) was seen more prominently in the myelin sheaths having larger diameters of axons. Oligodendrocyte and mitochondria were normal in number and appearance, and no increase in neurofilaments and microtubules appeared visible.

In TET-intoxicated rats (Figs. 13, 14), vacuoles were not only remarkably large, but also rupture of the thinned outer lamellae was often observed. Owing to the communication between the vacuoles and extracellular space, the extracellular space often became



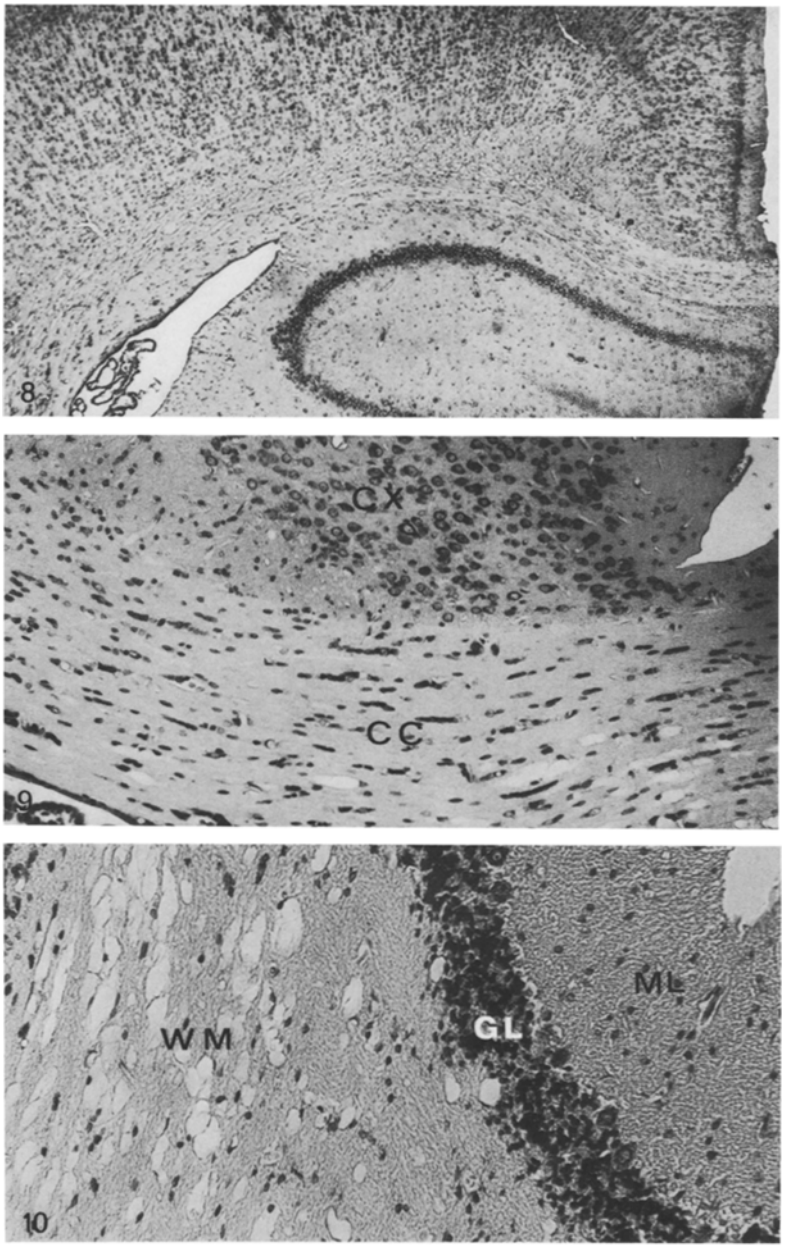




Figs. 5–7. Areas corresponding to **Figs. 2–4** in TET-treated rats show marked edema and sponginess in the white matter of the cerebral hemisphere (**Fig. 5**, ×30), the subcortical fibers and the corpus callosum (*CC*) (**Fig. 6**, ×120) and in the white matter (*WM*) of the cerebellum (**Fig. 7**, *GL* granule cell layer, *ML* molcular layer, ×120)

remarkably wide and confluent, resulting in destruction of the compact structure of the nervous tissue; this most distinctive feature of myelinated area in TET intoxication was seen in the corpus callosum. The distribution of myelin vacuoles in TET-intoxicated rats was focal rather than diffuse (Fig. 15). The basement membrane surrounding the blood vessels was often distended with the distension or rupture of astrocytic foot processes (Figs. 16, 17).

However, in TET-plus EGB-treated rats (Figs. 18, 19), the size of myelin vacuoles was much smaller, and rupture of myelin lamellae and large confluent vacuoles were rarely seen. Therefore, as compared to the distribution of myelin vacuoles in TET-intoxicated rats, the distribution in TET-plus EGB-treated rats appeared rather diffuse with myelin lamellae loosening up. The basement membrane surrounding the blood vessels was not as distended as in TET-intoxicated rats, but the endothelial basement membrane, upon which the endfeet of astrocytes rest, was sometimes scalloped with a slight distension of astrocytic foot processes (Fig. 20).

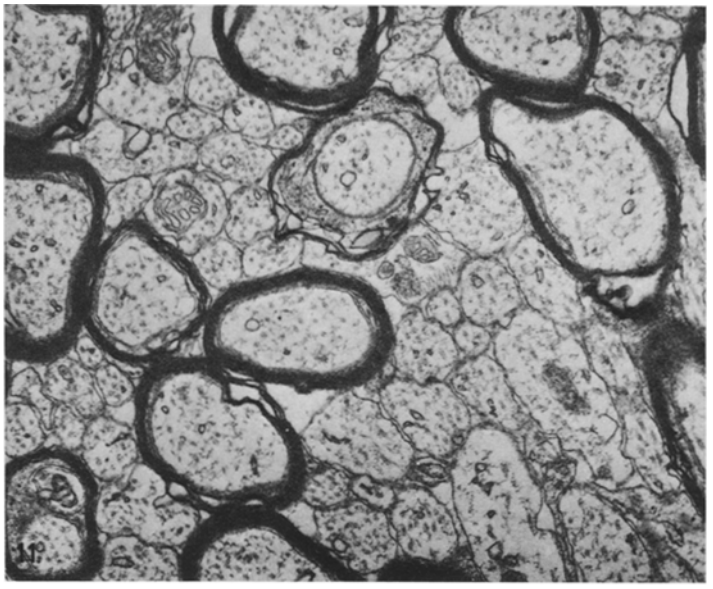


Figs. 8—10. Areas corresponding to **Figs. 2—4** and **5—7** in TET-intoxicated, EGB-treated rats. The development of vacuolization is markedly reduced in the subcortical white matter and the corpus callosum (**Figs. 8, 9**) and in the cerebellar white matter (**Fig. 10**)

Discussion

The effect of triethyltin (TET) on myelin has been well documented (Aleu et al. 1963; Hirano et al. 1968; Graham et al. 1976), and there is general agreement on the details, such as intramyelin vacuolation and splitting of myelin at the intraperiod line. These findings are confirmed in the TET-treated group of our study. In our material, these fine-structural features of the white matter in TET intoxication were seen most distinctively in the corpus callosum (A 30) and are consistent with the quantitative estimates of edema (Fig. 10, Table 2).

The results presented here reveal that the extract of Ginkgo biloba (EGB) prevents the full development of the cytotoxic edema induced by TET. EGB is not only capable of reducing the elevated water and electrolyte content of the edematous brain but also affords morphological improvements. Although intramyelin vacuolization was not completely prevented by EGB-treatment in this experiment, the size of the vacuoles was remarkably reduced. In addition, the



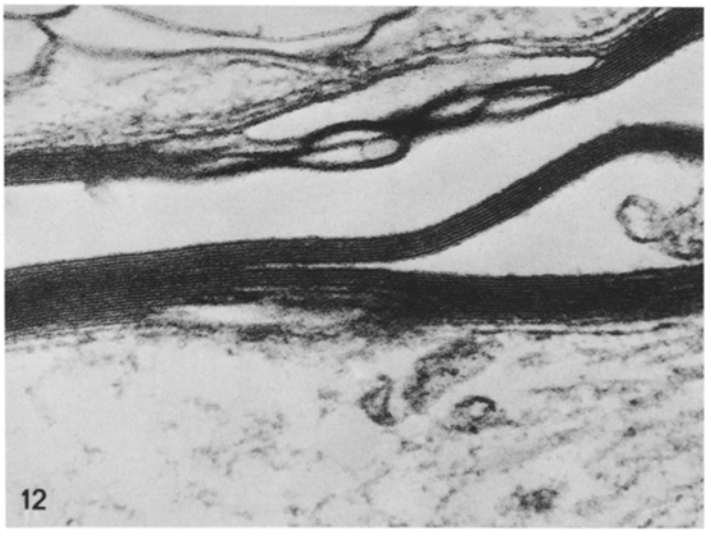


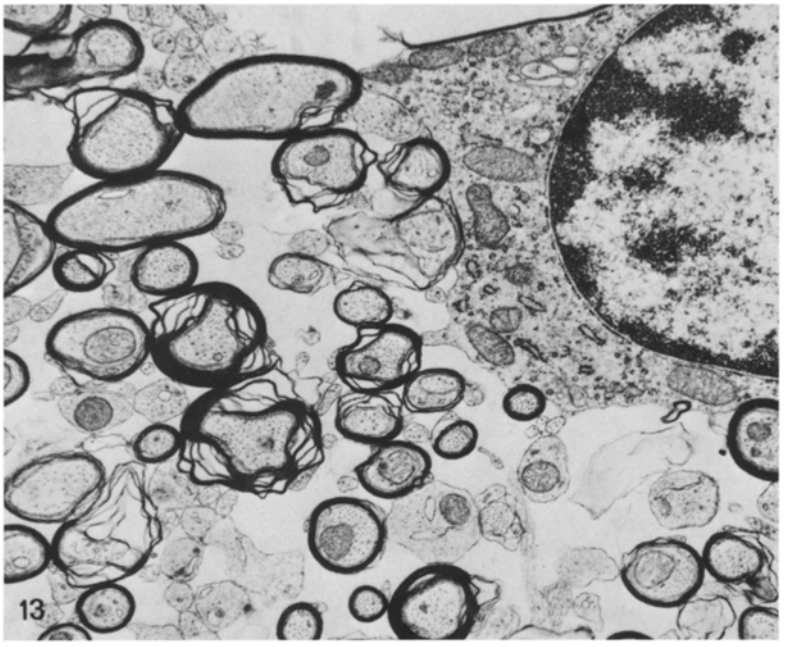
Fig. 11. Corpus callosum (A 30) in a control rat. Myelinated axons are compact. Electron micrograph; ×23,800

Fig. 12. Corpus callosum in TET-intoxicated rat. Splitting of myelin lamellae at the intraperiod line. EM; ×123,500

electron-microscopic studies demonstrate that the basement membranes and astrocytic foot processes are better preserved in the treated group.

EGB is a complex mixture (Weinges et al. 1968a, b) which is known to possess regulatory effects on blood vessels (Peter et al. 1966; Mußgnug and Alemany 1968; Heiss and Zeiler 1978). Recently, various other pharmacologic and clinical properties of the extract have been elucidated (Chatterjee and Trunzler 1981). These include effects on capillary permeability, ion transport and cerebral energy metabolism. Thus, Rapin and Le Poncin-Lafitte (1979) have shown that beneficial effects of EGB on cerebral edema induced by microembolization are due to the effects on cerebral blood flow, facilitating the maintenance of cerebral levels of glucose and ATP under ischemic conditions. Similarly, Karcher et al. (1984) have reported changes in brain energy metabolism and blood flow contributing to the protective effects of EGB against hypoxia. Etienne et al. (1982) have suggested independently that EGB modifies Na^+-transport across the cell membrane by an action on adrenergic receptors or by stimulating the Na^+, K^+-ATPase activity.

Elevation of Na^+ and water content of the cerebral tissue in TET-intoxicated animals is well documented and was also found in the present study. Thus, the reduction of this elevated electrolyte and water content in EGB-treated, TET-intoxicated rats could be due to the effects of the extract on Na^+-transport in a manner similar to that described by Etienne et al. (1982). Further, the reported studies directed toward



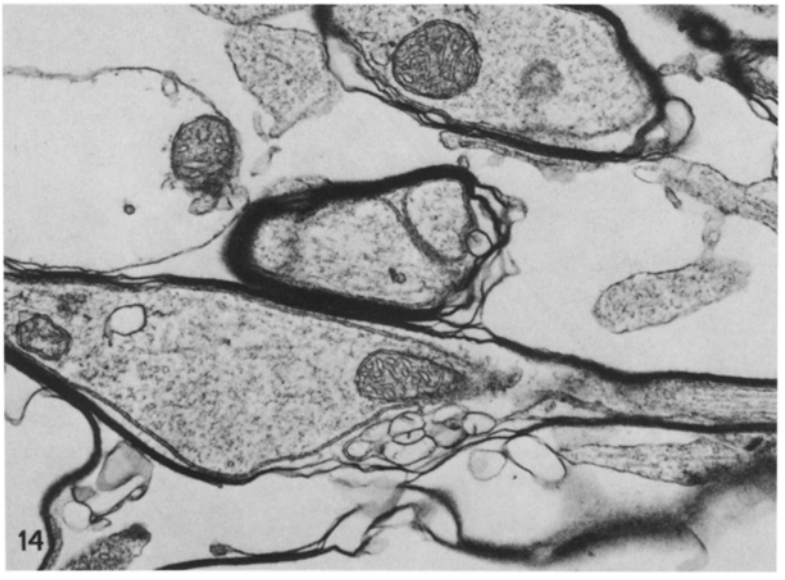
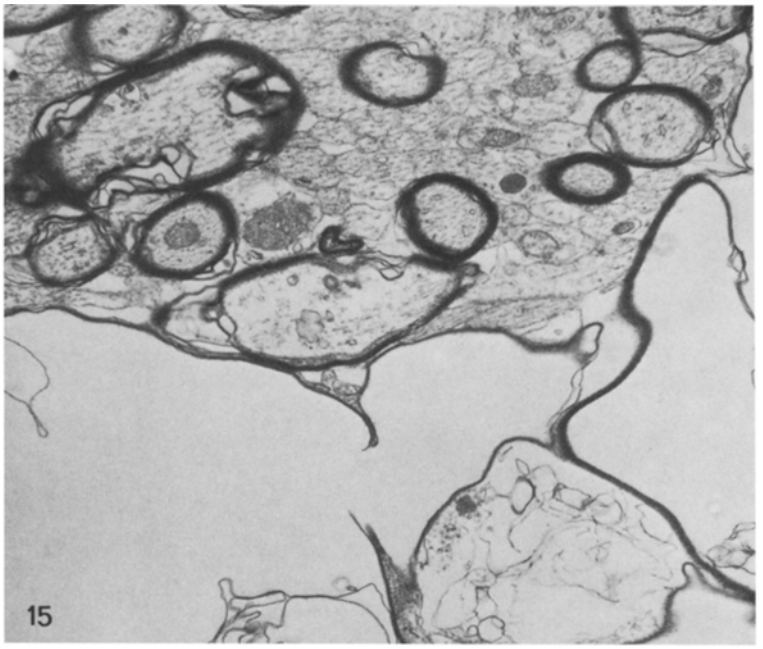


Fig. 13. Commissura anterior in TET-intoxicated rat. Extracellular space becomes confluent and wide, with rupture of the thinned outer myelin lamellae. Naked axon, cellular debris, and peeled off myelin lamellae appear floating in the extracellular space. EM; ×16,900

Fig. 14. Corpus callosum in TET-intoxicated rat. Myelin sheaths are stretched and peeled off. EM; ×23,900

understanding the biochemical mechanism and edematous effects of TET have revealed that this neurotoxic substance possesses several properties which are opposite to those reported for EGB: TET is known to inhibit various ATPase-activities (Wassenar and Kroon 1973; Lijinsky and Aldridge 1975), to reduce cerebral blood flow (Legrain and MacKenzie 1981), to diminish the synthesis of ATP (Cremer 1970), and to affect the permeability of membranes (Torack et al. 1970). It is conceivable, therefore, that the beneficial effects of EGB in this particular model are due to antagonistic actions on various biochemical processes altered by TET.

There is general agreement that the primary target of TET-toxicity is the myelin sheath. The blood-brain barrier (BBB) of TET-intoxicated animals is considered to be intact to the passage of macromolecules (Bakay 1965). There is, however, some debate about the TET-induced changes of the astrocytic processes or in the extracellular space. In several studies, transient swelling of astrocytes (Torack et al. 1970), or distension of astrocytic processes surrounding the blood vessels (Taylor et al. 1965) have been reported, but there have also been contradictory reports; i.e., describing no change of astrocytes (Jacobs et al. 1977), or a change of



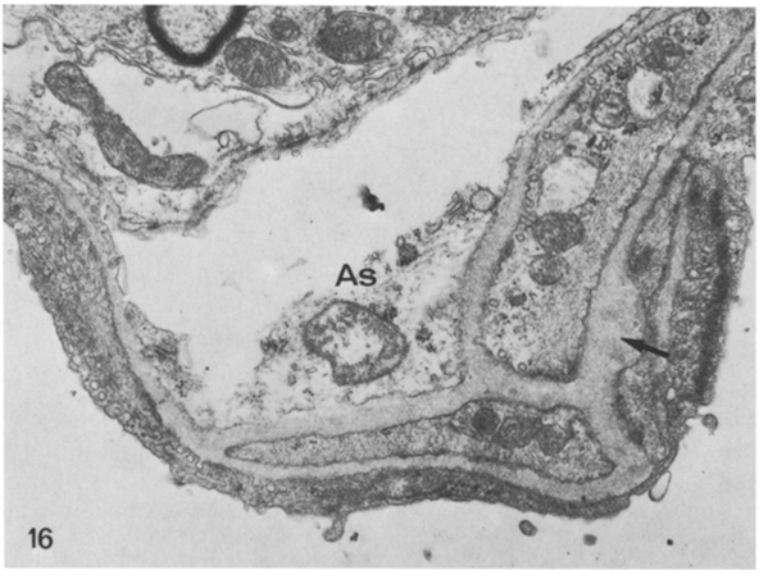
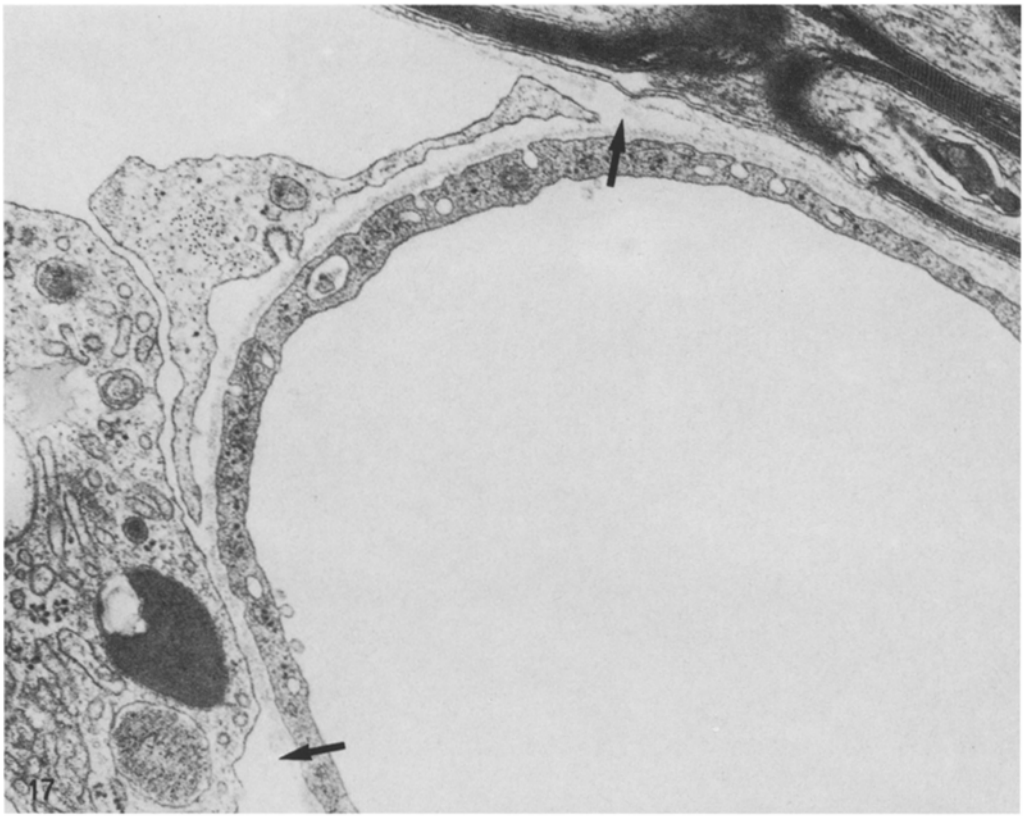


Fig. 15. Corpus callosum in TET-intoxicated rat. In spite of marked distension and rupture of myelin lamellae, the distribution of intramyelin vacuoles is focal. EM; ×16,900

Fig. 16. Corpus callosum in TET-intoxicated rat. Perivascular astrocytic foot processes (*As*) are widened with distension of the basement membrane (*arrow*). EM; ×16,900

astrocytes dependent on the TET dose (Watanabe 1977). Concerning the changes of the blood vessels and the extracellular space, no morphological alterations of blood vessels (Alev et al. 1963; Levy et al. 1965) and no enlargement of the extracellular space (Torack et al. 1970; Jacobs et al. 1977) have been observed, while there are reports describing a communication between the intramyelin vacuoles and the extracellular space which are caused by ruptures of the myelin lamellae (Taylor et al. 1965; Hirano et al. 1968). In our study, a confluent and wide extracellular space was observed, and the perivascular astrocytic foot processes and the basement membranes often appeared distended in TET-intoxicated rats, sometimes even with rupture of one or both (Figs. 16, 17). These findings suggest, therefore, that at least under our experimental conditions changes in the vascular permeability do occur after TET intoxication. The proposition that the edema fluid in the intoxicated rats originates from the circulating plasma or cerebrospinal fluid (Lock 1976) is in agreement with this suggestion. As EGB is known to influence the capillary permeability, it is likely that the scalloping of the astrocytic basement membrane as well as the relatively good preservation of foot processes in EGB-treated, TET-intoxicated rats (Fig. 20) might result from an increased Na^+ and water transfer by EGB into the capillaries.



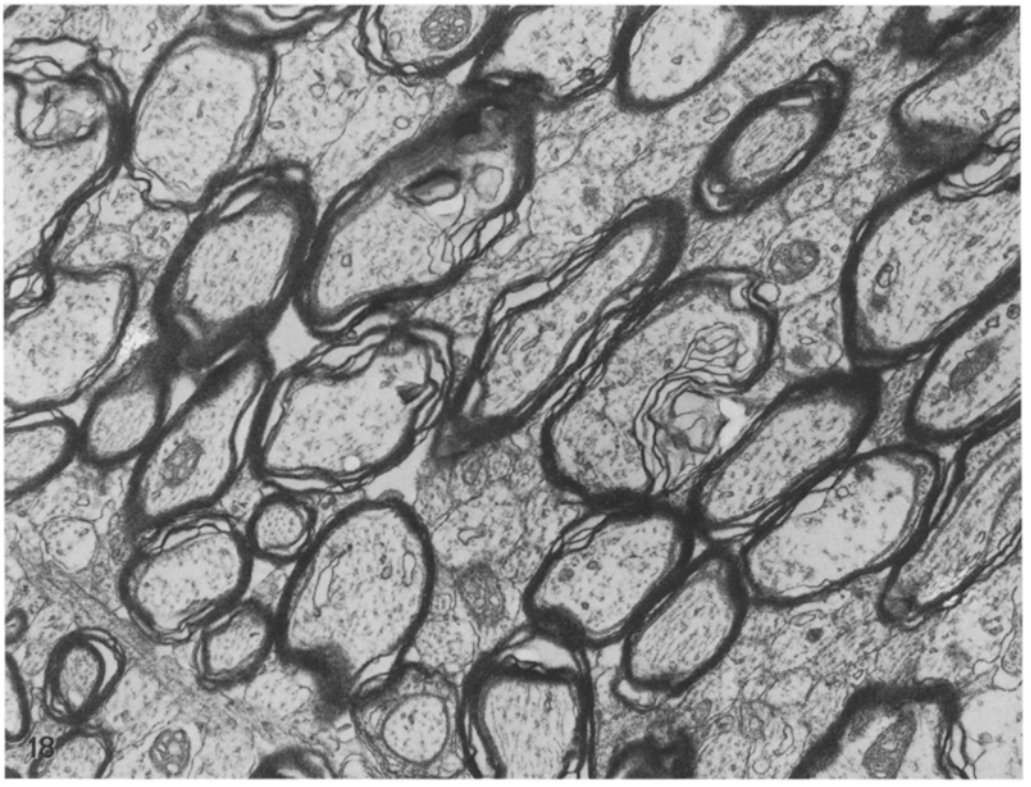
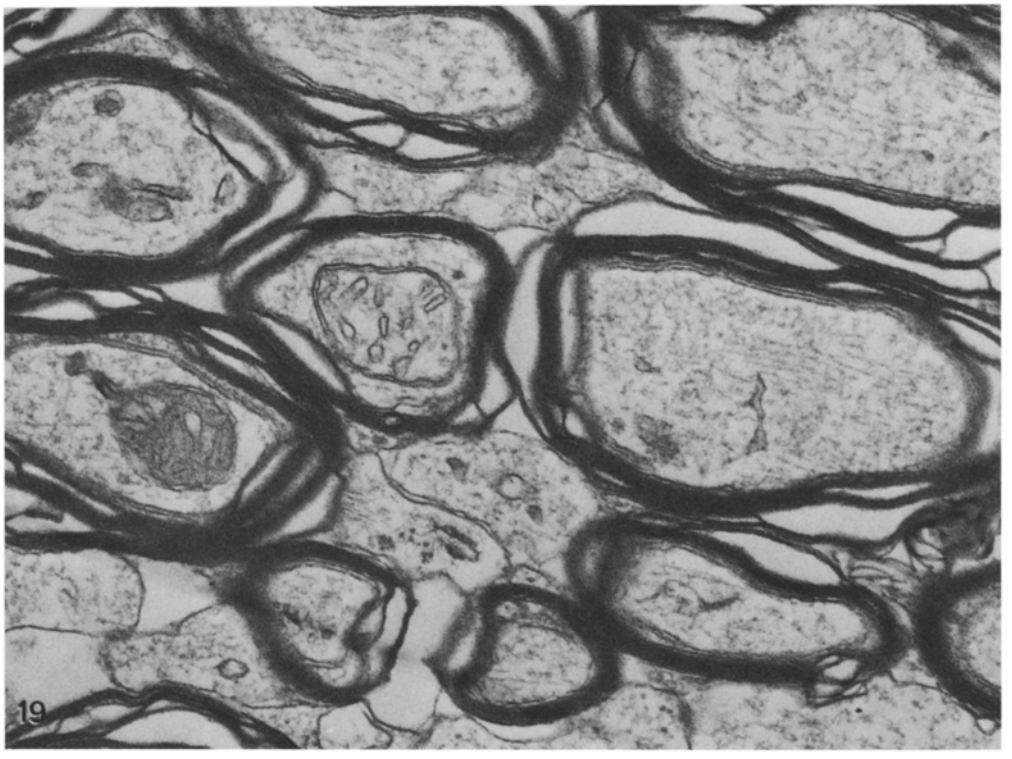


Fig. 17. Corpus callosum in TET-intoxicated rat. The basement membrane of the capillary (*arrow*) is discontinuous. EM; ×41,250

Fig. 18. Corpus callosum in TET- plus EGB-treated rat. Myelin sheaths show splitting and distension, but the compact structure of myelin sheaths is relatively well-preserved. EM; ×20,250



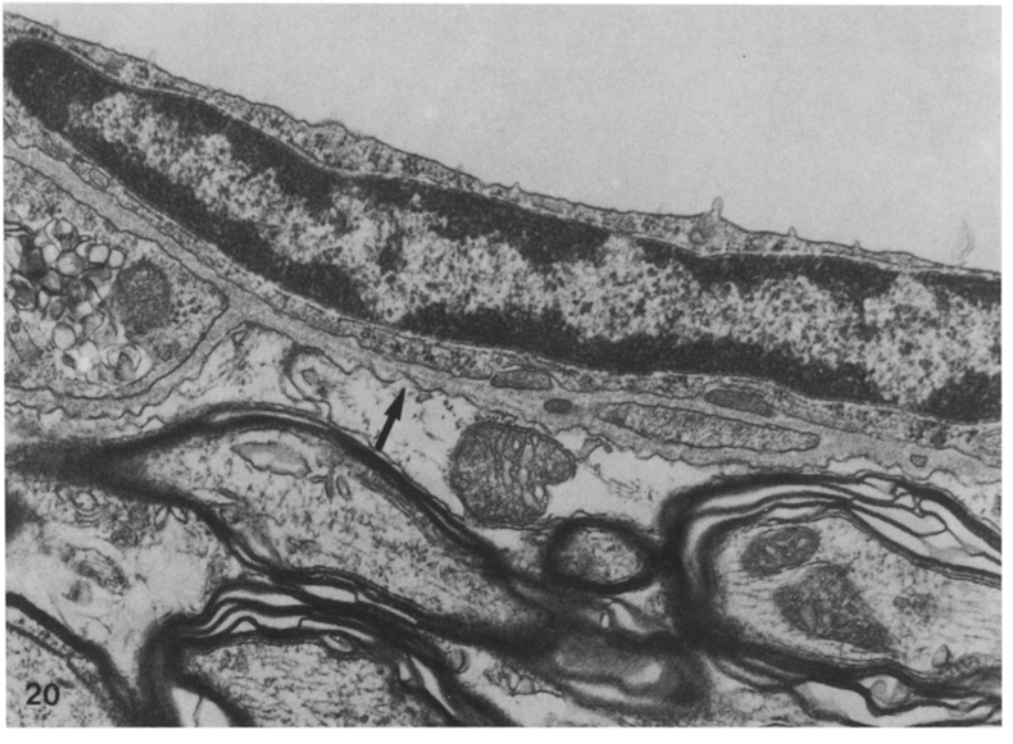


Fig. 19. Commissura anterior in TET- plus EGB-treated rat. The size of intramyelin vacuoles is much smaller than in TET-intoxicated rat. EM; ×41,250

Fig. 20. Commissura anterior in TET- plus EGB-treated rat. Astrocytic foot plate membrane at capillaries (*arrow*) is scalloped. EM; ×31,750

The effects of EGB on TET-induced edema are of a different nature from those reported for corticosteroids. Taylor et al. (1965) have shown that TET-intoxicated rats treated with corticosteroids present quantitative rather than qualitative morphological differences in comparison with control TET-intoxicated animals. In the case of EGB, treated animals show some qualitative as well as quantitative morphological differences. Thus, after corticoid treatment the localization of the edema in the white matter becomes more focal (Taylor et al. 1965), whereas after EGB-treatment the vacuolization of myelin sheaths becomes rather diffuse to the dramatic reduction in the large vacuoles. Here too, an influence on the capillary permeability may explain these beneficial effects, which, in turn, may be the consequence of a stimulation of ATPase or of an effect on ATP levels.

We conclude that EBG is effective in reducing the edematous changes and myelin damages induced by TET and thus may be of potential value for the treatment of cerebral edema and probably other diseases associated with myelin rupture. At present, no acceptable therapy for such disorders is available and thus clinical studies with EGB may be recommended. Although some speculations about the mechanism of action of EGB on TET-induced pathologic changes can be made, further studies are needed to clarify the situation.

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Received July 31, 1985/Accepted August 20, 1985