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Pathomorphological changes in rat brain choroid plexus due to administration of the amine-curing agent, bis(4-amino-3-methylcyclohexyl)methane

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Summary. Repeated oral administration of an amine-curing agent for epoxy resin, bis(4-amino-3-methylcyclohexyl)methane, gave rise to severe damage in the choroid plexus of rat brain. The damaged epithelium presented varying degrees of swelling and hydropic vacuolation on light microscopy, and varying numbers of vacuoles and inclusion bodies, frequently with lamellar structure, on transmission electron microscopy. Scanning electron microscopy of the choroid plexus disclosed some irregularity in the size of epithelial cells and occasional loss of microvilli. These changes in the choroid plexus were closely correlated with the dosage of the agent administered and the period of administration. In spite of the severe changes in the choroid plexus, no neurological abnormalities were observed in the animals during the experimental period.

Key words: Bis(4-amino-3-methylcyclohexyl)methane – Choroid plexus – Inclusion body – Hydropic vacuolation – Drug-induced lipidosis

Introduction

Epoxy resin has been widely used in industry as well as in daily life owing to its properties of insulation, adhesiveness, endurance and so forth. It is well known, however, that the material, including its amine-curing agent, occasionally gives rise to contact dermatitis in workers engaged in its polymerization (Hine et al. 1981). Since abnormalities similar to those in collagen diseases, such as scleroderma and polymyositis, have been reported (Yamakage et al. 1980), attention has been paid to the special toxic effects of this agent as an important industrial and public health problem. Having studied the causative agent of the disease, Ishikawa et al. (1980) reported that scleroderma-like lesions were produced on the back skin of rats by repeated intra-abdominal administration of an amine-curing agent for epoxy resin, bis(4-amino-3-methylcyclohexyl)methane (Fig. 1). We have also been investigating the subacute toxicity of the agent through oral administration to rats. In this process, striated muscle lesions were induced which were reminiscent of chloroquine myopathy with intrasarcoplasmic lamellar inclusion bodies (Oshima et al. 1984, 1986). At the same time, close attention was paid to conspicuous changes in the choroid plexus with hydropic vacuolation and concurrent deposition of inclusion bodies in the epithelial cells.

This paper, which is part of a series of publications on the toxicity of bis(4-amino-3-methylcyclohexyl)methane, focuses exclusively on the pathomorphological changes in the choroid plexus of the rat brain.

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Materials and methods

The detailed methods of our experiments have been described elsewhere (Oshima et al. 1984, 1986) and only a brief description is presented here.

Five-week-old male rats of the Fischer strain were used. They were given the amine-curing agent for epoxy resin, bis(4-amino-3-methylcyclohexyl)methane by gavage, dissolved in olive oil. Control animals were given olive oil alone in the same manner. In experiment A, the agent was given 8 times in 10 days at each dose level, 100, 75 and 50 mg/kg, and in experiment B, 17 times in 24 days at each dose level, 75 and 50 mg/kg. The animals in experiment C received 75 mg/kg of the agent in the same manner as in experiment B, and after the cessation of administration were maintained for 2 months on feed free from the agent. Each dose group was composed of five rats. The control groups, except for experiment C in which a control was not provided, were also composed of five animals.

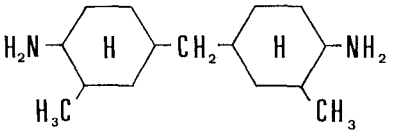

Fig. 1. Bis(4-amino-3-methylcyclohexyl)methane

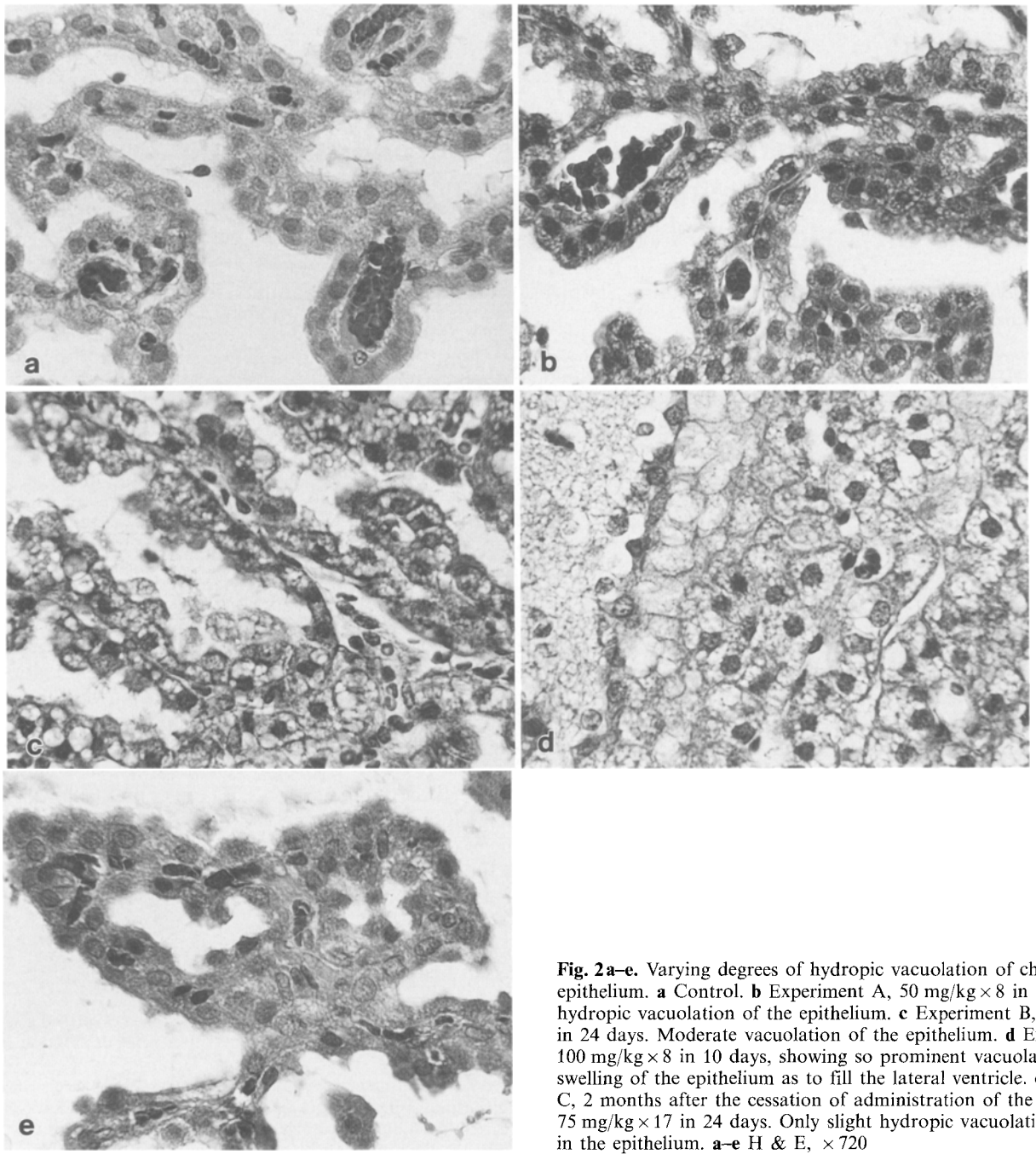

Fig. 2a–e. Varying degrees of hydropic vacuolation of choroidal epithelium. **a** Control. **b** Experiment A, 50 mg/kg × 8 in 10 days. Mild hydropic vacuolation of the epithelium. **c** Experiment B, 50 mg/kg × 17 in 24 days. Moderate vacuolation of the epithelium. **d** Experiment A, 100 mg/kg × 8 in 10 days, showing so prominent vacuolation and swelling of the epithelium as to fill the lateral ventricle. **e** Experiment C, 2 months after the cessation of administration of the agent at 75 mg/kg × 17 in 24 days. Only slight hydropic vacuolation is observed in the epithelium. **a–e** H & E, × 720

After the completion of administration in experiments A and B or 2 months after the last administration in experiment C, the animals were dissected under nembutal anaesthesia, and haematobiochemical and histopathological examinations were carried out. Light microscopic examinations were performed on all animals, but for electron microscopy, two animals were selected randomly from each group, and the choroid plexus of the lateral and third ventricles was examined. The methods for each technique were performed in the usual manner. For the electron microscopic examination, tiny pieces of the choroid plexus, taken immediately after the dissection of the animals, were immersed and fixed in 2% glutaraldehyde (pH 7.4), post-fixed in 1% osmium tetraoxide (pH 7.4), dehydrated in alcohol series and embedded in Epon. The ultra-thin sections were double-stained with uranyl acetate and lead citrate, and observed with a JEM 100-C or 100-S electron microscope. After fixation, dehydration, critical point drying and platinuum covering the blocks for scanning electron microscopy (SEM) were observed with a Hitachi S-500 electron microscope.

Results

The mean body weight gain of each group in the course of the experiments, and organ weights and haematobiochemical data at the time of dissection have already been

Table 1. Hydropic vacuolation of the choroidal epithelium

Experiment	Group	3+	2+	1+	−
A	100 mg/kg	5	0	0	0
	75	0	5	0	0
	50	0	1	4	0
	cont.	0	0	0	5
B	75 mg/kg	5	0	0	0
	50	0	3	2	0
	cont.	0	0	0	5
C	75 mg/kg	0	0	2	3

3+, Severe; 2+ moderate; 1+ mild; − no vacuolation

reported elsewhere (Ohshima et al. 1984, 1986), along with the precise descriptions of pathomorphological changes in skeletal muscles and brief descriptions of various organs and tissues including heart, liver, kidney and spleen. Suffice it to say here that no neurological abnormalities were found in the animals during the administration period and no statistically significant differences were observed between the mean brain weights of the animals at the time of dissection.

At light microscopy the changes in choroid plexus were as follows. Treated animals presented varying degrees of swelling and vacuolation of the choroidal epithelium (Fig. 2). The greater the dosage and the longer the administration period, the more prominent were these changes. The changes were directly proportional to the dosage and period (Table 1). In mildly affected cases, vacuolated cells were scattered in the epithelium (Fig. 2b), while in severely damaged cases, almost all of the epithelial cells showed marked swelling and vacuolation, and the swollen choroid plexus appeared to fill the ventricles (Fig. 2d). Both the lateral and third ventricles showed choroid plexus lesions of the same character, but the former seemed to be slightly more affected than the latter. The animals in experiment C, namely, those fed with feed free from the agent for 2 months after the administration of 75 mg/kg of the agent 17 times in 24 days showed nearly complete recovery, with two of the five animals showing mild hydropic vacuolation of the choroidal epithelium (Fig. 2e).

Electron microscopic examinations were carried out in two animals randomly selected from each dose group and the respective control groups. Transmission electron microscopy of the choroidal epithelium of control animals showed well-developed intracytoplasmic organelles and dense surface microvilli (Fig. 3), while the treated animals presented varying degrees of hydropic vacuolation, equivalent to those seen under light microscopy, and deposition of inclusion bodies of different electron densities, sizes and structures within the choroidal epithelium.

Hydropic vacuolation was represented by different numbers of intracytoplasmic vacuoles of varying sizes (Table 2, Figs. 4–6). Each vacuole was surrounded by a mono-layered membrane and often contained membranous debris and amorphous material. Vacuoles were occasionally scattered among the well-preserved intracytoplasmic organelles in animals that received a rather low dosage of the agent (Fig. 4) while in those given a higher dosage, this change was generally so marked that the cytoplasm of the epithelial cells was largely occupied by the vacuoles, as for example in the animals given 100 mg/kg × 8 in 10 days in experiment A (Fig. 5)

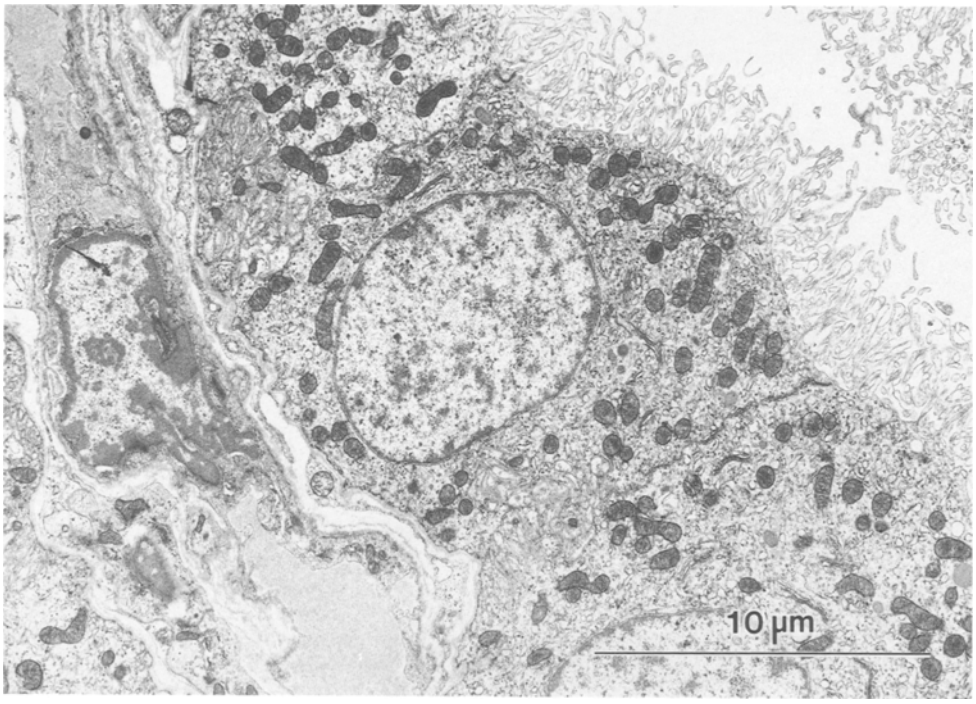

Fig. 3. Choroidal epithelium of a control animal with well-developed intracytoplasmic organelles and superficial dense microvilli. × 5700

Table 2. Hydropic vacuolation of the choroidal epithelium by transmission electron microscopy

Group		Epithelium	Endothelium
A	100 mg/kg	+++	–
	75	+++~++	–
	50	++	–
	cont.	–	–
B	75 mg/kg	++	–
	50	++	–
	cont.	–	–
C	75 mg/kg	–	–

+++, Marked; ++, moderate; +, mild; – no vacuolation

and 75 mg/kg × 17 in 24 days in experiment B (Fig. 6). The animals in experiment C no longer showed such vacuoles (Fig. 7).

In the animals in experiments A and B, inclusion bodies of different shapes, sizes and fine structures were found in varying numbers within the epithelial cells of the choroid plexus (Table 3, Figs. 4–9). Inclusion bodies with different morphologies often co-existed with each other within a single epithelial cell (Fig. 8). The shape of the bodies was generally spherical, but irregularly shaped ones were occasionally encountered (Fig. 9f). In addition, complicated structures composed of aggregated bodies were also found (Fig. 9a). The internal fine structures of the bodies were also diverse: many of the bodies showed myelin-like structures with varying degrees of electron density (Fig. 9a); some contained frayed membranes (Figs. 9d, h), some had marked electron density, making it impossible to distingush the fine structure (Fig. 9c); some had a rather complicated membranous structure (Fig. 9b), and some had myelin-like membranous structure surrounding electron-dense cores (Fig. 9g). The inclusion bodies generally were distributed among the intracytoplasmic organelles or vacuoles described above (Figs. 4 to 8). Although such bodies were occasionally encountered within the vacuoles, no relationship between the inclusion bodies and vacuoles was established.

Inclusion bodies were also observed in the animals in experiment C (Fig. 7). Most of them, however, lost their electron density to varying degrees, frequently containing membranous or myeline-like debris, and were different from those in experiments A and B in their fine structure, as shown in Fig. 9i and j.

Inclusion bodies were frequently found in the capillary endothelium of the choroid plexus (Table 3, Fig. 6), while no hydropic vacuolation was induced therein (Table 2). Kolmer cells, or epiplexus cells, that is, macrophages lying on the surface of the choroidal epithelium (Carpenter et al. 1970), which were occasionally seen in the electron micrographs, showed no significant changes.

In the animals given higher dosages of the agent, the microvilli of the epithelial cells were occasionally decreased in their distribution density and sometimes disappeared almost entirely (Fig. 5), a finding confirmed by SEM (Fig. 10). The epithelial cells were partially deprived of villi and presented smooth cell surfaces (Fig. 10b). In addition, SEM revealed some irregularities in the size of epithelial cells with mild intercellular dissociation and somewhat irregular and roughened appearance of the villi. Two months after administration of the agent was terminated, that is, in experiment C, the villi were distributed rather densely on the cell surfaces (Fig. 7).

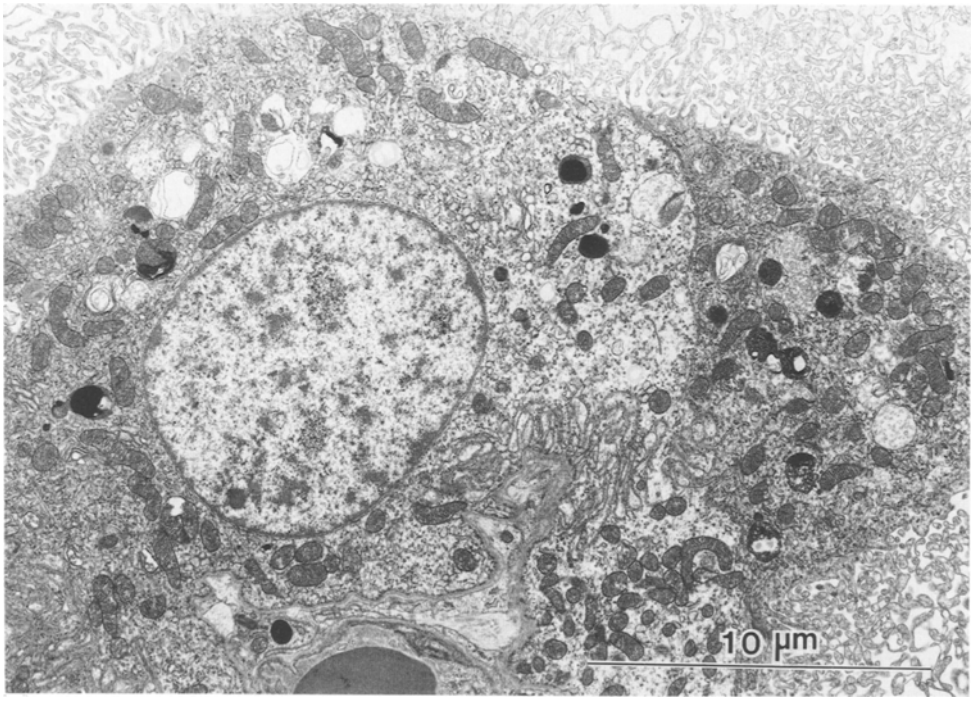

Fig. 4. Experiment A, 50 mg/kg × 8 in 10 days. A few small vacuoles and sporadically scattered inclusion bodies are seen in the cytoplasm of the choroidal epithelium. The microvilli are well sustained. × 5900

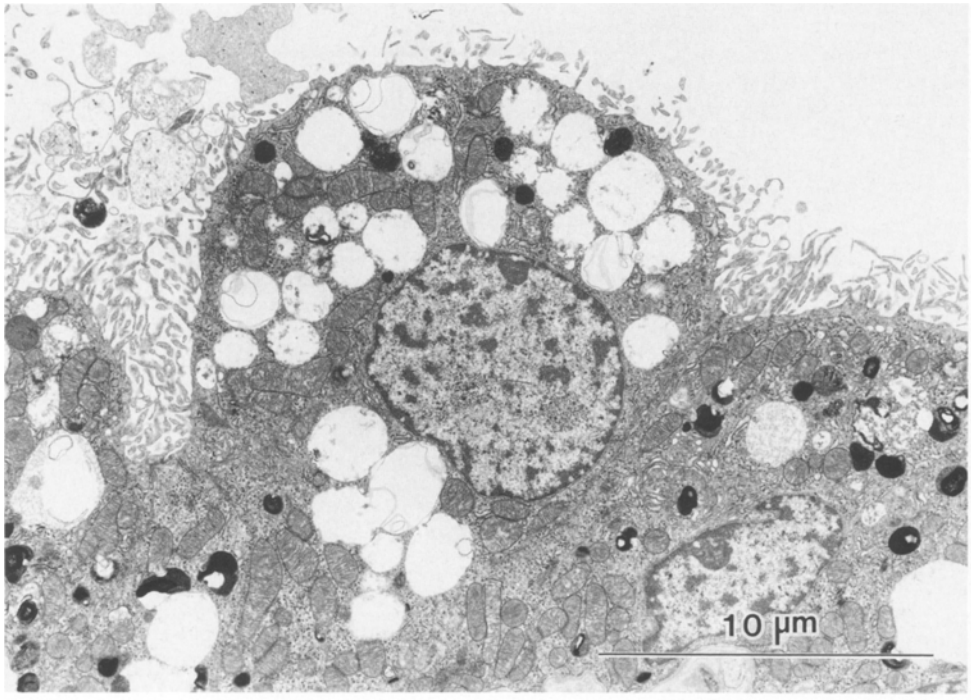

Fig. 5. Experiment A, 100 mg/kg × 8 in 10 days. Numerous vacuoles, some of which contain membranous debris, are scattered throughout the cytoplasm of the epithelial cells. The inclusion bodies are also scattered within the cell. The microvilli are sparse on the cell surfaces. × 5800

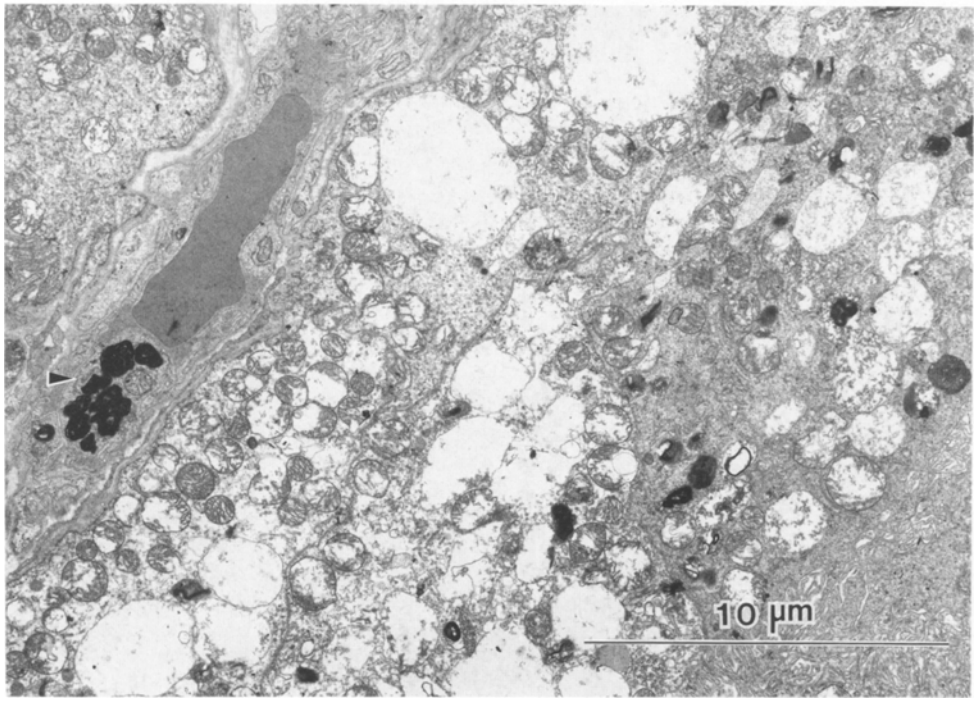

Fig. 6. Experiment B, 75 mg/kg × 17 in 24 days. The cytoplasm of the epithelial cells is replaced by numerous vacuoles with interspersed inclusion bodies. In the swollen capillary endothelium, an aggregate of electron-dense bodies is formed (*arrowhead*). × 6250

Discussion

The peculiar, characteristic changes in rat choroid plexus seen in our experiments were hydropic vacuolation of the choroidal epithelium concomitant with deposition of inclusion bodies.

The degree of hydropic vacuolation of the choroidal epithelium is directly related to the administered dose of the agent and the period of administration. Therefore, a causal relationship between the agent and the changes was evident. Since Benitz and Kramer's report (1968), a series of tertiary amines like piperamide and many others have been reported to give rise to hydropic vacuolation of the choroidal epithelium (Levine 1977; Wenk et al. 1979). Based on results obtained by experimental implantation of choroid plexus beneath the renal capsule, Levine suggested that tertiary amines caused hydropic vacuolation of the choroidal epithelium by a direct chemical interaction. The amine-curing agent we used, bis(4-amino-3-methylcyclohexyl)methane, is, however, a primary amine, different from those applied by Levine. This primary amine might have acted on choroid plexus

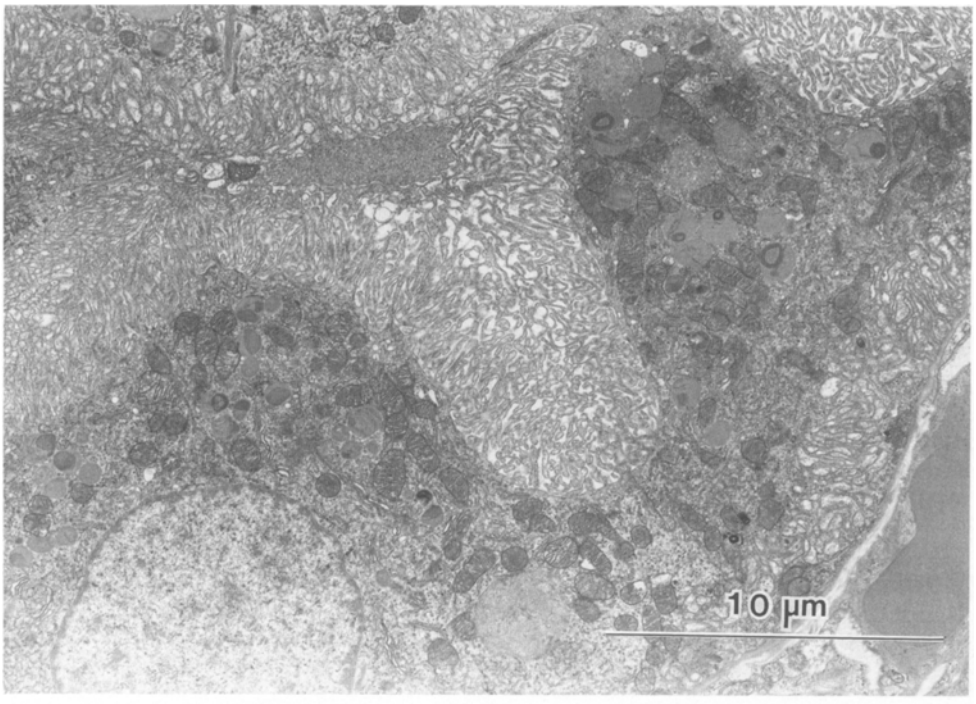

Fig. 7. Experiment C, 2 months after cessation of administration at 75 mg/kg × 17 in 24 days. Many round-shaped bodies of moderate electron density are interspersed among the well-developed intracytoplasmic organelles. Some of the bodies contain myelin-like structures. The villi are distributed densely on the cell surfaces. × 5800

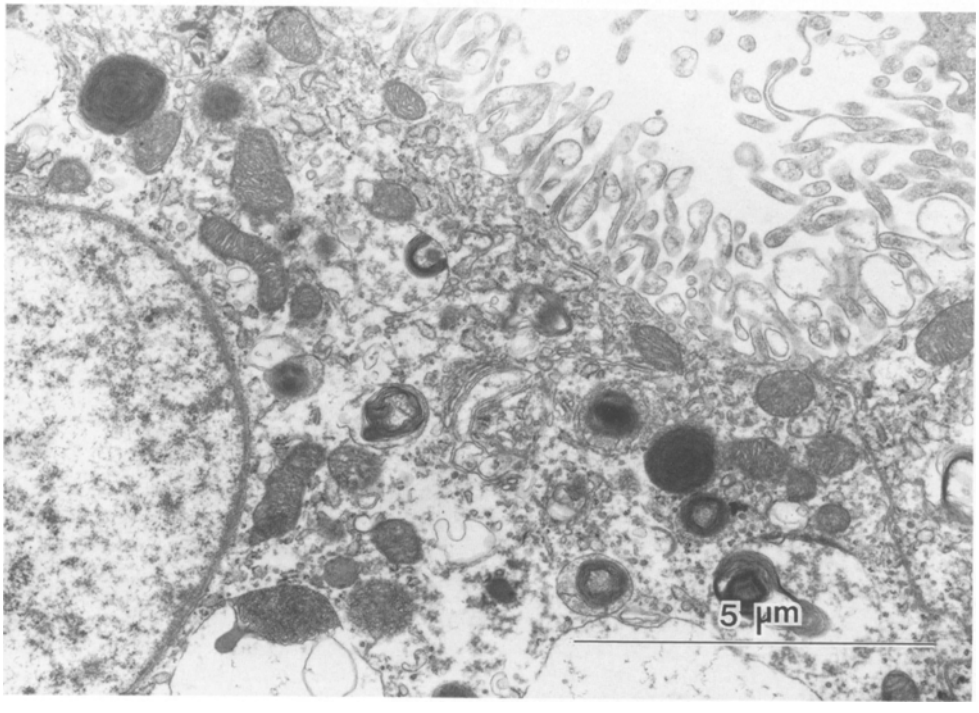

Fig. 8. Experiment B, 75 mg × 17 in 24 days. Inclusion bodies of various structures are scattered among the organelles in the apical portion of the epithelial cell. × 12400

to give rise to hydropic vacuolation in the same or in a similar way as that described by Levine. However, it is possible that the agent underwent in vivo transformation into a tertiary amine, which then attacked the choroid plexus. The main function of the choroid plexus is the production and secretion of cerebrospinal fluid (Welch 1967). If the mechanism of cerebrospinal fluid secretion is damaged by the agent, it is possible that the fluid accumulated within the cytoplasm of the choroidal epithelium to form vacuoles. Wenk et al. (1979) reported that the vacuoles formed within the choroidal epithelium of rats after treatment with tertiary amines were probably of lysosomal origin. We have no evidence to contradict their opinion, although it seems more likely that the vacuoles originated from the endoplasmic reticulum, which secures the passage of secretions (Alberts et al. 1989).

However, different degrees of deposition of inclusion bodies were seen within the choroidal epithelium. Similar inclusion bodies were also found by electron micros-

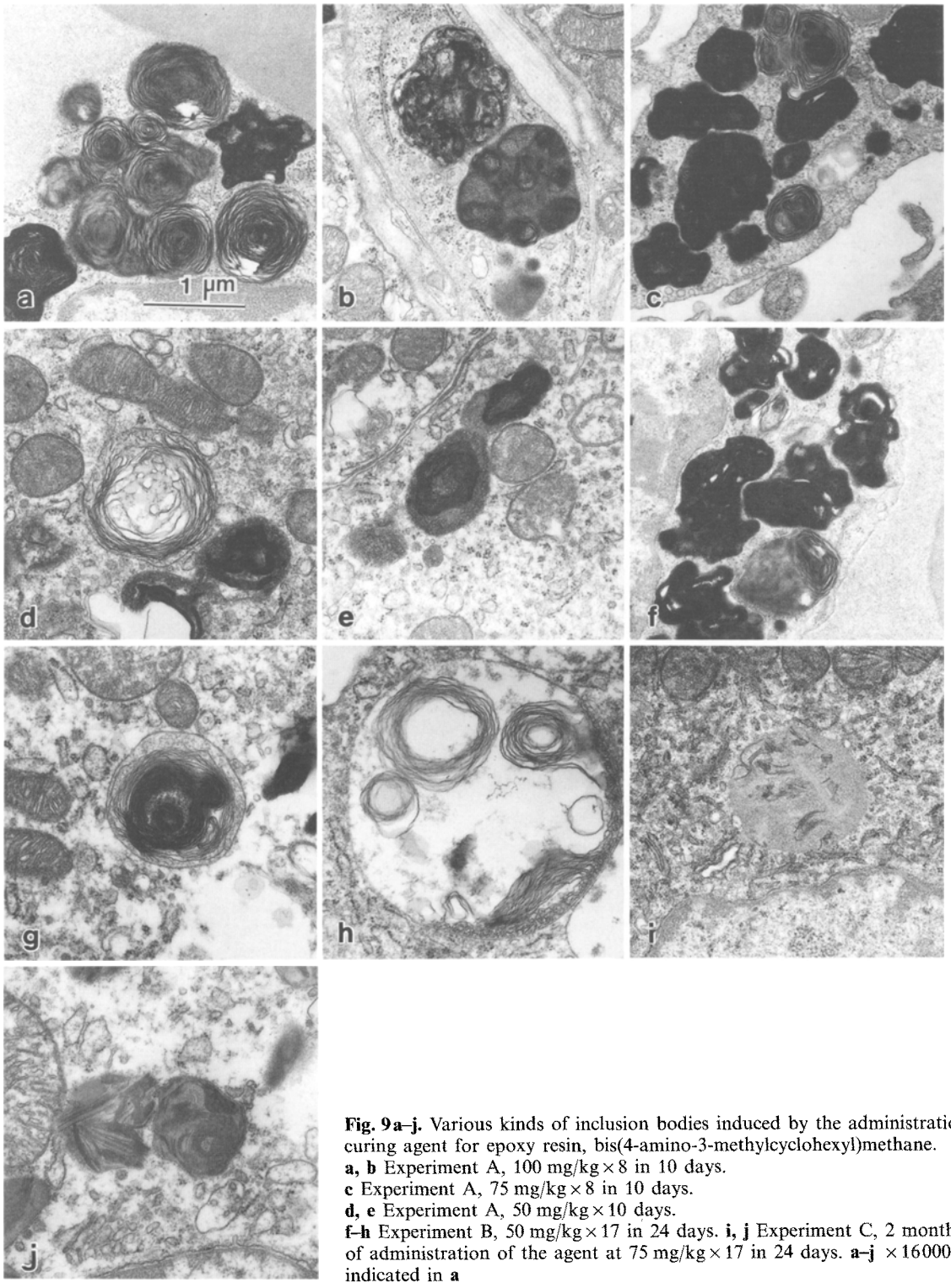

Fig. 9a–j. Various kinds of inclusion bodies induced by the administration of the amine-curing agent for epoxy resin, bis(4-amino-3-methylcyclohexyl)methane.
a, b Experiment A, 100 mg/kg × 8 in 10 days.
c Experiment A, 75 mg/kg × 8 in 10 days.
d, e Experiment A, 50 mg/kg × 10 days.
f–h Experiment B, 50 mg/kg × 17 in 24 days. **i, j** Experiment C, 2 months after the cessation of administration of the agent at 75 mg/kg × 17 in 24 days. **a–j** × 16000; the scale is indicated in **a**

copy in striated myofibres of skeletal muscles and heart, renal glomerular and tubular epithelia, hepatocytes, and splenic cells, although no light microscopic abnormalities were recognized apart from those in skeletal muscles (Ohshima et al. 1984, 1986). Therefore, this phenomenon seems to be a systemic disorder induced by the agent. Similar inclusion bodies have been found in many human storage diseases (Samuels et al. 1963; Schneck et al. 1969; Kamoshita et al. 1969): as membranous cytoplasmic bodies in Tay-Sachs disease and Niemann-Pick disease, and as zebra bodies in gargoylism. Furthermore, they can be induced as intracytoplasmic bodies with lamellated or crystalloid structures clinically (Itoh and Tsukada 1973) and experimentally (Chen and Yates

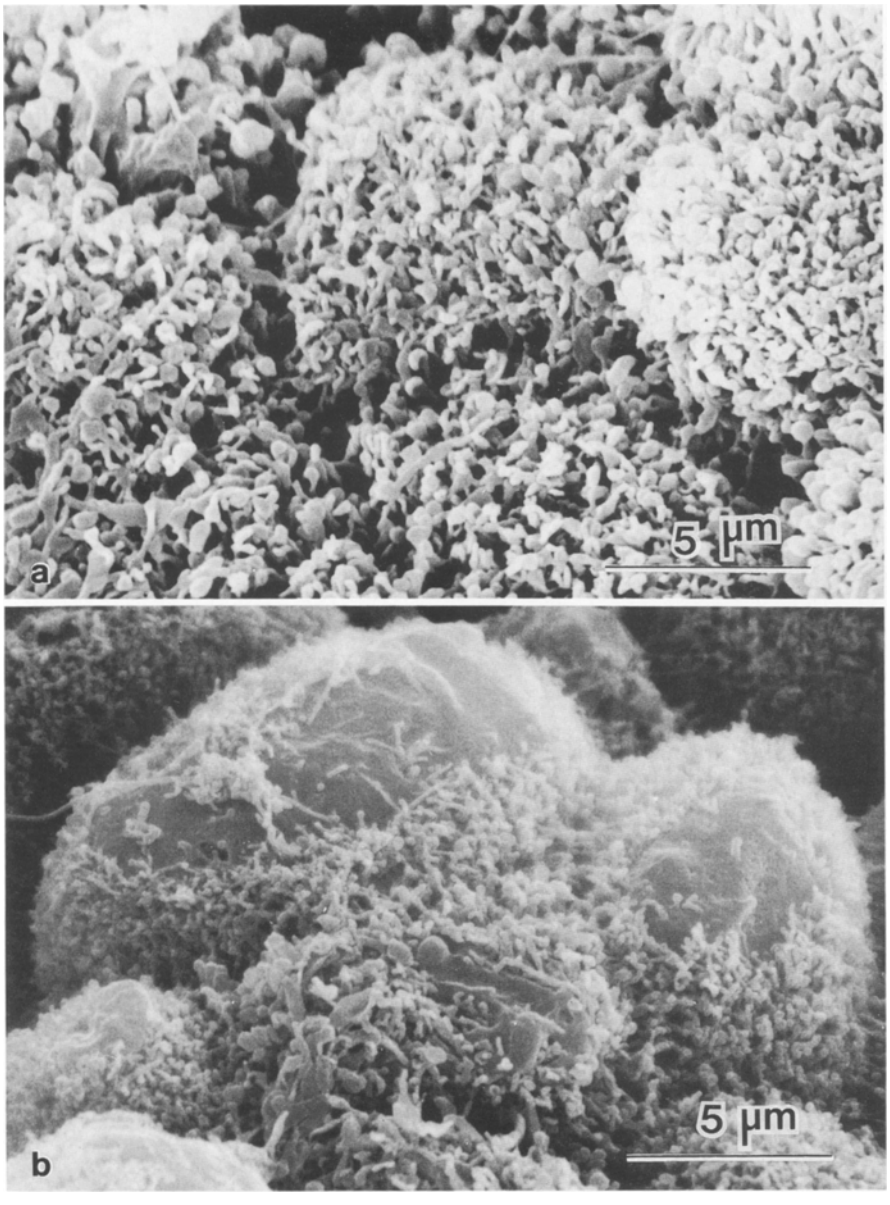

Fig. 10a, b. Scanning electron micrograph of the choroidal epithelium. **a** Control in which microvilli densely and uniformly cover the cell surfaces. **b** Experiment B, 50 mg/kg × 17 in 24 days. The surfaces of the epithelial cells are deprived of microvilli and the residual villous structures are somewhat rougher. × 5200

1967; Hruban et al. 1972; Suzuki et al. 1973; Tashiro et al. 1983) by the administration of amphiphilic drugs like, 4,4′-diethylamino-ethoxy-hexestrol, quinacrine, triparanol, perhexiline and many others, and have been described as drug-induced lipidosis. Takahashi et al. (1987) reported electron microscopic observations of inclusion bodies in the cultured fibroblasts of various sphingolipidoses. All of these inclusion bodies have been ascribed to an abnormal accumulation of materials within lysosomes. In human storage diseases, patients are devoid of intralysosomal hydrolytic enzymes pertinent to the metabolism of complex lipids or mucopolysaccharides. These accumulate within lysosomes to form characteristic fine structures without receiving enzymatic degradation. In the case of drug-induced lipidosis, Luellmann (Luellmann et al. 1978; Luellmann and Moesinger 1979) reported that drugs which are amphiphilic as well as lysosomotropic (de Duve et al. 1974) enter into cells in non-protonized form and penetrate into lysosomes, then become protonized and trapped in the acid milieu. Owing to the strong interaction, complexes composed of protonized amphiphilic drugs and certain polar phospholipids are formed. The lipid-drug complexes which no longer undergo enzymatic degradation give rise eventually to the formation of lamellated or crystalloid structures. The amine-curing agent for epoxy resin, bis(4-amino-3-methyl cyclohexyl)-methane, is an amphiphilic cationic agent and seems to be lysosomotropic. It might, therefore, form complexes with polar lipids within lysosomes and induce systemic lipidosis through the same process proposed by Luellmann et al. (1978).

Chen and Yates (1967) divided the cytoplasmic inclusion bodies found in smooth muscle fibres and parasym-

Table 3. Deposition of inclusion bodies

Group		Epithelium	Endothelium
A	100 mg/kg	+++	+++
	75	++	++
	50	++	++
	cont.	−	−
B	75 mg/kg	+++	+++
	50	+++	+++
	cont.	−	−
C	75 mg/kg	++	+

+++, Marked; ++, moderate; +, mild; − no deposition

pathetic cells of triparanol-treated hamsters into four types: type I, whorls of membranes; type II, labyrinthine aggregates of smooth membranes; type III, dense bodies with a reticular internal structure, and type IV, crystalline bodies showing a regular lattice pattern. In our experiments A and B, type I and its kindred inclusion bodies were mainly induced along with occasional ones belonging to type II or III. No type IV inclusion bodies were, however, encountered. Although Chen and Yates ascribed the different appearances of cytoplasmic bodies to their dehydration process, the possibility should be taken into account that the various structural patterns of the cytoplasmic inclusion bodies might reflect differences in the relative ratio of amphiphilic agents and polar lipids penetrating into each lysosome. The inclusion bodies found in experiment C were structurally different from those in experiments A and B. They appear to reflect long-standing, persistent digestion of the agent-lipid complexes within lysosomes.

No close relationship between the vacuoles and inclusion bodies was evident in our experiments, although on rare occasions a few inclusion bodies were encountered within the vacuoles or aggregated around the vacuoles. Except for choroidal epithelium, no hydropic vacuolation was demonstrated in other organs and tissues including skeletal muscle, liver, heart muscle, kidney, and spleen (Ohshima et al. 1984, 1986) in spite of the fact that inclusion bodies were found to varying degrees in these tissues. In the choroid plexus, inclusion bodies were formed in the endothelium of the capillaries within the connective tissue core, but no hydropic vacuolation was observed therein. Therefore, the formation of vacuoles and the deposition of inclusion bodies seemed to be separate, independent events. Hydropic vacuolation due to the action of the agent might be specific for the choroidal epithelium and be involved with the production of cerebrospinal fluid, the main function of the choroidal epithelium.

It is noteworthy that no neurological abnormalities were observed in any experimental animals in spite of varying degrees of damage to the choroidal epithelium. A large portion of cerebrospinal fluid is surely produced in choroid plexus, but some cerebrospinal fluid is thought to originate in other sites, for example the subarachnoid spaces and cerebral interstitium (Sato et al. 1975). The quantity of cerbrospinal fluid necessary to maintain the function of the central nervous system might be provided by sites other than the choroid plexus.

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