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The epidermis mitochondria ultrastructure evaluation of the etretinate-treated white rat

Etretinate belongs to the group of drugs known as retinoids which are vitamin A derivates. It is a representative of second-generation retinoids, i.e. a synthetic, aromatic analog of transretinoic acid. An indication for the oral therapy with etretinate (Tigason) are severe forms of psoriasis, genodermatoses and a number of other dermatological diseases. The administration of etretinate induces clinical effects and morphological alterations in the structure of both pathological and healthy epidermis in men and animals.

The aim of the present work was to examine the influence of etretinate (Tigason) long-term various doses treatment on the ultrastructural design of the mitochondria of white rat's epidermis.

MATERIAL AND METHODS

The studies were carried out on white Wistar rats of ca 300 g body weight. The animals were given the vitamin A derivate retinoid – etretinate, which is a synthetic, aromatic analog of transretinoic acid. The drug was administered intragastrically through a stomach tube over 28 days. The drug was administered in low doses causing no clinical effects in the animals. The rats made three experimental groups. The drug doses were: 2 mg/kg b.m./24 h in the experimental group I; 4 mg/kg b.m./24 h in the experimental group II; and 6 mg/kg b.m./24 h in the experimental group III. The control animals were given, respectively, distilled water. After the period of drug application animals were anaesthetized in ether narcosis and specimens of epidermis were taken up for observation in the transmission electron microscope Tesla BS 500.

RESULTS

The mitochondria turned out to be reacting to Tigason, even if they were administered in very small doses. In the experimental group I, the increase in both the mitochondria number and size and perinuclear mitochondria localization, was observed. These changes caused indentation of the nuclear areola towards the inside of the nucleus. In the mitochondria matrix microgranular material was found (Fig. 1). Such changes were

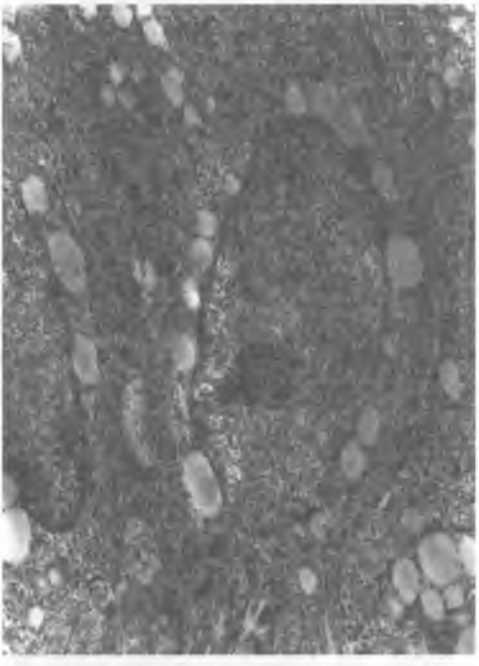

Fig. 1. Experimental group I. Cytoplasm contains enlarged mitochondria which, adhering to the nuclear areola, cause the latter's indentation towards the inside of the nucleus. The mitochondria matrix contains microgranular material. TEM x 4000

more intensive in the experimental groups II and III, yet they still concerned primarily the reproductive layer of the epidermis (Fig. 2). The structure of the internal membrane in the enlarged mitochondria was obliterated, and the mitochondria crests were deformed or imperceptible (Figs 1, 2, 3). In the experimental group these organelle were surrounded by contracted nuclei of the reproductive layer of the epidermis, containing chromatin of high electron density (Fig. 3). Changes in the ultrastructural design of the mitochondria correlated with the dose drug amount, and with the degree of ultrastructural alterations in other cell organelle of the epidermis reproductive layer. The increase in the

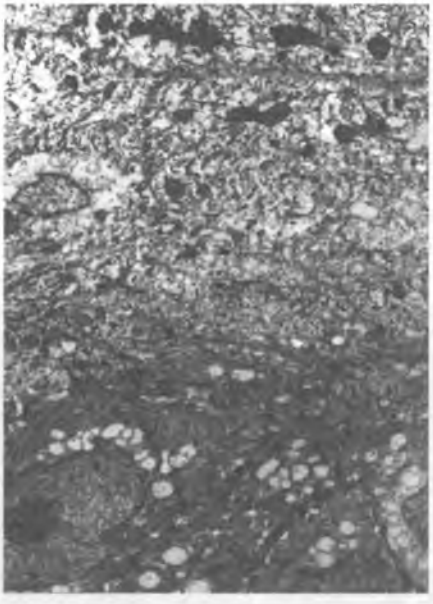

Fig. 2. Experimental group II. Epidermis. Basal layer contains numerous enlarged mitochondria accumulating around the contracted nucleus. TEM x 2000

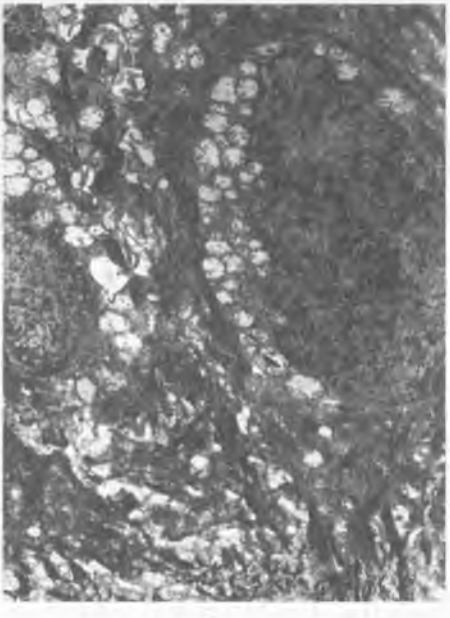

Fig. 3. Experimental group III. Basal layer of the epidermis. Mitochondria surround the contracted nucleus containing chromatin of high electron density. Mitochondria crests were seriously deformed. TEM x 4000

number and size of the mitochondria was probably the effect of hypertrophy and hyperproliferation of the epidermis cells. The alterations in the ultrastructural design were the result of increased energetic requirement.

DISCUSSION

The wide use of retinoids in dermatological treatment is the result of their regulatory impact on the proliferation process and the differentiation of the epithelium. The influence of these drugs on the cell is complex and differs in the healthy and pathologic epidermis (3). Retinoids control life processes of the cell through initiating or inhibiting gene expression (2). They initiate signal transduction where the mediator, acting as a transcription factor at the same time, is the nuclear receptor activated by the ligand. In reply to the signals received from the cells, the transcriptive factor, i.e. the nuclear receptor, regulates gene transcription, activating or inhibiting their expression (3). In healthy skin changes induced by a long-term administration of retinoids are observed mainly in the epidermis (1), whereas no significant impact on the morphological or ultrastructural design of healthy proper skin was revealed. Such alterations are found primarily in the reproductive layer of the epidermis and they concern mainly the nuclei of mitochondria cells and the intercellular junctions and spaces. In the foregoing experiment the increase in the number and size of the mitochondria was probably the effect of the epidermis cells hypertrophy and hyperproliferation, and the alterations in the ultrastructural design resulted from an increased energetic requirement of the cell and from intensified processes of oxidative phosphorylation.

CONCLUSIONS

An increase in the mitochondria number and size as well as changes in perinuclear localization were observed. These changes caused indentation of the nuclear areola towards the inside of the nucleus. In the mitochondria matrix microgranular material was found.

Application of etretinate modulates the ultrastructural status of the epithelial mitochondria. The dose of the administered drug correlates with the mitochondria ultrastructural design changes and the degree of ultrastructural alterations in the other organelle of the reproductive-layer cells of the epidermis, which were demonstrated in the foregoing experiment.

REFERENCES

1. Bhawan J., Gonzales Serva A.: Effects of tretinoin of photodamaged skin. Arch. Dermatoz., 125, 419, 5, 1991.
2. Czekaj P.: Interakcje receptorów hormonu tarczycy i pochodnych witamin A i D z DNA. Post. Biol. Kom., 23 (2), 261, 1996.
3. Trafna R., Majewski S.: Biologiczne podstawy działania retinoidów i witaminy D 3 w chorobach proliferacyjnych skóry. Przegl. Dermatol., 81, 573, 1994.

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SUMMARY

Etretinate belongs to the group of drugs known as retinoids which are vitamin A derivates. It is a representative of second-generation retinoids, i.e. a synthetic, aromatic analog of transretinoic acid. The administration of etretinate induces clinical effects and morphological alterations in the structure of both pathological and healthy epidermis in men and animals. The aim of the present work was to examine the influence of long-term various doses of etretinate (Tigason) treatment on the ultrastructural design of white Wistar rats epidermis mitochondria. The mitochondria turned out to be reacting to Tigason. The drug dose-dependent changes as well as the ultrastructural mitochondria design, and the degree of other ultrastructural reproductive epidermis layer alterations cell organelle were observed. The increase in the mitochondria number and size was noticed. We concluded that etretinate application modulates the ultrastructural status of the epithelial mitochondria, and the administered drug dose correlates with the mitochondria ultrastructural design changes and the degree of ultrastructural alterations in the other organelle of the epidermis reproductive-layer cells.

Zmiany ultrastrukturalne mitochondriów naskórka szczura białego poddanego działaniu etretinatu

Etretinat jest lekiem należącym do grupy pochodnych witaminy A. Jest on retinoidem drugiej generacji, tj. syntetycznym, aromatycznym analogiem kwasu transretinowego. Podawanie etretinatu prowadzi do zmian morfologicznych w obrębie zarówno zdrowego, jak i patologicznie zmienionego naskórka u ludzi i zwierząt. Celem pracy jest badanie wpływu długotrwałego podawania różnych dawek etretinatu (Tigason) na zmiany obrazu ultrastruktury mitochondriów naskórka szczura białego rasy Wistar. W przebiegu doświadczenia zaobserwowano zmiany obrazu ultrastruktury mitochondriów zależne od dawki leku.

Wystąpił wzrost liczby i wielkości mitochondriów, obserwowany przede wszystkim w warstwie rozrodczej naskórka. W wyniku przeprowadzonego doświadczenia stwierdzono, że mitochondria warstwy rozrodczej naskórka szczura białego są wrażliwe na podawanie etretinatu, a natężenie zmian ultrastrukturalnych zależy od dawki leku.