Histol Histopath (1987) 2: 213-216

Histology and Histopathology

The influence of bromocriptine on the ultrastructure of the biceps femoris muscle in mice

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Summary. Bromocriptine and other dopaminergic agonists drugs are used in Parkinson's disease.

In this paper we have studied the ultrastructure of striated muscle of mice after bromocriptine treatment.

There was a tremendous increase in the number and size of mitochondria, as well as a very notable increase in the cristae. Some ultrastructure changes were also noted at the neuromuscular junctions.

An explanation has been attempted in the light of other investigations concerning the relationship of microtubules and bromocriptine on the one hand, and microtubules and mitochondria on the other.

Key words: Bromocriptine — Mitochondria — Striated muscle

Introduction

Bromocriptine is an ergot derivative (Parkes, 1979) with dopaminergic properties in rodents and primates (Kartzinel et al., 1976). Since 1972 it has been employed therapeutically to reduce plasma prolactin concentration in galactorrhoea. At higher doses, it has also been given to supress growth hormone secretion in acromegaly (Calne et al., 1978). It is also known that bromocriptine lowers plasma norepinephrine in humans (Francis et al., 1983).

Currently bromocriptine and other dopaminergic agonists of this type are being investigated actively for their possible use in the treatment of Parkinson's disease (Bianchine, 1980), because these drugs have, in common, a direct vasodilator activity through vascular dopaminergic receptors (Francis et al., 1983) and the ability to improve skeletal muscle function by primary actions on the central nervous system.

We have also considered it worthwhile to study the morphology of striated muscle cells in C_3H mice after bromocriptine treatment.

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Materials and methods

A total of 20 female C_3H/Sy inbred mice, about 4 months of age, were used. The animals were obtained from the Experimental Department of the Theagenion Cancer Institute.

At the beginning of the experiment the animals were divided into two groups. The first one (10 animals) received bromocriptine and the second (10 animals) was the control group.

Each animal of the first group received intraperitoneally 0.1 mg/0.1 ml bromocriptine suspension for four weeks. The bromocriptine suspension was prepared by dissolving the drug initially in a minimal amount of ethanol and diluting to volume with 0.89% NaCl solution. The final suspension contained 2.5% ethanol or less. Control animals received the vehicle only.

At the end of the experiment, the animals were sacrificied by ether inhalation. Striated muscle tissue was obtained from the biceps femoris muscle, fixed in 2,5% glutaraldehyde-Sorrensen, post fixed in 1% osmium tetroxide, dehydrated through graded alcohol and embedded in Epon.

Thin sections on copper grids were stained with uranyl acetate, post stained with lead citrate and examined by electron microscope.

Results

By electron microscope we observed that the number of mitochondria greatly increased, being found under the sarcolemma (Fig. 1), in the perinuclear region (Fig. 2) or among the muscle fibers (Fig. 3). The mitochondria aggregated very closely, changing from round to angular, and their membranes, which were apposed to each other, appeared thicker than normal (Fig. 1). Size and shape of the mitochondria greatly varied, reaching giant dimensions

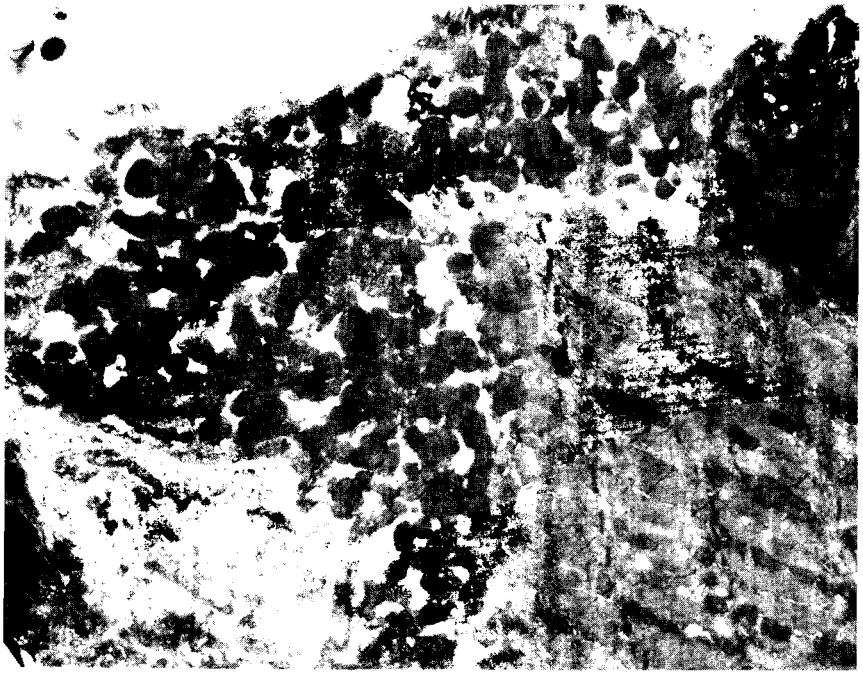

Fig. 1. Confluent bizarre-shaped mitochondria under the sarcolemma (S). Note the number of cristae, leaving very little mitochondrial matrix free. × 30,000

Fig. 2. Perinuclear aggregation of numerous mitochondria. × 5,000

Fig. 3. Giant mitochondria among the muscle fibers. The cristae fill the mitochondria leaving very little matrix. × 30,000

Fig. 4. Aggregation of giant bizarre-shaped mitochondria under the sarcolemma (S). The cristae are well-demarcated (arrow) only on well-oriented perpendicular planes. × 30,000

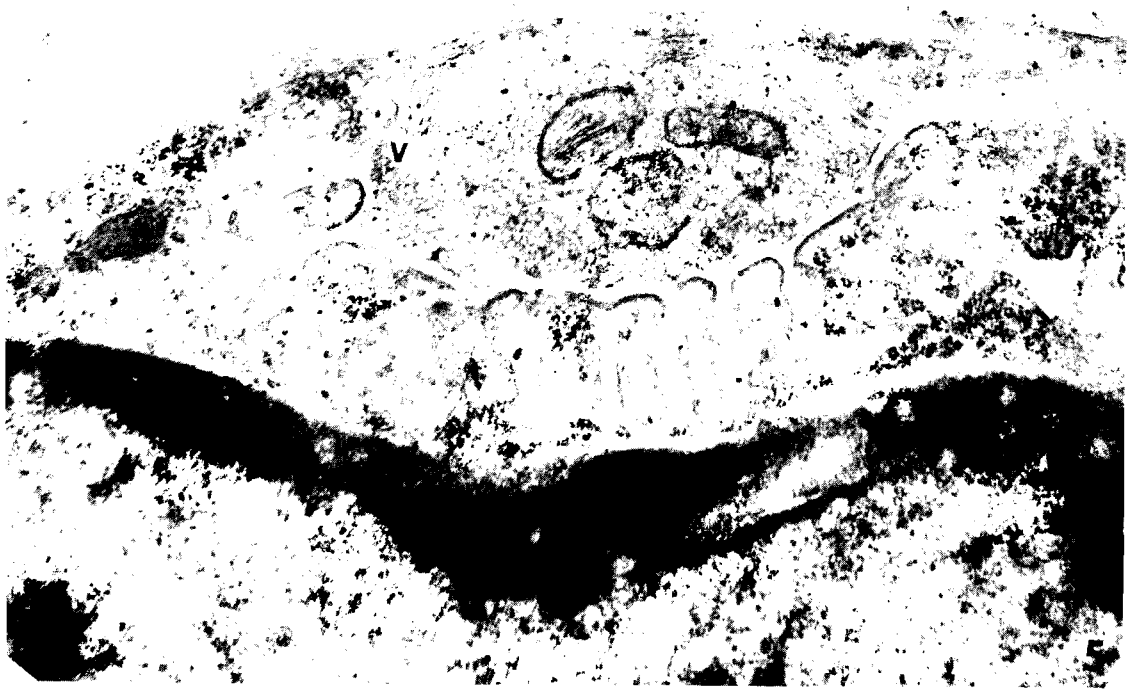

Fig. 5. Motor end plate. The synaptic vesicles (V) are numerous, with a foamy appearance. × 45,000

and bizarre forms (Figs. 1,3,4). The cristae also increased in number and length, forming closely-arranged long parallel lines. These cristae were well-depicted on perpendicular sections, but were undiscernable on oblique ones (Fig. 4). The cristae filled the whole mitochondrial body leaving little mitochondrial matrix free (Figs. 1,3,4).

There was also an increase in synaptic vesicles within the motor end plate (Fig. 5). These vesicles, all the same size, were small, clear and closely-packed.

Careful examination and comparison with the control animals did not show any of the above findings and no dilation of the muscle capillaries was noticed.

Discussion

Extensive biochemical studies of mitochondria have proved that they play a major role in the generation of energy for the survival and proliferation of cells (Racker, 1976).

Especially in muscle cells, where high levels of energy are necessary, mitochondria are the most important organelles. Mitochondrial clusters are also seen adjacent to the plasma membrane, often intimately associated with nuclei of the muscle cells or grouped at the motor end-plate region (Price, 1974).

Our results show that in muscle cells, bromocriptine affects the morphology and localization of mitochondria and increase their number, although the white fibers of the biceps femoris muscle, used in this work, are characterised by few mitochondria (Rhodin, 1974).

There is, on the other hand, a positive correlation between the metabolic activity of a tissue and the number and size of mitochondria and also the number, size, surface area and concentration of cristae (Ghadially, 1975). This correlation is an indication of the rate of oxidative metabolism within a given muscle. Thus, high energy transforming muscles have abundant mitochondria.

It is therefore, possible that the changes in mitochondrial distribution, number, shape and size, observed in our experiments, may reflect some biochemical and functional changes leading to a higher metabolic rate that may occur in the mitochondria of muscle cells after bromocriptine treatment, especially when it is considered that some striated muscles with high metabolic activity have an increased number of mitochondria (diaphragm - dragon fly).

It has also been observed that, afer bromocriptine treatment, there is an increase in centrioles or even the appearance of cilia in cells normally without them (Polyzonis, 1986 unpublished data).

Centrioles and cilia are made up from the same pool of building-blocks from which microtubules are built (Dustin, 1978) within the cell. On the other hand, electron microscopic studies by Johnson et al. (1980) have revealed an interaction between microtubules and mitochondria due to crossbridges between microtubules and adjacent mitochondria which may be involved in the maintenance of mitochondrial distribution and their migration.

The increase in mitochondria after the same treatment and the known relationship between mitochondria and microtubules (Johnson 1980) may well lead to the supposition that bromocriptine treatment leads to the formation of giant new mitochondria from similar building-blocks to those making up centrioles and cilia, as well as contributing to aggregation.

However, on the morphological basis above, it is not possible to explain any alteration in muscle fiber function.

Acknowledgements. The authors wish to thank the Sandoz L.T.D. for generously providing bromocriptine for the above experiments.

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Accepted February 3, 1987