REACTION OF NEURONS OF THE CEREBRAL CORTEX DURING REPARATIVE REGENERATION IN MAMMALS

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The study of regenerative processes in the central nervous system began about 100 years ago, yet the extent of the regenerative powers of the neuron still remains an unsolved problem. Some investigators consider that, being a highly differentiated cell, the mature neuron has lost its ability to proliferate by division. Others produce evidence supporting the view that the neuron still remains capable of amitotic and mitotic division. These opposite points of view are reflected in survey articles in the literature [6, 8]. In recent investigations of the regeneration of experimental brain wounds in mammals, ability of the neurons to undergo division could not be found [1, 4, 10], whereas other workers [2, 6, 8, 12] have found neurons in a state of mitotic division.

Some recent investigations using tissue cultures have also yielded evidence of the ability of neurons to undergo mitotic division in vitro [13].

We have studied reparative regeneration in the cerebral cortex of adult members of two species of laboratory animals—rats and cats.

EXPERIMENTAL METHOD

Experiments were carried out on 120 rats and 60 cats. Mechanical (with a fine scalpel) or thermal (with a red hot needle) injuries were inflicted in aseptic conditions after trephining the skull in the parietal region in the rats and in the region of the splenial and suprasylvial gyri in the cats. After the operation the soft tissues of the skull were sutured in layers. At different periods after the operation (from the 1st to the 30th day) the animals were sacrificed by instantaneous decapitation. Microscopic investigation of the focus of injury was carried out, using different histological and histochemical methods: staining with hematoxylineosin and methyl green—pyronine, iron-hematoxylin by Heidenhain's method, and by the methods of Nissl, Cajal, and Miyagiwa—Aleksandrovskaya. The use of these two species of animals enabled a comparative histological approach to be made to the study of the problem, taking account of the fact that the rat is distinguished by the high regenerative power of all its tissues, whereas the cat more closely resembles the primates by the character of its tissue reactions.

EXPERIMENTAL RESULTS

During the investigation of the neurons in the region of the wound margins pathological changes were observed in their cytoplasm and nucleus, varying in degree and in some cases irreversible: central and peripheral tigrolysis, acute swelling, vacuolation of the cytoplasm, lysis of the nucleolus, karyopycnosis, and karyolysis.

Soon after injury neurons with two nucleoli were found: one larger than the other. The cytoplasmic RNA and nuclear chromatin were very palely stained, the cytoplasm was swollen, and the nuclei were more indicative of neurons in a pathological state than of neurons about to undergo regenerative amitosis, as considered by I. I. Rampan [10].

At the same time progressive changes were observed in the astro- and oligodendroglia: hypertrophy of the processes and bodies, the appearance of binuclear forms as a result of division of the nucleus, and the presence of

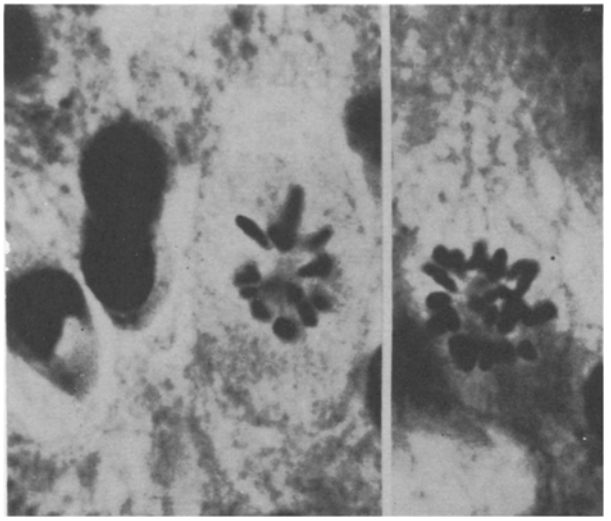

Fig. 1. Mitoses in neurons. Metaphase. Hematoxylin-eosin. Objective 100, ocular 10.

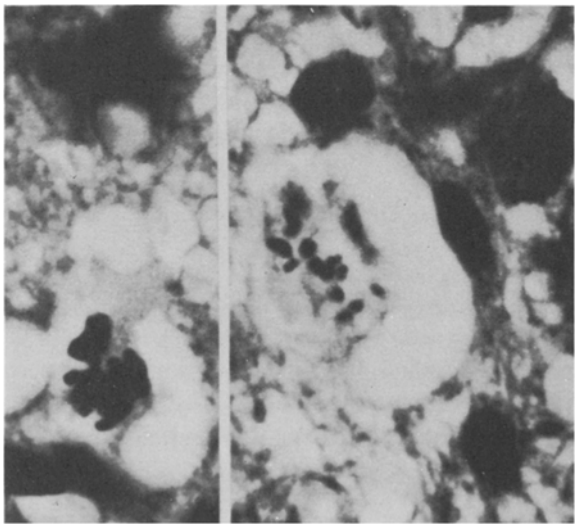

Fig. 2. Death of neurons in mitosis at stage of metaphase. Agglutination, deformation, and destruction of chromosomes. Vacuolation of cytoplasm. Hematoxylin-eosin. Objective 100, ocular 10.

"paired" cells and of twin cells as a result of division of the mother cell. In the region of the wound margins after the lapse of 7-10 days the formation of an astrocytic barrier from hypertrophied forms of astroglia was observed, confirming the presence of plastic properties in this type of glia [11]. The increase in the number of astroglial cells in the focus of injury to the brain in the white matter. In the subependymal zone in the rat small astrocytes appeared, with processes stretching out towards the site of injury.

The rate of regeneration was higher in the rats, in which the number of mitoses reached its maximum near the wound edges after 3-5 days, compared with 6-8 days after injury in the cats.

The study of the mitotic figures in wounds of the cerebral cortex revealed four types of cells in which mitotic figures were usually found:

1). Macrophages. The cytoplasm of these cells was granular, with tiny lipid inclusions and other phagocytosed materials, and they were round in shape. The RNA in their cytoplasm was distributed as finely dispersed granules. The chromosomes in the methaphase plate were grouped into a compact "aster." Macrophages undergoing mitotic division were situated in the zone of injury itself, at the site of necrosis of the brain tissue;

2). Endothelial cells of small vessels (capillaries and precapillaries situated in the region of the wound edges). These cells were round or oval in shape. They contained less RNA in their cytoplasm that did the macrophages, when stained with methyl green–pyronine. The RNA stained a weak, diffuse pink color. The chromosomes in the metaphase plate were compactly arranged;

3). Gliocytes (astrocytes, oligodendrocytes). Mitoses in these cells were encountered everywhere in the wound edges. The cells were medium sized and usually round in shape. Their cytoplasm contained less RNA than the cells of the vessel walls. The chromosomes were more loosely arranged in the metaphase plate than in the macrophages and the cells of the blood vessels;

4). Neurons. Neurons with mitotic figures were found everywhere in the wound edges. These were large, round cells, sometimes pyramidal in shape, and in some cases the base of their axon cone could be seen. Diffuse tigrolysis was observed in their cytoplasm, which stained a pale pink color with pyronine of approximately the same intensity as in the gliocytes mentioned above. In early prophase the large nucleolus characteristic of neurons could be seen, rich in RNA. The chromosomes were large and they were scattered haphazardly in the metaphase plate (Fig. 1).

In the first three cell groups described above, all stages of mitoses were found: pro-, meta-, ana-, and telophase. Sometimes, especially in the cells of the vessel walls, spindle-like threads and centrioles radiating from the poles could be seen.

We have previously reported that the final stages of mitosis (anaphase and telophase) cannot be found in

neurons. Neurons dying in the metaphase stage of mitosis were frequently seen, with the picture of deformation and agglutination of their chromosomes and solution of the cytoplasm (Fig. 2). Centrioles and spindle-like threads were never seen in the neurons.

Recent investigations, some using the electron microscope, have shown that there is doubt about the presence of a cell center in the neuron [15]. In particular, in articles surveying the fine structure of the neuron [3, 14], no mention is made of presence of this organoid.

We have put forward the suggestion that the absence of imperfect state of the cell center in the neuron is the reason for the absence of the final stages of mitosis. Other possible reasons for the failure of completion of mitosis may be given: lack of energy yielding products in the cell, absence of materials for construction of the mitotic apparatus, disturbances in the structure of the chromosomes themselves (absence of kinetochores, etc. [16]). Furthermore, abnormalities in the number of chromosomes in the somatic cells (2p)—polyploidy or aneuploidy—may cause the cell to lose its ability to complete its division. According to some reports [17], polyploidy is a rare event in differentiated mammalian tissues. Hence, the present investigation, while it demonstrated that the neuron can start the process of mitosis and can form chromosomes, did not solve the problem of the ability of the neuron to complete mitosis during reparative regeneration in the adult organism.

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