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REPAIR PROCESSES IN THE POSTISCHEMIC CEREBRAL CORTEX IN THE EARLY POSTRESUSCITATION PERIOD*

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After total ischemia pathological changes develop in the brain which frequently lead to so-called postresuscitation encephalopathies. In these conditions higher nervous processes are disturbed to some extent, and in man this affects his principal social quality, namely his intellect. The problem of restoring brain functions completely in the postresuscitation period is one of the most important aspects of modern resuscitation practice [3, 4, 7]. It will be quite evident that before a system of scientifically based measures for the treatment and prevention of these encephalopathies can be worked out, precise and reliable data are needed on the pathogenetic mechanisms lying at the basis of these diseases. Special attention here must be paid to repair processes in the postischemic brain in the early postresuscitation period, about which hardly anything was known until recently [2, 5]. This paper gives new data on reparative regeneration in the cerebral cortex on the 1st day of the postresuscitation period after total experimental ischemia in rats.

EXPERIMENTAL METHOD

Experiments were carried out on nine Norwegian male albino rats weighing 180-220 g, which were subjected to total ischemia for 10 min by cardiac arrest [1]. The animals were killed 1, 3, and 24 h after resuscitation, three animals in each group. Pieces of cortex were taken from the occipital, parietal, and frontal regions of the brain and fixed in 2% glutaraldehyde solution in 0.1 M phosphate buffer, pH 7.2. Subsequent treatment of the brain tissue for electron-microscopic study was carried out by the usual method. Ultrathin sections of the cerebral cortex were studied in the EM 10 CR electron microscope ("Opton," West Germany).

EXPERIMENTAL RESULTS

In the early postresuscitation period the brain tissues are exposed to the action of several unfavorable factors, of which the most important are hypoxia and endogenous toxins [6, 8], which leads primarily to pathological changes in cell membranes,

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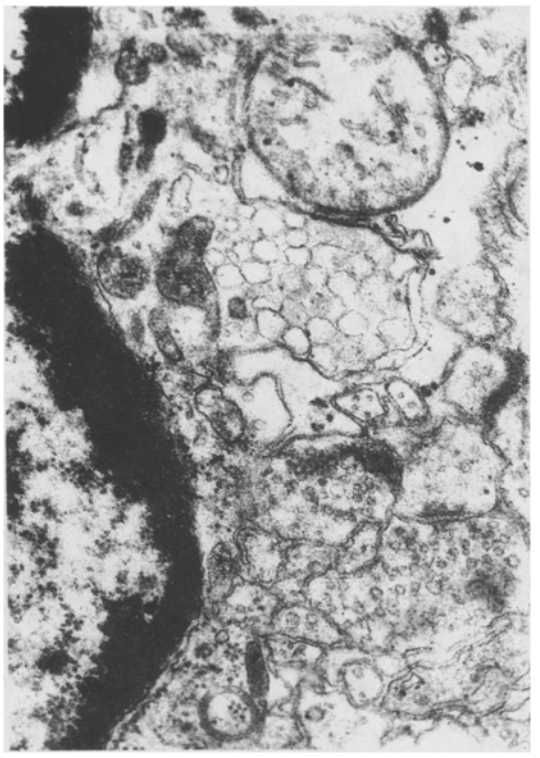

Fig. 1. Initial stage of formation of cone of growth on cell body from rat cere bral cortex. Total ischemia for 10 min, 3 h after resuscitation. 20,000×.

which become twisted and undergo desquamation. As a result of this, during the 1st hour of the postresuscitation period perivascular edema develops around the capillaries in the cerebral cortex. Plasma exuding from them accumulates in the interstitial spaces of the brain tissue, to form a zone of congestion around the capillaries, and this undoubtedly weakens exchange processes considerably between the bloodstream and tissue elements, thereby prolonging and maintaining cerebral hypoxia. However, after 2-3 h this perivascular edema, according to our observations, begins to diminish rapidly due to resorption of the edema fluid by the vascular pedicles of the astrocytic neuroglia, and it virtually disappears toward the end of the first day of the postresuscitation period.

During the first few hours after total ischemia, the nerve cell membranes are damaged particularly severely in the cerebral cortex, as we have demonstrated; membranes lining the cisterns of the endoplasmic reticulum and the nuclear membranes are most severely damaged, the plasma and mitochondrial membranes less severely. Profound changes in the structural organization of the cell membranes, especially the endoplasmic membranes, unavoidably lead to pathological disturbances of their permeability and to significant changes in ionic homeostasis in the cells, resulting in their internal edema. All these changes are an undoubted manifestation of severe damage to cerebral neurons, which may itself be the cause of further development and exacerbation of pathological processes in these cells, and in the case of decompensation, they may cause death of the nerve cell. During the first hours of the postresuscitation period, nerve cells in the cortex of the postischemic brain evidently still possess high biological activity and resistance, so that most of them survive and, according to our observations, they recover their membrane structures quite quickly, during the first day. An exceptional role in this process of reconstruction of the cell membranes in cerebral neurons is played by a special intracellular organelle — the lamellar apparatus of Golgi, which is in a state of marked hyperfunction in such neurons, as shown by the hypertrophy and hyperplasia of its structural elements. Nevertheless, in the first hours of the postresuscitation period a certain proportion of neurons and interneuronal synaptic connections in the postischemic cerebral cortex undergo destruction.

However, besides evident processes of destruction in the postischemic cerebral cortex, starting with the first few hours after resuscitation repair processes begin to develop progressively. They comprise both processes of intracellular repair [5] and processes of systemic regeneration of neuronal nets.

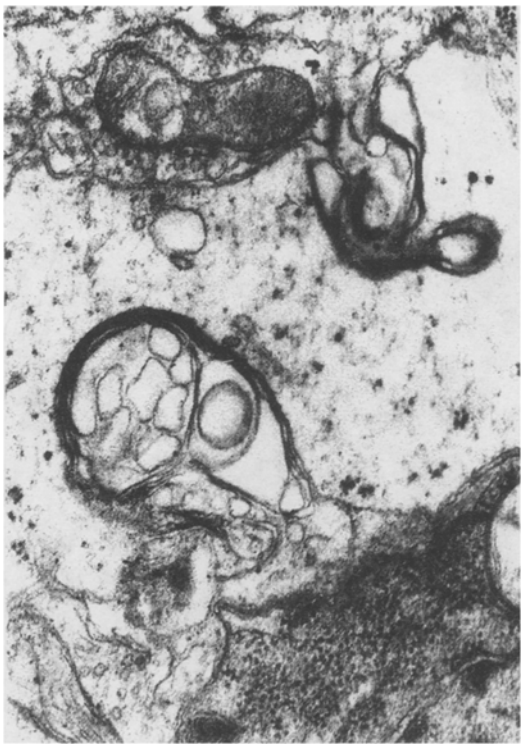

Fig. 2. New cellular process with typical cone of growth formed in body of cerebral neuron. Total ischemia of rat for 10 min, 3 h after resuscitation. 33,000×.

Intracellular repair processes develop in the postischemic brain as it were in two main directions. First, an increase in the energy potential of cells of the cerebral cortex and, in particular, its neurons, and second, considerable strengthening of the functions of their protein-synthesizing system, as is confirmed by the absolutely precise morphological criteria: an increase in the number of active mitochondria and polyribosomal complexes in the cytoplasm combined with hypertrophy of the nucleoli and uncoiling of the nuclear chromatin.

We would naturally wish to draw particular attention to repair processes connected with regeneration of nerve cell processes and with the formation of new neuronal nets in the cerebral cortex in the postresuscitation period, which demonstrate unequivocally not only the undoubtedly high plasticity of the postischemic brain, but also its exceptional ability to restore lost functional structures. We showed that 3 h after resuscitation many nerve cells in the cerebral cortex of the rats were able to carry out true regeneration (de novo formation) of their own processes, with the formation of typical cones of growth, which are an undoubted feature of the growing, regenerating nerve fiber. The formation of a new cellular process on a nerve cell in the cerebral cortex in the early postresuscitation period begins in precisely the same way as during embryonic development of the brain, namely with the formation of a special structure, the so-called cone of growth, on the cell body, with its characteristic collection of unique large transparent vesicles (Fig. 1). Insertion of the membranes of the special vesicles into the apical plasma membrane of the developing cellular process determines its rapid growth. The next photomicrograph shows the subsequent stage of development of such a process, when its growing tip, enlarged by the cone of growth at its apex, advances in the direction away from the surface of the nerve cell body, thus forming the base (neck) of the future dendrite (Fig. 2). These same cones of growth can be formed not only on the body of a nerve cell, but also in other regions of it, such as the terminal divisions of the axon — in its presynaptic region. The earliest stage of formation of typical cones of growth in the presynaptic part of an axon can be seen clearly in Fig. 3: in the immediate vicinity of the active zone of its synaptic junction with the dendritic spine. In their subsequent development these newly formed lateral branches of axons can establish new synaptic connections with other nerve cells [2]. Under these circumstances, however, it must be emphasized that these phenomena in the cerebral cortex of adult intact animals are observed extremely rarely.

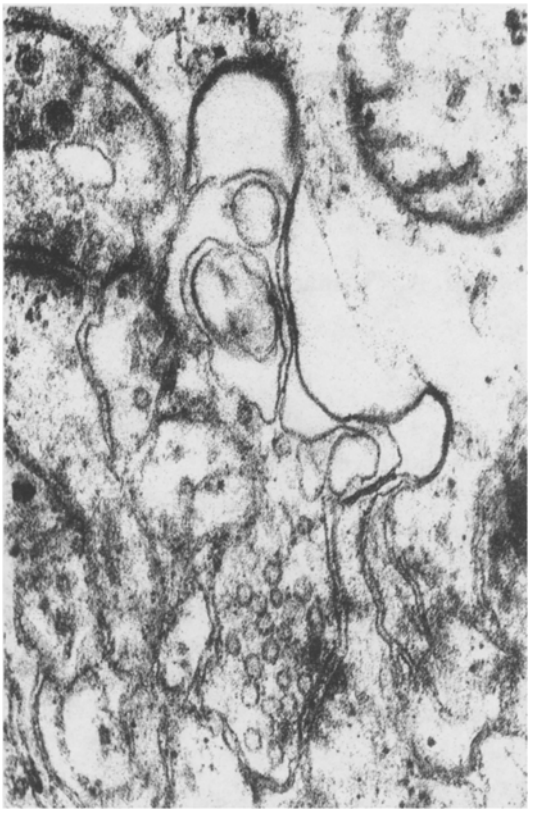

Fig. 3. Initial stage of formation of cones of growth in terminal part of axon, immediately next to active zone of its synaptic junction with dendritic spine. Occipital region of rat cerebral cortex, 3 h after resuscitation. 43,000×.

Repair processes, having started on the first days after resuscitation, continue to develop, according to our observations, with ever-increasing speed during the 1st and 2nd weeks after resuscitation [2]. At this time, the appearance of numerous cones of growth, which are absolutely definite evidence of the existence of sufficient regenerating nerve fibers, can often be observed here in the postischemic cerebral cortex. When, however, these nerve fibers reach their target cells, they form typical synaptic junctions with them [2]. As a result of this process of reparative synaptogenesis, the formation of new areas of neuronal nets, which may to some extent replace those which have died, and thereby bring about recovery of lost cerebral functions, takes place in the cerebral cortex. Consequently, the morphological evidence in this paper, confirming the possibility of early development of repair processes in the postischemic cerebral cortex, provides completely new prospects for the solution of the vital problem in present-day resuscitation practice, namely the complete rehabilitation of the postischemic brain.

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