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ASYMMETRIC DAMAGE OF THE CA1 SECTOR OF AMMON'S HORN AFTER SHORT-TERM FOREBRAIN ISCHEMIA IN MONGOLIAN GERBILS

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The studies were carried out on 98 three-month-old Mongolian gerbils, submitted to short-term (5 or 7.5 min) forebrain ischemia induced by bilateral ligation of common carotid artery. After 5-day survival animals were sacrificed by transcardiac perfusion with 10% formaldehyde. Paraffin brain sections were stained with cresyl violet and according to Klüver-Barrera method. Pickworth benzidine method was also applied to evaluate hippocampal vascular network.

Varying susceptibility of individual animals to the ischemic incident was found. This was expressed by differences in the intensity and extent of structural lesions of CA1 pyramidal neurons. No abnormalities were found in 41.7% of animals, total neuronal loss in the CA1 sector was observed in 33.3% of cases, while the partial neuronal loss appeared in the remaining 25% of animals. Asymmetric distribution of the neuronal changes observed in 18.4% of cases was a very striking feature. Differences of the angioarchitectonics of CA1 sector as compared with neighbouring parts of Ammon's horn were found. In the pyramidal cell layer very scarce fragments of the blood vessels were present. In adjacent cortical layers (stratum oriens and stratum radiatum) relatively dense capillary network was characterized by appearance of specific vascular loops and tangles localized on the border of stratum pyramidale.

It is supposed that particular spatial arrangement of the vascular network in pyramidal layer of CA1 sector, favouring appearance of local hemodynamic and rheologic abnoramalities after temporary brain ischemia, may play an essential pathogenic role in both, selective vulnerability of this neuronal population and individual variations in the intensity and distribution of the neuronal changes.

Key words: *temporary brain ischemia, hippocampus, CA1 neurons, selective vulnerability, vascular factor.*

The problem of selective vulnerability of Ammon's horn pyramidal neurons has a long history as far as its pathogenetic mechanism is concerned. The main lines of the discussion on the subject were established by prominent German neuropathologists: C. and O. Vogts (1925) and W. Spielmeyer (1925).

Vogts were linking selective sensitivity of hippocampal pyramidal neurons with their physico-chemical proprieties, using the name of "pathoclisis" to determine their changes induced by pathogenic factors. For Spielmeyer the main pathogenic role was played by vascular factor, indicating special angioarchitectonics in this part of the brain. The extensive studies, carried out in last two decades seem to speak in favour of Vogts pathoclisis concept understood in a modern terms as a complex of metabolic and functional proprieties of the particular groups of pyramidal neurons. The milestones posted along this way were observations indicating different reactions of various Ammon's horn neuronal populations to the same damaging factors, such as for instance, cerebral ischemia (Ito et al. 1975; Kirino 1982) or kainic acid (Nadler et al. 1978), as well as description of the phenomenon called delayed neuronal death, forming a special type of reaction of the pyramidal neurons from Ammon's horn CA1 sector to the short-term forebrain ischemia in Mongolian gerbils (Kirino 1982).

The further studies showed that damage and final breakdown of CA1 pyramidal neurons is preceded by their bioelectric hyperactivity (Suzuki et al. 1983b) with ultrastructural exponents of their metabolic activation (Mossakowski et al. 1989). It has been documented that neuronal hyperactivity is resulting from the influence of excitatory amino acid neurotransmitters, mostly glutamate, followed by intracellular calcium influx, which disturbs essential intracellular metabolic processes leading to irreversible neuronal damage (Drejer et al. 1985; Meldrum et al. 1985). Nociceptive role of excititoxic action of glutamate in this process, dependent on the specific synaptic organization of the CA1 sector (Collingridge et al. 1983) and an early damage of GABA-ergic interneurons (Gajkowska et al. 1989), was proven in experiments revealing cytoprotective effect on the pyramidal neurons of both glutaminergic deafferentiation of the area (Pulsinelli 1985) and application of specific NMDA receptor blockers (Simon et al. 1984).

This well documented theory, connecting specific reaction of CA1 neurons to the short-lasting ischemic insult with their glutaminergic innervation and calcium-induced metabolic alterations does not explain variability of the symmetry and intensity of neuronal damage observed in Mongolian gerbils after bilateral carotid artery occlusion. The asymmetry of neuronal lesions concerning both their extension and intensity, very seldom mentioned by most of the authors working on this experimental model, was relatively common feature in our material (Mossakowski, Gadamski 1985; 1987a, b).

This inclined us to evaluate this question quantitatively and to search for additional factor or factors which could explain this phenomen. We turned our attention to the Spielmeyer's vascular factor, moreover so as morphometric studies of Imdahl and Hossmann (1986) on capillary perfusion of the CA1 sector of Ammon's horn in Mongolian gerbils in normal and postischemic conditions suggested that protracted postischemic perfusion reduction may possibly play a role of an important factor in maturation of pathological changes.

MATERIAL AND METHODS

Experiments were performed on 98 Mongolian gerbils (*Meriones unguiculatus*), breed in animals quarter of the Medical Research Centre of PASci. Three-month-old male animals weighing ca 75 g were used. Transient forebrain ischemia was induced by bilateral common carotid artery ligation under halothane anesthesia in an open gas system consisting of a mixture of 70% of nitrogen and 30% of oxygen. The carotid arteries were exposed and Heifetz or Vasargile clips were placed on both of them for either 5 or 7.5 minutes. The animals were sacrificed by transcardiac perfusion with 10% neutral formalin 5 days after the ischemic insult, performed under ether anesthesia. The brains were postfixed in the perfusion fluid for 5 days and then cut into coronal blocks. Blocks containing dorsal hippocampus were embedded in paraffin. Sections 10 μm thick were stained with cresyl violet and according to the Klüver-Barrera method.

Morphologic observations were evaluated morphometrically by establishing mean number of pyramidal neurons in a 0.3 mm long segment of CA1 sector of Ammon's horn. The mean value was obtain from the total number of neurons in at least three segments of this length in 3 to 5 subsequent histologic sections from each animal. The results were then compared with mean value of CA1 pyramidal neurons in the reference animals (not subjected to any experimental procedure), which was 44.7 ± 2.5 cells. This value was considered to be 100%.

The morphometric categories used were the same as those applied in our previous studies (Mossakowski, Gadamski 1985; 1987a, b). No morphologic changes was when the average number of pyramidal cells was equal to that in the reference animals. Partial neuronal loss was characterized by the presence of varying proportion of the remaining pyramidal neurons. First-degree partial neuronal loss was characterized by 33.0 ± 4.7 cells (73.8%) preserved; second-degree – 23.6 ± 4.1 cells (52.7%) preserved; and third-degree – 15.7 ± 4.3 cells (35.0%) preserved. Total neuronal loss was characterized by replacement of the neuronal layer by proliferating glial cells with either no neurons or one to ten degenerating cells left in the entire CA1 segment.

For evaluation of the vascular network in particular CA1 hippocampal layers, 3 additional animals, not sujected to any experimental procedure, were used. Animals were sacrificed by decapitation under ether anesthesia. Brains were fixed by immersion in 10% neutral formalin and cut in frontal blocks. The blocks containing dorsal hippocampus were cut on freezing microtome. Sixty μm thick free floating sections were stained with benzidine method of Pickworth.

RESULTS

Frequency of morphological alterations of the pyramidal neurons in the CA1 sector was dependent on the duration of the ischemic incident. In the group of animals in which bilateral carotid artery occlusion lasted for 5 min total or

partial loss of pyramidal neurons with accompanying astrocytic proliferation was observed in 50% of cases. The ischemic incident lasting 7.5 min resulted in an increased proportion of damaged animals to 83.3%. Time-dependent differences in the intensity of the neuronal damage were also observed.

The mean data obtained from the whole experimental material comprising animals with 5 and 7.5 min forebrain ischemia were as follows:

– unchanged neuronal population in CA1 sector was observed in 41.7% of cases,

– total loss of CA1 pyramidal neurons was present in 33.3% of animals,

– partial neuronal loss of different degree was found in 25.0% of cases.

In 81.6% of animals with neuronal abnormalities in CA1 sector, the pathological changes were bilateral and symmetrical in their extent and intensity. In the remaining 18.4% asymmetrical distribution of CA1 sector changes was found. Four patterns of these abnormalities were distinguished:

1) entirely normal appearance of CA1 sector on one side with total neuronal loss on the contralateral side (Fig. 1),

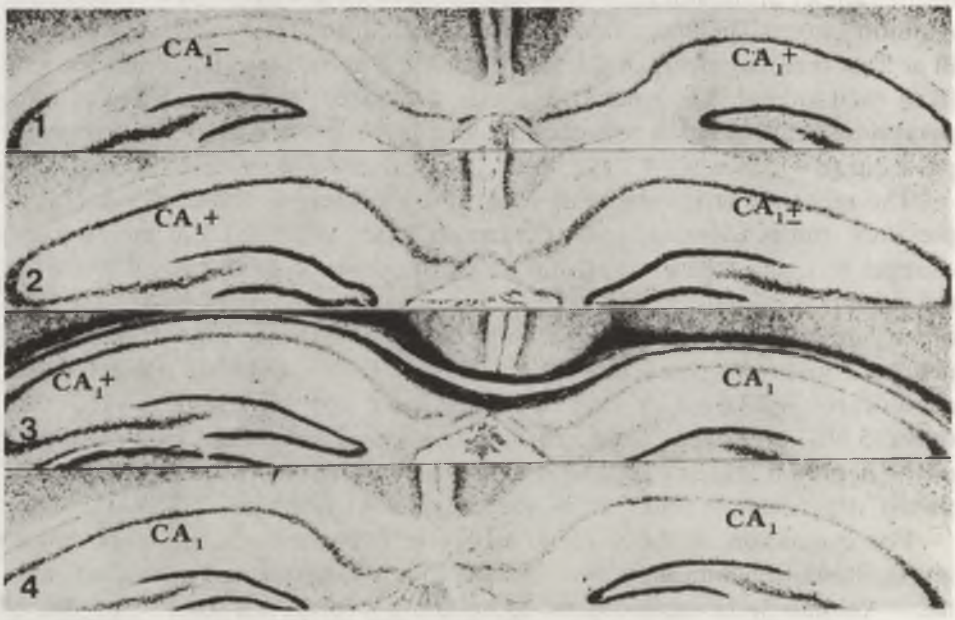

Fig. 1. Exp. animal: 5-min ischemia, 5-day survival. On the left side total loss of CA1 pyramidal neurons (CA_1-) with consecutive glial proliferation. On the right side unchanged neuronal population in the CA1 sector (CA_1+). Cresyl violet. × 60

Fig. 2. Exp. animal: 5-min ischemia, 5-day survival. On the left side entirely normal CA1 sector (CA_1+), on the contralateral side loss of *ca* 50% of pyramidal neurons ($CA_1\pm$). Cresyl violet. × 60

Fig. 3. Exp. animal: 7.5-min ischemia, 5-day survival. On the left side lateral half of the CA1 sector with entirely normal pyramidal cell population (CA_1+). Neuronal loss in the medial half and in the entire CA1 sector on the contralateral side. Klüver-Barrera. × 60

Fig. 4. Exp. animal: 7.5-min ischemia, 5-day survival. On the left side only 50% of CA1 sector pyramidal neurons are preserved, on the right side only 30% of neurons with normal morphological appearance. Cresyl violet. × 60

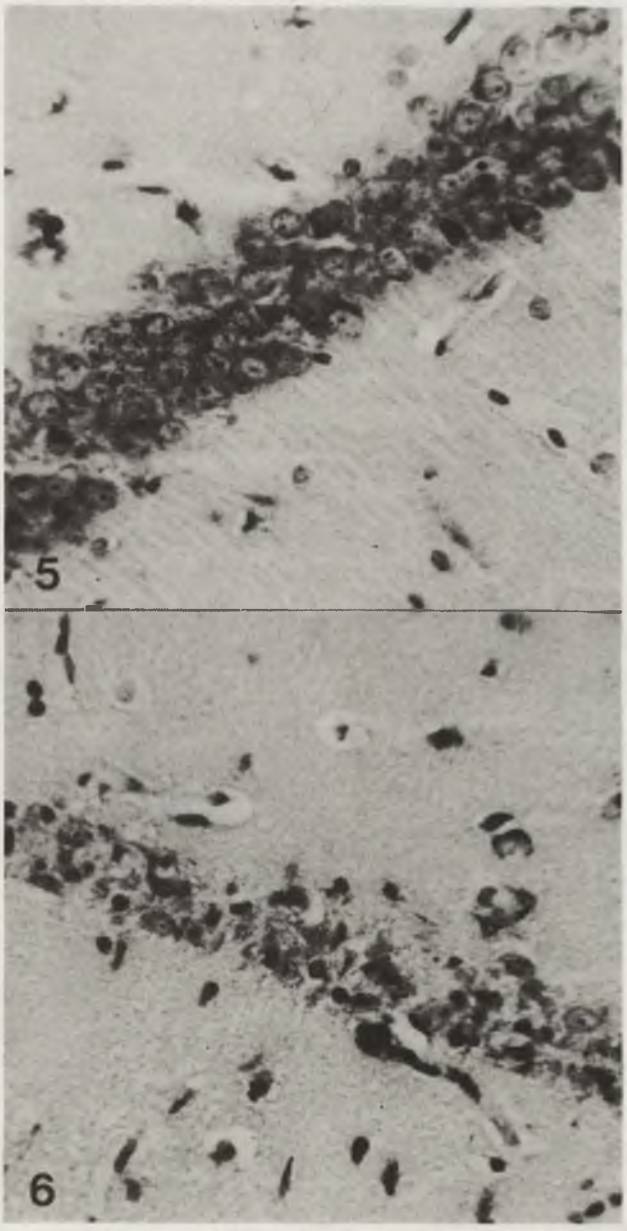

Fig. 5. Exp. animal: 7.5-min ischemia, 5-day survival. Normal population of CA1 sector. Cresyl violet. × 400

Fig. 6. Exp. animal: 5-min ischemia, 5-day survival. Pathological process totally mature: former pyramidal cell layer replaced by proliferating astrocytic glia. Cresyl violet. × 400

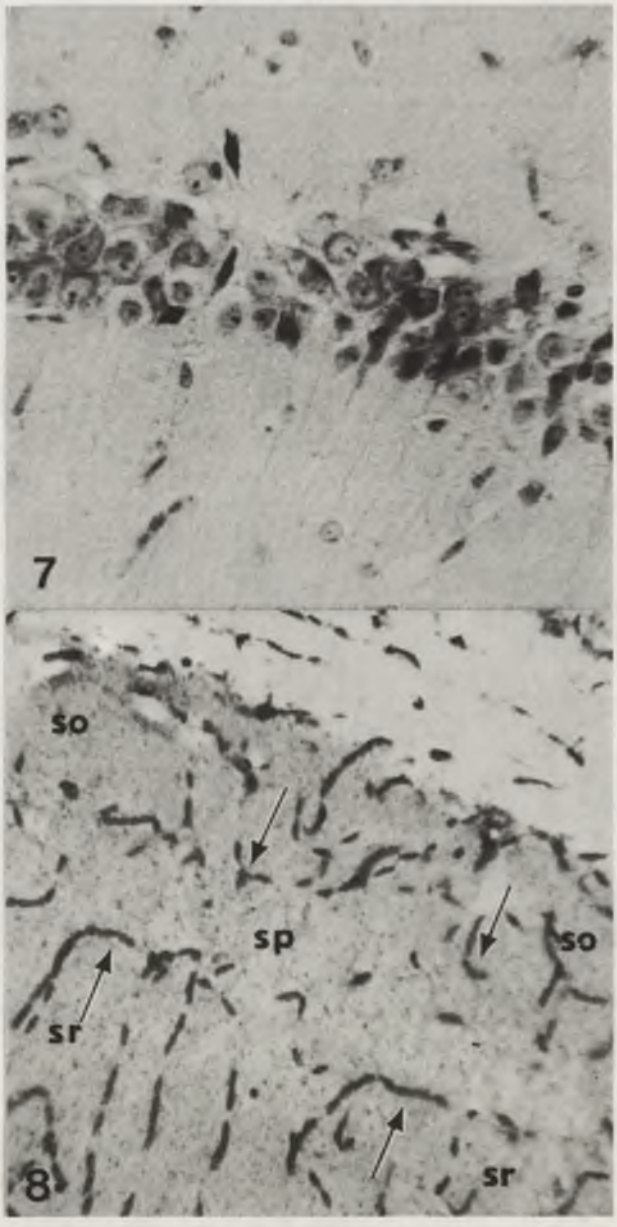

Fig. 7. Exp. animal: 5-min ischemia, 5-day survival. Immature pathological process: between normal pyramidal cells numerous neurons with feature of various types of degeneration. Cresyl violet. × 400

Fig. 8. Control animal. In the vascular network of *stratum oriens* (so) and *stratum radiatum* (sr) on the border of *stratum pyramidale* (sr) characteristic capillary loops (arrow) are visible. Scarce capillaries penetrating *stratum pyramidale*. Pickworth method. × 400

2) preserved pyramidal cells of CA1 sector on one side and their partial loss, ranging from 30 to 75% in the opposite hemisphere (Fig. 2),

3) total neuronal loss in the medial part of CA1 sector with normal appearance of its lateral half in one hemisphere and either normal or totally damaged neuronal population on the other side (Fig. 3),

4) partial, although varying in degree, loss of CA1 pyramidal neurons in both hemispheres (Fig. 4).

The asymmetry of neuronal loss was accompanied in some animals by remarkable variances in maturation rate of the pathological process. Except cases, in which no pathological changes of CA1 sector pyramidal neurons were present (Fig. 5), in most of the animals with the neuronal abnormalities, the pathological process reached full maturation, understood as either total or partial neuronal loss with accompanying astroglial proliferation (Fig. 6), within 5 days after brain ischemia. However, in 20% of these animals maturation of the pathological process seemed to be extended beyond this period, as indicated by differences in morphological picture of CA1 pyramidal neurons. On the background of highly rarefied pyramidal cell population, alongside with normally looking neurons, numerous pyramidal cells with features of degeneration (shrinkage, hyperchromasia, central chromatolysis of different intensity) were present (Fig. 7).

Benzidine staining visualized characteristic structure of hippocampal vascular network. In the CA1 sector it was moderately dense in both cortical layers neighbouring pyramidal cell bodies and strikingly scanty in the pyramidal layer (Fig. 8). Radially oriented vessels of *stratum radiatum* when approaching pyramidal layer binded in a characteristic way forming loops. Identical arrangement of capillaries was typical for *stratum oriens*. In *stratum pyramidale*, containing densely packed cell bodies of pyramidal neurons, only very few fragments of capillaries passing between them were seen. This sharply contrasted with other sectors of Ammon's horn in which relatively dense net of capillaries was observed in less populated pyramidal layers.

DISCUSSION

The results of our studies, contrary to the observation of Suzuki et al. (1983a, b), indicate that damage and loss of the pyramidal neurons in the CA1 sector of Ammon's horn is not a permanent finding in the temporary forebrain ischemia in the Mongolian gerbils. Data presented in this paper, are based on large and sufficient for statystical analysis number of observations to prove a marked variability of individual susceptibility of Mongolian gerbils to the ischemic incident, the phenomenon stressed by us in our earlier papers (Mossakowski, Gadamski 1985; 1987a, b). In the search for explanation of differences in the picture and extent of morphological damage to the CA1 sector neurons, first comes the question whether the operation was correctly performed, above all, whether the temporary closure of the common carotid

arteries was complete. The possibility of such a technical error seems to be excluded by the construction of Heifetz and Vasargil clips. The main argument, however, against reservations of this kind seem to be the asymmetrical lesions observed in our material. In this respect particularly noteworthy are cases in which, after 5 or 7.5 min of ischemia, neuronal loss was limited to the proximal half of the CA1 sector, whereas its distal half and the whole sector on the contralateral side remained intact. This type of asymmetry seems most convincing and ruling out completely any technical incorrectness.

The other factor underlaying great differences in our material may result from origin of animals from our own breeding, conducted on the principle of flock not strain, in which the use of a sibling population is rigorously excluded, and only distant relatives are used. It is possible that this way of breeding favours appearance of malformations, characteristic for this species in the intra- and extracerebral vascular network. This may find its reflection in the individually differentiated susceptibility to ischemia.

Our observations seem to indicate that severe damage of the pyramidal neurons should not be exclusively attributed to their special susceptibility to the ischemic incident as generally accepted in the literature, but in addition to the specific angioarchitectonics of CA1 sector. Particularly noteworthy is the dense cell arrangement in this segment, which hardly finds parallel not only in the remaining sectors of Ammon's horn but also in other parts of the CNS. The number of perfusing capillaries is found to be inversely proportional to the density of the neurons. The number of capillaries in the CA1 sector in Mongolian gerbils is 20% lower than in the neighbouring CA3 sector and in the cerebral cortex (Imdahl, Hossmann 1986). Similarly, Weiss et al. (1982) demonstrated on the basis of morphometric analysis, a remarkably lower density of the capillary network in the Ammon's horn in the rats as compared with that in the cerebral cortex. Quantitative differences in vascularization of particular hippocampal segments, demonstrated by Imdahl and Hossmann (1986) are supplemented by the specific configuration of capillaries, as visualized in our benzidine preparations, where they form loops in the hippocampal layers adjacent to pyramidal neurons. Such a configuration of capillaries may be conductive to the turbulence of the morphotic blood elements leading finally to the formation of microthrombi disturbing or totally blocking blood perfusion in the postischemic period. It seems that the microthrombi in these conditions are not transient thrombocyte aggregations, but are of an irreversible nature. This contension was supported by further observations of Imdahl and Hossmann (1986), who demonstrated that reduced volume of circulating blood in the CA1 sector persisted with a tendency to aggravation in time, up to the 7th day after transient forebrain ischemia in Mongolian gerbils.

Assuming the importance of the above mentioned hemodynamic disturbances in the development of morphological abnormalities in the CA1 sector, some additional factors resulting from brain ischemia should be taken into

consideration. These concern mostly the reaction of blood platelets. Drastic reduction of blood supply to the brain due to bilateral ligation of the carotid artery evokes a chain of functional and metabolic reactions, both local and systemic. Autoregulatory mechanisms set up in these pathological conditions result among others, in remarkable changes in the level of numerous biologically active substances such as adenosine, serotonin, catecholamines and others, which besides other consequences, may activate cell membranes of the blood platelets. This in turn, evokes a series of cellular reactions, including calcium ion translocation, changes in the adenyl cyclase activity, resulting in altered cyclic-AMP content as well as changes in the phospholipase activity reflecting on the functional state of the cell membrane, synthesis of prostaglandins and a number of other processes (Detwiler et al. 1978; Fitzpatrick, Gorman 1979; Serutton, Egan 1979). All those changes lead to the formation of thrombocyte aggregates and microthrombi both in the CNS and in other body organs. Hossmann et al. (1980) describing the relatively frequent appearance of microthrombi in various body organs as a consequence of brain ischemia, stressed their exceptional occurrence in the CNS. On the other hand, Pluta et al. (1992) had recently demonstrated the formation of microthrombi in the cerebral blood vessels resulting from global cerebral ischemia of the CNS. They were randomly distributed in various brain structures. Pluta (1992) believes that this pathological process is connected with disturbed functional balance between tromboxan and prostacyclin, reflecting altered relations between platelets and vascular endothelium.

The above mentioned mechanism referring to the hemodynamic and rheologic alterations as a pathogenic factors in the development of the ischemic brain damage, due to their general nature, can not explain by themselves selective involvement of the CA1 sector of Ammon's horn. However, concomitance of scarcity of vascularization and spacial arrangement of vascular network specific for this area, facilitating local hemodynamic disturbances on one hand, and changes in the functional state of thrombocytes on the other, may favor selective damage of the CA1 pyramidal neurons, exposed due to their innervation on the action of excitotoxic amino acid neurotransmitters. The participation of vascular factor seems to explain observed variations in the intensity and extent of cellular lesions. In that context we should admitt that the protective action of indomethacin, prostacyclin and calcium channel blocker – nimodipine against ischemic lesions of CA1 pyramidal neurons, observed in our previous studies (Mossakowski, Gadamski 1985; 1987a, b) can be, at least in part, attributed to the influence of these substances on the hemodynamic and rheologic changes occurring in this area.

Therefore, it seems justified to come back to the old neuropathological discussion concerning the role of metabolic and functional as well as vascular factors in the pathogenesis of the selective vulnerability of CA1 sector. The specific angioarchitectonics of this hippocampal structure facilitating local hemodynamic and rheologic abnormalities may play an important role in this process.

ASYMETRYCZNE USZKODZENIA ODCINKA CA1 ROGU AMONA PO KRÓTKOTRWAŁYM NIEDOKRWIENIU MÓZGU U CHOMIKÓW MONGOLSKICH

Streszczenie

Badania przeprowadzono na 98 trzymiesięcznych chomikach mongolskich, u których wywoływano 5- lub 7,5-minutowe niedokrwienie mózgu przez podwiązanie obu tętnic szyjnych. Czas przeżycia zwierząt po niedokrwieniu wynosił 5 dni. Parafinowe skrawki mózgu barwiono fioletem krezylu i wg metody Klüvera-Barrery. Oceniono również metodą benzydynową Pickwortha sieć naczyniową w hipokampie chomików nie poddanych żadnym zabiegom doświadczalnym.

Wykazano znaczne zróżnicowanie osobnicze wrażliwości zwierząt na niedokrwienie mózgu wyrażające się różnicami nasilenia strukturalnych uszkodzeń odcinka CA1 rogu Amona. U 41,7% zwierząt nie stwierdzono w tym obszarze żadnych zmian neuronalnych. Całkowity zanik neuronów CA1 stwierdzono u 25% zwierząt. Na szczególną uwagę zasługiwała niesymetryczność uszkodzeń komórek piramidowych sektora CA1 obserwowana w 18,4% przypadków.

Wykazano różnice angioarchitektoniki odcinka CA1 w porównaniu z sąsiednimi obszarami hipokampa. W warstwie piramidowej sektora CA1 występowały jedynie pojedyncze naczynia krwionośne. W przylegających do komórek piramidowych warstwach granicznej i promienistej tego sektora wykazano obecność charakterystycznych łuków i skrętów naczyń położonych na tle stosunkowo gęstej sieci kapilarnej. Były one nagromadzone na pograniczu warstwy komórek piramidowych.

Wysunięto przypuszczenie, iż specyficzne ukształtowanie przestrzenne sieci naczyniowej w sektorze CA1, sprzyjające miejscowym zaburzeniom hemodynamicznym w następstwie przebytego niedokrwienia mózgu, może stanowić istotny czynnik patogenetyczny kształtujący zarówno wybiórczą wrażliwość na niedokrwienie komórek piramidowych tego odcinka, jak i zróżnicowaną intensywność i rozległość uszkodzeń neuronalnych.

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