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ULTRASTRUCTURE OF NEURONS FROM THE CA_1 SECTOR OF AMMON'S HORN IN SHORT-TERM CEREBRAL ISCHEMIA IN MONGOLIAN GERBILS**

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Neurons of CA_1 sector of dorsal hippocampus are selectively vulnerable to cerebral ischemia. Their unique property as compared to other vulnerable brain areas, consists in a delayed pathological reaction, appearing several days after ischemic incident (Kirino 1982; Pulsinelli et al. 1982; 1984, 1985; Kirino et al. 1984a,b, 1985; Kirino, Sano 1984a; Yamaguchi, Klatzo 1984). As such it has been considered by some of the above mentioned authors as a novel type of neuronal alteration and distinguished under the name of delayed neuronal death (Kirino 1982; Kirino et al. 1984a,b). CA_1 neuronal damage and death are preceded by a relatively long period of bioelectric hyperactivation (Suzuki et al. 1983b, 1985). It has been postulated that lesion of CA_1 neurons is related to their specific synaptic innervation and may result from excitotoxic action of some amino acid neurotransmitters, mostly glutamate, released in excess during and/or after ischemic incident (Kirino et al. 1985; Pulsinelli 1985; Suzuki et al. 1985).

Delayed damage to CA_1 neurons as a result of short-term cerebral ischemia has been found both in Mongolian gerbils (Ito et al. 1975; Kirino 1982; Kirino et al. 1984b) and in rats (Pulsinelli, Brierley 1979; Pulsinelli et al. 1982; Kirino et al. 1984a). Its ultrastructural characteristics have been presented in the papers of Kirino et al. (1984b), Kirino and Sano (1984) and Petito and Pulsinelli (1983, 1984).

Some discrepancies in electron microscopic findings in both rodent species

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inclined us to repeat ultrastructural analysis of CA_1 neurons in the course of their damage due to short-term ischemia in Mongolian gerbils, with special reference to the state of their synaptic contacts. The literature concerning the latter is relatively scanty.

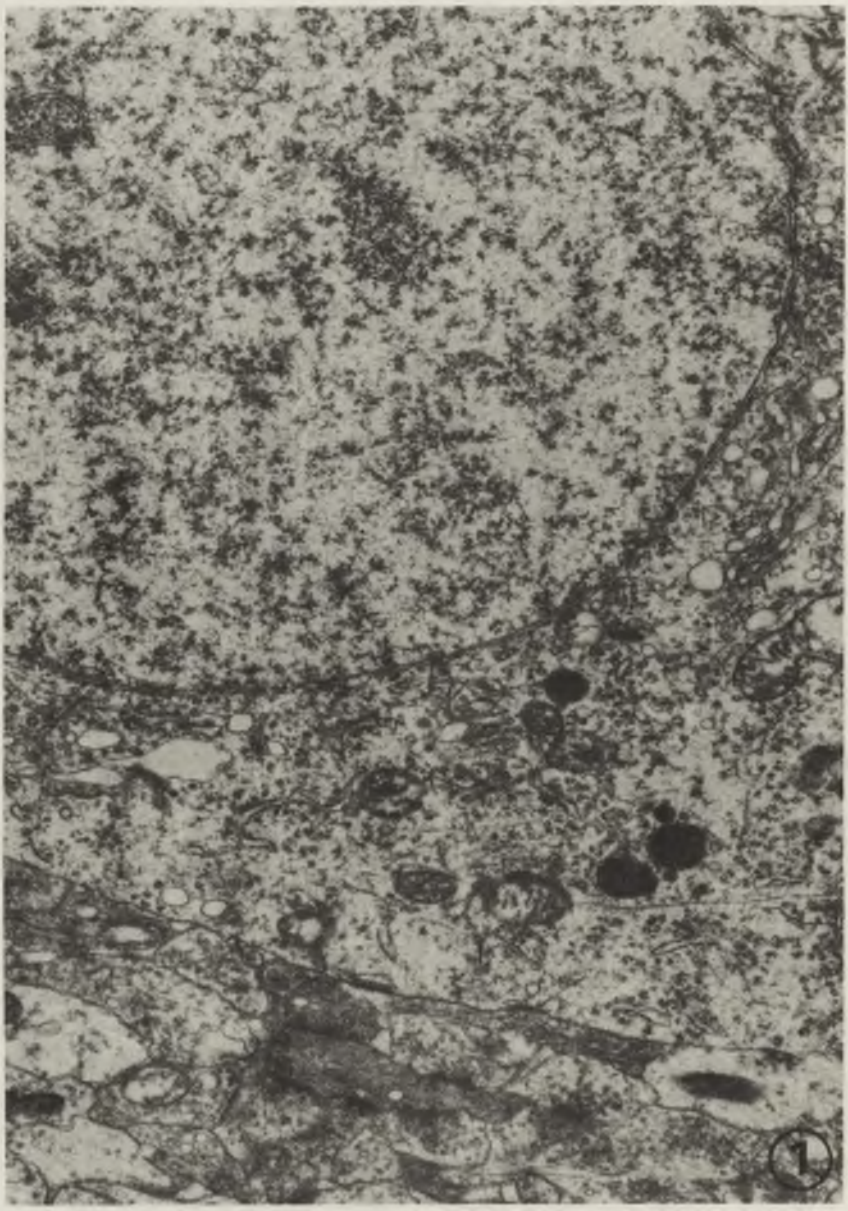

Fig. 1. Control animal. Electron microscopic picture of CA_1 pyramidal neuron. × 15300
Ryc. 1. Zwierzę kontrolne. Obraz mikroskopowo-elektronowy komórki piramidowej sektora CA_1 rogu Amona. Pow. 15300 ×

MATERIAL AND METHODS

Experiments were carried out on adult Mongolian gerbils weighing 70-80 g, which were subjected to short-term forebrain ischemia by occlusion of both common carotid arteries under halotan anesthesia. Common carotid arteries were exposed bilaterally through a midline cervical incision and Heifetz clips were put on both of them for 7.5 min. After that clips were removed for recirculation of the brain.

The animals were sacrificed in groups of 3 (1 control and 2 experimental) by transcardiac perfusion with 2.5 percent solution of glutaraldehyde in 0.1 M cacodylate buffer, pH 7.4 at 1, 2, 3, 4 and 5 days after the ischemic incident. Blocks of tissue containing all hippocampal layers were taken from CA_1 sector of dorsal Ammon's horn. They were additionally fixed for 1 h in 4 percent glutaraldehyde solution, washed in 0.1 M cacodylate buffer and then postfixed for 1 h in 2 percent osmium tetroxide in cacodylate buffer. They were dehydrated routinely in alcohol solutions, transfered to propylen oxide and embedded in Epon 812. Ultrathin sections were counterstained in uranyl acetate and lead citrate. Electron microscope JEM 7A was used for studies.

The electron microscopic observations in experimental animals were referred to the pictures from normal material of animals not subjected to any experimental procedure.

RESULTS

Normal pyramidal neurons of CA_1 sector, occupying dorsal hippocampus are ultrastructurally characterized by large typical neuronal nuclei and abundant cytoplasm rich in organelles such as rough endoplasmic reticulum, polyribosomes, medium-size mitochondria, well developed Golgi complex and relatively numerous lysosomes (Fig. 1). Their apical dendrites passing through *stratum radiatum* in the form of strong dendritic shafts with scanty dendritic spines, arborize profusely while reaching *stratum lacunosum moleculare* and *moleculare* where they form numerous synaptic contacts with axonal endings of different origin (Fig. 2).

During the first postischemic day CA_1 pyramidal neurons reveal marked dilatation of rough endoplasmic reticulum channels, containing delicate floccular material. So are cisternae and channels of Golgi complex. Some of the widened fragments of rough endoplasmic reticulum channels are deprived of ribosomes. A great part of the mitochondria appear normal. Axosomatic synapses surrounding neuronal perikarya are densely filled with small, round, light vesicles (Fig. 3), so are axodendritic synapses in *stratum lacunosum moleculare* (Fig. 4).

On the second day after ischemia, a great proportion of pyramidal neurons resemble those observed in the first day with a remarkable dilatation of the Golgi complex (Fig. 5). The new findings consist in the appearance of irregular agglomerations of electron dense material unbound by cytomembranes in the

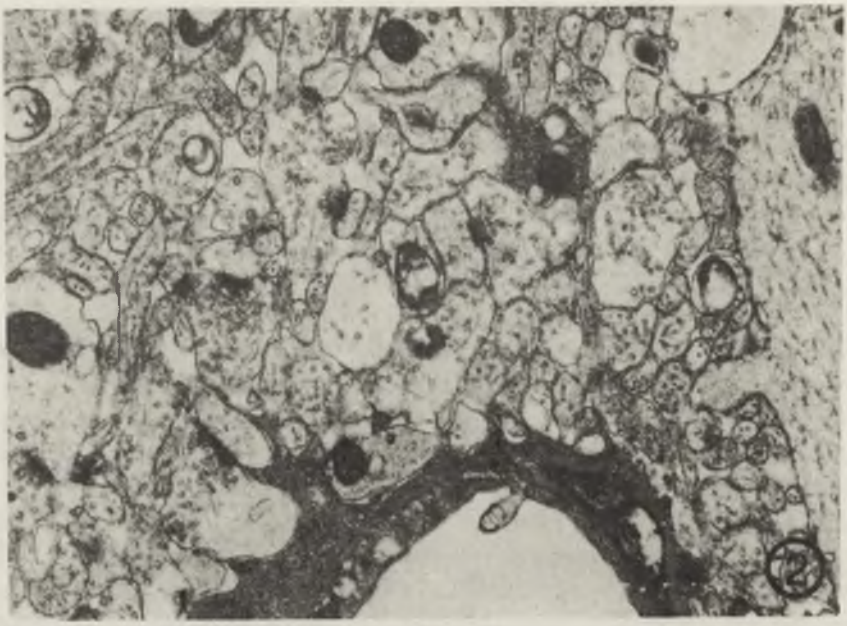

Fig. 2. Control animal. Numerous axodendritic and axospinal contacts in *stratum lacunosum moleculare* of CA_1 sector of Ammon's horn. × 9250

Ryc. 2. Zwierzę kontrolne. Liczne synapsy akso-dendrytyczne i aksonalno-kolcowe w warstwie zatokowo-drobinowej sektora CA_1 rogu Amona. Pow. 9250 ×

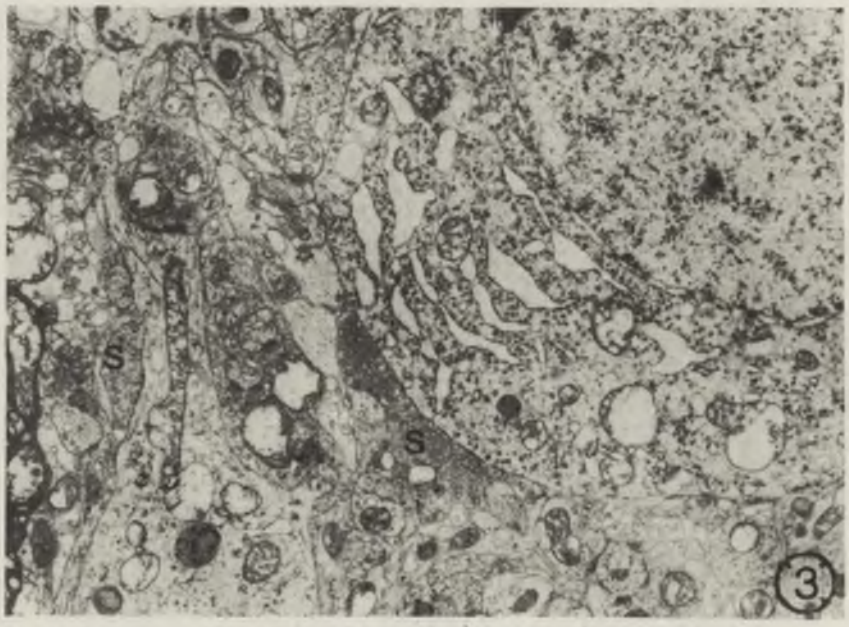

Fig. 3. Experimental animal — 1 day after ischemia. CA_1 pyramidal neuron with dilated channels of rough endoplasmic reticulum, containing floccular material. Some mitochondria in neuronal perikaryon and in neuropil elements are well preserved. Presynaptic bags (s) filled with spherical vesicles. × 8650

Ryc. 3. Zwierzę doświadczalne — 1 dzień po niedokrwieniu. Komórka piramidowa sektora CA_1 rogu Amona wykazująca znaczne poszerzenie kanałów szorstkiej siateczki śródplazmatycznej, zawierających kłaczkowaty materiał. Znaczna część mitochondriów w perykarionie neuronu i w elementach neuropilu nie wykazuje nieprawidłowości strukturalnych. Akso-somatyczne i akso-dendrytyczne zakończenia nerwowe (s) wypełnione okrągłymi pęcherzykami synaptycznymi. Pow. 8650 ×

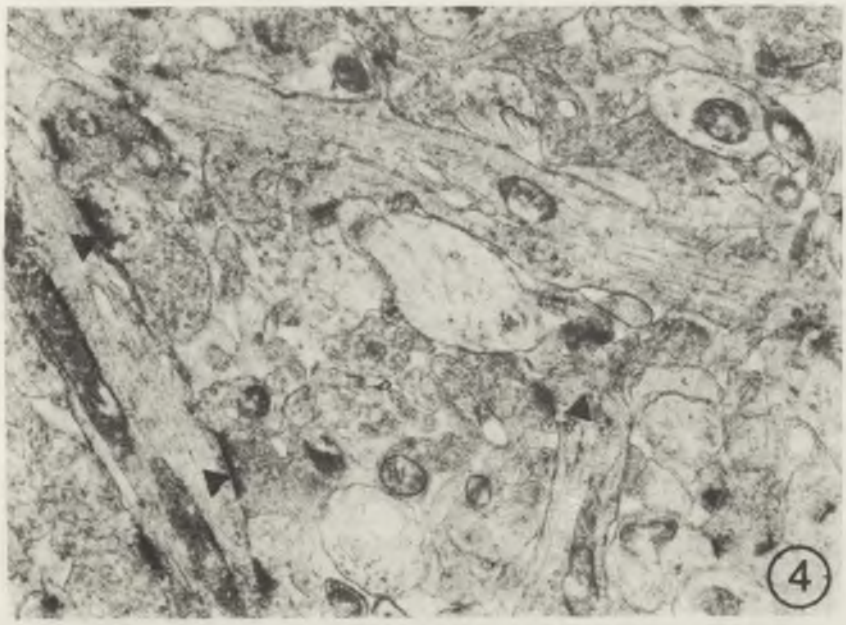

Fig. 4. Experimental animal — 1 day after ischemia. *Stratum lacunosum moleculare* with numerous axodendritic synapses with well preserved pre- and postsynaptic parts (arrows) × 9250

Ryc. 4. Zwierzę doświadczalne — 1 dzień po niedokrwieniu. Warstwa zatokowo-drobinowa sektora CA_1 rogu Amona z licznymi synapsami akso-dendrycznymi o dobrze zachowanych częściach pre- i postsynaptycznych (strzałki). Pow. 9250 ×

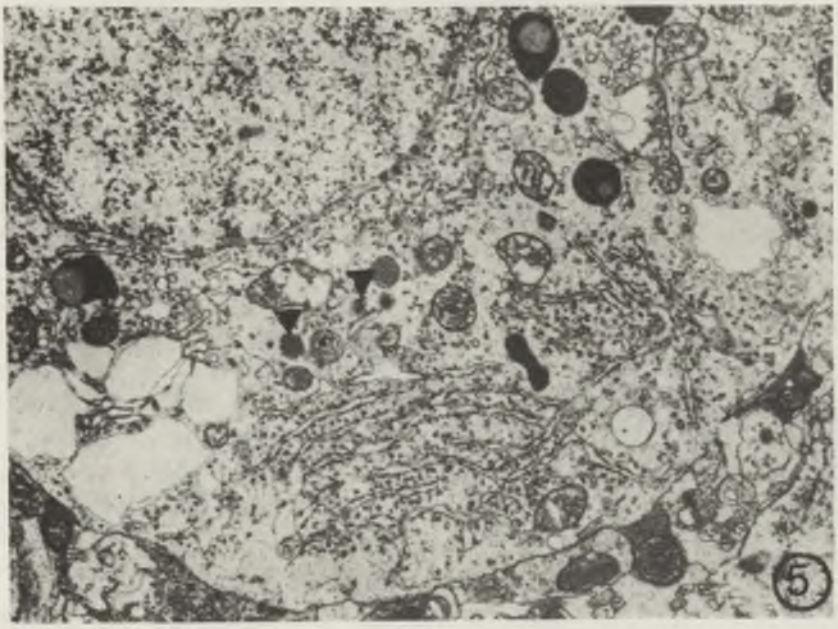

Fig. 5. Experimental animal — 2 days after ischemia. Pyramidal CA_1 neuron with well preserved mitochondria, greatly distended Golgi complex and groups of parallelly arranged channels of rough endoplasmic reticulum. Small clusters of dense material not bound by cytomembranes are visible in the neuronal cytoplasm (arrows). Note numerous dense bodies. × 8650

Ryc. 5. Zwierzę doświadczalne — 2 dni po niedokrwieniu. Piramidowa komórka nerwowa z sektora CA_1 z dobrze utrzymanymi mitochondriami, znacznie poszerzonymi zbiornikami zespołu Golgiego i grupami szeregowo ułożonych kanałów szorstkiej siateczki śródplazmatycznej. Drobne skupienia nieobłonionego elektronowo gęstego materiału (strzałki) zawarte są w cytoplazmie neuronu. Zwróć uwagę na obfite ciała gęste. Pow. 8650 ×

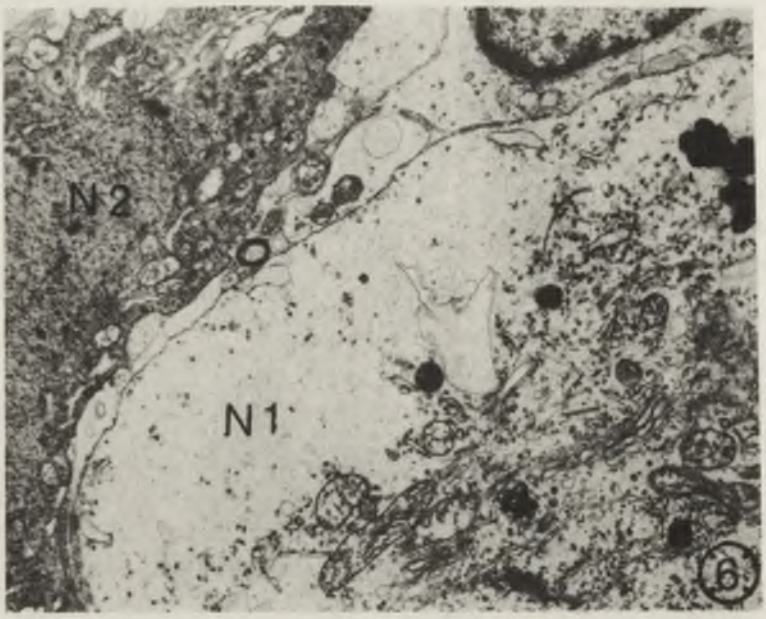

Fig. 6. Experimental animal — 2 days after ischemia. Fragments of two pyramidal neurons. Cytoplasm periphery of the first neuron (N^1) is devoid of organelles, which are grouped in perinuclear area. Fragmentation and denudation of channels of rough endoplasmic reticulum. Note prevalence of free ribosomes. Golgi complex well developed and remaining mitochondria are relatively well preserved. The second neuron (N^2) with features of typical ischemic changes. × 8650

Ryc. 6. Zwierzę doświadczalne — 2 dni po niedokrwieniu. Fragmenty dwóch piramidowych komórek nerwowych. Cytoplazma na obwodzie pierwszej z nich (N^1) pozbawiona jest całkowicie organelli skupionych w okołojądrowym polu cytoplazmy. Kanały szorstkiej siateczki śródplazmatycznej są pofragmentowane i w znacznej części pozbawione rybosomów. Przeważają wolne rybosomy. Aparat Golgiego jest mocno rozbudowany a zachowane mitochondria niezmienione. Druga komórka nerwowa (N^2) wykazuje typowe cechy zwyrodnienia niedokrwiennego. Pow. 8650 ×

neuronal cytoplasm (Fig. 5) and marked disaggregation of polyribosomes. Moreover, numerous pyramidal neurons reveal features of complete or partial disintegration of rough endoplasmic reticulum, mostly on the cell periphery. It is worth of mentioning that even in those neurons a great proportion of mitochondria are relatively well preserved. Among so altered neurons, some cells with typical ischemic changes are seen (Fig. 6). Most of the terminal boutons around neuronal perikarya are devoid of synaptic vesicles. Contrary to this synaptic terminals on scanty spines of dendritic shafts in *stratum radiatum* look normal (Fig. 7). Interneurons localized in *stratum oriens* appear unchanged.

On the third day most of the pyramidal neurons show features of far advanced disintegration of cytoplasm, concerning mostly endoplasmic reticulum and polyribosomes, with relatively good preservation of mitochondria. In numerous of them multilamellar structures appear, formed by membranes of

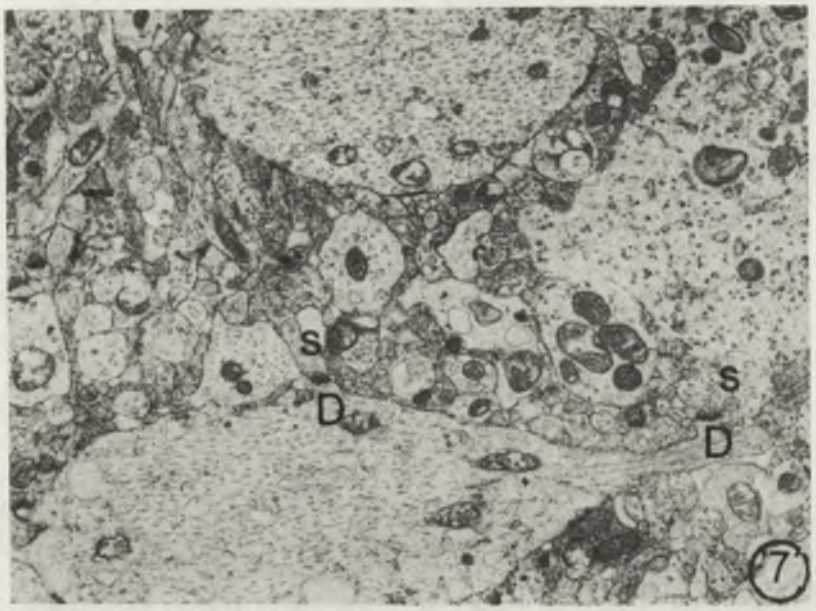

Fig. 7. Experimental animal — 2 days after ischemia. *Stratum radiatum*: Two dendritic shafts surrounded by apparently normal synaptic bags. S — synapses, D — dendritic spines. × 8650

Ryc. 7. Zwierzę doświadczalne — 2 dni po niedokrwieniu. Warstwa promienista. Dwa pnie dendrytyczne otoczone niezmienionymi zakończeniami nerwowymi. S — synapsy, D — kolce dendrytyczne. Pow. 8650 ×

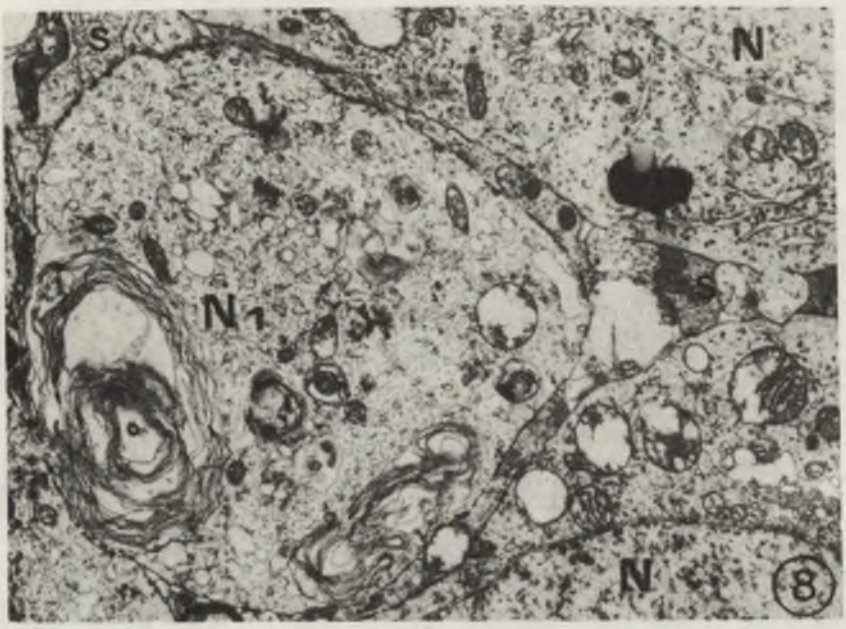

Fig. 8. Experimental animal — 3 days after ischemia. Fragments of 3 abnormal pyramidal cells (N) one of which (N_1) contains several multilamellar structures showing continuity with endoplasmic reticulum. Abundant free ribosomes are seen in cytoplasm. S — synapses. × 6650

Ryc. 8. Zwierzę doświadczalne — 3 dni po niedokrwieniu. Fragmenty 3 uszkodzonych komórek piramidowych (N). Jedna z nich (N_1) zawiera kilka ciał wieloblaszkowych, wykazujących łączność z siateczką śródplazmatyczną. W cytoplazmie widoczne są liczne wolne rybosomy niezwiązane ze strukturami siateczki śródplazmatycznej. S — synapsy. Pow. 6650 ×

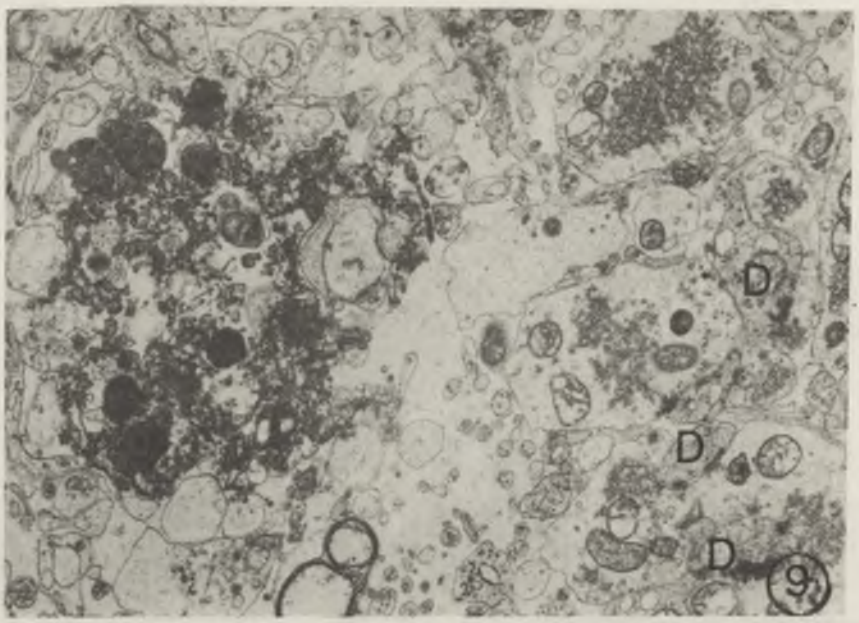

Fig. 9. Experimental animal — 4 days after ischemia. Clumps of cellular debris in the neuropile. Numerous synaptic bags without vesicles or abnormal vesicular arrangement. D — dendritic spines. × 8650

Ryc. 9. Zwierzę doświadczalne — 4 dni po niedokrwieniu. Skupienia produktów rozpadu komórkowego w neuropilu. Liczne zakończenia synaptyczne pozbawione pęcherzyków lub z nieprawidłowym układem pęcherzyków. D — kolce dendrytyczne. Pow. 8650 ×

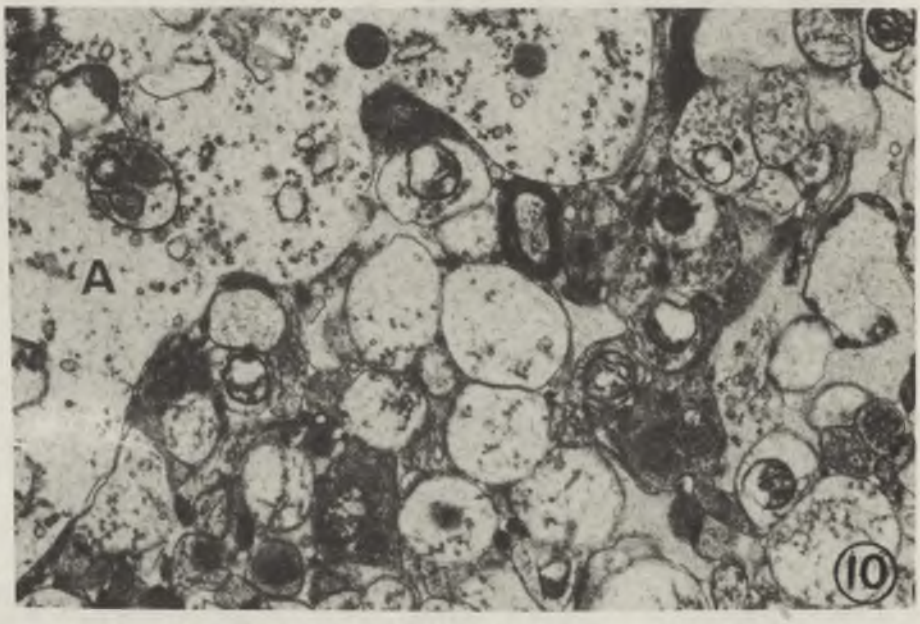

Fig. 10. Experimental animal — 4 days after ischemia. Severely damaged synaptic contacts in *stratum lacunosum moleculare* and fragment of swollem astrocyte (A). × 9250

Ryc. 10. Zwierzę doświadczalne — 4 dni po niedokrwieniu. Ciężko uszkodzone zespolenia synaptyczne w warstwie zatokowo-drobinowej oraz znacznie obrzmiała cytoplazma astrocyta (A). Pow. 9250 ×

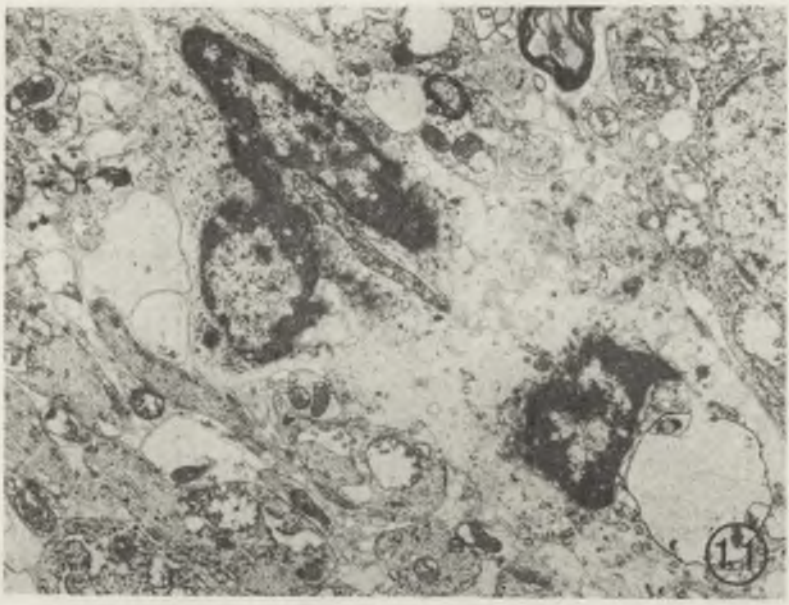

Fig. 11. Experimental animal — 5 days after ischemia. Dividing astroglial cell. × 8250
Ryc. 11. Zwierzę doświadczalne — 5 dni po niedokrwieniu. Dzieląca się komórka glejowa. Pow. 8250 ×

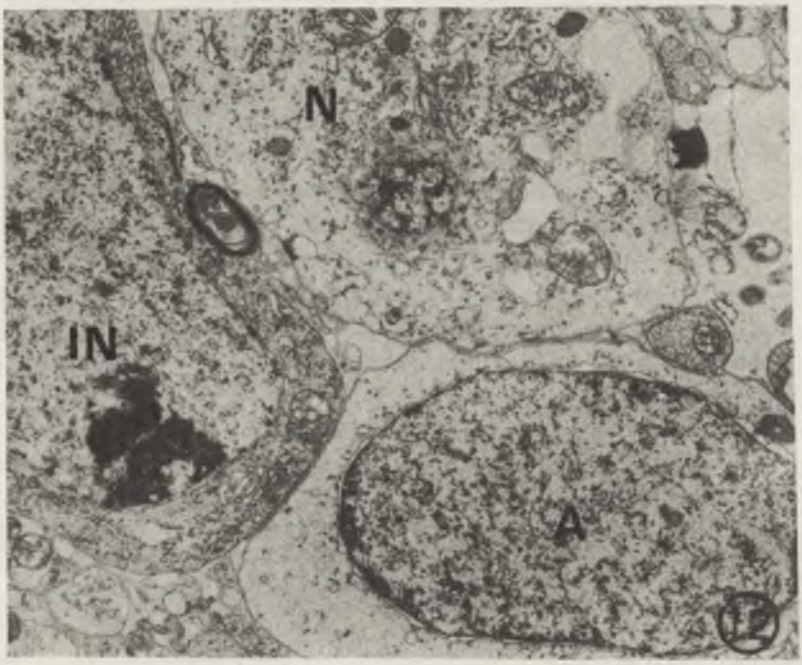

Fig. 12. Experimental animal — 5 days after ischemia. Fragments of degenerated pyramidal CA_1 neuron (N) and astrocyte (A) alongside with unchanged interneuron (IN). × 6800
Ryc. 12. Zwierzę doświadczalne — 5 dni po niedokrwieniu. Fragmenty uszkodzonego neuronu piramidowego (N), astrocyta (A) oraz niezmienionego interneuronu (IN). Pow. 6800 ×

endoplasmic reticulum, devoid of ribosomes (Fig. 8). Alongside typical ischemic neurons are present.

The fourth postischemic day is characterized by the appearance of numerous aggregations of cellular debris. The number of synaptic vesicles in the neighbouring axonal endings is greatly reduced and the arrangement of the residual ones is abnormal (Fig. 9). Synaptic contacts in *stratum lacunosum moleculare* are practically nonexistent (Fig. 10).

On the fifth postischemic day features of astroglial proliferation are prevailing. Some dividing astrocytes are seen (Fig. 11). Very seldom remnants of disintegrated pyramidal neurons, unchanged interneurons and swollen astrocytes lying alongside are seen (Fig. 12).

DISCUSSION

Our observations indicate that fine structural changes in the pyramidal CA_1 neurons of dorsal hippocampus following short-term forebrain ischemia are biphasic in nature.

The first stage appearing in the first postischemic day consists in morphological exponents of cell activation expressed by remarkable dilatation of channels of rough endoplasmic reticulum and cisternae of Golgi apparatus, containing delicate floccular material, above norm accumulation of ribosomes and increased contents of vesicles in all synaptic contacts of the pyramidal neurons, first of all in those formed on the dendritic arborizations in *stratum lacunosum moleculare* and neuronal somata in *stratum pyramidale*. The former are considered to be in a great proportion excitatory synapses with nerve endings from Schaffer's collaterals, originating in CA_3 sector (Andersen et al. 1966; Wieraszko 1983) while the latter represent inhibitory synapses with axon terminals of basket interneurons (Andersen et al. 1963).

The second stage, beginning on the second postischemic day is characterized by the appearance of exponents of the cellular damage, leading inevitably to neuronal disintegration and breakdown, observed on the fourth and fifth days after ischemia. These neuronal abnormalities corresponding to alterations described as features of delayed neuronal death are essentially different from typical ischemic changes, characterized by severe mitochondrial swelling, remarkable widening of rough endoplastic reticulum structures concomitant with condensation of ergastoplasm (Brown, Brierley 1972). Three components of typical fine structural picture of damaged CA_1 pyramidal neurons are to be pointed out: 1. relatively good preservation of mitochondria throughout almost the whole course of the cellular damage, ending with total breakdown of neuron, 2. dominating changes of endoplasmic reticulum taking the form of either ribosomal depletion and parallel arrangement of denuded endoplasmic membranes leading to the appearance of multilamellar formations with dlsaggregation of polyribosomes to monoribosomes or generalized fragmentation of endoplasmic reticulum and/or its disappearance; 3. in-

tracytoplasmic aggregation of unbound electron dense material, considered by Kirino and Sano (1984a,b), Petito and Pulsinelli (1983) and Pulsinelli (1985) as calcium deposits. Neuronal disintegration prevailing in further stages of the pathological process is accompanied with astrocytic proliferation.

Alongside with so damaged neurons, pyramidal cells with well-defined typical ischemic changes are present. Pyramidal neurons combining features of ischemic changes with those of delayed neuronal death appear rather seldom. It seems that the presence of those changes, rarely described by other authors (Kirino et al. 1985), may be related to the extention to 7.5 min time of forebrain ischemia in our experiments as compared with 5 min in experiments of Kirino (1985), Kirino and Sano (1984a) and Yamaguchi and Klatzo (1984). Kirino et al. (1985) emphasize that extension of ischemia to over 7—10 min results in the appearance in CA_1 sector of well-defined ischemic changes occurring in other vulnerable regions of the brain. In our material, prolonged ischemia may also be responsible for relatively frequent peripheral tigrolysis of the pyramidal CA_1 neurons. This type of changes, resulting from the cerebral ischemia have been observed in other, more severe experimental models (Mossakowski, Gajkowska 1984).

Dominating changes of CA_1 pyramidal neurons are in our material essentially similar to those described by Kirino et al. (1984, 1985), Kirino and Sano (1984b) and Petito and Pulsinelli (1983, 1984) in corresponding experimental conditions in gerbils and rats. However, the number of features of fine structural alterations present in our material differ from those described by others. Throughout the whole postischemic period content of endoplasmic reticulum structures was never increased. Exclusive localization of parallel arrays of endoplasmic reticulum in basal part of pyramidal cells was not a feature; they were usually spread at random in various parts of neuronal cytoplasm. There was in no case distinct partition of the cellular cytoplasm into perinuclear portion containing dense bodies and both changed and unchanged mitochondria, and peripheral one with abnormally arranged endoplasmic reticulum structures. In general the changes observed in our material resembled more those occurring in rats than in gerbils (Kirino et al. 1985).

However, the most fundamental difference consisted in that the alterations considered as exponents of cellular lesion appeared on the second postischemic day, being preceded by features of biological activation of neurons. Biphasic sequence of ultrastructural changes observed in our material is consistent with physiological behaviour of neurons. The first stage corresponds to their bioelectric hyperactivity observed in gerbils by Suzuki et al. (1983, 1985) and in rats by Lacy and Pulsinelli (1983). The second stage is concomitant with their bioelectric silence occurring in the second and subsequent postischemic days.

Parallel to cellular changes are alterations in the synaptic contacts of CA_1 neurons distributed both on their perikarya and different portions of the dendritic tree. The most significant abnormalities, appearing on the third postischemic day (one day delay as compared to perikaryal lesions), involve

axodendritic synapses on the dendritic arborization in *stratum lacunosum moleculare* corresponding to contacts with commissural axonal endings and those of Schaffer's collaterals (Andersen et al. 1966). Inhibitory synapses on neuronal perikarya, formed by axonal endings of basked cells and those on the dendric shafts in *statum radiatum* formed by fibres originating from granular neurons of the dentate gyrus are much less changed. This phenomenon is consistent with low sensitivity to ischema of the dentate granular cells and inhibitory interneurons which remain unchanged in the whole postischemic period. This observation confirms earlier morphological and biochemical findings of Johansen et al. (1983) and Francis and Pulsinelli (1982).

The mechanism of delayed neuronal death, involving selectively pyramidal neurons of CA_1 sector of Ammon's horn is far from being elucidated. Different from typical ischemic neuronal changes, pathomorphology of CA_1 neurons resulting from short-term cerebral ischemia, their physiological reaction, expressed by an early bioelectric hyperactivity alongside with alterations in their synaptic innervation appearing in an early postischemic period suggest different mechanism of their injury, which may be connected to a lesser degree with the ischemic incident and its metabolic consequences than with the excitotoxic action of excitatory neurotransmitters (Kirino et al. 1985; Pulsinelli 1985a; Suzuki et al. 1985). This opinion finds a strong support in observation of Pulsinelli (1985b), who had shown that deafferantation of hippocampus protects CA_1 pyramidal cells against ischemic injury. The most probable candidate to exert such excitotoxic action is glutamate (Olney et al. 1971; Van Harrveld, Fifkova 1971; Olney 1978; Meldrum, 1981). In case of CA_1-pyramidal neurons this may be connected with their rich glutaminergic innervation by Schaffer's collaterals, originating from pyramidal neurons of hippocampal CA_3 sector (Wieraszko 1983). The latter are characterized by low sensitivity to ischema, to which they respond with the so-called reactive changes (Ito et al. 1975; Bubis et al. 1976). The postischemic bioelectric hyperactivity is followed by intracytoplasmatic influx of calcium in selectively vulnerable neurons (Harris et al. 1981; Griffiths et al. 1982; Simon et al. 1984). This in turn may lead to irreversible metabolic and consecutively structural injury to nerve cells (Siesjö 1981). Observations concerning protective action of blockers of calcium entry channels in case of hippocampal lesions due to short-term ischemia support the opinion concerning the role of calcium in the development of delayed neuronal death (Mossakowski, Gadomski 1987).

ULTRASTRUKTURA NEURONÓW SEKTORA CA_1 ROGU AMONA CHOMIKA MONGOLSKIEGO W KRÓTKOTRWAŁYM NIEDOKRWIENIU MÓZGU

Streszczenie

Poddano analizie zmiany ultrastrukturalne sektora CA_1 rogu Amona u chomików mongolskich, spowodowane krótkotrwałym niedokrwieniem mózgowia. Doświadczenie przeprowadzono na dorosłych zwierzętach, którym zaciskano obustronne tętnice szyjne wspólne na okres 7,5 min.

Zwierzęta dekapitowano po 1, 2, 3, 4 i 5 dniach po niedokrwieniu. Pobierano wycinki tkanki zawierające wszystkie warstwy sektora CA_1 grzbietowego hipokampa.

Wyniki przeprowadzonych badań można podsumować następująco: Nieprawidłowości ultrastrukturalne neuronów sektora CA_1 mają dwojaki charakter. W pierwszym dniu po niedokrwieniu neurony piramidowe sektora CA_1 wykazują cechy aktywacji. Połączenia aksosomatyczne oraz zakończenia na dendrytach podstawnych i szczytowych są dobrze zachowane i zawierają dużą ilość pęcherzyków synaptycznych. W drugim dniu po niedokrwieniu w neuronach piramidowych sektora CA_1 pojawiają się zmiany patologiczne doprowadzające do ich śmierci. Stwierdzono dwa typy zmian ultrastrukturalnych w neuronach: 1. nieprawidłowości w budowie siatki śródplazmatycznej, prowadzące do jej zaniku oraz dezintegracji rybosomów oraz 2. odkładanie się elektronowo-gęstego, ziarnistego materiału w cytoplazmie. Mitochondria neuronów niemal do końcowych stadiów rozpadu komórki były prawidłowe. W końcowym okresie obserwacji stwierdzono brak synaptycznych połączeń zarówno na perykarionach neuronów, jak i na ich dendrytach szczytowych.

Odmienność obrazu patomorfologicznego neuronów sektora CA_1 w stosunku do typowego niedokrwiennego uszkodzenia komórek nerwowych, łącznie z ich czynnościową reakcją na niedokrwienie i zmiany w kontaktach synaptycznych, sugerują odmienny mechanizm ich uszkodzenia, który może być związany nie tyle z incydentem niedokrwiennym, lecz przede wszystkim z ekscytotoksycznym działaniem neurotransmiterów aminokwasowych.

УЛЬТРАСТРУКТУРА НЕЙРОНОВ СЕКТОРА CA_1 АММОНОВА РОГА МОНГОЛЬСКОЙ ПЕСЧАНКИ ПРИ КРАТКОВРЕМЕННОЙ ИШЕМИИ МОЗГА

Резюме

Исследовались ультраструктурные изменения нейронов сектора CA_1 Аммонова рога монгольских песчанок, вызванные кратковременной исхемией мозга. Эксперимент был проведен на взрослых животных, у которых производили двухсторонее пережатие общих сонных артерий на 7,5 минут. Декапитация производилась через 1, 2, 3, 4 и 5 дней после ишемии. Были взяты срезы ткани, содержащие все слои сектора CA_1 дорзального гиппокампа.

Результаты проведенных иследований можно подитожыть следующим образом: Ультраструктурные изменения нейронов сектора CA_1 имеют двоякий характер. В первый день после ишемии пирамидные нейроны сектора CA_1 проявляют черты активации. Аксосоматические синапсы и окончания на базальных и апикальных дендритах хорошо сохранены и обладают большим количеством синаптических пузырьков. На второй день после ишемии в пирамидных нейронах сектора CA_1 появляются патологические изменения, приводящие к их гибели. Обнаружены два типа ультраструктурных изменении нейронов:

1. нарушение структуры эндоплазматической сети, приводящее к ее деструкции и дезинтеграции рибосом и

2. накопление электронно-плотного зернистого материала в цитоплазме.

Митохондрии нейронов не были изменены почти до конечных стадий распада клетки. В заключительном периоде наблюдений обнаружено отсутствие синаптических связей как на телах клеток, так на их апикальных дендритах. Различие между патоморфологическими изменениями нейронов сектора CA_1 и типичным ишемическим повреждением нервных клеток вместе с их функциональной реакцией на ишемию и изменениями в их синаптических контактах, свидетельствуют об ином механизме их повреждения. Механизм этот связан, как кажется, не столько с воздействием ишемии но прежде всего с эксцитотоксическим действием аминокислот — нейромедиаторов.

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