cise explanation. One possible suggestion is that the changes described in the very small blood vessels of the skin are a manifestation of the physiological regeneration of the basis of the skin. Whereas the principles of renewal of the epidermis have been studied in adequate detail, little is known about the physiological regeneration of the connective-tissue basis of the skin. It is considered to be undertaken by fibroblasts producing collagen fibers. On the question of the origin of the fibroblasts themselves, the sources of their continuous renewal and replenishment of their composition – relations between their state such as between fibroblast and fibrocyte, much remains in dispute. It can be postulated that one mechanism of physiological regeneration of the basis of the skin is that, as a result of the transformations of the small vessels described above, pericytes leave the vessel walls and give rise to new populations of fibroblasts. In other words, it is suggested that the small vessels of the basis of the skin, which are continually "dying" and being reformed, constitute the main source and inducer of physiological regeneration of the cells and fibrous structures of the basis of the skin.

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CHANGES IN SYNAPSES IN SOME CORTICAL AND DEEP BRAIN FORMATIONS IN OLD RATS

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KEY WORDS: brain; aging; synapses.

A decrease in the number of synaptic junctions (SJ) has been demonstrated in the CNS of man and animals during aging [7, 9, 11]. The decrease in the number of synapses of different types is not uniform [7, 10, 14]. Numerous light-optical investigations have shown substantial changes in the postsynaptic components of synapses, namely dendrites and spines, which play an important role in the primary processing of information reaching the neuron and in the synaptic mechanisms of brain activity, during aging. There have been only isolated studies of age changes in the ultrastructure of interneuronal connections. In old animals a reduction in the density and total length of SJ [9], changes in the pre- and postsynaptic components of the synapses or even degeneration of dendritic and axonal profiles [3, 4, 8] have been observed, although other data have shown the absence of any age differences in synapse ultrastructure [10].

The aim of this investigation was to study the ultrastructure of synapses in different regions of the cortex and deep brain formations of old rats.

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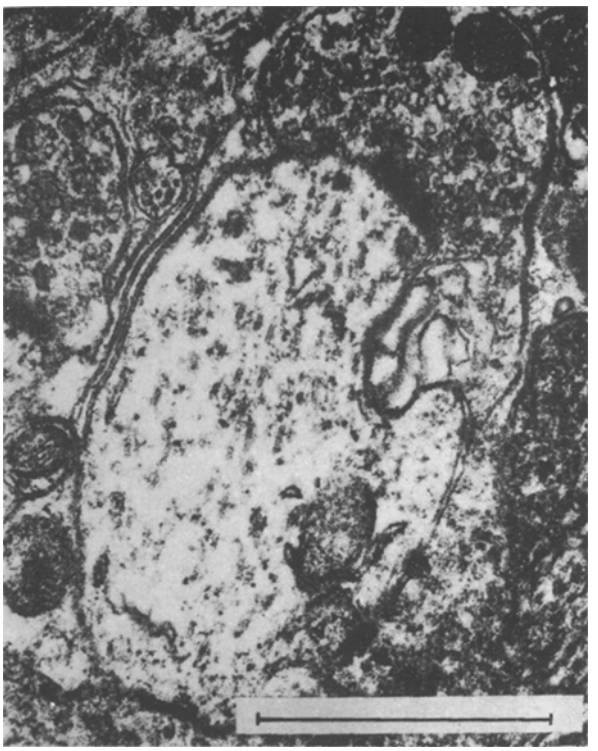

Fig. 1. Invagination of axon into dendrite in the region of SJ. Here and in Fig. 3: hypothalamus of an old rat (30 months).

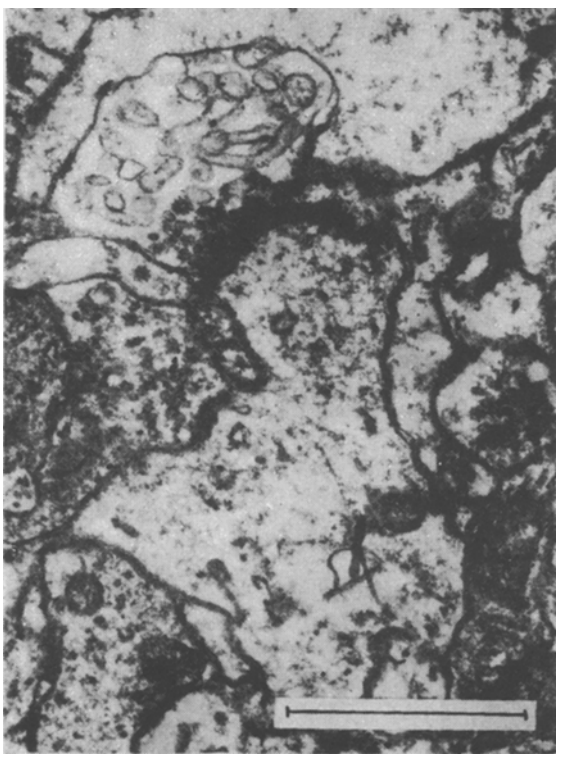

Fig. 2. Vacuolation of the presynaptic process of an axo-dendritic synapse. Limbic cortex of an old rat (30 months).

EXPERIMENTAL METHOD

The sensomotor, visual, parietal, and limbic cortex, the hippocampus, locus coeruleus, and hypothalamus of seven Wistar rats aged 28-30 months and weighing 500-700 g were studied. Material was treated by the formula adopted in the Laboratory of Brain Ultrastructure, Brain Institute, All-Union Mental Health Research Center, Academy of Medical Sciences of the USSR [1]. The material was examined and photographed on an electron microscope (Hitachi, Japan).

EXPERIMENTAL RESULTS

Comparative analysis of pathomorphological changes in the brain formations studied revealed considerable polymorphism of the ultrastructural changes in the processes and synapses and individual variability of these changes. In three of the seven rats the changes were well marked and were characterized by predominance of destructive processes in all the structural elements of the nerve tissue, by considerable gliosis and by phagocytosis of the structures. In the remaining rats degenerative changes and gliosis were much less marked, and signs of compensatory structural changes were more in evidence. Investigation of different cortical and deep brain formations also revealed absence of synchronization of the ultrastructural changes. The earliest changes evidently arise in the hypothalamus, hippocampus, and locus coeruleus, for the changes in those structures were more marked than in other parts of the CNS. Besides a considerable decrease in the number of synapses in all the brain formations studied, different changes also were observed in the region of the active zone of the synapse, as well as in the pre- and postsynaptic components of the synapses. Damage was more severe in the postsynaptic than in the presynaptic components of the synapse. Axon terminals appeared to be more or less intact.

Most dendritic profiles showed changes of the pale type; the ultrastructural changes were more marked in large and medium-sized dendrites than in small dendrites. The orientation of the microtubules and neurofilaments was disturbed, they were less numerous, fragmented, and destroyed, with the formation of finely granular material. Dendrites with patchy or total translucency of the dendroplasm, containing vacuoles of different shapes and sizes, membranes and myelin-like structures, and single electron-dense bodies were frequently found. Similar inclusions also were observed by Iontov and Shefer [3, 4] in the temporal cortex of old cats and in area 40 of the inferior parietal region of the human brain in old age. Occasionally invagination of part of an adjacent presynaptic component of the synapse into a dendrite was found. Such an invagination, containing structures resembling vacuoles, affected a small area of the contacting membranes (Fig. 1) or nearly the whole region of the presynaptic zone could invaginate into the dendrite, which was observed as a rule when there was marked destruction of the organelles in the dendroplasm. The functional significance of this phenomenon is not yet clear. Invagination of SJ into a dendrite, allowing direct access of the transmitter to the postsynaptic component, may perhaps be an extreme measure of compensatory character, aimed at maintaining the functions of the dendrite. On dendrites with changes of the pale type SJ were preserved, but they had a small "active zone" and accumulation of synaptic vesicles was observed in the presynaptic process. All these changes are considered to be an indication of the inactive state of the synaptic apparatus [2]. In a few dendrites changes were of the dark type. Synapses with dark postsynaptic dendrites as a rule were surrounded by swollen processes of astrocytes.

Many axon profiles in old rats preserved their ultrastructure. At the same time, presynaptic terminals with changes of pale and dark type were found. Axons with changes of the dark type usually had uneven outlines, and synaptic vesicles filled their whole cross-section. In the final stage the axon loses its connection with the postsynaptic component and is surrounded by swollen processes of astrocytes, as was observed by Iontov and Shefer [4] in the human cerebral cortex. Presynaptic processes with changes of the pale type were swollen, and in some of them there was patchy or, sometimes, total destruction of the axoplasm and mitochondria, and a reduction in the number of synaptic vesicles, with only single vesicles remaining near the presynaptic membrane. A marked increase in size of the vesicles and changes in their shape could also be seen, with the formation of curiously shaped vacuoles (Fig. 2), which was usually observed in the region of SJ which were invaginated into the dendrite. In individual presynaptic axons synaptic vesicles formed structures resembling networks close to the presynaptic membrane (Fig. 3).

As regards ultrastructural changes in the region of SJ itself, besides a decrease in area of the "active zone," in most synapses an increase in width of postsynaptic specialization of finely granular electron-dense material was detected. In all the old rats actively

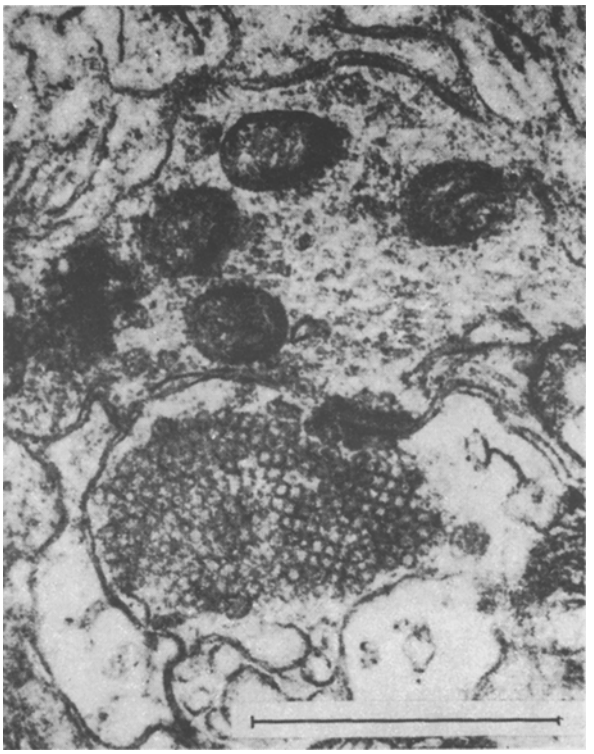

Fig. 3. Various forms of changes in synaptic vesicles (vacuolation and agglutination) in presynaptic process of an axo-dendritic synapse.

functioning synapses were found with an extensive SJ, concentration of synaptic vesicles near the presynaptic membrane, and the presence of hypertrophied mitochondria, which compensates to some degree the age-related death of synapses observed by some workers. Another sign of compensatory-adaptive restructuring of interneuronal connections with age is the presence of synapses of desmosome-like type with increased electron density of the contacting membranes, in whose presynaptic processes virtually no synaptic vesicles could be seen. The appearance of desmosome-like junctions in the cerebral cortex of old rats has been observed also by Pavlovskaya [6]. Since these synapses are characteristic of early ontogeny, their presence in old age is evidence of imperfection of the synaptic mechanisms of brain activity. Besides destructive changes, other workers studying interneuronal connections in the aging brain also have observed evidence of compensatory changes. It has been shown [12], for instance, that parallel with a decrease in the number of axo-somatic and axo-dendritic synapses, the number of dendro-dendritic synapses in old rats is increased.

The investigation thus revealed polymorphism of the ultrastructural changes in the various components of synapses in animals during aging. The ultrastructural changes revealed can evidently be the morphological basis of the reduction of afferentation and weakening of fundamental nervous processes observed in old age [5, 13].

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QUANTITATIVE ANALYSIS OF NEURONAL MOSAIC FORMATION IN THE MOUSE NEOCORTEX AND HIPPOCAMPUS

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KEY WORDS: neocortex; hippocampus; neurogenesis; autoradiography; computers.

The mosaic pattern of neurogenesis, reflected in the arrangement of concentrations of neurons intensely labeled with ^{3}H-thymidine, was described as a result of the writers' investigations with injection of ^{3}H-thymidine into mice at different times of embryogenesis, followed by analysis of the arrangement of the labeled cells in the neocortex and hippocampus of day-old mice [4, 5, 13]. It was concluded that the mosaic pattern of neurogenesis is determined by the nonsynchronized course of differentiation of cell groups in the ventricular zone of the embryonic brain, i.e., evidence was obtained of its discrete organization in the form of loci of neurogenesis.

The aim of the present investigation was to obtain mathematical confirmation of the nonrandomness of mosaic formation of neuronal groups in the cerebral cortex, to characterize this process quantitatively, and to compare its scale with the formation of the modular organization of the cortex.

EXPERIMENTAL METHOD

Pregnant female CBA mice were given a single intraperitoneal injection of ^{3}H-thymidine (10 μCi/g) on the 13th-19th day of pregnancy (E13-E19). At the age of 1 day, two or three mice from each mother were killed by decapitation. The cerebral hemispheres of mice receiving ^{3}H-thymidine from E15 to E19 were fixed in Karnovsky's fixative and embedded in Durcupan. When the isotope was injected during the period E13-19 the cerebral hemispheres were fixed in Carnoy's mixture and embedded in paraffin wax. One hemisphere from each animal was cut into frontal sections, the other into sagittal. Preparations with glued semithin (1 μ) or paraffin (6 μ) sections were covered with type M emulsion and, after standard autoradiographic processing, were stained with 1% toluidine blue solution in 2.5% sodium carbonate solution or with 0.1% cresyl violet. The arrangement of the centers of the nuclei of the intensely labeled neurons in area 6 of the frontal region of the neocortex and in area CA1 of the dorsal hippocampus was mapped on an NU-2E microscope with projection screen. Mapping in the neocortex was carried out on frontal semithin brain sections from mice receiving ^{3}H-thymidine from E15 through E17, whereas mapping in the hippocampus was carried out on paraffin and semithin frontal brain sections from animals receiving the isotope from E13 through E17. Cells were recorded as intensely labeled if the number of grains of silver above the nucleus varied from maximal to half that number of grains per section. Maps of areas 6 and CA1 from two animals at each time of the experiment studied were analyzed mathematically to discover nonrandom groups of intensely labeled neurons. For this purpose an approach was used which enables the regularity of neurogenesis to be assessed in brain structures organized on the principle of a rec-

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