Development of Synapses as the Basis of Their Involution

L. E. Frumkina, N. I. Yakovleva, and N. N. Bogolepov

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Gaining information that can help in understanding the morphological basis of normal and pathological aging is an important task of neurobiology and medicine today. It is well known that aging is an involutional process that shares many features with the early stages of ontogeny [2]. In the available literature, however, we could not find an answer to the question as to what underlies the mechanisms responsible for the involution of interneuronal connections. In an attempt to answer this question we compared the changes which synapses of the human brain undergo in normal aging and in vascular disease with those observed in our previous studies on the development of synaptic junctions in experimental animals during ontogeny. This could also shed light on the plasticity of the nervous system and offer new prospects for devising ways to prevent various forms of age-related pathology.

MATERIALS AND METHODS

Materials for this study were brains of individuals aged 36, 39, 50, 70, and 72 years who had died from ischemic heart disease and of persons aged 73 and 83 years whose death was not associated with any vascular disorders - a total of 10 brains taken 2.5-4.5 h after death. Various cortical and subcortical structures were examined and photographed using Hitachi H-600 and H11E electron microscopes. The material for electron microscopy was prepared in the usual way and embedded in Epon-812.

Laboratory of Brain Ultrastructure, Institute of Brain Research, Russian Academy of Medical Sciences, Moscow

RESULTS

Analysis of the data obtained showed that the human brain at all ages studied contains considerable numbers of desmosome-like and mixed junctions (Fig. 1, *b* and *f*). In our material, desmosome-like junctions (connections) varied both in length, which not infrequently was due to the unequal sizes of the processes forming a given junction, and in the size of the fibrillary thickenings, which were equal on both sides of the synaptic membranes in some cases and larger on the side of a particular synaptic membrane (most often postsynaptic) in others. Some desmosome-like junctions contained, in the presynaptic terminal, a small number of synaptic vesicles at the fibrillary thickening, while others did not contain any synaptic vesicles.

Mixed junctions consist of a desmosome-like connection and a specialized part which is symmetrical or asymmetrical. Synaptic vesicles are located only within the specialized part of a mixed junction. The relative lengths of the desmosome-like and specialized parts are variable.

Of special note are the rough and smooth microvesicles found in some synaptic endings of the brain. Such microvesicles were first described by us [1,3] in a study of the synaptogenesis of cortical structures in brains of experimental ani-

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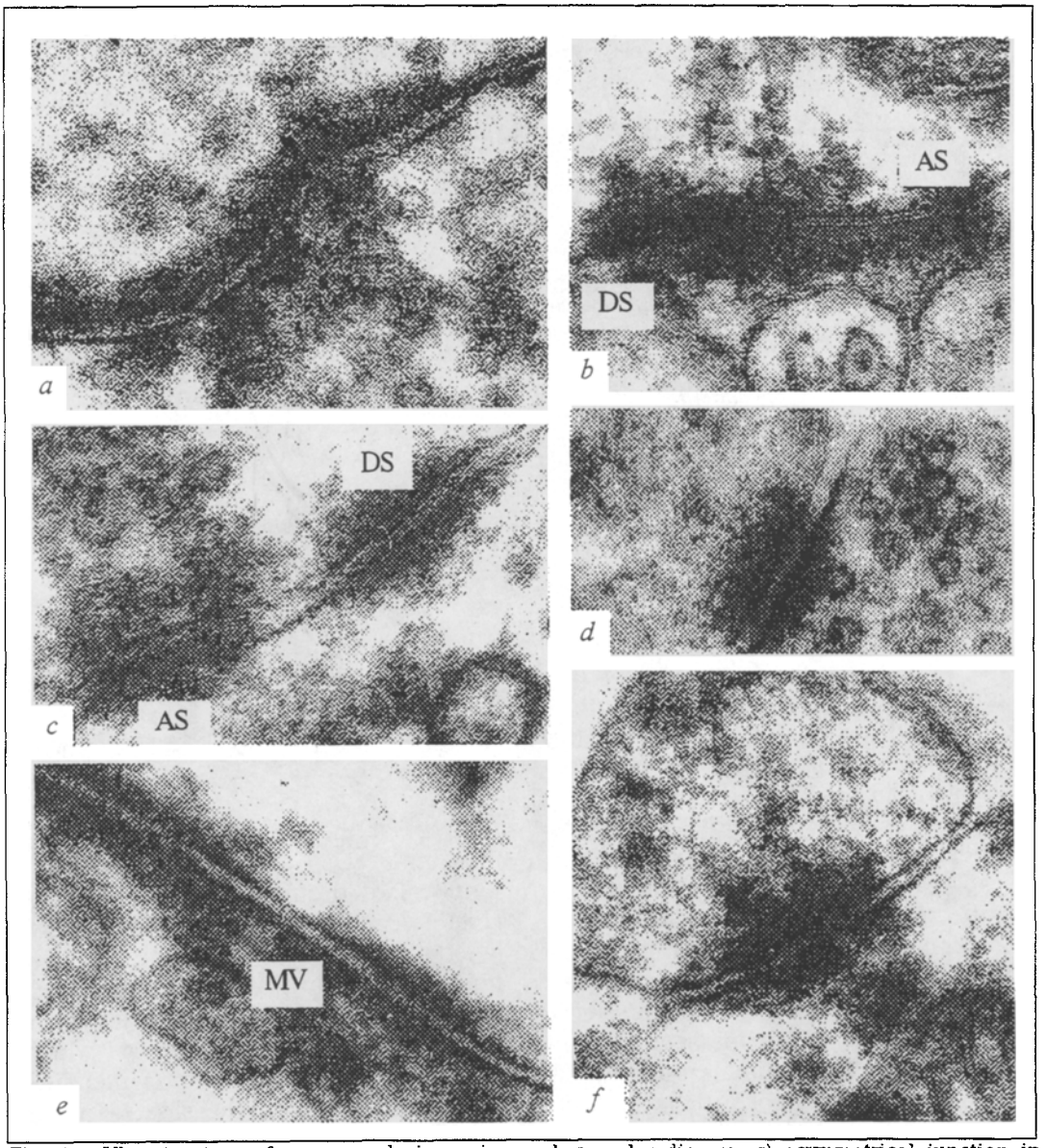

Fig. 1. Ultrastructure of synapses during aging and vascular disease. *a*) asymmetrical junction in temporal region of cortex from a 36-year-old individual; *b*) mixed junction consisting of a desmosome-like (DS) and an asymmetrical (AS) connection; synaptic vesicles are absent. Caudate nucleus of a 72-year-old individual; *c*) mixed junction with synaptic vesicles located in the zone of an asymmetrical synapse. Temporal region of cortex from a 39-year-old individual; *d*) desmosome-like junction; a few synaptic vesicles can be seen in the area of fibrillary threads, but most of them are situated far from the presynaptic membrane. Precentral region of cortex of a 70-year-old individual; *e*) mixed junction; microvesicles (MV) are located in the zone of the presynaptic membrane. Temporal region of cortex of an 83-year-old individual; *f*) avesicular desmosome-like junction. Temporal region of cortex of a 39-year-old individual. *a*-*f* ×100,000.

mals. Unlike in developing synapses, rough microvesicles in this study of human brains were observed at presynaptic membranes only (Fig. 1, *d*), whereas smooth microvesicles were seen, just as in developing synapses, within pre- and postsynaptic thickenings, in the presynaptic cleft, on the outer membrane of granular and agranular synaptic vesicles, or lying freely in the axoplasm. It is important to note that such microvesicles occurred only in functionally active synapses.

Thus, as shown by the present study, structural changes in synapses in the form of desmosome-like and mixed junctions identical in ultrastructure to those found in developing synapses during ontogeny (Fig. 2, *a*-*e*) occur in the human brain during aging and in vascular disease. Hence it may be concluded that in the process of aging or in vascular disease synapses undergo changes indicative of their involution, a process opposite to that by which synapses arise in ontogeny. However,

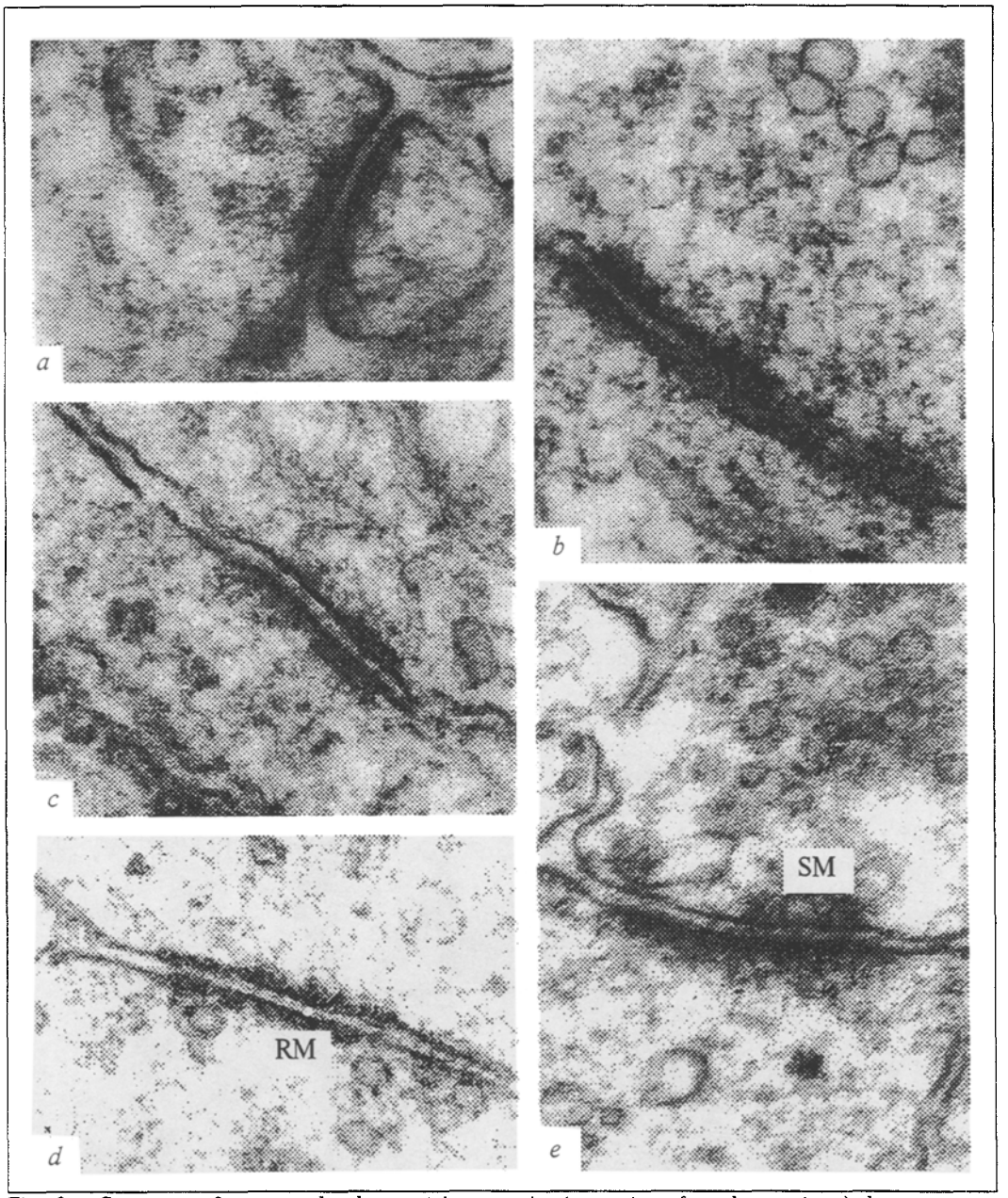

Fig. 2. Sequence of synapse development in sensorimotor cortex of newborn rats. *a*) desmosome–like avesicular junction; *b*) desmosome–like junction; synaptic vesicles are located far away from it; *c*) mixed avesicular junction consisting of a desmosome–like and a symmetrical connection. *d*) mixed junction consisting of a desmosome–like connection and a symmetrical synapse. In the desmosome area, microvesicles with a rough surface (RM) can be seen; *e*) specialized asymmetrical synapse; synaptic vesicles and microvesicles with a smooth surface (SM) occur at the presynaptic membrane. *a–e* ×100 000.

whereas desmosome-like junctions are precursors of mature synapses in ontogeny, they represent the end result of synaptic transformation in the aging or diseased human brain. The functional role of desmosome-like junctions is more or less equivalent in both cases and consists in electrical conduction of impulses. However, the presence of desmosomes during synaptogenesis is due to the absence of chemical transmission over a particular period, whereas in the human brain their emergence may be regarded as a compensatory/adaptive response to the functional depletion or degeneration of synapses or to the death of other synaptic junctions. Broader opportunities for chemical and electrical conduction arise in mixed junctions, which in the aging or diseased human brain, as in ontogeny, represent a transitional step between a functional synapse of an asymmetrical or symmetrical type and a desmosome. In a mixed junction, the desmosome-like connection appears to

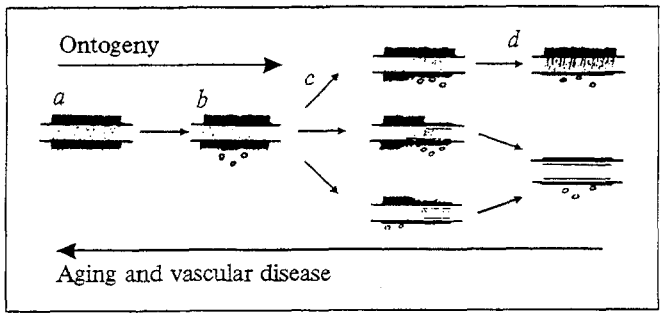

Fig. 3. Schematic representation of possible mechanisms by which synapses develop in early ontogeny and of the involution of synaptic junctions during aging and vascular disease. *a* – desmosome–like connection; *b* – desmosome–like connection with synaptic vesicles; *c* – different types of mixed junctions; *d* – formation of symmetrical and asymmetrical specialized synapses.

protect the remaining portion of the chemical synapse from fatigue and under favorable circumstances can probably again become a functional synapse. Desmosomes play a similar role in certain other forms of pathology, for example various types of stress [4,5]. The formation of desmosomes in the aging or diseased human brain may therefore be looked upon not as an abnormal phenomenon, but rather as one element of a plastic reorganization taking place in synapses.

The occurrence of rough microvesicles in synaptic endings of the human brain confirms that these structures participate in synapse formation, as we have already reported [1,3]. During ontogeny, however, rough vesicles form through twisting of the desmosomal fibrillary threads, followed by incorporation of these into the membranous packing of the junction, whereas in the human brain the desmosome is formed as a result of untwisting of the microvesicles, i.e., by a process that is the reverse of that by which synapses develop in early ontogeny (Fig. 3).

The foregoing leads to the following conclusions:

1) in the human brain during aging and vascular disease, synapses undergo ultrastructural changes indicative of their involution;

2) involution of synapses results from the plasticity of interneuronal connections which underlies the compensatory/adaptive changes occurring in the brain as a whole;

3) the mechanism of synapse involution is a mirror image of the mechanism by which synaptic junctions develop during early ontogeny;

4) the morphological expression of synapse involution is the desmosome.

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