ANALYSIS OF THE TYPES OF REACTIVE CHANGES IN NERVE FIBERS

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UDC 612.338

The morphological features of varicose corpuscles discovered along the course of the peripheral nerve fibers in man and animals in the final stages of ontogeny were studied. The properties of the varicose corpuscles were compared with those of reactive varicose deformities observed experimentally when the blood supply was disturbed. In view of the features of similarity between the varicose corpuscles and varicosities and the presence of intermediate forms, the former can be regarded as reactive structures. However, a considerable time and the participation of surrounding tissue were required for their formation.

KEY WORDS: *peripheral nervous system*; *varicose corpuscles*; *reactivity*.

The study of the nervous apparatus of the small intestine of animals and man in the final stages of ontogeny [5] has shown that distinctive varicose corpuscles of uncertain origin lie along the course of the nerve fibers. In their external appearance they differ considerably from the amyloid corpuscles described previously [3].

The present investigation was carried out to make an experimental study of the nature of these corpuscles.

EXPERIMENTAL METHOD

Three series of experiments were carried out. In series I varicose corpuscles in the small intestine of 39 dogs aged 12-17 years and the small intestine of 15 persons aged 70-86 years were investigated. In series II the nervous apparatus of the small intestine was studied in dogs aged 2-5 years under conditions of experimental hypoxia produced by ligation of three adjacent mesenteric arteries (6 experiments). The animals were killed on the second or third day after the operation. In series III an intravital microscopic analysis was made of reactive changes in nerve fibers surviving under hypoxic conditions using teased frog's nerves as the model (15 experiments). All the material was fixed and treated by the Bielschowsky–Gros method. The intravital investigations were carried out with the use of a phase-contrast system.

EXPERIMENTAL RESULTS

Direct observations showed that the varicose corpuscles are arranged in groups of 3 to 9 at a time on a short length of fiber. They are commensurate in size with nerve cells. Usually their diameter is 9-20 times greater than that of their axon. The corpuscles are often arranged asymmetrically relative to the axis of the fiber (Fig. 1a), and they may be fusiform, circular, spherical, or racemose in shape. Frequently they are found where fibers branch dichotomously (Fig. 1b) or in the region of preterminals (Fig. 1c). In some cases (Fig. 1a) reactive proliferation of the surrounding tissue (glia, possibly) is found around the varicose corpuscles.

Experience of the study of reactive changes in nervous structures shows that "pools of axoplasm" and varicosities are found most frequently in the region of preterminals and ramifications of nerve processes [2, 7, 8, 9]. Proliferation of cells surrounding nerve fibers is also included in the category of reactive changes. This phenomenon is evidently widespread. It has been observed recently, for example, in a study of the formation of Pacinian corpuscles [4].

Laboratory of Functional Neuromorphology, I. P. Pavlov Institute of Physiology, Academy of Sciences of the USSR, Leningrad. Department of Histology and Embryology, Samarkand Medical Institute. (Presented by Academician V. N. Chernigovskii.) Translated from Byulleten' Éksperimental'noii Biologii i Meditsiny, Vol. 83, No. 2, pp. 240-243, February, 1977. Original article submitted April 21, 1976.

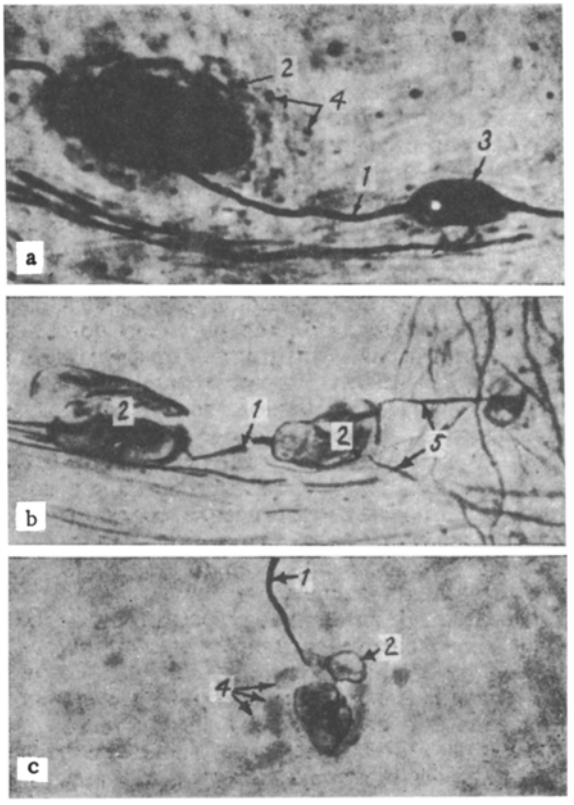

Fig. 1. Varicose corpuscles of nerve fibers of the small intestine in a dog aged 16 years: a) proliferation of glial cells; b) varicose corpuscle in region of branching of fiber; c) varicose corpuscles on terminal fiber; 1) axons; 2) varicose corpuscles; 3) varicosity; 4) nuclei of glial cells; 5) branches of axons. Here and in Fig. 2, impregnation by Bielschowsky—Gros method; 400×.

There are thus adequate grounds for regarding varicose corpuscles as belonging to the group of reactive changes. Sometimes varicose corpuscles can be found side by side with ordinary varicosities on the same fiber (Fig. 1a). These varicosities differ in size and in some cases, they appear as intermediate states in the process of corpuscle formation. Typical varicosities differ from varicose corpuscles in their smaller size, their more elongated shape, and the symmetry of their parts relative to the axis of the fiber.

Assuming that corpuscles can be formed, in principle, from ordinary varicosities, attempts were made to reproduce this process under acute experimental conditions. Since in old age disturbances of the hemodynamics become particularly important, it was decided to use various degrees of ischemia as the pathogenic factor (experiments of series II). Some nerve fibers of the ischemized portion of the small intestine showed varicose deformities. Three main types of varicosities were distingushed: dashed, fusiform, and drop-like (Fig. 2).

The dashed and fusiform structures evidently correspond to different stages of formation of varicosities. They are found on axons of medium and large caliber and of uniform type and have numerous intermediate forms. The drop-like varicosities are situated usually on thin fibers and they are distinguished by several features in which they resemble varicose corpuscles. They are usually asymmetrical and they may project considerably from one side of the fiber. In size they are much larger (6-8 times) in diameter than the axon on which they lie. Their study shows that they are varicose corpuscles in miniature. However, they differ from varicose corpuscles not only in their absolute size, but also by the fact that they are formed on the thinnest nerve fibers whereas varicose corpuscles are derivatives of thick and medium nerve fibers.

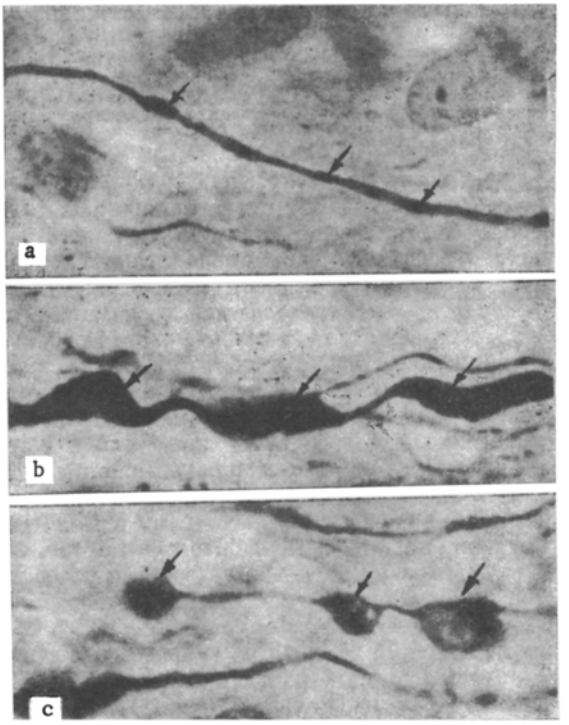

Fig. 2. Types of varicosities of nerve fibers of dog small intestine during ischemia. a, b, c) Dashed, fusiform, and drop-like varicose expansions (varicosities indicated by arrows).

The attempt to obtain an increase in size of the varicosities on the large nerve fibers by increasing the severity of ischemia was unsuccessful. Indeed, the number of fibers showing varicose changes was actually reduced under these circumstances. In an area of intestine with distinct visual signs of gangrene (on the second day after ligation of the mesenteric arteries and their anastomoses along the mesenteric border of the intestine) nearly all the fibers appeared as well-impregnated smoothly outlined bands. This pattern very closely resembles the state frequently described in pathological histology known as mummification of axons [1]. Unfortunately the genesis of this phenomenon is still unknown and this makes it very difficult when attempting to distinguish pathohistological and normal pictures of fibers in fixed preparations impregnated with silver nitrate, more especially because the myelin sheath is very rarely demonstrated by this method.

It might be hoped that further information on the connection between the processes of origin and development of varicosities and varicose corpuscles could be obtained by the intravital study of the nerve fiber, more especially since the structures of the axon and myelin sheath are clearly visible under these circumstances. Morphological observations on nerve fibers surviving under conditions of hypoxia revealed considerable differences in the character of varicose deformation of the thick and thin fibers. In the myelinated nerve fibers of large diameter the varicosities are formed by swelling of the Schmidt—Lantermann myelin incisures, which are pressed inside the axon to form the isthmus between varicosities (Fig. 3a). Consequently the varicosity does not project beyond the outlines of the fiber, for its diameter is not significantly greater than the original diameter of the axon. In fact, it is a varicosity of the axial cylinder only [10]. Varicosities of thin myelinated fibers, on the other hand, project considerably beyond the outline of the fiber and the isthmus between them appears to be thinner. These features distinguishing the varicose deformity of the nerve fibers can be explained on the grounds that the axoplasm of reactively changed fibers consists of two components [11]. Aggregation of the filamentous-tubular material of the axoplasm of the damaged fiber leads to the release of the liquid fraction, which, because of surface tension forces, tends to form drops on the solid fibrillary band thus formed [6, 11, 14]. In fibers with a thin myelin sheath, Laplacean forces are able to overcome its resistance and to form such drops on a thin filament. In thick fibers, on the other hand, it

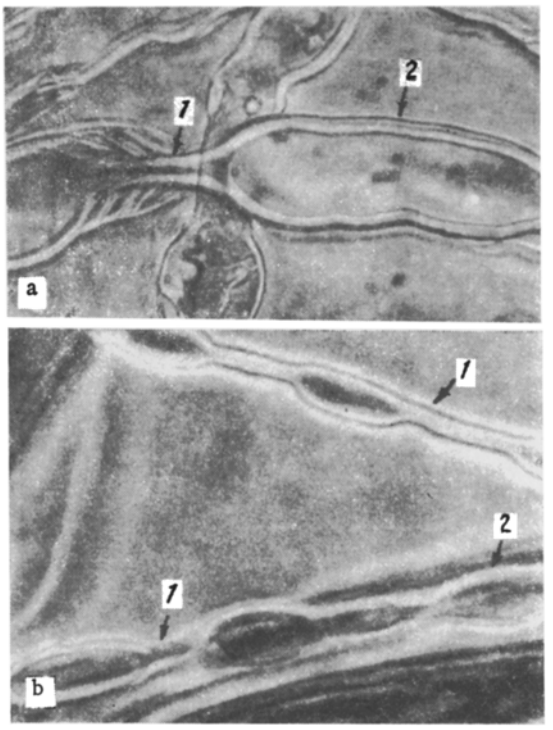

Fig. 3. Varicose deformities of thick and thin nerve fibers surviving in a state of hypoxia: a) thick myelinated fiber; b) thin nerve fibers. 1) Isthmus between varicosities; 2) varicosities. Intravital microscopy in phase contrast 400×.

is impossible to overcome the resistance of the membrane and the outlines of the fiber remain smooth, but the diameter of the varicosities of the axial cylinder cannot exceed the diameter of the fiber.

Consequently, so that varicosities of large nerve fibers can be converted into massive varicose corpuscles such as were described in the experiments of series I, certain changes in the myelin sheath must first take place. It is evidently not by accident that varicose corpuscles are frequently located in the region of branching of nerve fibers (Fig. 1), where protrusion of the axoplasm is facilitated by the well-marked gap between adjacent Schwann cells [13]. The gathering of satellites found in the region of varicose corpuscles (Fig. 1a) may perhaps also be evidence of some damage to the glia, preceding protrusion of the axoplasm and formation of the varicose corpuscles. If this is in fact so, it becomes clear why varicosities of thin nerve fibers resemble varicose corpuscles in certain features. For this complex process of formation of varicose corpuscles to take place, much time and special conditions are evidently necessary. This must evidently be a chronic process, as is shown by the proliferation of glia ground the corpuscles. It could not therefore be reproduced under acute experimental conditions. Varicose corpuscles have so far been described only in aging people and animals. It can accordingly be postulated that, by virtue of all the arguments presented above, there are good grounds for regarding varicose corpuscles as a manifestation of chronic senile changes in the nervous system.

It must be remembered that such a severe disturbance of the microgeometry of the fiber cannot but affect its functions. As has been shown on a mathematical model of the fiber [12], such deformities lead to sharp changes in the function of the fiber and can completely block its conduction.

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EXPERIMENTAL TOXIC PULMONARY EDEMA IN ALBINO MICE WITH INFLUENZA

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UDC 616.988.75-092.9-06:616.24-005.98

Toxic edema of the lungs during influenza develops 3 h after infection of mice with concentrated influenza viruses adapted to lung tissue. The toxic action of the viruses is manifested by filling of the alveoli with a liquid exudate, by the development of stasis in the pulmonary vessels, by eosinophilic necrosis of the epithelium of the bronchioles, and also by destruction of cells of the cortical layer of the thymus. The model thus developed can aid with the understanding of fulminating forms of influenzal infection in man terminating in death.

KEY WORDS: *influenza*; *pulmonary edema*.

The toxicity of influenza virus has so far been studied in experiments on volunteers or in mice by intravenous, intracerebral, or parenteral methods of infection [1, 3, 5, 7]. Under these conditions no severe lung lesions develop. Yet we know that one of the leading manifestations of the toxicosis with severe influenza in man is toxic hemorrhagic edema of the lungs [2, 4, 6].

The object of this investigation was to develop a model of experimental toxic pulmonary edema in albino mice with influenza.

EXPERIMENTAL METHOD

Two hundred mice were infected intranasally, under ether anesthesia, with one of the following strains of influenza virus in a dose of 10^{-3} in 0.05 ml: A/Hong Kong/68 (H_3N_2), A/Victoria/72 (H_3N_2), A/Leningrad/72 (H_3N_2), all avirulent for mice, and A/37/11 (H_1N_0), A/Hong Kong/68 (H_3N_2), and A/Leningrad/32/49 viruses adapted to mouse lungs. The animals were killed 3 days after infection, the trachea and lungs were removed with sterile precautions, cut into small pieces and disintegrated by ultrasonic treatment, and the virus was

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Translated from Byulleten' Éksperimental'noi Biologii i Meditsiny, Vol. 83, No. 2, pp. 243-244, February, 1977. Original article submitted June 2, 1976.