DIFFERENTIATION AND MIGRATION OF NEUROBLASTS IN THE DEVELOPING HUMAN SPINAL CORD DURING THE FIRST HALF OF PRENATAL ONTOGENY

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UDC 611-82-018.82-013

Processes of differentiation and migration of neuroblasts in the developing human spinal cord were studied in the first half of its prenatal ontogeny by Golgi's method. The dynamics of development of the neuroblast from the neuroepithelial matrix cell to the fully developed neuron was studied. It is postulated that a special process of the neuroblast may play the role of channel of oriented migration of its nucleus toward the site of the final topologic position of the future neuron.

KEY WORDS: neuroblast; differentiation and migration of neuroblasts; spinal cord; human prenatal ontogeny.

Processes of differentiation, especially migration of neuroblasts, are a still unsolved problem. None of the existing motions of neurogenesis, whether the classical [1-3] or modern [4-6], can satisfactorily explain how neuroblasts differentiate as soon as they reach their definite location in the nervous system. The main reason for this is the extremely inadequate study which has been made so far of migration processes of neuroblasts; the situation is particularly unsatisfactory as regards the human nervous system. The objects of the present investigation were accordingly to make a detailed study of all the consecutive stages of differentiation and migration of neuroblasts in the provisional human spinal cord during the first half of its prenatal ontogeny.

EXPERIMENTAL METHOD

Experiments were carried out on 112 human embryos and fetuses aged from 5 to 22 weeks of intrauterine development. Their age was determined on the basis of clinical and anthropometric data. The material was treated by Golgi's method, the most suitable method for the needs of the investigation because it enabled the neuroblasts with all their processes to be completely demonstrated.

EXPERIMENTAL RESULTS

The earliest forms of differentiating neuroblasts in the developing spinal cord of human embryos could be detected by Golgi's method starting from the age of 5 weeks. Observations showed that neuroblasts of this type were located entirely in the layer of neuroepithelial cells. In this period of development they were radially elongated cells, the medial segments of which, just as in the case of neuroepithelial cells, projected into the lumen of the presumptive spinal canal and were bathed by the fluid contained in that canal. Their basal part, on the other hand, taporing to a cone, changed into a relatively thick, slightly curved, smoothly outlined long process, terminating in a characteristic expansion — a cone of growth (Fig. 1A, B). It is the presence of this leading (or axial) process that distinguishes the neuroblast significantly from the neuroepithelial cell and, in the writers' opinion, it can serve as a definite morphological feature to indicate that differentiation of the future nerve cell has begun.

During the subsequent development of the neuroblast its leading process gradually lengthened. Winding among the cells of the presumptive spinal cord, it was directed to the place in which the soma of the maturing nerve cell occupied its definite position. As

Laboratory of Development of the Human Nervous System, Institute of Human Morphology, Academy of Medical Sciences of the USSR, Moscow. (Presented by Academician of the Academy of Medical Sciences of the USSR A. P. Avtsyn.) Translated from Byulleten' Éksperimental'noi Biologii i Meditsiny, Vol. 87, No. 4, pp. 352-354, April, 1979. Original article submitted July 5, 1978.

0007-4888/79/8704-0361$07.50

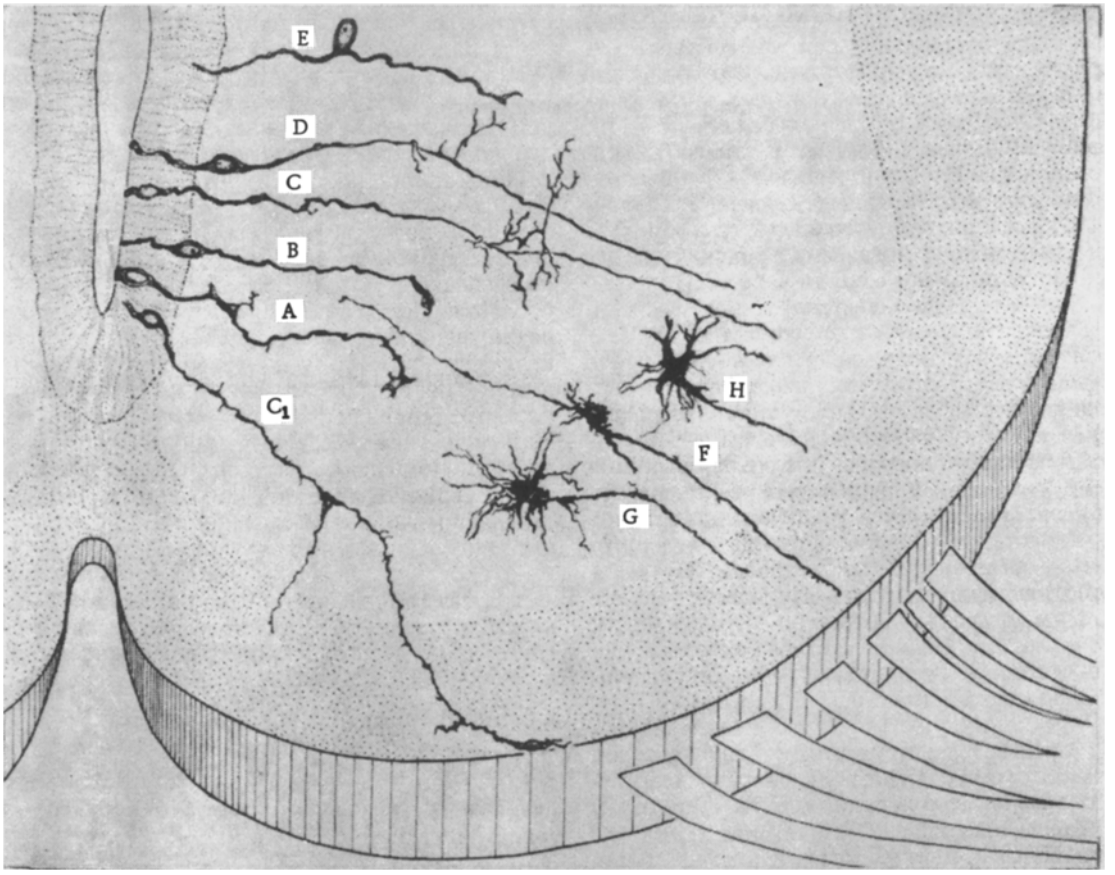

Fig. 1. Composite chart of development of neuroblasts of human spinal cord in first half of prenatal ontogeny. Explanation in text.

the process advanced further it gave off side branches which formed often intensively branched arborizations (Fig. 1C, D). The function of these side branches of the leading process is not completely understood. Most probably they must play the role of provisional dendrites, enabling the neuroblasts even in the early stages of its development to establish connections (principally synaptic) with other developing nerve cells.

Having reached the zone of the definitive topological position of the perikaryon of the future nerve cell, the leading process did not stop there, although sometimes it formed cytoplasmic expansions in that region, giving off provisional dendrites. The process itself, continuing to grow, advanced along the paths which was later followed by the axon of the mature neuron.

This phenomenon could be seen most clearly in the case of motoneuroblasts of the spinal cord. Their leading processes, even in the early stages of cell differentiation, could be traced directly to the point of entry of the anterior roots into the presumptive spinal cord (Fig. $1C_1$, F).

Simultaneously with growth of the leading process of the neuroblast, definite changes also took place in the region of its perikaryon. The nucleus gradually began to move inside the cell in the lateral direction, toward the outer border of the neuroepithelial layer (Fig. 1B). The medial part of the cell under these circumstances became long and narrow and was converted into a distinctive type of peripheral process, apparently stretching beyond the neuroblast, which in the course of a certain period of time could remain structurally connected with the neuroepithelial matrix layer and even directly with the lumen of the spinomedullary canal (Fig. 1D, E). In this period the cell naturally assumed the shape of a bipolar neuroblast.

In this stage of neuronal differentiation migration of the nucleus began to take place along the leading process of the neuroblast to the location of its definite position. Its nucleus in this period was usually elongated, with well-marked nucleoli; around the nucleus

was a very small, intensely stained belt of cytoplasm. In the course of migration the nucleus could occupy an eccentric position in the process (Fig. 1E). As the nucleus advanced along the process, its medial part sooner or later lost its connection with the lumen of the spinomedullary canal and was reduced. In some cases observed, this process could go on to such a degree that the cell became unipolar in shape.

Migration of the nucleus within the cell cytoplasm is not itself an exceptional phenomenon: It has frequently been described in the most widely different cells, including developing neurons [7]. However, it is important to stress in this case that migration of the nucleus took place along a special process of the neuroblast, as far as the place destined for the maturing nerve cell in the definite nervous system.

It is difficult at present to determine what sources compel the nucleus of the neuroblast to migrate along its process. However, the recent discovery of true contractile proteins in neurons and glial cells [8-11] and also the unusually rich development of microtubules in the differentiated neuroblast and their direct connection with the nuclear membrane [12] suggests that the mechanisms responsible for migration of the neuroblast nucleus along its process are most probably based on interaction between its microtubular and microfilamentous systems.

After the nucleus of the neuroblast migrating along the leading process has reached the place of its definite position, the final stage of morphological and functional modification of the neuroblast takes place, namely its conversion into a young neuron. Under these circumstances its nucleus grew in size considerably and became round. Besides an increase in the size of the nucleus, the volume of cytoplasm surrounding it and forming the body of the neuron also increased. More and more new cytoplasmic processes (dendrites) began to emerge from the perikaryon. Present in large numbers, thin, and slightly winding, at first they gave off few if any branches and followed a radial course from the cell body (Fig. 1G), but the axon could already be clearly identified among them. Consequently, at this stage of development clear differentiation of all the main components of the nerve cell — soma, dendrites, and axon — takes place.

Further development of the nerve cell led to an increase in the size of its body and to a change in the general structure of the dendritic tree. The number of cytoplasmic processes gradually decreased, they became thicker, they started to branch dichotomously, and to grow, so that they became converted into typical dendrites characteristic of the mature motoneuron (Fig. 1H). The medial part of the basal process continued to connect the neuroblast for some time longer with the layer of neuroepithelial cells — with the place from which its migration began (Fig. 1). However, it gradually either atrophied or was converted into one of the dendrites of the maturing neuron.

Hence, on the basis of the results described above the following hypothesis can be put forward regarding the differentiation and migration of neuroblasts in the developing human spinal cord.

In the writer's opinion, neuroblasts develop directly from neuroepithelial cells through a continuous and gradual process of their specific differentiation; each group of neuroblasts, including motoneuroblasts, must correspond, it is expected, to a definite population of neuroepithelial cells which occupies a special region in the matrix layer of the neural tube. The first distinct morphological sign of the conversion of such a cell into a developing neuroblast is the appearance of a rapidly growing process at its basal end. This so-called leading process grows toward the site of the definite position of the future nerve cell. Moreover, the nucleus of the neuroblast already begins to migrate along it, as if along a specially constructed canal. Having reached the zone of its final location, the nucleus remains there and the volume of cytoplasm around it increases appreciably, so that the soma of the nerve cell with its system of emergent dendrites is gradually formed. During further maturation of the neuroblast its leading process is converted into a typical axon, forming synaptic connections with its target cells (neurons, muscle fibers, and so on). Consequently, as a result of these interconnected processes, the nerve cell developing from the neuroblast occupies its own strictly determined position in the definite nervous system.

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MICROCIRCULATION IN THE SEROUS MEMBRANES OF RATS WITH SPONTANEOUS GENETIC HYPERTENSION

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UDC 616.12-008.331-021.3-092.9-07:616.76-005-072.7

A comparative study was made of the microcirculation (MC) of the serous membranes of rats with spontaneous genetic hypertension (SHR) and rats with normal blood pressure (Wistar). The disturbance of MC in hypertension was shown to affect the system as a whole, as shown by structural changes in each of its components (arterioles, precapillaries, capillaries, postcapillaries, venules, lymphatic capillaries and postcapillaries, nerve fibers), and the lesions were generalized, for the changes in all serous membranes studied were of the same kind. The similarity of the changes in MC of the serous membranes of SHR rats and of persons dying from essential hypertension confirms the hypothesis that the changes in MC are stereotyped and relatively specific for hypertension. The specificity of the hypertensive changes in MC is expressed as severe vascular changes of a special kind, whereas the nonspecific changes consist of a combination of intra- and perivascular changes accompanied by only minimal vascular changes, representing the universal response of MC to various stresses.

KEY WORDS: microcirculation; spontaneous genetic hypertension; essential hypertension.

Progress in the study of structural and functional organization of the microcirculation (MC) under normal and pathological conditions has necessitated the compiling of a nosological classification of its changes [7]. Two types of responses of the microvessels have been postulated: 1) stereotyped, observed in various pathological states, and 2) relatively specific for each disease, indicating that the disease leaves a functional and morphological imprint on all structures of MC [5, 6]. To detect specific changes in the microvessels both in the patient during life and in autopsy material, the investigator must make allowance for various additional conditions: age and the presence of atherosclerosis, complications of the underlying disease, and accompanying diseases and their complications [10, 11]. The influence of these conditions on the character of the changes in MC can be excluded by creating an experimental model of the disease. The most adequate model of essential hypertension in man is spontaneous genetic hypertension in rats of the SHR (spontaneously hypertensive rats) line [4, 15].

The object of this investigation was to study the MC of serous membranes in rats of this line in order to distinguish changes due to hypertension and to confirm the concept that stereotyped and relatively specific responses of the microvessels may take place in this disease.

Laboratory of General Pathological Anatomy, Institute of Human Morphology, Academy of Medical Sciences of the USSR, Moscow. (Presented by Academician of the Academy of Medical Sciences of the USSR A. P. Avtsyn.) Translated from Byulleten' Éksperimental'noi Biologii i Meditsiny, Vol. 87, No. 4, pp. 355-358, April, 1979. Original article submitted May 12, 1978.

 0007-4888/79/8704-0364$07.50