ADENYLATE CYCLASE ACTIVITY IN THE CAPILLARY WALL AND HAIR CELLS IN EXPERIMENTAL CARCINOGENESIS

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Avtsyn and Yablonovskaya [1, 2] have drawn attention to a unique capsule around a DMBA (9,10-dimethyl-1,2-benzanthracene) pellet implanted in the brain of rabbits, and later of mice and rats. Further investigations in this direction showed that the pellet of carcinogen was surrounded as early as 24 h after the beginning of the experiment initially by mesenchymal cells with no processes, but which later acquired powerful outgrowths and small additional processes of cytoplasm. These processes make contact with the surface of the carcinogen. Because of these properties, these cells have been conventionally described as hair cells. It was soon found that hair cells are constantly formed around a DMBA pellet in all organs of tissues, and that they are thus a regular early stage in the process of chemical carcinogenesis [2, 3]. Meanwhile, it has been suggested on the basis of morphological observations that resorption and metabolism of DMBA take place in these cells [3, 5, 6], accompanied by activation of particular metabolic reactions and by ultrastructural changes in the capillary wall of the capsule [7].

In this investigation the object was to study by an electron-cytochemical method changes in some metabolic processes in the hair cells and in the capillary walls under the influence of the polycyclic hydrocarbon DMBA.

EXPERIMENTAL METHOD

Altogether 10 control and 10 experimental animals were used. Material was taken 1, 3, and 7 days after implantation of a DMBA pellet into the rat's brain. Pieces of brain in direct contact with the pellet were fixed in 1% glutaraldehyde solution in cacodylate buffer (pH 7.4) with the addition of 4.5% glucose for 1 h. Adenylate cyclase was detected by a modified method in [8]. Two incubation media were used: mixture 1) with the addition of sodium fluoride (control) and mixture 2) without sodium chloride (experiment). The material was dehydrated in acetones of increasing strength by the usual electron-microscopic methods. The unstained preparations were examined in the electron microscope.

EXPERIMENTAL RESULTS

One day after the beginning of the experiment young hair cells were found in the perivascular zone close to the carcinogen pellet. At this period their cytoplasm was poorly supplied with organelles. The presence of poorly developed cisterns of granular cytoplasmic reticulum and the solitary ribosomes were evidence of an inadequate level of intracellular protein translation activity. Electron-histochemical investigation revealed very low activity of adenylate cyclase on the plasmalemma in the hair cells (Fig. 1).

No adenylate cyclase activity was detected in the wall of the regional capillaries in the zone of implantation of the carcinogen, on membranes of the endotheliocytes and in the basal layer of the capillaries, in either the experimental or the control animals.

In the course of 3 to 7 days gradual differentiation of the hair cells took place and organelles, particularly protein-synthesizing organelles, such as the granular cytoplasmic reticulum and free ribosomes, developed in them. Processes of cytoplasm, making contact with the carcinogen, also appeared. In this period the hair cells began to carry out phagocytosis of particles of the carcinogen. The latter, in the form of electron-dense fragments, also

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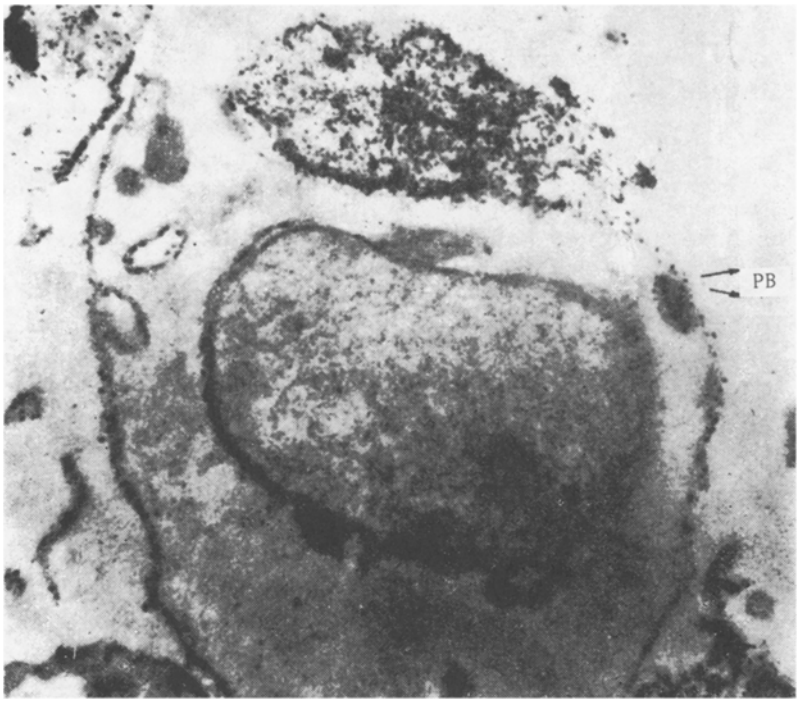

Fig. 1. Adenylate cyclase activity on plasmalemma of hair cell 1 day after implantation of DMBA. PB) Pellet bed (arrows), 25,000 ×.

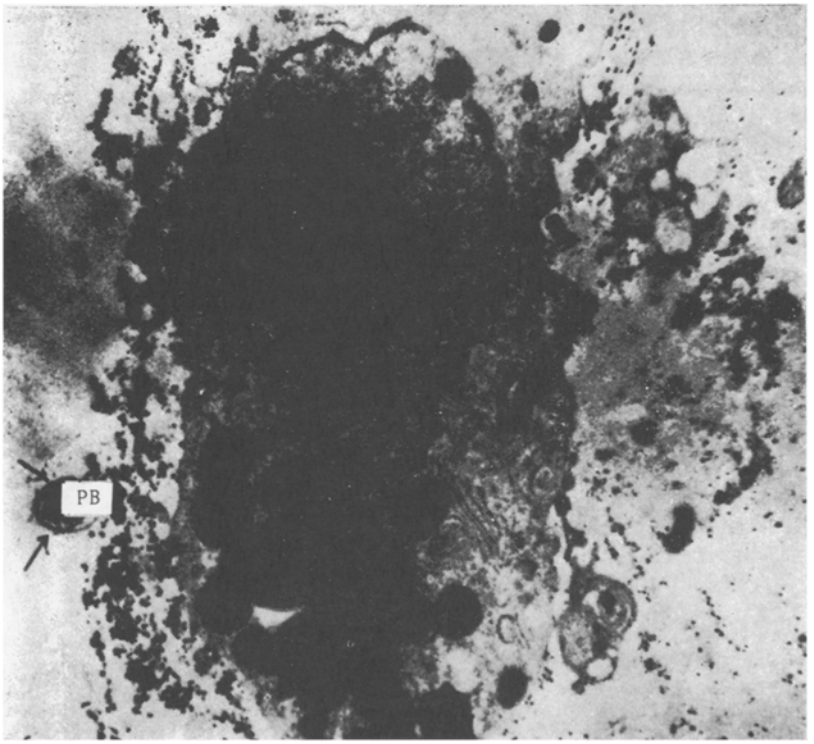

Fig. 2. Adenylate cyclase activity on plasmalemma of hair cell 7 days after implantation of DMBA. 12,500 ×. Remainder of legend as in Fig. 1.

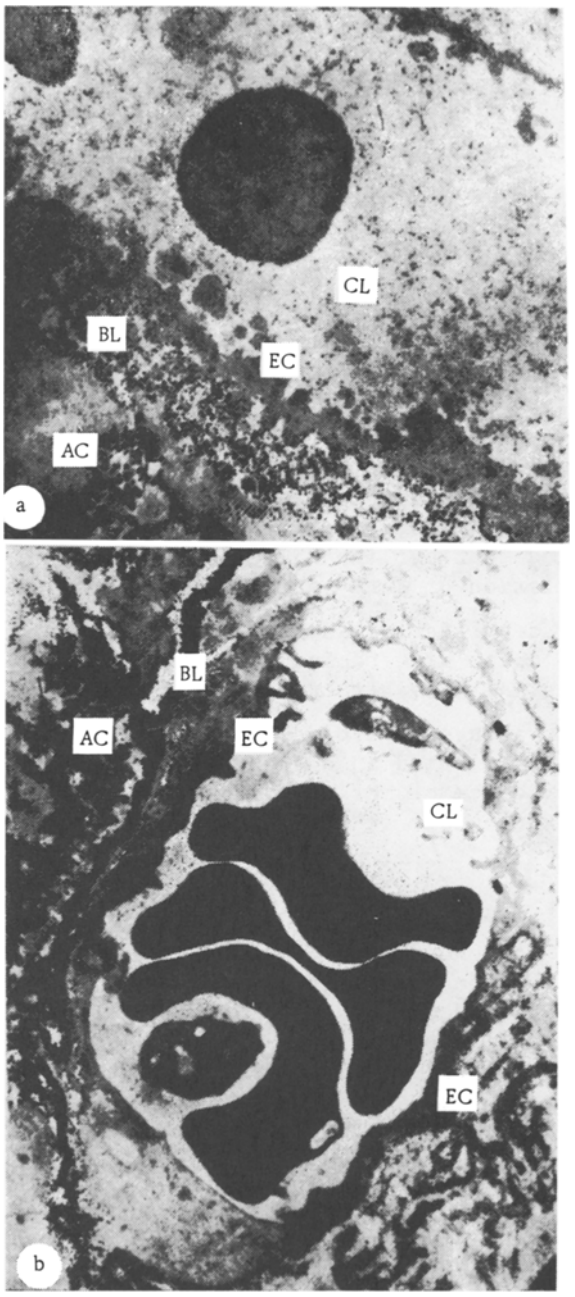

Fig. 3. Adenylate cyclase activity on basal plasmalemma of endothelial cells (EC) and in basal layer (BL) of capillary wall facing DMBA. a) Three days after beginning of experiment; b) 7 days after beginning of experiment. CL) Capillary lumen; AC) adventitial cells. 12,500 ×.

was found in their cytoplasm [6, 7]. Meanwhile, adenylate cyclase activity on the membranes of the hair cells was intensified and was particularly clearly revealed on the side facing the DMBA pellet (Fig. 2).

At the same period a gradual increase in enzyme activity was observed in the wall of the regional capillaries on the side facing the DMBA pellet. The intensification of adenylate cyclase activity was particularly marked on the basal part of the plasmalemma of the endothelial cells and also in the basal layer of the capillaries. Activity of the enzyme also could be detected on membranes of the adventitial cells of the capillaries (Fig. 3).

In the control in which sodium fluoride was added, a uniform distribution of enzyme was observed in the wall of the capillaries, irrespective of their orientation relative to the carcinogen.

The electron-cytochemical investigation of adenylate cyclase activity in the hair cells in the early stages (from 1 to 7 days) thus showed a gradual increase in activity of the enzyme on the cell membranes and, in particular, on the cytoplasmic membranes on the side facing the DMBA pellet.

Among the main substances taking part in the general system of self-regulation of the activity of the cells and tissues of the body are hormones, binding with special receptors on the cell surface. Under these circumstances adenylate cyclase located in the cell membrane becomes activated and, in turn, this leads to activation of cyclic AMP, which has been shown to activate many intracellular enzymes [4, 8, 10]. These biochemical investigations, and also the results of our own observations, suggest that the polycyclic carcinogenic hydrocarbon DMBA, which has a steroid-like structure, can stimulate the adenylate cyclase of the hair cell. The cyclic AMP synthesized as a result of this effect, activates metabolic processes in the cell [9] and thereby accelerates the development of the hair cell. There is evidence in the literature that cyclic AMP effects processes of lipolysis in adipose tissue [10]. In this connection it can be suggested that cyclic AMP causes breakdown of triglycerides in the hair cell, followed by the accumulation of fatty acids and water in it.

The intensification of adenylate cyclase activity of the endothelial cells and the basal layer of the capillary wall on the side facing the carcinogen is also evidence of early activation of metabolic processes in these structures under the influence of DMBA.

Consequently, changes in adenylate cyclase activity in the hair cells and capillary wall in a focus of carcinogenesis, reflected in a gradual increase in activity throughout the period of the experiment, are evidence of early involvement of the hair cells and capillaries in the pregliomatous process taking place in the CNS under the influence of DMBA.

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