STRUCTURAL CHANGES IN THE TUBULAR EPITHELIUM OF ALLOGRAFTED HUMAN KIDNEYS AFTER TRANSPLANTATION

V. N. Blyumkin and A. E. Ivanov

UDC 616.61-089.843-07: 616.612-018.7-076.5

The structure of allografted cadaveric human kidneys (AK) was studied between 4 months and 6 years after transplantation. In AK which kept on functioning well until death of the patients from causes unconnected with failure of the grafts, a weak cellular immune response and moderate sclerosis of the intertubular connective tissue were observed. Cytological reconstruction of the epithelium of the proximal tubules consisted of the formation of numerous polykaryocytes with a hypertrophied brush border. This phenomenon ("proximal polykaryocytosis") is interpreted as a manifestation of the regenerative powers of the epithelium of the proximal tubules of AK in the late stages after transplantation. Chronic moderate hypoxia of AK is a favorable factor for reconstruction of the epithelium of the proximal portion of the nephron. In AK with unsatisfactory function associated with the development of chronic rejection, not responding to treatment, an intensive cellular immune response was observed, with the development of coarse sclerosis, resulting in atrophy of most of the tubules of AK.

KEY WORDS: allografted cadaveric kidneys; mitotic activity; tubular epithelium.

In previous publications [1-3] the writers stated that in the early period of existence of allografted human cadaveric kidneys (AK) in the recipients mitoses appear, which are not found in the renal tubules of healthy subjects. Certain distinguishing features of mitosis in the AK epithelium were described: variations of mitotic activity, shifts in the formula of mitosis, and the appearance of pathological mitoses [1, 2]. Mitotic activity was highest during the first months after transplantation. It fell in the 2nd month, and toward the end of the 3rd month hardly any mitoses could be found in the tubules of AK. Recently the writers have studied changes in the structure of the tubular epithelium of AK taking place in late stages after transplantation. These changes are described below.

EXPERIMENTAL METHOD

The test objects were 24 AK which had survived in the recipients for between 4 months and 6 years (autopsy and biopsy material). The material was fixed in 10% neutral formalin and embedded in paraffin wax. Sections 3-7 μ thick were stained with hematoxyline-eosin, picrofuchsin, orcein, and toluidine blue and the PAS reaction was carried out. The AK were divided into two groups. Group 1 included 14 AK which continued to function satisfactorily until the patient's death, which was not due to graft failure but resulted from influenzal phenumonia, tuberculous meningitis, bleeding from steroid ulcers of the stomach and intestine, and so on. Group 2 consisted of 10 AK whose function had been unsatisfactory for a long time before removal or before the patient's death in connection with chronic rejection which did not respond to immunodepressive treatment.

EXPERIMENTAL RESULTS

Macroscopic changes in AK of group 1 were slight. The kidneys were a little enlarged and their surface smooth. In the cut surface the boundary between the cortex and medulla was clearly identified. The general pattern of the organ was preserved. Microscopically, slight proliferation of the intertubular connective tissue was observed. The arrangement of the tubules was normal; there was no difficulty in identifying the different parts of the nephrons. The structure of the intramural arteries and veins was only slightly changed. The cellular immune response in most AK of this group was weak. Most of the malpighian bodies retained their normal structure; some glomeruli were moderately sclerosed. Against this background characteristic cyto-

Laboratory of Pathomorphology, Institute of Transplantology and Artificial Organs, Ministry of Health 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. 88, No. 9, pp. 355-358, September, 1979. Original article submitted February 6, 1979.

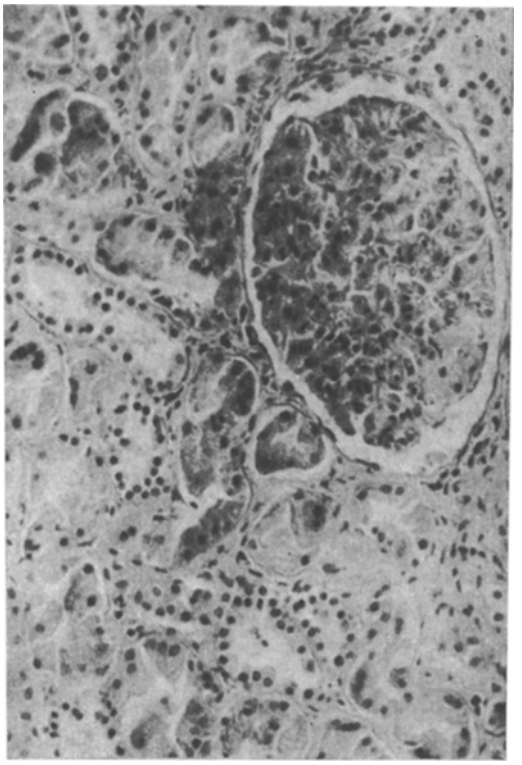

Fig. 1. Allografted kidney with good function after 3 years 7 months in the recipient. Cortex. Structure of parenchyma well preserved. Moderate sclerosis of intertubular connective tissue. Cellular immune response absent. Numerous polykaryocytes in proximal tubules. Hematoxylin-eosin, 160×.

logical structural changes were observed in the epithelium of the proximal portion of the nephrons. Cells with many nuclei – polykaryocytes – appeared (Figs. 1 and 2). The number of nuclei in some polykaryocytes reached 30-40. The polykaryocytes accounted for 6-10% of the total number of cells lining the proximal tubules. The total number of nuclei contained in the polykaryocytes was 15-80% of the total number of nuclei in all epithelial cells of the proximal tubules counted in sections in different AK of group 1. Sections through some proximal tubules showed that the lumen was lined entirely by polykaryocytes. The brush border of the polykaryocytes was hypertrophied, evidence of the high functional activity of the epithelial cells undergoing structural changes.

A different picture was found when AK of group 2 were studied. They were greatly reduced in size and their weight did not exceed 100 g. The organ was firm in consistency and regions of contracted AK could be seen in the cut section, and the boundary between the cortex and medulla could not be identified. Histological examination revealed considerable sclerotic changes in AK. Collagen muscles ran in different directions through the cortex, forming wide partitions between small areas of atrophic parenchyma. The total number of malpighian bodies was sharply reduced; most of the preserved renal glomeruli were sclerosed and deformed, and devoid of capillary loops, in which the number of endothelial cell nuclei were sharply reduced and the mesangium was thickened. Some malpighian bodies showed hyalinosis: the space in Bowman's capsule was obliterated, its parietal layer considerably thickened, and outside it there was a well-marked layer of PAS-positive material. Marked sclerotic changes were observed in the walls of the arteries. Localized foci or more general areas of infiltration of plasma cells and lymphocytes were constantly found in the stroma. Advanced atrophic changes in the tubular epithelium, in the form of flattening or shrinking of the epithelial cells and karyopycnosis, were characteristic of this group of AK. In places the tubules were converted into narrow bands and islands consisting of small epithelial cells with hyperchromic nuclei. All these changes made it impossible to differentiate between the different portions of the nephrons. The structural changes described above were evidence of the functional insufficiency of the AK of group 2.

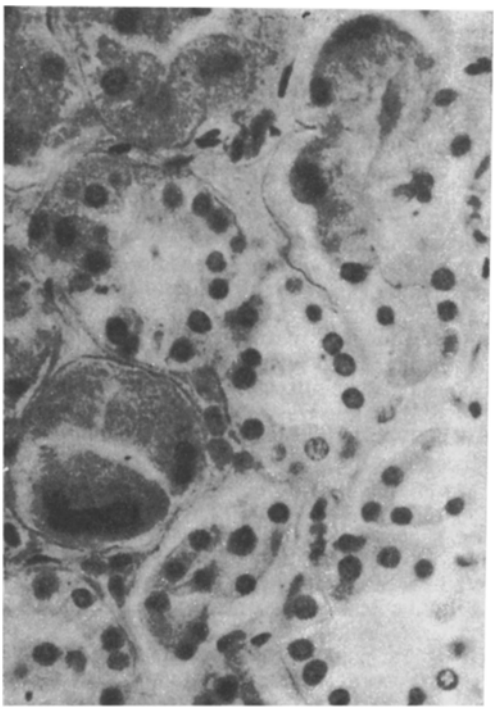

Fig. 2. Region of cortex of the same kidney. Polykaryocytes in proximal tubules. Hematoxylin-eosin, 400×.

It is now known that the functional state of the tubules of AK is an important factor in the maintenance of homeostasis in the recipients [4, 5]. For this reason the study of cytological structural changes and cell proliferation in the tubular epithelium of AK is very important. On the basis of previous investigations and the results of the present study definite conclusions can be drawn regarding the special features distinguishing regeneration of the tubular epithelium of the human AK at different times after transplantation. In the early stages [1, 2, 6] the principal method of regeneration is mitosis. Despite the fact that mitotic activity varied in different cases within wide limits, there were nevertheless sufficient grounds for postulating mobilization of the "proliferative pool" of the tubular epithelium of AK during the first months after transplantation. The problem of the possible trigger mechanisms of this process has already been discussed previously [1-3]. The morphological manifestation of regenerative activity of the tubular epithelium of AK in the late stages after transplantation (under conditions of prolonged immunodepression) is the phenomenon of polykaryocyte formation in the proximal part of the nephron. The nature of these cells and the cause of their appearance in certain pathological states has already been discussed elsewhere [7-9]. It has been concluded from an analysis of extensive data that the appearance of polykaryocytes in the proximal tubules is a unique manifestation of the regenerative powers of this part of the nephron during chronic oxygen deficiency [8]. The present results support this hypothesis. Polykaryocytes were found in the proximal tubules of well functioning human AK after a period of more than 4 months in the recipient. In these cases the cellular immune response in AK was weak, but signs of moderate sclerosis of the intertubular connective tissue were observed, and this may probably have been the cause of development of moderate chronic hypoxia of the tubular epithelium. As a result of this process conditions were created that were favorable for regenerative reorganization of that part of the nephron that was most sensitive to oxygen deficiency, namely its proximal portion (i.e., for the formation of polykaryocytes). Possibly largely on account of these structural changes the AK of group 1 were able to take part in the maintenance of the recipients' homeostasis. In cases when chronic rejection could not be overcome by therapeutic measures and signs of severe sclerosis developed (the AK of group 2), profound destructive changes developed in the tubular epithelium of AK. The AK thereupon lost their function.

The phenomenon described above, for which the name "proximal polykaryocytosis" is suggested, requires further special study. This phenomenon is perhaps one of the important morphological criteria of the functional state of the tubular epithelium of AK in the late stages of their existence in the recipient.

LITERATURE CITED

1. V. N. Blyumkin, in: Transplantation of the Kidney and Artificial Organs [in Russian], Moscow (1976), p. 98.
2. V. N. Blyumkin and A. E. Ivanov, Byull. Éksp. Biol. Med., No. 12, 78 (1973).
3. A. E. Ivanov and V. N. Blyumkin, in: Immunodepression during Organ Transplantation [in Russian], Moscow (1973), p. 176.
4. M. Ya. Ratner, in: Current Problems in Transplantology and Artificial Organs [in Russian], Moscow (1975), p. 17.
5. M. Ya. Ratner, V. V. Serov, and N. A. Tomilina, Renal Dysfunctions [in Russian], Moscow (1977).
6. W. J. Dempster and M. A. Williams, Br. Med. J., 1, 18 (1963).
7. G. Holle, Zbl. Allg. Path. Path. Anat., 102, 581 (1963).
8. J. Orlowska, Patol. Pol., 24, 409 (1973).
9. A. Tilp, Über die Regenerationsvorgänge in der Nieren des Menschen, Jena (1912).

EFFECT OF SODIUM HYDROXYBUTYRATE ON MYOCYTE ULTRASTRUCTURE IN STRIATED MUSCLE TISSUE DURING PHYSICAL EXERTION

N. N. Kleimenova, R. U. Ostrovskaya, and V. A. Arefolov

UDC 615.31:547.473.2'133].015.4:612.74

The ultrastructure of myocytes in the rat myocardium and skeletal muscles was studied during physical exertion in a control group and after preliminary administration of sodium hydroxybutyrate for 2 weeks. A single exposure to maximal physical exertion was shown to cause considerable changes in the fine structure of the cardiomyocytes and, to a rather lesser degree, in the myocytes of skeletal muscles. These changes consisted of masked intermyofibrillary edema, swelling of the mitochondria, and a sharp decrease in the glycogen level. Sodium hydroxybutyrate, if given for 2 weeks beforehand, prevents the changes described above in the myocytes. Normalization of structure observed under the influence of the compound can evidently be attributed to the character of its metabolic conversion and its effect on energy metabolism.

KEY WORDS: sodium hydroxybutyrate; physical exertion; ultrastructure of the myocardium and skeletal muscles.

Sodium hydroxybutyrate has been shown to be capable of increasing the resistance of the body to various types of hypoxia [1, 5, 6] and to accelerate recovery processes under conditions of minimal rest after physical exertion [3]. Sodium hydroxybutyrate prevents the increase in the lactate concentration in the tissues of the brain and heart characteristic of hypoxia and also considerably restricts the increase in the lactate/pyruvate ratio caused by hypoxia [7]. Under the influence of sodium hydroxybutyrate the accumulation of toxic products of nitrogen metabolism is prevented [2]. Since considerable physical exertion causes metabolic changes in muscle tissue, accompanied by accumulation of lactic acid and ammonia and by a decrease in the glycogen concentration, it was decided to study the effect of sodium hydroxybutyrate on the ultrastructure of myocytes of cardiac and skeletal muscles.

EXPERIMENTAL METHOD

Experiments were carried out on 25 noninbred albino rats weighing 170-180 g. The control group, consisting of 10 rats, was compelled to swim carrying a load equal to 6% of the body weight in water at a tempera-

Laboratory of Pharmacology of the Nervous System and Laboratory of Neurochemical Pharmacology, Institute of Pharmacology, Academy of Medical Sciences of the USSR, Moscow.

(Presented by Academician of the Academy of Medical Sciences of the USSR V. V. Zakusov.) Translated from Byulleten' Éksperimental'noi Biologii i Meditsiny, Vol. 88, No. 9, pp. 358-361, September, 1979. Original article submitted January 16, 1979.

0007-4888/79/8809-1080$07.50