MORPHOLOGY AND PATHOMORPHOLOGY

HUMAN MYOCARDIAL HYPERTROPHY AND CARDIOMYOCYTE PLOIDY

V. Ya. Brodskii, A. M. Aref'eva, N. V. Panova, I. G. Gvazava, and D. S. Sarkisov

UDC 612.17.014.22:612.6.05].08

KEY WORDS: human cardiomyocytes; polyploidy.

High ploidy of the myocytes in the hypertrophied human heart has been observed in several cytophotometric studies [7-9]. It has been suggested that in man, unlike in the rat, which has been completely studied in different experiments [5], hypertrophy is accompanied by entry of the myocytes into the mitotic cycle in the adult period. In a more recent study of ploidy of myocytes in the normal myocardium considerable individual variability was found [3]. The average ploidy in the anterior wall of the ventricle varied from 3.2 to 7.3 c (where c denotes the DNA content in the haploid set of chromosomes), and in the posterior wall it could be about 8-9 c. In this hexadecaploid cells were predominant in the heart wall. It was suggested that high ploidy in hypertrophy in adults may be the result of enhanced polyploidization of the myocytes during proliferation, which ended in childhood.

EXPERIMENTAL METHOD

The myocardium of seven patients with pathology of the heart and blood vessels was studied. The heart of two of these patients was not hypertrophied, although scars were found in the left ventricle (Table 1). In another two cases hypertrophy of the left ventricle was the result of general atherosclerosis with myocardial infarcts. Three patients had congenital heart disease with hypertrophy of the left or right ventricle, and these patients were young. All these patients had died from heart failure. Small pieces of the tunica media of the myocardium of the left or right ventricle were fixed in formalin solution, made up in phosphate buffer, pH 7.0 (1:10) for 2-3 weeks. The muscle was then dissociated into separate cells [1] and stained by Feulgen's method and with Naphthol yellow [10]. The conditions of photometry of DNA on a Vickers M-86 scanning integrating densitometer were: objective 100 times, scanning probe 0.4 illumination of the preparation by light with a wavelength of about 580 nm.

EXPERIMENTAL RESULTS

The average ploidy of the myocytes (and, correspondingly, the set of their classes) in the unhypertrophied ventricle and also in the hypertrophied ventricle of the adults were within the limits of variability of the normal myocardium (Table 1). In one case with considerable postinfarction hypertrophy (i.e., acquired by the patient when an adult), the average ploidy was close to the extreme values for the normal posterior wall. A significant number of myocytes was found with 16 sets of chromosomes (8 c × 2), and cells with 32 sets were found also (Fig. 1). In the remaining cases of late hypertrophy the average ploidy corresponded to the average values for the normal myocardium.

The examples of congenital heart disease, accompanied by hypertrophy, differed sharply from these cases. The average ploidy of the myocytes was far outside the limits of normal variability. Cells with 32 sets of chromosomes, especially 16 c × 2, predominated, but cells of even higher ploidy were found – up to 64 c × 2, which are not normally found (Fig. 2).

Laboratory of Cytology, N. K. Kol'tsov Institute of Developmental Biology, Academy of Sciences of the USSR. Department of Pathological Anatomy, A. V. Vishnevskii Institute of Surgery, Academy of Medical Sciences of the USSR, Moscow. (Presented by Academician of the Academy of Medical Sciences of the USSR D. S. Sarkisov.) Translated from Byulleten' Éksperimental'noi Biologii i Meditsiny, Vol. 113, No. 2, pp. 196-198, February, 1992. Original article submitted May 23, 1991.

0007-4888/92/0002-0259$12.50

TABLE 1. Average Ploidy of Ventricular Myocytes in Different Cases of Pathology of the Human Heart

Age, years	Weight, g			Description	Average ploidy, c
	of heart	of LV	of RV		
68	500	210	—	General atherosclerosis, coronary	
				Scars in posterolateral wall	5,7
53	740	340	—	General atherosclerosis, lower limbs. Scars in posterior wall	9,3
44	520	170	—	General atherosclerosis, coronary. Extensive foci of infarcts in postero-lateral wall	5,9
43	630	180	—	Rheumatic mitral heart disease, established 3 years before death. Scars in posterolateral wall	8,8
22	550	150	200	Congenital defect. Tetralogy of Fallot, interatrial septal defect	7,0 13,2
28	850	340	—	Rheumatic heart disease established at 9 years of age. Mitral incompetence. Stenosis	23,2
19	620	100	240	Congenital heart disease. Marked stenosis of outlet of right ventricle	6,4 21,0

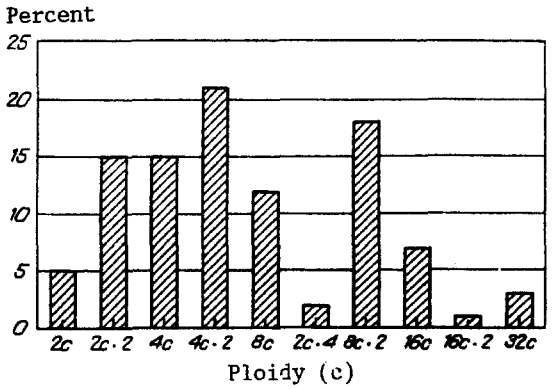

Fig. 1. Ploidy classes of myocytes (2 c – diploid cells, 2 c × 2 – binuclear cells with diploid nuclei, 4 c – mononuclear tetraploid cells, 2 c × 4 – tetranuclear cells with diploid nuclei, etc.) in adult with hypertrophied left ventricle (weight 340 g), average ploidy 9.3 c.

Incidentally, in the example shown in Fig. 2 the weight of the left ventricle was exactly the same as in the example in Fig. 1, namely 340 g.

The composition of the myocytes in the right, hypertrophied, ventricle and in the left ventricle with normal weight, in the case of congenital stenosis of the outlet of the right ventricle is shown in Fig. 3. In the left ventricle both the ratio between the classes of myocytes and their average ploidy were indistinguishable from normal. In the right ventricle cells with high ploidy predominated, and the average ploidy (21 c) went far beyond the limits of normal.

Proliferation of the ventricular myocytes is complete in man by the age of 8-12 years [2]. The difference of 4 years most probably signifies natural variability of the times of proliferation (polyploidization) rather than an error of observation. This may be one cause of the individual variability in cardiomyocyte ploidy found in adult individuals [3]. Congenital

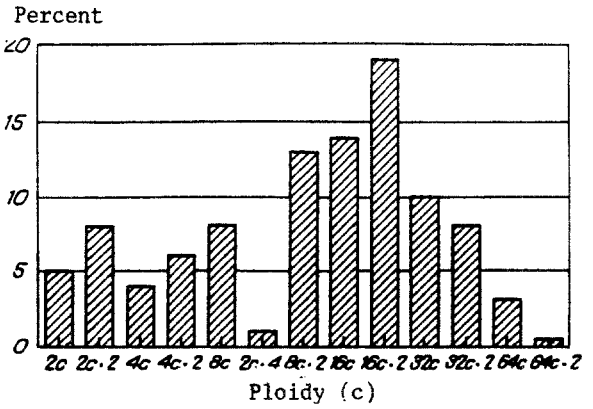

Fig. 2. Ploidy classes of myocytes in hypertrophied left ventricle in patient with congenital heart disease. Weight of ventricle the same as in Fig. 1, average ploidy 23.2 c.

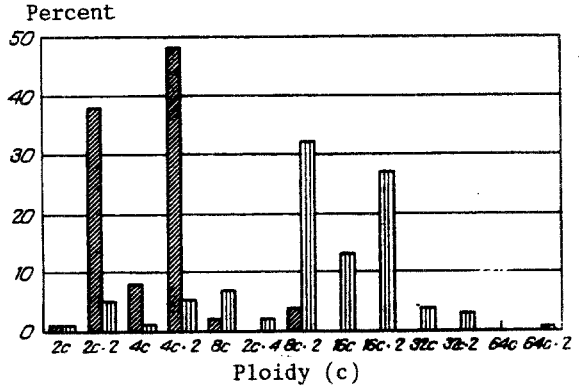

Fig. 3. Ploidy classes of myocytes in left ventricle of normal weight (100 g), average ploidy 6.4 c (obliquely shaded columns) and in right hypertrophied (weight 240 g) ventricle of the same heart, average ploidy 21 c (vertically shaded), in patient with congenital heart disease (Table 1).

heart disease, discovered before the age of 12 years, i.e., before polyploidization has ended, may be an additional factor in multiplication of the genome. Postnatal growth of the heart is known to be determined by both multiplication and polyploidization of the myocytes in the early period after birth, and mainly, by hypertrophy of the cytoplasm of postmitotic cells. In mice and rats growth of the cytoplasm takes place almost throughout life, but in man, only while the heart grows [2]. In patients with diseases of the cardiovascular system, the considerable weight of the ventricle associated with comparatively low ploidy of the myocytes may be the result of hyperplasia of structures and an increase in mass of the cytoplasm in nonproliferating cells. The very high ploidy in other cases of a pathological increase in weight of the heart leads to doubling of the mass of the cells on polyploidization, and later, after departure from the cycle, these polyploid cells grow more rapidly than diploid cells. Ventricular myocytes do not lose their ability to enter the mitotic cycle, although under normal conditions this ability is virtually not exhibited in adult rats, and during functional stress (for example, after myocardial infarction) it is manifested extremely weakly [5]. Nevertheless, in extreme emergency situations, accompanied by hypertrophy, some degree of additional polyploidization can be assumed. We have not yet seen such a case.

In congenital heart disease polyploidization takes place mainly in childhood within the strictly defined 12 years of the normal period. In postinfarct hypertrophy in adult individuals additional polyploidization is absent: polyploidy differed within the limits of the strongly varying normal value. The results confirm the view that prolonged intensification of

myocardial function in the adult individual is typically maintained not by stimulation of proliferation, but by hyperplasia of the structures and hypertrophy of the cytoplasm in nondividing myocytes [6].

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EFFECT OF SENSITIZATION ON GUINEA PIG SLOW MUSCLE WITH DISTURBANCE OF NEUROTROPHIC CONTROL

V. V. Valiullin, A. M. Devyataev, R. R. Islamov, M. E. Valiullina, and A. Yu. Teplov

UDC 616.74-02:616-056.3]-092.9-078.33

KEY WORDS: slow muscle; sensitization; denervation; immunohistochemistry; myosins.

The influence of neurotrophic control on various structural and functional characteristics of muscle fibers (MF) has been studied quite adequately. Repeated investigations have shown that disturbance of neurotrophic control modifies the phenotype of the skeletal muscles [4, 13]. It has been found, for instance, that division of the motor nerve (denervation) affects the set of myosins in MF, and that in fast muscles the content of the slow light chain 1 (LC1) increases, whereas in slow muscles, on the contrary, the concentration of LC3, characteristic of fast myosin, is increased. Unfortunately, virtually all studies of the protein composition of MF when neurotrophic control is disturbed had been undertaken by electrophoretic methods [9], but when isoforms of contractile proteins with closely similar electrophoretic parameters are present, interpretation of the results can be very difficult. The immunologic approach, using antibodies (AB) to concrete proteins or to their fragments [6] must therefore be regarded as the most adequate approach for identification of contractile proteins. Besides neurotrophic control, phenotypes of skeletal muscles are determined also by hormonal influences. There have been many investigations into the endocrine regulation of skeletal muscle function, which have shown that both hormone excess and hormone deficiency can modify various characteristics of skeletal muscles [2, 14]. For instance, hypo- and hyperthyroid-

Department of Histology and Embryology and Department of Pathological Physiology, S. V. Kurashov Kazan' Medical Institute.

(Presented by Academician of the Academy of Medical Sciences of the USSR A. P. Avtsyn.) Translated from Byulleten' Éksperimental'noi Biologii i Meditsiny, Vol. 113, No. 2, pp 198-200, February, 1992. Original article submitted March 19, 1991.

0007-4888/92/0002-0262$12.50