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RESPONSE OF CARDIOMYOCYTES OF THE RIGHT HEART TO TRAUMA OF THE LEFT

G. B. Bol'shakova

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A myocardial infarct in the left ventricle was produced in adult rats weighing 120-160 g by ligation of the left coronary artery; the left atrium was injured; or a mock operation was performed and the pericardium was removed. On the fifth day after the operation dividing myocytes were found in the right atrium (mitotic index 0.7-8.8‰) and in the subepicardial zone of the right ventricle (mitotic index 0.8-2.9‰). In old rats weighing 300-430 g, on the third day after the various types of injury to the myocardium, mitotic activity was found in the myocytes of the left auricle (1-5.1‰), and in one of eight cases in the right auricle (4.2‰); single mitoses also were found in the subepicardial zone of the left ventricle.

KEY WORDS: myocardial infarct; division of cardiomyocytes; right heart.

This investigation is a continuation of previous work [2] which showed that in response to injury to the left heart (infarct of the ventricle, trauma to the atrium) and, in some cases, in response to a mock operation also, certain cardiomyocytes in the left atrium and the supepicardial zone of the left ventricle start to divide by mitosis. With these observations in mind it seemed important to study the response of the right, intact side of the same heart. There is evidence in the literature of an increase in the number of myocytes of the rat atrium synthesizing DNA in infarction of the left ventricle [4], but no quantitative characteristics of their mitotic activity are given in the paper cited.

The object of this investigation was to study the level of proliferation of the myocytes of the right heart after trauma to the left heart.

EXPERIMENTAL METHOD

An infarct of the myocardium of the left ventricle was produced in adult noninbred albino rats weighing 120-160 g, the left atrium was injured, or a mock operation was performed with removal of the pericardium only. From the 49 rats 29 were chosen, in which mitoses were comparatively numerous in the left heart in

Laboratory of Growth and Development, Institute of Human Morphology, Academy of Medical Sciences of the USSR, Moscow.

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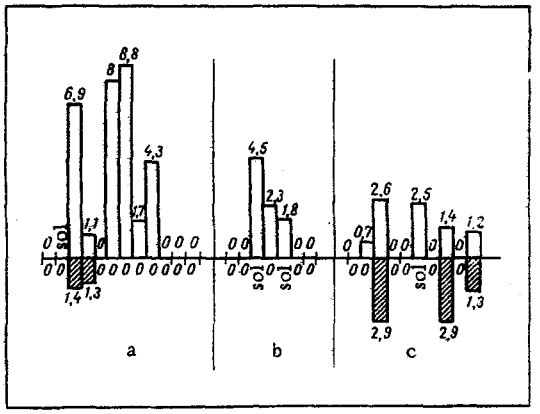

Fig. 1. Mitotic index (in $^0/_{00}$) of myocytes of right heart of individual animals after various injuries to left heart: a) ligation of coronary artery; b) injury to atrium; c) mock operation. Unshaded columns represent right atrium, shaded columns supepicardial zone of myocardium of right ventricle. 0) Mitoses absent, sol) solitary mitoses.

response to injury. The control group consisted of 10 intact animals of the same weight. The rats were killed on the fifth day after the operation at 10 a.m.

Various injuries were inflicted on the myocardium of eight old noninbred albino rats (body weight 300-430 g) also: In three animals a ligature was applied to the left coronary artery at the level of the atrium, in one the coronary artery was ligated in the region of the upper third of the left ventricle, in two rats the ligature was applied to the wall of the left atrium, in one rat to the left auricle, and in one rat the pericardium was removed without any additional procedures (mock operation). The old rats were killed on the third day after the operation at 10 a.m.

The hearts were fixed in Carnoy's fluid and embedded in paraffin wax. Longitudinal sections 5-7 μ thick were stained with hematoxylin and counterstained with eosin and picrofuchsin. The number of mitoses was counted in 3000-4000 muscle nuclei from the atrium and subepicardial zone of the ventricle. The mitotic index (MI) was expressed in promille.

EXPERIMENTAL RESULTS

The right heart responded to injury to the left heart by mitotic division of the myocytes (Fig. 1). An interesting discovery was that the degree of proliferation of the myocytes of the uninjured right atrium was frequently higher than that of the left atrium. For example, in three rats surviving a myocardial infarct of the left ventricle, MI for the left atrium was 3.5, 3.7, and 2.6$^0/_{00}$, and for the right atrium 4.3, 8.1, and 8.8$^0/_{00}$, respectively (Fig. 2a). The myocytes of the right atrium are evidently no less capable of proliferating than the myocytes of the left atrium. This was also confirmed by the fact that removal of the pericardium (mock operation) in 5 of 10 cases induced mitoses in the right atrium (MI 0.7-2.6$^0/_{00}$), whereas in the left atrium of rats undergoing the mock operation mitoses appeared in only two cases.

The subepicardial zone of the myocardium of the right ventricle also proved to be sensitive. In eight cases mitoses were found in the myocytes there (Fig. 2c), and in most cases MI corresponded to that for the left subepicardial zone, varying between 0.8 and 2.9$^0/_{00}$. Mitoses in the myocytes of the subepicardial zone of the right ventricle probably arose as a direct response to injury irrespective of the response of the myocardium of the left ventricle, for in five of eight cases no proliferation of the myocytes was found in the left subepicardium of the same hearts. The cause of the appearance of mitoses in these zones of the heart evidently requires special investigation.

In the control group of intact animals, no mitoses were found in either the left or the right heart. This indicates that the mitoses observed in the cardiomyocytes were most likely reactive in character and appeared in response to the operation.

The myocardium of the old animals was injured by the same methods as the myocardium of the young rats. In six of eight cases division of the myocytes of the left atrium was observed (Fig. 2b). The mitotic activity was comparatively high and MI reached 5.1$^0/_{00}$ (ligation of the coronary artery at the level of the atrium).

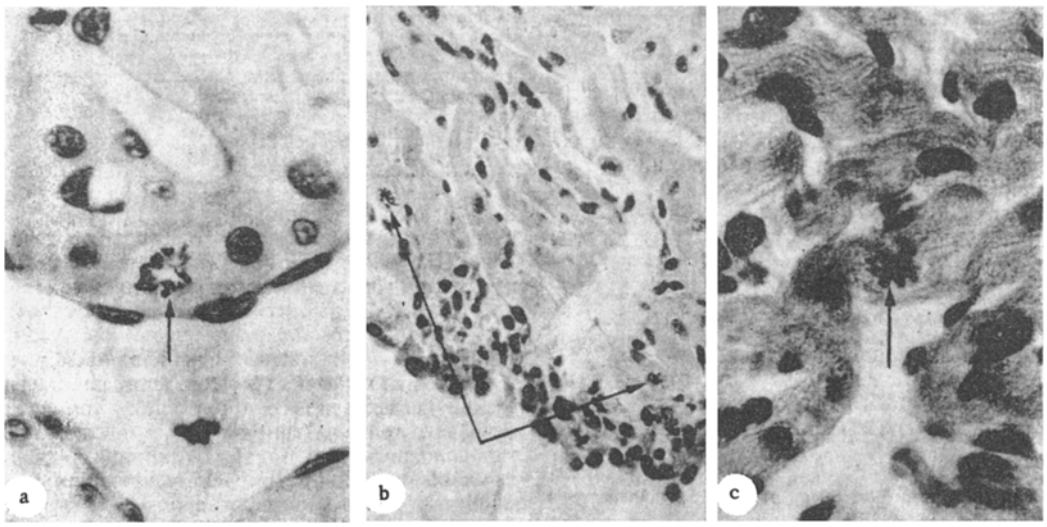

Fig. 2. Mitoses (arrows) of cardiomyocytes: a) in right atrium (stained with hematoxylin and counterstained with picrofuchsin, 1100×); b) in left auricle of heart of old rat (hematoxylin–eosin, 500×); c) in subepicardial zone of right ventricle (hematoxylin–eosin, 1100×).

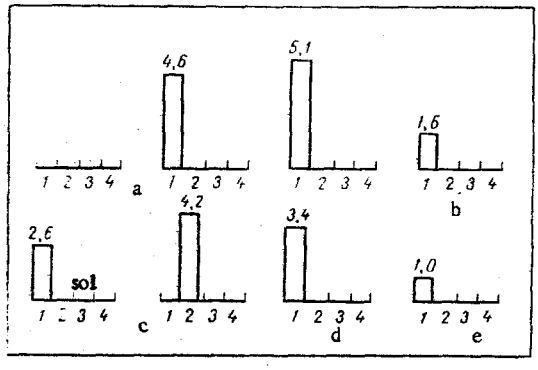

Fig. 3. Mitotic index (in $^0/_{00}$) of myocardium of old rats in different series of experiments: a) ligation of coronary artery in atrium; b) ligation of auricle; c) ligation in wall of atrium; d) ligation of coronary artery in upper third of ventricle; e) mock operation. 1) Left atrium; 2) right atrium; 3) subepicardial zone of left ventricle; 4) subepicardial zone of right ventricle. sol) Solitary mitoses.

In the right auricle mitoses were found in one of eight cases (ligature to the wall of the atrium, MI = 4.2$^0/_{00}$). In the myocardium of the subepicardial zone of the left ventricle solitary mitoses were observed in only one case (Fig. 3).

With age the cardiomyocytes thus do not lose their ability to divide. This is in agreement with the observations of Skuba [3], who found that recovery of the myocardium in old animals follows the same course as in young, the only difference being that the rate is slower because of a reduction in the rate of premitotic DNA synthesis.

In all the cases described above, one regular feature was observed: The appearance of mitoses was connected with inflammation and thickening of the epicardium [2].

It can be concluded from these results that the myocytes of the right heart are no less able to proliferate than the myocytes of the left heart [1, 2]. The heart thus responds to injury as an integral system, and not just locally.

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AUTORADIOGRAPHIC STUDY OF DNA SYNTHESIS IN RATS WITH EXPERIMENTAL MYOCARDIAL INFARCTION

V. R. Babaev

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Tritium-labeled thymidine was injected into rats with an experimental myocardial infarct and the number of DNA-synthesizing nuclei was determined in various parts of the heart. Myocardial infarction activated DNA synthesis to some extent in the nuclei of monocytes lying at the periphery of the focus of injury. However, there was no doubt about the extremely low density of labeling in the muscle nucleus. Increasing the dose and giving three injections of thymidine-^{3}H did not increase the number of labeled muscle cell nuclei. Activation of proliferation of the connective tissue cells was observed in all parts of the heart. The number of connective-tissue nuclei synthesizing DNA was increased after 24 h, reached a maximum on the second day, and remained above the control level until the end of the experiment.

KEY WORDS: myocardial infarct; DNA synthesis; cardiomyocytes.

The most debatable problem in the subject of regeneration of the myocardium is the possibility of DNA synthesis in the nuclei of the muscle cells of the ventricle of the adult mammalian heart. Although Grove et al. [10] and Sasari et al. [15] found an increase in the number of polyploid cardiomyocyte nuclei and in the number of muscle cells in the hypertrophied rat heart, autoradiographic investigations with tritium-labeled thymidine (thymidine-^{3}H) have yielded the opposite results. For instance, in addition to data pointing to the absence of DNA-synthesizing myocyte nuclei in the hypertrophied [4, 9] and infarcted [1] myocardium of adult animals, in other investigations activation of DNA synthesis has been reported in some muscle cells of the ventricles [3], especially cells near the focus of injury [11, 12].

Meanwhile, during the electron-autoradiographic study of DNA synthesis in cardiomyocytes after physical exertion, nuclei with a small number of grains were found, and their appearance could be attributed to slow synthesis of nuclear DNA [5]. This is in agreement with the view that an increase in the level of differentiation of the myocardial myocytes is accompanied by a marked increase in the duration of the main periods of the cell cycle [2, 13].

It thus appeared interesting to use autoradiographic techniques to study the topography of DNA-synthesizing nuclei of the ventricles of the rat heart in relation to a focus of infarction.

EXPERIMENTAL METHOD

An infarct was produced in the myocardium of 20 noninbred male albino rats weighing 90-100 g by suture and ligation of the left coronary artery. The animals were killed 1, 2, 3, 5, 7, 15, and 20 days after the begin-

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