AGE DIFFERENCES IN POSTSTRESS REPAIR OF MYOCARDIAL DNA

V. K. Vasil'ev and F. Z. Meerson

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Injuries to DNA develop and its reparative synthesis is induced in various organs of animals exposed to stress [2]. However, the effect of the animals' age on the severity of these injuries and the intensity of reparative DNA synthesis has not hitherto been studied.

The aim of this investigation was to make a sedimentation analysis of the degree of polymerization and analysis of reparative synthesis of myocardial DNA in rats of two age groups under normal conditions and after exposure to stress.

EXPERIMENTAL METHOD

Male Wistar rats aged 2 months (weight 190-210 g) and 13 months (weight 520-600 g) were used. Immobilization stress was induced as described previously [7] and sedimentation analysis and analysis of reparative synthesis were in accordance with the method in [3].

EXPERIMENTAL RESULTS

It will be clear from Fig. 1 that the molecular weight of DNA decreased with age whereas its heterogeneity increased, in agreement with age in the literature [8]. Poststress accumulation of low-molecular-weight fragments (fractions of gradients Nos. 13-17) in myocardial DNA also was discovered. The fraction of low-molecular-weight fragments appearing in DNA 8 h after the beginning of stress was greater in young than in adult animals. Since sedimentation analysis gives an idea of the degree of polymerization of DNA only at a certain moment, incorporation of a radioactive precursor of DNA in the course of its reparative synthesis is a more reliable test of injury and repair of DNA, for the radioactive label remains in it even after completion of repair of a certain region of DNA as evidence of the previous existence of injury.

As Figure 2 shows, analysis of poststress reparative DNA synthesis revealed distinct differences in the character of DNA repair between animals of the two age groups. Poststress activation of reparative DNA synthesis in young animals took place more rapidly than in adult animals, in agreement with data in the literature on an age increase in latent period between presentation of the inducing factor and the corresponding metabolic response [5]. The results also showed that activation of reparative synthesis in adult rats had a lower amplitude (than the corresponding analogs in the literature [6]). Poststress reparative synthesis of myocardial DNA in animals of the older age group was more prolonged than in young rats. It is a noteworthy fact that the areas of the figures (Fig. 2) included between lines of the control level and experimental curves, which show incorporation of the label throughout the period of additional reparative DNA synthesis induced by stress, are almost equal for the two age groups (the difference is under 10%). It can therefore be concluded that the DNA repair system of young animals, although it develops considerable power, on the whole functions in order to abolish poststress DNA injuries on a far larger scale than the corresponding system in animals of the older age group.

To explain the slowing of adaptive biosynthesis and, in particular, of induced DNA reparative synthesis with age, a number of possible causes may be mentioned [1, 4]. A decrease in the number of active genes through injury or blocking under these circumstances seems to be the most likely cause capable of explaining to a definite degree the age pro-

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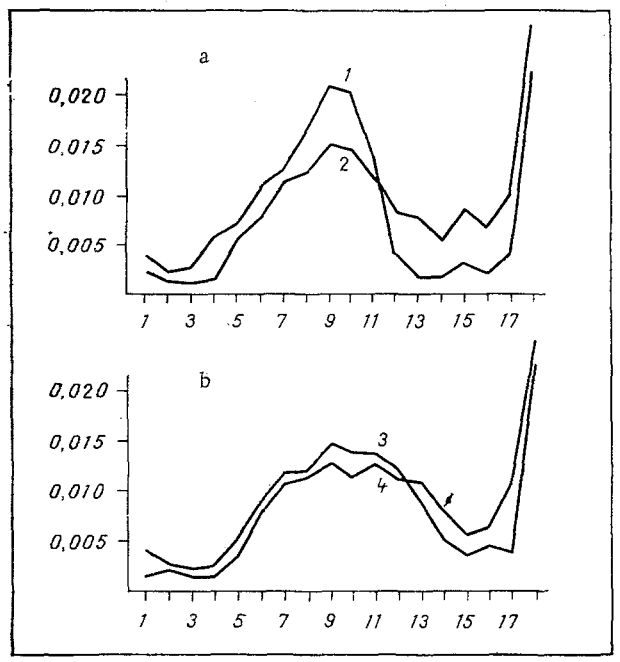

Fig. 1. Sedimentation profiles of myocardial DNA in a 5-20% alkaline sucrose gradient. Abscissa, No. of fractions of gradients; ordinate, optical density at 260 nm. a) 2 months, b) 13 months; 1) normal, 2) stress, 3) normal, 4) stress. Direction of sedimentation from right to left. High absorption at peak of gradients due to low-molecular-weight components of nucleus, including ribonucleotides — products of alkaline hydrolysis of RNA.

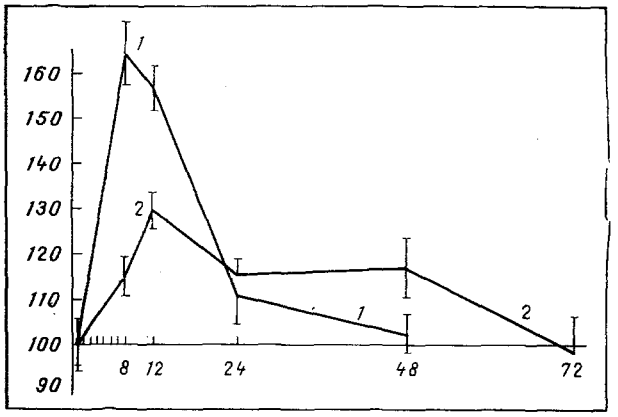

Fig. 2. Poststress reparative incorporation of [^{3}H]thymidine into myocardial DNA (in % of control level). Abscissa, time after beginning of exposure to stress (in h); ordinate, incorporation of [^{3}H]-thymidine (in % of control). 1) 2 Months (control level of incorporation of radioactivity 247 cpm/mg DNA), 2) 13 months (control level of incorporation of radioactivity 254 cpm/mg DNA). Dose of radioactivity injected during hour before sacrifice was 250 Ci/100 g body weight. During 30 min before intraperioteneal injection of radioactive label, hydroxyurea was injected in doses of 50 mg/100 g [3]. Group of three animals was used to obtain each experimental point. Scatter of data represented by standard deviation of arithmetic mean of three determinations.

longation of poststress reparative DNA synthesis demonstrated in the present investigation. Injuries accumulating with age evidently do not leave untouched the genes which control DNA repair, and this must be reflected in the correctness of reparative synthesis. When the results of this investigation are analyzed, it can be accepted that repair of myocardial DNA in the older age group takes place in several stages and may perhaps include correction (resynthesis) of individual repaired DNA regions initially insufficiently correctly synthesized, and this requires extra time. This hypothesis is in agreement with the character of the time course of poststress reparative synthesis of myocardial DNA from the comparative age aspect (Fig. 2). During the first days after stress, in the course of induced reparative synthesis for a period of 2 days 88% of radioactivity is incorporated into DNA of animals of the younger age group, compared with only 33% of additional radioactivity incorporated into DNA of animals of the older group in the course of induced synthesis for 3 days. Consequently, prolongation of poststress DNA repair takes place with age.

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EFFECT OF EMOTIONAL-PAINFUL STRESS ON MYOCARDIAL CONTRACTILITY IN PROLONGED HYPOKINESIA

A. I. Saulya

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Prolonged hypokinesia leads to arrest of growth and, in particular, to cessation of the increase in weight of the heart in rats [1, 4, 5]. A reduction in weight of the heart by more than one-third is due to the fact that the heart muscle consists of cardiomyocytes with a smaller volume than in the control. The ratio of area of sarcolemma to weight of the cell is increased for these cardiomyocytes. The quality of coupling of excitation with contraction and the functional capacity of the myocardium are increased correspondingly [4]. The problem of how acute stress is reflected in cardiac contracility of these animals has not hiterto been studied.

The aim of this investigation was to study the effect of emotional painful stress (EPS) on contractility of the heart muscle of animals previously exposed to a state of prolonged hypokinesia.

EXPERIMENTAL METHOD

Experiments were carried out on 64 male Wistar rats weighing 180-200 g, divided into four groups: 1) control (n = 21), 2) EPS (n = 10), 3) hypokinesia (n = 21), and 4) hypokinesia + EPS (n = 12). Hypokinesia for 60 days was produced by keeping the animals in special restraining cages. At the end of the period of hypokinesia the body weight of the

Kishinev Medical Institute.

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