Thus bone marrow cells produce a group of substances with a wide range of molecular weight (0.3-150.0 kD) possessing a marked analgesic action and depressing a severe pain syndrome of spinal origin induced by a GPEE in the dorsal horns of the lumbosacral segments of the spinal cord. The possibility cannot be ruled out that high-molecular-weight substances contained in fraction 1 and possessing analgesic properties are precursors of low-molecular-weight bone marrow peptides. It is an interesting fact that, unlike the commercial preparation myelopide, medullary peptides with both higher and lower molecular weight give an analgesic effect in much lower concentrations. Another important property of the myelopeptides is the absence of muscle-relaxing and narcotic effects in the realization of their analgesic effect. These properties distinguish myelopeptides in principle from known narcotic analgesics of the morphine type.

The facts described above offer prospects of the creation of effective and harmless analgesics, and also of preparations with combined immunostimulating and analgesic action, on the basis of bone marrow peptide molecules.

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ABOLISHING STRESS-INDUCED ACTIVATION OF MYOCARDIAL REPARATIVE DNA SYNTHESIS BY AN INCREASED LOAD ON THE HEART

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Under the influence of emotional—painful stress (EPS) damage to DNA and a subsequent increase in the rate of its reparative synthesis are observed in the heart cells [4]. Meanwhile the rate of replication rises in the heart cell nuclei [6]. As a result of compensatory hyperfunction of the heart (CHH) caused by coarctation of the aorta, the replication rate also is increased [13], but reparative DNA synthesis under these circumstances has not been studied. Moreover, it is not clear to what extent the rate of DNA synthesis during CHH in the heart cells depends on the increase in their function, and to what extent on operative stress, which inevitably arises in surgically created coarctation of the aorta and in other models of CHH.

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TABLE 1. Rate of Reparative DNA Synthesis in Heart Cell Nuclei

Experimental conditions	Number of counts per minute per milligram DNA
Control	1500
CHH	
After 12 h	1400
After 24 h	1600
After 48 h	1500
Operation without coarctation of the aorta:	
After 12 h	2250
After 24 h	2600

Legend. Each value is the result of averaging of three experiments (three hearts in one experiment).

The aim of this investigation was to compare the effects of operative stress, i.e., the operation without creation of coarctation of the aorta, and of the same operation concluding with constriction of the aorta and the development of CHH, on the DNA replication rate in myocardial cells.

EXPERIMENTAL METHOD

Experiments were carried out on male Wistar albino rats weighing 200-220 g. Compensatory hyperfunction of the heart was induced by coarctation of the aorta by the Beznak–Kogan method. The operation was performed under superficial ether anesthesia. A longitudinal incision was made through skin and muscles in the midline about 35 mm long. The internal organs and muscles were drawn apart and a ligature applied beneath the aorta 10 mm away from the diaphragm. The aorta was slightly lifted and its area of cross section was reduced by 75% by means of a metal coil. The muscles and skin were then sutured in layers. The operation but without coarctation of the aorta was performed in a similar way but without application of the coil to the aorta. The animals were investigated 12, 24, and 48 h after the operation. The rate of DNA synthesis was judged from incorporation of ^{3}H-thymidine, injected intraperitoneally into the animals in a dose of 50 μCi/100 g body weight. The duration of exposure was 2 h. To study reparative synthesis of nuclear DNA the rats were given an intraperitoneal injection of hydroxyurea, an inhibitor of replication, in a dose of 50 mg/100 g body weight 30 min before the injection of ^{3}H-thymidine. The heart cell nuclei were isolated from the heart tissues by Pogo's method with certain modifications [8*]. The tissues were washed to remove blood with 0.25M sucrose solution containing 0.010 M Tris-HCl (pH 7.5) and 0.003 M $MgCl_2$, and homogenized in the same buffer with the addition of Triton X-100 (final concentration 0.5%) in a homogenizer of Dounce type. The homogenate was centrifuged at 2000 g for 10 min. DNA in the nuclei was determined by the method [sic]. The radioactivity of the samples was measured in Bray's fluid in a scintillation counter and expressed as the number of counts per minute per milligram DNA.

EXPERIMENTAL RESULTS

Hydroxyurea inhibited DNA synthesis in the heart cells by 88%. This is comparable with data in the literature obtained during investigations of other cells [6]. The rate of synthesis of nuclear DNA in the presence of the hydroxyurea block can be regarded as the rate of its repair. The results of a study of reparative DNA synthesis in cell nuclei in the myocardium, while engaged in compensatory hyperfunction of the heart and in animals undergoing the operation but without coarctation of the aorta are given in Table 1. They show that during CHH 12, 24, and 48 h after coarctation of the aorta the rate of DNA repair in the myocardial cell nuclei was unchanged. Meanwhile, in animals undergoing the operation but without coarctation of the aorta the rate of reparative DNA synthesis in the heart cell nuclei was sharply increased. For instance, during the first day after the operation these values exceeded the control by 50-74%.

When this fact is evaluated it must be recalled that an increase in the rate of reparative DNA synthesis was found previously in heart and liver cells in EPS [4, 6]. It can accordingly be concluded that the burst of reparative DNA synthesis is a regular feature of the response of organs to any sufficiently strong stressor. It is generally considered that activation of reparative DNA synthesis is due to injury to its structure. In fact, breaks in the

*Not given in Literature Cited.

DNA molecule in EPS have been demonstrated on the basis of lowering of its sedimentation rate [4]. An increase in ^{3}H-thymidine incorporation during stress when replication is inhibited evidently takes place at the sites of these breaks. Thus the burst of reparative DNA synthesis under the influence of stress indicates enlargement of the breaks in the DNA molecule, i.e., transient injury which can be eliminated by repair. Injuries to DNA during stress can be induced by the action of free radicals, the formation of which is increased due to activation of lipid peroxidation [5], brought about by an increased concentration of catecholamines. In surgical operations the plasma adrenalin concentration exceeds initial values by up to 20 times [2]. There are data in the literature on direct damage to the structure of DNA by catecholamines; moreover, it is stated that incorporation of ^{14}C-adrenalin into the DNA molecule is directly proportional to the number of breaks in it. There are also indications that oxidation products of catecholamines block cell division [1].

Unlike animals undergoing the operation but not coarctation of the aorta, the rate of DNA repair at the same times of investigation, in cell nuclei of the hyperfunctioning heart was unchanged. This suggests that the enhanced contractile function of the myocardium in coarctation of the aorta, despite exposure to operative stress, stabilizes the structure of DNA in the cardiomyocyte nuclei. When the possible mechanism of stabilization of the genetic matrix at a time of increased function of the cell is assessed, it must be recalled that marked hyperfunction induces abrupt changes in myocardial RNA metabolism, new protein factors increasing the rate of transcription are formed, and embryonic isozymes accumulate [7]. During hyperfunction of the heart the spectrum of myocardial cell proteins changes. We also know that proteins in principle stabilize DNA structure. It can therefore be tentatively suggested that special proteins, stabilizing the DNA molecule and protecting it from the damaging action of stress, accumulate in the heart when the load on it is increased.

Thus considerable activation of reparative DNA synthesis is observed in the myocardial cell nuclei of animals exposed to operative stress just as it is as a result of EPS. This process is evidence that this is a regular phenomenon in the response of the animal to stress. Cardiac function, when enhanced as a result of constriction of the aorta, prevents a burst of reparative synthesis and, consequently, prevents stress-induced damage to DNA.

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