ROLE OF NONCORONARY MYOCARDIAL DAMAGE IN SUDDEN DEATH AT VARIOUS STAGES OF POSTNATAL DEVELOPMENT

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Sudden cardiac death (SCD) is one of the most important manifestations of ischemic heart disease. In a high proportion of cases it is caused by electrical instability and the development of ventricular fibrillation of the heart and it is not accompanied by the morphological picture of myocardial infarction. Frequently SCD develops in patients with no evident cardiovascular pathology [15]. In most cases of SCD, however, microfocal metabolic lesions [4], in whose development an important role is played by hypercatecholaminemia, are observed in the myocardium. On the one hand, we know that hypercatecholaminemia is characteristic of experimental stress of varied nature, in which a lethal outcome is a possibility [3, 7, 9, 11], and on the other hand, sudden death as the outcome in patients with cardiovascular pathology is often accompanied by emotional collisions and stress situations. With the more rapid rates of scientific and technological progress at the present time, there is an increase in psychoemotional overloads not only on persons of mature age, but also on young and old people. That is why the study of a model of stress with a lethal outcome may provide one method of investigation of the pathogenesis of SCD. The aim of this investigation was to study correlation between myocardial damage and the response of the adrenal medulla in the condition known as "catecholamine stress" with a lethal outcome in animals of different ages.

EXPERIMENTAL METHOD

Noradrenalin hydrotartrate (NAH) is a dose of 2 mg/kg body weight was injected subcutaneously into noninbred albino rats of both sexes aged 1 and 3 weeks (young rats) and into male rats, comprising sexually immature (age 1.5 months), mature (6 months), and old (over 24 months). The animals were decapitated under superficial ether anesthesia 6 h after injection of catecholamine (CA). Some rats died during the first 20 min of the experiment, and accordingly, a group of mature animals, decapitated 20 min after injection of NAH, was chosen for comparison. The heart and adrenal gland (left) were quickly removed from the decapitated and dying rats. The hearts were fixed in 10% buffered formalin solution and embedded in paraffin wax. Histotopographic frontal sections through the heart 5-7 μ thick were stained by Lie's and Regaud's methods to reveal contracturally damaged myocytes, which were studied visually and counted in the whole area of a section through both ventricles, stained by Regaud's method, and the result expressed per unit area, which was taken to be the area of cross-section of the right ventricle. The adrenals were frozen in petroleum benzine, cooled to −70°C. Sections 10 μ thick, dried in a current of warm air, were treated for 3 h in paraform vapor with 60% humidity and embedded in polystyrene. To determine the CA concentration, the sections through the adrenal medulla were subjected to fluorometry on the LYUMAM-IZ luminescence microscope with FMEL-14.U2 fluorometric attachment, adjusted to detect fluorescence of condensation products of CA with paraformaldehyde, which was measured in conventional units. The results of quantitative investigation were subjected to statistical analysis by Student's t test.

EXPERIMENTAL RESULTS

The presence of contracturally injured cardiomyocytes, whose morphology corresponded to that described previously [9, 10], was discovered. When the myocardium of rats aged 1 and

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TABLE 1. Number of Damaged Cardiomyocytes in Ventricular Myocardium of Rats after Injection of NAH (M ± m)

Age of animals, months	6 h after injection of NAH		Animals which died	
	left ventricle	right ventricle	left ventricle	right ventricle
1½	109,0±42,7 (5)	45,0±10,5 (5)	97,2±33,0 (7)	52,3±10,9 (7)
6	132,0±38,7 (8)	105,0±23,0 (8)	281,0±43,9 (5)	166,0±64,1 (5)
Over 24	43,5±12,8 (4)	17,5± (4)	133,3±19,2 (4)	76,00±20,0 (4)

Legend. Number of animals given between parentheses.

3 weeks was studied, no damaged cardiomyocytes were found in it. None of these likewise died after injection of NAH.

In mature rats decapitated 20 min after injection of NAH, the left ventricle was found to contain 34.0 ± 8.8 and the right ventricle 24.3 ± 6.1 damaged cardiomyocytes, and after 6 h their number had increased by 3.9 and 4.3 times respectively ($p < 0.01$; Table 1). The degree of damage to the myocardium 6 h after the beginning of the experiment in the old rats was significantly less than in adult animals in both ventricles (by three times in the left and by 2.3 times in the right; $p < 0.01$).

In the mature rats which died the number of damaged cells in both ventricles was significantly greater than in animals decapitated 20 min after injection of NAH (by 8.3 times in the left ventricle and by 6.8 times in the right; $p < 0.01$). This is evidence of the greater degree of injury to the myocardium and, consequently, the higher sensitivity of the dying rats to exogenous NAH than of the surviving rats.

Conversely, in the immature and old rats which died, the number of damaged cells in the left ventricle was 2.9 and 2.1 times less respectively ($p < 0.01$) than in the mature rats. In other words, besides lower sensitivity of the mature and old rats to a toxic dose of NAH, as shown by the smaller number of damaged cells in the surviving rats than in the case of mature animals, rats of these age groups had lower ability to adapt themselves in response to stress, for even the much less marked degree of damage in them than in the adult rats was accompanied by a lethal outcome.

The absence of damaged cardiomyocytes and of lethal outcomes in the younger animals (1 and 3 weeks) deserves special attention. This phenomenon contradicts the view that the stress-realizing system are fully developed in animals of this age [2]. In our opinion, this phenomenon may be associated with inability of the animal in the early stages of postnatal ontogeny to respond to stress with a coordinated and exaggerated response of the sympathicoadrenomedullary, cardiovascular, and other systems of the body. This is probably why in reviews and monographs devoted to the question of sudden death in early childhood, there is virtually no mention of SCD of such origin [1, 6]. The insignificant degree of cardiac damage in rats aged 1-3 weeks may also be attributed to the fact that, besides the fully developed neuronal uptake of NAH at this age [12], with its protective action against an excess of CA [14], the sensitivity of the actively growing cardiomyocytes to the injurious action of monoamines is low because of increased synthesis of DNA, RNA, and protein in them [5, 8]. Finally, the possibility cannot be ruled out that because of immaturity of the contractile apparatus of the cardiomyocytes they cannot respond to injury by hypercontracture.

The lower degree of myocardial damage in the old rats than in those of the mature age group was due to an age-related structural change in the cardiomyocytes, accompanied by thickening and altered permeability of the sarcolemma, reduction of the capacity of the sarcoplasmic reticulum and mitochondria for Ca^{++}, leading to a change in its concentration in the sarcoplasm and, evidently, to inability of the concentration of this cation to rise quickly under these conditions, which is essential for the development of contracture in response to the action of an injurious agent. Finally, the decrease in sensitivity of the heart to NAH in old rats may be connected with elevation of its blood concentration, accompanied by a decrease in the number of adrenoreceptors of the sarcolemma [13].

TABLE 2. CA Concentration in Adrenal Medulla of Rats Dying after Injection of NAH (in conventional fluorescence units; M ± m)

Age, months	Control	Dying animals
$1^1/_2$	48,7±1,45	39,1±1,1
6	54,2±1,6	40,65±1,6
Over 24	43,4±2,7	16,1±0.8

Reduction of the sensitivity of the myocardium of the old animals to a toxic dose of NAH compared with that of mature and immature animals was observed against the background of much greater activation of their adrenal medulla in the case of a lethal outcome. For instance, whereas in adult and immature rats under these circumstances the CA concentration fell by only 1.25-1.3 times ($p < 0.05$), in old animals it fell by 2.7 times ($p < 0.01$, Table 2).

Incidentally, in adult animals surviving 20 min after injection of NAH, the CA concentration in the adrenal medulla was the same as in the control, namely 55.1 ± 1.6 conventional fluorescence units. A lethal outcome is evidently linked with marked activation of the adrenal medulla and by a more severe degree of myocardial damage than in animals which survive. The possibility cannot be ruled out that the changes discovered were due to the longer duration of agony of the spontaneously dying animals.

This investigation thus demonstrated considerable variability of the sensitivity of animals to catecholamine stress during ontogeny. It is low in young rats, increases gradually toward the period of sexual maturation, and then falls again during aging. In the period of sexual maturation and in old age animals have less ability to adapt themselves in response to the action of extremal factors than adult animals.

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