EFFECT OF NUCLEOSIDES ON THE CONTRACTILE FUNCTION OF THE MYOCARDIUM IN THE EMERGENCY STAGE OF COMPENSATORY HYPERFUNCTION OF THE HEART

(UDC 616.12-007.61-008.45-085.754.3-07:616.127-009.1-072.7)

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Translated from Byulleten' Éksperimental'noi Biologii i Meditsiny, Vol. 61, No. 4, pp. 16-18, April, 1966
Original article submitted November 27, 1964

Substances playing an important role in energy and nuclear metabolism—the nucleosides and their corresponding purine and pyrimidine bases—are known to exert a marked influence on the contractile function of the isolated mammalian heart in conditions of overloading [1-10].

In the present investigation the effect of uridine and uracil and of inosine and hypoxanthine on the contractile function of the heart was studied in the emergency stage of compensatory hyperfunction of the heart (CHH) in experimental aortic stenosis

EXPERIMENTAL METHOD

Experiments were conducted on 55 male rabbits weighing 2.5-2.8 kg. The animals were divided into 6 groups with 8-12 rabbits in each group. Group 1 consisted of intact animals; group 2 of rabbits in which stenosis of the aortic orifice was created 60 h before the main experiment by a method described previously, resulting in a decrease of 67% in its cross section [1]; group 3 consisted of intact rabbits receiving three intravenous injections of uridine (each of 50 μM) during the 60 h before the experiment; group 4 consisted of intact animals receiving three intravenous injections of a mixture containing 50 μM each of uridine, uracil, inosine, and hypoxanthine during the 60 h before the main experiment; group 5 consisted of animals in which aortic stenosis was created 60 h before the main experiment, and during this period three intravenous injections of uridine, each of 50 μM, were given; group 6 consisted of animals in which aortic stenosis was created 60 h before the main experiment, and during this period three intravenous injections were given of a mixture containing 50 μM each of uridine, uracil, inosine, and hypoxanthine.

The object of the basic experiment, carried out by a uniform technique, was to determine the maximal strength of contraction which could be developed by the left ventricle of the animals of each of the 6 groups. For this purpose, under pentobarbital anesthesia (40-60 mg/kg intravenously) and with artificial respiration using air, the thorax was widely opened. A special device was placed under the initial part of the ascending aorta, acting by the principle of a bayonet plug and enabling the aorta to be compressed instantaneously. Through the region of the apex of the heart a No. 12 needle was passed into the cavity of the left ventricle, and connected to an electromanometer by means of a catheter. Complete compression of the ascending aorta distally to the point of branching of the coronary arteries continued for 10 sec and was carried out twice; the interval between the first and second compressions of the aorta was 5 min. The initial pressure before compression of the aorta varied from 80-120 mm Hg.

The index of the maximal strength of contraction of the left ventricle was the maximal systolic peak—the maximal height of the systolic pressure in the left ventricle during complete compression of the aorta. In normal animals this index shows little variation, so that its changes in the emergency stage of CHH (60 h after the creation of aortic stenosis) and under the influence of chemical factors were significant.

Influence of Emergency State of CHH, Nucleosides, and Purine Bases on Maximal Pressure in the Left Ventricle during Compression of Aortic Orifice

Group of animals	No. of animals	Pressure in left ventricle (in mm Hg), M±m		P_{II}
		first compression	second compression	
Intact (1)	12	224±8.8	210±10	
With emergency stage of CHH (2)	9	192±15.4	173±12	$P_{2-1} < 0.05$
Intact, receiving uridine (3)	8	206±10.3	186±19.4	
Intact, receiving uridine, uracil, inosine, hypoxanthine (4)	9	215±8.8	205±8.1	
With emergency stage of CHH, receiving uridine (5)	8	212±12.6	205±11.6	$P_{5-1} > 0.05$
With emergency stage, receiving uridine, uracil, inosine, and hypoxanthine (6)	9	220±7.1	202±7.7	$P_{6-1} > 0.05$

EXPERIMENTAL RESULTS AND DISCUSSION

The maximal systolic pressure in the left ventricle during total compression of the aorta in animals in the emergency stage of CHH was 14% lower than in the intact animals (see the table). It is also clear from the table that the administration of uridine lowered the maximal systolic peak in the intact rabbits and elevated it distinctly in the animals in the emergency stage of CHH. This increase did not lead, however, to the complete normalization of the systolic peak in the emergency stage of CHH— it remained 5% lower than in the control animals. The administration of a mixture of uridine, uracil, inosine, and hypoxanthine had no significant effect on the magnitude of the maximal systolic peak in the intact animals, but led to an increase in its value in the animals in the emergency stage of CHH by 15%. This means that this particular combination of chemical factors completely overcame the defect in the contractile function of the left ventricle appearing in the emergency stage of CHH.

It is clear from the table that the level of the maximal systolic pressure was lower during the second compression of the aorta in the animals of all the groups than during the second compression. However, despite this difference, evidently caused by fatigue of the myocardium, the experimental results were essentially the same as those obtained during the first compression.

The first stage (emergency) of CHH is characterized by a sharp increase in breakdown of the myocardial proteins [2, 11] and in the utilization of the energy of the terminal phosphate bonds of ATP for functional and plastic purposes simultaneously [4]. The increased breakdown of protein and ATP is a factor stimulating protein synthesis and ATP formation. However, in the presence of a marked degree of acute hyperfunction of the heart, which was created by experimental aortic stenosis, the tempo of this stimulation was inadequate for the efficient functioning of both energy and plastic processes. As a result of this lag of the level of protein synthesis and energy formation behind the level of function, a sharp fall in the concentrations of glycogen and CP in the myocardium, signs of cloudy swelling and fatty degeneration [1, 2], destruction of the mitochondria [3], pathological changes in the ECG, and signs of functional insufficiency of the heart were regularly observed 48 h after the formation of the aortic stenosis. The last of these phenomena was observed in the present experiments, in which it took the form that the maximal level of the contractile function of the left ventricle, as determined from the maximal systolic peak, was depressed in the emergency stage of CHH after compression of the aortic orifice by 14% compared with normal.

To increase the rate of mobilization of the protein synthesizing and energy-forming apparatus, and thereby to reduce the observed defect in the contractile function of the myocardium, the natural course was to use the factors stimulating energy formation and the synthesis of nucleic acids and proteins. The results showed that the simultaneous administration to the animals of large doses of uridine, uracil, inosine, and hypoxanthine overcame the defect in the contractile function of the myocardium arising regularly in the emergency stage of CHH.

The fact that uridine, inosine, and their corresponding bases overcome the defect of the myocardial contractile function arising from the creation of an experimental heart lesion in an otherwise intact animal suggests the urgent need for study of the therapeutic value of the clinical administration of certain nucleosides and nucleoside triphosphates and of substances stimulating the synthesis of nucleic acids, such as folio and orotic acids, vitamin B_{12}, and

so on. The most promising line of attack on this problem would seem to be the study of the influence of a combination of these stimulants with the cardiac glucosides on the contractile function of the failing heart.

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