EFFECT OF PRELIMINARY ADMINISTRATION OF PROSTAGLANDIN E_2 AND THE PROSTAGLANDIN SYNTHESIS INHIBITOR INDOMETHACIN OF MYOCARDIAL CONTRACTILITY AFTER STRESS

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KEY WORDS: stress; indomethacin; prostaglandin E_2; isolated atrium; contractility.

Prostaglandins of the E group (PGE) are known to block adrenergic effects [8-10]. Accordingly, their preliminary administration regularly prevents injury to the gastric mucosa due to the above effects resulting from stress [5], and induction of PG biosynthesis by administration of excess arachidonic acid limits the stress reaction and thereby inhibits fibrillation of the heart and lowers the mortality of waking animals with experimental infarction [6]. It therefore seems probable that the PG system plays an important role in the maintenance of resistance of the body as a whole and of the heart in particular to stress-induced injury to adrenergic nature and, consequently, preliminary administration of PGE may have a cardioprotective effect, whereas inhibition of PGE synthesis may aggravate injury to the heart as a result of exposure to stress.

To test this hypothesis we studied the effect of preliminary administration of indomethacin, an inhibitor of PG biosynthesis, or of PGE_2 on the disturbance of myocardial contractility which usually arises during stress [3].

EXPERIMENTAL METHODS

Experiments were carried out on male Wistar rats weighing 180-220 g, divided into six groups: 1) intact animals (control), 2) rats exposed to stress resulting from prolonged immobilization, 3) intact animals receiving indomethacin (5 mg/kg, intraperitoneally), 4) rats treated with indomethacin and then exposed to stress, 5) intact animals receiving PGE_2 (5 mg/kg, intraperitoneally), and 6) animals receiving PGE_2 and then exposed to stress. Stress was induced by immobilizing the animals in the supine position for 6 h. Extensibility and contractility of the isolated papillary muscles of the left ventricle were investigated by the methods described previously [2, 3]. Extensibility of the muscle was estimated as the increase in its length in response to an increase in the load by every 100 mg; the increase in muscle length was expressed as a percentage of its initial length. Contractility of the muscle was determined as the amplitude of contraction, calculated as the ratio of isotonic shortening of the muscle to its initial length, in %. The results were subjected to statistical analysis by Student's test. The indomethacin was obtained from Sigma (USA) and the PGE_2 was of Soviet origin, synthesized in the Institute of Chemistry, Academy of Sciences of the Estonian SSR (Professor Yu. E. Lille).

RESULTS

As in previous investigations [3], preliminary long-term stress led to a decrease in the extensibility of the papillary muscles, combined with depression of the amplitude of contractions (Figs. 1 and 2). Severe immobilization stress preceded by indomethacin administration (Fig. 1) caused a more marked decrease in extensibility and the amplitude of contraction of the papillary muscle than without indomethacin. Preliminary administration of PGE_2 (Fig. 2) increased extensibility of the papillary muscles somewhat but had hardly any effect on the amplitude of contractions in intact animals. Injection of PGE_2 before the animals were exposed to stress largely prevented the stress-induced decrease in extensibility of the papillary

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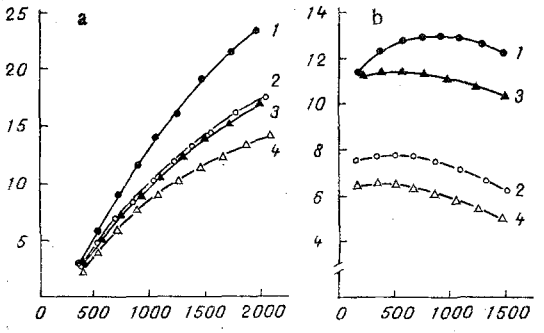

Fig. 1. Effect of preliminary administration of indomethacin on disturbance of extensibility and depression of amplitude of contractions of papillary muscle from stressed animals. Abscissa, stretching load (in mg/mm^2); ordinate: a) increase in length of muscle (in % of initial length taken as 100), b) amplitude of contractions (in % of initial length of muscle taken as 100). 1) Control, 2) stress, 3) indomethacin, 4) indomethacin + stress.

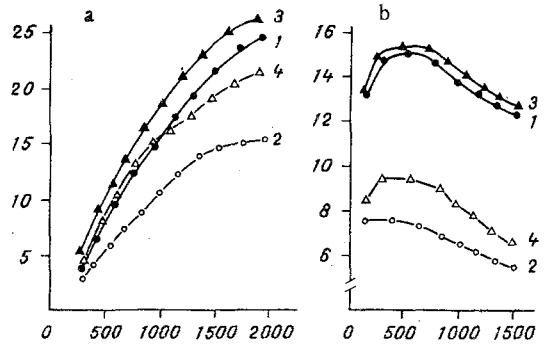

Fig. 2. Effect of preliminary administration of PGE_2 on disturbance of extensibility and depression of amplitude of contractions of papillary muscle of stressed animals. 1) Control, 2) stress, 3) PGE_2, 4) PGE_2 + stress. Remainder of legend as to Fig. 1.

muscles: The muscle extensibility curve for animals receiving PGE_2 before stress coincided almost completely with the control (Fig. 2a). The amplitude of contraction in rate of this group also was greater than after stress not preceded by PGE_2 administration (Fig. 2b).

Thus preliminary administration of indomethacin aggravated the disturbances of extensibility and contractility of the myocardium usually arising through exposure to severe stress, whereas preliminary injection of PGE, on the other hand, reduced these disturbances, i.e., had a prophylactic action.

The cardioprotective effect of PGE in stress, revealed by these experiments, is evidently attributable not only to their ability to block the effects of catecholamines [8-10], but also to the fact that PG reduce catecholamine uptake by the myocardium, and also weaken vasoconstrictor reactions. It has in fact been shown that preliminary administration of PGE reduces adrenalin uptake by the rabbit myocardium, and that indomethacin increases this uptake by 20%, while simultaneously potentiating the damaging action of this catecholamine [1]. It has also been shown that PG depress vasoconstrictor reactions during adrenergic effects, but inhibition of their synthesis, on the contrary, potentiates the adrenergic vasoconstrictor response [4].

When the antistressor protective effect of PG in stress is assessed, it must be recalled that stress is an inevitable companion of ischemic heart disease, and that the now familiar data showing that PG limit the zone of ischemia in myocardial infarction in man [7] can evidently be largely explained by their antistressor action described above.

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FORMATION OF A "PRO-OXIDANT" BOUNDARY ZONE AND ITS ROLE IN INTENSIFICATION OF LIPID PEROXIDATION IN AN AREA OF MYOCARDIAL ISCHEMIA AND INFARCTION

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A phenomenon known as the "free-radical peroxide paradox" (FRPP) during the development of myocardial ischemia and infarction was described in 1975 [6]. It is that, despite the oxygen deficiency present in the region of ischemia and the developing myocardial infarct, free-radical lipid peroxidation (LPO) is for a long time intensified. Its pathogenetic role has been proved, for inhibition of LPO by means of antioxidants reduces the severity and size of a myocardial infarct [6, 7, 9, 10]. Subsequent investigations confirmed these observations [9, 15]. The mechanism of FRPP has not yet been explained.

The writers postulate a definite connection between intensification of LPO in an area of ischemia and infarction with the formation of a "pro-oxidant" boundary zone (POBZ) at its periphery, which differs from other zones of the infarct in that, first, the blood flow (and, consequently, the oxygen supply) in it is partially restored and, second, the cardiomyocytes in this zone have largely lost their ability to utilize oxygen. This paper gives the results of experiments which confirmed this hypothesis.

EXPERIMENTAL METHODS

A model of myocardial ischemia and infarction was produced in noninbred male albino rats weighing 180-250 g by the method developed previously [3]. The left coronary artery was ligated by 3-5 mm below the left angle of the base of the infundibulum. The possible formation of a POBZ was studied by injecting the coronary vessels with latex microspheres (LM) and by the histochemical reaction for dehydrogenase activity (DA) using nitro-BT, followed by morphometry. By means of these methods, the area of the zone in which the vessels did not fill with LM, i.e., the unperfused (not supplied with blood) zone (UPZ) (one group of rats), the area of the zone not giving a positive reaction with nitro-BT, the so-called dehydrogenase-free zone (DFZ), corresponding to the zone of injury (ZI) (2nd group of rats), and also the difference between the area of the DFZ and UPZ, consisting of the zone without DA, but having patent vessels, communicating with the vascular bed of the normal myocardium, were determined. This last difference corresponds to the POBZ. The coronary vessels were injected with a suspension of blue LM into rats killed under anesthesia. The final concentration of LM was (2.6-3.2) $\times 10^6/mm^3$, and their diameter as a rule (in 83% of LM) was 4.38-8.7 μ. The suspension

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