EFFECT OF INDOMETHACIN ON THE DEVELOPMENT OF CARDIAC DAMAGE INDUCED IN RATS BY NORADRENALIN

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KEY WORDS: Isolated rat heart; noradrenalin injury; creatine phosphokinase; indomethacin; prostaglandins.

An important role is nowadays ascribed to noradrenalin (NA) in the pathogenesis of myocardial infarction [8, 11]. Experiments on animals have shown that injection of large doses causes necrosis of the myocardium [7]. In experiments in vitro injury to the rat heart has been produced by the use of physiological concentrations of NA [15]. Data have recently been published to show that catecholamines are connected with prostaglandins (PG) in the heart. It has been shown that NA activates PG biosynthesis, and that PG regulate synaptic neurotransmission, secretion, and uptake of catecholamines by the heart [1, 3-5].

To solve the problem of the role of PG in the process of injury to the heart by NA, in the investigation described below the effect of indomethacin, an inhibitor of PG biosynthesis, on the sensitivity of the rat heart to NA-induced injury was studied.

EXPERIMENTAL METHOD

Male Wistar rats weighing 350-450 g were used. A model of the isolated perfused rat heart was used for the investigation. The model and the conditions of reproduction of injury to the heart by NA in vitro were described fully previously [14, 15]. All the animals were divided into two groups. The animals of one group received indomethacin in phosphate buffer in a dose of 5 mg/kg body weight, whereas the animals of the other group received the same volume of phosphate buffer. The heart was removed 1 h after injection of indomethacin or buffer from the animal and connected to the perfusion apparatus. After the heart had worked for 10 min, a single injection of NA up to a final concentration of 10^{-6} M and (or) of indomethacin to a final concentration of $2.8 \cdot 10^{-8}$ M was given into the perfusion fluid. When both these drugs were used, indomethacin was injected 2 min before NA. Perfusion continued for 47 min after the time of injection of NA. The degree of noradrenalin injury was judged from the outflow of creatine phosphokinase (CPK) from the heart into the recirculating perfusion fluid toward the end of perfusion. Activity of the enzyme was assessed spectrophotometrically and expressed in international units of activity per unit volume [13].

To assess PG biosynthesis the heart was perfused by Langendorf's method without recirculation of the perfusion fluid. Perfusion continued for 25 min, and during the last 5 min the coronary perfusion fluid was collected for analysis of the PG concentration. Indomethacin was injected into the perfusion fluid 10 min after the beginning of perfusion. Since PG do not accumulate in the tissues in the course of their synthesis, their outflow from the heart reflects the activity of their de novo biosynthesis. After extraction with ethylacetate and column chromatography on silicic acid, the content of PG-E ($PG\text{-}E_1 + PG\text{-}E_2$) was assayed by a radioimmunologic method, using kits from Clinical Assay Inc., U.S.A. [6]. The quantity of PG-E synthesized in the course of 5 min was expressed in nanograms per gram wet weight of heart tissue.

The minute volume of the left ventricle (MVLV) and the velocity of the coronary flow (VCF) were measured by collecting the perfusion fluid in a measuring cylinder and expressed in ml/min. The results were subjected to statistical analysis by Student's t-test.

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TABLE 1. Effect of Indomethacin on MVLV, VCF, and Outflow of CPK from Isolated Perfused Heart during Injury by NA (M ± m)

Group of hearts	MVLV, ml/min		VCF, ml/min		CPK, i.u./liter
	time, min				
	0	47	0	47	45
Control	34±1	35±2	20±1	19±1	33±4
Indomethacin in vitro	38±1	38±2	19±1	18±1	23±3
Indomethacin in vivo	37±2	37±2	20±1	19±1	28±4
NA	37±1	29±1*	18±1	18±1	188±20*
Indomethacin in vitro+HA	38±2	28±1*	18±1	18±1	177±19*
Indomethacin in vivo+HA	37±1	19±3*	19±1	18±1	306±25*

Legend. Each group consisted of 6 to 8 hearts. *P < 0.05 compared with control.

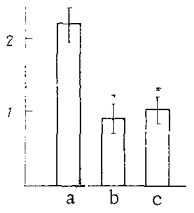

Fig. 1. Effect of indomethacin on outflow of PG-E from isolated rat hearts. a) Control group of hearts; b) injection of indomethacin in vitro; c) injection of indomethacin in vivo. *P < 0.01 compared with control. Control and experimental groups each consisted of 9 hearts. Ordinate, PG-E concentration (in ng/g tissue/5 min).

EXPERIMENTAL RESULTS

The results in Table 1 show that injection of indomethacin, both in vivo and in vitro, caused no change in MVLV or VCF of the isolated perfused heart and did not affect the outflow of CPK from it. This indicates that indomethacin has no toxic action on the heart in the concentrations used.

Injection of NA caused a decrease in MVLV and a considerable increase in the outflow of CPK into the perfusion fluid. NA, if given after previous injection of indomethacin in vitro, did not change these parameters. If NA was injected after indomethacin in vivo, this led to a further decrease in MVLV ($P < 0.01$) and further outflow of CPK ($P < 0.005$) compared with the experiment in which no indomethacin was given. The outflow of CPK from the heart is an indicator of the degree of injury to the heart both in experiments in vivo and in the model of NA-induced injury to the rat heart in vitro [9, 15]. Hence it can be concluded that injection of indomethacin into the rat increased the sensitivity of its heart to noradrenalin injury.

The mechanism of action of indomethacin is by inhibiting PG biosynthesis; it was therefore necessary to study the effect of indomethacin in the doses used, on PG biosynthesis.

The results of investigation of PG biosynthesis in the rat heart showed that injection of indomethacin both in vivo and in vitro caused a decrease in the basal outflow of PG-E from the heart (Fig. 1). It should be pointed out that of the broad spectrum of PG synthesized in the heart, only PG-E were investigated. This was sufficient to answer the question of whether the whole PG spectrum was inhibited, on the basis of the well-known fact that indomethacin inhibits the key enzyme of the multienzyme complex prostaglandin synthetase, namely cyclooxygenase, at the stage of formation of cyclic endoperoxides, which are the substrate for the whole spectrum of PG [2]. The fact that indomethacin does not change VCF may also indicate that PG under

normal conditions are not involved in the regulation of coronary vascular tone. Other investigators have reached the same conclusion [10, 12]. However, it is possible that conditions in vitro are not sufficiently adequate for the study of the effect of PG on coronary vascular tone.

The results of this investigation showed that only if indomethacin is injected in vivo is an intensification of noradrenalin-induced injury observed, although PG biosynthesis is inhibited by administration of indomethacin both in vivo and in vitro. Inhibition of PG biosynthesis evidently affects certain processes of regulation of cardiac metabolism at the whole body level. Indications have recently appeared that PG regulate synaptic neurotransmission and may affect processes of secretion and uptake of catecholamines by the heart [1, 3, 4]. Disturbance of one of these processes probably leads in this case to an increase in the sensitivity of the heart to noradrenalin injury in vitro.

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EFFECT OF LITHIUM PREPARATIONS ON CARDIAC ARRHYTHMIAS DUE TO STROPHANTHIN*

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The efficacy of lithium preparations in psychiatric practice is linked with the ability of lithium to inhibit activity of the central adrenergic apparatus [2, 3, 6, 13, 14]. Autonomic imbalance, in the genesis of which an important role is played by activation of the sympathetic nervous system, can lead as we know to disturbances of cardiac rhythm [5]. One example of disturbances of this sort is the arrhythmias induced by administration of large doses of cardiac glycosides. According to observations made by various workers, the genesis

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