ANTIARRHYTHMIC ACTION OF TETRODOTOXIN IN THE LATE STAGE OF EXPERIMENTAL MYOCARDIAL INFARCTION

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The action of tetrodotoxin (TT), which blocks the fast inward sodium current, on arrhythmias developing 24 h after occlusion of the coronary artery in ten dogs was studied. After intravenous injection of TT in a dose of 0.5-3.0 μg/kg body weight the number of ventricular extrasystoles was significantly reduced, and in four animals the sinus rhythm was completely restored. The maximal antiarrhythmic effect occurred 3-5 min after injection. It is suggested that the development of arrhythmias and the antiarrhythmic action of drugs in the late stage of myocardial infarction are connected with the fast inward sodium current.

KEY WORDS; myocardial infarction; arrhythmias; tetrodotoxin.

Disturbances of rhythm in the early stage of experimental myocardial infarction (the first few minutes after occlusion of the coronary artery) are associated with slow conduction, for these arrhythmias can be abolished by substances depressing the slow inward current [6, 13, 14].

The mechanism of arrhythmias in the late stage of infarction, which begins 6-8 h after ligation of the coronary artery and continues for 2-3 days [8, 13], is not yet known. In this connection it is an interesting fact that substances which are effective antiarrhythmics in the late stage of infarction, namely etmozin [1, 3, 7], mexiletine [5], etc. – possess the common property of inhibiting the fast inward sodium current of myocardial fibers [4, 12]. Moreover, it has been shown in the case of antiarrhythmics of the phenothiazine series that the longer the drug inhibits the sodium current, the longer its antiarrhythmic action in the late stage of infarction continues [2]. These observations suggest that the appearance of arrhythmias in the late stage of infarction is somehow connected with the fast sodium channels and that the antiarrhythmic action of drugs in this period is due to their ability to influence the fast inward sodium current. In the present investigation, in order to study the role of a decrease in the fast inward current in the production of the antiarrhythmic effect in the late stage of infarction, the action of tetrodotoxin (TT), a specific blocker of the fast inward current, was investigated. The antiarrhythmic activity of TT was discovered previously in arrythmias induced by aconitine and by glycoside poisoning [9].

EXPERIMENTAL METHOD

Experiments were carried out on mongrel dogs on both sexes weighing 8-20 kg. Under pentobarbital anesthesia (30-35 mg/kg, intravenously) and artificial respiration, the thorax was opened under sterile conditions through the fourth left intercostal space. The pericardium was then opened and the left descending coronary artery was freed from surrounding tissues for a distance of 1-2 cm from the auricle of the left atrium. Ligation of the artery was carried out in two stages by Harris' method [8]. For subsequent intravenous injection a polyethylene catheter was introduced into the external jugular vein, channeled under the skin, and secured in the neck. The thorax was closed and the animal's natural breathing restored. The ECG in standard lead II was recorded 22-24 h after the operation and, if marked arrhythmia was present, TT was injected. The initial dose of TT was 0.5 μg/kg; the action of TT in doses of 1, 2, and 3 μg/kg was then tested. The corresponding quantities of TT were dissolved in 5-10 ml physiological saline and injected in the course of 1 min. The minimal dose causing a marked antiarrhythmic effect (a reduction in the number of extrasystoles by more than 50%) was taken to be the threshold. The ECG was recorded before and during injection of TT and

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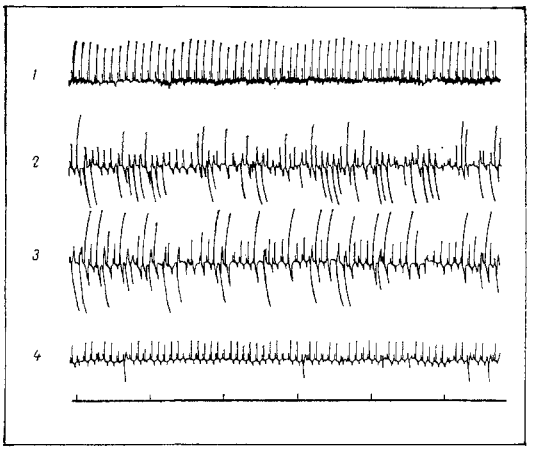

Fig. 1. Antiarrhythmic effect of TT 24 h after occlusion of coronary artery. 1) ECG before operation; 24 h after operation; 3) after injection of 1 μg/kg TT; 4) after injection of 2 μg/kg TT; 3 and 4) 3rd minute after injection. Time marker 5 sec.

throughout the period of its action. To reduce the central action of TT, chloralose (100 mg/kg) was injected intravenously into the animals. Injection of chloralose had virtually no effect on the arrhythmia. The intervals between injections of TT were 1 h.

EXPERIMENTAL RESULTS

The results of one typical experiment are given in Fig. 1. They show that 24 h after occlusion of the coronary artery marked ventricular extrasystoles developed. As a result of injection of 2 μg/kg TT the number of ventricular extrasystoles was significantly reduced. In half that dose, TT had virtually no antiarrhythmic action. In all ten experiments the percentage of ventricular ectopic excitations was determined both before injection of TT and at the time of development of maximal antiarrhythmic effect. The threshold doses of TT in different experiments were between 0.5 and 3 μg/kg. Injection of TT in these doses considerably reduced the percentage of ventricular extrasystoles [on average from 80 ± 4.5 to 6.6 ± 2.3 ($P < 0.001$)]. The sinus rhythm was fully restored in four animals. The maximal effect was achieved toward 3-5 min after injection of TT. On average the effect was reduced to half the maximal value after 22 min.

The results indicate clearly that TT effectively depresses ventricular arrhythmias arising 24 h after occlusion of the coronary artery. The explanation of the mechanisms of the antiarrhythmic action of TT is closely linked with the mechanism of arrhythmias in the late stage of the infarct. However, since the causes of development of arrhythmias under these conditions are not yet known, all that can be done at present is to examine some of the possible situations in which a decrease in the sodium current may be the cause of cessation of the arrhythmias.

One of them is that in the late stage of an infarct the mechanism of the arrhythmias is similar to that of the disturbances of rhythm arising during the action of the alkaloid aconitine on the myocardium. Voltage clamp experiments have shown that aconitine changes the properties of the fast sodium channels, delays their inactivation, and causes the development of an inward current between values of the potentials in which under normal conditions no such current is present. TT completely blocked the action of aconitine and suppressed the inward current evoked by it [13]. Furthermore, in experiments on the cat heart in vivo, cardiac arrhythmias induced by aconitine were abolished by intravenous injection of TT [9]. Taken as a whole, these results suggest that in the late stage of infarction changes in the properties of the fast sodium channels resembling those of aconitine poisoning arise in the zone of ischemia. In that case the antiarrhythmic action of TT is linked with the fact that it directly suppresses the ectopic focus of excitation.

Another possible way in which TT may act directly on the ectopic fucus stems from the results of experiments which showed that the steepness of diastolic depolarization is much greater in Purkinje fibers isolated from the zone of the infarct than in fibers isolated from areas of intact myocardium [10]. If the increased ability of Purkinje fibers to contact automatically is the cause of ectopic activity in the late stage of the infarct, a decrease in the inward current under the influence of TT may abolish the automatic activity as a result of inhibition of phase 0 of the transmembrane action potential of these fibers.

The antiarrhythmic action of TT can also be exhibited in the case when arrhythmias in the late stage of infarction are due to the circulation of excitation. It has recently been shown that in dogs in the late stage of infarction, cells of the working myocardium generate a sodium-dependent action potential which, spreading at reduced speed over the nonhomogeneous myocardium, can induce circulation of excitation [11]. In that case a decrease in the velocity of conduction of excitation as a result of a decrease in the sodium current under the influence of TT can lead to a conduction block and can stop the arrhythmia.

It can be concluded that the fact that arrhythmias can be abolished by the action of TT, a specific blocker of the fast inward sodium current, discovered by this investigation will help to reveal the true causes of development of arrhythmias and of the antiarrhythmic effect of drugs in the late stage of myocardial infarction.

LITERATURE CITED

1. N. V. Kaverina, Z. P. Senova, Yu. I. Vikhlyaev, et al., Farmakol. Toksikol., No. 6, 693 (1970).
2. V. V. Lyskovtsev, Z. P. Senova, I. A. Juriavicus, et al., Byull. Éksp. Biol. Med., No. 3, 243 (1979).
3. L. V. Rozenshtraukh, R. L. Ver'e, and B. Laun, Vestn. Akad. Med. Nauk SSSR, No. 10, 52 (1978).
4. I. A. Juriavicus, L. V. Rozenshtraukh, A. I. Undrovinas, et al., Kardiologiya, No. 9, 118 (1978).
5. J. D. Allen, R. G. G. James, J. G. Kelly, et al., Postgrad. Med. J., 53, Suppl. 1, 35 (1977).
6. P. F. Cranefield, A. L. Wit, and B. F. Hoffman, Circulation, 47, 19 (1973).
7. P. Danilo, W. B. Langan, M. R. Rosen, et al., Europ. J. Pharmacol., 45, 127 (1977).
8. A. S. Harris, Circulation, 1, 1318 (1950).
9. T. F. Huang, Eur. J. Pharmacol., 26, 77 (1974).
10. R. Lazzara, N. El-Sherif, R. R. Hope, et al., Circulat. Res., 42, 740 (1978).
11. R. Lazzara, R. R. Hope, N. El-Sherif, et al., Am. J. Cardiol., 41, 872 (1978).
12. E. M. Vaughn Williams, Postgrad. Med. J., 53, Suppl. 1, 30 (1977).
13. A. L. Wit and J. T. Bigger, Jr., Postgrad. Med. J., 53, Suppl. 1, 98 (1977).
14. D. P. Zipes, H. R. Besch, Jr., and A. M. Watanabe, Circulation, 51, 761 (1975).

ACTIVATION OF LIPID PEROXIDATION DURING PAINFUL EMOTIONAL STRESS

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Accumulation of primary and secondary lipid peroxidation (LPO) products were investigated by ultraviolet spectrophotometry and fluorescence of Schiff bases in various tissues of Wistar rats subjected to painful emotional stress (PES). The quantity of LPO products was shown to increase under the influence of PES mainly in the heart, and also significantly, although to a lesser degree than in the heart, in skeletal muscles and brain. The increase in content of hydroperoxides in all the organs studied was smaller than the increase in the content of fluorescent Schiff bases, the end products of LPO.

KEY WORDS: painful emotional stress; lipid peroxidation.

The role of emotional stress in the etiology of human diseases is widely known, but the actual metabolic link through which the harmful action of high concentrations of catecholamines and glucocorticoids in stress is effected requires further study. One of the main mechanism of injury to cell structures is activation of lipid peroxidation (LPO) [2, 3]. It was shown recently that after painful emotional stress (PES) an increase

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