activation – were virtually unchanged under the influence of ethmozine. It was suggested on the basis of these findings that ethmozine, like tetrodotoxin, acts from outside the cell membrane, reducing the number of channels capable of conducting $Na^+$. In the present investigation, when intracellular and extracellular perfusion of single heart cells was used, direct proof was obtained that ethmozine acts predominantly from the outside of the sarcolemma.

Lignocaine has a more complex action on electrical activity of heart tissue. For instance, besides the reduction in $\dot{V}_{max}$ and, consequently, of $I_{Na}$ also, under the influence of lignocaine the action potential of the Purkinje fibers was significantly shortened [3, 4], evidence that lignocaine affects not only $I_{Na}$, but also other ionic currents. The action of lignocaine on $I_{Na}$ cannot be reduced purely to depression of maximal conductance, but it is accompanied by a significant increase in the reactivation constant of $I_{Na}$ [5, 11]. It has been shown on internally perfused squid giant axons [9] and Purkinje cardiac cells [7] by iontophoretic application of lignocaine that inhibition of $I_{Na}$ by lignocaine is connected mainly with the intracellular action of this drug. Comparison of the action of lignocaine and ethmozine on $I_{Na}$ from inside and outside the heart cell in the present investigation showed that the sites of action of these two antiarrhythmics on the cell membrane are different.

## LITERATURE CITED


1. L. V. Rozenshtraukh, R. Raffi, V. Élkharar, et al., Kardiologiya, No. 5, 63 (1979).
2. I. A. Yuryavichyus, L. V. Rozenshtraukh, A. I. Undrovinas, et al., Kardiologiya, No. 9, 118 (1978).
3. M. F. Arnsdorf and J. T. Bigger, Jr., J. Clin. Invest., 51, 2252 (1972).
4. J. T. Bigger, Jr. and W. J. Mandel, J. Clin. Invest., 49, 63 (1970).
5. C. M. Chen, L. S. Gettes, and B. C. Katzung, Circulat. Res., 37, 20 (1975).
6. P. Danilo, W. B. Langan, M. R. Posen, et al., Eur. J. Pharmacol., 45, 127 (1977).
7. J. I. Gliklich and B. F. Hoffman, Circulat. Res., 43, 638 (1978).
8. P. G. Kostiuk, O. A. Krishtal, V. I. Pidoplichko, et al., Neuroscience, 3, 327 (1978).
9. T. Narahashi and D. T. Frazur, J. Pharmacol. Exp. Ther., 171, 32 (1970).
10. Y. Rajs, M. Sundberg, N. Danell, et al., Exp. Cell Res., 115, 183 (1978).
11. F. M. Weld and J. T. Bigger, Jr., Circulat. Res., 37, 630 (1975).


# EFFECT OF ETHIMIZOLE AND PROPYLNORANTIPHEIN ON ACTIVITY OF RESPIRATORY ENZYMES OF THE MYOCARDIUM AFTER NEUROGENIC INJURY


V. V. Bul'on



UDC 616.127-008.931:577.152.1]-02:615.214.31

KEY WORDS: neurogenic injury to the myocardium; respiratory enzymes; ethimizole; propylnorantiphein.


One of the main causes of development of neurogenic trophic disorders of the internal organs is insufficiency of energy metabolism in the damaged tissues [5, 11]. Ethimizole,* an imidazole dicarboxylic acid derivative, accelerates the healing of gastric ulcers and has a preventive and therapeutic action in neurogenic lesions of heart muscle [6, 7]. The writer showed previously that ethimizole considerably accelerates energy forming processes in the CNS of healthy animals [4].

The object of the present investigation was accordingly to study the effect of ethimizole and of another imidazole-dicarboxylic acid derivative, propylnorantiphein, on some indices of metabolism of the myocardium

*1-ethylimidazole-4,5-dicarboxylic acid-bis-methylamide.


Laboratory of Experimental Pharmacology, Department of Pharmacology, Institute of Experimental Medicine, Academy of Medical Sciences of the USSR, Leningrad.


(Presented by Academician of the Academy of Medical Sciences of the USSR S. V. Anichkov.) Translated from Byulleten' Éksperimental'noi Biologii i Meditsiny, Vol. 90, No. 8, pp. 180-182, August, 1980. Original article submitted October 16, 1979.




0007-4888/80/9008-1080$07.50

after neurogenic injury. Components of the respiratory chain such as succinate dehydrogenase (SDH) and cytochrome oxidase (CO), whose activity under normal conditions is particularly high in the myocardium, undergo considerable changes in the presence of lesions of the heart muscle of neurogenic character [3].

## EXPERIMENTAL METHOD

Experiments were carried out on male rabbits weighing 3-3.5 kg. Neurogenic injury to the myocardium was induced by electrical stimulation of the arch of the aorta for 3 h by means of an electrode introduced through the right common carotid artery [1]. Immediately after electrical stimulation and 48 h later, activity of SDH and CO in the mitochondria of the heart was determined spectrophotometrically [2, 10]. Ethimizole and propylnorantiphein were injected intraperitoneally in a dose of 2 mg/kg, 30 min before the beginning of electrical stimulation of the animals. Intact rabbits served as the control.

## EXPERIMENTAL RESULTS

The results of investigation of myocardial respiratory enzyme activity over a period of time confirmed previous observations showing an increase in SDH activity and a decrease in CO activity immediately after electrical stimulation of the aortic arch for 3 h [3]. On subsequent days of development of the trophic lesion of the heart muscle there was a marked decrease in the catalytic properties of SDH. The activity of this enzyme 48 h after electrical stimulation was 30% below normal. The increase in SDH activity immediately after electrical stimulation of the aortic arch of the animals could evidently be regarded as a metabolic reaction aimed at maintaining the energy supply of the damaged myocardium. In the myocardium with neurogenic injury a decrease was found in the total nicotinamide coenzyme (NAD + NADP) content and a change in their relative proportions in favor of the reduced forms [8]. In the modern view, NAD and NADP are primary hydrogen acceptors in the respiratory chain. The level of these compounds in the cell, and the ratio between their oxidized and reduced forms, largely determine the intensity of oxidative processes in the heart muscle. The decline in oxidized forms of nicotinamide nucleotides and predominance of reduced forms blocks the respiratory chain in its initial stage and leads to disturbance of oxidation of most substrates of energy metabolism involving NAD and NADP [9]. With these facts in mind, it may be suggested that the increase in SDH activity in these experiments, when the content of nicotinamide coenzymes was low, represented a compensatory intensification of the function of another process supplying electrons to the respiratory chain, in which the main role is played by succinate and the flavoprotein SDH.

The decline in SDH activity on subsequent days of development of neurogenic injury to the heart (after 48 h) is evidence of disturbance of the compensatory mechanism aimed at maintaining the energy metabolism of the injured myocardium.

Unlike SDH, the catalytic properties of which underwent biphasic changes in the injured myocardium, CO activity changed in one direction only. Inhibition of the activity of this enzyme, which was observed immediately after electrical stimulation of the aortic arch, also persisted 48 h later.

Administration of ethimizole before the beginning of electrical stimulation of the aortic arch had a protective action on the myocardial oxidative enzymes. In animals receiving ethimizole, SDH and CO activity after electrical stimulation differed only a little from that in intact rabbits (Table 1).

Our observations on the prophylactic effect of ethimizole agree with the results of investigations in which ethimizole prevented disturbances of myocardial metabolism by restoring the normal levels of lactic acid,

TABLE 1. Effect of Ethimizole and Propylnorantiphein on Activity of Oxidative Enzymes (in optical density units/mg protein/h) in the Myocardium 3 h after the Beginning of Electrical Stimulation of the Aortic Arch (M ± m)

| Experimental conditions | SDH ($n$=11) | CO ($n$=10) |
|---|---|---|
| Control | 18,2±1,5 | 51,1±2,0 |
| Stimulation | 28,5±1,9 | 30,5±2,2 |
| Ethimizole + stimulation | 22,0±1,4 | 47,0±1,3 |
| Control | 17,1±1,7 | 54,4±3,8 |
| Stimulation | 27,2±2,3 | 33,2±2,4 |
| Propylnorantiphein + stimulation | 18,9±0,6 | 51,5±5,3 |

creatine phosphate (CP), and inorganic phosphate, and prevented changes in the electrocardiogram of the myocardium in this pathological state [8]. Propylnorantiphein also had a similar prophylactic effect. As Table 1 shows, propylnorantiphein prevented the increase in SDH activity and the decrease in CO activity in the heart, observed immediately after electrical stimulation of the aortic arch, to the same degree as ethimizole.

In neurogenic injury to the myocardium significant changes thus arise in various components of the respiratory chain, leading to a disturbance of the formation of high-energy compounds. It was shown previously that during trophic disturbances of neurogenic character in heart muscle tissue, at different times of observation (3, 24, and 48 h) uncoupling of oxidative phosphorylation and a decrease in the concentrations of ATP and CP are observed [3, 5]. There is no doubt that the changes described are a molecular mechanism of disturbance of myocardial function of the utmost importance during neurogenic injury to the organ.

Administration of ethimizole and propylnorantiphein – preparations stimulating energy metabolism of the CNS – has a beneficial effect on neurogenic injury to the myocardium accompanied by energy deficiency.

## LITERATURE CITED


1. S. V. Anichkov, I. S. Zavodskaya, E. V. Moreva, et al., Neurogenic Trophic Disturbances and their Pharmacotherapy [in Russian], Leningrad (1969).
2. V. S. Asatiani, Enzymic Methods of Analysis [in Russian], Moscow (1969), p. 428.
3. V. V. Bul'on, Byull. Éksp. Biol. Med., No. 7, 13 (1978).
4. V. V. Bul'on and E. V. Moreva, Byull. Éksp. Biol. Med., No. 2, 185 (1977).
5. I. S. Zavodskaya, E. V. Moreva, and N. A. Novikova, Effect of Neurotropic Agents on Neurogenic Injuries of the Heart [in Russian], Moscow (1977), pp. 79-113.
6. O. N. Zabrodin, Farmakol. Toksikol., No. 5, 566 (1975).
7. V. B. Isachenko, N. A. Novikova, and V. A. Kovaleva, Farmakol. Toksikol., No. 5, 606 (1972).
8. É. A. Migas, Byull. Éksp. Biol. Med., No. 10, 408 (1978).
9. T. V. Fetisova and R. A. Frol'kis, Biochemistry of Myocardial Infarction [in Russian], Kiev (1976), pp. 55-78.
10. S. J. Cooperstein and A. Lazarov, J. Biol. Chem., 189, 665 (1951).
11. J. S. Zavodskaya (I. S. Zavodskaya) and E. V. Moreva, in: Conference on Experimental Ulcer, Budapest (1976), pp. 243-250.


# EFFECT OF ISOPROTERENOL ON ADENYLATE CYCLASE ACTIVITY IN ADIPOCYTES OF SPONTANEOUSLY HYPERTENSIVE RATS


M. B. Reznikova and Yu. V. Postnov



UDC 616.12-008.331.1-055.5/.7:616-018.26-008.931-02:615.217.22

KEY WORDS: hypertension; adrenalectomy; fat cells; isoproterenol.


It was shown previously that the cellular response to the action of hormones (insulin, adrenalin, ACTH) in the adipose tissue of spontaneously hypertensive rats (SHR) differs from the response of the same cells in normotensive animals [3]; this difference in the case of adrenalin and insulin, however, appeared only after adrenalectomy. The change in "sensitivity" of fat cells of hypertensive animals to the action of the above-mentioned hormones is evidently connected with a change in the content of cyclic nucleotides, which is controlled mainly by adenylate cyclase (AC), the enzyme controlling synthesis of cyclic AMP, and by phosphodiesterase, which controls the rate of breakdown of cyclic AMP and cyclic GMP.

---


Department of Pathomorphology, Fourth Main Board, Ministry of Health of the USSR, Moscow.


(Presented by Academician of the Academy of Medical Sciences of the USSR E. I. Chazov.) Translated from Byulleten' Éksperimental'noi Biologii i Meditsiny, Vol. 90, No. 8, pp. 182-184, August, 1980. Original article submitted October 30, 1979.




0007-4888/80/9008-1082$07.50