Since $PGE_2$ formation in the aqueous humor, a subsequent rise of IOP, and the development of an inflammatory reaction are observed in clinical practice in connection with operations and the use of lasers [7, 8], the results of this investigation may provide an experimental basis for the clinical study of carnosine as a means of reducing the development of reactive hypertension associated with laser therpay and ophthalmic surgical operations.

## LITERATURE CITED


1. A. Ya. Bunin, A. A. Yakovlev, L. A. Kondé, and N. A. Komlev, Vestn. Oftal'mol., No. 3, 24 (1975).
2. A. Ya. Bunin, A. F. Brovkina, V. N. Ermakova, and N. V. Makarskaya, Vestn. Oftal'mol., No. 3, 55 (1983).
3. V. N. Ermakova, Uch. Zap. Mosk. Nauchno-Issled. Inst. Glaznym Bolezn., No. 13, 208 (1967
4. V. N. Ermakova, Vestn. Oftal'mol., No. 1, 11 (1981).
5. S. E. Severin, A. A. Boldyrev, and A. M. Dupin, Vopr. Med. Khim., 30, No. 3, 32 (1984).
6. L. Z. Bito, R. R. Nichols, and R. A. Baroody, Exp. Eye Res., 34, No. 3, 325 (1982).
7. D. F. Cole and W. G. Unger, Exp. Eye Res., 17, No. 4, 357 (1973).
8. R. Gailitis, G. A. Peyman, J. Pulido, et al., Ophthal. Surg., 17, No. 8, 467 (1986).
9. V. S. Gulevitsch and S. Amiradzhibi, Ber. Dtsch. Chem. Ges., 33, 1902 (1900).
10. N. Kineshiro, J. Nihon. Univ. Sch. Dent., 13, No. 1, 1 (1971).
11. Y. Kitazawa and M. E. Langham, Nature, 219, 1376 (1968).
12. A. H. Neufeld and M. L. Sears, Exp. Eye Res., 17, 445 (1973).
13. S. Tsuneo and N. Kineshiro, J. Nihon Univ. Sch. Dent., 16, No. 1, 18 (1974).
14. M. B. Waitzman and C. D. King, Am. J. Physiol., 212, 329 (1967).


# FUNCTIONAL CHANGES IN THE MYOCARDIUM AND MEDULLARY RETICULAR FORMATION IN CARDIOGENIC STRESS TREATED WITH LITHIUM NICOTINATE


L. B. Aksel'rod, V. I. Kresyun, I. N. Moiseev, D. M. Sukolovskaya, L. S. Kravchenko, D. G. Rasina, and L. L. Kadyrova



UDC 616.127-005.8-036.11-06:613.863]-07: 616.127-008.3+616.831.8-018.24-008.1

KEY WORDS: stress; ischemia; lithium nicotinate; antibodies; reticular formation.


Acute ischemic heart damage causes pain and emotional-painful stress, which aggravates the course of infarction and may not only potentiate progression of ischemic damage, but may also cause damage to nonischemic areas of the myocardium [2].

The aim of this investigation was to study the character of damage to the myocardium and medullary reticular formation during experimental myocardial infarction (MI) and also to investigate the possibility of pharmacologic correction of the lesions with the aid of the atypical tranquilizer lithium nicotinate (Litonit), discovered at the N. I. Pirogov Odessa Medical Institute.

## EXPERIMENTAL METHODS

Experiments were carried out on 35 dogs with experimental MI. Before induction of MI, the ECG of all the dogs was recorded in the usual 12 derivatiions on the 1st, 3rd, and 6th days. To judge immunologic reactivity, the passive hemagglutination test [11, 12] and the lymphocyte blast transformation test (LBTT) [13] were used. At the end of the investigations MI was produced surgically (by ligation of the descending branch of the left coronary artery). The operation was performed under intravenous pentobarbital anesthesia (5% solution


Department of Pharmacology and Central Research Laboratory, N. I. Pirogov Odessa Medical Institute.


(Presented by Academician of the Academy of Medical Sciences of the USSR A. V. Val'dman.) Translated from Byulleten' Éksperimental'noi Biologii i Meditsiny, Vol. 105, No. 4, pp. 453-455, April, 1988. Original article submitted June 1, 1987.




0007-4888/88/0004-0542$12.50

TABLE 1. Number of Altered Nerve Cells per 100 Normal Cells in Medullary Reticular Formation of Dogs of Experimental and Control Groups (M ± m)

| Group of animals | Type of staining of cell | | Vacuolated neurons |
|---|---|---|---|
| | hyperchromic | hypochromic | |
| Control | 6,76±0,45* | 4,30±0,35 | 4,27±0,50 |
| Exptl. | 5,08±0,71 | 3,29±0,46 | 3,29±0,46 |

Legend. *$p < 0.05$.

30-40 mg/kg) with artificial ventilation of the lungs. On the 1st day after production of the infarct, dogs of the experimental group were treated with lithium nicotinate. The compound was injected intramuscularly in a dose of 10 mg/kg daily for 6 days. The animals were then killed with hexobarbital and succinyl choline, and pieces of heart muscle were taken for biochemical, histological, and histochemical investigations. The concentration of malonic dialdehyde (MDA) was determined in the zone of infarction [6]. Succinate dehydrogenase (SDH) and Ca-ATPase activity, and concentrations of lipids and acid mucopolysaccharides (including glycogen) were determined histochemically; the PAS reaction was performed and acid phosphatase determined [5]. Survey sections were stained with hemaoxylin and eosin and by Van Gieson's method. Part of the medulla was removed at the same time. Sections of the medulla 10 μ thick were stained with thionine by Nissl's method. The state of the nerve cells in the brain of animals of the control and experimental groups was characterized by counting the number of altered neurons (hyper- and hypochromic, vacuolated) per 100 normal cells under magnification of 10 × 20.

## EXPERIMENTAL RESULTS

Ligation of the descending branch of the left coronary artery in the dogs gave rise to an anterior septal infarct, accompanied by ventricular extrasystoles.

The experiments showed that lithium nicotinate, in the dose used, had no antiarrhythmic action: on the 3rd and 6th days the percentage of animals with extrasystoles was about the same. However, during the course of infarction differences were observed in the dogs of the experimental and control groups. Whereas toward the end of observation normalization of the ECG parameters and scar changes and disturbances of the coronary circulation were found equally often, myocardial anoxia was observed only in the untreated dogs (22.2 ± 13.8%), and it was not observed in a single case in the animals treated with lithium nicotinate ($p < 0.05$). This result must evidently be attributed to the beneficial effect of lithium nicotinate on post-stress disturbances of myocardial energy metabolism, and damage to membrane mechanisms and calcium transport. According to data in the literature, lithium nicotinate has a normalizing effect on the energy supply to brain mitochondria [1]. Treatment with lithium nicotinate caused inhibition of free-radical lipid oxidation in the myocardium of the dogs, when activated by infarction. The MDA concentration in the zone of infarction of the control dogs was 0.035 ± 0.016 μmole/g, compared with 0.021 ± 0.004 μmole/g after treatment with lithium nicotinate ($p < 0.01$).

According to the results of the histochemical tests, activity of SDH, LDH, and ATPase was absent in the zone of total ischemia in dogs of both groups. The area of dystrophic changes revealed relative to SDH activity was more extensive than that revealed by LDH activity, evidence of a switch of tissue respiration from the aerobic type to glycolysis. However, no significant differences were found (in the experimental and control groups) in metabolism of the zone of infarction or in the character of repair processes.

The microscopic investigations showed that as a result of the use of lithium nicotinate the number of hyperchromic neurons was significantly reduced in dogs with experimental MI in the nuclei of the medullary reticular formation, and a tendency was found for the number of hypochromic and vacuolated cells to decrease compared with the control (Table 1).

The formation of hyperchormic nerve cells in brain tissues has been described during exposure of the CNS to various factors: fatigue produced by prolonged swimming [10], acoustic

stress [3], alcoholization of animals [4], and as a result of the action of trifluperazine [8]. Despite the absence of unanimity, there are convincing arguments in support of a link between the functional state of nerve cells and the intensity of their staining [3, 7, 9]. Considering data in the literature, it can be postulated that the decrease in the number of hyperchromic neurons found in the present investigations in the medullary reticular formation of dogs of the experimental group is the result of the positive action of lithium nicotinate on cell metabolism.

A beneficial action of lithium nicotinate on humoral immunity was observed in these experiments. The titer of anticardial antibodies was increased in all dogs with infarction. However, the antibody titer was lower after treatment with lithium nicotinate. Whereas in the untreated dogs on the 3rd day after production of experimental infarction the antibody titer rose from 2.5 ± 0.3 to 38.4 ± 5.8 (an increase of 16 times compared with the initial level), after treatment with lithium nicotinate it increased from 2.7 ± 0.4 to 24.8 ± 4.6 (by 9.5 times, $p < 0.001$). Toward the end of observation the antibody titer in dogs of the control group was 32.6 ± 6.4 (increased by 13 times), whereas after treatment with lithium nicotinate it was 26.4 ± 5.1 (increased by 10.1 times; $p < 0.001$).

In the period immediately after infarction the level of functional activity of the T lymphocytes in response to stimulation by phythohemagglutinin was reduced in all the dogs, and in dogs of the experimental group, T-cell function was depressed much more than in the control. By the 6th day the number of blast forms of lymphocytes was increased, and much more so in the experimental than in the control group. The LBTT with antigen from the infarcted and intact heart on the 3rd day revealed enhancement of the specific immune response in all the dogs, which was more marked in the case of the antigen from the infarcted heart. By the 6th day blast formation with the specific antigen was reduced in all the dogs.

Thus lithium nicotinate, which has a protective action against stress that is realized through stabilization of the membranes and stimulation of energy metabolism, has a favorable effect on the course of MI and of its biochemical and immunologic manifestations.

In cardiogenic stress due to experimental MI, complex relations are created between nervous-reflex, humoral, and immunologic factors, which may be realized both in the heart and in the brain.

By the use of lithium nicotinate, activity of free-radical lipid preoxidation was reduced in the zone of myocardial infarction, the time course of infarction improved, a favorable trend of immunologic reactivity was established, and the compound had a beneficial action on metabolsim of the medullary reticular formation.

It can be concluded from these investigations that lithium nicotinate is indicated in the treatment of cardiogenic stress induced by myocardial infarction.

## LITERATURE CITED


1. V. I. Kresyun, Vest. Akad. Med. Nauk SSSR, No. 11, 31 (1984).
2. F. Z. Meerson, V. I. Lifant'ev, and V. V. Malyshev, Vopr. Med. Khim., No. 1, 119 (1984).
3. S. Nichkov and G. N. Krivitskaya, Acoustic Stress and Cerebro-Visceral Disturbances [Russian translation], Moscow (1969).
4. A. G. Pearse, Histochemistry: Theoretical and Applied, Longman, New York (1962).
5. É. N. Popova, Zh. Nevropatol. Psikhiat., No. 12, 1674 (1979).
6. I. D. Stal'naya and T. G. Garishvili, Modern Methods in Biochemistry [in Russian], ed. V. N. Orekhovich, Moscow (1977), pp. 66-68.
7. V. P. Tumanov and M. D. Malamud, Changes in the Central Nervous System in Response to Thermal, Radiation, and Combined Trauma [in Russian], Kishinev (1977).
8. L. E. Frumkin and É. N. Popova, Functional and Structural Bases of Systemic Activity and Mechanisms of Plasticity of the Brain [in Russian], No. 4, Moscow (1975), pp. 418-421.
9. N. E. Yarygin and V. N. Yarygin, Pathological and Adaptive Changes in the Neuron [in Russian], Moscow (1973).
10. V. N. Yarygin and A. S. Pylaev, Tsitologiya, No. 4, 464 (1976).
11. S. Boyden, Meth. Med. Res., 10, 152 (1964).
12. D. Hungerford, J. Donnal, and S. Beck, Am. J. Hum. Genet., 11, 215 (1959).
13. G. Middelbrock and P. Dubos, J. Exp. Med., 88, 66 (1948).