Role of δ-Opiate Receptors in Development of Ischemic Arrhythmias

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In acute experiments on anesthetized cats, the selective δ-opiate receptor agonist DSLET has a pronounced antiarrhythmic effect on ischemic heart rhythm disturbances. This effect is probably related to inhibition of the sympathetic heart rhythm regulation, because the antifibrillation effect of DSLET is not mediated via the vagus nerves, but on the other hand DSLET considerably modulates cardiac adrenoreactivity.

Key Words: *DSLET; δ-opiate receptors; myocardial ischemia; cardiac arrhythmias; autonomic nervous system*

Nonselective agonists of opiate receptors (OR) dalargin (δ- and μ-receptors) and β-endorphin (δ-, δ-, ε-, and κ-receptors) produce an antiarrhythmic effect in ischemic myocardium under conditions of preserved autonomic innervation of the heart [6-8]. However, it is unclear what specific role in the antiarrhythmic effect is given to particular type of OR. Our aim was to study the effect of the selective δ-opiate receptor agonist DSLET on the development of ischemic arrhythmias and the role of the autonomic nervous system in this process.

MATERIALS AND METHODS

Experiments were carried out on 67 cats of both sexes weighing 2-4 kg anesthetized with Nembutal (40 mg/kg intraperitoneally). Myocardial ischemia was produced by clamping the circumflex branch of the left coronary artery near its orifice with the help of a controllable tourniquet. The development of arrhythmias was observed during 15-min arterial occlusion and subsequent 15-min reperfusion periods. Under these conditions, idioventricular rhythm disturbances were observed in 72% animals, while ventricular tachycardia and ventricular fibrillation developed in 28 and 55% cats, respectively [6]. ECG and blood pressure in femoral artery were recorded with a Biocomb-8 polyphysiograph (Orion/EMG). Single and grouped extrasystoles, ventricular tachycardia, and ventricular fibrillation were recorded and analyzed. The selective δ-OR agonist DSLET (Laboratory of Peptide Synthesis, Russian Cardiology Research-and-Production Complex) was infused intravenously in a dose of 20 μg/kg during the coronary occlusion (CO) period. Seven experimental series were carried out: series I (n=9) — CO and infusion of DSLET under conditions of intact cardiac innervation; series II (n=8) — CO+DSLET + transection of the vagus nerves (VN) on the neck and cardiac branches of the stellate ganglia (5 min prior to CO); series III (n=10) — CO+cardiac denervation as in series II without DSLET; series IV (n=10) — CO+DSLET+differential block of myelinated VN fibers (cooling to 6°C [13]). To this end VN was separated from sympathetic nerves and placed on a cooling platform with a thermistor recording the nerve temperature. The platform was carefully isolated from the adjacent tissues and the nerve was cooled to 6°C with a cooling fluid propelled by a vacuum pump for 5 min before CO and during the ischemia and reperfusion periods; series V (n=10) — CO as in series IV without DSLET; series VI (n=8) — CO+DSLET+ transection of the VN on the neck 5 min before CO;

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and series VII (n=12) — cardiac sensitivity to norepinephrine (NE) was assessed by changes in the left ventricular pressure, dynamics of the chronotropic reaction, and the integral index of cardiac activity [12] in response to a standard dose of NE (1 μg/kg) injected into the right ventricle before and on minutes 5 and 15 of DSLET or Ringer's solution infusion. The cardiac reactions were analyzed 20 and 180 sec postinjection corresponding to the maximum and minimum heart responses [5]. The significance of differences was evaluated by the χ^2 and sign tests.

RESULTS

In the first series, the initial systolic, diastolic, pulse, and mean pressure values were, respectively, 124.5±3.8, 85.7±3.8, 38.9±2.6, and 98.6±3.7 mmHg, while the initial HR was 150.5±9.4 beats/min. Insignificant decrease in the hemodynamic indices was observed at the early period of myocardial ischemia (30 sec after CO). In control cats (ischemia without DSLET) a pronounced decrease in blood pressure was observed 30 sec after CO [6]. Our findings indicate that DSLET prevents the decrease in blood pressure induced by myocardial ischemia. This is a positive sign because the incidence of ventricular fibrillation directly correlates with the pressure drop at the early stage of ischemia [3]. DSLET decreased the occurrence of CO-induced idioventricular rhythm disturbances 2-fold in comparison with the control, in particular, the occurrence of ventricular tachycardia and ventricular fibrillation decreased 2-fold and 5-fold, respectively (Fig. 1, *a* and 2, *a*). Thus, DSLET produced a pronounced antiarrhythmic effect against all ischemic rhythm disturbances, decreased the occurrence of grouped extrasystoles and ventricular tachycardia, and prevented ventricular fibrillation (p<0.05).

Bearing in mind that extracardiac nervous control plays an important role in the pathogenesis of ischemic arrhythmias [4,9-11], we studied the participation of the autonomic nervous system in the antiarrhythmic effect of DSLET. To this end, in series II CO was preceded by bilateral transection of VN and cardiac branches of the stellar ganglion. Under these conditions, the occurrence of idioventricular rhythm disturbances in ischemic myocardium was the same as in the experiments with CO performed against the background of limited sympathetic and parasympathetic cardiac regulation without DSLET (Fig. 1, *b* and 2, *b*). These finding indicate that denervation of the heart abolishes the antiarrhythmic effect of DSLET. Therefore, the protective effect of selective δ-agonist on ischemic arrhythmias is not related to intracardiac arrhythmogenic mechanisms, but is mediated via the autonomous nervous system.

The next step was to study the role of sympathetic and parasympathetic autonomic regulation in the antiarrhythmic effect of DSLET. Taking into consideration the key role of afferent traffic via myelinated VN fibers in the genesis of ischemic arrhythmias [4, 10], in series IV myocardial ischemia was produced in DSLET-treated cats under conditions of blockade of myelinated VN fibers. In these experiments the incidence of CO-provoked ventricular fibrillation and ventricular tachycardia was 2-fold lower than in the absence of DSLET (Fig. 1, *c* and 2, *c*). These findings suggest that the protective effect of DSLET against severe ischemic arrhythmias is not related to myelinated fibers in VN.

An important role in the electrical stability of the ischemic myocardium is played by efferent subdivision of the parasympathetic nervous system [9]. In series VI, CO and DSLET injection were preceded by bilateral VN transection. Under these conditions, the incidence of CO-induced ventricular fibrillation was 2-fold lower in DSLET-treated cats than in cats with ischemic hearts deprived of parasympathetic innerva-

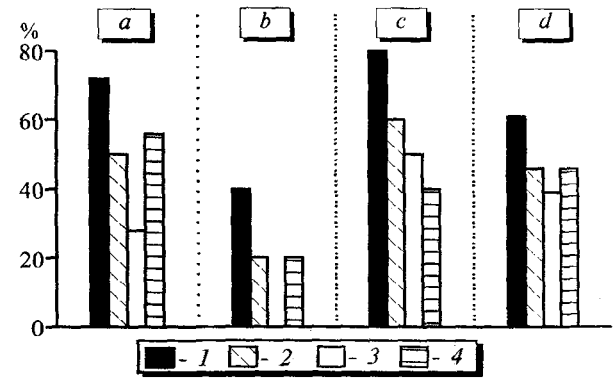

Fig. 1. Occurrence of ischemic rhythm disturbances in denervated heart. Here and in Fig. 2: *a*) intact cardiac innervation; *b*) transection of the vagus nerves and cardiac branches of the stellate ganglion; *c*) blockade of vagal myelinated fibers; and *d*) bilateral vagus nerve transection. *1*) idioventricular rhythm disturbances; *2*) grouped extrasystoles; *3*) ventricular tachycardia; *4*) ventricular fibrillation.

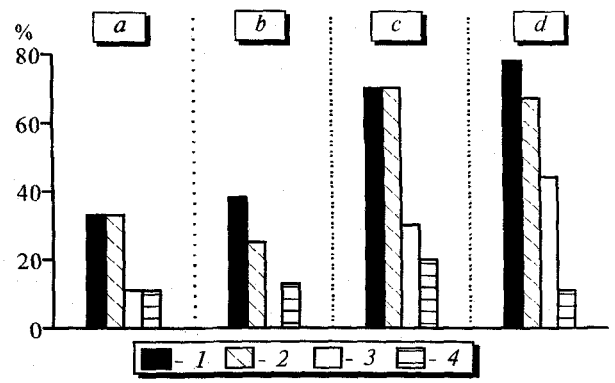

Fig. 2. Occurrence of ischemic rhythm disturbances in denervated heart in DSLET-treated cats.

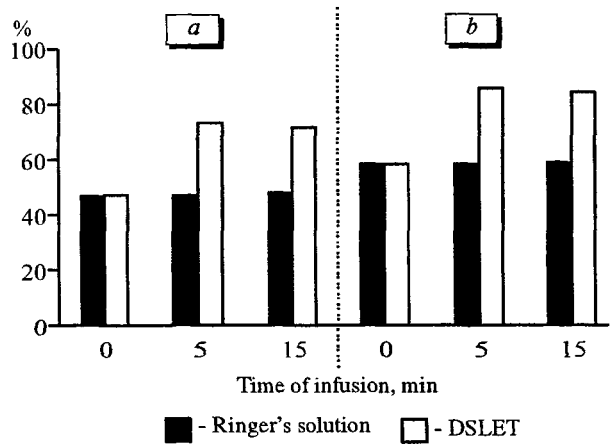

Fig. 3. Changes in left ventricular pressure (*a*) and Opie index (*b*) in response to norepinephrine under conditions of Ringer's solution or DSLET infusion.

tion and receiving no DSLET (Fig. 1, *d* and 2, *d*). This indicates that the antifibrillation effect of DSLET is not mediated via the efferent vagal fibers.

There is evidence that pulse activity in the cardiac inferior nerve sharply increased immediately before fibrillation, which means drastic activation of the sympathetic influences on the heart [2]. On the other hand, synthetic leu-enkephalin analog decreased the content of NE in the left ventricle under conditions of acute cardiac ischemia [1]. To evaluate the role of sympathetic signals in the antifibrillation effect of DSLET, in series VII we studied the effect of this agent on cardiac response to NE. Cardiac reactions to a standard dose of NE administered against the background of Ringer's solution infusion served as the control. In control cats, adrenoreactivity of the myocardium remained unchanged: the cardiac responses to a standard dose of NE were the same before and after beginning of Ringer's saline infusion. By contrast, infusion of DSLET potentiated cardiac response to a standard dose of NE on the 5th and 15th minutes in 100% experiments (Fig. 3).

There is inverse dependence between NE concentration in the heart and the number of β-adrenoceptors that determine its adrenoreactivity [15]. Enhanced cardiac adrenoreactivity presumably results from inhibition of the cardiac sympathetic influences by DSLET. Since the antifibrillation effect of DSLET in the ischemic myocardium is not mediated through the vagal system and intracardiac mechanisms, it may be hypothesized that this effect is mediated by the sympathetic part of the autonomic nervous system.

Thus, activation of δ-OR by the selective agonist DSLET produces a pronounced protective effect against ischemic rhythm disturbances, which implies an important role of these receptors in cardiac rhythm modulation during acute myocardial ischemia. The antiarrhythmic effect of DSLET is probably related to inhibition of the sympathetic arrhythmogenic mechanisms, which is confirmed by the presence of δ-OR in sympathetic postganglionic neurons [14].

REFERENCES

1. L. A. Alekminskaya, Yu. B. Kondrat'ev, V. D. Slepushkin, *et al., Patol. Fiziol.*, No. 1, 16-18 (1986).
2. N. V. Kaverina, N. V. Darinskii, and S. Yu. Berdyaev, *Vestn. Akad. Med. Nauk SSSR*, No. 5, 21-28 (1982).
3. G. I. Kositskii, S. D. Mikhailova, S. L. Gorozhanin, *et al., Ibid.*, No. 12, 67-69 (1985).
4. G. I. Kositskii, S. D. Mikhailova, and T. M. Semushkina, *Byull. Eksp. Biol. Med.*, **98**, No. 12, 653-655 (1984).
5. P. F. Litvitskii, *Ibid.*, **92**, No. 8, 17-20 (1981).
6. S. D. Mikhailova, T. M. Semushkina, and N. A. Bebyakova, *Kardiologiya*, No. 1, 13-15 (1991).
7. S. D. Mikhailova, G. I. Storozhakov, N. A. Bebyakova, and T. M. Semushkina, *Byull. Eksp. Biol. Med.*, **122**, No. 8, 176-178 (1996).
8. S. D. Mikhailova, G. I. Storozhakov, N. A. Bebyakova, and T. M. Semushkina, *Ibid.*, **123**, No. 5, 509-511 (1997).
9. L. V. Rozenshtraukh, A. V. Zaitsev, F. M. Pertsov, *et al., Kardiologiya*, No. 10, 28-33 (1994).
10. F. P. Yasinovskaya, *Ibid.*, No. 11, 54-59 (1969).
11. A. Malliani, P. J. Schwartz, and A. Zanchetti, *Am. Heart J.*, **100**, No. 5, 705-715 (1980).
12. L. Opie, *Br. Heart J.*, **33**, 129-137 (1971).
13. A. S. Paintal, *Physiol. Rev.*, **53**, 159-227 (1973).
14. Y. O. Taiwo and J. D. Levine, *J. Neurosci.*, **11**, No. 4, 928-932 (1991).
15. Sh. Yamada, H. Yamamura, and W. Roeske, *Circulation*, **60**, No. 2, 275-278 (1979).