Prevention of Experimental Epinephrine-Induced Arrhythmias with Agonists of δ_1- and δ_2-Opiate Receptors

Yu. B. Lishmanov, D. S. Ugdyzhekova, and L. N. Maslov

Translated from *Byulleten' Eksperimental'noi Biologii i Meditsiny*, Vol. 124, No. 9, pp. 286-288, September, 1997
Original article submitted July 22, 1996

Agonists of δ_1- and δ_2-opiate receptors prevent epinephrine-induced arrhythmias in rats after intracerebroventricular administration. The antagonist of δ-opiate receptors ICI 174,864 blocks antiarrhythmic effect of the selective agonist of δ-opiate receptors DTLET and exhibits no antiarrhythmic activity by itself. It is shown that antiarrhythmic effect of DTLET is associated with increased vagal tone.

Key Words: δ_1- *and* δ_2-*opiate receptors; arrhythmia*

Recent studies show that the probability and severity of arrhythmias developed under extreme conditions are strongly influenced by the functional state of the stress-limiting systems of the organism [4]. We think that the endogenous opioid system plays a key role in this phenomenon [2]. However, there is controversy over the role of opioid peptides in the formation of higher cardiac resistance to arrhythmogenic influences. It was demonstrated that ligands of opiate receptors (OR) produce both antiarrhythmic [3,13] and arrhythmogenic [3,10] effects. This controversy may be due to functional heterogeneity of central OR. Previously, we showed that intracerebroventricular (ICV) administration of μ-OR agonists increases cardiac resistance to arrhythmogenic influences, while stimulation of central κ-OR potentiates arrhythmias [3].

In the present study we assessed the contribution of central δ-OR to the processes determining heart resistance to epinephrine-induced arrhythmias.

MATERIALS AND METHODS

Experiments were carried out on male Wistar rats weighing 250-300 g. A stainless steel cannula was implanted in the lateral brain ventricle 5-7 days before induction of arrhythmias. The operation was performed under barbamil anesthesia (50 mg/kg intraperitoneally) using a SEZh-5 stereotaxic apparatus (*Konstructor*, Kiev): AP -1.5 mm, L +2.0 mm, and V -3.5 mm relative the bregma [12]. To check up the localization of the cannula 5 μl methylene blue was injected into it before decapitation. Arrhythmia was modeled by intravenous infusion of 120 μg/kg epinephrine (Sigma) after ethyl ether anesthesia. The ECG (standard lead II) was recorded for 5 min after the infusion. The ligands of OR were dissolved *ex tempore* in 0.9% NaCl and 10 μl of the solution was infused at a rate of 5 μl/min 30 min prior to epinephrine. The following OR agonists and antagonists (Chiron Mimotopes Peptide Systems) were used:

1) selective δ-agonist H-Tyr-D-Thr-Gly-Phe-Leu-Thr-OH (DTLET) in a dose of 14 μg/rat [15];

2) selective agonist of δ_1-OR H-Tyr-D-Pen-Gly-Phe-D-Pen-OH (DPDPE) in doses 10 and 50 μg/rat [11,14];

3) selective agonist of δ_2-OR H-Tyr-D-Ser-Gly-Phe-Leu-Thr (DSLET) in doses 10 and 50 μg/rat [8,11,14];

4) selective blocker of δ-OP N,N-diallyl-Tyr-Aib-Aib-Phe-LeuOH — [N,N-diallyl-Tyr1, Aib2,3]-Leu-enkephalin (ICI 174,864) in a dose of 25 μg/rat

Department of Experimental Cardiology, Institute of Cardiology, Siberian Division of the Russian Academy of Medical Sciences, Tomsk

0007-4888/97/0009-0873$18.00

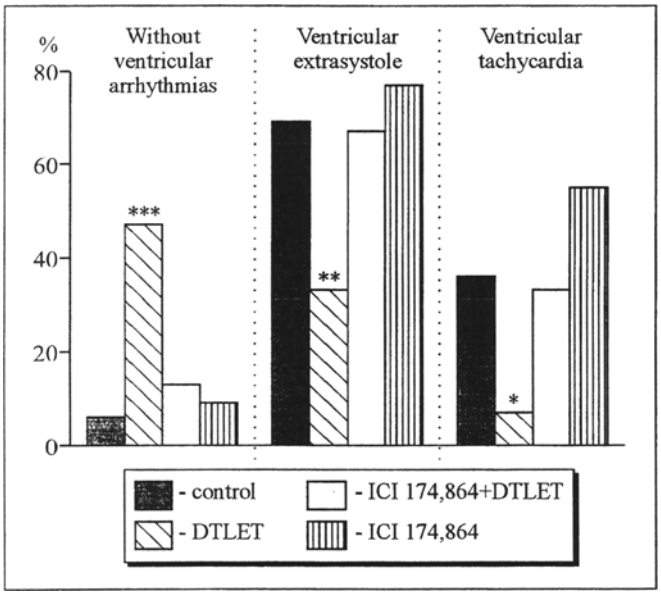

Fig. 1. Effect of the δ-OR antagonist ICI 174,864 on antiarrhythmic effect of DTLET. Here and in Fig. 2: *p<0.05, **p<0.025, ***p<0.001 compared with the control. Ordinate: percent of animals with and without arrhythmias.

[5,6]. The blocker is a weak organic acid poorly soluble in water, therefore, during its dissolution pH was adjusted to 7.0 with 0.01 N NaOH. The choice of dose and time of administration of the preparations was based on the published data on dose-dependent analgesic and cardiotropic effects of ICV administered opioid peptides [6,8]. Preliminary experiments showed that ICV administration of 0.9% NaCl produces a moderate antiarrhythmic effect. Therefore, before administration of epinephrine control animals were given 10 μl normal saline ICV instead of opioids. The results were processed statistically using the χ^2 test.

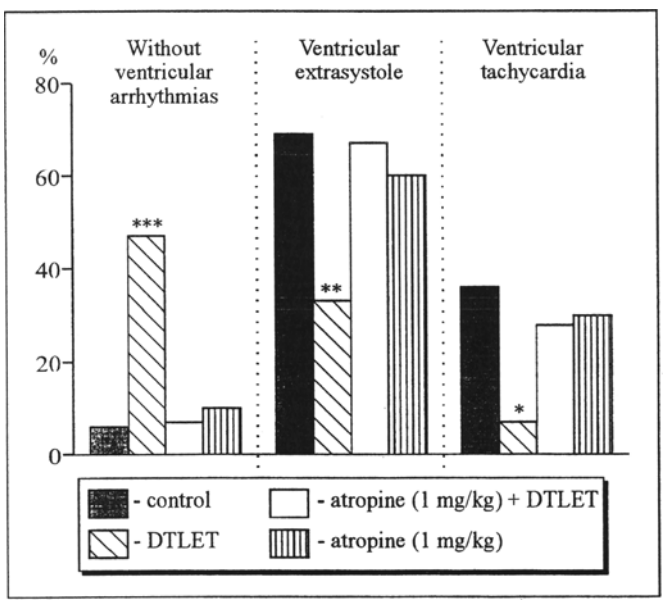

Fig. 2. Effect of atropine on antiarrhythmic effect of DTLET.

RESULTS

The selective agonist DTLET exhibited antiarrhythmic activity after ICV administration (Table 1), significantly decreasing the occurrence of cardiac arrhythmias, particularly of ventricular tachycardia, which often causes sudden death [9]. This finding is consistent with our previous observations that the δ-OR agonist DADLE produces antiarrhythmic effects [3].

The δ-OR antagonist ICI 174,864 abolished the antiarrhythmic effect DTLET (Fig. 1) and exhibited no antiarrhythmic activity by itself, indicating that the antiarrhythmic effect of DTLET specifically depends on activation of δ-OR.

Two types of δ-OR (δ_1 and δ_2) have been identified; activation of these OR subtypes results in different physiological effects [1,11,14]. Therefore, we decided to determine the contribution of δ_1- and δ_2-OR to the formation of increased cardiac resistance to epinephrine-induced arrhythmias. The selective agonist of δ_1-OR DPDPE had no significant effect on the occurrence of rhythm disturbances in a dose of 10 μg/rat, while at 50 μg/rat DPDPE reduced it by 4.5-fold. This indicates that the agonists of δ_1-OR receptors possess antiarrhythmic activity. Similar effects were observed after ICV administration of DSLET, a selective agonist of δ_2-OR, at the same doses.

Thus, stimulation of central δ_1-OR and cerebral δ_2-OR with their ligands in a dose of 50 μg/rat increases cardiac resistance to epinephrine-induced arrhythmias. At the same time, the effects of agonists of δ_1- and δ_2-OR are weaker than the antiarrhythmic effect of DTLET. At the maximum dose for ICV administration (50 μg), these agonists only increased the percent of rats without arrhythmias. It can be suggested that the higher antiarrhythmic activity of DTLET is due to its interaction with both δ_1- and δ_2-receptors. The hypothesis that the affinity of DTLET for neuronal δ-OR is higher than that of DPDPE and DSLET is quite logical.

What mechanism is responsible for the antiarrhythmic effects of δ-agonists? It can be suggested that OR ligands modulate functional activity of the autonomic nervous system. Indeed, pretreatment with atropine almost completely abolished antiarrhythmic effect of DTLET (Fig. 2). At the same time, atropine by itself had no effect on epinephrine-induced arrhythmias. This indicates that antiarrhythmic effect of the δ-OR agonist is associated with increased tone of *n. vagus*, which was demonstrated for other opioid peptides [7,13].

TABLE 1. Effects of OR Agonists and Antagonists on the Occurrence of Epinephrine-Induced Arrhythmias

Peptide, dose	n	Without ventricular arrhythmias	Ventricular extrasystole	Ventricular tachycardia	Ventricular fibrillation
Control (normal saline)	35	2 (6)	25 (69)	13 (36)	1 (3)
DTLET, 14 μg	15	7 (47)***	5 (33)**	1 (7)*	0
DPDPE, 10 μg	15	0	13 (87)	7 (47)	1 (7)
50 μg	15	4 (27)*	7 (47)	4 (27)	0
DSLET, 10 μg	20	2 (10)	14 (70)	5 (25)	2 (10)
50 μg	15	4 (27)*	10 (67)	8 (53)	0

Note. *n* = number of animals in experiment. Percent of the total number is given in parentheses. *$p<0.05$, **$p<0.025$, ***$p<0.001$ compared with the control.

From our results it can be concluded that 1) activation of central δ_1- and δ_2-opiate receptors increases heart resistance to arrhythmogenic influences and 2) antiarrhythmic effect of DTLET, a selective agonist of δ-OR, is due to increased vagal tone.

This study was supported by Dr. P. S. Hillery, National Institute on Drug Abuse (NIDA, USA).

REFERENCES

1. E. Dikenson, *Eksp. Klin. Farmakol.*, **57**, No.6, 3-12 (1994).
2. Yu. B. Lishmanov and L. M. Maslov, *Opioid Neuropeptides, Stress and Adaptive Protection of the Heart* [in Russian], Tomsk (1994).
3. Yu. B. Lishmanov, L. M. Maslov, and D. S. Ugdyzhekova, *Eksp. Klin. Farmakol.*, **58**, No. 4, 26-28 (1995).
4. F. Z. Meerson and I. Yu. Malyshev, *Phenomenon of Adaptive Stabilization of Structures and Heart Protection* [in Russian], Moscow (1993).
5. R. Cotton, M. G. Giles, L. Miller, *et al., Eur. J. Pharmacol.*, **97**, 331-332 (1984).
6. A. Cowan, X. Zhu, and F. Porreca, *Neuropeptides*, 5, 311-314 (1985).
7. E. Frey, G. Avril, and E. Hartung, *Cah. Anesthesiol.*, **29**, No. 5, 591-598 (1981).
8. G. Gacel, M.-C. Fournie-Zaluski, and B. P. Roques, *FEBS Lett.*, **118**, No. 2, 245-247 (1980).
9. A. Gradman, P. Deedwania, R. Cody, *et al., J. Am. Coll. Cardiol.*, **14**, 564-570 (1989).
10. A. Y. S. Lee, *Int. J. Cardiol.*, **27**, No. 2, 145-151 (1990).
11. A. Mattia, S. C. Farmer, A. E. Takemori, *et al., J. Pharmacol. Exp. Ther.*, **260**, 518-525 (1992).
12. G. Paxinos and C. Watson, *The Rat Brain in Stereotaxic Coordinates*, New York (1982).
13. S. W. Rabkin, *Life Sci.*, **45**, No. 12, 1039-1047 (1989).
14. M. Sofuoglu, P. S. Portoghese, and A. E. Takemori, *Eur. J. Pharmacol.*, **216**, 273-277 (1992).
15. J.-M. Zajac, G. Gasel, F. Petit, *et al., Biochem. Biophys. Res. Commun.*, **111**, No. 2, 390-397 (1983).