Central κ_1-Opiate Receptors and Mechanisms of Arrhythmias

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

Translated from *Byulleten' Eksperimental'noi Biologii i Meditsiny,* Vol. 127, No. 1, pp. 57-59, January, 1999.
Original article submitted April 21, 1998

Intracerebroventricular infusion of κ_1-opiate receptor agonists potentiated cardiac arrhythmias elicited by epinephrine. This effect was completely reversed by the κ_1-receptor antagonist norbintaltorphymine and the ganglioblocker hexamethonium. Norbintaltorphymine also exhibited an antiarrhythmic activity. It is suggested that endogenous ligands of κ_1-receptors play an important role in the regulation of arrhythmias.

Key Words: *κ-opiate receptors; arrhythmias*

Opioid peptides are involved in regulatory mechanisms of cardiac arrhythmic activity [1,2,12]. According to published data, antiarrhythmic activity is inherent to both agonists [1,2,12] and antagonists [5] of opiate receptors (OR). This discrepancy can be explained by the existence of different types of OR with different roles in the regulation of arrhythmic activity. We have shown that stimulation of central μ-OR increases the cardiac resistance to arrhythmogenic stimuli [1]. The question about the involvement of central κ_1-OR in the regulation of heart electrical stability remained unsolved. The objective of the present work was to evaluate the role of κ_1-OR in the regulation of arrhythmogenesis.

MATERIALS AND METHODS

Experiments were carried out on male Wistar rats weighing 250-300 g. Five to seven days before the experiment a stainless steel cannula was stereotaxically implanted into the lateral ventricle (AP 1.5 mm; L+2.0 mm, V— 3.5 mm) and fixed on the skull with dental cement. The operation was performed under barbiturate anesthesia (50 mg/kg, intraperitoneally) using a SEZH-5 stereotaxis apparatus (Konstruktor, Ukraine). To verify the position of the cannula, methylene blue (5 μl) was injected through the cannula at the end of the experiment.

Arrhythmias were provoked by intravenous injection of 120 μg/kg epinephrine (Sigma) under ethylester anesthesia. The ECG in standard lead II was recorded for 5 min after the injection. The OR ligands were *ex tempore* dissolved in normal saline and infused intracerebroventriculary (icv) in a volume of 10 μl at a rate of 5 μl/min 30 min prior to intravenous epinephrine. The following drugs were used: the nonselective κ_1-agonist [D-Ala^2]-dynorphin A1-13 [6] (Bio-Pro, Novosibirsk) in a dose of 30 μg/rat; the specific κ_1-OR agonist U50488H, trans-(±)-3,4-dichloro-N-methyl-N-(2-[1-pyrrolidinyl]cyclohexyl)-benzeneacetamide [14], generously given by Dr. P. F. VonVoigtlander (Upjohn Company), 35 μg/rat; the selective antagonist of κ_1-OR norbinaltorphumyne (NBPh) [11] (Research Triangle Institute] in a dose of 10 μg/rat, and the nonselective μ-OR antagonist naloxone [4,8] (Sigma), 20 μg/rat. The doses and administration schedules were determined from the reported data on dose-dependent analgetic and cardiotropic effects of opioid peptides after icv administration [1,6,8,12]. Hexamethonium was injected intravenously in a dose of 10 mg/kg [3]. Our preliminary tests showed that icv infusion of 10 μl saline induced a moderate antiarrhythmic effect, therefore the control groups were comprised of animals given 10 μl 0.9% NaCl prior to the norepinephrine injection. To avoid potential effects of

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

0007-4888/99/0001-0050 $22.00

seasonal variations in physiological responses, each experimental group with 1 or 2 drugs tested was compared with its own control group. The data were analyzed statistically using the χ^2 test.

RESULTS

The nonselective agonist of κ_1-OR dynorphin potentiated cardiac ventricular arrhythmias (Table 1). The incidence of ventricle fibrillations increased 4 times after intracerebral administration of this peptide.

Since some effects of dynorphin are not mediated by OR [13], in an additional series of experiments we examined its effects on the epinephrine-induced fibrillations in the presence of naloxone, a nonselective OR antagonist. When administered prior to dynorphin, naloxone completely prevented its potentiating effects, which confirmed the specific nature of dynorphin's proarrhythmic activity. Naloxone did not affect arrhythmias induced by norepinephrine (Table 1).

As dynorphin is a nonselective κ_1-agonist, in further experiments we studied the effects of U50488H, a highly selective agonist of κ_1-OR. This compound showed strong proarrhythmic activity, dramatically increasing (16 times) the occurrence of ventricle tachycardia and aggravating fibrillations (Table 1). Intracerebroventricular infusion of the specific κ_1-antagonist NBPh prevented this proarrhythmic effect U50488H (Table 1). Interestingly, NBPh suppressed ventricular tachycardias and fibrillations. Therefore, stimulation of central κ_1-OR diminished cardiac resistance to arrhythmogenic effects, while their blockade prevented the development of arrhythmias caused by epinephrine injection. These findings suggest the involvement of the central κ_1-OR in tonic regulation of the electrical stability of the myocardium.

The mechanisms of proarrhythmic effects of κ_1-OR agonists remain unclear. Any direct effects of OR ligands on the myocardium after an icv injection could be excluded, since the blood-brain barrier is practically impermeable to opioid peptides [11], and the concentration of U50488H after icv infusion in peripheral blood is too low to affect the peripheral structures [8, 14]. It can be suggested that proarrhythmic effects of κ_1-agonists are mediated by the autonomic nervous system that plays an important role in the regulation of electrical stability of the myocardium [7]. Indeed, hexamethonium in a dose of 10 mg/kg, which is sufficient for complete blockade of peripheral autonomic neurotransmission [3], not only prevented the proarrhythmic effects of the agonists, but significantly lowered the responsiveness to epinephrine (increased the number of rats without arrhythmias) and reduced the occurrence of ventricular tachycardias (Table 1). Its antiarrhythmic activity may result from nonspecific blockade of proarrhythmogenic effects of κ_1-OR agonists and its own weak antiarrhythmic effects.

From our results it can be concluded that 1) the proarrhythmic effects of dynorphin and U50488H arise from activation of central κ_1-OR; 2) central κ_1-OR are

TABLE 1. Effects of Opiate Receptor Ligands and Hexamethonium on Epinephrine-Induced Arrhythmias

Animals	*n*	Without VE	VE	VT	VF
Control	25	7 (28)	12 (48)	2 (8)	5 (25)
Naloxone	12	2 (17)	7 (58)	0	2 (17)
Dynorphin	15	3 (20)	10 (67)	1 (7)	9* (60)
Control	18	1 (4)	11 (53)	5 (27)	2 (11)
Naloxone+dynorphin	15	4 (27)	4 (27)	2 (13)	2 (13)
Control	20	1 (5)	17 (85)	1 (5)	0
U50488H	15	0	15 (100)	12*** (78)	8*** (56)
Control	15	0	12 (80)	8 (53)	4 (27)
NBPh	15	0	13 (92)	2** (14)	1* (7)
NBPh+U50488H	15	2 (13)	9 (60)	1* (7)	0**
Control	14	0	12 (86)	3 (21)	0
Hexamethonium+U50488H	15	5**(33)	10 (67)	2 (13)	0
Control	20	3 (15)	16 (80)	12 (60)	3 (15)
Hexamethonium+dynorphin	15	0	11 (73)	4** (27)	1 (7)
Control	34	3 (9)	13 (38)	15 (44)	2 (6)
Hexamethonium	19	2 (10)	2** (10)	11 (58)	1 (5)

Note. *VE*: ventricular extrasystola; *VT*: ventricular tachycardia; VF: ventricular fibrillation; *$p<0.01$; **$p<0.05$; ***$p<0.001$ compared with the control. Percent ratio is given in parentheses.

involved in tonic regulation of cardiac resistance to arrhythmogenic influences; 3) proarrhythmic effects of κ_1-agonists are associated with modulation in the autonomic nervous system.

This study was supported by the Russian Foundation for Basic Sciences (grant No. 98-04-4810), by Dr. P. Hillary from the National Institute on Drug Abuse (USA), and Dr. P. F. VonVoigtlander from the Upjohn Company (USA).

REFERENCES

1. Yu. B. Lishmanov and L. N. Maslov, *Opioid Neuropeptides, Stress and Cardioprotective Adaptation* [in Russian], Tomsk, (1994).
2. Yu. B. Lishmanov, L. N. Maslov, and D. S. Ugdyzhekova, *Eksperim. Klin. Farmacol.*, **58,** No. 4, 26-28 (1995).
3. P. P. Denisenko, in *Gangliolytics and Blockers of Neuromuscular Synapses* [in Russian], Leningrad (1958).
4. V. Dauge, P. Rossignol, and B. P. Roques, *Psychopharmacology* (Berlin), **96,** No. 3, 343-352 (1988).
5. X. D. Huang, A. Y. S. Lee, T. M. Wong, *et al., Br. J. Pharmacol.*, **87,** 475-477 (1986).
6. D. N. Jones and S. G. Holtzman, *Eur. J. Pharmacol.*, **215,** No. 2-3, 345-348 (1992).
7. B. Lowen, R. A. DeSilva, and R. Lenson, *Am. J. Cardiol.*, **41**, 979- 985 (1978).
8. M. J. Millan, A. Czlonkowski, A. Lipowski *et al., J. Pharmacol. Exp. Ther.*, **251,** No. 1, 342-350 (1989).
9. W. Pardridge and L. Mietus, *Endocrinology,* **109,** No. 4, 1138-1143 (1981).
10. G. Paxinos and C. Watson, *The Rat Brain in Stereotaxic Coordinates,* New York (1982).
11. P. S. Portoghese, A. W. Lipkowsky and A. E. Takemori, *Life Sci.*, **40,** 1287-1291 (1987).
12. S. W. Rabkin, *Clin. Exp. Pharmacol. Physiol.*, **20**, 95-102 (1993).
13. A. E. Takemori, H. H. Loh, and N. M. Lee, *J. Pharmacol. Exp. Ther.*, **266,** No. 1, 121-123 (1993).
14. P. F. VonVoigtlander and R. A. Lewis, *Ibid.*, **246,** No. 1, 259-262 (1988).