Central κ_1-Opiate Receptors and Mechanisms of Arrhythmogenesis

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Agonists of κ_1-opiate receptors injected in brain ventricle potentiate arrhythmogenic effect of adrenaline. Antagonist of κ_1-opiate receptors norbinaltorphimine or ganglioblocker hexamethonium completely abolish proarrythmic effects of κ_1-agonists. Norbinaltorphimine possesses intrinsic antiarrhythmic activity.

Key Words: *κ_1-opiate receptors; arrhythmias*

It is known that opioid peptides play a role in the regulation of extracardial mechanisms of arrhythmogenesis [2,11]. However, published data concerning this problem are contradictory: antiarrythmic activity has been reported for both agonists [2,11] and antagonists [4] of opiate receptors (OR). These discrepancies are probably due to the existence of various types of OR and their different roles in the regulation of arrhythmogenesis.

We have previously demonstrated that stimulation of central μ-OR improves heart resistance to arrythmogenic influences [2]. However, the role of κ_1-OR in the regulation of electrical stability of the heart remains unclear.

The aim of the present study was to elucidate the role of κ_1-OR in the regulation of arrythmogenesis.

MATERIALS AND METHODS

Experiments were carried out on male Wistar rats weighing 250-300 g. A hole cannula made of stainless steal was implanted into the lateral brain ventricle 5-7 days before induction of arrhythmia and fixed to the scull with cement phosphate. The operation was performed under barbamil narcosis (50 mg/kg, i.p.) using an SEZh-5 stereotactic apparatus (*Constructor* Research and Manufacturing Association, Ukraine) at AP=—1.5 mm, L=+2.0 mm, and V=—3.5 mm from bregma. For verification of the cannula position, 5 μl methylene blue was injected into the brain ventricle.

Cardiac arrhythmias were modeled by intravenous injection of adrenaline (Sigma) in a dose of 120 μg/kg body weight. The animals were preliminary narcotized with ethyl ether; ECG (standard lead II) was recorded for 5 min postinjection. Ligands of OR were *ex tempore* dissolved in 0.9% NaCl and infused in a volume of 10 μl 30 min prior to adrenaline (5 μl/min infusion rate). The following ligands were used: the κ_1-agonist [D-Ala^2]-dynorphin A 1-13 [5] (BioPro, Novosibirsk) in a dose of 30 μg/rat, the selective agonist of κ_1-OR U50488H — trans-(±)-3,4-dichloro-N-methyl-N-(2-[1-pyrrolidinyl]cyclohexyl)benzeneacetamide [13] in a dose of 35 μg/rat kindly provided by Dr. P. F. Von Voigtlander (Upjohn Company), the selective κ_1-blocker norbinaltorphimine (NBP) [10] (Research Triangle Institute) in a dose of 10 μg/rat, and the nonselective blocker of μ-OR naloxone [3,7] (Sigma) in a dose of 20 μg/rat. The doses and time of injection were chosen on the basis of published data on dose-dependent analgesic and cardiotropic effects of opioid peptides after intracerebroventricular administration [2,5,7,11]. The ganglioblocker hexamethonium was injected intravenously in a dose of 10 mg/kg [1]. Previous experi-

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TABLE 1. Effect of Ligands of OR and Hexamethonium on Adrenaline-Induced Arrhythmias

Drugs	Number of animals	Without ventricular extrasystoles	Ventricular extrasystoles	Ventricular tachycardia	Ventricular fibrillation
Control	25	7 (28)	12 (48)	2 (8)	5 (25)
Naloxone	12	2 (17)	7 (58)	0	2 (17)
Dynorphin A 1-13	15	3 (20)	10 (67)	1 (7)	9* (60)
Control	18	1 (4)	11 (53)	5 (27)	2 (11)
Naloxone+dynorphin A 1-13	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)
NBP	15	0	13 (92)	2** (14)	1* (7)
NBP+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 A 1-13	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. Percentage is shown in parentheses; *$p<0.01$, **$p<0.05$, *$p<0.001$ in comparison with the control.

ments showed that intracerebroventricular injection of 10 μl 0.9% NaCl exerts a moderate antiarrhythmic effect; therefore, control animals received 10 μl 0.9% NaCl prior to adrenaline. In order to minimize the effect of seasonal fluctuations in physiological reactions on experimental results, the control groups were repeatedly composed for 1-2 experimental series. The data were processed using χ^2 test.

RESULTS

Experiments showed that nonselective κ_1-agonist dynorphin aggravates ventricular arrythmias and increases 4-fold the occurrence of ventricular fibrillation (VF) in comparison with the control.

Some effects of dynorphin are not mediated through activation of OR [12]; therefore, in special experimental series dynorphin was injected against the background of the nonselective OR blocker naloxone. Naloxone completely abolished dynorphin-induced potentiation of adrenaline-induced VF. Hence, the used agonist of κ_1-OR exhibits a specific proarrythmogenic effect. Naloxone alone had no effect on adrenaline-induced arrythmias (Table 1).

Since dynorphin is a nonselective κ_1-agonist, in further experiments we used the high-selective agonist of κ_1-OR U50488H. This preparation exhibited a pronounced proarrhythmic activity; it increased 16-fold the occurrence of ventricular tachycardia and promoted the development of VF (Table 1). Preliminary intracerebroventricular injection of the selective κ_1-antagonist NBP completely abolished the proarrythmic effect of U50488H (Table 1). Interestingly, NBP alone also prevented the development of ventricular tachycardia and VF in experimental animals in comparison with the control group. Hence, stimulation of the central κ_1-OR reduces heart resistance to arrythmogenic influences, while blockade of these receptors prevents the development of adrenaline-induced arrythmias. This implies the participation of central κ_1-OR in tonic regulation of electrical stability of the heart.

However, the mechanism of proarrythmic effect of κ_1-agonists remained unclear. Upon intracerebroventricular administration the direct effect of OR ligands on the myocardium can be excluded, since opioid peptides cannot cross the blood-brain barrier [10], and final blood concentration of U50488H after intracerebral infusion is very low to produce any effect on peripheral organs [7,13]. We assumed that the antiarrythmic effect of κ_1-agonists is due to modulation of the vegetative nervous system, which plays an important role in the regulation of electrical stability of the myocardium [6]. Indeed, 10 mg/kg hexamethonium sufficient for total blockage of neurotransmission in vegetative ganglia [1] not only completely abolished the antiarrythmic effect of κ_1-agonists, but also increased the number of animals without ventricular arrythmias and reduced the occurrence of ventricular tachycardia (Table 1). It can be hypo-

thesized that we observed two effects: nonspecific inhibition of the proarrythmogenic action of κ_1-agonists and weak antiarrythmic effect of hexamethonium. Such an effect of ganglioblockers has not been previously reported.

Thus, the following conclusions can be made from our findings: the proarrythmic effect of dynorphin and U50488H is mediated through central κ_1-OR; central κ_1-OR are involved into tonic regulation of heart resistance to arrythmogenic influences; the proarrythmic effect of κ_1-agonists is due to their modulating action on the vegetative nervous system.

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