PATHOLOGICAL PHYSIOLOGY AND GENERAL PATHOLOGY

Central Opioid Receptors in the Pathogenesis of Adrenal Arrhythmias

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The effect of intraventricular administration of opioid peptides on the frequency and severity of ventricular arrhythmias is studied after intravenous injection of epinephrine. It is found that the selective μ-agonist DAGO and the nonselective σ-agonist DADLE decrease the frequency and severity of arrhythmias. On the other hand, the selective σ-agonist DSLET and the κ-agonist dinorphine A 1-13 potentiate adrenal arrhythmias.

Key Words: *opioid receptors; opioid peptides; arrhythmia*

The prevention and treatment of disorders of the cardiac rhythm are still problematic. Peripheral and central components of the autonomic nervous system play a considerable role in arrhythmogenesis [1,10,12]. It is commonly believed that the endogenous opioid system markedly modulates the state of the sympathetic and parasympathetic tone [1,2,5,7, 10,14,15], a fact which has prompted scientists to study the role of the endogenous opioid system in arrhythmogenesis [1,8,9,11,14,16]. Endogenous opioid peptides (OP) promote the development of arrhythmias [8,9,16], but can possess antiarrhythmic activity as well, according to the data of Rabkin [14] and our own findings [11]. Such a contradiction stems in our view to the fact that the majority of studies performed by Wong and co-workers were carried out on the isolated perfused heart, whereas Rabkin used central administration of OP *in vivo* [14].

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We consider that the final arrhythmogenic or, on the contrary, the antiarrhythmogenic effect of OP is determined by the interaction between the administered ligand and various types and subtypes of central and peripheral opioid receptors (OR).

The aim of the present study was to analyze the role of central μ-, σ-, and κ-OR in the genesis of adrenal arrhythmias.

MATERIALS AND METHODS

Experiments were carried out on male Wistar rats weighing 250-300 g. Five to seven days prior to the induction of arrhythmia a hollow stainless steel cannula was implanted in the lateral ventricle of the rat brain and fixed on the cranial surface with dental cement. The operation was performed under amytal sodium anesthesia (50 mg/kg i.p.) using an SEZh-5 stereotaxic apparatus (Konstruktor Scientific Conglomerate, Ukraine). The coordinates used were as follows: AP 1.5, L +2.0, V 3.5 mm as related to the bregma [13]. Five microliters of a dye were administered intracerebroventricularly (ICV) to all animals before decapitation to pinpoint the localization of the cannula.

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TABLE 1. Effect of Opioid Peptides on the Frequency of Development of Adrenal Arrhythmias

Peptides	*n*	VE	Animals with VE, %	VT	Animals with VT, %	VF	Animals with VF, %
Control	25	12	48	2	8	4	16
DAGO	15	1*	7	–	–	–	–
DADLE	15	2*	13	–	–	–	–
DSLET	20	16*	80	3	15	6	30
Dinorphine A 1–13	15	10	67	1	7	9*	60

Note. *n*: number of experimental animals. Asterisk denotes reliable differences as compared to the control (administration of epinephrine). VE: ventricular extrasystoles; VT: ventricular tachycardia; VF: ventricular fibrillation. Peptides were administered at 20 nmol per rat.

Arrhythmia was simulated by i.v. administration of epinephrine at 90 μg/kg body weight under ether anesthesia. The electrocardiogram (ECG) was recorded in the second standard lead for 5 min after the injection.

OR ligands dissolved in 0.9% NaCl *ex tempore* were then infused in a volume of 10 μl at a rate of 5 μl/min 30 min prior to epinephrine. The σ-OR agonist [D-Ala2, D-Leu5]-enkephalin (DADLE) [3,17], the selective μ-OR agonist [D-Ala2, N-Met-Phe4, Gly5-ol]-enkephalin (DAGO) [4], the selective σ-agonist [D-Ser2, Leu5, Thr6]-enkephalin (DSLET) [13,17], and the nonselective κ-agonist [D-Ala2]-dinorphine A 1-13 [6] (Vektor-Bioprodukt) were used. All peptides were administered at 20 nmol per rat. The choice of schedule and of the dose of preparation were guided by the reported dose-dependent analgetic and cardiotropic effects of OP injected ICV [2,5]. Naloxone was administered ICV at 55 nmol per rat [5]. Atropine was injected i.v. in a dose of 1 mg/kg [14]. Our preliminary experiments showed that ICV administration of 10 μl 0.9% NaCl may produce a moderate antiarrhythmic effect itself, and therefore the control animals received 10 ml 0.9% NaCl ICV instead of opioids before epinephrine injection. Results were processed statistically using the χ^2 method

RESULTS

DAGO, the selective μ-OR agonist, exhibited the greatest antiarrhythmic activity when injected ICV (Table 1), as is in agreement with Rabkin's data [14]. The same properties were more weakly pronounced in the σ-OR agonist DADLE. In contrast, the highly selective σ-OR ligand DSLET possessed a moderate antiarrhythmogenic activity. The κ-OR agonist dinorphine A 1-13 potentiated the development of cardiac rhythm disorders as well. The arrhythmogenic effect of dinorphine and the antiarrhythmic action of the κ-agonist were demonstrated by Lee and Wong *in vitro* on the isolated perfused heart [8,16]. Our findings attest that not only the peripheral but also the central κ-OR participate in arrhythmogenesis.

Such substantial differences in the effects of DADLE and DSLET might be related to the different degree of selectivity of these ligands. In fact, the selectivity of DSLET is known to be twice that of DADLE, which can simultaneously interact with μ-OR [3,17].

Evidently, it is the activation of μ-receptors which ultimately produces the antiarrhythmic effect of DADLE. The data on the antiarrhythmic properties of the selective μ-agonist DAGO confirm this notion. A comparison of the arrhythmogenic effect of DSLET and of dinorphine reveals that the σ-agonist DSLET potentiates the development of ventricular extrasystoles only, which are relatively mild. At the same time, the κ-agonist dinorphine induces lethal ventricular fibrillation in rats.

Activation of the sympathetic component of the autonomic nervous system is known to favor the development of arrhythmia [10], while an increase of the vagus tone, on the contrary, prevents this [12]. It may be assumed that the capacity to modulate the activity of the indicated components of the autonomic nervous system underlies the arrhythmogenic or antiarrhythmic effect of OP [1,5,7,11, 14,15]. It is remarkable, that opinions differ as to the role of the endogenous opioid system in the regulation of the central component of the autonomic nervous system. Thus, according to Laubie and Schmitt [7], OP administered ICV increase the tone of *n. vagus*. At the same time, according to Van Loon and co-authors [15], the intraventricular administration of OP stimulates the release of catecholamines from the adrenals and sympathetic terminals.

In view of the above, it may be assumed that μ-agonists (DAGO and, to a lesser degree, DADLE) are able to increase the vagus tone and

thereby to prevent electrical instability of the heart. Indeed, in a separate experimental series we established that pretreatment with the M-cholinoblocker atropine completely abolished the antiarrhythmic effect of DAGO and DADLE. In contrast, σ-(DSLET) and κ-(dinorphine) agonists may potentiate the development of arrhythmia via activation of the sympathetic component of the autonomic nervous system (or due to a decrease of the vagus tone) and the arrhythmogenic effect is more pronounced in dinorphinee than in DSLET, which suggests an important role of the central κ-OR in arrhythmogenesis.

Thus, the findings testify that different subtypes of opioid receptors play a diverse role in arrhythmogenesis, namely: activation of the central μ-OR promotes a rise of the electrical stability of the heart, while the stimulation of central σ- and κ-receptors lowers the resistance of the heart to the arrhythmogenic effect of epinephrine. The capacity of opioid peptides to modulate the state of the autonomic nervous system probably underlies the observed effects.

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