Correction of Electrical Instability of the Heart with Opiate Receptor Ligands

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Peripheral injections of the μ-opiate receptor agonist DALDA, κ-opiate receptor agonist spiradoline, and δ-opiate receptor blocker DuP734 significantly increased the ventricular fibrillation threshold in animals with modeled postinfarction cardiosclerosis or stress-induced damage to the heart.

Key Words: *opiate receptors; stress; cardiosclerosis; arrhythmias*

Ventricular fibrillation and sudden death are the most serious complications of ischemic heart disease and myocardial infarction. There are numerous reports on the development of fatal electrical instability of the myocardium in patients without coronary symptoms survived severe stress or long-term psychoemotional strain [5]. However, the mechanisms underlying the development of cardiac electrical instability remain poorly understood.

We have previously demonstrated that some ligands of μ-, κ-, and σ-opiate receptors (OR) exhibit antiarrhythmic activity and prevent the development of stress-induced cardiac damage [1,2]. However, it remains unknown whether these agents correct pre-existent electrical instability of the heart.

The aim of the present study was to explore the possibility of using OR ligand for correcting of experimental electrical instability the heart.

MATERIALS AND METHODS

Experiments were carried out on male Wistar rats weighing 150-250 g. The animals were divided into 3 groups. Ventricular fibrillation threshold (VFT) was measured either immediately after stress (24-h immobilization in the supine position (group 1) or 30-45 days after experimental occlusion of the descendent coronary artery as described previously [4] (group 2). Intact rats (group 3) served as the control. For evaluation of VFT the heart was stimulated with anodal square electrical pulses (2 msec) delivered during the susceptible phase of the cardiac cycle using a ES-50-1 cardioverter defibrillator. The minimal current inducing ventricular fibrillation was taken as VFT. The following OR ligands were injected 15 min before measuring VFT: peripheral μ-OR agonist DALDA ([D-Arg^2, Lys^4]-dermorphin (1-4)-amide, 0.1 mg/kg, intravenously), σ-OR blocker DuP734 (1-(cyclopropylmethyl)-4-(2'-(4''-fluorophenyl-2'-oxoethyl)piperidine-HBr, 1 mg/kg, intraperitoneally), and selective κ_1-OR agonist U62066E spiradoline (5α,7α, 8β-(+)-3,4-dichloro-N-methyl-N-(7-(1-pyrrolidinyl)-1-oxaspiro-(4,5)dec-8-yl)-benzeneacetamide, 8 mg/kg, intraperitoneally). In a dose of 1 mg/kg DuP734 inhibited both central and peripheral σ-OR [10]. The U62066E dose (8 mg/kg) was chosen on the basis of published data of its analgesic effects [11].

DALDA was provided by the National Institute on Drug Abuse (USA), DuP734 was donated by Dr. P. Gilligan (DuPont Merck Sharp, USA), and U62066E was kindly provided by Dr. P. F. Von-Voigtlander (The Upjohn Company, USA).

The data were processed statistically using the Student *t* test.

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RESULTS

In rats subjected to stress and in animals with postinfarction cardiosclerosis, VFT decreased 2-fold in comparison with the control, indicating electrical instability of the myocardium (Figs. 1 and 2). Injection of the μ-OR agonist DALDA significantly increased VFT in rats subjected to immobilization stress (by 30%) and in animals with postinfarction cardiosclerosis (by 37%). We assume that this antifibrillatory effect of DALDA is related to the inhibition of calcium entry into cardiomyocytes, since activation of μ-OR is accompanied by blockage of slow Ca^{2+} channels [9].

A similar effect was produced by the κ_1-OR agonist spiradoline. It completely abolished electrical instability induced by stress or cardiosclerosis (Figs. 1 and 2). This effect can also be attributed to the inhibition of slow Ca^{2+} entry into cardiomyocytes. This assumption is based on experiments demonstrating the possibility of inhibiting slow Ca^{2+} channels with κ-OR agonists [8]. However, modulation of other ionic channels with κ-OR agonists cannot be excluded [7].

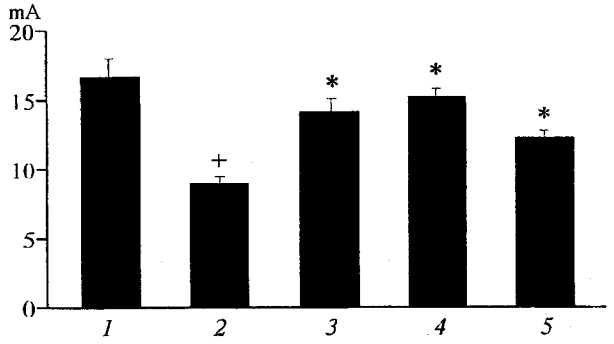

Fig. 1. Effects of DALDA (*3*), DuP734 (*4*), and spiradoline (U62066E, *5*) on the fibrillation threshold in animals with postinfarction cardiosclerosis (n=18). Here and on Fig. 2: *1*) intact rats, *2*) rats with cardiosclerosis without injections. $^{*}p<0.05$, $^{**}p<0.01$ compared with *1*, $^{*}p<0.01$ compared with *2*.

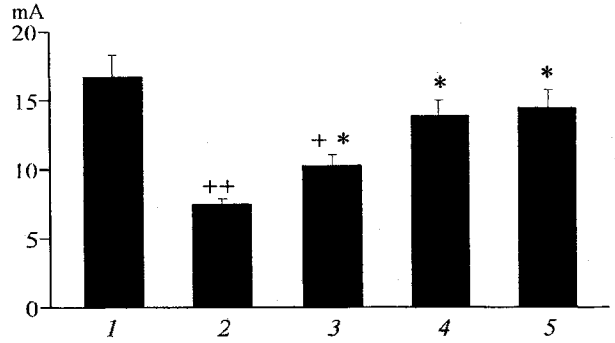

Fig. 2. Effects of DALDA (*3*), DuP734 (*4*), and spiradoline (U62066E, *5*) on the fibrillation threshold in animals with stress-induced damage to the myocardium.

Improvement of electrical stability of the heart was also noted under conditions of σ-OR blockade. Injection of the σ-OR antagonist DuP734 significantly increased VFT in rats subjected to stress (approximately 2-fold) and in animals with cardiosclerosis (by 71%). This allowed us to hypothesize that tonic σ-OR stimulation plays a pathogenetic role in the development of electrical instability of the myocardium resulting from its postischemic heterogeneity or stress-induced damage. The observed antiarrhythmic effects of the σ-OR blocker DuP734 are probably realized though the restriction of the cardiomyocyte membrane permeability for Ca^{2+} ions, since σ-OR agonists have been reported to activate Ca^{2+} transport across the sarcolemma [6].

Our previous findings suggest that, unlike the nonselective ε-OR ligand β-endorphin, whose antifibrillatory effect is mediated through the vagus nerves [3], antiarrhythmic effects of μ-, κ-, and σ-OR ligands do not depend on the autonomic nervous system [1,2]. In light of this, modulation of the cardiomyocyte membrane ionic (primarily Ca^{2+}) channels is the key mechanism of the opiatergic improvement of cardiac electrical stability. This concept is confirmed by published data [3,6-9] and our previous experiments [2], where DALDA, spiradoline, and DuP734 exhibited antiarrhythmic activity in modeled adrenaline and $CaCl_2$-induced arrhythmias primarily associated with enhanced Ca^{2+} entry into cardiomyocytes.

Thus, our findings suggest that μ- and κ-OR agonists and σ-OR blockers provide a prospective basis for the development of new pharmacological preparations for effective correction of cardiac electrical instability associated with stress and postinfarction cardiosclerosis. There are strong grounds to believe that endogenous σ-OR stimulators actively participate in tonic regulation of arrhythmogenesis.

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