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Esmolol activates endogenous neurokinin activity inhibiting infarction-induced arrhythmias in rats: Novel mechanisms of anti-arrhythmia

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ABSTRACT

Endogenous neurokinin and adrenergic mechanisms might co-participate in the pathology of acute myocardial infarction (MI). This study sought to investigate the role of endogenous neurokinin and its relationship with β_1-adrenergic mechanism in the infarction induced arrhythmias.

In 60 min of MI in rats, the contents of substance P (SP), a native agonist of neurokinin 1 receptor (NK1-R), norepinephrine (NE), NK1-R and β1-adrenergic receptor in the myocardium at risk of ischemia were examined and the ventricular arrhythmias were analyzed. The effects of pretreatment with D-SP (152 ng/kg), a specific antagonist of NK1-R, esmolol (10 mg/kg), a specific blocker of β_1-adrenergic receptor, and a combination of the two blockers were studied. The results showed that the overlaps of up-regulation of NE, SP and the increase of ventricular arrhythmias were observed. D-SP exacerbated the episodes and duration of VT & VF by 54% and 104%, respectively (all $P < 0.05$). Esmolol inhibited the morbidity rate, the episodes and the duration of VT & VF by 66%, 92% and 95%, respectively. Surprisingly, esmolol significantly attenuated the arrhythmogenic effect of D-SP throughout the MI, beyond the time span of esmolol action, during which a significant up-regulation of the NK1-R (by 19%, $P < 0.05$) was detected.

In conclusion, the findings of this study may indicate an anti-arrhythmic effect of endogenous neurokinin mechanism, through the activation of which, via up-regulation of NK1 receptor, esmolol may exert its anti-arrhythmic action at the early time of acute myocardial infarction.

1. Introduction

Acute myocardial infarction (MI) provokes cardiac arrhythmias ranging from mild sinus arrhythmia to ventricular tachycardia (VT), ventricular fibrillation (VF) and sudden cardiac death. It was found that the cardiac arrhythmias at an early time of MI [1] were timely overlapped with the massive increase of catecholamine in myocardium [2], suggesting an involvement of the sympathetic mechanism with ventricular arrhythmias [3], although some of the aspects remain controversial, which indicates that the β-adrenergic stimulation possesses pro-arrhythmic features [4], while the α-adrenergic activity is of anti-arrhythmic property [5,6].

Meanwhile, cardiac sensory afferent nerves were activated at the early time of MI, presenting marked increases of some neuropeptides, including substance P (SP), in the sensory neurons of the spinal dorsal root ganglia, spinal cord [7,8] and in myocardium [9,10], which may raise a possibility of a co-participation of the neurokinin and sympathetic mechanism in the pathology of myocardial infarction.

SP is an important member of the neurokinin family, playing important roles in the regulation of cardiac performance during acute myocardial ischemia and reperfusion, via neurokinin 1 receptor (NK1-R) [11,12]. Encouraging evidence indicating an interaction of sympathetic and sensory nervous activities in the anti-arrhythmia was reported by Zhou et al., presenting that the stimulation of peripheral afferent nerves could inhibit ventricular arrhythmias induced by the excitation of sympathetic system (by hypothalamic stimulation) during MI [13].

Based on the findings, we tested the hypothesis that normal activities of adrenergic and neurokininergic mechanisms may play important roles in the homeostasis of cardiac rhythm through investigating (1) the feature of the activation of the endogenous neurokinin 1 mechanisms at an early time of MI, (2) its role in the infarction-induced arrhythmias and (3) its relationship with endogenous β_1-adrenergic mechanism.

Abbreviations: D-SP, [D-Arg[1], D-Phe[5], D-Trp[7,9], Leu[11]]-substance P; SP, substance P; NE, norepinephrine; NK1-R, neurokinin 1 receptor; β1-AR, β1-adrenergic receptor.

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2. Materials and methods

Male Sprague–Dawley rats, weighing 260 g–280 g, were used in this study, which was approved by the Institutional Animal Care and Use Committee of Shanxi Medical University and conformed to the guidelines for the care and use of laboratory animals (National Institute of Health Guide for the Care and Use of Laboratory Animals, NIH Publications No. 80–23, revised 1996) [14].

2.1. Protocol

In 60 min of MI, the study was carried out to investigate (1) the relationship among the changes of the contents of norepinephrine (NE), substance P in the myocardium at risk of ischemia and the incidence of ventricular arrhythmias, following permanent coronary artery occlusion (CAO) by ligation of the left anterior descending branch of coronary artery, (2) the difference in the incidence and severity of ventricular arrhythmias including ventricular ectopic beats (VEB), ventricular tachycardia (VT) and fibrillation (VF) induced by the CAO in the presence and the absence of the antagonism of endogenous neurokinin-1 and β_1-adrenergic actions, respectively and simultaneously and (3) the difference in the expressions of neurokinin 1 receptor and β_1-adrenergic receptor (β1-AR) in the presence and the absence of the antagonisms of endogenous β_1-adrenergic and neurokinin-1 actions, respectively.

The antagonist of β_1-adrenergic receptor, esmolol (Qilu Pharmaceutical Co. Ltd., Jinan, Shandong, China) was intravenously injected (10 mg/kg, in 0.3 ml) at 5 min prior to the CAO, while the NK1-R blocker, [D-Arg^1, D-Phe^5, D-Trp^{7,9}, Leu^{11}]-substance P (D-SP, Sigma-Aldrich Corp. St. Louis, Missouri, USA) was given (152 ng/kg, in 0.3 ml, i.v.) at 15 min before the CAO. The timing of the administration of esmolol and D-SP was selected according to the half-life of the drug action and results of previous study [12].

2.2. MI model

The CAO and the sham surgery were carried out under anesthesia as we previously reported [8,12]. The coronary artery occlusion was confirmed by changes in the color of the myocardium (Fig. 1A) and the elevation of the ST-segment in the electrocardiogram (ECG, multi-physiological signal processing system, RM 6240BD, Chengdu, China) immediately following ligation of the coronary artery and by autopsy at the end of each test (Fig. 1C–G). The ECG, intra-ventricular pressures and heart rate were monitored and recorded throughout the experiment and analyzed. During the experiments any animal with constant

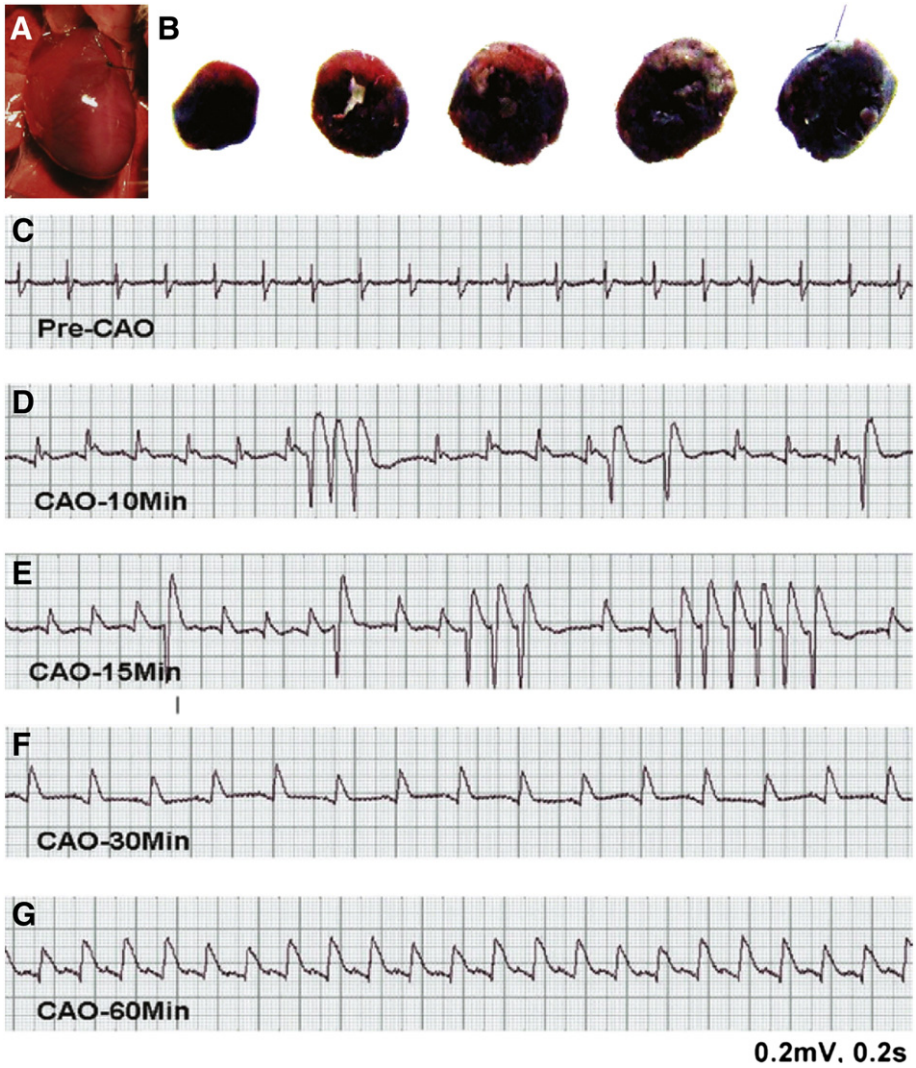

Fig. 1. A and B show the myocardium (area) at risk of ischemia of the left ventricle after the CAO. C–G indicate the ECG of pre-CAO and at 10 min, 15 min, 30 min and 60 min after the CAO presenting the elevation of ST segment and ventricular arrhythmias.