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Stereospecific blocking effects of naloxone against hemodynamic compromise and ventricular dysfunction due to myocardial ischemia and reperfusion

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Abstract

Endogenous opioid peptides subserve regulatory roles in cardiovascular function and are released upon myocardial ischemia contributing to the development of ischemic arrhythmias and cardiogenic shock, which are reversed by the opioid antagonist naloxone. Since the hallmark of myocardial infarction is the impairment of hemodynamics and ventricular function, we evaluated further if blockade of opioids reverses the ischemia induced hemodynamic compromise, and if the effects are mediated by opioid receptors. Thirty-two mongrel dogs were anesthetized and artificially ventilated. Median thoracotomy was performed, the heart exposed, and the left anterior descending coronary artery isolated for subsequent occlusion and reperfusion. All cardiac parameters were recorded on an Electronics for Medicine recorder through the intracardiac catheters advanced from femoral vessels. Results indicate that naloxone significantly reversed the ischemic and reperfusion induced reduction in aortic, left ventricular and pulmonary arterial pressures, and left ventricular dp/dt. The inactive (+) stereoisomer of naloxone was without effect. These data demonstrate that opioids may have a role in the pathophysiology of myocardial infarction, mediated by opioid receptors, and provide new insight and strategies for the understanding and treatment of ischemic heart disease.

Keywords: Naloxone; Stereoisomer; Opioid; Hemodynamic; Ventricular function; Myocardial infarction

1. Introduction

The endogenous opioid system includes three major families of peptides; dynorphin (derived from pre-proenkephalin B), endorphins (derived from pre-proopiomelanocortin) and enkephalins (derived from pre-proenkephalin A). Multiple forms of endogenous opioid peptides (EOPs) are derived from these major precursors and many of them possess potent cardiovascular properties.

EOPs and their receptors are widely distributed throughout the body, including the heart [1–3]. They subserve important roles in cardiovascular

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regulation and are released upon various cardiovascular stress situations such as shock [4], heart failure [5] and myocardial ischemia [6], which might contribute to the respective detrimental effects. In an isolated heart preparation, it has been shown that morphine decreases the myocardial contractility and heart rate [7]. β-Endorphin, likewise, has been demonstrated to cause cardiac arrhythmias and to decrease myocardial contractility [8] in the isolated perfused rat heart. In an in vivo preparation, administration of morphine, β-endorphin or dynorphin intravenously or intrasisternally produced hypotension and bradycardia [9]. Under certain conditions such as shock, stroke, heart failure and myocardial ischemia, blood pressure and heart rate can be altered in response to the opiate antagonist naloxone [10]. It is believed that EOPs are released during these various pathophysiologic states which induce detrimental changes in hemodynamic variables, and this may be blocked by treatment with opiate antagonists. The above findings strongly suggest a possible regulatory role played by EOPs in the cardiovascular system.

During myocardial ischemia, it has been shown that naloxone markedly attenuates the ischemic arrhythmias in conscious and anesthetized rats [5], suggesting that EOPs are involved in the arrhythmogenesis induced by myocardial ischemia. We have also found that naloxone reversed the ischemic arrhythmias, bradycardia and cardiogenic shock that resulted from acute coronary artery occlusion in the rat [11].

It is known that aside from the above deleterious complications, the hallmark of myocardial infarction is the impairment of hemodynamics and ventricular function. Therefore, we evaluated further if blockade of EOPs reverses the hemodynamic compromise due to myocardial ischemia and reperfusion, and if the effects are mediated by opioid receptors.

2. Materials and methods

Thirty-two mongrel dogs of either sex weighing between 15 and 20 kg were used and divided into four groups. They were anesthetized with pentobarbitone sodium (60 mg/kg) intravenously. Tracheal intubation was performed and the dog was artificially ventilated (16–18 strokes/min; 300 ml/kg/min). The femoral artery and cephalic vein were cannulated for recording blood pressure and heart rate, and for administration of drugs, respectively. Standard lead II electrocardiogram was monitored continuously.

Under fluoroscopic guidance, a thermodilution Swan-Ganz catheter was advanced from the femoral vein to the right heart for the measurement or right atrial (RA), pulmonary artery (PA) and pulmonary wedge (PW) pressures. A pigtail catheter was advanced from a femoral artery to the left heart for the measurement of systolic (Ao (syst)) and diastolic (Ao (diast)) left ventricular pressures. All cardiac pressures were monitored and recorded on VR-12 Electronics for Medicine recorder through the catheters connected to a pressure transducer (Statham). Maximum first derivative of left ventricular pressure (LV dp/dt) was measured with a RC differentiator.

After placement of the right and left cardiac catheters in the correct positions (which would later not be altered during the entire experimental period), a median thoracotomy was performed. The heart was exposed by cutting open the pericardium. The left anterior descending coronary artery (LAD) was isolated. A suture with a short polyethylene tubing threaded around it was placed under the artery. The dog was allowed to equilibrate for 30 min when the preinjection hemodynamics were stabilized normally. Afterwards, saline as control, naloxone (with opiate antagonistic properties; Sigma; at the doses of 0.92 and 2.75 μmol/kg), or (+) naloxone (without opiate antagonistic properties) at the dose of 2.75 μmol/kg were infused intravenously over a period of 10 min, respectively. At 2 min after the start of infusion, occlusion of the LAD was performed by applying tension on the suture and clamping immediately above the tubing. Occlusion was maintained for 20 min followed by reperfusion for 30 min, by simply releasing the clamp above the polyethylene tubing surrounding the artery. The hemodynamic parameters during ischemia (at 5, 10 and 20 min) and reperfusion (at 5, 10, 20 and 30 min) were recorded. In this manner, the effects of the stereoisomers of naloxone on ventricular func-

tion and circulatory dynamics during coronary rtery occlusion and reperfusion could be valuated.

Analysis of variance followed by multiple comparison was used to compare the difference in time course changes in heart rate, mean arterial pressure, aortic, left ventricular, RA, PA and PW pressures, and LV dp/dt between control and treated groups, and between the groups receiving 2.75 μmol/kg of naloxone and (+) naloxone, respectively. A P-value <0.05 was considered as tatistically significant.

3. Results

Fig. 1 shows the effects of the stereoisomers of naloxone on the changes in arterial blood pressure and heart rate following coronary artery occlusion and reperfusion. Myocardial ischemia and reperfusion invariably caused a markedly decrease in both blood pressure and heart rate. Pretreatment with naloxone (2.75 μmol/kg) before coronary artery occlusion and reperfusion significantly reversed the reduction in both blood pressure and heart rate. A lower dose of naloxone also reversed significantly the reduction in blood pressure (but not heart rate), but to a lesser extent as compared with the higher dose of naloxone. The effects of naloxone in reversing the reduction in blood pressure and heart rate following myocardial ischemia and reperfusion seemed to be dose related. Pretreatment with (+) naloxone was however without effect.

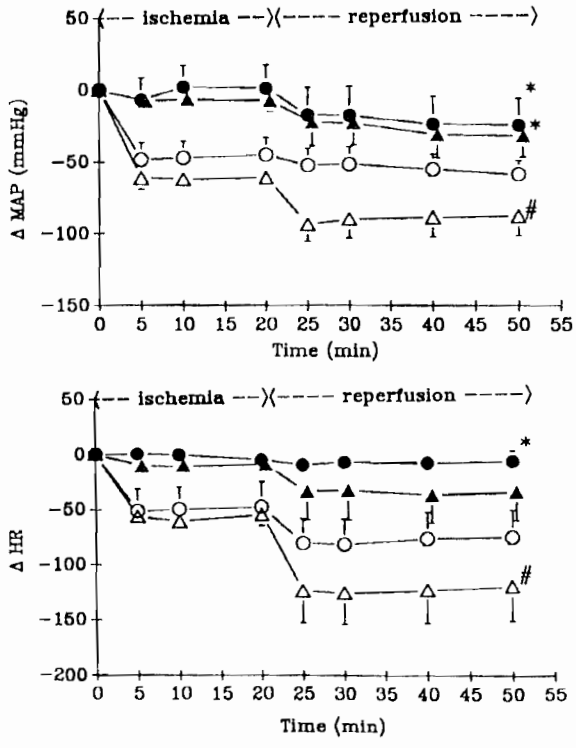

Fig. 1. Effects of the stereoisomers of naloxone on the changes in mean arterial pressure (ΔMAP) and heart rate (ΔHR) following coronary artery occlusion and reperfusion in the dog. (○) control; (▲) naloxone 0.92 μmol/kg; (●) naloxone 2.75 μmol/kg; (Δ) (+) naloxone 2.75 μmol/kg. Values represent the means ± S.E.M. $^{*}P < 0.05$ vs. control; $^{\#}P < 0.05$ vs. 2.75 mol/kg naloxone by analysis of variance.

Results of the investigations on hemodynamics and ventricular function are illustrated in Fig. 2. In the control group, there were pronounced reductions in Ao (syst), Ao (diast), LV (syst), LV (diast), RA, PA and PW pressures following coronary artery occlusion and reperfusion. LV dp/dt was also significantly diminished. In marked contrast to the control, the reduction in the aortic, left ventricular and PA pressures, and LV dp/dt were significantly reversed after pretreatment with naloxone followed by coronary artery occlusion and reperfusion. These cardiovascular effects of naloxone appeared to be dose-related. A lower dose of naloxone reversed the reductions in aortic, left ventricular and PA pressures, and LV dp/dt following coronary artery occlusion and reperfusion, but to a lesser extent as compared with the higher dose of naloxone. On the other hand, pretreatment with (+) naloxone was not effective in reversing the hemodynamic compromise and ventricular dysfunction due to myocardial ischemia and reperfusion. Their hemodynamic effects were similar to the control but statistically different from the group receiving naloxone.

4. Discussion

It is well-known that aside from ischemic arrhythmias, bradycardia and cardiogenic shock, the hallmark of coronary artery occlusion and reperfusion is the impairment of hemodynamics and ventricular function, all of which being the

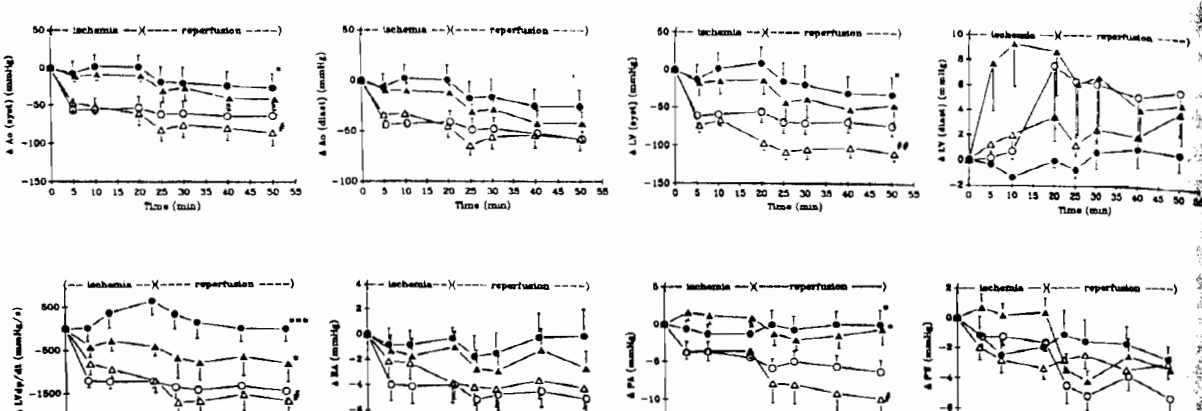

Fig. 2. Effects of the stereoisomers of naloxone on the changes in hemodynamics and ventricular function following coronary artery occlusion and reperfusion in the dog. (○) control; (▲) naloxone 0.92 μmol/kg; (●) naloxone 2.75 μmol/kg; (△) (+) naloxone 2.75 μmol/kg; Ao (syst), systolic aortic pressure; Ao (diast), diastolic aortic pressure; LV (syst), systolic left ventricular pressure; LV (diast), end-diastolic left ventricular pressure; LV dp/dt, first derivative of left ventricular pressure; RA, right atrial pressure; PA, mean pulmonary arterial pressure; PW, pulmonary wedge pressure. Values represent the means ± S.E.M. $^{*}P < 0.05$; $^{***}P < 0.001$ vs. control; $^{\#}P < 0.05$; $^{\#\#}P < 0.01$ vs. 2.75 μmol/kg naloxone by analysis of variance.

most common fatal complications secondary to myocardial infarction. Similar observations were made in the present study in the dog in which coronary artery occlusion and reperfusion led to a marked hemodynamic compromise and ventricular dysfunction, as evidenced by the pronounced reduction in heart rate, arterial blood pressure, aortic, left ventricular, RA, PA and PW pressures, and LV dp/dt.

We have demonstrated an improvement in hemodynamics and ventricular function, characterized by a reversal of the above deleterious effects, in anesthetized dogs subjected to coronary artery occlusion and reperfusion. This observation is compatible with the previous findings that administration of naloxone improved survival in various forms of shock via a mechanism which resulted in an increase in blood pressure, cardiac output, stroke volume and cardiac contractility [4]. In the present study, pretreatment with naloxone restores the heart rate, arterial blood pressure, aortic and left ventricular pressures, probably by blocking and attenuating the bradycardia and the depressor effects of EOPs which are believed to be release as a consequence of myocardial ischemia and reperfusion [7]. The elevation in PA pressure after treatment with naloxone may be caused by an increase in venous return. Machuganska et al. [12] have demonstrated that naloxone significantly inhibited the reduction in cardiac output following coronary artery occlusion in the rat. The increase in LV dp/dt may have been due to the tendency toward elevated cardiac output and Ao (syst) pressure, or because of a direct inotropic effect of naloxone [13]. The above protective effects of naloxone, moreover, are stereospecific, since its (+) isomer, which lacks opiate antagonistic actions, does not block the ischemia and reperfusion induced impairment of hemodynamics and ventricular function.

The efficacy of the opiate antagonist naloxone as a modifier of physiological events has been used as a tool to infer EOPs in various system. From that perspective, the effects of the two stereoisomers of naloxone, as demonstrated in the present study, strongly implicate EOPs as a factor in the pathophysiology of myocardial infarction, mediated by opioid receptors through opioid an-

tagonism. Our results are also consistent with the ›othesis that EOPs may be released from the .rt upon myocardial ischemia and reperfusion thus causing ischemic arrhythmias, bradycardia, cardiogenic shock or, as shown in this study, impaired cardiac pressures and ventricular function. Naloxone, by virtue of its antagonistic action against opiates, rectifies these fatal complications secondary to myocardial ischemia and reperfusion, thus suggesting an important role of EOPs in ›emic heart disease. Further studies are needed lefine the roles of EOPs and the therapeutic values of opiate antagonists in myocardial infarction.

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