Plasma Levels of Endogenous Opioid Peptides in Patients with Acute Myocardial Infarction

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SUMMARY

There is substantial evidence that cardiac opioid receptors are activated during arrhythmias induced by administration of opioid peptides or myocardial ischemia, supporting the hypothesis that endogenous opioid peptides (EOP) are involved in myocardial infarction. This prospective clinical trial is designed to determine whether the ischemia-induced arrhythmias and extent of the infarct are related to the release of the EOP β-endorphin in patients with acute myocardial infarction. Two groups were included in the study, patients with acute myocardial infarction, and healthy volunteers who served as controls. The results indicate that, compared to the controls, there was augmentation of ischemic arrhythmias and ischemic damage as assessed by serum creatine kinase activity, accompanied by an elevated level of β-endorphin, in patients with acute myocardial infarction. The above data strongly indicate that EOP are indeed involved in the pathophysiology of myocardial infarction, and suggest these peptides have an important role in ischemic heart disease. (Jpn Heart J **36**: 421–427, 1995)

Key words: Endogenous opioid peptide Myocardial infarction Cardiac arrhythmia Creatine kinase β-endorphin

THE endogenous opioid system includes three major families of peptides; dynorphin (derived from preproenkephalin B), endorphins (derived from preproopiomelanocortin) and enkephalins (derived from preproenkephalin A). Multiple forms of opioid peptides are derived from these major precursors and many of them possess potent cardiovascular properties.

Endogenous opioid peptides (EOPs) and their receptors are present in brain areas important for cardiovascular control, in the heart, in autonomic ganglia and in the adrenal medulla.[1–3] This widespread distribution and localization of EOPs throughout the cardiovascular system exerts biological activities which

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influence and regulate the cardiovascular functions, both centrally and peripherally, including a direct action of EOP on the heart. Exogenous EOPs have been found to induce different effects on blood pressure and heart rate depending on the route of administration.[4,5] EOPs may also act directly on the heart causing cardiac arrhythmias (for a review, see ref.[6]). It has been shown that when administered directly into the heart, both β-endorphin[7] and dynorphin[8] caused cardiac arrhythmias in the isolated perfused rat heart preparation.

There is good evidence that EOPs may be released from the pituitary gland during various cardiovascular stress situations such as shock[9] and myocardial ischemia,[10] which might contribute to their respective detrimental effects. For instance, the opioid antagonist naloxone has been shown to reverse hypotension in patients with cardiogenic or septic shock.[11] It has also been demonstrated that naloxone reversed the ischemic arrhythmias that resulted from acute coronary artery occlusion and/or reperfusion in the rat and dog, in both *in vitro* and *in vivo* preparations.[10,12,13] According to Sawynok et al,[14] more compelling proof of a role of EOPs in any situation requires several lines of evidence that include the demonstration of a direct release of EOPs. The present study therefore aims at elucidating whether or not the endogenous opioid system is activated during acute myocardial infarction.

Patients and Methods

Protocols: Consecutive patients who were admitted to the intensive care unit of Taichung Veterans General Hospital, Taichung, Taiwan, Republic of China, with an admission diagnosis of acute myocardial infarction within 4 hours of the onset of chest pain were considered for entry into this prospective study. Informed consent was obtained from all patients after the nature of the trial had been fully explained. On admission, history, physical examination, an electrocardiogram (ECG), and a blood sample for MB isoenzyme of creatine kinase (CK-MB) determination were obtained. Definite myocardial infarction was subsequently confirmed if all of the following criteria were fulfilled: (1) typical chest pain of more than 30 minutes' duration; (2) CK-MB of more than twice the upper limit of the normal value; (3) appearance of new Q wave or loss of R waves or ST segment elevation followed by T wave inversion in at least 2 leads of the standard 12-lead ECG.

We checked for the inclusion criteria and for the absence of any exclusion criteria prior to enrolling the patients. Inclusion criteria were as follows: age < 75 years; no past history of myocardial infarction; chest pain > 30 minutes but < 4 hours duration; ECG ST elevation > 1 mm in > 2 contiguous anterior chest leads. Exclusion criteria were the following: age > 75 years; various severe sys-

temic diseases (neurological, renal, hepatic or bronchopulmonary); valvular or myocardial cardiopathy; current antiarrhythmic treatment; complications on entry including acute (Killip's class 3 and 4) or chronic heart failure; pulmonary edema; hypotension (systolic blood pressure, 90 mmHg); bradycardia (< 50 beats/min); proven myocardial infarction, chronic arrhythmias, or both before acute myocardial infarction; atrioventricular disturbances; complete bundle branch block; sustained ventricular tachycardia, ventricular fibrillation and hypokalemia.

Two groups were finally included in the study, healthy volunteers who served as controls and patients with acute myocardial infarction.

Arrhythmias/ECG recordings: All patients were monitored electrocardiographically by trained coronary care nurses. In addition, a 2-channel continuous Holter recording (model 8500 Holter recorder, Marquette Co., USA) was begun in the intensive care unit as soon as possible when a patient was included in the study and continued for 24 hours. Holter ECG tapes were analyzed by computer with manual overread (Arrhythmia & Pacer Analyzer, Marquette Co., USA), and printout analysis was applied to complicated parts of the recordings. All arrhythmias were recorded and every hour a rhythm strip was obtained and subsequently evaluated by a cardiologist. Ventricular premature contractions (VPC) were counted manually on a complete recording printout, and we counted the episodes of NOC and couplets separately from those occurring during the runs of ventricular tachycardia (VT). The term VT was used when > 6 consecutive VPCs occurred. Heart rate was measured from the ECG tracings, and blood pressure was measured by cuff sphygmomanometer.

MB-CK determination: Blood was collected on arrival of the patients at the intensive care unit and then serially at 5 hour intervals for 24 hours. Serum CK-MB was assayed by an Abbott biochromatic analyzer (Abbott Laboratories) using a standard uv test kit (A-Gent CK-VAC kit, Abbott Laboratories).

Plasma β-endorphin measurement: Blood samples for β-endorphin analysis were taken on admission before any drug was given. Five m*l* of blood were drawn into a polyethylene syringe, divided and placed immediately into iced test tubes. Test tubes containing EDTA as an anticoagulant were centrifuged at 0°C for 15 minutes using 760 × g. Plasma was obtained from centrifuged samples, frozen immediately and stored at −20°C or lower until extraction and assay. For the extraction and determination of β-endorphin, a commercial radioimmunoassay kit (Incstar Corp., USA) was used.

Statistical analysis: Data are expressed as mean ± standard error of mean. The chi-square test was used to analyze the difference in the number of patients having ventricular arrhythmias between controls and patients with myocardial infarction. Student's t test was used to test the differences in the number, onset

Table. Ventricular Arrhythmias Analyzed from Twenty-four Hour Holter EKG Recording

	n	VPC	Couplets	VT
Healthy volunteers (as control)	8	0	0	0
Acute myocardial infarction patients	8	8*	2	1

n = number of patients; VPC = ventricular premature contractions; VT = ventricular tachycardia; *$p < 0.001$ vs control by chi-square test.

and duration of arrhythmias, and the maximal CK-MB and β-endorphin levels between the healthy volunteers and patients with myocardial infarction. Repeated-measure analysis of variance was used to compare the differences in time course changes in arterial pressure, heart rate and CK-MB activity between control and myocardial infarction groups. A p value of less than 0.05 was considered statistically significant.

Results

The baseline characteristics of the healthy volunteers ($n = 8$) and of patients with acute myocardial infarction ($n = 8$) were similar. No patient had previous infarction. The admission heart rates, and systolic and diastolic pressures were similar. The groups were well matched with no significant differences with respect to age, sex ratio or other important variables.

The Table shows the occurrence of ventricular arrhythmias in the two groups during the 24 hours of Holter ECG monitoring. No arrhythmia was detected in the healthy volunteers. However, in patients with acute myocardial infarction, all had VPC ($p < 0.001$), 2 had couplets and 1 had VT.

During the 24 hours after admission, the means of maximal CK-MB activities were 42.80 ± 12.14 in the controls and 774.10 ± 123.79 IU/l ($p < 0.05$) in the myocardial infarction group. Moreover, the means of β-endorphin levels were 3.8 ± 0.7 in the healthy volunteers and 10.3 ± 0.6 pmole/l in patients with acute myocardial infarction ($p < 0.05$).

Discussion

It is well known that acute myocardial infarction leads to ischemic arrhythmias and augmentation of ischemic damage as assessed by serum CK-MB activity. Similar effects were observed in the present study in which acute myocardial infarction patients invariably had ventricular arrhythmias and marked elevation of maximal CK-MB activity. Most importantly, however, these ischemic events were accompanied by an increased level of the EOP, β-endorphin.

Previous animal studies have indicated that opiates and opioids can induce cardiac arrhythmias with or without myocardial infarction.[6] The first observation of the ability of opioids to induce cardiac arrhythmias was made by Lee et al[7,8] who demonstrated that, when administered directly into the heart, the EOPs β-endorphin and dynorphin both caused cardiac arrhythmias in the isolated perfused rat heart preparation. Subsequently, the effects of opioids on the induction of cardiac arrhythmias in animal models of myocardial infarction have been examined. Wu et al[15] have further shown that opioids markedly potentiated the ischemia induced arrhythmias, hypotension and bradycardia in the rat subjected to acute coronary artery ligation. In this study, both arrhythmias and elevated concentrations of β-endorphin were observed in acute myocardial infarction patients. The results are compatible with the previous notion that EOP may be involved in cardiac arrhythmogenesis as well as in the pathophysiology of myocardial infarction.

Morphine or opioids have also been shown to accentuate myocardial ischemia in myocardial infarction, as evidenced by an increase in ST-segment elevation,[16] and a larger dimension of the myocardial infarct following coronary artery ligation.[17,18] It is known that the release of CK-MB reflects the infarct size which is related to the severity of cardiac arrhythmias.[19,20] The above observations are compatible with our findings that patients with acute myocardial infarction had a greater release of CK-MB, which was related to a greater severity of cardiac arrhythmias and a higher level of β-endorphin.

Significant effort has been made to understand the roles of opioids on the cardiovascular system and on the ischemic myocardium. It has been shown that EOPs and their receptors are widely distributed throughout the body, including the heart.[1 3] They subserve important cardiovascular regulatory function and are released during various cardiovascular stress situations such as shock, heart failure, and myocardial infarction, contributing to the respective detrimental effects.[9,10] There is substantial evidence that cardiac opiate receptors are activated during arrhythmias induced by administration of opioid peptides or myocardial ischemia, supporting the hypothesis that EOPs are involved in cardiac arrhythmogenesis and in myocardial infarction. To support the involvement of EOPs in a particular physiological process, however, a number of criteria have been suggested.[14] These include the demonstration of, first, cross tolerance with morphine; second, similar responses with other opiate antagonists; third, the lack of an effect with non-antagonist isomers; fourth, agents that agonize or antagonize EOPs potentiate or attenuate the response, respectively, and fifth, a direct release of EOPs. There are several pieces of evidence suggesting that EOPs are involved in myocardial ischemia. Firstly, isolated perfused hearts of rats chronically treated with morphine exhibit tolerance to dynorphin or ischemia and

reperfusion in induction of arrhythmias.[21] Secondly, the opioid antagonists, naloxone,[12] naltrexone[22] and MR2266[23] have been shown to attenuate arrhythmias during ischemia and reperfusion in the isolated rat heart. Thirdly, the antiarrhythmic effects of naloxone are stereospecific because naloxone's (+) isomer (without any opiate antagonistic property) is not effective in reversing ischemia induced arrhythmias, hypotension and bradycardia in the rat.[24] Fourthly, dynorphin and naloxone potentiated and attenuated, respectively, ischemia induced arrhythmias, bradycardia and cardiogenic shock in rats subjected to coronary artery ligation.[15] The above strongly indicate that EOPs are involved in the pathophysiology of myocardial infarction. The most important issue outstanding, therefore, is the demonstration of a direct release of EOPs. Though there are limitations in this study population with a limited number of patients (this was due to the trial design), the striking results of this initial study, however, clearly indicate that in patients with acute myocardial infarction the ischemic events of ischemic arrhythmias and augmentation of CK-MB activity were accompanied by elevated levels of β-endorphin, supporting the previous notion that EOP may be involved in the pathophysiology of myocardial infarction. Further investigation is needed to identify the types of EOP that are released, and to elucidate the events that occur following myocardial ischemia.

In conclusion, β-endorphin is elevated in acute myocardial infarction patients, and the endogenous opioids probably contribute to the circulatory dysfunction observed in acute myocardial infarction. As acute myocardial infarction patients are characterized by chest pain, EKG changes, cardiac enzyme elevation, ischemic arrhythmias, creatine kinase elevation, hypotension and bradycardia, further studies are also warranted to delineate the relative importance or correlation of various hemodynamic parameters that may have significant effects on β-endorphin release.

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