IJC Heart & Vessels 4 (2014) 135–137

Contents lists available at ScienceDirect

IJC Heart & Vessels

journal homepage: http://www.journals.elsevier.com/ijc-heart-and-vessels

Improved survival rate after myocardial infarction using an inducible cholesterol efflux (iCE) peptide: FAMP

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ARTICLE INFO

Article history:
Received 7 November 2013
Received in revised form 13 May 2014
Accepted 18 May 2014
Available online 25 May 2014

Keywords:
Peptide
Myocardial infarction
Treatment
Sudden death

ABSTRACT

Background: There have been no previous reports that apolipoprotein (apo) A-I mimetic peptide improves survival rate after myocardial infarction (MI).
Method and results: Male C57Bl/6J mice were subjected to left coronary artery permanent ligation as a model of MI. We synthesized a novel 24-amino acid apoA-I mimetic peptide-type5 (FAMP5), which potently removes cholesterol via specific ATP-binding cassette transporter A1 (ABCA1). FAMP5 was associated with a significantly improved survival rate by protecting against cardiac rupture compared to the control. mRNA levels for eNOS, Gata-4, CTGF and ANP were significantly increased in the hearts of the FAMP5-treated group, while that for MCP-1 decreased.
Conclusion: This is the first report that high-density lipoprotein (HDL) therapy with FAMP5 improved the survival rate after MI.

1. Introduction

Percutaneous coronary intervention (PCI) has dramatically improved the short-term survival rate after myocardial infarction (MI) over the past two decades. Despite the fact that patients have benefited from the use of PCI after MI, the incidence of myocardial rupture has not decreased [1,2]. We synthesized a novel 24-amino acid apoA-I mimetic peptide without phospholipids, known as Fukuoka University apoA-I Mimetic Peptide (FAMP) of inducible cholesterol efflux (iCE) peptide, which potently removes cholesterol in vitro via ABCA1 [3,4], in addition to its endothelial-protecting, anti-oxidation, and anti-inflammation action [5,6]. While high-density lipoprotein (HDL) has been shown to have pleiotropic effects against cardiac events, it is still remaining unclear whether apoA-I mimetics can influence a hard endpoint and the survival rate after MI.

2. Methods

Eight- to 10-week-old male C57Bl/6J mice were subjected to left anterior coronary artery permanent ligation by 6-0 silk suture for 1 week as an experimental model of MI. Twenty-four hours later, we assigned the animals into 3 groups. Control mice were injected intraperitoneally (i.p.) with 300 μl of PBS on 1, 3 and 5 days post operation. Type 5 of FAMP (FAMP5) was injected i.p. at 10 mg/kg (FAMP5-L as low dose-FAMP5) or 50 mg/kg (FAMP5-H as high dose-FAMP5) on 1, 3 and 5 days post operation. The experiments complied with the regulations of the Committee on Ethics in the Care and Use of Laboratory Animals. All results are expressed as the mean ± standard deviation (SD) and p values <0.05 were considered to be statistically significant.

2.1. Synthesize of FAMP5

The design of the Fukuoka University apoA-I Mimetic Peptide (FAMP) is based upon the general structure of the amphipathic α-helical repeats in apoA-I with its separation of polar and nonpolar residues on the two faces of the helix and distribution of charged residues. FAMP (FAMP5: H-ALEHLFTLYEKALKALEDLLKKLL-OH), was synthesized by Fmoc (N-[9-fluorenyl] methoxycarbonyl)-based solid-phase peptide synthesis using an automated peptide synthesizer, Pioneer and Model 433A, from Applied Biosystems, Inc.

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http://dx.doi.org/10.1016/j.ijchv.2014.05.005

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	Control (n=7)	FAMP5 -L(n=8)	FAMP5 -H(n=8)
HR (beat/min)	530 ± 23	556 ± 33	563 ± 22
SBP (mmHg)	84 ± 9	86 ± 6	84 ± 10
DBP (mmHg)	51 ± 2	50 ± 5	46 ± 3
MBP (mmHg)	34 ± 2	32 ± 2	29 ± 4
TC (mg/dl)	77 ± 22	83 ± 19	78 ± 16
HDL-C (mg/dl)	30 ± 6	30 ± 4	28 ± 2
Infarct size (%)	45 ± 5	46 ± 6	48 ± 4

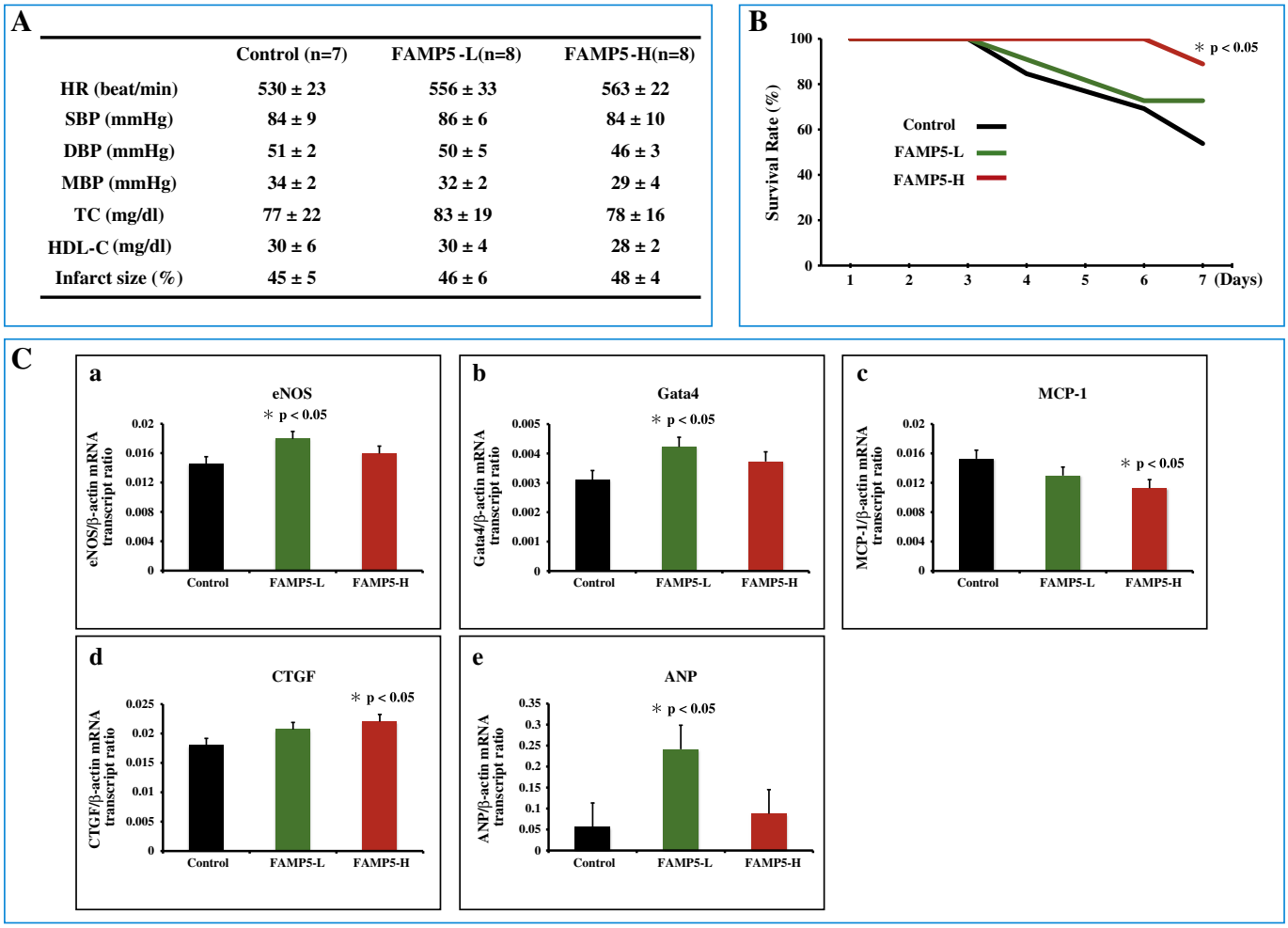

Fig. 1. A. Lipoprotein profiles and hemodynamics. B. Survival rate after MI. *p < 0.05 vs. control group, by the Cochran–Armitage test. C. mRNA expression, (a) to (e), in the mouse heart after MI. Comparisons were made by ANOVA followed by Tukey's test.

3. Results

There was no difference in the lipid profile after treatment with FAMP5. Hemodynamic parameters and LV infarct size were also similar in the 3 groups (Fig. 1-A). However, the survival rate during the acute phase after MI in the FAMP5-H group (8/9, 89%) was much better than those in the FAMP5-L (8/11, 73%) and control (7/13, 54%) groups. Interestingly, we could find that in all cases of death after MI, except for one mouse in the FAMP5-L group, the cause of death was cardiac rupture (Fig. 1-B). We then evaluated mRNA expression in the heart. FAMP5-H showed significant reductions in MCP-1 mRNA levels, and a trend was seen in the FAMP5-L group. In addition, mRNA levels of angiogenic compounds (eNOS, Gata-4) were significantly up-regulated by FAMP5-L, and a trend was seen in the FAMP5-H group. CTGF and ANP were significantly up-regulated in both the FAMP5-H and FAMP5-L groups.

4. Discussion

The novel finding in this study is that FAMP5 significantly improved the survival rate after MI, particularly by preventing cardiac rupture. Not only did FAMP5 change the hemodynamics, but also infarct size was identical in our models. In addition, FAMP5 did not alter the lipid profile at all, even at a high dose. Coronary events have not been adequately prevented by statins, and therapeutic options for increasing HDL functionality have stepped into the spotlight, albeit little progress has been made. The use of an apoA-I mimetic peptide is much simpler for therapeutic purposes than increasing the mass of HDL or apoA-I. FAMP5 was associated with changes in mRNA levels of eNOS, Gata-4, ANP, MCP-1 and CTGF (Fig. 1-C), and CTGF was previously reported as one of the main factors related to cardiac rupture after MI [7]. It has been reported that FAMP5 improved atherosclerotic lesion through a suppressed inflammation and enhanced HDL function [3]. These results suggest that FAMP5 might play a role in maintaining heart muscle structure after acute myocardial infarction. Myocardial infarction that triggers a robust inflammatory response, which is essential for cardiac repair, is also involved in the pathogenesis of remodeling subsequently heart failure. In conclusion, these results indicate that our FAMP5 might prevent cardiac rupture, which improves the survival rate in the acute phase after MI, through anti-inflammatory and vasculoangiogenic effects in the heart, i.e., by raising HDL-functionality.

Conflict of interest

Eiji Yahiro, Emi Kawachi and Setsuko Ando have no conflicts of interest to disclose. Research and education grants, consulting, and promotional speaking (Yoshinari Uehara, Shin-ichiro Miura, Keijiro Saku) are from MSD Co., Bayer, and Eli Lilly, Co. (clinical research grant), and Keijiro Saku and Shin-ichiro Miura are Directors of NPO Clinical and Applied Science, Fukuoka, Japan. Keijiro Saku has Endowed Department of Molecular Cardiovascular Therapeutics (Yoshinari Uehara, Shin-ichiro Miura), Fukuoka University, supported by MSD Co., Ltd.

Acknowledgments

This work was supported by grants-in-aid from the Ministry of Education, Culture, Sports, Science, and Technology (Nos. 24591123 and25461141).

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