Post-infarct treatment with [Pyr1]apelin-13 exerts anti-remodelling and anti-apoptotic effects in rats’ hearts

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Abstract

Background: Ischaemic heart disease is the main cause of mortality in the world. After myocardial infarction (MI) cardiomyocytes apoptosis and ventricular remodelling have occurred. Apelin is a peptide that has been shown to exert cardioprotective effects.

Aim: The aim of this study was to investigate the anti-apoptotic and anti-remodelling effects of [Pyr1]apelin-13 in the rat model of post-MI.

Methods: Thirty-six male Wistar rats were randomly divided into three groups: (1) sham, (2) MI, and (3) MI treated with [Pyr1]apelin-13 (MI+Apel). MI animals were subjected to 30-min ligation of the left anterior descending coronary artery (LAD) and 14 days of reperfusion. Twenty-four hours after LAD ligation, [Pyr1]apelin-13 (10 nmol/kg/day, i.p.) was administered for five consecutive days. Hypertrophic parameters, left ventricular (LV) remodelling, and gene expression of Apel, apelin receptor (Apelr), Bax, caspase-3 (Casp-3), and Bcl-2 by real-time polymerase chain reaction and cardiomyocytes apoptosis by TUNEL immunostaining were assessed on day 14 post-MI.

Results: Post-infarct treatment with [Pyr1]apelin-13 improved myocardial hypertrophic and LV remodelling parameters and led to a significant increase in the expression of Apel, Apelr, and Bcl-2, and a decrease in the expression of Bax and Casp-3. Furthermore, treatment with [Pyr1]apelin-13 decreased cardiomyocyte apoptosis.

Conclusions: [Pyr1]apelin-13 has anti-hypertrophic, anti-remodelling, and anti-apoptotic effects via overexpression of Apel, Apelr, and Bcl-2 and reduces gene expression of Bax and Casp-3 in the infarcted myocardium, which can in turn lead to repair myocardium.

Key words: [Pyr1]apelin-13, left ventricular remodelling, cardiac hypertrophy, myocardial apoptosis, rat

INTRODUCTION

Myocardial infarction (MI) is the most usual representation of cardiovascular disease [1]. It is one of the leading causes of morbidity and mortality in our world, and many patients experience disabling symptoms, despite intense therapeutic approaches and pharmacotherapies [1, 2]. MI is caused by deprivation of oxygen and nutrients to the myocardial tissue, which results in the induction of the cardiomyocytes apoptosis [3]. It is well documented that unexpected occlusion of the coronary artery causes acute myocardial ischaemia and apoptosis of cardiomyocytes, which leads to progressive replacement of myocardium by fibrosis and left ventricular (LV) dilatation [2].
After MI, pathological changes in the geometry, organisation, composition, and structure of myocardial tissue, such as dilatation of the ventricular chamber and wall thinning, are initiated, which are known as ventricular remodelling. At first it is beneficial, leading to continuing reduction of cardiac function and finally, after days and weeks, it causes heart failure (HF) [4, 5]. Owing to the quantitative and qualitative changes in cardiomyocytes, LV contractile function is impaired after MI [6]. Many studies have shown that apoptosis (programmed cell death) of cardiomyocytes is one of the mechanisms leading to ventricular remodelling in animal models and human disease [5, 7, 8]. One common mechanism of remodelling is hyper activation of caspase families. Activation of these proteases may cause disintegration of various key cellular proteins, thereby resulting in the loss of contractile proteins and hence reduction of cardiac muscle cell function [6].

In the clinical setting, ischaemia and/or reperfused cardiomyocyte protection against cell death is a useful strategy [9]. Thus, it seems that reduction of cell loss and apoptosis after MI may preserve cardiac function and structural integrity, and thereby prevent or delay ventricular dysfunction and onset of post-MI heart failure.

Apelin, a relatively recently discovered adipocytokine from bovine stomach tissue extracts is an endogenous peptide ligand for apelin angiotensin receptor-like 1 (AP) [10]. Its beneficial effects, such as reduction of infarct size, improvement of myocardial function, and contractility against myocardial acute ischaemia and ischaemia/reperfusion (I/R) injuries, have been shown in some studies [11–13]. Apelin is widely expressed in the endothelium, binds to G protein-coupled receptor (AP) in endothelial cells, myocardial cells, and smooth muscle cells and activates its following signalling pathways such as PI3K/Akt, activation of nitric oxide (NO) synthases (eNOS), and NO production [14–16]. Apelin/AP system (expression of apelin and AP) in the serum and myocardial tissue) has been downregulated in severe and uncompensated HF in experimental and clinical studies [17, 18]. Low serum apelin levels following MI have also been documented in a clinical study in which the control was 76% and the MI group was 45% [19].

Post-MI treatment with apelin has shown to improve cardiac contractility and function against myocardial acute ischaemia and I/R injuries [20]. Acute intramural (focal) MI was produced by ligating the LAD with 6-0 polypropylene suture approximately 1–2 mm distal from its origin for 30 min. The same procedure of thoracotomy, without the LAD ligation, was done in sham-operated rats. 
Pyr 1 apelin-13 (10 nmol/kg/day, Sigma) was dissolved in normal saline and administered i.p. 24 h after MI once a day for five days [21]. Normal saline was given to the sham and MI animals. Post-operatively, rats were hydrated with normal saline (s.c.) and received buprenorphine (0.05 mg/kg) as an analgesic. Tetracycline was used as postoperative antibiotic.

Assessment of myocardial hypertrophy
Fourteen days after surgery, all animals were anesthetised with thiopental sodium, the hearts were removed and hypertrophic parameters were measured. For this, the chest was opened and the hearts were arrested by intraventricular injection of KCl (10%) in diastole. The animals were sacrificed under deep anaesthesia and the hearts and lungs were rapidly removed, washed in normal saline, blot dried, and weighed. Heart weight (HW), lung weight (LW), heart-weight-to-body-weight ratio (HW/BW), and lung-weight-to-body-weight ratio (LW/BW), an indicative of the pulmonary congestion that followed by HF, measured as a cardiac hypertrophy parameters.

Assessment of LV remodelling
After washing in normal saline and weighing, hearts were fixed in formalin 10% for 24–48 h and embedded in paraffin. 6-μm transverse sections were prepared using a microtome and stained with haematoxylin and eosin (H&E, Sigma-Aldrich Co., MO, USA) for assessment of LV remodelling.
digital images of H&E-stained hearts were prepared using Adobe Photoshop CS software (Ver. 7.0, Adobe System, San Jose, CA, USA) to measure septal wall and LV free wall (in millimetres). Internal diameter (ID), external diameter (ED), infarcted wall thickness (IWT), and non-infarcted wall thickness (NIWT) of LV were calculated by measuring the size of these parameters.

**Real-time polymerase chain reaction (RT-PCR)**

After 14 days of MI, the myocardial samples (n ≥ 4 in each of three groups) were immediately removed, rinsed in PBS, frozen in liquid nitrogen, and stored at −80°C for gene expression assessment. An RNX-Plus kit was used for total RNA extraction from the frozen peri-infarct area and border zone of the LV free wall (Cat. No: RN7713C, Cinnagen, Iran). Complementary DNA (cDNA) was synthesised from 1000 ng of total RNA using a Rocket Script RT PreMix (BioNeer). cDNA samples were then used as templates for qRT-PCR. Rotor-Gene 6000 (Qiagen) was used for quantification of gene expression. RT-PCR analysis was done by AccuPower 2 × Green star quantitative PCR Master Mix (BioNeer). GAPDH was used as the housekeeping standard. The relative expression of Apel, Apelr, Casp-3, Bax, and Bcl-2 were calculated using the 2−ΔΔCT method [4]. Sequences of the specific primer are listed in Table 1.

**TUNEL assay**

For assessing apoptosis, 6-μm tissue sections were deparaffinised and terminal deoxynucleotidyl transferase-mediated dUTP nick end-labeling (TUNEL) was performed by using an “in situ cell death detection kit” (Roche, Mannheim, Germany) according to the manufacturer’s protocol. The relative number of apoptotic cells per section was counted with a light microscope under ×400 magnification in peri-infarct area using 10 randomly selected fields from eight sections per animal (n = 6 hearts/group). In each section, the numbers of cardiomyocytes and TUNEL positive nuclei were blindly counted using coded slides. Apoptosis was expressed as the mean percentage of TUNEL-positive nuclei. Haematoxylin staining was used for counterstaining.

**Statistical analysis**

All data are presented as mean and standard error of mean (means ± SEM). SPSS software (Version 15.0, SPSS Inc., Chicago, IL) was used for statistical analysis. One-way ANOVA was used to compare mean differences among three groups followed by Tukey post-hoc test. Statistical significant was considered as p < 0.05.

**RESULTS**

**The effect of apelin on myocardial hypertrophic parameters**

Fourteen days after surgery, our results showed that there was no significant difference in the BW among the experimental groups (Table 2). The HW and LW in the MI group increased in comparison with the sham animals (p < 0.05 and p < 0.001, respectively). There were, however, increases in HW/BW and LW/BW ratios in the untreated MI animals as compared with sham animals (p < 0.001), suggesting greater pulmonary congestion. Five days of treatment with apelin-13 led to significant reduction of HW and LW compared to the MI group (p < 0.05 and p < 0.001, respectively). In addition, apelin could decrease HW/BW and LW/BW in comparison with MI animals (p < 0.001). Except for LW/BW (p < 0.05), our data analysis showed that treatment with apelin could reverse other parameters to the level of sham animals.
Effect of apelin on myocardial remodelling

Histological sections of MI hearts showed LV dilation, wall thinning, increased the spaces between cells, changes in cardiomyocytes structure and shape, and leukocyte infiltration. H&E staining showed that treatment with apelin-13 for five days could prevent these changes (Fig. 1). Statistical analysis of LV remodelling parameters showed significant increases in ID (p < 0.05), ED (p < 0.001) and NIWT (p < 0.01) in MI animals when compared with the sham group (Table 3). Treatment with apelin markedly reduced ID (p < 0.05) and

Table 2. Hypertrophic parameters.

<table>
<thead>
<tr>
<th>Groups</th>
<th>Body weight (BW) [g]</th>
<th>Heart weight (HW) [g]</th>
<th>Lung weight (LW) [mm Hg]</th>
<th>Heart weight to body weight (HW/BW)</th>
<th>Lung weight to body weight (LW/BW)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sham</td>
<td>285.6 ± 5.372</td>
<td>0.941 ± 0.0325</td>
<td>1.266 ± 0.0398</td>
<td>3.29 ± 0.0653</td>
<td>4.429 ± 0.0685</td>
</tr>
<tr>
<td>MI</td>
<td>279 ± 8.503</td>
<td>1.172 ± 0.0143*</td>
<td>1.748 ± 0.0693***</td>
<td>4.21 ± 0.079***</td>
<td>6.26 ± 0.086***</td>
</tr>
<tr>
<td>MI + Apelin</td>
<td>288 ± 7.635</td>
<td>0.999 ± 0.007*</td>
<td>1.386 ± 0.027***</td>
<td>3.475 ± 0.075***</td>
<td>4.811 ± 0.0786***</td>
</tr>
</tbody>
</table>

Data are presented as means and standard error of mean (means ± SEM); MI — myocardial infarction; *p < 0.05 and ***p < 0.001 vs. sham group; †p < 0.05 and ‡p < 0.001 vs. MI group.

Table 3. Remodeling parameters of left ventricle

<table>
<thead>
<tr>
<th>Groups</th>
<th>External diameter [mm]</th>
<th>Internal diameter [mm]</th>
<th>Infarcted wall thickness [mm]</th>
<th>Non-infarcted wall thickness</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sham</td>
<td>8.46 ± 0.328</td>
<td>2.134 ± 0.102</td>
<td>0.000 ± 0.000</td>
<td>4.142 ± 0.115</td>
</tr>
<tr>
<td>MI</td>
<td>9.822 ± 0.417*</td>
<td>4.12 ± 0.382***</td>
<td>1.192 ± 0.109</td>
<td>3.024 ± 0.157**</td>
</tr>
<tr>
<td>MI + Apelin</td>
<td>8.984 ± 0.32</td>
<td>3.05 ± 0.231*</td>
<td>2.048 ± 0.069***</td>
<td>3.227 ± 0.226**</td>
</tr>
</tbody>
</table>

Data are presented as means and standard error of mean (means ± SEM); MI — myocardial infarction; *p < 0.05, **p < 0.01 and ***p < 0.001 vs. sham group; †p < 0.05 and ‡p < 0.001 vs. MI group.

Figure 1. Histological changes of myocardial tissue on day 14 after myocardial infarction (MI) (n = 6). Transverse sections of the hearts from apex to base stained with haematoxylin and eosin. Upper: bar 5 mm, magnification ×7 and lower: magnification ×400.
IWT (p < 0.001) when compared to the MI group. Moreover, except for NIWT, apelin could reverse ED and ID to the same levels in sham animals.

The effect of apelin on gene expression
We investigated the potential mechanisms for the action of apelin on the mRNA expression of apoptotic and anti-apoptotic genes. A total of 15 hearts were used for RT-PCR analysis of mRNA expression of Apel, Apelr, Bax, Casp-3, and Bcl-2. Figure 2 shows that induction of MI significantly increased Apelr, Bax, and Casp-3 in the peri-infarct area and border zone of LV compared with sham animals. Five days of treatment with apelin-13 significantly increased Apel, Apelr, and Bcl-2 when compared to sham and MI animals (p < 0.001 for all of

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**Figure 2.** Effects of apelin-13 on Apel, Apelr, Bax, Casp-3, and Bcl-2 mRNA expression in left ventricle (LV) of sham and peri-infarct area and border zone of LV of myocardial infarction (MI) and MI+Apelin groups 14 days after surgery (n = 4). Data are presented as means ± standard error of mean; **p < 0.01 and ***p < 0.001 vs. sham group; ***p < 0.001 vs. MI group
them), and decreased Casp-3 and Bax in MI+Apel animals when compared to MI animals (p < 0.001 for all of them). Our results also showed that induction of MI increased Apelr expression in comparison with the sham group (p < 0.001). In addition, analysis of data revealed that in the apelin-treated group, expression of Bax could not reach the level of the sham animals (p < 0.01), but it was lower than in the MI group.

**Effect of apelin on cardiomyocytes apoptosis**
TUNEL staining was used for detecting cardiomyocytes apoptosis. As shown in Figure 3A and 3B, there were few apoptotic cells (shown with arrows [TUNEL-positive]) in the border zone and peri-infarct area in the sham group (2.417 ± 0.455), while the percentage of TUNEL-positive cardiomyocytes increased in MI animals (24.167 ± 2.040). After treatment with apelin-13 TUNEL-positive cardiomyocytes were markedly reduced (7.833 ± 0.946) as compared with the MI group (Fig. 3B). Representative photographs of stained sections demonstrated that apelin-13 has an anti-apoptotic effect in the LV after induction of MI (Fig. 3A).

**DISCUSSION**
In the present study, we investigated the anti-hypertrophic, anti-remodelling, and anti-apoptotic effects of apelin-13 on the LV myocardium in the post-MI rat model. This study showed that five days of treatment with apelin-13, after acute intramural (focal) MI induction, decreased cardiac hypertrophy and myocardial remodelling parameters and decreased apoptosis by increasing mRNA expression of Apel, Apelr, and Bcl-2 and decreasing expression of Casp-3 and Bax 24 h after induction of MI.

Our previous studies showed that five days of pharmacological treatment with apelin-13, 24 h after induction of MI, has long-term cardioprotective effects through antioxidant effects and production of NO, and it has angiogenic and anti-fibrotic effects [21]. In this study, along with our previous studies [16, 21], we have further studied the anti-apoptotic, anti-remodelling, and anti-hypertrophic effects of apelin-13 in improving myocardial function and preserving its structural integrity.

After MI severe loss of myocardium causes higher loading conditions that in turn induce remodelling of the infarcted border zone and peri-infarcted region of the myocardium. Necrosis of the cardiomyocytes and higher loading condition activate a cascade of intracellular signalling pathways, which induce changes such as myocardial dilatation, hypertrophy, and the formation of collagen scar tissue [22]. In this study we showed that physiological parameters of HF (HW/BW and LW/BW ratios) were improved by apelin-13. Indeed, the MI animals had significant heart hypertrophy (increased HW/BW) and index of HF (increased LW/BW) in comparison with the sham group. Treatment with apelin-13 led to significant reduction of these ratios, in addition to the improvement of HW (as myocardial hypertrophic parameter) and LW compared to the
apelin-13 and mechanism of post-infarct protection

MI group. Elevation of lung weight in MI animals in comparison with the sham group (a good marker of LV insufficiency) and reduction of it in MI-treated animals with apelin-13 have been shown. In addition, HW increased in MI animals, and treatment with apelin-13 reduced it, which may show its anti-hypertrophic effects. Cell death of cardiomyocytes in the ischaemic myocardium occurred, and the remaining cardiomyocytes underwent hypertrophic growth for compensation of myocardial function, and this may cause an HW increase in the MI group. Apelin improves these parameters to the same levels in sham group, except for LW/BW. As a result, our data indicates that pharmacotherapy with apelin-13 improves cardiac hypertrophy and HF, and it seems that it protects myocardium against detrimental remodelling.

After myocyte injuries, the infarct size increases and causes wall thinning and ventricular dilatation [22, 23]. Our results also showed that apelin-13 given 24 h after MI for five days could improve myocardial structure and remodelling parameters, as shown in Figure 1. It prevents dilatation of LV myocardium and wall thinning (Fig. 2). Apelin-13 increases wall thickness and decreases the internal diameter of LV. Early LV dilatation and early LV wall thinning in MI animals can represent infarct expansion, and apelin-13 via improvement of remodelling parameters prevents infarct expansion. Based on our previous studies showing that apelin reduced infarct size and improved myocardial function, it is likely that apelin via anti-remodelling and anti-hypertrophic effects preserves myocardial structure and allows for a more viable myocardium. In the previous study, our results showed that apelin decreased collagen deposition and formation of fibrosis in the post-MI rats. We also reported that apelin enhanced neoangiogenesis. Therefore, these effects (anti-fibrotic and angiogenic) may prevent deleterious LV remodelling after MI and reduce ventricular dilatation and cardiac hypertrophy.

Apoptosis can be triggered by several stimuli, and it is an important modulator of reperfusion injury [9], which was also reduced in this study by five days of pharmacotherapy with apelin-13. This was observed with reduction of TUNEL-positive cells and decreased expression of Casp-3 and Bax, as well as increased Bcl-2. It has been reported that apelin reduces apoptosis in the I/R model of the isolated heart [24]. Thus, one mechanism of the effects apelin on myocardial remodelling following MI and the reduction of infarct size that was reported in the previous study [21] might be its anti-apoptotic action and prevention of cell death. The anti-apoptotic effect of apelin-13 24 h after LAD ligation probably extends for a long time and contributes to the following reduction of LV remodelling via impeding total cell loss to the level required for late MI expansion, LV dilatation, and wall thinning. Consequently, treatment at that time may directly affect subsequent LV remodelling. LV dilatation in the MI group is probably associated with an increase in wall stress, which causes further apoptosis. Although we did not asses wall stress, we suggest that apelin indirectly reduces apoptosis due to reducing LV stretch and tension and subsequent LV dilatation.

It is reported that activation of PI3K/Akt signalling pathway can protect cells against apoptosis and delivers a cell survival signal [2, 25]. Accumulating studies are reporting that the cardioprotective effects of apelin against I/R injuries occur through activation of PI3K/Akt/eNOS and ERK signalling pathways [11, 26, 27]. With the knowledge about the PI3K/Akt signalling pathway against apoptosis [2, 25] and the effect of apelin on the activation of PI3K/Akt [11, 26, 27], we suggest that apelin, via expression and activation of its receptor (Apelr), could activate this signalling pathway and therefore reduce cardiomyocytes apoptosis. This was indicated by decreasing the number of TUNEL-positive cells and decreasing the expression of Bax and Casp-3 and increasing Bcl-2 expression. This in turn improves myocardial hypertrophy and remodelling and results in maintaining myocardial tissue integrity. In line with this study, Li et al. [28] reported that myocardial injection of apelin overexpressing bone marrow cells immediately after MI in mice decreased apoptosis. They also reported that treatment with apelin-13 (1 mg/kg/day) for three days before MI and for 14 days post-MI decreased myocardial apoptosis and hypertrophy [29].

In the previous study we showed that post-infarct treatment with apelin-13 increases mRNA expression of VEGFA, Kdr, Ang-1, Tie2, and eNOS in the LV myocardium on day 14 post-MI. Therefore, we can suggest that apelin-13 binds to Apelr, and increases Apel, Apelr, by increasing the expression of VEGFA, Kdr, Ang-1, Tie2, and eNOS, and it may increase survival of cardiomyocytes and prevent apoptosis. Through these mechanisms, apelin can preserve myocardial integrity, and can limit remodelling and hypertrophy of the myocardium.

CONCLUSIONS

In summary, administration of apelin-13 for five days beginning 24 h after induction of MI can decrease myocardial hypertrophy and LV remodelling. Furthermore, it can decrease cardiomyocytes apoptosis by decreasing the expression of Bax and Casp-3 and increasing Bcl-2 expression. Thus, apelin-13 through its anti-apoptotic action preserves structural integrity and decreases cardiac hypertrophy and LV remodelling. Based on these results and our previous studies, and the results from other studies about cardioprotective effects of apelin against MI and I/R, and improvement of LV function, apelin can be used and studied in the clinical setting.

Acknowledgements

This study was financially supported by AJA University of Medical Sciences and Tehran University of Medical Sciences (Tehran, Iran).

Conflict of interest: none declared
References


Wpływ leczenia za pomocą [Pyr\textsuperscript{1}]apeliny-13 na zmniejszenie remodelingu i apoptozy w sercach szczurów

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Streszczenie

Wstęp: Choroba niedokrwienna serca jest główną przyczyną zgonów na świecie. Po zawale serca (MI) obserwuje się apoptozę kardiomiocytów i remodeling komór. Wykazano, że białkowa substancja, apelina, ma działanie kardioprotekcyjne.

Cel: Badanie przeprowadzono w celu oceny ochronnego działania [Pyr\textsuperscript{1}]apeliny-13 w postaci zmniejszenia apoptozy i remodelingu w szczurzym modelu MI.

Metody: Trzydzieści sześć szczurów Wistar płci męskiej podzielono losowo na trzy grupy: (1) grupa kontrolna, (2) grupa z MI oraz (3) grupa z MI poddana leczeniu za pomocą [Pyr\textsuperscript{1}]apeliny-13 (MI+Apel). U części zwierząt podwieszano na 30 min tętnicę przednią zstępującą lewą (LAD), po czym nastąpił 14-dniowy okres reperfuzji. [Pyr\textsuperscript{1}]apelinę-13 (10 nmol/kg/d., i.p.) podawano przez 5 kolejnych dni, przy czym pierwszą dawkę podano 24 h po podwiązaniu LAD. Po 14 dniach od MI oceniono wskaźniki przerostu mięśnia sercowego i remodelingu lewej komory (LV), a także ekspresję genów Apel, receptor apeliny (Apelr), Bax, caspase-3 (Casp-3) oraz Bcl-2 metodą polimerazowej reakcji łańcuchowej (PCR) w czasie rzeczywistym i apoptozę kardiomiocytów metodą immunobarwienia TUNEL.

Wyniki: Leczenie za pomocą [Pyr\textsuperscript{1}]apeliny-13 u zwierząt po MI spowodowało poprawę parametrów przerostu mięśnia sercowego i przebudowy LV, a także istotne zwiększenie ekspresji genów Apel, Apelr i Bcl-2 oraz zmniejszenie ekspresji genów Bax i Casp-3. Ponadto stosowanie [Pyr\textsuperscript{1}]apeliny-13 wpłynęło na zmniejszenie apoptozy kardiomiocytów.

Wnioski: [Pyr\textsuperscript{1}]apelina-13 zmniejsza przerost mięśnia sercowego i remodeling oraz ma działanie przeciwapoptotyczne poprzez zwiększenie ekspresji genów Apel, Apelr i Bcl-2 oraz zmniejszenie ekspresji genów Bax i Casp-3 w objętym zawałem miokardium, co może prowadzić do naprawy uszkodzonego mięśnia sercowego.

Słowa kluczowe: [Pyr\textsuperscript{1}]apelina-13, remodeling lewej komory, przerost mięśnia sercowego, apoptoza kardiomiocytów, szczur

Kardiol Pol 2017; 75, 6: 605–613

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