Elevated adropin: A candidate diagnostic marker for myocardial infarction in conjunction with troponin-I

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Myocardial infarction (MI; “heart attack”) can cause injury to or death of heart muscle tissue (myocardium) owing to prolonged ischemia and hypoxia. Troponins and CK-MB are released from heart muscle cells during MI. It has been demonstrated that energy expenditure is regulated by adropin expressed in the endocardium, myocardium, and epicardium. We hypothesized that adropin is released into the bloodstream during myocardial muscle injury caused by MI, so the serum level rises as myocytes die. Therefore, we examined the association between adropin expression and myocardial infarction in isoproterenol-induced myocardial infarction. Rats were randomly allocated to six groups. After treatment they were decapitated and their blood and tissues were collected for adropin measurement. Changes in adropin synthesis in rat heart, kidney and liver tissues in isoproterenol (ISO)-induced MI were demonstrated immunohistochemically. Serum adropin concentrations were measured by ELISA, and troponin-I, CK and CK-MB concentrations by autoanalysis. The results demonstrated that cardiac muscle cells, glomerular, peritubular and renal cortical interstitial cells, hepatocytes and liver sinusoidal cells all synthesize adropin, and synthesis increased 1–24 h after MI except in the liver cells. The findings elucidate the pathogenesis of MI, and the gradual increase in serum adropin could be a novel diagnostic marker and serve as an alternative to troponin-I measurement for diagnosing MI.

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Introduction

Cardiovascular disease (CVD) remains the most common cause of death and disability in both developed and developing countries [11]. The category includes congestive heart disease, high blood pressure, and myocardial infarction (“heart attack”), which results from a reduction of coronary blood flow extensive enough to make the oxygen supply to myocardial tissues insufficient [8,24]. Ischemia (restriction in blood supply) and consequent oxygen shortage, if left untreated for long enough, can cause myocardial cell death and necrosis [4,7]. Myocardial infarction (MI) is currently diagnosed by integrating the history of the presenting illness, prolonged chest pain, “silent infarct”, painless infarct, a typical electrocardiogram (ECG) pattern involving the development of pathological Q waves, and a rapid rise and fall of CK-MB and the typical rise and gradual fall of troponin-I [4,7]. Troponin-I was first described as a biomarker specific for acute myocardial infarction (AMI) in 1987 [10] and is now the biochemical “gold standard” for diagnosing AMI according to a consensus of the American College of Cardiology (ACC) and European Society of Cardiology (ESC) [1,28]. Early diagnosis is vital if irreversible heart tissue injury is to be avoided [4,7,28]. Therefore, we need new early-appearance, accurate, precise, readily accessible, cost-effective cardiac markers for better diagnosis and prognosis of MI. Several million patients annually seek care in emergency, cardiology and cardiovascular surgery departments when chest pain or other symptoms suggest an acute coronary syndrome (ACS), but only ∼10% are subsequently confirmed to have AMI [21].

A new metabolic hormone, adropin, was isolated in 2008 by Kumar et al. from liver and brain [19] and could be linked with
AMI, since in addition to pancreatic, liver, brain and kidney tissues, adropin synthesis was demonstrated immunologically in the endocardium, myocardium, and epicardium [6]. After adropin is released into blood, it plays various roles, such as nitric oxide bioavailability, apoptosis and energy homeostasis, heart failure and a novel predictor of coronary atherosclerosis [reviewed, 5, 22, 33]. Some researchers have also noted a positive correlation between plasma adropin levels and flow-mediated dilatation values [31]. Adropin levels are also significantly lower in patients with cardiac syndrome X (CSX) than healthy subjects, and lower serum adropin is an independent risk factor for CSX [9, reviewed, 5].

On the basis of the foregoing information, we hypothesized that the adropin synthesized in the endocardium, myocardium, and epicardium [6] could serve as a new biological marker for diagnosis and prognosis of myocardial ischemia, because injury to heart muscle cells is likely to release adropin into the bloodstream. In order to test our hypothesis, AMI in rats was experimentally induced by isoproterenol [1–(3,4-dihydroxyphenyl)-2-isopropyl amino ethanol] hydrochloride, a synthetic catecholamine and adrenergic agonist that causes severe stress in the myocardium resulting in infarct-like necrosis of the heart muscle [25]. Impaired cardiac function is also detrimental to the kidney (cardiorenal interaction) in clinical [3] and experimental [27] settings, and AMI causes significant abnormality in liver function [30]. Therefore it is important to check renal and liver adropin expression in the experimental model of MI induced by isoproterenol in rats. However, no study to date has reported the fate of adropin in ISO-induced AMI. Hence, the first aim was to compare adropin expression in cardiac muscle, kidney and liver tissues in rats with ISO-induced MI against controls immunohistochemically. The second aim was to measure ISO-induced changes in serum creatine kinase (CK), myocardial muscle creatinine kinase (CK-MB) and troponin-I concentrations by autoanalysis and adropin concentrations by ELISA.

Materials and methods

All protocols of animal experiments used for this study accorded with the principles set out by the Institutional Animal Ethics Committee (FUIAC; issue: 2013-4-69) at our university and with the policy of the European convention for the protection of vertebrate animals. All animals were acclimatized for one week before the experiment began, being fed a standard pellet diet and given water ad libitum. The rats (2.5 months old) were divided into six treatment groups of six animals each: group I (control), group II (1 h), group III (2 h), group IV (4 h), group V (6 h), and group VI (24 h). The rats were housed in cages in an animal facility with a 12-h dark/light cycle and controlled temperature and humidity. Water and food were administered unrestricted throughout the study. MI in groups III, IV, V, and VI was induced by single subcutaneous injections of ISO (200 mg/1000 g body weight) dissolved in normal saline. Iso-proterenol (ISO) hydrochloride (cat. no. IS627) was purchased from Sigma Chemical Co., St. Louis, MO, USA. This ISO dose and injection route is known to cause significant alterations in biochemical parameters and also moderate heart tissue necrosis [18]. At the end of the experimental periods, the rats were decapitated under ketamine–HCl (75 mg/kg) and 10 mg/kg xylazine–HCl anesthesia and serum adropin levels and tissue adropin immunoreactivity were measured. To check whether MI had occurred, histological sections were prepared and examined by light microscopy to assess gross myocyte injury, and serum levels of CK, CK-MB and troponin-I, which are superior biochemical markers of MI, were measured. Other relevant details of experimental MI were described previously [2,18]. Cardiac, renal and liver tissues were resected, cleaned for immunohistochemistry (IHC) washed in ice-cold saline, fixed in 10% formaldehyde and embedded in paraffin. Blood samples were divided into two aliquots, one for classical biochemical parameters and the other for adropin measurement. Blood was collected in plain biochemical tubes containing 500 KIU aprotinin to protect from proteolysis, and centrifuged at 4000 rpm (1792 × g) at RT for 5 min. Sera were collected and stored at −80 °C until adropin levels were measured.

Masson staining

After one day in 10% formaldehyde, the blocks were dehydrated and embedded in paraffin, cut into 4–5 μm slices, heated overnight in a 60 °C incubator, and then dewaxed and stained with Masson dye. One slice was chosen from each rat and examined under a microscope. This Masson trichrome staining was used for histological evaluation. Histological injury scores were allotted according to a previously published classification method (0: absence, +1: weak, +2: medium, +3: strong), noting the increments of inflammatory cells, congestion, fibrosis, edema, disruption of tissue integrity and necrosis [18]. The overall tissue injury score was calculated from 10 randomly selected microscopic fields in four to six individual sections per heart using a camera attached to an Olympus B ×50 microscope.

Immunohistochemistry

The avidin–biotin–peroxidase complex (ABC) was used for immunohistochemistry as per Hsu et al. [16] with minor modifications [18]. All procedures were followed exactly as described previously except for the primary antibody step. Briefly, paraffin-embedded 4–5 μm sections were cut, deparaffinized and passed through a graded alcohol series. They were incubated in citrate buffer A (pH 6.0) and heated in a microwave oven (750 W; 7 min + 5 min) to recover antigenicity, then for 1 h with the primary antibody. The adropin primary antibody was diluted 1/400 (anti-adropin antibody, ab12800 Abcam, Cambridge, UK), applied, and incubated in a humid environment for 60 min at RT. As a control for antibody specificity, the primary antibody step was omitted. The primary antibody was highly specific against the proteins under examination and did not cross-react with related molecules. There were positive reactions when the sections were incubated with the substrate 3-amino-9-ethylcarbazole (AEC) + AEC chromogen (AEC Substrate, TA-015 and HAS, AEC Chromogen, TA-002-HAC, Lab Vision Corporation, USA) and counterstained with Mayer’s hematoxylin, then covered with lamellae to make permanent preparations. These preparations were examined under a light microscope and photographed using an attached camera (Olympus B × 50, Tokyo, Japan). Immunohistochemical staining was scored for both intensity and prevalence on a scale of 0 to +3 (0: absence, +1: weak, +2: medium, +3: strong).

Serological measurements

Serum adropin was measured using commercial ELISA kits (cat no: EK-032-35) and procedures (Phoenix Pharmaceuticals, Belmont, CA, USA). The lowest detectable concentration of adropin was 0.1 ng/mL, with intra- and inter-assay variations of 10 and 15%, respectively. Sample absorbance at 450 nm was measured with an ELX 800 ELISA reader. Serum CK and CK-MB levels were measured by autoanalysis (Advia 1800 Chemistry System, Siemens Healthcare Diagnostics Inc. Tarrytown, NY, USA) using Advia Chemistry commercial kits, and serum troponin-I concentration by chemiluminescence using a Siemens IMMULITE 2000 XPI Immunoassay System (Siemens Healthcare Diagnostics Inc. Flanders NJ, USA) and commercial kits (Siemens Healthcare Diagnostics Products Ltd. Llanberis, United Kingdom).
Statistical analysis

SPSS 21 (SPSS Inc., Chicago, IL) was used for statistical analysis. The normality distribution of the variables was tested using the one sample Kolmogorov–Smirnov test. The mean ± 2 standard deviation of adropin values were used for selecting cut-off points in order to verify sensitivity and specificity. Statistical differences within groups were compared using the Mann–Whitney U test, followed by post hoc Bonferroni comparisons. Spearman’s test was used to establish correlations. All data were expressed as mean ± SD. Differences were considered statistically significant when p < 0.05.

Results

Histopathological injury confirmed MI [Fig. 1a (control), b (1 h), c (2 h), d (4 h), e (6 h), f (24 h)], as described by other researchers ([1] and [20]). Heart tissues from control rats appeared normal under the light microscope (Fig. 1a). Inflammatory cell numbers (black arrows) were higher at 1 h (Fig. 1b), 2 h (Fig. 1c), 4 h (Fig. 1d) and 6 h (Fig. 1e) than in controls (Fig. 1a). At 24 h (Fig. 1f) there was a remarkable increment of inflammatory cells (black arrows), congestion (red arrows), edema, and disruption of tissue integrity (black stars). Table 1 summarizes the histological injury scores for the whole experimental period (1 h, 2 h, 4 h, 6 h and 24 h) in rats with ISO-induced MI and in controls.

Immunohistochemical staining revealed that cardiac muscle cells have moderate (+2) adropin immunoreactivity (red arrows) in control rats (Fig. 2a). Compared with the control (Fig. 2a) and sham groups (data not shown), adropin increased markedly (+3) in the heart muscle cells (red arrows) at 1 h (Fig. 2b), 2 h (Fig. 2c), 4 h (Fig. 2d), 6 h (Fig. 2e) and 24 h after MI was induced.

Adropin expression was also followed in the kidneys after ISO-induced MI. Adropin was observed in the glomeruli (red arrows) and the renal cortex in all rats. The adropin immunoreactivity in the control group was +1 in the glomerular region (Fig. 3a). It increased markedly (+3) in the renal cortices (red arrows) at 1 h (Fig. 3b), 2 h (Fig. 3c), 4 h (Fig. 3d), 6 h (Fig. 3e) and 24 h (Fig. 3f) after induction of MI.

In the livers of all the rats with ISO-induced MI, adropin was found in the sinusoidal cells (red arrows). Immunohistochemical staining revealed that liver tissues had moderate (+2) adropin immunoreactivity (red arrows) in control rats (Fig. 4a). Adropin staining in the sinusoidal cells did not differ from controls at 1 h (Fig. 4b), 2 h (Fig. 4c), 4 h (Fig. 4d), 6 h (Fig. 4e) or 24 h (Fig. 4f) (red arrows).

The control level of serum CK was 554.2 ± 78.3 IU/L but the level rose gradually in ISO-induced MI rats (Fig. 5) to 645.3 ± 53.6 IU/L at 1 h, 789.1 ± 31.4 IU/L at 2 h, 1147.1 ± 79.9 IU/L at 4 h, and 1689 ± 82.6 at 6 h; there was a decrease to 539.1 ± 46.7 IU/L at 24 h. The control level of serum CK-MB was 228.5 ± 33.5 IU/L, but the level rose gradually in ISO-induced MI rats (Fig. 5) to 250.1 ± 69.7 IU/L at 1 h, 419 ± 63.9 IU/L at 2 h, 637.3 ± 29.1 IU/L at 4 h, and 921 ± 76.2 IU/L at 6 h; at 24 h it was 245 ± 35.1 IU/L.

The control level of serum troponin-I was 10.80 ± 2.04 ng/mL but the level gradually increased (Fig. 6) in ISO-induced MI rats to 27.85 ± 4.88 ng/mL at 1 h, 38.17 ± 3.69 ng/mL at 2 h, 48.16 ± 4.02 ng/mL at 4 h, and 35.48 ± 5.54 at 6 h; at 24 h it was 13.51 ± 2.12 ng/mL.

The control level of serum adropin was 21.66 ± 4.06 ng/mL, but the level gradually increased (Fig. 7) in ISO-induced MI rats to 33.73 ± 3.19 ng/mL at 1 h, 39.98 ± 5.65 ng/mL at 2 h, 37.16 ± 3.5 ng/mL at 4 h, and 36.56 ± 4.13 at 6 h; at 24 h it was 32.43 ± 2.38 ng/mL. There was a positive correlation between the adropin and troponin-I concentrations (r = 0.518, p = 0.000).

Both troponin-I and adropin are cardiac markers used to diagnose myocardial infarctions and their blood levels increase after a myocardial infarction. The predictive sensitivity and specificity for MI was 83% and 100, respectively when used a peak adropin (second hour) cutoff value of 29.78 ng/mL (>90th percentile level). The predictive sensitivity and specificity for MI was 100% and 100, respectively when used a peak troponin-I (fourth hour) cutoff value of 14.88 ng/mL (>90th percentile level).
Discussion

Acute myocardial infarction (AMI) remains a leading cause of death in both developed and developing countries [11]. The major causes of death in AMI patients are prolonged ischemia, hypoxia, reinfarction and cardiac rupture [32]. To avoid irreversible heart tissue injury, an early diagnostic test for AMI is essential [4,10]. Recently, it has been found that the hormone adropin is produced in the endocardium, myocardium, and epicardium [6]. Therefore, we hypothesized that adropin could be used as a marker protein for early diagnosis in conjunction with CK, CK-MB and troponin-I because we expected rapid release of adropin from cardiac tissue injured by AMI. In order to test our hypothesis, an animal model was used in which AMI was induced by injection of ISO. Histological examination of ISO-injected rats demonstrated MI-related injury of heart tissues (Masson's trichrome staining) throughout the period of observation (control, 1 h, 2 h, 4 h, 6 h and 24 h). Compared to the control, there were slight increases of inflammatory cells (black arrows) at 1 h and 2 h; remarkable increments of inflammatory cells at 4 h (black arrows) and 6 h; and at 24 h there were remarkable increments of inflammatory cells (black arrows), congestion (red arrows), edema, and disruption of tissue integrity (black stars). Similar histological injuries after ISO-induced MI have been reported by Kuloglu et al. [18]. The CK, CK-MB and troponin-I levels in the control and isoproterenol-treated rats were also comparable to the values reported by other researchers [12,34].

In the second part of this experiment we found that adropin synthesis was higher in the endocardium, myocardium, and epicardium of ISO-induced MI rats than in controls. The heart tissue injury in ISO-induced MI rats comprised edema and disruption of tissue integrity and was irreversible [18,20]. These infarcted tissues need to maintain energy (glucose) homeostasis [13], which could explain the increase in adropin expression. Our results indicate that adropin could influence the regulation of metabolic pathways during prolonged ischemia and hypoxia in ISO-induced MI rats; in the ischemic region, adenosine triphosphate synthesis (required for contraction, relaxation, and ion homeostasis) is markedly reduced due to the lack of oxygen and washout of metabolic products [13]. Any reduction in ATP synthesis quickly results in systolic and diastolic dysfunction, quickly followed by irreversible injury [17]. Previous studies also demonstrated a correlation between the elevation of adropin and the severity of heart failure [22], and a negative correlation between adropin and the left ventricular ejection fraction [22].

Adropin potentially has the capacity to protect the endothelium by upregulating endothelial NO synthase expression through the vascular endothelial growth factor (VEGF) receptor 2 (VEGFR2)-phosphatidylinositol 3-kinase-Akt and VEGFR2-extracellular signal regulated kinase 1/2 pathways [19, reviewed 5]. Also, adropin within the heart tissues could be increased in order to protect heart tissue in MI, thereby improving the energy status of the myocardium by maintaining glucose homeostasis and restoring

Table 1
Histological injury scores for the whole observation period (control, 1 h, 2 h, 4 h, 6 h and 24 h) after ISO-induction of MI.

<table>
<thead>
<tr>
<th>Groups</th>
<th>Increments of inflammatory cells</th>
<th>Congestion</th>
<th>Fibrosis</th>
<th>Edema</th>
<th>Disruption of tissue integrity</th>
<th>Necrosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>0 ± 00</td>
<td>0 ± 00</td>
<td>0 ± 00</td>
<td>0 ± 00</td>
<td>0 ± 00</td>
<td>0 ± 00</td>
</tr>
<tr>
<td>1 h</td>
<td>1.50 ± 0.54e</td>
<td>0 ± 00</td>
<td>0 ± 00</td>
<td>0 ± 00</td>
<td>0 ± 00</td>
<td>0 ± 00</td>
</tr>
<tr>
<td>2 h</td>
<td>1.50 ± 0.54e</td>
<td>0 ± 00</td>
<td>0 ± 00</td>
<td>0 ± 00</td>
<td>0 ± 00</td>
<td>0 ± 00</td>
</tr>
<tr>
<td>4 h</td>
<td>2.33 ± 0.81e</td>
<td>0 ± 00</td>
<td>0 ± 00</td>
<td>0 ± 00</td>
<td>0 ± 00</td>
<td>0 ± 00</td>
</tr>
<tr>
<td>6 h</td>
<td>2.16 ± 0.75e</td>
<td>0 ± 00</td>
<td>0 ± 00</td>
<td>0 ± 00</td>
<td>0 ± 00</td>
<td>0 ± 00</td>
</tr>
<tr>
<td>24 h</td>
<td>2.67 ± 0.52e</td>
<td>2.50 ± 0.56hde</td>
<td>0 ± 00</td>
<td>2.66 ± 0.52hde</td>
<td>1.83 ± 0.98hde</td>
<td>0 ± 00</td>
</tr>
</tbody>
</table>

Control vs. (a) 1 h (MI); (a) 2 h (MI); (abc) 4 h (MI); (abc) 6 h (MI) and (abcde) 24 h (MI); p < 0.05.

Fig. 2. Immunohistochemical staining of adropin in the cardiac tissues in rats with ISO-induced MI and controls. Adropin was markedly increased (+3) in the heart muscle cells (red arrows) at 1 h (b), 2 h (c), 4 h (d), 6 h (e) and 24 h (f) after induction of MI compared with control (a). (For interpretation of the references to color in this figure legend, the reader is referred to the web version of the article.)
myocardial glycogen stores. The clinical importance of these changes could lie in a positive relationship between maintained glucose homeostasis, glycogen stores, and contractile function in rats with ISO-induced MI. Thus, we tentatively suggest that adropin synthesis within the heart tissues provides a reliable indicator of heart tissue injury in the context of MI in rats.

In this study, we also found that serum adropin rises as early as 30 min post-infarct and peaks at 2 h; the adropin concentrations at 4, 6 and 24 h post-infarct were still 1.3–1.4 times higher than controls. Thus, blood adropin levels can remain elevated for 24 h after MI. The animal adropin data presented here are not consistent with recent results of Yu et al. [35], who reported that single timing serum adropin levels were lower in human subjects with acute myocardial infarction (AMI) compared with stable angina pectoris (SAP) patients or controls [35]. Furthermore, the time course of changes in adropin levels parallels that of troponin-1. These
findings demonstrate that serum adropin is much highly cardiac specific and therefore a candidate marker protein for early diagnosis in conjunction with troponin. During MI, myocardial tissues need much energy and oxygen in order to avoid hypoxia, enlargement of the infarcted region, and further impairment of cardiac function [13,17]. After MI, energy and oxygen demand are increased in myocardial tissues [13]. In order to maintain and regulate energy homeostasis in tissues, especially heart tissues, adropin production (in liver, kidney, heart, etc.) could be increased; in particular, injury to heart muscle cells releases adropin into the bloodstream. Therefore, changes in the adropin source lead to a large increase and then a fall in the serum level. The blood level of adropin increases within 1 h after MI, peaks at 2 h, and starts to decrease after 4 h but remains higher than control even at 24 h. Other peptides have previously been assessed as biomarkers reflecting MI, including copeptin [23] and natriuretic peptide [26].

We also measured the CK and CK-MB levels, which started to increase 1 h after MI and peaked at 6 h. In human subjects following myocardial injury, the initial CK and CK-MB rise occurs 4–9 h after the onset of chest pain, peaks at 24 h, and returns to baseline at 48–72 h [14,15]. In the present animal experiment we followed up 24 h and we caught the highest peak at 6 h, and then the CK and CK-MB decreased up to 24 h after MI. It has previously been reported that CK-MB elevations return to baseline within 36–48 h, in contrast to troponins and possibly adropin, which could serve as an alternative to troponins for diagnosing MI in clinical practice; its best clinical use in future could be the most appropriate timing of serial measurements. Our animal studies revealed considerable promise for adropin as a diagnostic biomarker in a range of MI-related conditions.

The relationship between kidney, liver and cardiovascular risk is longstanding and impaired cardiac function is known to be detrimental to the kidney (cardiorenal interaction) in clinical [3] and in experimental [18,27] settings. MI also causes significant hepatic impairment [30]. Therefore, we checked renal and liver adropin expression immunohistochemically in the experimental model of ISO-induced MI model in rats. Adropin immunoreactivity in liver tissue did not differ between the experimental MI model and the control rats, but adropin immunoreactivity (severity 3+) was greater at all-time points (1 h, 2 h, 4 h, 6 h and 24 h after MI) in the renal tissues of the experimental MI rats than in controls. This change could represent a compensatory mechanism to help maintain energy regulation and glucose homeostasis; during ischemia, when oxygen availability is limited, energy expenditure should be strictly controlled to protect the most essential cellular functions in non-ischemic regions (such as the kidneys). Such regions require more rapid ATP synthesis and therefore more rapid substrate oxidation [29]. The elevated levels of adropin in the serum and kidney tissues could reduce the glucose intolerance that occurs in response to metabolic stress (such as MI) and mediate substrate oxidation in order to generate energy. Thus, increased adropin could contribute to protecting tissues from ischemia by regulating energy better.

In conclusion, the present study demonstrated that acute ISO injection into experimental animals induces MI, as confirmed by histological heart injury scores and CK, CK-MB and troponin-I levels, the traditional gold standard test for AMI. Immunological staining revealed that adropin synthesis was dramatically increased in heart and kidney tissues during MI. Adropin was probably released into the blood mainly from injured heart muscle, since its serum level was higher in MI than control animals. Also, its level was elevated as early as 1 h post-infarct. The cardiac specificity of adropin could therefore make it an ideal marker for retrospective diagnosis of infarction, in addition to troponin-I. However, the diagnostic performance of each of these cardiac markers (adropin and troponin-I) was not significantly superior to each other.

Conflict of interest

The authors declare that they have no conflict of interest.

References


