Involvement of galectin-3 in cadmium-induced cardiac toxicity

Galektin-3'ün kadmiyuma bağlı kardiyotoksisiteye katılımı

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ABSTRACT

Objective: Accumulation of the wide spread environmental toxin cadmium (Cd) in tissues results in toxicity. Heart is one of the most effected tissues. Cd exposure induces inflammation in effected tissues. The present study was focused to evaluate roles of tumor necrosis factor alpha (TNF-α) and interleukin-6 (IL-6) in Cd toxicity and their relationships with galectin-3 levels.

Methods: In this experimental study, male Wistar rats were divided randomly to control and experimental groups. Experimental group was exposed to Cd at the dose of 15 ppm for 8 weeks (n=10/group). Inflammatory status in hearts was evaluated with measurement of tissue TNF-α and IL-6 levels. Histopathological examination of heart was carried out by light microscopy. Heart tissue caspase-3 level was used to identify apoptosis. Tissue galectin-3 level was evaluated by ELISA. Statistical difference between groups was evaluated by unpaired Student t-test, correlation was analyzed by Pearson's test.

Results: Heart sizes were increased after Cd toxicity. A significant increase in galectin-3 tissue levels was seen after Cd toxicity, this was accompanied with a significant increase in the TNF-α (control: 402±39, Cd: 793±26 pg/g tissue, p<0.001) and IL-6 (control: 150±78, Cd: 325±65 pg/g tissue, p<0.001) levels. Histopathological examination under light microscope suggested a combination of ongoing necrosis and apoptosis. Increased caspase-3 levels were measured after Cd toxicity (control: 12±2, Cd: 18±3 pmol/μg/min, p<0.001).

Conclusion: Chronic Cd administration induces inflammation and apoptosis in rat hearts. Cadmium causes increased galectin-3 production from heart tissue. The formation of TNF-α due to Cd exposure may likely trigger this mechanism. *(Anadolu Kardiyol Derg 2011; 11: 479-84)*

Key words: Cadmium, heart, galectin-3, caspase-3, tumor necrosis factor alpha, interleukin-6

ÖZET

Amaç: Çevresel toksinlerden biri olan kadmiyumun dokularda birikimi ciddi toksiteye neden olur. Kalp en sık etkilenen organlardan biridir. Kadmiyuma maruz kalma dokularda enflamasyonla sonuçlanır. Bu çalışmada kadmiyum toksitesinin kardiyak dokuda proenflamatuvar sitokinlerden tümör nekrozis faktör-alfa (TNF-α) ve interlökin-6 (IL-6) düzeylerine etkisi ve doku galektin-3 düzey değişiminin belirlenmesi hedeflenmiştir.

Yöntemler: Bu deneysel çalışmada, erkek Wistar sıçanlar randomize kontrol ve deney grubuna ayrılmış, deney grubu 8 hafta, günlük 15 ppm kadmiyuma maruz bırakılmıştır (n=10/grup). Kalp dokusunda enflamasyon doku TNF-α ve IL-6 düzeyleri ile belirlenmiştir. Kardiyak doku histolojik olarak incelenmiştir. Dokuda apoptozis caspase-3 düzeyleri ile belirlenmiştir. Galektin-3 düzeyi ELISA ile ölçülmüştür. Gruplar arası farklar t-testi, korelasyon Pearson's testi ile değerlendirilmiştir.

Bulgular: Kadmiyum uygulanan grupta makroskopik olarak kardiyomegali gözlenmiştir. Dokuda TNF-α (kontrol: 402±39, Cd: 793±26 pg/g doku, p<0.001), IL-6 (kontrol: 150±78, Cd: 325±65 pg/g doku, p<0.001) ve galektin-3 düzeyleri belirgin artmıştır. Histopatolojik incelemede kadmiyum kalp dokusunda belirgin nekroz ve apoptoza neden olduğu gözlenmiştir. Doku kaspaz-3 düzeyleri artmıştır (kontrol: 12±2, Cd: 18±3 pmol/μg/dk, p<0.001).

Sonuç: Kadmiyum toksitesi kalp dokusunda enflamasyona, apoptoza neden olmaktadır. Kadmiyum kardiyak dokuda galektin-3 düzeyini arttırmaktadır. Dokudaki enflamasyonun artması galektin-3 düzeyinin artışına neden olan mekanizmalardan biri olabilir.
(Anadolu Kardiyol Derg 2011; 11: 479-84)

Anahtar kelimeler: Kadmiyum, kalp, galektin-3, caspase-3, tümör nekrozis faktör - alfa, interlökin-6

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Introduction

Cadmium (Cd) exposure occurs widely in general population, especially low-level chronic exposure through smoking and dietary sources, but it is known also as one of most toxic environmental and industrial pollutants. Cadmium accumulates in the body because of slow excretion. Cd causes toxicity in different organs, heart is one of the most effected tissues and oxidative damage usually occurs after Cd toxicity (1-4). Many mechanisms are defined to explain pathophysiology of the Cd toxicity; inflammation is one of them (5).

Galectins are a large family of animal lectins that contain carbohydrate-recognition domains consisting of amino acids that are responsible for carbohydrate binding (6). Galectins can behave as a pro-inflammatory or anti-inflammatory mediator by modulating the physiology and responses of immune cells, including macrophages, T and B cells, neutrophils, eosinophils and mast cells (7). Galectin-3 has also antiapoptotic effect and tumor associated immune and inflammatory responses (8). It was shown that galectin-3 also takes part in the mechanism of the ischemia-induced damages (9), it behaves as an inflammatory substance. Latest studies focused on the involvement of galectin-3 in cardiac failure, cardiac remodeling and in the fibrotic process (10). Galectin-3 is accepted as a novel biomarker in cardiac failure progress (11). Recent studies showed that environmental cadmium exposure is associated with cardiovascular disease, significantly increased stroke and heart failure prevalence (12).

Role of galectin-3 during Cd toxicity has not been reported yet. Additionally, its relationship with tumor necrosis factor alpha (TNF-α) is still unclear.

This study was designed to evaluate role of galectin-3 in the cardiac toxicity of Cd and whether their levels correlated with inflammatory markers such as TNF-α level and interleukin-6 (IL-6).

Methods

Study animals

Twenty adult male Wistar rats (150-200 g) were used for toxicity model. Rats were divided randomly control and Cd toxicity groups (n=10). Animals were housed at Ankara University Animal Laboratory under controlled light (12L: 12D) and temperature with free access to food and water. All aspects of animal handling and surgery were conducted in accordance with appropriate animal experiments criteria established by Helsinki Declaration by the permission of Ankara University, Faculty of Medicine, Ethical Committee.

Experimental design

The rats were given 15 ppm of Cd in their drinking water (cadmium chloride dissolved in distilled water) for 8 weeks. Cd-chloride ($CdCl_2$, anhydrous) was obtained from Sigma (St. Louis, MO, USA). At the end of 8 weeks the rats were sacrificed under anesthesia, and their hearts were taken out for further evaluations. Half of the hearts were used for determination of Cd concentrations; the other half was used for measurements of protein levels. All tissue samples were stored at -80°C until they were used for evaluation.

Histological examination

Following the removal of hearts, they weighted and sizes of left and right ventricular wall thickness and atrioventricular opening diameters of them were measured and recorded. After fixation in 10% buffered formalin, tissue samples were dehydrated and embedded in paraffin, cut at about 5 µm thick and stained with hematoxylin-eosin. Samples were evaluated under light microscope (Olympus, Japan) with X50-100 magnification.

Biochemical determinations

Protein extracts were prepared from fresh tissue samples in Brij 150 lysis solution which contains a cocktail of protease inhibitors aprotinin (2 µg/ml), leupeptine (2 µg/ml), pepstatine (2 µg/ml), PMSF (2 µg/ml). Chemicals were obtained from Sigma unless otherwise stated. Lysis solution was added as two folds of tissue weight by volume and homogenized (Powergen 125, Fisher, PA, USA).

Measurement of cytokine levels

Tissue supernatants were harvested and analyzed for TNF-α, interleukin-6 (IL-6) and galectin-3 in triplicate using an ELISA kit (Cytolab/PeproTech, Israel). The lower detection limits of the assay were 16 pg/ml for TNF-α, 30 pg/ml for IL-6 and 200 pg/ml for galectin-3.

Tissue cadmium levels

Half of the hearts were used for determination of the Cd concentration by flame-less atomic absorption spectrophotometry (AAS). All reagents and chemicals were of analytical grade or higher purity. Trace pure nitric acid (HNO_3; Merck, NJ, USA) as well as Cd standard solutions assigned for atomic absorption spectrometry (Sigma, Mo, USA) were used in metals analysis.

The weighed heart tissue slices were dry mineralized at 450°C in an electric oven. After ashing, the samples were dissolved in 10 ml of 1 M HNO_3. Cadmium was determined by flameless AAS method with electro thermal atomization in a graphite cuvette.

Caspase-3 levels

Protein content of homogenates was determined with Bradford method. Then 100 µg of proteins were diluted with assay buffer (50 mM HEPES, pH 7.4, 100 mM NaCl, 0.1% CHAPS, 10 mM DTT, 2 mM EDTA, 2 mM EGTA, Triton X-100, 0.1%) and incubated at 25°C with the colorimetric substrates (Sigma, Mo, USA): Ac-DEVD-pNA. Final concentration was 200 µM for all substrates in 96-well microtiter plates. Cleavage of the p-nitroaniline (pNA) dye from the peptide substrate was determined by the measurement of absorbance of pNA at 405 nm in a micro-

plate reader. Results were calibrated with known concentrations of p-NA and expressed in picomole substrate cleaved/minute and per microgram protein at 25°C.

Statistical analysis

Statistical analyses were performed using SPSS version 10.0 software for Windows (SPSS Inc, Chicago, Il, USA).

Data were evaluated first for homogeneity of variance with Shapiro-Wilk test. Student's t-test (unpaired) was used for comparison of continuous variables between control and cadmium exposure groups. Correlations between galectin-3 and cardiac measurements and TNF-α level within the same tissues were evaluated with Pearson's test. Results were expressed as mean±SD. $p<0.05$ was accepted as statistically significant.

Results

After 8 weeks Cd exposure no mortality occurred. Cd concentrations of the heart tissue control and cadmium toxicity groups were 2.28±0.26; 52.77±1.95 ng/g tissue (mean±SD), respectively.

Histological examination

Hearts were evaluated under light microscope. Heart sizes increased after Cd toxicity. Ventricular wall thickness and atrioventricular opening diameters increased significantly in Cd toxicity group (Table 1). Heart size ($r=0.834$, $p<0.01$) and right ventricular thickness ($r=0.944$, $p<0.001$) were found to be significantly correlated with tissue galectin-3 levels in rat hearts.

Hearts of the Cd group are hypertrophied (Fig. 1). Myocardium was in normal aspect in control group (Fig. 2.1). Some degenerative differences were observed in cadmium treated group such as congestion in the vessels (Fig. 2.2), nuclear lysis, vacuolization of cytoplasm and irregularity (Fig. 2.3) of myofibrils (Fig. 2.4).

Biochemical evaluations

As seen in the Fig. 3-5 our results showed that chronic cadmium administration in rats caused marked increases in the caspase-3, TNF-α, IL-6 and galectin-3* levels ($p<0.001$, $p<0.05$*, Table 2). Tissue levels of TNF-α, galectin-3 were strongly correlated with each other ($r=0.872$, $p<0.0001$).

Discussion

In this study, we aimed to evaluate roles of proinflammatory cytokines TNF-α, IL-6 and galectin-3 during 8 weeks of Cd toxicity. Oral Cd administration in rats results in increased TNF-α, IL-6 production in heart tissue in correlation with increased galectin-3 levels. Our results showed that Cd induces caspase activated apoptosis, causes degenerative changes in rat hearts. It is known that Cd exposure causes severe damage in different organs of the body. Heart is one of them. We found degenerative changes during histopathological evaluation of the hearts in Cd group. Cadmium induced apoptosis in cardiomyocytes. It was supported by increased caspase-3 levels in Cd group.

Several immunological and non-immunological mechanisms of Cd toxicity have been proposed. Pathological proinflammatory and pro-apoptotic stimuli, like TNF-α can cause activation of caspase cascades and apoptosis by direct or indirect processing of caspase-3. Tumor necrosis factor-α and IL-6 levels increased and correlated with caspase-3 levels in Cd group. The cardiotoxicity of the Cd seems as it was mediated by inflammation. Although conflicting results were found related to immunomodulatory actions of Cd (13-15), its effect is seemed to be dose and time dependent. It was found that high doses of Cd suppress

Table 1. Cardiac sizes of control and cadmium - induced toxicity groups

Variables	Control group	Cadmium group	p*
Heart weights, gr	1.04±0.10	1.66±0.06	<0.0001
Left ventricular wall thickness, mm	3.8±0.5	4.0±0.6	>0.05
Right ventricular wall thickness, mm	2.3±0.5	1.3±0.2	0.004
Left atrioventricular opening diameter, mm	1.02±0.09	1.2±0.13	0.028
Right atrioventricular opening diameter, mm	1.02±0.07	1.28±0.07	<0.0001

Data are presented as mean±SD
*Unpaired t test

Table 2. TNF-α, IL-6 and caspase-3 levels after chronic Cd exposure

Variables	Control group	Cadmium group	p*
TNF-α, pg/g tissue	402±39	793±26	<0.001
IL-6, pg/g tissue	150±78	325±65	<0.001
Caspase-3 levels, pmol/µg/min	12±1.4	18±1.3	<0.001

Cd - cadmium, IL-6 - interleukin-6, TNF-α - tumor necrosis factor alpha
Data are presented as mean±SD
*Unpaired t test

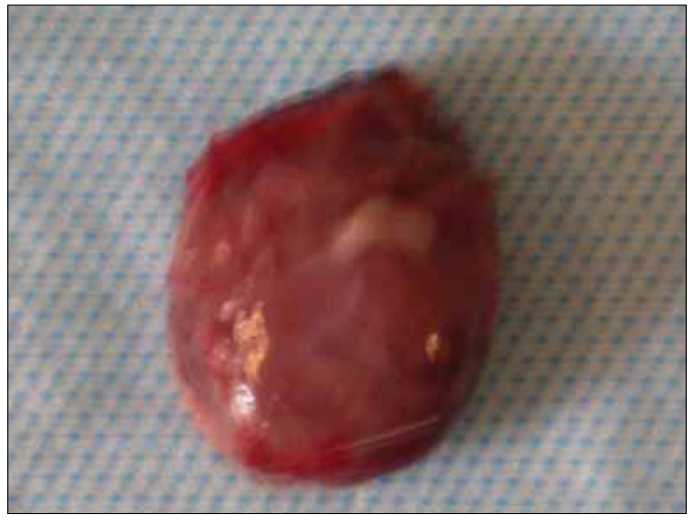

Figure 1. Gross appearances of control (A) and Cd (B) induced hearts
Cd - cadmium

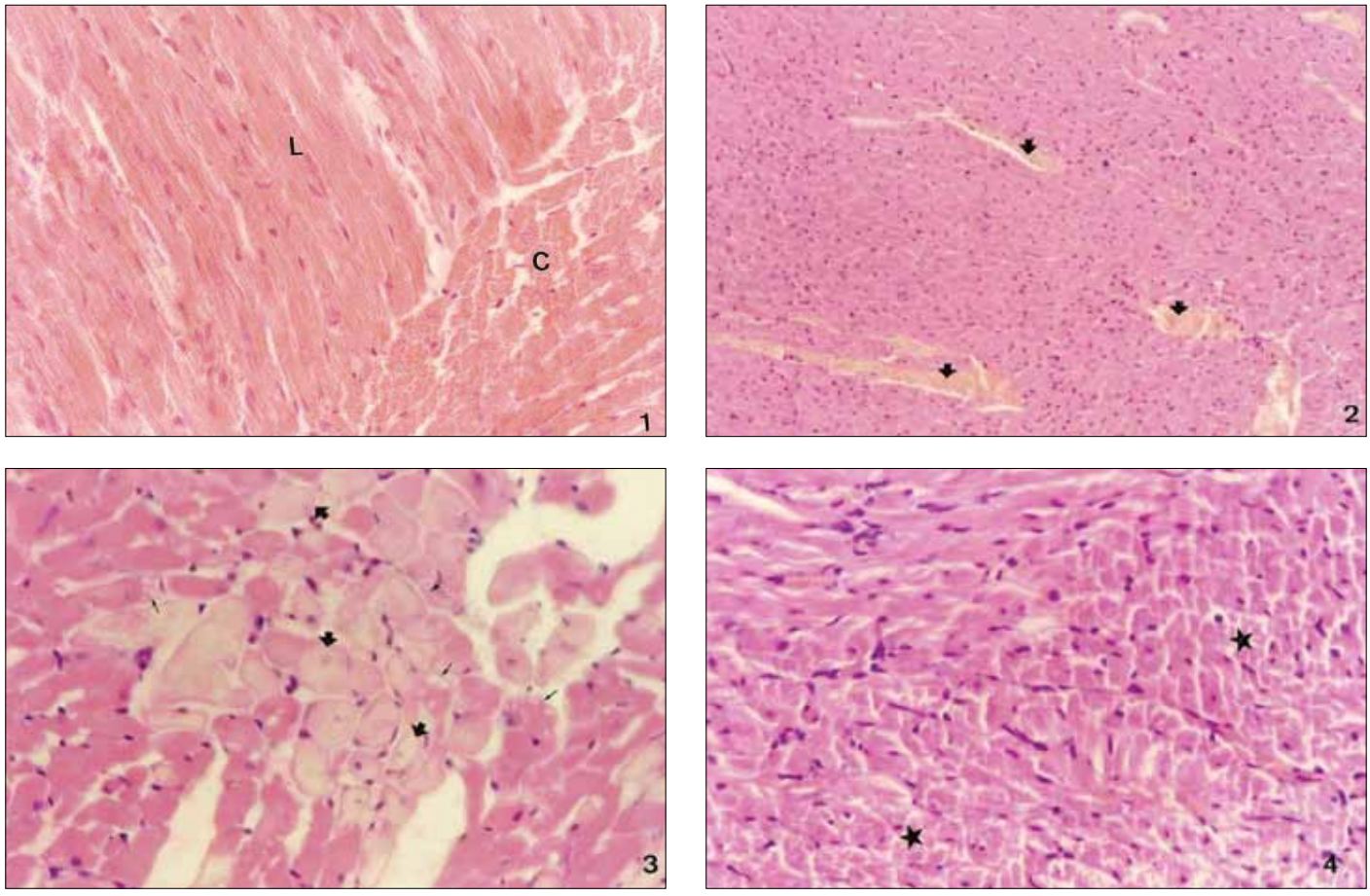

Figure 2. 1. Myocardium of control group. Longitudinal (L) and cross (C) sectioned myocardial cells are seen in normal aspect (H&E, X100) 2. Myocardium of cadmium treated group exhibiting congestion in the vessels (arrow) (H&E, X50) 3. Myocardium of cadmium treated group exhibiting degenerative changes with nuclear lysis (thick arrow) and vacuolization of cytoplasm (thin arrow) in some areas (H&E, X100) 4. Myocardium of cadmium treated group exhibiting irregularity of myofibrils particularly more clear in cross section (asterisk). (H&E, X100)

immune response where as with lower doses immune stimulatory effects become more prominent. A growing body of evidence links macrophage activation and fibrosis to the pathogenesis of heart failure. Studies are increasing that link macrophage activation and fibrosis to the pathogenesis of heart failure. Accordingly, there has been increasing interest in developing therapeutic agents with anticytokine properties in patients with heart failure (16).

A role for galectin-3 in the pathophysiology of heart failure has been reported recently. Galectin-3 could induce primary immune response and cytokine production and has important roles in metastasis, migration, inflammation, fibrosis, and in the main mechanisms take part in pathogenesis and progress of heart failure (6, 7, 10). Galectin-3 is chemo-attractant for leukocytes. It is important for modulation of integrins and metalloproteinases (6, 7). Deficiencies in accumulation of inflammatory cells, decreased response to peritonitis, lower levels of NF-κB response and decreased inflammatory cell survival were seen in galectin-3 deficient mice (17). Increased myocardial galectin-3 expression is seen during progression to heart failure. The up-regulation of myocardial galectin-3 has been demonstrated in a rat model of heart failure prone hypertensive hearts (18), interferon γ -induced murine chronic active myocarditis and cardiomyopathy together with TNF-α, IL-12 and the macrophage-attracting chemokines MCP1 and MIP1-α (19).

Cardiac remodeling is an important determinant of the clinical outcome of heart failure, as it is linked to disease progression and poor prognosis. Increased inflammation and fibrosis are main determinants of ventricular remodeling. Resent findings support the involvement of galectin-3 in cardiac remodeling and in the fibrotic process and, as suggested by two recent experimental studies of liver and kidney fibrosis (20, 21). There is evidence that inflammation contributes to end organ damage. It has shown that N-acetyl-seryl-aspartyl-lysyl-proline (Ac-SDKP) prevents inflammation, cell proliferation and fibrosis in the heart and kidney in a ANG II-induced hypertension model. They found that galectin-3 expression increased in left ventricular remodeling together with inflammatory markers IL-6, transforming growth factor-β (TGF-β), and TNF-α (22). Liu et al. (23) recently showed that the co-infusion of Ac-SDKP with galectin-3 into the pericardial sac, inhibited fibrosis and inflammation and decreased cardiac dysfunction.

Together, the experimental data underlying the potentially important role that galectin-3 may play in cardiac remodeling,

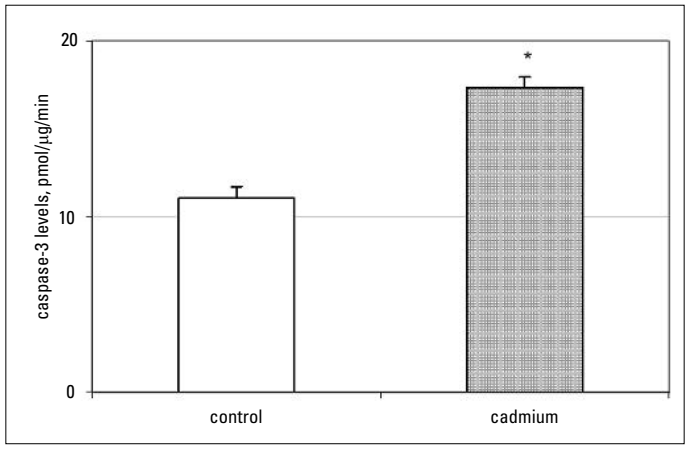

Figure 3. Caspase-3 levels of chronic Cd exposure and control groups
Cd - cadmium
Results are presented as mean±SD, * p<0.001 in comparison to control value

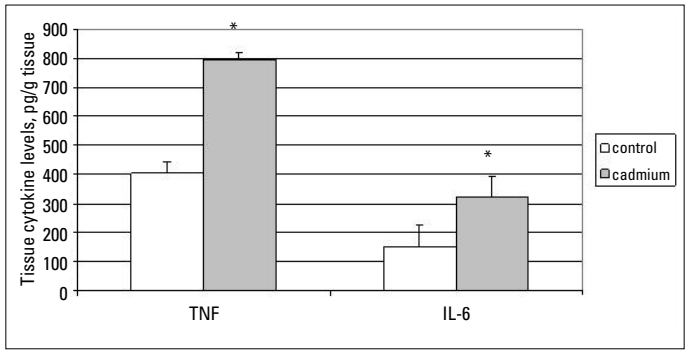

Figure 4. TNF-α and IL-6 levels after chronic Cd exposure
Cd - cadmium, IL-6 - interleukin-6, TNF-α - tumor necrosis factor alpha
Results are presented as mean±SD, * p<0.001 in comparison to control value

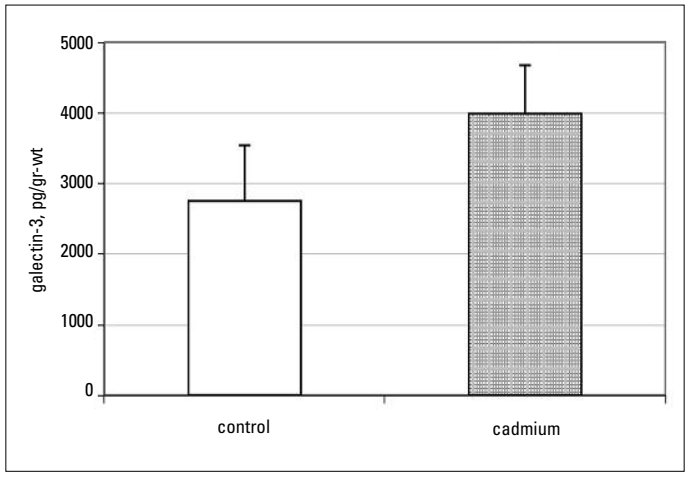

Figure 5. Galectin-3 levels after chronic Cd exposure.
Cd - cadmium
Results are presented as mean±SD, *p<0.05 in comparison to control value

and interference with galectin-3 levels seems to effectively reverse cardiac remodeling. Galectin-3 over expression causes changes in the expression levels of cell cycle regulators, including cyclin D1, which is important for myocardial fibrosis and heart failure. Nuclear galectin-3 expression is associated with cell proliferation, and this effect is mediated through enhanced cyclin D1 promoter activity (24). Galectin-3 has ability to bind to cardiac fibroblasts and it induces fibroblast proliferation via the activation of cyclin D1. The exact myocardial localization of galectin-3 has not been known exactly. However, immunohistochemistry and confocal microscopy analyses of hypertrophied rat myocardium showed that galectin-3 binding sites were localized predominantly to the myocardial matrix, in macrophages and fibroblasts. Galectin-3 is necessary for normal phagocytic activity. In hypertrophied hearts and during active myocarditis, significant infiltrations of activated macrophages were observed and galectin-3 was found to be co-localized with macrophages (18).

Heart sizes and ventricular hypertrophy were found significantly correlated with tissue galectin-3 levels in rat hearts, and there was strong correlation between tissue TNF-α and galectin-3 levels. Taken together, with from available clinical data, plasma and/or serum galectin-3 is increased in acute and chronic heart failure and previous animal studies our results support the idea of the involvement of galectin-3 in cardiac remodeling and inflammation. Galectin-3 might be of particular value to predict prognosis and as a novel biomarker in cardiac pathologies even in toxicities.

Study limitations

The functional analysis of heart, in case of ventricles and valves was not evaluated in this study. Echocardiographic analysis might give more information about Cd induced damage in rat hearts.

Conclusion

Our results support the concept of considering galectin-3 as a new target for therapeutic intervention and prognostic biomarker in different heart dysfunction and pathologies. Further studies will explain the pathophysiological mechanisms of the involvement of galectin-3 in Cd induced toxicity in heart.

Conflict of interest: None declared.

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