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Research Article

Effect of Candesartan Combined with Rosuvastatin on Myocardial Fibrosis in Rats with Alcoholic Cardiomyopathy by Mediating LOX-1 Expression

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Abstract: ***Objective:*** To analyze the effect of candesartan and rosuvastatin on myocardial fibrosis in rats with alcoholic cardiomyopathy by mediating the expression of lectin-like oxidized low-density lipoprotein receptor-1 (LOX-1). ***Methods:*** The rats were selected as experimental samples, and these rats were randomly divided into observation group and alcohol feeding group (abbreviated as "alcohol group") and desartan combined with rosuvastatin intervention + alcoholic cardiomyopathy group (Referred to as the "intervention group"), the observation group is fed normally, the alcohol group is fed with alcohol, and the intervention group uses two drugs on the basis of the alcohol group to intervene. After 16 weeks of the three groups of experiments, analyze the results of the three groups of experiments. Myocardial structure, myocardial fibrosis and myocardial function. ***Results:*** After 16 weeks, the left ventricular short axis shortening rate (FS) and left ventricular ejection fraction in the alcohol group were lower than those in the observation group, while the collagen volume fraction (CVF) and left ventricular end-diastolic diameter (LVEDd) were higher than those in the observation group, The expression of LOX-1 in the intervention group was lower than that in the alcohol group, and the degree of fibrosis was reduced. The expression of LOX-1 in the alcohol group was higher than that in the observation group, and the degree of fiber increased. At the same time, the expression of TN-X and smad-3 protein in the alcohol group (86%± 7%, 83%±9%) were higher than those in the observation group (32%±10%, 30%±7%), while the expression of smad-7 protein (36%±8%) was lower than that in the observation group (78%± 9%), $P<0.05$ among the three groups of experiments, and there is statistical significance among the groups. ***Conclusion:*** Candesartan combined with Rosuvastatin can reduce myocardial fibrosis in rats with alcoholic cardiomyopathy by mediating the expression of LOX-1.

Keywords: Candesartan; Rosuvastatin; LOX-1; Rat alcoholic; Cardiomyopathy; Myocardial fibrosis

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Alcohol cardiomyopathy is a disease in the cardiovascular field in recent years. Its incidence rate is also increasing. After research, most of the alcoholic heart failure patients are accompanied by myocardial remodeling, and myocardial fibrosis is a pathological change which often occurs in the process of myocardial remodeling. In the myocardium interstitial fibrosis is the result of heart failure [2].In the study, we found that tenogenin is a glycoprotein, which mainly constitutes the extracellular matrix. There are six subtypes, which are tenogenin-r (TN-R), TN-X, TN-C, TN-N, TN-Y and TN-W. However, up to now, tn-x is only limited to a variety of animal and human tissues, and can be prominently expressed in skeletal muscle and cardiac extracellular matrix.

Tn-x is mainly derived from fibroblasts, which is a glycoprotein component of extracellular matrix and can co mediate the process of fibrosis with collagen. In this study, lectin like oxidized low density lipoprotein receptor-1 (LOX-1) as a receptor promoter gene, through the comparative method, continuous analysis of different methods on LOX-1 protein expression, get different degrees of fibrosis, so as to get the effect of candesartan combined with rosuvastatin on myocardial fibrosis in alcoholic cardiomyopathy rats.

1 Material and methods

1.1 Animal model

Sixty male rats of our institute were selected as the research sample, with the weight of (250 ± 50) g. all the animals were divided into intervention group, alcohol group and observation group, with 20 rats in each group. The alcohol group was fed with alcohol for one week, the alcohol content was 10%, and the 60% alcohol was given by gavage once a day, with the standard of 5ml / kg; In the second week, by the same method, only 60% alcohol standard was changed to 10 ml / kg for gavage twice; In the 3-16 week interval, 20% alcohol was used for drinking at will every day, while 60% alcohol was given by gavage twice a day, 15ml / kg. On the basis of alcohol group, candesartan 1mg / kg / D combined with rosuvastatin 1mg / kg / D + alcoholic cardiomyopathy was used in the intervention group, while the rats in the observation group were fed normally.

1.2 Detection of left ventricular function

The left ventricular function including LVEDd, FS and LVEF was measured by Doppler echocardiography.

1.3 Immunohistochemistry and protein expression

In the process of immunohistochemistry, the computer pathological image analysis system was used for modular analysis. Under the high-power microscope, the protein expression of TN-X, LOX-1, the proportion of SMAD-3 and smad-7 were selected and calculated, and the average value was taken as the relative content of the three indicators. Western blotting was used to detect the expression of the three indicators.

1.4 Statistical methods

The data obtained in this study were statistically processed by SPSS 20.0 software. The comparison among the three groups was tested by t test and chi square test. When the test results were $P<0.05$, the difference was statistically significant.

2 Results

2.1 Ultrasound results

After 16 weeks, cardiac function and CVF value of rats in normal control group and alcoholic cardiomyopathy group were detected respectively. It was found that CVF and LVEDd of alcohol group were higher than those of observation group, while FS and LVEF were lower. The comparison of relevant data is shown in Table 1.

Table 1. Comparison of relevant data between two groups of experiments

Group	LVEF(%)	LVEDd (mm)	FS(%)	CVF(%)
Alcohol group	40±5	7.2±0.8	17.2±2.6	8.1±1.8
Observation group	58±9	4.6±0.2	44.6±3.2	3.2±1.3

As for Masson chromosome, the alcohol group compared with the other three groups, collagen hyperplasia, blue deep staining, as shown in Figure 1.

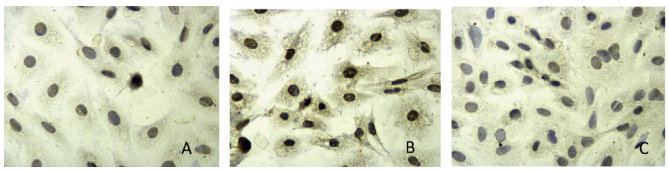

Figure 1. Masson chromosome. A: Normal control group; B: Alcoholic cardiomyopathy group; C: Drug intervention group.

2.2 The expression of TN-X, LOX-1 protein, smad-3 and smad-7 immunohistochemical staining

Among the three groups, the expression of LOX-1 in the intervention group was lower than that in the alcohol group, the degree of fibrosis was alleviated, the expression of LOX-1 in the alcohol group was higher than that in the observation group, the degree of fibrosis was aggravated, the expression rates of tn-x, LOX-1 protein and smad-3 in the alcohol group were higher than those in the observation group, the expression rates of TN-X (86% ± 7% vs 32% ± 10%), LOX-1 protein (82% ± 8% vs 61% ± 7%), smad-3

(83% ± 9% vs 30% ± 7%), and the correlation values of smad-7 were lower than those in the observation group The observation group (36% ± 8% vs 78% ± 9%) had statistical significance ($P < 0.05$).

2.3 Western blot detection index

The expression of LOX-1 protein and smad-3 index in the alcohol group was higher than that in the observation group, and only smad-7 was lower than that in the observation group. There were statistically significant differences in the three indexes between the two groups ($P<0.05$). The expression of LOX-1 and smad-3 protein in the drug intervention group was lower than that in the alcohol group, and the expression of smad-7 was higher than that in the alcohol group. There were statistically significant differences in the three indexes between the two groups ($P<0.05$), as shown in Figure 2.

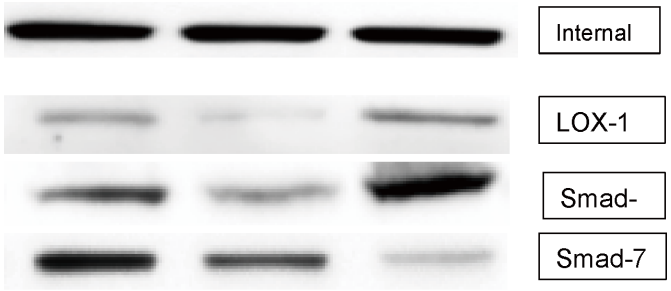

Figure 2. Western blot detection index

Normal control drug; Intervention group; Alcoholic cardiomyopathy group

3 Discussion

Candesartan is a kind of angiotensin II, which can be hydrolyzed into active metabolite in vivo AT1 receptor antagonist, which can reduce systolic and diastolic blood pressure, peripheral vascular resistance and left ventricular myocardial weight, has no obvious effect on ejection fraction, renal blood flow, cardiac output and renal vascular resistance. Candesartan can be used alone or in combination with other drugs. Rosuvastatin has a certain inhibitory effect on HMG-CoA reductase, which has been studied in rat and human liver microsomes as well as cloned and purified human HMG and CoA reductase fragments[1]. Related studies have shown that rosuvastatin has a stronger drug effect than other statins, and the research results in rat and human liver microsomes are extremely similar, which can adapt to hypercholesterolemia, hypercholesterolemia and related cardiovascular diseases, and reduce the risk of myocardial infarction[2-3].

In this study, through the comparison of the three groups of experiments, the rats were fed with alcohol for 16 weeks, and the LVEF, LVEDd and other related indicators were analyzed, which promoted the collagen proliferation and increased the protein expression of TN-X and LOX-1.The experimental results show that, through the analysis and comparison of three groups of experiments, the expression of LOX-1 protein in the alcohol group is higher than that in the observation group, and the degree of fibrosis in the alcohol group is heavier than that in the observation group. Compared with the alcohol group and the intervention group, the expression of LOX-1 protein in the alcohol group is higher than that in the intervention group, but the degree of fibrosis in the intervention group is lower than that in the alcohol group[4]. Therefore, by analyzing the protein expression of TN-X, LOX-1 and SMAD-3 and smad-7, it is concluded that the protein expression of TN-X, LOX-1 and SMAD-3 can promote fibrosis remodeling, and TN-X and LOX-1 are not only mediators, but also mediators of cell and matrix fibrosis together with collagen fibers. After research, TN-X and LOX-1 may promote the metabolism of fatty acids in myocardium together with alcohol, resulting in the disorder of myocardial energy synthesis, which easily leads to myocardial ischemia and hypoxia, and release cytokines and inflammatory mediators, thus indirectly promoting the secretion of TN-X and LOX-1 and myocardial fibrosis[3]. At the same time, the increase of some soluble inflammatory mediators in blood circulation is also a factor that stimulates the secretion of TN-X by related cells and organs.

In conclusion, through the comparison of three groups of experiments, LOX-1 expression increased in alcoholic cardiomyopathy group, which aggravated myocardial fibrosis of alcoholic cardiomyopathy and made the condition of alcoholic cardiomyopathy more serious. Compared with LOX-1 expression in alcoholic cardiomyopathy group, candesartan combined with rosuvastatin reduced alcoholic cardiomyopathy of rats It is in line with the main direction of this study to down regulate the expression of LOX-1 protein in myocardial fibrosis. Therefore, candesartan combined with rosuvastatin

has a positive effect on myocardial fibrosis in rats with alcoholic cardiomyopathy by mediating the expression of LOX-1, which is worthy of promotion and application.

References

[1] Li Q. Efficacy of rosuvastatin and clopidogrel bisulfate in the treatment of coronary heart disease [J]. CME, 2021,13 (03): 134-137.

[2] Chen W. Effect of candesartan combined with spironolactone on cardiac function and hemodynamics in patients with chronic heart failure [J]. World Composite Medicine, 2020,6(11): 181-183.

[3] Liu YC. Effect of candesartan combined with amiodarone on cardiac function and serum inflammatory factors in patients with heart failure and atrial fibrillation [J]. Chinese Modern Doctor, 2020,58 (31): 47-50.

[4] Zeng LT, Fan GQ, Ouyang QG, *et al*. Study on LOX-1 as a potential lung specific aging marker [J]. Journal of Medical Research, 2020, 49(7): 22-26.