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Short Communication

Effect of sodium houttuyfonate on myocardial hypertrophy in mice and rats

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Abstract

Objectives The aim of the study was to determine the effect of sodium houttuyfonate on myocardial hypertrophy and its mechanism of action in mice and rats.

Methods A mouse model of myocardial hypertrophy was established by subcutaneous injection with isoproterenol. Mice were randomly divided into five groups: normal control; isoproterenol control; isoproterenol plus metoprolol; isoproterenol plus low- and high-dose sodium houttuyfonate. A rat model of myocardial hypertrophy was established by intraperitoneal injection with L-thyroxine. Rats were randomly divided into five groups: normal control; L-thyroxine control; L-thyroxine plus captopril; L-thyroxine plus low- and high-dose sodium houttuyfonate. At the end of the experiments, the left ventricular weight index and heart weight index were determined in mice and rats, the size of cardiomyocytes was measured in rats and the concentrations of cAMP in plasma and angiotensin II in ventricular tissue of mice were detected by radioimmunoassay. The endothelin-1 concentration was measured by radioimmunoassay and the hydroxyproline content was measured by a digestive method in ventricular tissue of rats.

Key findings After 7–9 days of treatment, sodium houttuyfonate significantly reduced the left ventricular weight index and heart weight index in mice and rats with myocardial hypertrophy, decreased the size of cardiomyocytes in rats, and reduced the content of cAMP and angiotensin II in mice with myocardial hypertrophy. It also decreased the endothelin-1 concentration and the hydroxyproline content in ventricular tissue in rats.

Conclusions Sodium houttuyfonate can inhibit myocardial hypertrophy in mouse and rat models by restricting the activity of the sympathetic nervous system and decreasing the levels of angiotensin II and endothelin-1 in ventricular tissue.

Keywords angiotensin II; cAMP; endothelin-1; hydroxyproline; myocardial hypertrophy; sodium houttuyfonate

Introduction

Chronic heart failure is the endpoint of many types of cardiovascular disease. In patients with chronic heart failure, the myocardium adapts to an increased workload due to haemodynamic overload and resumes function through the compensated hypertrophy of individual cells, leading to left ventricular hypertrophy and remodelling. Initially, ventricular hypertrophy is beneficial for the heart to pump blood. However, chronic ventricular hypertrophy is an independent risk factor for heart failure, myocardial infarction, sudden death and other cardiovascular events. The degree of myocardial hypertrophy correlates well with mortality in patients with heart failure.[1,2] The search for drugs to inhibit myocardial hypertrophy and remodelling could lead to an important breakthrough in the prevention of myocardial infarction, heart failure and other cardiovascular diseases.

Sodium houttuyfonate ($CH_3(CH_2)_8COCH_2CHOHSO_3Na$), a general and economical compound, is synthesized by combining sodium bisulfite with decanoyl acetaldehyde ($CH_3(CH_2)_8COCH_2CHO$), which is a major compound in the volatile oil of the Chinese herb *Houttuynia cordata* Thunb. Sodium houttuyfonate can be synthesized entirely and economically.[3]

Sodium houttuyfonate presents many biological activities, including antibacterial activity, dilation of blood vessels, increase of urinary excretion and myocardium

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protection. Sodium houttuyfonate has been widely used in China for the clinical treatment of bronchitis and upper respiratory infection for many years. Experimental studies have demonstrated the broad biological activity of sodium houttuyfonate, including its antibacterial function[4,5] and adjuvanticity function[6]. Based on its ability to dilate blood vessels and its restraining effect on the spasmodic coronary artery, *H. cordata* can be used in cases of coronary heart disease.[7] *H. cordata* and decanoyl acetaldehyde can also be used in treating pulmonary heart disease,[8,9] owing to their ability to reduce pulmonary artery hypertension by dilating capillary vessels.[7] *H. cordata* can also protect the myocardium against injury induced by endotoxin.[10] However, the effect of sodium houttuyfonate on inhibiting myocardial hypertrophy has not been reported. In this study, we demonstrate for the first time *in vivo* that sodium houttuyfonate attenuates myocardial hypertrophy induced by isoproterenol in mice and L-thyroxine in rats.

Materials and Methods

Animals

Male Kunming mice (20–22 g) and male Sprague-Dawley rats (150–170 g, specific pathogen-free animals) were supplied by Shanghai Experimental Animal Center, Chinese Academy of Sciences, China. All animals were maintained under constant conditions: temperature 23 ± 1°C; humidity 40 ± 5%; 12-h light/dark cycle. All animals received humane care and had free access to a standard diet and drinking water. The animal experiments were approved by the Animal Care and Use Committee of Shanghai University of Traditional Chinese Medicine.

Drugs

Sodium houttuyfonate (lot no. 070103) was supplied by Shanghai Qingping Pharmaceutical Co., Ltd (Shanghai, China). Isoproterenol injection (lot no. 5E20010) was from Shanghai Harvest Pharmaceutical Co., Ltd (Shanghai, China). Metoprolol (lot no. 0605002) was from AstraZeneca Pharmaceutical Co., Ltd (Wuxi, China). L-Thyroxine (lot no. WA1331) was from Sigma Chemical Co. (St Louis, MO, USA) and captopril tablets (lot no. 061005) were from Shanghai Hengshan Pharmaceutical Co., Ltd (Shanghai, China).

Effect of sodium houttuyfonate on myocardial hypertrophy induced by isoproterenol in mice

Mice were randomly divided into five groups: the normal control group; the isoproterenol control group; the isoproterenol plus metoprolol (60 mg/kg) group; and the isoproterenol plus low (90 mg/kg) and high (180 mg/kg) dose sodium houttuyfonate groups. Mice in the normal control group were subcutaneously administered with 0.9% NaCl injection and the other mice were subcutaneously injected with isoproterenol daily at a dose of 2 mg/kg for 7 days. Mice in the drug treatment groups were administered with the appropriate drugs intragastrically for 7 days, while mice in the normal control group and the isoproterenol control group were treated with drinking water intragastrically for 7 days. All animals were weighed at the beginning and the end of the experiment.

Measurement of plasma cAMP concentration in mice

At the end of the experiment, blood samples were collected from the carotid artery into cuvettes containing the anticoagulant ethylene diamine tetraacetic acid. Whole blood was centrifuged (4°C, 2325*g*, 10 min) to recover plasma and stored at –70°C before assay. The cAMP concentration in plasma was determined by a radioimmunological assay. Plasma cAMP was expressed as concentration/ml plasma.

Measurement of cardiac indices in mice

Mouse bodyweight was recorded at the end of the experiment after fasting for 16 h. After collection of blood samples, all animals were killed by cervical dislocation. The hearts were taken out and then the left ventricle was separated from the atria, aorta and adipose tissue. Heart weight and left ventricle weight (LVW) were measured and then left ventricular weight index (LVWI) and heart weight index (HWI) were estimated by calculating heart weight/bodyweight or LVW/bodyweight ratio. The myocardial tissue was divided into several parts, rapidly frozen in liquid nitrogen and then stored at –70°C until assay.

Measurement of angiotensin II concentration in left ventricular tissue of mice

Ventricular tissue (40 mg) was homogenized with 2 ml cool 0.9% NaCl and centrifuged (4°C, 1780*g*, 15 min). The supernatants were analysed with an iodine [^{125}I] angiotensin II radioimmunoassay kit (Beijing Puerweiye Biology and Technology Co. Ltd, Beijing, China). The sensitivity of the assay was 10 pg/ml. The interassay variation was less than 10% and the intra-assay variation was less than 5%. Tissue angiotensin II was expressed as concentration/mg protein of ventricular tissue.

Effect of sodium houttuyfonate on the myocardial hypertrophy induced by L-thyroxine in rats

Rats were randomly divided into five groups: the normal control group; the L-thyroxine control group; the L-thyroxine plus captopril (40 mg/kg) group; L-thyroxine plus low (50 mg/kg) and high (100 mg/kg) dose sodium houttuyfonate groups. Rats in the normal control group received an intraperitoneal injection of 0.9% NaCl daily, while the other rats received an intraperitoneal injection of L-thyroxine daily at a dose of 0.25 mg/kg for 7 days. From the first day, rats in the drug treatment groups were administered intragastrically with the appropriate drugs for 9 days, while rats in the normal control group and the L-thyroxine control group were administered intragastrically with drinking water for 9 days.

Measurement of cardiac indices in rats

At the end of the experiment, all rats were weighed after fasting for 16 h and anaesthetized with urethane (1.0 g/kg i.p.). The hearts were taken out immediately and the left ventricle

was separated from the atria, aorta and adipose tissue. Heart weight and LVW were measured. HWI and LVWI were estimated by calculating heart weight/bodyweight or LVW/bodyweight ratio. The myocardial tissue was divided into several parts, rapidly frozen in liquid nitrogen and then stored at –70°C until assay.

Histological examination

The superior part of the left ventricular tissue was immersed in formalin (10% formaldehyde) then dehydrated and embedded in paraffin. Segments of ventricle were cut into 5-μm thick slices and heated overnight in a 60°C incubator. The sections were stained with haematoxylin and eosin for measurement of myocyte cross-section size. Each sample slice was photographed with an Olympus BX51 camera connected to a microscope (magnification 400×) and computer. They were analysed with image-Pro Plus 6.0 software (Media Cybernetics, Bethesda, MD, USA). About 30 cells per sample slice were randomly selected to calculate the average area of a single cell.

Measurement of endothelin-1 and hydroxyproline concentration in ventricular tissue of rats

Ventricular tissue (100 mg) was homogenized with 1 ml cool 0.9% NaCl and centrifuged (4°C, 1780*g*, 15 min). The supernatants were analysed with an iodine[^{125}I] endothelin-1 radioimmunoassay kit (Beijing Puerweiye Biology and Technology Co. Ltd). The sensitivity of the assay was 5 pg/ml. The interassay variation was less than 15% and the intra-assay variation was less than 10%. Tissue endothelin-1 was expressed as concentration/mg protein of ventricular tissue. The hydroxyproline content in the supernatants was measured by colorimetry with a spectrophotometer at a wavelength of 550 nm. The hydroxyproline concentration was expressed as concentration/mg protein of ventricular tissue.

Statistical analysis

All values are expressed as mean ± SD. Statistical analysis was performed by one-way analysis of variance for multiple comparisons, followed by Dunnett's test to evaluate the difference between two groups using SPSS 13.0 software. Values of $P < 0.05$ were considered statistically significant.

Table 1 Effect of sodium houttuyfonate on the cAMP concentration in plasma

Group	*n*	Dose (mg/kg)	cAMP (pmol/ml)
Normal control	9	–	60.850 ± 17.506
Isoproterenol control	11	–	167.654 ± 72.445**
Isoproterenol + sodium houttuyfonate	11	90	48.583 ± 17.155††
Isoproterenol + sodium houttuyfonate	11	180	45.099 ± 10.019††
Isoproterenol + metoprolol	11	60	71.580 ± 31.504††

Myocardial hypertrophy was induced by isoproterenol in mice. Results are presented as mean ± SD. $^{**}P < 0.01$, significantly different compared with the normal control group; $^{\dagger\dagger}P < 0.01$, significantly different compared with the isoproterenol control group.

Results

Effect of sodium houttuyfonate on myocardial hypertrophy induced by isoproterenol in mice

The cAMP concentration in plasma of mice in the isoproterenol control group was significantly higher than that of mice in the normal control group ($P < 0.01$). Treatment with 90 and 180 mg/kg sodium houttuyfonate or 60 mg/kg metoprolol for 7 days significantly reduced the cAMP concentration ($P < 0.01$) (Table 1).

Isoproterenol increased the HWI and the LVWI of mice in the isoproterenol control group compared with the normal control group ($P < 0.01$). After the mice were treated with sodium houttuyfonate (90 and 180 mg/kg) or metoprolol (60 mg/kg) for 7 days, the HWI and the LVWI were significantly reduced ($P < 0.05$) (Table 2).

In the isoproterenol control group, the angiotensin II concentration of the left ventricular tissue was significantly increased compared with the normal control group ($P < 0.01$). Treatment with sodium houttuyfonate (90 and 180 mg/kg) or metoprolol (60 mg/kg) significantly reduced the angiotensin II concentration ($P < 0.01$) (Table 3).

Effect of sodium houttuyfonate on myocardial hypertrophy induced by L-thyroxine in rats

L-Thyroxine increased the HWI and LVWI of rats in the L-thyroxine control group compared with the normal control group ($P < 0.01$). The HWI and the LVWI were reduced

Table 2 Effect of sodium houttuyfonate on cardiac indices in mice

Group	*n*	Dose (mg/kg)	Left ventricular weight index (mg/g)	Heart weight index (mg/g)
Normal control	11	–	3.418 ± 0.202	4.410 ± 0.226
Isoproterenol control	11	–	3.861 ± 0.197**	4.959 ± 0.234**
Isoproterenol + sodium houttuyfonate	11	90	3.687 ± 0.185†	4.663 ± 0.185††
Isoproterenol + sodium houttuyfonate	11	180	3.657 ± 0.201†	4.733 ± 0.219†
Isoproterenol + metoprolol	11	60	3.435 ± 0.287††	4.508 ± 0.300††

Myocardial hypertrophy was induced by isoproterenol in mice. Results are presented as mean ± SD. $^{**}P < 0.01$, significantly different compared with the normal control group; $^{\dagger}P < 0.05$, $^{\dagger\dagger}P < 0.01$, significantly different compared with the isoproterenol control group.

Table 3 Effect of sodium houttuyfonate on angiotensin II concentration of ventricular tissue in mice

Group	*n*	Dose (mg/kg)	Angiotensin II (pg/mg protein)
Normal control	11	–	48.754 ± 8.687
Isoproterenol control	11	–	67.816 ± 6.244**
Isoproterenol + sodium houttuyfonate	11	90	42.610 ± 7.539††
Isoproterenol + sodium houttuyfonate	11	180	50.265 ± 8.970††
Isoproterenol + metoprolol	11	60	45.295 ± 11.100††

Myocardial hypertrophy was induced by isoproterenol in mice. Results are presented as mean ± SD. $^{**}P < 0.01$, significantly different compared with the normal control group; $^{††}P < 0.01$, significantly different compared with the isoproterenol control group.

after the rats were treated with sodium houttuyfonate (50 and 100 mg/kg) or captopril (40 mg/kg) ($P < 0.05$) (Table 4).

The sections were stained with haematoxylin and eosin and photographed (Figure 1). The average transverse area of a single myocardial cell in the L-thyroxine control group was significantly larger than that in the normal group ($P < 0.01$), but it was attenuated in the sodium houttuyfonate and captopril groups ($P < 0.01$) (Table 5).

In the L-thyroxine control group, there was a significant increase in the hydroxyproline content compared with the normal control group ($P < 0.01$). Treatment with sodium houttuyfonate (50 mg/kg) or captopril (40 mg/kg) for 9 days significantly reduced the hydroxyproline content ($P < 0.05$) (Table 6).

The endothelin-1 concentration of left ventricular tissue in the L-thyroxine control group was significantly increased compared with the normal control group ($P < 0.01$). Treatment with sodium houttuyfonate (50 and 100 mg/kg) or

Table 4 Effect of sodium houttuyfonate on cardiac indices in rats

Group	*n*	Dose (mg/kg)	Left ventricular weight index (mg/g)	Heart weight index (mg/g)
Normal control	9	–	2.802 ± 0.166	3.666 ± 0.180
L-Thyroxine control	10	–	3.977 ± 0.291**	5.191 ± 0.330**
L-Thyroxine + sodium houttuyfonate	10	50	3.712 ± 0.262†	4.886 ± 0.346†
L-Thyroxine + sodium houttuyfonate	10	100	3.702 ± 0.181†	4.820 ± 0.226††
L-Thyroxine + captopril	10	40	3.435 ± 0.366††	4.519 ± 0.501††

Myocardial hypertrophy was induced by L-thyroxine in rats. Results are presented as mean ± SD. $^{**}P < 0.01$, significantly different compared with the normal control group; $^{†}P < 0.05$, $^{††}P < 0.01$, significantly different compared with the L-thyroxine control group.

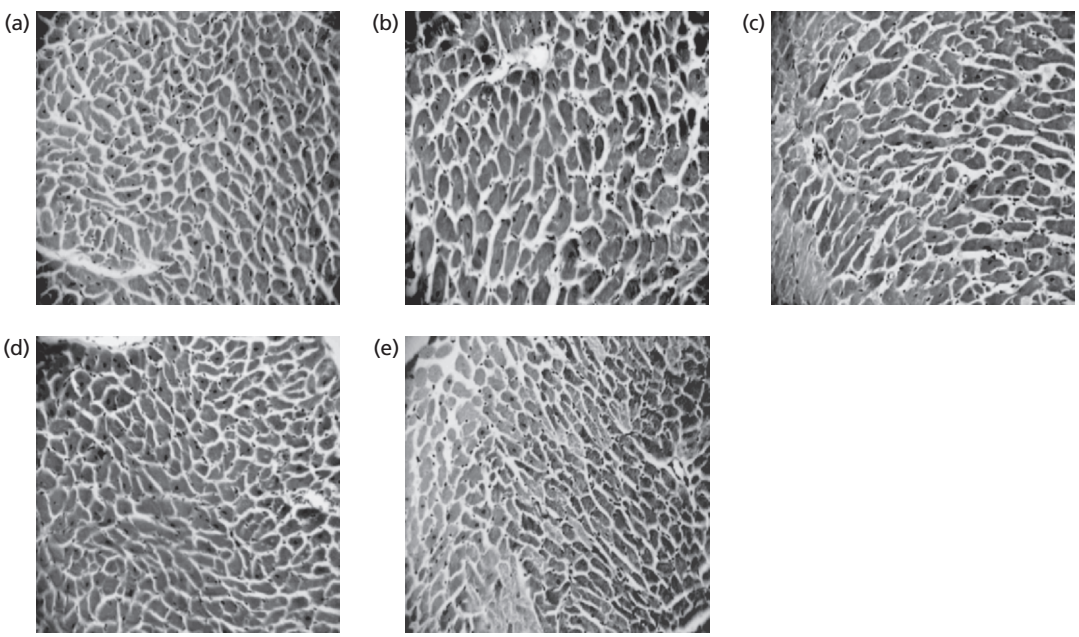

Figure 1 Effect of sodium houttuyfonate on the transverse area of myocardial cells. Myocardial hypertrophy was induced by L-thyroxine in rats. (a) Normal control group; (b) L-thyroxine control group; (c) L-thyroxine plus 50 mg/kg sodium houttuyfonate group; (d) L-thyroxine plus 100 mg/kg sodium houttuyfonate group; (e) L-thyroxine plus 40 mg/kg captopril group.

Table 5 Effect of sodium houttuyfonate on the transverse area of single myocardial cells in rats

Group	*n*	Dose (mg/kg)	Area of single myocardial cell (μm^2/cell)
Normal control	6	–	2349.7 ± 349.3
L-Thyroxine control	6	–	3447.7 ± 451.9**
L-Thyroxine + sodium houttuyfonate	6	50	2558.3 ± 456.6††
L-Thyroxine + sodium houttuyfonate	6	100	2470.0 ± 434.9††
L-Thyroxine + captopril	6	40	2212.6 ± 159.0††

Myocardial hypertrophy was induced by L-thyroxine in rats. Results are presented as mean ± SD. **$P < 0.01$, significantly different compared with the normal control group; $^{\dagger\dagger}P < 0.01$, significantly different compared with the L-thyroxine control group.

Table 6 Effect of sodium houttuyfonate on hydroxyproline concentration of ventricular tissue in rats

Group	*n*	Dose (mg/kg)	Hydroxyproline (μg/mg protein)
Normal control	9	–	0.378 ± 0.083
L-Thyroxine control	10	–	0.490 ± 0.080**
L-Thyroxine + sodium houttuyfonate	10	50	0.400 ± 0.0396††
L-Thyroxine + sodium houttuyfonate	10	100	0.440 ± 0.109
L-Thyroxine + captopril	9	40	0.351 ± 0.147†

Myocardial hypertrophy was induced by L-thyroxine in rats. Results are presented as mean ± SD. **$P < 0.01$, significantly different compared with the normal control group; $^{\dagger}P < 0.05$; $^{\dagger\dagger}P < 0.01$, significantly different compared with the L-thyroxine control group.

Table 7 Effect of sodium houttuyfonate on endothelin-1 concentration of ventricular tissue in rats

Group	*n*	Dose (mg/kg)	Endothelin-1 (pg/mg protein)
Normal control	9	–	45.312 ± 24.752
L-Thyroxine control	10	–	123.810 ± 36.455**
L-Thyroxine + sodium houttuyfonate	10	50	71.179 ± 27.274††
L-Thyroxine + sodium houttuyfonate	10	100	56.239 ± 21.895††
L-Thyroxine + captopril	9	40	51.929 ± 16.265††

Myocardial hypertrophy was induced by L-thyroxine in rats. Results are presented as mean ± SD. **$P < 0.01$, significantly different compared with the normal control group; $^{\dagger\dagger}P < 0.01$, significantly different compared with the L-thyroxine control group.

captopril (40 mg/kg) for 9 days significantly reduced the endothelin-1 concentration ($P < 0.01$) (Table 7).

Discussion

Myocardial hypertrophy is an independent risk factor for many cardiovascular events, and the degree of myocardial hypertrophy correlates well with mortality in patients with heart failure. The degree of cardiac hypertrophy in animal models is usually assessed by the increase of HWI, LVWI and the transverse area of cardiomyocytes.[11–14] In our study, the myocardial hypertrophy induced by isoproterenol in mice and by L-thyroxine in rats was clearly demonstrated by the increase in HWI, LVWI and the transverse area of cardiomyocytes. Treatment with sodium houttuyfonate restrained the increase of the HWI, LVWI and the transverse area of cardiomyocytes, suggesting that sodium houttuyfonate contributes to the attenuation of myocardial hypertrophy.

Studies have indicated that the progressive development of myocardial hypertrophy is related to neuroendocrine activation.[15,16] Neuroendocrine activation begins early after myocardial injury. In patients with heart failure, the neuroendocrine activation was expressed more intensively.[17] The activated neurohormones include the sympathetic system, the renin angiotensin system, aldosterone and endothelin.[18]

Restraining the neuroendocrine activation and the release of hormones are important factors in the treatment of myocardial hypertrophy. Animal studies and clinical trials have shown that neuroendocrine blockers, including β-blockers and angiotensin converting enzyme inhibitors, can attenuate ventricular hypertrophy.

In heart failure, sympathetic nervous system activation in the heart is excessively increased.[19] Excessive stimulation of β- and α-1 receptors leads to transcription factor production and gene expression changes, leading to myocardial hypertrophy.[18] Isoproterenol is one of the stimulators of β-adrenergic receptors. It has been reported that isoproterenol administered for 7 days to rats can induce cardiomegaly,[20] and it has been frequently used as a pharmacological inducer in animal studies of cardiac hypertrophy.[12,13] Myocardial hypertrophy induced by isoproterenol demonstrates the increase of left ventricle weight,[12,13] which is relative to cardiac content of protein, β-myosin heavy chain level, RNA/DNA ratio and hydroxyproline. Moreover, isoproterenol-induced myocardial hypertrophy involves growth of both muscle and connective tissue, and left ventricular pressure after hypertrophy induction is significantly increased.[21–24] Excitation of β-receptors activates adenylate cyclase, which converts ATP to cAMP, leading to protein kinase A activation and ultimately resulting in hypertrophy.[18] Our results showed that the cAMP concentration in plasma of mice treated with isoproterenol was significantly increased compared with that of normal mice. This indicates that sympathetic activation is stimulated by isoproterenol. The cAMP concentration in mice treated with sodium houttuyfonate was significantly reduced compared with that in isoproterenol control mice. Metoprolol, a β-adrenergic receptor blocker, also reduced the cAMP concentration. This result suggested that the inhibition by sodium houttuyfonate of myocardial hypertrophy induced by isoproterenol was related to its control of sympathetic activation.

The renin angiotensin system plays a key role in the pathophysiology of myocardial hypertrophy.[25] In the renin angiotensin system, angiotensin II is one of the principal effectors and mediators. It can affect cardiovascular structure, growth and fibrosis.[26,27] Inhibition of angiotensin

II synthesis with an angiotensin converting enzyme inhibitor has been demonstrated to be beneficial in modifying the progress of human cardiovascular remodelling disease.

Isoproterenol can induce differential expression of angiotensin converting enzyme[24] and endogenous angiotensin II has a major function in maintaining isoproterenol-induced myocardial hypertrophy.[23] In our study, isoproterenol induced a significant increase in the angiotensin II concentration. Treatment with sodium houttuyfonate for 7 days reduced the angiotensin II concentration, indicating that the function of sodium houttuyfonate in antagonizing myocardial hypertrophy correlated with its inhibition of the renin angiotensin system.

The correlation between thyroid disease and cardiopathy, that is the importance of the cardiac manifestations in thyrotoxicosis, has been widely acknowledged, particularly the influence of thyroid hormones in relation to myocardial hypertrophy.[28,29] L-Thyroxine can induce an increase in the total amount of nucleic acids in the myocardium and enhancement of the RNA synthesis rate in rats,[30] and can increase protein synthesis in the heart.[14]

Most factors that induce myocardial hypertrophy cause simultaneous changes in haemodynamics. Thyroid hormones have a different effect on haemodynamics. Chronic hyperthyroidism has typically been associated with simultaneous increases in blood pressure. However, in short-term treatment, thyroid hormones do not affect haemodynamic parameters.[14,31] This indicates that at the early stage of the cardiac hypertrophy, haemodynamic parameters do not change obviously, and our study confirmed this.

L-Thyroxine-induced myocardial hypertrophy is a widely used model of myocardial hypertrophy.[31–33] The myocardial hypertrophy in the L-thyroxine treated group was demonstrated by the increase in the LVWI and HWI, which were about 41% greater than in the normal group. The results of both direct and indirect actions of thyroid hormone on the myocardium are expressed by the increase in protein synthesis.[14] Otherwise, thyroid hormones can alter the collagen matrix.[34] The area of myocytes was 46.7% greater than that of the normal control group. The high hydroxyproline concentration suggested cardiac fibrosis. It plays a pivotal role in the transition from compensation to decompensation of heart function.[35]

After rats were treated for 9 days with sodium houttuyfonate, the cardiac indices, the mean transverse area of the myocytes and hydroxyproline content of the left ventricular tissue were significantly reduced. These results confirm that sodium houttuyfonate attenuates the hypertrophy and fibrosis induced by L-thyroxine.

Endothelin-1 is a potent vasoconstrictor hormone, which takes part in the pathogenesis of myocardial hypertrophy. There are endothelin-1 receptors in cardiac tissue.[36] Plasma endothelin-1 levels are increased in symptomatic patients with chronic heart failure.[37] In our experiment, L-thyroxine increased the endothelin-1 concentration of left ventricular tissue, while treatment with sodium houttuyfonate significantly reduced it. This results indicates that the function of sodium houttuyfonate in antagonizing myocardial hypertrophy correlated with its inhibition of myocardial fibrosis and the reduction of endothelin-1 in rats.

Conclusions

Sodium houttuyfonate can inhibit myocardial hypertrophy induced by isoproterenol in mice and by L-thyroxine in rats. Sodium houttuyfonate can also decrease the concentration of hydroxyproline in ventricular tissue of rats, which suggests that it could prevent cardiac fibrosis. The beneficial effects of sodium houttuyfonate are at least in part mediated by restraining the activation of the renin angiotensin system, the activity of the sympathetic nervous system and endothelin-1. This suggests that several regulatory pathways participate respectively or correlatively in the effect of sodium houttuyfonate in attenuating myocardial hypertrophy.

Declarations

Conflict of interest

The Author(s) declare(s) that they have no conflicts of interest to disclose.

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References

1. Fuster V *et al*. The natural history of idiopathic dilated cardiomyopathy. *Am J Cardiol* 1981; 47: 525–531.
2. Schillaci G *et al*. Continuous relation between left ventricular mass and cardiovascular risk in essential hypertension. *Hypertension* 2000; 35: 580–586.
3. Yang J *et al*. Synthesis of sodium houttuyfonate. *West China J Pharm Sci* 2005; 20: 30–31.
4. Cheng X *et al*. Initial study on sodium houttuyfonate (injectable powder): antimicrobial activity *in vitro*. *Lishizhen Med Materia Med Res* 2005; 16: 465–466.
5. Zhao Z *et al*. Antimicrobial activity of berberine hydrochloride, sodium houttuyfonate and allicin *in vitro*. *Chin J Clin Pharmacol* 2005; 21: 119–121.
6. Wang D *et al*. Studies on adjuvanticity of sodium houttuyfonate and its mechanism. *Int Immunopharmacol* 2002; 2: 1411–1418.
7. Wang JY, Fan SK. Clinical application of herba houttuyniae injection. *Beijing J Tradit Chin Med* 1999; 4: 61–62.
8. Gan B. Observation on the effect of herba houttuyniae injection treatment in cases with pulmonary heart disease (in acute period) through atomizing inhalation. *J Chin Physician* 2004; 32: 45–46.
9. Guan LP, Xia SX. Observation on the effect of herba houttuyniae injection treatment in 92 cases with pulmonary heart disease. *J Clin Pulmonary Med* 2004; 9: 369
10. Wang HH *et al*. Experimental study on herba houttuyniae injection against myocardial injury induced by endotoxin. *Chin J Pathophysiol* 2004; 20: 387–390.
11. Iaccarino G *et al*. Beta-adrenergic receptor kinase-1 levels in catecholamine-induced myocardial hypertrophy: regulation by beta- but not alpha1-adrenergic stimulation. *Hypertension* 1999; 33: 396–401.
12. Morisco C *et al*. Beta-adrenergic cardiac hypertrophy is mediated primarily by the beta(1)-subtype in the rat heart. *J Mol Cell Cardiol* 2001; 33: 561–573.
13. Hohimer AR *et al*. Repeated daily injections and osmotic pump infusion of isoproterenol cause similar increases in cardiac mass

but have different effects on blood pressure. *Can J Physiol Pharmacol* 2005; 83: 191–197.
14. Kuzman JA *et al*. Rapamycin prevents thyroid hormone-induced cardiac hypertrophy. *Endocrinology* 2007; 148: 3477–3484.
15. Schlaich MP *et al*. Relation between cardiac sympathetic activity and hypertensive left ventricular hypertrophy. *Circulation* 2003; 108: 560–565.
16. Burns J *et al*. Relationship between central sympathetic drive and magnetic resonance imaging-determined left ventricular mass in essential hypertension. *Circulation* 2007; 115: 1999–2005.
17. Dúbrava J, Cagán S. Neurohumoral activation and remodeling after acute myocardial infarct and the effect of angiotensin-converting enzyme inhibitors. *Bratisl Lek Listy* 1993; 94: 88–93.
18. Remme WJ. Pharmacological modulation of cardiovascular remodeling: a guide to heart failure therapy. *Cardiovasc Drugs Ther* 2003; 17: 349–360.
19. Esler M *et al*. Assessment of human sympathetic nervous system activity from measurements of norepinephrine turnover. *Hypertension* 1988; 11: 3–20.
20. Szabó J *et al*. Experimental cardiac hypertrophy induced by isoproterenol in the rat. *Acta Physiol Acad Sci Hung* 1975; 46: 281–285.
21. Taylor PB, Tang Q. Development of isoproterenol-induced cardiac hypertrophy. *Can J Physiol Pharmacol* 1984; 62: 384–389.
22. Tang Q *et al*. Catecholamine induced cardiac hypertrophy. *Can J Cardiol* 1987; 3: 311–316.
23. Golomb E *et al*. Angiotensin II maintains, but does not mediate, isoproterenol-induced cardiac hypertrophy in rats. *Am J Physiol* 1994; 267: H1496–H1506.
24. Ocaranza MP *et al*. Isoproterenol and angiotensin I-converting enzyme in lung, left ventricle, and plasma during myocardial hypertrophy and fibrosis. *J Cardiovasc Pharmacol* 2002; 40: 246–254.
25. Weir MR, Dzau VJ. The renin-angiotensin-aldosterone system: a specific target for hypertension management. *Am J Hypertens* 1999; 12: 205S–213S.
26. Adams KF, Jr. Pathophysiologic role of the renin-angiotensin-aldosterone and sympathetic nervous systems in heart failure. *Am J Health-Syst Pharm* 2004; 61: S4–S13.
27. Duprez DA. Role of the renin-angiotensin-aldosterone system in vascular remodeing and inflammation: a clinical review. *J Hypertens* 2006; 24: 983–991.
28. Kahaly GJ, Dillmann WH. Thyroid hormone action in the heart. *Endocr Rev* 2005; 26: 704–728.
29. Klein I, Danzi S. Thyroid disease and the heart. *Circulation* 2007; 116: 1725–1735.
30. Karsanov NV *et al*. Regulation of RNA synthesis in the rat heart in L-thyroxine toxicosis and hypothyroidism; the role of RNA-polymerases and the template activity of chromatin. *Ukr Biokhim Zh* 1986; 58: 8–15.
31. Hu LW *et al*. Myocardial ultrastructure in cardiac hypertrophy induced by thyroid hormone – an acute study in rats. *Virchows Arch* 2005; 446: 265–269.
32. Sanford CF *et al*. Synthesis and degradation of myocardial protein during the development and regression of thyroxine-induced cardiac hypertrophy in rats. *Circ Res* 1978; 43: 688–694.
33. Fernandes ML *et al*. Spironolactone effects on myocardium changes induced by thyroid hormone in rats. *Arq Bras Cardiol* 2007; 89: 398–402.
34. Heide SM *et al*. Metabolism of thyroid hormones in cultured cardiac fibroblasts of neonatal rats. *J Endocrinol* 2002; 174: 111–119.
35. Brown RD *et al*. The cardiac fibroblast: therapeutic target in myocardial remodeling and failure. *Annu Rev Pharmacol Toxicol* 2005; 45: 657–687.
36. Slătineanu L *et al*. Correlation between plasma level of endothelin-1 and heart remodeling in dilated cardiomyopathy. *Rev Med Chir Soc Med Nat Iasi* 2007; 111: 345–351.
37. Kinugawa T *et al*. Plasma endothelin-1 levels and clinical correlates in patients with chronic heart failure. *J Card Fail* 2003; 9: 318–324.