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Pharmacological and Nonpharmacological Treatments for Cardiac Hypertrophy

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Abstract

Cardiac hypertrophy is an adaptive response of the heart to a large variety of extrinsic and intrinsic stimuli, including maladaptive remodeling in response to pathological conditions or to a physiological stimulus such as exercise training. In spite of the cardiac remodeling, classical features differ the pathological and physiological cardiac hypertrophy, in which the pathological remodeling has been associated with several cardiovascular diseases such as heart failure, a major cause of morbidity and mortality. However, there is still no consensus regarding therapies for the treatment of cardiac hypertrophy. In line with the imperative need for new strategies for its treatment, this review is focused on the importance of cholinergic signaling regulation by conventional and alternative drug therapies as well as in the beneficial contribution of exercise as a nonpharmacological approach.

Keywords: Cardiac hypertrophy; Cardiovascular diseases; Cholinergic signaling; Natural products; Physical training; Aerobic and resistance exercise

Introduction

Hypertrophic remodeling accompanies many forms of heart disorders, including ischemic disease, hypertension, and heart failure, affecting the morbidity and mortality worldwide [1]. Despite several signaling pathways are involved in the onset and progression of cardiac hypertrophy, β-adrenergic signaling pathway emerges as one of the major players of maladaptive remodeling in the heart [2]. Nevertheless, in contrast to the pathological cardiac remodeling the physiological hypertrophy is found in athletes of many modalities of sports, due to neurohormonal, endothelial, and electrophysiological mechanisms, in which has been positively correlated with increased cardiovascular morbidity and mortality [3]. In spite of the unfavorable prognostic in patients with cardiac diseases, intense research efforts have been developed to promote novel strategies that may improve the efficiency of cardiac hypertrophy therapies. In this mini-review, we briefly highlighted the importance of cholinergic signaling regulation by conventional and alternative drug therapies as well as the beneficial contribution of exercise as a nonpharmacological approach for the treatment of cardiac diseases.

Pharmacological treatments for cardiac hypertrophy

A distinctive hallmark of cardiac hypertrophy is the autonomic imbalance, particularly through increased sympathetic activity associated with parasympathetic tone withdrawal [4]. Indeed, activation of parasympathetic cholinergic activity in the heart plays a pivotal role in the cardiac function and may have beneficial implications in the development of cardiac hypertrophy and heart failure [5,6]. Recently, it was demonstrated that cardiomyocyte expresses all components of cholinergic machinery [7] and, the local synthesis of acetylcholine (ACh) by ventricular myocyte plays a protective role against the deleterious effects of chronic adrenergic stimulation *in- vitro* and *in-vivo*. Altogether, these studies support the notion that enhanced cholinergic function represents a cardioprotective action, by opposing sympathetic actions at both pre- and post-junctional levels.

A growing body of evidence has shown a beneficial correlation of augmented systemic ACh levels through cholinesterase inhibitors treatment with decreased cardiac disease [8]. Accordingly, pyridostigmine, a cholinesterase inhibitor, inhibited cardiac remodeling induced by isoproterenol,

a β-adrenergic receptor agonist, by restoration of ACh availability. Moreover, short-term treatment of pyridostigmine has been also linked with decreased ventricular arrhythmias in patients with congestive heart failure [9]. Although the precise mechanisms by which cholinesterase inhibitors promote cardiac protection is still not fully understood, the direct enhancement of ACh levels appears as adecisive factor in the reduced cardiac remodeling and dysfunction [10]. In line with this hypothesis, amelioration of hypertrophic response induced by transverse aortic constriction has been shown in mice orally treated with choline via a mechanism dependent of a specific miRNA, miR-133a.

Some therapeutic areas, including the field of cardiovascular diseases, has not benefited as broadly from natural product discovery programs. However, there are a few notable exceptions. Recently, our group has uncovered a new mechanism involved in the cardioprotective action of Ginkgo biloba. Our results demonstrate that Ginkgo biloba counteracts the deleterious cardiac actions of sustained β-adrenergic receptor activation by preventing autonomic imbalance, myocardial remodeling, aberrant electrocardiographic waveforms and ventricular dysfunction. The main finding of this study was that part of the remarkable anti hypertrophic effect of Ginkgo biloba occurs by activation of the M2/NO pathway [11]. As the most abundant flavonoid present in Ginkgo biloba, quercetin (3,3',4',5,7-pentahydroxyflavone) has been demonstrated to possess multiple beneficial biological actions including anti oxidative [12], anti-inflammatory [13] and anti hypertrophic effect [14].

Accordingly, the cardioprotective action of quercetin against cardiac hypertrophy induced by pressure overload occurs via reduction of oxidant status and inhibition of ERK1/2, p38 MAP kinase, Akt and GSK-3β activities. Intriguingly, it was recently shown that quercetin activates β-adrenoceptors in isolated ventricular myocytes, leading to increased L-type Ca2+ current and cell-wide intracellular Ca^{2+} transient without changes in Ca^{2+} sparks, in which has been in involved in the onset of arrhythmias [15].

Nonpharmacological treatments for cardiac hypertrophy

Despite cardiac hypertrophy is mainly associated with a pathological remodeling. Physical training, well known to improve aerobic capacity or increase strength, also promotes cardiac remodeling, producing distinct morphometric changes, depending on the type of training performed. However, regardless of the exercise modality, aerobic or strength, both promote the improvement of cardiac function, unlike the pathological hypertrophy (known as athlete's heart).Thus, in view of the evidence and increased knowledge showing the beneficial effects of exercise on the cardiovascular system [16,17], physical training has been suggested as a compelling nonpharmacological strategy for treatment and/or prevention of the development of pathological cardiac hypertrophy [18].

Even in the face of increasing research investigating the outcomes of strength training, few studies have explored its effects on pathological cardiac hypertrophy. Alves et al. [19] demonstrated in an experimental model of heart failure that strength training for eight weeks, with progressive intensity (65 to 75% of maximal overload), led to an improvement of hemodynamic function, reduction of collagen deposition in the left ventricle, enhancement of anti-inflammatory profile and, consequently, attenuation of cardiac hypertrophy. However, the mechanism by which strength training promotes this improvement was not investigated. Aerobic training has been also recommended for treatment of pathological cardiac hypertrophy [20]. Intriguingly, this modality of exercise was able to convert pathological into physiological cardiac hypertrophy by reduction of collagen deposition, apoptosis and increasing capillary density of the myocardium through, at least in part, by down regulation of calcineurin activity.

Moreover, restoration of left ventricular systolic function induced by aerobic training has been associated with increased SERCA2a expression, leading to an enhancement of Ca2+ reuptake into the sarcoplasmic reticulum of cardiomyocytes and thus, representing an underlying mechanism involved in the exercise-mediated cardio protection. Interestingly, in a recent and robust randomized clinical trial [21] investigating the effects of moderate-intensity aerobic training in patients with hypertrophic cardio myopathy, it was found that the training did not trigger deleterious effects, such as sustained ventricular arrhythmia, sudden cardiac arrest, appropriate defibrillator shock or death. In sharp contrast, moderate-intensity aerobic training led to a further improving the aerobic capacity, which is an important prognosis of reduces the risk of death in patients with hypertrophic cardiomyopathy. Furthermore, physical training in both modalities, aerobic and strength, has been shown to positively regulate renin angiotensin aldosterone system [22,23], a pivotal mechanism involved in the pathological cardiac hypertrophy, as well as a critical modulator of the autonomic nervous system [16,24]. Recent evidence [25] also points the influence of epigenetic regulation of myomiRs induced by aerobic training, mainly through inhibition of miR-208a and miR-208b, which are involved in the development of pathological cardiac hypertrophy [26]. In a meta-epidemiological [27] study of 16 meta-analyses including 305 randomized controlled trials with 339 274 participants, it was found that despite having fewer trials evaluated exercise than drugs and fewer people participated in exercise trials, exercise was predicted with similar effectiveness than drug interventions.

Conclusion

Despite the regulation of cholinergic signaling appears as a novel, unexplored and promising signaling pathway

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involved in the treatment of cardiac diseases, clinical trials are certainly needed to further evaluate the potential benefits of pharmacological therapies derived, or not, from natural sources at different stages of cardiac hypertrophy. As an alternative tool, exercise training, in both modalities, has been shown to modulate several signaling pathways that are closely involved in the treatment of cardiac hypertrophy. Thus, albeit it is necessary more studies to investigate the mechanism by which exercise training causes beneficial actions, the best settings of exercise training, such as intensity and volume, emerge as critical adjustments for prescription of safer cardiovascular limits. Moreover, although not discussed here, the current therapies for cardiac hypertrophy and/or heart failure are based on clinical features and symptomatic alleviation. Thus, the formidable advances in molecular technologies, mainly high-throughput sequencing, have allowed the identification of potential genes involved in the development and/or progression of cardiomyopathy, in which certainly deserve great attention.

References

1. Frey N, Katus HA, Olson EN, Hill JA (2004) Hypertrophy of the heart: a new therapeutic target? Circulation 109(13): 1580-1589.
2. Krenek P, Kmecova J, Kucerova D, Bajuszova Z, Musil P, et al. (2009) Isoproterenol-induced heart failure in the rat is associated with nitric oxide-dependent functional alterations of cardiac function. Eur J Heart Fail 11(2): 140-146.
3. Pelliccia A, Maron MS, Maron BJ (2012) Assessment of left ventricular hypertrophy in a trained athlete: differential diagnosis of physiologic athlete's heart from pathologic hypertrophy. Prog Cardiovasc Dis 54(5): 387-396.
4. Desai MY, Watanabe MA, Laddu AA, Hauptman PJ (2011) Pharmacologic modulation of parasympathetic activity in heart failure. Heart Fail Rev 16(2): 179-193.
5. Gavioli M, Lara A, Almeida PW, Lima AM, Damasceno DD, et al. (2014) Cholinergic signaling exerts protective effects in models of sympathetic hyperactivity-induced cardiac dysfunction. PLoS One 9(7): e100179.
6. Li M, Zheng C, Sato T, Kawada T, Sugimachi M, et al. (2004) Vagal nerve stimulation markedly improves long-term survival after chronic heart failure in rats. Circulation 109(1): 120-124.
7. Rocha RC, Roy A, Resende R, Ladeira MS, Lara A, et al. (2012) Non-neuronal cholinergic machinery present in cardiomyocytes offsets hypertrophic signals. J Mol Cell Cardiol 53(2): 206-216.
8. Zhao Y, Wang C, Wu J, Wang Y, Zhu W, et al. (2013) Choline protects against cardiac hypertrophy induced by increased after-load. Int J Biol Sci 9(3): 295-302.
9. Behling A, Moraes RS, Rohde LE, Ferlin EL, Nobrega AC, et al. (2003) Cholinergic stimulation with pyridostigmine reduces ventricular arrhythmia and enhances heart rate variability in heart failure. Am Heart J 146(3): 494-500.
10. Roy A, Guatimosim S, Prado VF, Gros R, Prado MA (2015) Cholinergic activity as a new target in diseases of the heart. Mol Med 20: 527-37.
11. Mesquita T, Jesus I, Santos J, Almeida G, Vasconcelos C, et al. (2017) Cardioprotective action of Ginkgo biloba extract against sustained β-adrenergic stimulation occurs via activation of M2/NO pathway. Front Pharmacol 8(220).
12. Wang W, Sun C, Mao L, Ma P, Liu F, et al. (2016) The biological activities, chemical stability, metabolism and delivery systems of quercetin: A review. Trends in Food Science & Technology 56: 21-38.
13. Jin HB, Yang YB, Song YL, Zhang YC, Li YR (2012) Protective roles of quercetin in acute myocardial ischemia and reperfusion injury in rats. Mol Biol Rep 39(12): 11005-11009.
14. Han JJ, Hao J, Kim CH, Hong JS, Ahn HY, Lee YS (2009) Quercetin prevents cardiac hypertrophy induced by pressure overload in rats. J Vet Med Sci 71(6): 737-43.
15. Santos MS, Oliveira ED, Santos MA, Cruz JS, Gondim AN, et al. (2016) Dissection of the Effects of Quercetin on Mouse Myocardium. Basic Clin Pharmacol Toxicol 120(6): 550-559.
16. Macedo FN, Mesquita TR, Melo VU, Mota MM, Silva TL, et al. (2016) Increased Nitric Oxide Bioavailability and Decreased Sympathetic Modulation Are Involved in Vascular Adjustments Induced by Low-Intensity Resistance Training. Front Physiol 7: 265.
17. Mota MM, Mesquita TR, Braga STL, Fontes MT, Lauton SS, et al. (2015) Endothelium adjustments to acute resistance exercise are intensity-dependent in healthy animals. Life sciences 142: 86-91.
18. McMullen JR, Jennings GL (2007) Differences between pathological and physiological cardiac hypertrophy: novel therapeutic strategies to treat heart failure. Clin Exp Pharmacol Physiol 34(4): 255-262.
19. Alves JP, Nunes RB, Stefani GP, Dal Lago P (2014) Resistance training improves hemodynamic function, collagen deposition and inflammatory profiles: experimental model of heart failure. PLoS One 9(10): e110317.
20. Garciarena CD, Pinilla OA, Nolly MB, Laguens RP, Escudero EM, et al. (2009) Endurance training in the spontaneously hypertensive rat: conversion of pathological into physiological cardiac hypertrophy. Hypertension 53(4): 708-714.
21. Saberi S, Wheeler M, Bragg GJ, Hornsby W, Agarwal PP, et al. (2017) Effect of Moderate-Intensity Exercise Training on Peak Oxygen Consumption in Patients With Hypertrophic Cardiomyopathy: A Randomized Clinical Trial. JAMA 317(13): 1349-1357.
22. Barauna VG, Magalhaes FC, Krieger JE, Oliveira EM (2008) AT1 receptor participates in the cardiac hypertrophy induced by resistance training in rats. Am J Physiol Regul Integr Comp Physiol 295(2): R381-387.
23. Oliveira EM, Sasaki MS, Cerencio M, Barauna VG, Krieger JE (2009) Local renin-angiotensin system regulates left ventricular hypertrophy induced by swimming training independent of circulating renin: a pharmacological study. J Renin Angiotensin Aldosterone Syst 10(1): 15-23.
24. Sanches IC, Conti FF, Bernardes N, Brito JO, Galdini EG, et al. (2015) Impact of combined exercise training on cardiovascular autonomic control and mortality in diabetic ovariectomized rats. J Appl Physiol 119(6): 656-662.
25. Soci UP, Fernandes T, Barauna VG, Hashimoto NY, Mota GF, et al. (2016) Epigenetic control of exercise training-induced cardiac hypertrophy by miR-208. Clin Sci (Lond) pii: CS20160480.
26. Satoh M, Minami Y, Takahashi Y, Tabuchi T, Nakamura M (2010) Expression of microRNA-208 is associated with adverse clinical outcomes in human dilated cardiomyopathy. J Card Fail 16(5): 404-410.
27. Naci H, Ioannidis JP (2013) Comparative effectiveness of exercise and drug interventions on mortality outcomes: metaepidemiological study. Br J Sports Med 49(21): 1414-1422.

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