Parasitology

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Could pre-infection exercise training improve the efficacy of specific antiparasitic chemotherapy for Chagas disease?

Elda Gonçalves Santos[1], Reggiani V. Gonçalves[2], Thaiany G. Souza-Silva[1], Izabel R. S. C. Maldonado[3], Eliziária C. Santos[4], André Talvani[5], Antônio J. Natali[6] and Rômulo D. Novaes[2]

[1]Department of Structural Biology, Institute of Biomedical Sciences, Universidade Federal de Alfenas, Alfenas, MG, 37130-001, Brazil; [2]Department of Animal Biology, Universidade Federal de Viçosa, Viçosa, MG, 36570-000, Brazil; [3]Department of General Biology, Universidade Federal de Viçosa, Viçosa, MG, 36570-000, Brazil; [4]School of Medicine, Universidade Federal dos Vales do Jequitinhonha e Mucuri, Diamantina, MG, 39100-000, Brazil; [5]Department of Biological Science and NUPEB, Universidade Federal de Ouro Preto, Ouro Preto, MG, 35400-000, Brazil and [6]Department of Physical Education, Universidade Federal de Viçosa, Viçosa, MG, 36570-000, Brazil.

Research Article

Cite this article: Santos EG, Gonçalves RV, Souza-Silva TG, Maldonado IR S C, Santos EC, Talvani A, Natali AJ, Novaes RD (2019). Could pre-infection exercise training improve the efficacy of specific antiparasitic chemotherapy for Chagas disease? *Parasitology* 1–10. https://doi.org/10.1017/S0031182019000970

Received: 14 May 2019
Revised: 21 June 2019
Accepted: 2 July 2019

Key words:
Cardiovascular pathology; complementary therapy; experimental chemotherapy; oxidative stress; *Trypanosoma cruzi*

Author for correspondence:
Rômulo Dias Novaes,
E-mail: romuonovaes@yahoo.com.br, romulo.novaes@unifal-mg.edu.br

Abstract

Considering a potential exercise-drug interaction, we investigated whether exercise training could improve the efficacy of specific antiparasitic chemotherapy in a rodent model of Chagas disease. Wistar rats were randomized into five groups: sedentary and uninfected (CT); sedentary and infected (SI); sedentary, infected and treated (SIT); trained and infected (TI); trained, infected and treated (TIT). After 9-weeks running training, the animals were infected with *T. cruzi* and followed up for 4 weeks, receiving 100 mg kg^{-1} day^{-1} benznidazole. No evidence of myocarditis was observed in CT animals. TI animals exhibited reduced parasitemia, myocarditis, and reactive tissue damage compared to SI animals, in addition to increased IFN-γ, IL-4, IL-10, heart non-protein antioxidant (NPA) levels and glutathione-s transferase activity ($P < 0.05$). The CT, SIT and TIT groups presented similar reductions in parasitemia, cytokines (IFN-γ, TNF-α, IL-4, IL-10, IL-17 and MCP-1), inflammatory infiltrate, oxidative heart damage and antioxidant enzymes activity compared to SI and TI animals, as well as reduced heart microstructural remodeling ($P < 0.05$). By modulating heart inflammation and redox metabolism, exercise training exerts a protective effect against *T. cruzi* infection in rats. However, the antiparasitic and cardioprotective effects of benznidazole chemotherapy are more pronounced, determining similar endpoints in sedentary and trained *T. cruzi*-infected rats.

Introduction

Chagas disease is a neglected anthropozoonosis caused by the protozoan parasite *Trypanosoma cruzi* (Pérez-Molina and Molina, 2018). It is estimated that at least 8 million people are currently infected by *T. cruzi* worldwide, and symptomatic clinical forms of Chagas disease are responsible for around 10 000 deaths every year (WHO, 2019). This disease is endemic in South and Central America, where oral and vector (triatomine insects) transmission routes are the main routes of contamination (Nogueira *et al.*, 2018; Pérez-Molina and Molina, 2018). However, there are increasing cases of infection in non-endemic areas, mainly due to the migration of infected individuals, congenital transmission (mother to fetus), and iatrogenic events related to laboratory accidents, blood transfusion and transplantation of infected organs (Bern, 2015; WHO, 2019). Recent estimates suggest at least 350 000 cases of infection in North America (Echeverria and Morillo, 2019) and 181 181 cases in European countries (Antinori *et al.*, 2017).

Chagas cardiomyopathy is the most severe and disabling manifestation of *T. cruzi* infection (Bern, 2015). It is associated with extensive inflammatory processes, oxidative damage, cardiomyocytolysis, necrosis, progressive heart fibrosis, electromechanical insufficiency, heart failure and death (Bern, 2015; Pérez-Molina and Molina, 2018). Chagas disease is the leading cause of nonischemic cardiomyopathy and the third highest indication for heart transplantation in Latin America (Mendonça *et al.*, 2018; Nogueira *et al.*, 2018). Chronic Chagas cardiomyopathy (CCC) is associated with a worse prognosis and 2.48-times greater risk of death than noninfectious cardiomyopathies (Freitas *et al.*, 2005; Nogueira *et al.*, 2018).

After more than four decades, benznidazole (Bz) is still the first-line drug for the etiological treatment of *T. cruzi* infection (Urbina, 2010; Nogueira *et al.*, 2018). However, this drug has high toxicity and low cure rates (10–20%) after the parasites have spread and established quiescent amastigote reservoirs in multiple tissues (Urbina, 2010; Mendonça *et al.*, 2018). As the prospect of new drugs for the treatment of *T. cruzi* infection is not promising, supporting drugs (e.g. antiarrhythmic, anti-inflammatory and antioxidant drugs) (Santos *et al.*, 2015; Novaes *et al.*, 2016*a*; Mendonça *et al.*, 2018) and non-pharmacological strategies (e.g. exercise training) (Novaes *et al.*, 2016*b*, 2017; Lucchetti *et al.*, 2017) have been proposed to increase host resistance against *T. cruzi*. Unlike cardiomyopathies with noninfectious etiologies, exercise training