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Review

Mode of action of natural and synthetic drugs against *Trypanosoma cruzi* and their interaction with the mammalian host☆

Juan Diego Maya [a], Bruce K. Cassels [b], Patricio Iturriaga-Vásquez [b], Jorge Ferreira [a], Mario Faúndez [a], Norbel Galanti [a], Arturo Ferreira [a], Antonio Morello [a,*]

[a] *Instituto de Ciencias Biomédicas, Facultad de Medicina, Universidad de Chile, P.O. Box 70000, Santiago 7, Santiago, Chile*
[b] *Departamento de Química, Facultad de Ciencias, Universidad de Chile, Chile*

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Abstract

Current knowledge of the biochemistry of *Trypanosoma cruzi* has led to the development of new drugs and the understanding of their mode of action. Some trypanocidal drugs such as nifurtimox and benznidazole act through free radical generation during their metabolism. *T. cruzi* is very susceptible to the cell damage induced by these metabolites because enzymes scavenging free radicals are absent or have very low activities in the parasite. Another potential target is the biosynthetic pathway of glutathione and trypanothione, the low molecular weight thiol found exclusively in trypanosomatids. These thiols scavenge free radicals and participate in the conjugation and detoxication of numerous drugs. Inhibition of this key pathway could render the parasite much more susceptible to the toxic action of drugs such as nifurtimox and benznidazole without affecting the host significantly. Other drugs such as allopurinol and purine analogs inhibit purine transport in *T. cruzi*, which cannot synthesize purines de novo. Nitroimidazole derivatives such as itraconazole inhibit sterol metabolism. The parasite's respiratory chain is another potential therapeutic target because of its many differences with the host enzyme complexes. The pharmacological modulation of the host's immune response against *T. cruzi* infection as a possible chemotherapeutic target is discussed. A large set of chemicals of plant origin and a few animal metabolites active against *T. cruzi* are enumerated and their likely modes of action are briefly discussed.

Keywords: Review; *Trypanosoma cruzi*; Nifurtimox; Benznidazole; Glutathione; Trypanothione; Immune system; Natural antichagasic compounds; Macrophages; Nitric oxide; Prostaglandins

Contents

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* Corresponding author. Independencia 1027, P.O. Box 70000, Santiago 7, Santiago, Chile. Tel.: +56 2 9786071; fax: +56 2 7355580.
E-mail address: amorello@med.uchile.cl (A. Morello).

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In 1909 Carlos Chagas, a Brazilian scientist, discovered a parasitic flagellate that he named *Trypanosoma cruzi* and which is the causative agent of American trypanosomiasis, now known as Chagas'disease. Chagas' disease affects 24 million people from Southern California to Argentina and Chile (Chagas, 1909; WHO Expert Committee on the Control of Chagas Disease, 2002). The most important mode of transmission of the disease is associated with the feces of several species of triatomine bugs that are strictly hematophagous. Blood transfusion also plays a role in Chagas' disease transmission, since serological tests in blood banks of areas where the disease is endemic give 10–50% positivity, and of that percentage around 10% of the blood contains infective parasites. This disease has been present in the American continent for more than 9000 years (Aufderheide et al., 2004).

1. The life cycle of *T. cruzi*

The parasite's biological cycle includes three fundamental forms characterized by the relative positions of the flagellum, kinetoplast, and nucleus (Prata, 2001): (1) Trypomastigotes: 20 μm long, fusiform, subterminal kinetoplast, constitute the infecting form, and are found in mammalian blood and the hindgut of triatomine bugs; they do not multiply. In mammals they are the disseminators of blood-borne infection (Prata, 2001). (2) Epimastigotes: Also 20 μm long, kinetoplast anterior to the nucleus, fusiform. They represent the parasite's multiplicative form in the triatomid's intestine, and are the predominant form in culture. For this reason it is the form most commonly used in biochemical studies (Prata, 2001). (3) Amastigotes: Approximately 2 μm in diameter, round, without an emergent flagellum. They multiply by means of binary fission inside mammalian host cells, producing their rupture, and liberating trypomastigotes into the bloodstream that can once again invade any nucleated cell (Prata, 2001). They can be grown in culture in muscle cells, fibroblasts, and macrophages among others (Faúndez et al., 2005; Morello, 1988).

2. Epidemiology

American trypanosomiasis or Chagas' disease is a major public health concern in Latin America. It takes second place after malaria in prevalence and mortality due to vector-associated diseases (WHO Expert Committee on the Control of Chagas Disease, 2002). At least 25 million people are considered to be at risk of exposure to infection, with a total estimate of 8 million infected cases, with Chile contributing to this number with 150,000 presumably infected cases (WHO Expert Committee on the Control of Chagas Disease, 2002). Furthermore, according to World Health Organization reports, mortality rates vary from 8% to 12% depending on the country studied, age, patients' health conditions, and treatment received (WHO Expert Committee on the Control of Chagas Disease, 2002). This report also states that recent studies have shown approximately 200,000 new cases per year and 21,000 deaths per year associated with Chagas' disease (WHO Expert Committee on the Control of Chagas Disease, 2002).

Chagas' disease is controlled at present through the elimination of the vectors with insecticides; better housing and educational campaigns are also fruitful approaches. Chagas' disease, as well as other parasitic diseases, is associated with poverty and low educational levels. The development of vaccines has thus far been unsuccessful. The chemotherapy of Chagas' disease is inadequate since the treatment of patients with the drugs nifurtimox and benznidazole presents serious toxic side effects; there are also doubts as to whether these drugs are capable of achieving parasitological cure. Gentian violet (Hiratake et al., 2002) is used to treat transfusion blood, its main disadvantage being the purple colouring of the blood and the staining of the patients' tissues. Hundreds of *T. cruzi* "strains" have been isolated from different countries and geographical zones. Important differences in resistance or susceptibility to drugs in use, in laboratory experimentation, or in clinical studies, have been described among different strains of the parasite. This situation makes the development of new antichagasic drugs even more difficult (Morello et al., 1994).

Currently, most antiparasitic drugs are considered orphan drugs with the main exception of antimalarials. Economic considerations of the pharmaceutical industry outweigh all others, because of the very low return of the developmental costs. Therefore, it is necessary to find alternative and cheaper ways to approach the treatment of Chagas' disease. This could be achieved by increasing the activity of the antichagasic drugs presently used or by modifying the host's immune response, which would render current therapies more effective.

3. Treatment of Chagas' disease

3.1. Clinical approach

The drugs currently used to treat Chagas' disease are nifurtimox (4[(5-nitrofurfurylidene)amino]-3-methylthiomorpholine-