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Mini-review

Trends in research of antitrypanosomal agents among synthetic heterocycles

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ABSTRACT

To date treatment of trypanosomiasis urgently requires new effective and non-toxic drugs. The article covers some of the achievements in the search for new antitrypanosomal agents; also the "validated" biological targets used in the antitrypanosomal agents design are outlined. The major part of the manuscript focuses on the synthetic small molecules, such as thiosemicarbazone and thiazole (as their cyclic analogues) derivatives, benzofuran derivatives, heterocycles bearing nitro group etc. Also, the attractiveness of metal complexes and well known drugs as sources for antitrypanosomal agent design is discussed.

1. Introduction

Trypanosomes are unicellular parasitic protozoa belonging to the *Trypanosoma* genus (Kinetoplastea, Excavata) [1]. Different species of trypanosomes infect a variety of different vertebrates, including humans. Most of them are transmitted by different insects and cause such diseases as Human African Trypanosomiasis (HAT) also known as sleeping sickness, and American trypanosomiasis or Chagas disease.

On the African continent a number of *Trypanosoma* species and subspecies are economically significant causing human and animal diseases, which are an obstacle to human welfare, affecting cattle rearing and agricultural development. HAT only occurs in sub-Saharan Africa. It is caused by two subspecies of *Trypanosoma brucei* (*T. b.*), namely *T. b. gambiense* and *T. b. rhodesiense*. Animals can host these parasites and represent an important reservoir of infection for the tsetse flies that transmit the disease [2]. HAT caused by *T. b. gambiense* (95% of reported cases) occurs only in 36 sub-Saharan Africa countries where tsetse flies are present. *T. b. rhodesiense* is found in Eastern and Southern Africa. Nowadays, this form represents less than 5% of reported cases and causes an acute infection. First signs and symptoms are observed few months or weeks after infection. The disease develops rapidly and invades the central nervous system (CNS). If left untreated the disease caused by either of the two parasites leads to coma and death. However, even if diagnosed in time, the pharmacological treatment of HAT may be in some cases ineffective, because of side effects and length of treatment. After continued control efforts, the number of cases reported in 2009 has dropped below 10 000 for the first time in 50 years. This trend was maintained in 2010 with 7139 new cases reported [2,3].

Chagas disease caused by *Trypanosoma cruzi* is a devastating human disease in Latin and South America with more than 10 million infected people. It is transmitted to man by infected faeces of a blood-sucking triatomine bug through skin breaks during blood meal or through mucous membranes, occasionally causing outbreaks with contaminated food. Transmission through blood transfusion, pregnancy and delivery are also possible, and less frequently, through organ transplantation or laboratory accidents. Chagas disease was once confined to the Region of the Americas but it has now spread to other continents, specialy due to blood transfusion transmission [4]. Since the Chagas disease was discovered in 1909 numerous studies have been carried out to investigate the pathogenesis of acute and chronic phases of the disease, but the underlying mechanisms are still debated. Undeniable remains the statement that *T. cruzi* multiplies in the host's cells in the amastigote form that differentiates into the infective trypomastigote form, which is released after the host-cell rupture causing inflammatory reactions leading to megaesophagus, megacolon and cardiac conduction disturbances. In one case the lesion

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formation during the chronic stage is associated with the parasite circulation in the organism. A second possible pathogenetic mechanism lies in the immune response of the host's organism, which is independent of the parasite persistence [5,6]. Earlier autoimmune reactions were believed to be the primary factors leading to the lesions associated with the chronic stage. Recent investigations showed that the persistence of parasites in the organism also contribute to the inflammatory processes leading to cardiac or gastrointestinal complications. Therefore success of the treatment depends greatly on the elimination of *T. cruzi* from the organism [6].

2. Trypanosomiasis: current therapy

2.1. HAT pharmacological treatment

Nowadays four main drugs are used for the treatment of early stage and late-stage HAT: suramin, pentamidine, melarsoprol and eflornithine (Fig. 1). Unfortunately, since eflornithine was approved by the FDA in the 90s [7], no new drugs were marketed. Effectiveness of HAT treatment is reduced by the long duration of treatment and the serious side effects of drugs. An additional problem is the way of drugs administration, which is only by intramuscular or intravenous route. Given the low standard of living in endemic areas more efficient and simple in the application would be oral drug forms [8,9]. Choice of treatment depends on the stage of the disease and the parasite subspecies.

First-line treatment for the early stage of *T. b. gambiense* HAT, the heamolymphatic stage, is pentamidine first used in 1940. Despite non-negligible undesirable effects (hypoglycaemia, prolongation of the QT interval on electrocardiogram, hypotension and gastrointestinal features), pentamidine is in general well tolerated. Early-stage of *T. b. rhodesiense* HAT is treated with suramin, which was discovered in 1921 and, although usually effective, especially when given early in the disease, can result in potential complications such as renal failure, skin lesions, anaphylactic shock, bone marrow toxicity and neurological complications such as peripheral neuropathy [9–11].

Treatment of the late-stage HAT, the meningoencephalitic stage, when the trypanosomes had invaded CNS, is more problematic because drugs need to cross the blood–brain barrier to reach the parasite. Such drugs are toxic and complicated to administer [8,9]. The only drug being effective at present for the late-stage *T. b. rhodesiense* HAT is the trivalent organoarsenic compound melarsoprol, which acts on trypanothione, a parasite molecule that maintains an intracellular reducing environment [12]. Although melarsoprol is no longer used as first line treatment for *T. b. gambiense* HAT, it remains the most widely used drug for treatment of the second-stage of *T. b. gambiense* HAT in resource-poor countries where eflornithine is not available or affordable [9]. Melarsoprol is very toxic being responsible of a post-treatment reactive encephalopathy, leading to an overall mortality from treatment of about 5% [13,14]. An increase of resistance to melarsoprol has been observed in several foci particularly in Central Africa. Eflornithine, an ornithine decarboxylase inhibitor, had been known to be effective for the late-stage *T. b. gambiense* HAT since 1981 and was designated as an orphan drug [7,10,13,14]. Because of effective efforts and partnership between WHO and pharmaceutical companies, intravenous eflornithine was made widely available to patients around 2001 [13,14]. An important advance was the development of the nifurtimox–eflornithine combination therapy (NECT), which is now becoming the standard first-line treatment for the CNS-stage of *T. b. gambiense* HAT, with intravenous melarsoprol now being used as second line treatment for this disease form [3,15].

2.2. Pharmacological treatment of Chagas disease

Unfortunately, despite the impressive advances in understanding the biology of *T. cruzi*, the only drugs currently available for Chagas disease treatment are nifurtimox (NF) and benznidazole (BNZ) developed empirically in the 1960s and 1970s. These compounds are active in the acute stage of Chagas disease (up to 80% efficacy), and BNZ has also recently been shown to be efficacious in early chronic infections but of limited efficacy against established chronic-stage disease [16]. NF acts by increasing of free radical species (mainly superoxide anions and H_2O_2) and electrophilic metabolites production [17], as well as increase of oxygen consumption in *T. cruzi* [18]. It has been shown that not only the metabolic action of the drug on *T. cruzi*, but also its incorporation and transport into the parasite are of great importance in its efficiency. There are strains with some resistance to NF, which differ by a lower drug intake and transportation, rather than by the amount

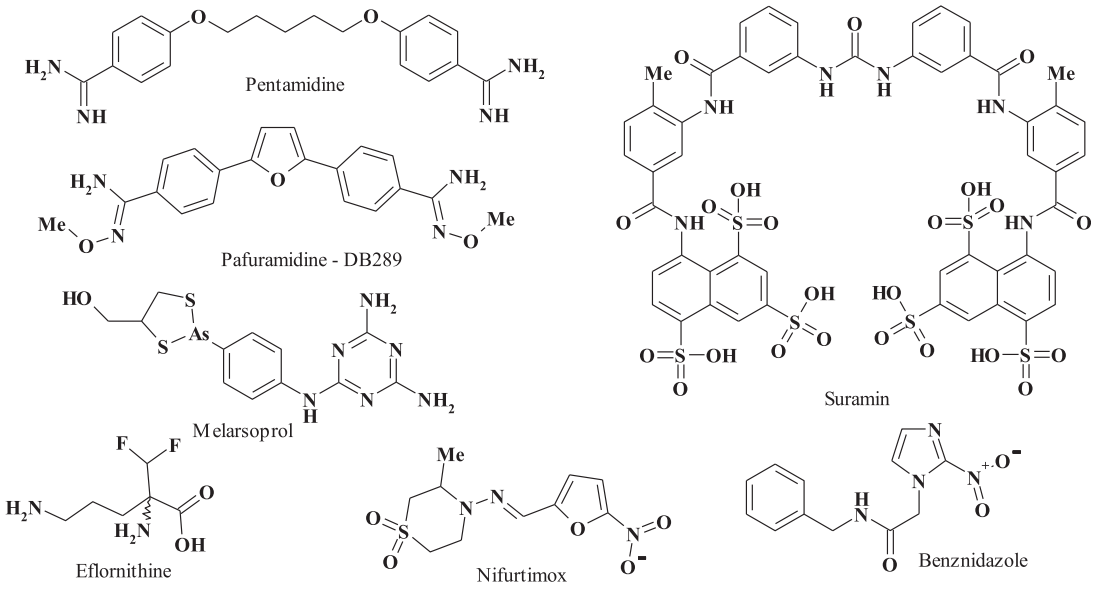

Fig. 1. Structure of antitrypanosomal drugs and drug-candidate.