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SHORT COMMUNICATION

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Chemotherapeutic approaches to protozoa: Kinetoplastida – current level of knowledge and outlook

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Classification of agents with activities against kinetoplastida in three main pathogen-based groups

1. Agents with activity against *Trypanosoma brucei*.
   a. Carbohydrate and/or energy metabolism. Suramin: inhibition of glycosomal proteins (Fig. 1).
   b. DNA metabolism. Melarsoprol: inhibition of trypanothione reductase (Fig. 2), further inhibition of various glycolytic enzymes with essential thiol groups. Diminazene aceturate, quinapyramine, pentamidine: inhibition of trypanothione metabolism (Fig. 2) and/or interaction with the

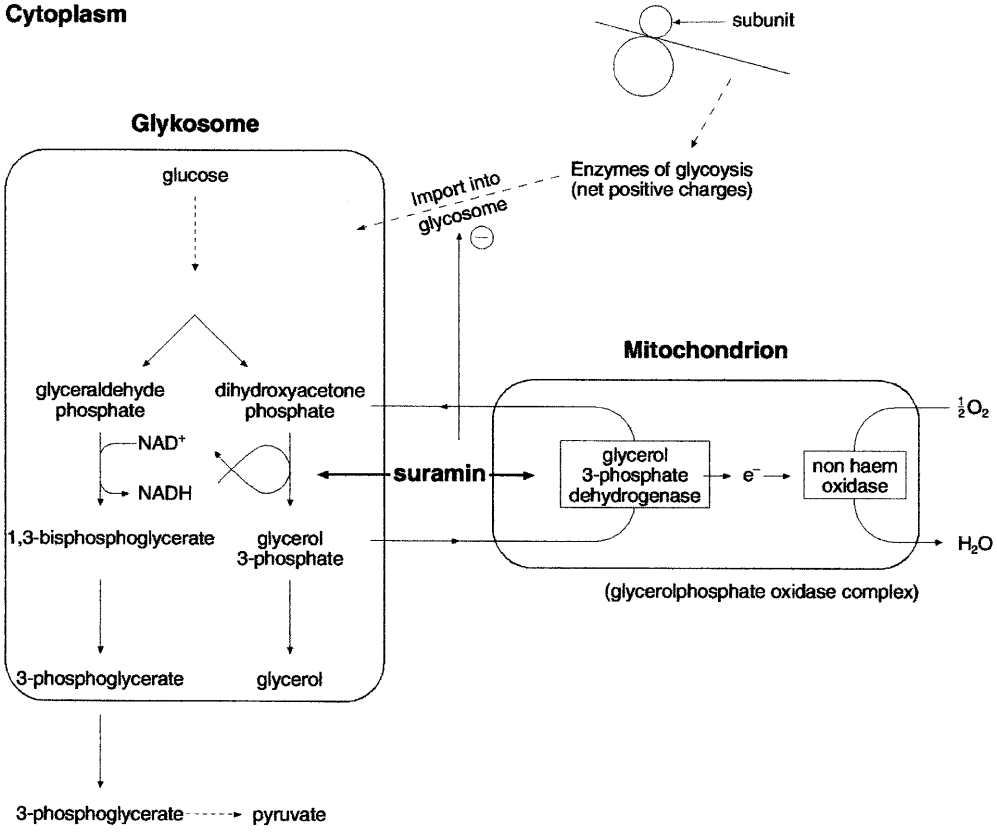

Fig. 1 Model to show the mechanism of action of suramin

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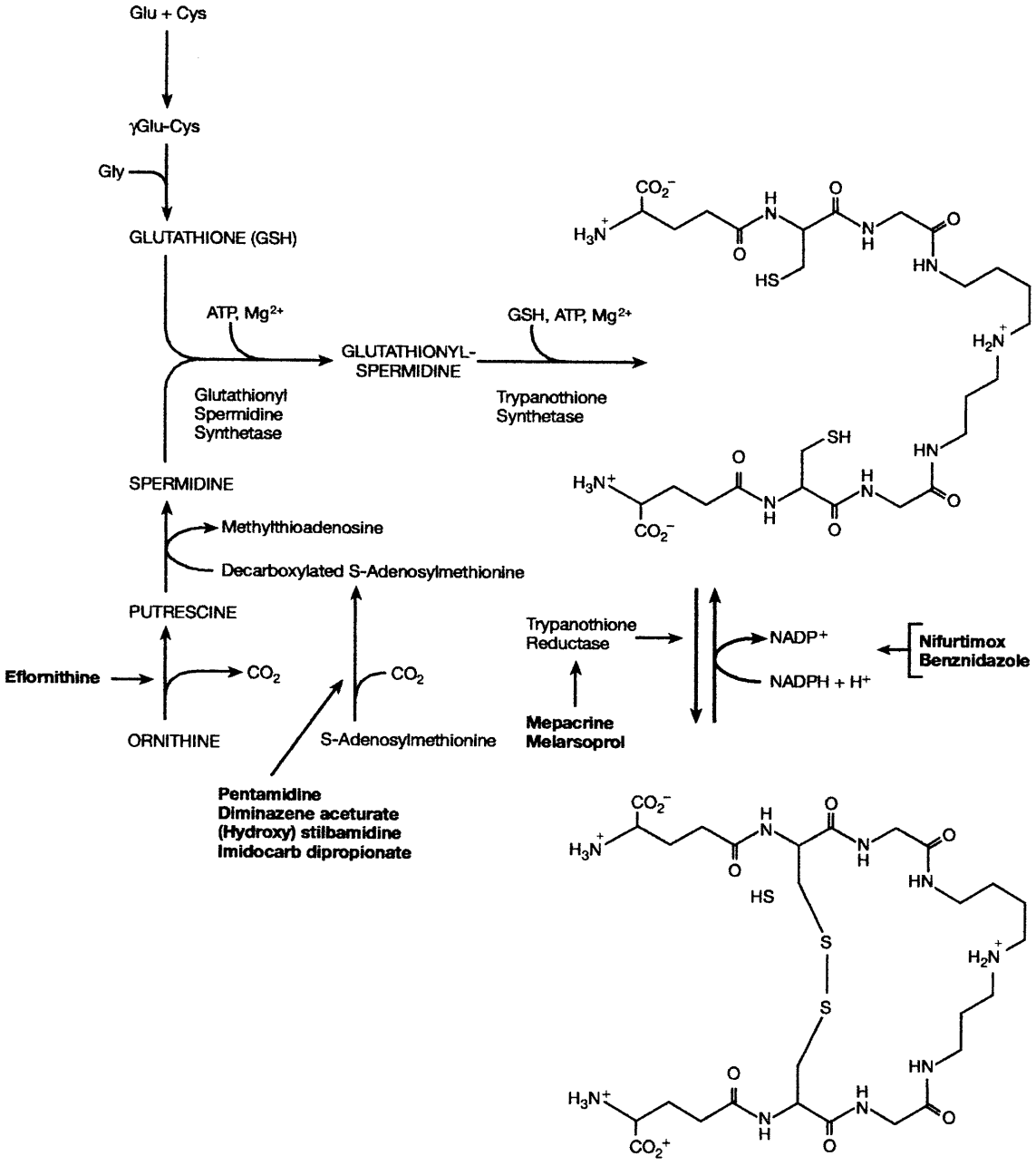

Fig. 2 Model to show the effects of drugs on trypanothione metabolism

DNA minicircle. Elfornithine: inhibition of ornithine decarboxylase and interference with trypanothione metabolism (Fig. 2).

2. Agents with activity against *Leishmania* species.
   a. Carbohydrate and/or energy metabolism. Sodium stibogluconate (= meglumine antimonate), stibophen: inhibition of glycolytic enzymes with essential thiol groups and possibly trypanothione reductase?
   b. DNA metabolism. Diamidines (pentamidine, stilbamidine): inhibition of trypanothione metabolism (Fig. 2) and/or interaction with the DNA minicircle. Allopurinol: inhibition of the incorporation of adenosine into DNA.
   c. Protein synthesis. Paromomycin: inhibition of bacterial protein synthesis (also in *Leishmania* spp?).
   d. Membrane integrity. Amphotericin B: interaction with ergosterol in the membrane, increases permeability of plasma membrane to ions and small molecules. Miltefosine: as a phosphocholine analogue (hexadecylphosphocholine), affecting cell-signalling pathways and membrane synthesis.

Table 1 Spectrum of agents with efficacy against kinetoplastida. *xxx* High efficacy against at least some development stages and various species, *xx* partial efficacy in terms of development stages and species, *x* low efficacy, *E* experimental efficacy

Year of Launch	Drug	*Trypanosoma brucei*	*Leishmania* spp	*Trypanosoma cruzi*
T*rypanosoma brucei*				
1920	Suramin	xxx[a]		x
1949	Melarsoprol	xxx[b]		
About 1958	Diminazene aceturate	xxx	xE	
	Quinapyramine	xxx[a]		
1990	Eflornithine	xxx[b]	xx	
Leishmania species				
	Glucantime (meglumine antimonate)		xxx	
1937	Sodium stibogluconate		xxx	
	Stibophen		xxx	
1950/1984	Pentamidine	xxx [a)]	xx	
1942?	Stilbamidine	xxx	xx	
	Allopurinol	xE	xx	
1999?	Paromomycin		xx	
1962/1996	Amphotericin B		xxx	
1990's	Miltefosine[c]		xxx	
Trypanosoma cruzi				
1984	Nifurtimox	xxx		xxx
1981	Benznidazole			xxx

[a] Efficacy in the acute (blood) phase
[b] Efficacy in the chronic (liquor) phase
[c] In clinical trial against visceral leishmaniasis

3. Agents with activity against *Trypanosoma cruzi*. DNA metabolism. Nifurtimox, benznidazole: activation by trypanothione reductase (?; Fig. 2), formation of free nitroanion radicals, interference with DNA (?).

Summary

The possibilities for treating haemoflagellate infections (African trypanosomiasis) are very limited (Table 1; Mehlhorn and Schrevel 1995; Croft 1997; Hunter 1997; Wang 1997; Trouiller and Olliaro 1998). All the available drugs have severe side-effects in humans and animals. Vaccination is not really an option, in view of the wide antigen variability. At present, there are several drug combinations in clinical trials: suramin/eflornithine, suramin/metronidazole, suramin/pentamidine, melarsoprol/pentamidine, melarsoprol/nifurtimox and nifurtimox/eflornithine. Some of these combinations were successful in treating resistant *Trypanosoma brucei rhodesiense* and/or *T. b. gambiense* infections (Keiser et al. 2001). In leishmaniasis, the tendency is still to resort to the old antimony compounds, with their severe side effects. At present, miltefosine is in clinical phase and is the first oral drug against visceral leishmaniasis (Jha et al. 1999). Two drugs are currently used against Chagas' disease, although these do not cure chronic effects. There is no prospect of novel drugs in this indication either (Pecoul et al. 1999; Morel 2000).

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