POLYAMINE METABOLISM AS A CHEMOTHERAPEUTIC TARGET IN TRYPANOSOMATID PROTOZOA

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Polyamines, such as putrescine, spermidine and spermidine, regulate growth and differentiation in a variety of cells and are valuable drug targets to parasitic protozoa. *Trypanosoma cruzi* cannot synthesize putrescine and relies on its uptake from the extracellular milieu, whereas *Leishmania* growth can be inhibited by polyamine biosynthesis antagonists. Here we evaluated the physiological and biochemical effects of the putrescine analogue 1,4-diamino-2-butanone (DAB) on *T. cruzi* and *L. amazonensis*. DAB inhibited growth of *T. cruzi* promastigotes with IC_{50} = 0.14mM whereas on *T. cruzi* epimastigotes its IC_{50} was about 1.2mM. Treatment of *T. cruzi* with 10mM DAB reduced putrescine concentration by nearly 50%, inhibited both ornithine decarboxylase (ODC) activity and also [H^3]-putrescine uptake by promastigotes. DAB also caused mitochondrial destruction and cell disorganization, assessed by transmission electron microscopy, as well as on its function, demonstrated by diminished MTT reduction in *T. cruzi* and in *L. amazonensis*. In both parasites, DAB treatment induced lipid peroxidation, dose-dependently as 5 mM DAB slightly enhanced peroxidation, whereas 10 mM DAB significantly reduced it. Murine macrophages infected with *L. amazonensis* amastigotes treated with DAB showed that parasite loads were significantly lowered. These results indicate that putrescine is required for these parasites and its metabolism may comprise a useful chemoterapic target.

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