Correspondence

Potential utility of disulfiram against leishmaniasis

Sir,

The trypanothione biosynthetic pathway, common to the trypanosomatid family of protozoa (which includes *Leishmania* and *Trypanosoma*), is absent in the host systems. This pathway constitutes an important target for chemotherapy against leishmaniasis. The trypanothione pathway combines two metabolic pathways – the polyamine biosynthetic pathway and the glutathione pathway. Since glutathione (GSH) is involved in a number of vital functions within cells, chiefly defence against oxidative damage, GSH inhibition is a potential means for chemotherapy of these parasites. Moreover, GSH depletion in macrophages leads to increased nitric oxide (NO) production, which has leishmanicidal action. Buthionine sulfoximine (BSO), an inhibitor of GSH synthesis, has been shown to exert an inhibitory effect on *Leishmania donovani* growth. On the other hand, resistance of *Leishmania donovani* to sodium stibogluconate is related to the expression of host and parasite gamma-glutamylcysteine synthetase, which produces GSH. Resistance of *L. major* and *L. tropica* to glucantime (meglumine antimonate) an antileishmanial agent, was also attributed to higher GSH levels.

Intracellular parasitic protozoans of the genus *Leishmania* depend for their survival on the elaboration of enzymic and other mechanisms for evading toxic free radical damage inflicted by their phagocytic macrophage host. One such mechanism may involve superoxide dismutase (SOD), which detoxifies reactive superoxide radicals produced by activated macrophages. These results indicate that SOD is a major determinant of intracellular survival of *Leishmania*.

Disulfiram (Antabuse) is a dithiocarbamate (DC) used as an adjunct in the treatment of chronic alcoholism. In the presence of GSH, disulfiram is reduced to *N,N*-diethylthiodicarbamate (DDC) nonenzymatically, with a stoichiometric relationship of 2:1. DIS does not deplete total glutathione but significantly reduces the GSH/GSSG (oxidised glutathione) ratio. It is suggested that DDC forms a complex with copper, either intracellularly or extracellularly, which is toxic to malarial parasites which are also intracellular parasites like *Leishmania*. Moreover, disulfiram is an inhibitor of SOD. Another useful effect of this agent is the inhibition of P-glycoproteins by its metabolites. P-glycoproteins are operative in mediating drug resistance in *Leishmania* and other protozoans, followed by development of cross-resistance to many structurally and functionally unrelated drugs.

Disulfiram may thus prove to be effective against leishmaniasis. Combining this agent with glucantime could potentiate the therapeutic response of the latter and help in reducing the resistance of the parasites against it.

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References


