

Zeitschrift: Acta Tropica
Herausgeber: Schweizerisches Tropeninstitut (Basel)
Band: 44 (1987)
Heft: 4

Artikel: Competent metabolic utilization of hydrogen peroxide by trypanosomes
: short communication
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DOI: <https://doi.org/10.5169/seals-313876>

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Competent metabolic utilization of hydrogen peroxide by trypanosomes

Short communication

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Many trypanosomatids have been reported to be deficient in their ability to metabolize H_2O_2 and be particularly sensitive to H_2O_2 oxidant stress (Docampo and Moreno, 1984) due to their lack of the glutathione peroxidase and catalase. Recently, however, it has been demonstrated that *Trypanosoma brucei* possesses a novel trypanothione-dependent enzymic system for metabolizing H_2O_2 (Penketh, 1986; Penketh and Klein, 1986). This finding has led us to question the generally accepted idea that trypanosomes are particularly sensitive to H_2O_2 oxidant stress.

T. brucei rhodesiense bloodstream trypomastigotes were purified as described by Lanham (1968). *T. cruzi* strain epimastigotes and trypomastigotes were prepared and purified as described by Widmer (1986) and Piras et al. (1982), respectively. Levels of parasitemia were determined using a Neubauer haemocytometer at a magnification of 200 \times . Erythrocyte morphology was examined in thin wet smears at magnifications of 200–1000 \times . The toxicity of H_2O_2 to mice and to *T. b. rhodesiense* was determined as follows. Female CD-1 25–35 g mice were injected intravenously (i.v.) with glucose oxidase (GO) in 50 μl of phosphate buffered saline. The LD_{50} dose of glucose oxidase was determined to be 3.8–4.5 mg/kg (133 units/mg; Sigma). When catalase (180 mg/kg, 11,000 units/mg; Sigma) was co-administered, mice tolerated doses of 45.0 mg/kg of GO with no deaths (0/4). In the absence of catalase, however, doses of 5.5 mg/kg were 100% lethal (8/8). This finding indicates that H_2O_2 production is the major toxic product of GO treatment. Mice given an LD_{50} dose of GO generally died within 24 h or they survived.

Mice were infected with *T. b. rhodesiense* (2×10^6 cells i.p.) and the doubling time of the organisms was determined by following the increase in parasitemia. A mean doubling time of 6.8 h ($n = 24$, $\text{SD} = 0.6$) was observed and all of the mice died approximately 3 days after infection with parasitemias of greater than 10^9 cells/ml. In a further experiment 14 mice were infected with 2×10^6 parasites and after 24 h were injected with 3.8 mg/kg of GO. Parasitemia levels were then followed in these animals. Approximately 70% (9/14) of the animals survived the GO treatment. However, they all died approximately 3 days after infection with maximal parasitemias. A mean doubling time of 7.1 h ($n = 9$, $\text{SD} = 1.3$) was calculated. At all times the parasites were of normal appearance. Since both

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trypanosomes (in acutely infected mice) and erythrocytes reside in the bloodstream, both cell types should be exposed to equivalent steady state H_2O_2 concentrations. Although trypanosomes appeared to be unaffected by GO administration, erythrocytes were adversely affected unless catalase, 180 mg/kg, was co-administered. Within 12 h of GO treatment, virtually all of the erythrocytes were of echinocyte I–IV morphology indicating major cytoskeletal changes had occurred within these cells. H_2O_2 has been previously shown to cause cytoskeletal damage (Ragu et al., 1986) and inhibit cellular volume-regulation (Rosenberg and Mathews, 1973). This suggests that the oxidant defense mechanisms of the erythrocytes had been compromised even though these cells are not normally considered to be deficient in defenses against H_2O_2 .

The quantities of H_2O_2 metabolized in 1 min by *T. b. rhodesiense* trypomastigotes (5×10^7 cells/ml), *T. cruzi* epimastigotes (2×10^7 cells/ml) and trypomastigotes (2×10^7 cells/ml), using an initial H_2O_2 concentration of 20 μM , were measured as described previously (Penketh and Klein, 1986). Rates of H_2O_2 metabolism of 3.5 nmol/ 10^8 cells/min ($n = 5$, $\text{SD} = 0.6$), 18.3 nmol/ 10^8 cells/min ($n = 3$, $\text{SD} = 1.5$) and 48.2 nmol/ 10^8 cells/min ($n = 3$, $\text{SD} = 1.9$), respectively, were obtained. Rates of H_2O_2 metabolism in 11 other trypanosomatids have been determined (Penketh et al., 1987), and rates comparable to or greater than those found in *T. b. rhodesiense* were observed.

In view of these findings, trypanosomes cannot be considered deficient in their ability to metabolize H_2O_2 or particularly sensitive to H_2O_2 stress. The very high rate of H_2O_2 metabolism in *T. cruzi* trypomastigote forms compared to epimastigote forms probably has a pathophysiological function, and correlates with their previously reported greater resistance to the phagocytic killing mechanism and the oxidant stress in the form of H_2O_2 (Tanaka et al., 1983).

Declaration. All animal procedures described are in compliance with USA regulations.

Acknowledgments. P.G.P., C.L.P., and A.C.S. acknowledge support from USPHS Grant AI15742 and a grant from the MacArthur Foundation. – W.P.K. K. acknowledges support from the Wolfson Foundation.

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