

Synergistic enhancement of a copper chelator, bathocuproine disulphonate, and cysteine on in vitro growth of *Plasmodium falciparum* in glucose-6-phosphate dehydrogenase-deficient erythrocytes

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Abstract

In vitro growth of *Plasmodium falciparum* is restricted in glucose-6-phosphate dehydrogenase (G6PD)-deficient erythrocytes (RBC), as a result of oxidative stress. Bathocuproine disulphonate (BCS), a copper chelator, as well as cysteine have been shown to synergistically stimulate the in vitro growth of various mammalian cells and Trypanosoma under oxygenated conditions. We examined the effects of these two chemicals on the in vitro growth of *P. falciparum* in G6PD-deficient RBC, and found that addition of BCS and cysteine synergistically enhanced the growth of the *P. falciparum* FCR-3 strain in these RBC to the same level as in normal RBC. However, BCS or cysteine alone had no stimulatory effect. To explain this synergistic enhancement, changes in thiol, NADPH and glutathione contents were investigated. After addition of cysteine alone, thiol content in the medium decreased rapidly, but when BCS was added, it was maintained at about 35% at 24 hours after incubation, suggesting that BCS stimulates parasite growth in G6PD-deficient RBC by inhibiting copper-mediated oxidation of cysteine in the medium. In these RBC, no increase in NADPH level, but a slight increase in glutathione, was observed in the presence of both BCS and cysteine. The slight increase of glutathione, was probably due to incorporation of cysteine from the medium, although this could not fully explain the synergistic growth enhancement. These findings taken together suggest that cysteine incorporated into G6PD-deficient RBC may help maintain the thiol groups in many proteins, such as membrane proteins, hemoglobin and enzymes, and plays an important role in maintaining an appropriate culture state necessary for parasite growth. We also examined the effects of BCS and cysteine on adaptation of wild isolates of *P. falciparum* to in vitro cultivation using the candle jar method. Although there was no drastic effect on growth enhancement, the presence of BCS and cysteine accelerated the appearance of schizonts in many isolates.