Thesis Title : Inhibition of growth and polyamines biosynthesis in P. falciparum by berenil and methylglyoxal bis(guanylhydrazone)

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ABSTRACT

Berenil and MGBG, inhibitors of S-adenosylmethionine decarboxylase effectively inhibited growth of P. falciparum in culture with EC_{50} after 48 h exposure to the drugs of 0.41 and 2.4 μM respectively. EC_{50} as determined by [^{3}H] hypoxanthine uptake was 0.9 and 4.7 μM for berenil and MGBG respectively. Both drugs blocked development of the parasites from trophozoites to schizonts. Berenil and MGBG inhibited DNA, RNA and protein synthesis in P. falciparum. The EC_{50} for inhibiting these macromolecular synthesis of berenil was about 6-9 times higher than that of MGBG. Addition of exogenous polyamines, i.e., putrescine, spermidine or spermine at concentration of 1 mM could not reverse the inhibitory effects of berenil and MGBG on both growth and macromolecular synthesis of P. falciparum.

P. falciparum contained 8-15% putrescine, 70-80% spermidine and 8-15% spermine and the concentrations of these polyamines were

highest at schizont stage. Exposure of the parasites culture to berenil or MGBG resulted in a decrease in polyamine content in the parasites, especially spermidine decreased to 25% and 64% after exposure to 5 μM berenil and 25 μM MGBG for 30 h. Polyamine biosynthesis from either [^{3}H] ornithine or [^{14}C] putrescine in the parasites was inhibited by both berenil and MGBG. The results suggested that both drugs also inhibited the transport of [^{14}C] putrescine from red cells into the parasites.

These results suggested that inhibition of polyamines, especially spermidine biosynthesis by berenil and MGBG had led to inhibition of DNA, RNA and protein synthesis in P. falciparum, and as a result, growth of the parasites was inhibited. Nevertheless, the mechanism of actions of berenil and MGBG might not be specific to only polyamine biosynthesis, since the inhibitory effects of these drugs could not be reversed by addition of exogenous polyamines. Thus, berenil and MGBG might also inhibit growth of P. falciparum by other mechanisms which are still not known.