MECHANISM OF ANTIMALARIAL ACTION

OF

TETRACYCLINE

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ABSTRACT

Tetracycline showed a time-dependent antiparasitic activity on Plasmodium falciparum growth in vitro. It did not directly inhibit merozoite reinvasion processes and had no effect on normal erythrocytes. Cultivation of the infected erythrocytes in the presence of a therapeutic level of tetracycline resulted in a marked decrease in dihydroorotate dehydrogenase activity, but without or with a little effect on glutamate dehydrogenase activity. Dihydroorotate dehydrogenase was found mainly in the particulate fraction of parasite extract and presumed to be mitochondrial, whereas glutamate dehydrogenase, shown to be cytoplasmic in origin, was found mainly in the supernatant of parasite extract. The decrease in dihydroorotate dehydrogenase activity was not due to the direct effect of tetracycline but was shown to be due to the defect in the respiratory chain linked to it. Tetracycline could further enhance the $^{45}Ca^{2+}$ uptake by Plasmodium falciparum-infected erythrocytes after 16 h of drug-treatment, but only when the serum was omitted from the medium. This phenomenon may be due to the effect of tetracycline on the parasite, possibly on parasite mitochondria combined with the effect of ATP depletion of the infected cells. Tetracycline uptake was also greater in the infected erythrocytes, but no stoichiometry between [^{3}H]-tetracycline uptake and $^{45}Ca^{2+}$ uptake by tetracycline-treated infected cells was observed, indicating that tetracycline-enhanced $^{45}Ca^{2+}$ uptake was not

due to the uptake of tetracycline-Ca^{2+} chelating complexes. By using two dimensional polyacrylamide gel electrophoretic technique, a protein of 95K, pI 4.5 was shown by its sensitivity to tetracycline and resistance to cycloheximide to be of possible mitochondrial origin. It is concluded that the action of tetracycline on the malaria parasite may be directed to the mitochondria, probably through its effect on mitochondrial protein synthesis.