THE EFFECT OF CHLOROQUINE ON MACROMOLECULE SYNTHESIS AND OXYGEN UPTAKE IN ESCHERICHIA COLI

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It is known that chloroquine will interact with nucleoproteins in vitro and until recently it was generally believed that chloroquine exerts its anti-plasmodial action by interfering with replication of DNA. However, there is now a good deal of evidence to suggest that interaction of 4-aminoquinolines such as chloroquine with plasmodial nucleic acid may provide only part of the answer to their efficacy against the malaria parasite (Pinder 1973).

Chloroquine has been shown to inhibit the growth of E. coli (Wiseman 1972) and in this communication the effect of chloroquine on the incorporation into macromolecules of precursors of cell wall, protein, RNA and DNA by this organism together with its effect on oxygen uptake are reported.

All experiments were carried out in a Tris minimal salts medium at pH 7.7 (Rye and Wiseman 1966). Growth was measured by changes in absorbance and cell wall, protein, RNA and DNA syntheses by the incorporation of ^{3}H-diaminopimelic acid, ^{14}C-alanine and ^{35}S-sulphate, uracil-5-^{3}H and ^{14}C-thymidine into cold trichloroacetic acid insoluble material respectively. Oxygen uptake was measured using Rank oxygen electrodes.

The addition of 1×10^{-4}M chloroquine to cultures caused a 50% decrease in growth rate after about 50 mins, the rates of synthesis of cell wall, protein and RNA were all inhibited to the same extent as the rate of increase in absorbance but the rate of DNA synthesis was inhibited to a lesser extent. Oxygen uptake was decreased immediately but then slowly increased until after about 120 mins it was increasing at the same rate as the increase in absorbance.

4×10^{-4}M chloroquine was slowly bactericidal after an initial period of about 50 mins during which viable and total cell counts remained virtually constant although the absorbance and the mean cell size both increased.

During the first 50 mins with this concentration cell wall synthesis paralleled the increase in absorbance but protein and RNA synthesis were both inhibited more than the increase in absorbance. Synthesis of all three materials ceased when the increase in absorbance ceased after about 50 mins. DNA synthesis occurred at the same rate as the increase in absorbance during the first 50 mins and continued for at least 30 mins even after the absorbance had ceased to increase. Oxygen uptake decreased until a plateau of residual respiration equivalent to about 22% of the initial rate was reached after 80 mins.

These findings suggest that simple inhibition of DNA synthesis is not responsible for the growth inhibitory activity of chloroquine against E. coli and that protein and RNA syntheses and respiration are more sensitive to the drug.

Pinder, R.M. (1973). "Malaria". Scientechnica Publishers Ltd.
Rye, R.M. and Wiseman, D. (1966) J. Pharm. Pharmacol., 18, (Suppl). 114-118
Wiseman, D. (1972). Ibid. 24, (Suppl), 162P.