Effects of antimalarial drugs on phospholipase A_2

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Antimalarial drugs of the chloroquine-type inhibit lipolytic processes in fat tissue *in vitro* (Markus & Ball, 1969) and phospholipase activity in various tissues (Blackwell, Flower, Nijkamp & Vane, 1978) including the malarial parasite (Cenedella, Jarrell & Saxe, 1969). Several of these drugs have been used in the treatment of rheumatoid conditions. We report the effects of three antimalarial drugs, chloroquine, mepacrine and primaquine, on the activity of a crude phospholipase A_2 enzyme obtained from an inflammatory peritoneal exudate (Fransen, Dobrow, Weiss, Elsbach & Weglicki, 1978).

Phospholipase A_2 activity was assayed against E. coli labelled with [1-^{14}C]-oleate. Greater than 95% of the incorporated label was in the 2-position of membrane phospholipids. Radiolabelled E. coli were autoclaved for 15 min at 2.7 kg/cm^2 to inactivate endogenous bacterial phospholipases and render the membrane more susceptible to enzymic attack. Assays were performed at pH 6.0 in tris buffer 4×10^{-2} M containing calcium 5×10^{-3} M at 37°C for 5 min. Lipid products were extracted, separated by TLC and areas of plates containing radioactive lipids were scraped off and radioactivity determined by scintillation counting.

All three drugs inhibited the enzymic hydrolysis of E. coli phospholipids. IC_{50} for mepacrine was 33×10^{-5} M, primaquine was twice and chloroquine five times less active. In addition the drugs chloroquine and mepacrine showed a stimulation of hydrolysis at approximately 20-fold lower doses, whilst at doses above those causing maximum inhibition a reversal of the inhibitory effects was seen.

The antimalarial drugs examined are amphiphilic cationic drugs. Other drugs of this general type inhibit phospholipase enzymes, possibly by effects on the substrate (Kunze, Nahas, Traynor & Wure, 1976). In relation to this we have studied the effects of the drugs on the stability of guinea-pig red blood cells to hypotonic haemolysis. All three drugs again showed paradoxical dose-dependent inhibitory and stimulatory effects.

The findings described may be of relevance to the use of the drugs in the treatment of malaria and rheumatoid diseases and in their effects in causing drug-induced lipidoses.

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The transport of cimetidine across the rat small intestine *in vitro*

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Cimetidine, an H_2-receptor blocking drug, is well absorbed in man, rat and dog after oral dosing (Taylor & Cresswell, 1975; Burland, Duncan, Hesselbo, Mills, Sharpe, Haggie & Wyllie, 1975). However, absorption is often discontinuous and does not follow first-order kinetics. The aim of this study was to investigate whether cimetidine is actively absorbed across the small intestine of the rat.

The everted-sac method, based on that described by Wilson & Wiseman (1954) was used. Sacs were prepared from the small intestine and randomised with respect to position along the intestine. In some experiments the solution on the mucosal side initially contained cimetidine (40 μmol/l, 200 μmol/l, 400 μmol/l) in Krebs-Henseleit bicarbonate-buffered saline (pH 7.2); in other experiments, cimetidine in