

Abstract:

The antifolate anticancer drug methotrexate (MTX) has potent activity against *Plasmodium falciparum* in vitro. Experience of its use in the treatment of rheumatoid arthritis indicates that it could be safe and efficacious for treating malaria. We sought to establish a murine malaria model to study the mechanism of action and resistance of MTX and its analogue aminopterin (AMP). We used *Plasmodium berghei*, *Plasmodium yoelii yoelii*, *Plasmodium chabaudi* and *Plasmodium vinckei*. None of these species were susceptible to either drug. We have also tested the efficacy of pyrimethamine in combination with folic acid in *P. berghei*, and data indicate that folic acid does not influence pyrimethamine efficacy, which suggests that *P. berghei* may not transport folate. Since MTX and AMP utilise folate receptor/transport to gain access to cells, their lack of efficacy against the four tested murine malaria species may be the result of inefficiency of drug transport.