

Abstract

The folate derivatives folic acid (FA) and folinic acid (FNA) decrease the in vivo and in vitro activities of antifolate drugs in *Plasmodium falciparum*. However, the effects of 5-methyl-tetrahydrofolate (5-Me-THF) and tetrahydrofolate (THF), the two dominant circulating folate forms in humans, have not been explored yet. We have investigated the effects of FA, FNA, 5-Me-THF, and THF on the in vitro activity of the antimalarial antifolates pyrimethamine and chlorcycloguanil and the anticancer antifolates methotrexate (MTX), aminopterin, and trimetrexate (TMX), against *P. falciparum*. The results indicate that these anticancers are potent against *P. falciparum*, with $IC_{50} < 50$ nM. 5-Me-THF does not significantly decrease the activity of all tested drugs, and none of the tested folate derivatives significantly decrease the activity of these anticancers. Thus, malaria folate metabolism has features different from those in human, and the exploitation of this difference could lead to the discovery of new drugs to treat malaria. For instance, the combination of 5-Me-THF with a low dose of TMX could be used to treat malaria. In addition, the safety of a low dose of MTX in the treatment of arthritis indicates that this drug could be used alone to treat malaria.