Artemisinin and Heme

A recent Letter to the Editor (R. K. Haynes, D. Monti, D. Taramelli, N. Basilico, S. Parapini, and P. Olliaro, Letter, Antimicrob. Agents Chemother. 47:1175, 2003) presented cogent evidence that artemisinin and its derivatives do not inhibit hemozoin formation in vitro. However, the authors misinterpreted these data to conclude that “binding of artemisinins with Fe(III)PPIX is not necessary for antimalarial activity.” The authors show that heme [Fe(III)PPIX] may not be the important alklylation target; however, their data do not shed light on the role of heme as the drug activator.

The authors cite an article published by my group (1) and state that we “proposed that artemisinins kill the parasite through inhibition of hemozoin formation.” In fact we found (and stated) exactly the opposite. In whole living parasites, artemisinin did not cause a reduction in hemozoin content. Since other studies showed that the artemisinin was activated by Fe(III)PPIX to become a potent alklylating agent which reacted with both Fe(III)PPIX and proteins (2, 3, 5, 6), we concluded that proteins were more important alkylation targets than Fe(III)PPIX.

Work by 19 other research groups in 11 countries (summarized in reference 4) has corroborated the importance of heme in the activation of artemisinin and its derivatives. The results from this paper are consistent with the current hypothesis that heme is only the activator of artemisinin, not its target.

REFERENCES


Steven R. Meshnick
Departments of Epidemiology and Microbiology & Immunology
University of North Carolina
Chapel Hill, NC 27599-7435
Phone: (919) 966-7414
Fax: (919) 966-2089
E-mail: meshnick@unc.edu

Authors’ Reply

Meshnick notes that while “cogent evidence” is presented in our letter (R. K. Haynes, D. Monti, D. Taramelli, N. Basilico, S. Parapini, and P. Olliaro, Letter, Antimicrob. Agents Chemother. 47:1175, 2003) that artemisinin does not inhibit hemozoin formation, his work was misquoted and erroneous conclusions were drawn as to how artemisinin compounds work. Indeed, we are aware of Meshnick’s demonstration of the lack of inhibition of hemozoin formation by artemisinin, and members of our group cited his results in other work (6). In our letter, the papers by Asawamahasakda et al. (Haynes et al., Letter [reference 1]), Pandey et al. (7), and our own group (Haynes et al., Letter [reference 2]) were cited together to demonstrate the problem with the hemozoin theory, whereby artemisinin would exert its antimalarial effect through heme-artemisinin adducts inhibiting heme polymerization (4, 7).

With reference to the “potent [protein] alkylating ability” in the above response, Meshnick nicely demonstrated that uptake of radiolabeled artemisinin into intraparasitic hemozoin constitutes 75% of total administered artemisinin; thus, heme is indeed a substantial target (3). Model studies also indicate that 85 to 90% of artemisinin forms adducts with heme (8). Thus, a correlation has been drawn between interaction of artemisinin derivatives with heme and antimalarial activity (8, 9). However, we believe we have provided conclusive evidence to support the view, shared by other authors, that these compounds cannot kill the parasite by interacting with heme. The artemisinin derivative 10-deoxohydroartemisinin does not inhibit hemozoin formation in vitro and yet is a potent inhibitor of parasite growth (Haynes et al., Letter).

A further case against the heme activation pathway is provided by the lack of inhibition of phase I-metabolizing CYP enzymes by artemisinin, in which the prostatic heme hydroxylates the periphery of the molecule without interfering with the trioxane nucleus (1).

A number of groups supports a nonheme iron activation process (reviewed in reference 11). Meshnick himself showed that iron chelators antagonize the antimalarial effect of artemisinin (5), a result which is not easily reconciled with a heme activation mechanism (6). Also, that the putative parasiticidal agents are “carbon-centered radicals” generated from the artemisinins by heme or iron(II) (11) is discounted on the basis that Fe(III) (formed by reductive cleavage of the peroxide) oxidizes such radicals to carbocations (2). This has been verified for antimalaria-active peroxides (10).

More work is indeed required in order to acquire a satisfactory understanding of antimalarial activity of this remarkable compound class. Nevertheless, the weight of evidence currently suggests that a specific, as yet unknown target is involved (6). It further follows that interactions of the artemisinin antimalarials with heme and free iron(II) represent competitive decomposition pathways, and thus, if it were possible to design derivatives in which degradation of the trioxane by heme or free iron(II) is inhibited, highly active derivatives would be obtained.

REFERENCES

are crucial mediators of the ability of artemisinin to inhibit heme polymerization. Chem. Biol. 9:321–332.


