Journal of Biomedical and Pharmaceutical Research
Available Online at www.jbpr.in
CODEN: - JBPRAU (Source: - American Chemical Society)
PubMed (National Library of Medicine): ID: (101671502)
Review Article
Volume 8, Issue 5: September-October: 2019, 68-70
ISSN (Online): 2279-0594
ISSN (Print): 2589-8752

# PLASMEPSIN INHIBITORS; IS $PLA_2$ ENZYME THE NATURAL INHIBITOR IN HUMANS AGAINST PLASMEPSINS PRODUCED BY MALARIAL PARASITE IN THEIR ERYTHROCYTIC CYCLE?

**Manoj G Tyagi**
Department of Pharmacology, KM Medical College, Mathura, (U.P.)

**Article Info:** Received 07 September 2019; Accepted 30 September. 2019
**DOI: https://doi.org/10.32553/jbpr.v8i5.655**
**Corresponding author:** Manoj G Tyagi
**Conflict of interest statement:** No conflict of interest

**ABSTRACT:**
Malaria is a mosquito-borne infectious disease that affects humans and other animals. Most deaths in malarial infection are caused by *P. falciparum* because *P. vivax*, *P. ovale*, and *P. malariae* generally cause a milder form of malaria. Within the red blood cells, the parasites multiply further, again asexually, periodically breaking out of their host cells to invade fresh red blood cells. Several such amplification cycles occur. Thus, classical descriptions of waves of fever arise from simultaneous waves of merozoites escaping and infecting red blood cells. Plasmepsin is a hemoglobin-degrading enzyme produced by the plasmodium parasite. It is an aspartic acid protease having 2 aspartic acid residues in the active site. On the other hand phospholipase A2 levels are increased in malarial infection and this may possibly provide protection against the effects of plasmepsin. This review examines the importance of this enzyme and interaction with plasmepsin.

## INTRODUCTION

Malaria kills millions of people every year and new control measures are urgently needed. The recent demonstration that effector genes can be introduced into the mosquito germ line to diminish their ability to transmit the malaria parasite offers new hope toward the fight of the disease (1). Because of the high selection pressure that an effector gene imposes on the parasite population, development of resistant strains is likely to occur (2). Why some children have higher $PLA_2$ enzyme activity is unknown. $PLA_2$ activity is tightly regulated by host responses including TNFα and reactive oxygen species (ROS), both of which can be elevated during severe malaria. Thus the $PLA_2$ pathway and its metabolites may be acting directly on brain microvasculature endothelial cells or indirectly through their effects on cell signaling or energy metabolism (3). Phospholipid metabolism may affect plasmepsin induced effects on the haemoglobin and increased levels of phospholipases found in those infected with the plasmodium species may be a natural protection against the detrimental effects of the malarial parasite. This review examines the possibilities of such an interaction.

### Phospholipid metabolism in the Plasmodium species:

Phospholipid synthetic pathways can provide key information to find and understand the evolution of eukaryotes. Indeed, few phospholipid pathways occur in eukaryotes, which can be parallel redundant routes. The conservation or withdrawal of these routes, throughout evolution, also provide clues to understand membrane lipid dynamics in relation to cell development and, possibly, in the case of infectious pathogens, to introduce novel therapeutical treatments. Consequently, some genes, are markers of complete pathways. However in the case of the malarial parasite, the biosynthesis of phosphatidylcholine (PC), the most abundant membrane phospholipid (PL) in *P. falciparum*, is a remarkable example of the level of parasitic adaptation and dependence toward its host and represents a promising target for novel chemotherapies (4-5). The biosynthesis of phosphatidylcholine (PC), the most abundant membrane phospholipid (PL) in *P. falciparum*, is a remarkable example of the level of parasitic adaptation and dependence toward its host and represents a promising target for novel chemotherapies . In *P. falciparum*, PC can be synthesized de novo by two major routes using

choline (Cho) or ethanolamine (Etn) as precursors (6-7). Incorporation of the three precursors in uninfected erythrocytes was absent or very low in human erythrocytes but significant and marked in some cases in rodent erythrocyte preparations, probably due to the presence of reticulocytes from mouse blood. In the case of infected cells, the values were corrected for the activity of unparasitized cells present in each preparation. Incorporation of the polar heads into the three main PLs and the water-soluble intermediate metabolites was always substantially higher in infected cells than in control unparasitized erythrocytes. On the other hand, the aquaglyceroporins are the only known glycerol channels in mammals. Roles for aquaglyceroporins in lipid metabolism have recently been proposed in adipocytes and liver. According to an article by Dr Peter Agre aquaporin glycerol channels may play an important role in the lipid metabolism and survival of the parasites in the red blood cells and it is possible that high levels of phospholipases in the those having the malarial fever may interact with plasmepsin and prevent its deleterious effects on the haemoglobin and as well as prevent the destructive activity through effects on the aquaporin glycerol channels (8-9). The intracellular molecular mechanism of haem crystallization in an aqueous protein-rich environment, whether by histidine-rich proteins, polar membrane lipids or neutral lipids, has not been fully substantiated (10-11). Bendrat et al. (12) first implicated polar lipids, later substantiated by Dorn et al. (13) with acetonitrile extracts of trophozoites promoting haem crystallization.

**Phospholipase $A_2$ from venom and its antimalarial actions:**

PLA2 will be equally effective in curtailing transmission in this most important parasite-vector combination (14). Whereas reports of attempts to interfere with *Plasmodium* transmission by expression of defensin or single-chain antibodies. The binding of phospholipases to their substrates, such as aggregated phospholipids and membrane surfaces, is independent of their enzymatic activity . Indeed, it has been shown that PLA2 inhibited *Plasmodium* development even when its enzymatic activity was inhibited, suggesting that PLA2 acts primarily via its binding to exposed membrane lipids. Similar antimalarial activity has been shown by venom of some snake species. Two $PLA_{2s}$ from the whole venom were purified and characterized, and their in vitro antiplasmodial activity against P. falciparum was investigated. Cytotoxicity on peripheral blood mononuclear cells (PBMC) and acute toxicity in mice were also evaluated. Results indicate that catalytically-active and inactive PLA2s isolated from B. asper venom are cytotoxic against P. falciparum and, thus have the potential as antimalarials (15).

**Conclusion:**

This question that phospholipid metabolism and increased levels of PLA2 enzyme in the patients affected by malarial parasite may be a natural protectant against plasmepsin should now be investigated through appropriate studies. This is particularly of interest in patients of the African continent where majority of young persons succumb to the menace of malaria. It should be noted that, in *P. berghei*, the PMT pathway is absent and the three enzymes involved in *de novo* PC synthesis are essential implicating that choline is crucial for parasite survival. To conclude, several studies have focused on the malaria asexual blood stages and it could be interesting to extend these labelling assays to gametocytes from different *Plasmodium* species. The analysis of phospholipid content of malaria liver and mosquito stages could also be performed to shed light on other host-parasite interactions, and its effects on the plasmepsin the haemoglobin degrading protease.

**References:**


1. Griffiths MJ, Ndungu F, Baird KL, Muller DP, Marsh K, Newton CR. Oxidative stress and erythrocyte damage in Kenyan children with severe *Plasmodium falciparum* malaria. Br J Haematol. 2001;113:486–91
2. Vadas P, Taylor TE, Chimsuku L, Goldring D, Stefanski E, Pruzanski W, Molyneux ME.Increased serum phospholipase A2 activity in Malawian children with falciparum malaria. Am J Trop Med Hyg. 1993 Oct;49(4):455-9.
3. Ito, J., Ghosh, A., Moreira, L.A., Wimmer, E.A. & Jacobs-Lorena, M. (2002) *Nature,* 417**,** 452-455
4. Ishikawa S, Uozumi N, Shiibashi T, Izumi T, Fukayama M, Shimizu T, Watanabe J, Nogami S. Lethal malaria in cytosolic phospholipase A2- and phospholipase A2IIA-deficient mice. Am J Trop Med Hyg. 2004 Jun;70(6):645-50
5. Farooqui AA, Horrocks LA. Phospholipase A2-generated lipid mediators in the brain: the good,

the bad, and the ugly. Neuroscientist. 2006; 12:245–60.

**6.** Vial, H., and C. Mamoun. 2005. Plasmodium Lipids: Metabolism and Function. *In* Molecular Approach to Malaria. I. Sherman, editor. ASM Press, Washington DC. 327–352.

**7.** Vial, H. J. , S. Wein, C. Farenc, C. Kocken, O. Nicolas, M. L. Ancelin, F. Bressolle, A. Thomas, and M. Calas. 2004. Prodrugs of bisthiazolium salts are orally potent antimalarials. *Proc. Natl. Acad. Sci. USA.*101: 15458 – 15463

**8.** Agre P, King LS, Yasui M, Guggino WB, Ottersen OP, Fujiyoshi Y, Engel A, Nielsen S (2002) J Physiol 542:3–16.

**9.** D Promeneur, Y Liu, J Maciel, P Agre, L S. King, and N Kumar. Aquaglyceroporin PbAQP during intraerythrocytic development of the malaria parasite Plasmodium berghei. PNASc, 2007 vol. 104 no. 7 2211–2216

**10.** Sullivan, Jr, D. J., Gluzman, I. Y. and Goldberg, D. E. (1996) Plasmodium hemozoin formation mediated by histidine-rich proteins. Science 271, 219–222

**11.** Egan, T. J. (2002) Physico-chemical aspects of hemozoin (malaria pigment) structure and formation. J. Inorg. Biochem. 91, 19–26

**12.** Bendrat, K., Berger, B. J. and Cerami, A. (1995) Haem polymerization in malaria. Nature 378, 138–139

**13.** Dorn, A., Vippagunta, S. R., Matile, H., Bubendorf, A., Vennerstrom, J. L. and Ridley, R. G. (1998) A comparison and analysis of several ways to promote haematin (haem) polymerisation and an assessment of its initiation in vitro. Biochem. Pharmacol. 55, 737–74

**14.** Luciano A. Moreira, Junitsu Ito, Anil Ghosh, Martin Devenport, Helge Zieler, Eappen G. Abraham, Andrea Crisanti, Tony Nolan, Flaminia Catteruccia and Marcelo Jacobs-Lorena. Bee venom phospholipase inhibits malaria parasite development in transgenic mosquitoes. *J. Biol. Chem., 2002*

**15.** Juan Carlos Quintana Castillo, Leidy Johana Vargas, Cesar Segura, José María Gutiérrez and Juan Carlos Alarcón Pérez.*In Vitro* Antiplasmodial Activity of Phospholipases A2 and a Phospholipase Homologue Isolated from the Venom of the Snake Bothrops asper.Toxins 2012, 4, 1500-1516;