Review Article

A REVIEW OF MANIPULATIONS IN PLASMODIUM – MOSQUITO INTERACTIONS

Adedotun A Adedolapo[1], Morenikeji Olajumoke A[2]

SUMMARY

A key requirement for transmission of malaria parasite is an infected blood meal that initiates parasites transmission cycle. The malaria parasite and its mosquito require differing biting rates of mosquito to ensure parasite transmission success and mosquito reproductive success. The trade-off existing between mosquito biting rate and survival further constrains the attempts by both partners to minimize their successes. This review discusses the attempts by malaria parasites to enhance the transmission and the defense system of its vector to resist infection. This article is a review of several articles obtained from the Internet, www.pubmed.com, medline and several authors via e-mail.

KEY WORDS: Malaria Transmission, Plasmodium SPP.

Pak J Med Sci October - December 2008 (Part-II) Vol. 24 No. 6 898-901

How to cite this article:

Adedotun AA, Morenikeji OA . A review of manipulations in plasmodium–mosquito interactions. Pak J Med Sci 2008;24(6):898-901.

INTRODUCTION

Malaria, every year, results in 300-500 million clinical cases, one million deaths and is responsible for about 20% of all deaths among children under five years in Africa.[1] Malaria parasites, *Plasmodium* spp, require female anopheline mosquitoes as vectors for sexual development and transmission to vertebrates. These female mosquitoes require a blood meal from a vertebrate host to obtain nutrients to sustain oogenesis and reproduce. *Anopheles gambiae*, a highly anthropophilic mosquito, is the principal vector of human malaria in Africa.[2]

Upon ingestion, parasite gametocytes are rapidly activated to produce gametes in the mid gut of mosquitoes. Fertilization follows, leading to formation of a motile ookinete which penetrates the mid gut. The ookinete ceases its migration upon reaching the basal lamina separating the mid-gut and haemocoel compartments. Here the ookinete undergoes differentiation into the oocyst form. Oocysts grow over a period of days to produce many sporozoites each. These sporozoites are released into the haemolymph to colonize the salivary gland. They reach the salivary duct to be injected into a vertebrate host during mosquito blood feeding.[3]

A long held view among parasitologists is that infection by malaria parasites does not harm their mosquito vectors. Both partners benefit from increased survival and an increased rate of blood feeding – the mosquito to

1. Miss. Adedotun Adedolapo A, Postgraduate Student,
2. Dr. Morenikeji Olajumoke A, Lecturer,
1-2: Department of Zoology, University of Ibadan, Nigeria.

Correspondence

Dr. Morenikeji Olajumoke A,
E-mail: jumokemorenikeji@yahoo.co.uk
jumoke.morenikeji@mail.ui.edu.ng

* Received for Publication: January 24, 2008
* Revision Received: January 26, 2008
* Revision Accepted: October 17, 2008

increase its reproductive success and the parasite to ensure its own transmission.[4] However, mosquitoes face trade-offs during blood feeding.[5] On one hand, fecundity of the mosquito increases with increased rate of blood feeding because of the strong positive correlation that exists between the amounts of blood imbibed by the mosquito and the number of eggs it lays.[6] On the other hand, blood feeding increases the risk of mosquito mortality since mosquitoes are likely to be killed by the irritated vertebrate host while feeding or trying to feed, or by predators due to mosquito's increased mass. This trade-off constrains the mosquito while the malaria parasite's attempt to maximize their successes. Coupled to this constraint is the difference in the frequency of blood feeding required by mosquito and malaria parasite to maximize their successes. Koella[7] described a simple model of mosquito reproductive success and *Plasmodium* transmission success as a function of mosquito biting rate. It was concluded that the parasite's success is maximal at a biting rate that is higher than required for maximal mosquito's success, as long as transmission increases more rapidly with fecundity with biting rate.

This article discusses the evolutionary consequences of the differing frequencies of mosquito blood feeding required by mosquito and its malaria parasite.

Manipulation of mosquito by malaria parasite: In *Plasmodium*-mosquito interactions, it is in the interest of both partners that the mosquito survives for a long time (at least until the infectious sporozoites have developed) and bite frequently.[4] However, since the biting rate that is optimal for the mosquito is not optimal for the malaria parasites; *Plasmodium*, therefore tries to manipulate several aspects of its mosquito vector's biting behaviour in a way that should increase its own transmission success.[8] This mode of manipulation is stage specific i.e. it is dependent on the parasite's developmental stage.

The oocyst is the non-transmissible stage of *Plasmodium*. It must develop for several days in the mosquito mid-gut wall before it can produce sporozoites, the only stage that can be transmitted to the vertebrate host. The only way to increase overall transmission during this developmental period is to increase its mosquito vector's survival of which experiments have investigated. The persistence with which *Anopheles stephensi* mosquitoes attempt to feed on human host is decreased if they are infected with oocysts of the parasite *P. yoeli nigeriensis* as opposed to a higher persistence in sporozoite – infected mosquitoes.[9] Corroborating this is the finding by Koella and co-workers[10] that oocyst of *P. gallinaceum* decreased the blood volume that *Aedes aegyti* takes up for it to be satiated. *Plasmodium* infected mosquitoes took up less blood than uninfected mosquitoes if they had been starved for 6 days (when parasites would have developed into oocysts) (Fig-1).

The amount of blood is expressed as the residual after controlling; in particular, for the amount of time the mosquitoes were allowed to feed. In infected mosquitoes, the parasites had developed into mature oocysts after 6 days and into sporozoites after 12 days.[10]

At the sporozoite stage, the parasite's interest lies in its mosquito vector's frequent biting while the mosquito vector is more interested in its own survival. This is because the parasite's transmission increases more rapidly with biting frequency than mosquito fecundity.

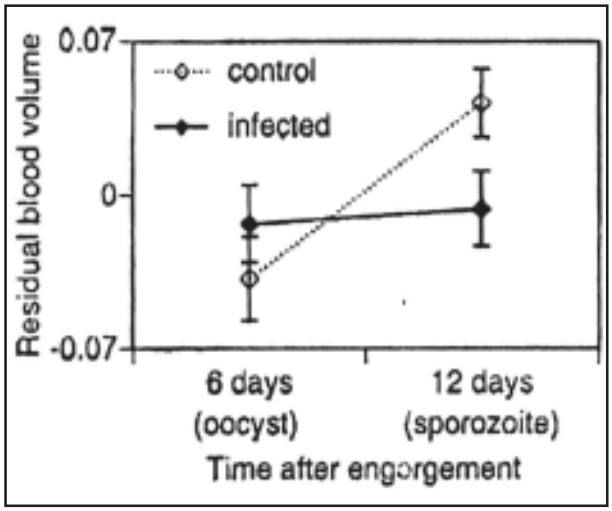

Figure-1: Amount of blood imbibed by *Plasmodium*-infected mosquitoes 6 or 12 days after the previous engorgement.

So also, transmission of parasite occurs during biting while oviposition occurs days after biting.[4] Behavioural manipulations have been observed in both laboratory and field experiments that malaria parasites manipulated mosquitoes to bite more. Sporozoite infection in mosquitoes caused an increase in the duration of probing and number of probes.[11] Sporozoite infected mosquitoes were also more persistent in biting.[9] Koella and co-workers[10] showed that sporozoites increased the volume of blood required by their mosquito vectors to be satiated and quit host seeking, thereby causing the mosquito vector to bite more.

The gametocyte stage, although a vertebrate stage of *Plasmodium*, has also been implicated in the behavioural manipulation of mosquitoes to aid *Plasmodium* transmission. Lacroix and co-workers[8] investigated this issue and showed in a semi-natural experiment that children infected with gametocyte stages of *Plasmodium* attracted twice as many mosquitoes to themselves as the uninfected children and those harboring asexual stages (Fig-2). However, when infected children were treated, all children had similar attractiveness to mosquitoes. Of all these manipulations, only that of the sporozoite stage has a known mechanism. *Plasmodium* sporozoites reduce the apyrase activity of the mosquito vector thereby causing difficulties in obtaining a full blood meal. The result of this is biting more often.[12]

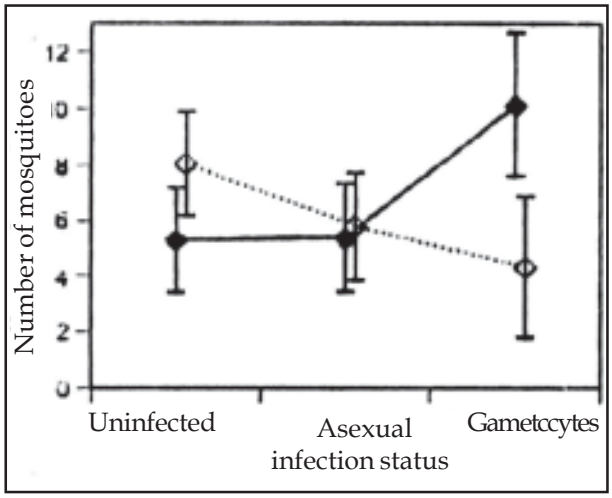

Figure-2: Effect of *P. falciparum* infection in children on their attractiveness to *An. gambiae* (8)

Resistant mechanism in mosquito: The insect innate defense system represents a potentially formidable obstacle to the survival and growth of infecting microorganisms and eukaryotic parasites, in particular those which, like *Plasmodium*, undergo profound developmental changes associated with the invasion of multiple host tissues.[13] The innate immune response of mosquito is activated during mid gut invasion[14] and there is increasing evidence that the mosquito mid gut is an immune-competent organ inducing several immune markers in response to *Plasmodium* infection.[15] Several types of defence mechanisms have been documented in mosquitoes against *Plasmodium.* These are melanotic encapsulation of *Plasmodium* ookinetes at a later stage as they initiate oocyst development,[16] lysis of migrating ookinetes within the mid-gut epithetial cells[17] and destruction of parasites by mosquito immune system peptides. These responses are genetically as well as morphologically distinct,[13] so that one would expect resistance to spread in a mosquito population infected by malaria parasites. However, defence reactions, with melanization being the most studied, are rare in infected field-caught mosquitoes.[18,4] This could be due to the fitness cost of immune response, for instance, defense reactions that result in the melanotic encapsulation of parasites are reproductively costly. Both melanization and egg tanning require tyrosine, so a competition for limited resources ensues ultimately resulting in a reproductive cost (lower fecundity) for the mosquito.[19] Another reason for this lack of immune response in national populations could be down-regulation or evasion of mosquito immune system by *Plasmodium*.[19]

CONCLUSIONS

The epidemiological success of *Plasmodium* is partly due to its very high intensity of transmission. This intense transmission is largely due to the parts of *Plasmodium*'s life cycle that takes place within its mosquito vector, particularly the interaction between the lifespan of mosquito, the duration of the parasite's development and mosquito biting rate.[8] The

knowledge of *Plasmodium*-mosquito interactions is thus of epidemiological importance.

It is also clear that parasite transmission depends on the molecular and cellular interactions acting at different levels of parasite's lifecycle in vector. Understanding these interactions and identifying the molecules involved will provide valuable information that can be exploited in designing novel transmission blocking strategies for vector borne pathogens.[20]

REFERENCES

1. The World Malaria report 2005. Geneva: World Health Organization. http://rbm.who.int/wmr2005/
2. Barillas-Mury C, Kumar S. Plasmodium – mosquito interactions: a tale of dangerous liason. Cellul Microbiol 2005;7(11):1539-45.
3. Touray MG, Warburg A, Laughinghouse A, Kretti AU, Miller LH. Developmentally regulated infectivity of malaria sporozoites for mosquito salivary gland and the vertebrate host. J Exp Med 1992;175:1607-12.
4. Schwartz A, Koella JC. Trade-offs, conflicts of interest and manipulation in Plasmodium – mosquito interactions. Trends Parasitol 2001;17:189-94.
5. Roitberg BD, Gordon I. Does the *Anopheles* blood meal-fecundity curve, curve? J Vec Ecol 2004;3(1):83-6.
6. Hurd H, Hogg JC, Renshaw M. Interactions between blood feeding, fecundity and infection in mosquitoes. Parasit Today 1995;11:411-6.
7. Koella JC. An evolutionary view of the interactions between anopheline mosquitoes and malaria parasites. Microbes and Infect 1999;1:303-8.
8. Lacroix R, Mukabana WR, Gouagna LC, Koella JC. Malaria Infection Increases Attractiveness of Humans to Mosquitoes. PLoS Biol 2005;3(9):e298.
9. Anderson RA, Koella JC, Hurd H. The effect of *Plasmodium yoelii nigeriensis* infection on the feeding persistence of *Anopheles stephensi* Liston throughout the sporogonic cycle. Proc R Soc Lond B Biol Sci 1999;266:1729-33.
10. Koella JC, Rieu L, Paul REL. Stage specific manipulation of a mosquito's host-seeking behaviour by the malaria parasite *Plasmodium gallinaceum*. Behav Ecol 2002;13:816-20.
11. Koella JC, Sorensen FL, Anderson R. The Malaria parasite *Plasmodium falciparum* increases the frequency of multiple feeding of its mosquito vector *Anopheles gambiae*. Pro R Soc Lond Sen B 1998;265:763-8.
12. Rossignol PA, Ribeiro JMC, Spielman A. Increased intradermal probing time in sporozoite infected mosquitoes. Am J Trop Med Hyg 1984;33:17-20.
13. Richman AM, Dimopoulos G, Seeley D, Kafatos FC. *Plasmodium* activates the innate immune response of *Anopheles gambiae* mosquitoes. Embo J 1997;16:6114-9.
14. Osta MA, Christophides GK, Katafos FC. Effects of Mosquito genes on *Plasmodium* developments. Sci 2004;303:2030-2.
15. Han YS, Thompson J, Katafos FC, Barillas-Mury C. Molecular interactions between *Anopheles stephensi* midgut cells and *Plasmodium berghei:* The time bomb theory of ookinete invasion of mosquitoes. Embo J 2000;19(22):6030-40.
16. Collins FH, Sakai RK, Vermick KD, Paskewitz S, Seeley DC, Miller LH, et al. Genetic selection of a *Plasmodium*-refractory strain of the malaria vector *Anopheles gambiae*. Sci 1986;243:607-10.
17. Vermick KD, Fujioka H, Seeley AC, Tandler B, Aikawa M, Miller LH. *Plasmodium gallinaceum*: A refractory mechanism of ookinete killing in the mosquito *Anopheles gambiae*. Exp Parasitol 1995;80:583-95.
18. Naire O, Markianos K, Volz J, Odul F, Toure A, Bagayoko M, et al. Genetic loci affecting resistance to human malaria parasite in a West African mosquito vector population. Sci 2002;298:213-6.
19. Beernsten BT, James AA, Christensen BM. Genetics of Mosquito Vector Competence. Microbiol Mol Biol Rev 2000;64(1):115-37.
20. Osta MA, Katafos FC, Christophides GK, Vlachon D. Innate immunity in the malaria vector *Anopheles gambiae*. Comparative and function genomics. J Exp Biol 2004;207:2551-63.