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Plasmodium and mosquito behavior: A review

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Abstract
This study was conducted at Department of Zoology, University of Gujrat, Pakistan during April 2016-July 2016. The data for the last two decades regarding Mosquito behavior and *plasmodium* was compiled through a thorough review of research articles published in various journals of international repute. The main purpose of this review is to differentiate between *plasmodium* infected and uninfected female mosquito. *Plasmodium* manipulate the host to increase its own transmission. The most obvious changes induced in mosquito due to *plasmodium* is increase in its biting rate towards human host. Infected female bite more than uninfected female. *Plasmodium* increases the vector longevity for its own survival. The fecundity of *plasmodium* infected mosquito is greatly reduced. There is a modification in the head region of mosquito and protein expressions in infected and uninfected mosquito are different. So when we differentiate between infected and uninfected mosquitoes the control measures are very easy. Then we will focus on only infected mosquito and it will save the cost and time as well as environmental hazards are reduced.

Keywords: Host manipulation, mosquito behavior, *Plasmodium*

Introduction
Many harmful parasite induced diseases are transmitted by blood sucking insects [7]. Now a day's people facing many health problems which are related to emerging and re-emerging vector borne diseases [2]. Many efforts and steps have been taken to manage and eradicate the mosquito but it kill many people every year by malaria [4]. Over 200 million people are affected all over the world each year and 770 thousand deaths occurred per year [28]. Malaria is the oldest disease as it infected our ancestors before the origin of human being. Recently its influence is greater than any other infectious agent [13]. Malaria is more common in tropical and subtropical areas of the world in Asia, America and Africa [9]. Malaria is a major communicable disease and transmitted by female *Anoheline* mosquito species [5]. Due to malaria about 2-5% human deaths occurred in 20th century. In 2000, 20% of all deaths are considered by malaria in Africa. Most cases of malaria in humans are due to *Plasmodium falciparum. P. falciparum* is transmitted by blood meal when female Anopheles bite. Female Anopheline depends upon the blood for their reproduction [14]. In anopheles species *Anopheles gambaie* is important as a *plasmodium* vector [10]. The intensity of malarial transmission depends upon the vector feeding rate and survival time of adult female [14]. In the world about 3,500 species of mosquito are present [1]. Mosquito is a serious pest of public that transmit pathogens and spread many diseases such as malaria, yellow fever, west Nile fever etc. [1]. *Plasmodium* is a causative agent of malaria and it completes its life cycle in the host (mosquito) [4]. The pest that transmit pathogens are called vector and mosquito is a major pest than any other group [2]. Mosquito is the only vector that is responsible for the transmission of malaria [3]. It means mosquito is an obligate vector for malaria transmission. The vector success is depends upon its high reproductive capacity and its biological fitness [15]. *Plasmodium* development in the mosquito is very complex process and it requires two epithelial layers for crossing that are mid gut and salivary gland. To cross from these epithelial layers there is a requirement of specific interaction between *plasmodium* and surface molecules of epithelial layer [4]. Host manipulation is a well-known process in vector borne parasites. For control measures it is necessary to differentiate between infected and uninfected female mosquito [20]. Parasite changes the host phenotype and increase its own fitness. And chances that larvae transmit from intermediate host to next host increases. These are different from passive changes in host behavior due to any infection. Active changes in host behavior increase the parasite fitness but it is hard to differentiate that either it is alter behavior due to parasitism or adaptation against the parasite [6].

Plasmodium have the ability to change the behavior of their host and as a result it increases their transmission efficiency [3]. It also increases vector longevity, amount of contact between vector and host and reduce vector reproductive output [7]. Parasitologists considered that some genes are responsible for the alteration of the host behavior and when these genes express in host they alter the phenotype of the host. Parasite secretes some chemicals or induce their production in the host than these chemicals act upon the central nervous system and manipulate the behavior of the host [3]. Behavioral changes in the infected mosquito provide benefit to the *plasmodium*. Host behavioral changes after infection is a true compromise between parasite and host [8].

Objective

- To understand the changes induced in mosquito by *plasmodium*.
- To check the difference between infected and uninfected mosquito.

***Plasmodium* Life Cycle**

There are two distinct phases of *plasmodium* life cycle. Asexual phase in humans and sexual phase in mosquito. Asexual phase started when infected female mosquito inject the sporozoites through biting in blood than these sporozoites migrate to liver, they invade hepatocytes, this is the hepatic stage of parasitic life cycle. In the liver they multiply in number and differentiate in to schizonts and containing thousands of hepatic merozoites. Then these merozoites come into the blood and invade red blood cells and replicate this stage is known as erythrocytic stage of plasmodium life cycle. Some of these blood parasites develop in to gametocytes asexually and transmit to Host mosquito when mosquito bite and take blood meal. But in some cases sporozoites don't develop into schizonts and remain uninucleate stage and called hypnozoite and remain for weeks, months or even years [11]. Gametocytes in the human host may be male gametocyte or female gametocyte. Then sexual phase begin when female mosquito take these gametocytes. Male gametocyte differentiates and fertilize the female gametocyte in mosquito. Then parasite become ookinete, penetrate to mosquito gut and form oocyst. Then parasite multiplies asexually and form hundreds of sporozoites in the oocyst. Then these sporozoites release from oocyst and reach to salivary glands then penetrate into the walls of salivary glands and reach to stored saliva of mosquito. Now they are ready for transmission to vertebrate host when female mosquito take another blood meal [12]. In infected mosquito oocyst developed in 6 days and sporozoite developed in 12 days [45].

Manipulations in Mosquito Behavior

The special requirement for malaria transmission through female mosquito is an infected blood meal [45]. Mosquito is not a mechanical vector of its parasite *(plasmodium*) but responsible for the growth, development and reproduction of plasmodium. So majority of vectors (mosquito) die before they take a blood meal which are transmitted by infected parasite [7]. Some scientists considered that the vector Anopheles is unaffected by the activities of the *plasmodium* [17]. But it is not true, parasite try to manipulate the mosquito life history and its feeding pattern to increase its own transmission [16]. The biting rate which is sufficient for mosquito is not sufficient for parasite so it manipulate its host to increase transmission [45]. The phenotype of female is changed when she feed on infected human [44]. But in some cases host manipulation may reduce other functions such as growth [43]. Some behavioral changes can be adaptations against the parasite but not all behavioral changes are parasitic adaptations, some changes induced by the *plasmodium* to increase its own transmission and its reproductive success [17].

Increased Contact between Vector and Host

Mosquito seek the host due to three main reasons (1) for appetite (2) attraction (3) activation and orientation [51]. Attraction, activation and orientation are the mosquito response due to human odor, visual cues, and heat and to lesser extent are water vapors and sound [51]. Human odor is an important factor for contact between vector and host [22]. And it is the dominant indication to locate the blood meal. It is the olfactory mediated response for looking for the host [28]. Some chemicals are present in human odor and infected female mosquito show different behavior to those chemicals [22]. Mosquito respond to lactic acid, fatty acid, carbon dioxide, [47] ammonia, acetone, octanol, phenolic components of urine and sweat [51] are associated to host. Mosquito also respond to heat and visual cues [47]. The mosquito odorant receptor's response to human odor is developmental stage specific [44]. Female is more attracted toward emanating human skin than clear substrate [28]. Infected female is three times more attracted toward humans than uninfected female [22]. And similarly infected human host have more attraction for mosquito. The symptoms of malaria make easier and safer transmission. Symptoms include rise in body temperature, sweating, increased Carbon dioxide output which are attractant for mosquito and mosquito will not be swatted [49]. But it depends upon the blood meal. If female ingests blood meal which is less than the threshold blood meal than she continues for seeking the host. But if they ingest great volume of blood meal than she rest until blood meal is digested [24]. And this fasting is beneficial for parasite. Because when female not feeding she is not swatted. Due to hunger parasites migrate to salivary glands of mosquito. So we can say that when female is hungrier the more they feed and chances to finding new host are greater [46]. Taking of blood meal is not depended upon the infection status. The blood feeding behavior also not depends upon the age of female [27]. When a female mosquito take a blood from infected human it is not readily able to bite another human because at that time parasite is not infectious it undergo some developmental stages to become infectious. At that time female mosquito is less attracted to human host and have less feeding rate. Probing duration is shorter and she probes less frequently. Then *plasmodium* develop in midgut for 10-14 days. Then parasite reach to the salivary glands through hemolymph and stored in the saliva now female mosquito is able to bite another human host [18]. Saliva helps to locate the blood vessels of human host [25]. At this stage she is more attracted toward human host [18]. Some pheromonal cues in humans attract the mosquito at gametocyte stage. Three groups of children were placed in tent, one uninfected, one infected with gametocytes, and other is infected with non-infected malarial stage. And it was observed that mosquito is more attractant toward gametocyte infected children [49].

Biting Rate

Due to change in feeding behavior of mosquito parasite easily transmitted from one human to other [29]. Feeding patterns

depends upon the host preference, availability of host, requirement of blood, and vector density [31]. Intensity of malaria transmission depends upon the multiple or mixed blood meal from two or more than two hosts which belong to same species or different species [31] and it depends upon how much person is infectious, mosquito number and its survival, duration of feeding cycle, tendency of biting, time of parasite development in the mosquito [33] number of gametocytes inoculated and index of malaria stability [35]. The biological characteristics of mosquito also interact with climate and affect the malarial transmission [38]. There is a close relationship between seasonal variations and differences from house to house in malaria transmission [40]. There is great effect of temperature on gonotrophic cycle, and development of ovaries. These variables are sensitive to temperature. Malarial transmission also varies according to temperature. By decreasing the time of gonotrophic cycle increase the vector and host contact and increase malaria transmission [41]. And interrupted the blood feeding will increase the malaria transmission but it is argued that interrupted blood feeding don't increase parasite transmission because small number of gametocytes are ingested and infection rate also less [31]. Malaria infection occurs not only due to blood feeding but probing the host skin also cause the malaria. The sporozoites that are injected in the skin stay five minutes in the skin and then migrate toward the blood vessels [32]. Biting rate vary with time and it is higher in wet season [39]. Rate of landing and biting is three times greater in infected female [22]. Greater percentage (81%) of infected and less percentage (38%) of uninfected females are involved in biting purpose [27]. Mosquito usually don't bite when eggs are developing. And digestion of blood meal takes several days so at that time mosquito search a safe place for resting. Mosquito rest in cattle sheds, houses, vegetation, outdoors and on natural sites. Anopheles mosquito bite at the time of dawn and dusk. Each species have specific biting hours and indoor and outdoor preference also vary [21]. Feeding behavior of mosquito changes according to developmental stage [23]. Biting rate increases not only on same individual but also on different host [48]. Biting rate depends upon the developmental stage of the parasite; when they are at sporozoite stage they are ready for transmission to the vertebrate host, and parasite increases the biting rate of its vector [19]. At sporozoite stage mosquito require large amount of blood meal [45]. Salivary apyrase (anticoagulant injected with saliva) [50] activity is reduced to third at the mature sporozoite stage. But those regions that are invaded by sporozoites have normal apyrase activity. Salivary apyrase produced in equal amount in sporozoite infected and uninfected female mosquito. Due to sporozoite infection vector did not locate the blood vessels of host so it bite again and again [25] to top up its blood meal [50] and increased host contact [25]. Due to increased biting rate more sporozoites are deposited in skin than blood due to inability of finding blood vessels [26]. In contrast when they are at the oocyte stage they are not ready for transmission, it reduces the contact between vertebrate host and vector and as a result decreases the biting rate [19].

Vector Longevity

The mean longevity between infected and uninfected mosquitoes is significantly different [53]. By changing the resource management and increase available nutrients and avoid reproductive cost would increase the vector longevity [51]. Mosquito don't bite at the oocyst stage the main reason for not biting at this stage is that oocyst increase the mosquito survival. Oocyst stage inhibit the host seeking behavior [24]. Survival of mosquito is neither depended upon the age [34] nor its size [36]. There are some evidences which show that parasite induced infection increase the mortality of infected female mosquito. The reason of mortality is difficulty of obtaining blood and increased biting rate, the irritated host and by predators when mosquito mass increases [45] (host defensive mechanism) may involve and it cause the mortality [29]. In infected mosquito there are two mortality stages while in non-infected mosquito only one mortality stage. In infected mosquito mortality is high at rupturing of oocyst and then rupturing of salivary glands [53].

Reduced Fecundity

In *plasmodium* infected mosquito fecundity has been reduced [58]. Because when fecundity increased it limit the resources that are used for the survival, and laying eggs may increase the risk of mortality. Reduced fecundity might the immune response of mosquito or it is an accidental by-product of infection. Fecundity also reduced due to manipulation of vitello-endocrine system of mosquito [57]. Reduced production of eggs may increase the life of the host and nutrients released from blood used both host and parasite that would otherwise use for oogenesis [54]. It is adaptive strategy of the parasite aimed at redirecting resources towards longevity [55]. But longevity of mosquito due to parasite is highly controversial [56]. There is a negative correlation between parasite burden and the number of oocysts. Significantly less number of viable larvae are produced by infected female mosquito as compared to uninfected female [54]. Parasite is interested in its own survival and transmission rather than mosquito fecundity. So when mosquito bite its oviposition is delayed. Some evidences show that fecundity of infected female mosquito increases due to due to increased rate of blood feeding because there is a positive correlation between blood feeding and egg laying [45]. The infected female has relatively low EPG as compared to uninfected female [44].

Decrease in Population Size

When biting rate increases it will reduce the size of vector population which are required to sustain the parasite, so it making difficult to eliminate the parasite. The mechanism behind this is that parasite impairs the vector's ability to obtain a full blood meal and therefore induces the vector to bite several times before it is fully engorged. Because it's difficult to obtain full blood meal because blood flow through the foregut is impaired. So it probes several times, as probing is infectious several hosts can be infected by one mosquito. Sporozoites of parasite (plasmodium) reduces the apyrase activity in the salivary glands of infected mosquito and as result the ability of mosquito to locate the blood is impaired and it probe longer and multiple times than uninfected mosquito. Transmission is likely to be increased during probing. Infected mosquitoes not easily interrupt their feeding when they are disturbed, or that they are more likely to continue their feeding if they have been interrupted. But it is not clear that increased biting frequency will increase the transmission of parasite [60].

Modification of Head Proteome

There is a modification in the head region of mosquito which indicate the different protein expressions in infected and uninfected mosquito [52]. Malaria parasite causes modification to the head proteome of its host. Level of 12 protein spots altered in the infected mosquito. These proteins potentially

identified and classified. These proteins belonged to metabolic, synaptic, molecular chaperone, signaling, and cytoskeletal groups. Behavioral modification is due to change in ATP synthesis: (I) directly through the potential roles of ATP as neuromodulators and (ii) indirectly through modifications of cellular energy metabolic mechanisms that subsequently have detrimental effects on neuronal cells [59]. Changing the expression of 12 proteins in mosquito head [52]. For example protein that is involved in olfactory system it change the sense of smell in infected mosquito. It changes the olfactory mechanism to bind the airborne stimulants [52]. Some biochemical pathways changed in infected mosquito [49]. Parasite inhibit some of the processes in the host so it is less chosen by others [51].

Resistance Mechanism in Mosquito

Sometimes parasites invade the multiple host tissues and the innate defense system of mosquito may activate and it restarted the parasite development. Immune response mostly active when parasite invade the midgut. Mid gut act as immune competent organ which have several immune markers. Many types of resistance mechanisms are present in mosquito melanotic encapsulation of ookinetes when they begin oocyst development, destruction of migrating ookinetes in midgut epithelium and parasites are destroyed by immune system peptides. However defense reaction with melanization are rare. Melanization egg production require tyrosine so competition rises for limited resources and it reduced fecundity [45].

Control Measure

The main focus in control measure is to interrupt the transmission of *plasmodium* parasite from one human to other [37]. Nets treated with insecticides reduced the malarial transmission [42].

Conclusion

The alterations of mosquito behavior have major impact on malaria transmission. All these changes increase the transmission. But in some cases the altered behavior of mosquito is only the adaptation against the parasite. The altered behavior of mosquito is either due to infection, mosquito immune response, or the interaction between these two. So when we understand the altered behavior of mosquito then in the malarial control process we target the manipulated phenotype.

Recommendations

There is further work required on the mortality pattern associated with blood feeding. Some evidences which show that parasite induced infection increase the mortality of infected female mosquito. There are many views about the vector longevity. According to some evidences plasmodium increase the vector longevity for its own survival. But the mechanism is not clear.

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