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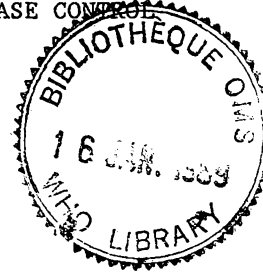
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ENGLISH ONLY
 (avec résumé en français)

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INNOVATIVE APPROACHES TO VECTOR-BORNE DISEASE CONTROL

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1. Introduction

In view of the difficulties now being faced by vector-borne disease control in the areas of pesticide use, chemotherapy/prophylaxis and vaccine development, it is strongly indicated to intensify the search for other, innovative methods.

The field is a wide one, including such current topics as improved environmental management methods, new biological control agents and refined methods of pesticide use and application.

Several opportunities for new approaches, however, clearly lie in the area of vector physiology including, for example, immunological (both active and passive), metabolic and structural barriers to ookinete and sporozoite development and movement.

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A few selected avenues of research, which apply mainly (but not exclusively) to mosquito disease vectors, are outlined below under four broad headings:

- (a) invertebrate vector immune systems;
- (b) reaction of mosquitos to mammalian antibodies raised against mosquito tissues;
- (c) the significance of symbionts in vector reproduction and susceptibility to infection; and
- (d) possible effect of antibodies ingested along with the bloodmeal on the development of the disease organism in the vector.

2. Invertebrate vector immune systems

Cellular and humoral immune mechanisms are present in Diptera and other insects, and research in this field has been making progress in the last few years (Lackie, 1986). It is therefore reasonable to expect that such progress will eventually provide the possibility of manipulation of these mechanisms for interruption of disease transmission in a manner parallel to that of the mammalian host immune system.

Cellular reactions include phagocytosis, nodule formation and cellular encapsulation, while humoral reactions consist of humoral encapsulation and the formation of antibacterial proteins and other antibiotic factors.

In addition, the recent demonstration of stable integration and expression of a bacterial gene in the malaria vector Anopheles gambiae (Miller et al., 1987) further emphasizes the possibility of manipulating the physiology of mosquito populations, and this may eventually lead to important advances in vector-borne disease control.

3. Reaction of mosquitos to mammalian antibodies raised against mosquito tissues

In the past there have been relatively few attempts to investigate this question in Diptera. These have included examination of the effects in such species as Anopheles stephensi (Alger & Cabrera, 1972), Aedes aegypti (Sutherland & Ewen, 1974), Stomoxys calcitrans (Schlein & Lewis, 1976) and Sarcophaga falculata (Schlein et al., 1976).

In general it was found that the more specific and refined the antigen, the greater the immunopathological impact of the antibodies raised. Thus, in An. stephensi, the mortality rates of mosquitos which fed on rabbits injected with midgut antigen were higher than those of mosquitos which fed on rabbits injected with whole mosquito antigens. In respect of the midgut tissue antigen, four possible reasons are put forward to explain its greater impact:

- (a) mechanical damage to cells in the digestive tract;
- (b) inhibition of a protease or other specific enzyme;
- (c) reduction of the absorptive surface of the gut lining by binding together of the microvilli; and
- (d) death of the bacterial flora in the gut.

It is clear, however, that even by using midgut alone, a competing series of antigens may still be involved. Clearance of the bacterial flora of the gut is considered further in section 4 below.

In experiments with Ae. aegypti, where whole mosquitos were used as antigen material, reduced fecundity was observed, but not increased mortality. It would therefore seem to be worthwhile to continue these types of trial with different vector species and more refined antigen material.

One further important principle was established in the course of some of these early observations, namely that the gut wall does not bar the passage of serum immunoglobulins taken in with the bloodmeal. This is examined in section 5 below.

4. The significance of symbionts in vector reproduction and susceptibility to infection

It has been shown that symbionts, consisting of rickettsia-like organisms, play an important role in tsetse fly reproduction, that they may provide their fly hosts with certain vitamins of the B group and that their removal causes sterility (Nogge, 1976). It has also been demonstrated that tsetse may be made aposymbiotic by allowing them to feed on rabbits which have been immunized specifically with symbionts (Nogge, 1978). Further, results from both field and laboratory reared tsetse show a strong association between susceptibility to trypanosome infection and presence of rickettsia-like symbionts (Maudlin & Ellis, 1985).

Recently these rickettsia-like organisms have been cultivated in vitro using a mosquito cell line derived from Ae. albopictus (Welburn et al., 1987).

The presence of rickettsia-like organisms, primarily Wolbachia spp., in mosquitos has been recorded by several workers (Ferguson & Micks, 1961; Micks et al., 1961; Wright & Wang, 1980), but the possible biological effects of such infections have been considered mainly in relation with cytoplasmic incompatibility (Magnin & Pasteur, 1987a,b; Yen & Barr, 1983). However, some observations have been made on a possible connection with filarial infections in the Ae. scutellaris complex and in Culex quinquefasciatus (Duhropf & Trpis, 1981; Trpis et al., 1981; Curtis et al., 1983).

While there was some indication of a possible correlation of absence of rickettsia with refractoriness to infection with Brugia malayi in Ae. scutellaris, no such correlation was apparent in the Wuchereria infection of Culex quinquefasciatus.

Despite the above observations on the effects of rickettsial symbionts on susceptibility of tsetse to trypanosomes and of some culicines to filariae, there appears to be a serious gap in our knowledge concerning the possible effects of symbionts on anopheline susceptibility to infection with plasmodia in general, and human plasmodia in particular.

Observations have been made in which certain gut flora did not interfere with sporozoite production, and in fact appeared to play a role in larval and adult nutrition, and even in providing some components for growth of the parasite (Jadin, 1967).

On the other hand observations on a situation where the "rickettsia-like organisms" were evidently more pathogenic to the anopheline host tended to lead to the opposite conclusion (Davies et al., 1971).

This suggests a complexity in the relationships between symbionts/other gut flora/the vector/the vertebrate pathogen, thus emphasizing the need for proper clarification. This type of investigation should, of course, also include other vector-borne diseases such as Chagas' disease, leishmaniasis, plague and arboviruses.

Should there happen to be a parallel with the rickettsiae/tsetse/trypanosome interaction in other vector/parasite combinations, then important new approaches would be opened up for:

- (a) vector control per se by upsetting the vector/symbiont relationship; and
- (b) development of a "transmission-blocking" vaccine based on a purified antigen derived from the symbiont.

The possibility of cultivation of these rickettsia-like organisms has already been noted.

It may also be worth investigating whether symbionts play any role in insecticide resistance, and whether they themselves are affected by exposure to pesticides.

5. Possible effects of antibodies ingested along with the bloodmeal on the development of the disease organism in the vector

It has been shown by several authors that, in certain haematophagous insects, some elements of the bloodmeal may be absorbed directly into the haemolymph without being digested (Wigglesworth, 1943; Nogge, 1971). This may possibly be due to a process of pinocytosis in the midgut epithelium (Smith et al., 1969).

What is of particular interest in this respect is that serum immunoglobulins taken in by a biting fly in the bloodmeal have also been demonstrated to pass from the gut into the haemolymph. Where these antibodies have been raised against selected fly tissues, they were specifically demonstrated in the tissues which had been used as immunizing antigen. Further, it has also been shown that antibodies unrelated to fly antigens can pass through the insect gut wall and still react with their specific antigens (Schlein & Lewis, 1976; Schlein et al., 1976).

It is therefore very likely that, for example, human antisporezoite antibodies can also pass through the anopheline gut epithelium and enter the haemocoel of the insect. The question immediately arises as to:

- (a) whether such antibodies can enter the haemolymph in a sufficiently high concentration to affect mature sporozoites in the haemocoel (i.e. to give a "transmission-blocking" effect); and
- (b) whether the persistence of such antibodies is sufficiently long for their concentration in the haemolymph to be increased by successive bloodmeals containing the antibody.

The above and other similar questions require urgent clarification, both in relation to existing natural levels of antisporezoite antibody and to situations in which these levels may be boosted by use of a vaccine.

6. Conclusion

The selected topics considered in this paper may illustrate some of the many opportunities for investigation of potentially novel approaches to vector-borne disease control and the key position occupied by vector physiology in this respect.

RESUME

APPROCHES INEDITES DE LA LUTTE CONTRE LES MALADIES TRANSMISES PAR DES VECTEURS

Etant donné les difficultés auxquelles on se heurte actuellement pour lutter contre les maladies transmises par les vecteurs, que ce soit dans le domaine des pesticides, de la chimiothérapie/prophylaxie ou de la mise au point de vaccins, il est impératif d'intensifier la recherche de nouvelles méthodes. Sont examinées dans cet article quelques orientations de recherche qui s'appliquent principalement (mais non exclusivement) aux maladies transmises par les moustiques; on peut les classer selon quatre catégories :

- a) Systeme immunitaire des vecteurs invertébrés. On peut raisonnablement s'attendre à ce que les progrès réalisés dans ce domaine permettent d'envisager la possibilité de jouer sur ces mécanismes pour interrompre la transmission de la maladie, comme on le fait déjà avec le système immunitaire du mammifère hôte.
- b) Réaction des moustiques aux anticorps mammaliens produits contre leurs tissus. Cette question a été relativement peu étudiée chez les diptères; on a trouvé qu'en général, plus l'antigène est spécifique, plus l'impact immunopathologique des anticorps qu'il suscite est important.
- c) Importance des symbiotes dans la reproduction des vecteurs et leur sensibilité à l'infection. On a montré que des symbiotes, qui sont des micro-organismes de type rickettsies, jouent un rôle important dans la reproduction de la mouche tsé-tsé et que leur élimination provoque la stérilité. En outre, chez des tsé-tsé élevées en laboratoire ou capturées sur le terrain, on a observé une forte association entre la sensibilité à l'infection par le trypanosome et la présence de symbiotes de type rickettsies. S'il existait un parallèle avec l'interaction rickettsies/tsé-tsé/trypanosome dans d'autres associations vecteur/parasite, de nouvelles perspectives importantes s'ouvriraient alors pour : i) la lutte antivectorielle en elle-même, par la destruction de la relation vecteur/symbiote; et ii) la mise au point d'un vaccin "bloquant la transmission", basé sur un antigène purifié dérivé du symbiote.
- d) Effets éventuels des anticorps ingérés avec le repas de sang sur le développement chez le vecteur du micro-organisme pathogène. Il faut sans tarder élucider cette question, en ce qui concerne d'une part les concentrations naturelles d'anticorps antiparasitaires et d'autre part les cas dans lesquels ces concentrations peuvent être amplifiées par l'emploi d'un vaccin.

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