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Review

About factors that determine trypanotolerance and prospects for increasing resistance against trypanosomosis

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The current threat of African trypanosomosis on sustainable livestock production and food security coupled with failure of tse-tse fly control, chemotherapy and chemoprophylaxis to control the present resurgence of the disease has increased the imperative need for increasing trypanotolerance in livestock. The innate ability of trypanosome infected animals to control anaemia and development of parasitaemia are some of the indicators of trypanotolerance. In the last few years, research had aimed at identifying the various factors involved in trypanotolerance. Even though haematopoietic and anti-trypanosome serum lytic factors have been associated with ability to control the development of anaemia and parasite respectively, trypanotolerance is a genetically defined complex mechanism involving factors which are not yet well known. Recent molecular based research using mice and cattle identified genomic regions controlling trypanotolerance in animals. Although these biotechnologies have not been able to identify the complete pool of genes involved in trypanotolerance, they have raised the hope of producing synthetic breeds of animals with higher trypanotolerance level, and enhancing the tolerance of susceptible breeds.

Key words: Biotechnologies, livestock, mechanisms, trypanotolerance.

INTRODUCTION

African animal trypanosomosis has been described as a major obstacle to sustainable livestock production and food security, and an important factor of underdevelopment in sub-saharan Africa (Onyiah, 1997; Swallow, 2000). The disease has assumed greater global importance with the spread of mechanically transmitted non-tse-tse trypanosomosis due to *Trypanosoma vivax*, to ten out of 13 countries of the South American continent (Jones and Davila, 2001) and parts of Asia. African trypanosomosis has been described as probably being the single most devastating disease in Africa in terms of poverty and lost of agricultural production amounting to 3 billion pounds annually (Hursey, 2000). Furthermore, it is estimated that 50 million cattle are at risk of becoming infected with trypanosomosis leading to more than 3 million livestock deaths yearly, losses in calving, reduction in livestock numbers, drop in meat and milk off-take and reduced work efficiency of draft animals and profitability of mixed farming (Budd, 1999; Hursey, 2000).

We recently observed that trypanosomosis is a major cause of culling of animals form herps and has impact on the physical condition of cattle at slaughter and consequently, the market value (Abenga et al., 2002). In a recent resurgence in tsetse menace and

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trypanosomosis, about 83% mortality rate was observed in a Fulani herd near Saminaka, North Central Nigeria and seasonal migration of semi-nomadic herdsmen from the area (Abenga et al., 2004). The most important species of trypanosome that cause disease in livestock include *Trypanosoma vivax*, *T. congolense* and *T. brucei brucei* (Ikede, 1981), and are widely distributed in agroecological zones of Sub-Saharan Africa. Other species, *T. simiae* and *T. evansi* cause diseases in pigs (Leach and Roberts, 1965) and camels (Scot, 1973) respectively.

About 22 species of tsetse flies, (*Glossina*) principal vectors of trypanosomosis in Africa, infests 75% of the Nigerian land mass, the most important species being, *Glassina morsitans submorsitans, G. tachinoides* and *G. longipalpis* (Onyiah, 1997). The principal methods of control of animal trypanosomosis include integrated tsetse control, chemotherapy and chemoprophylaxis, and use of trypanotolerant animals. The major shortcoming of these methods of control has been described. These include the complicating roles of non-tsetse mechanical vectors such as African tabanids (Desquesnes and Dia, 2003) and stomoxys (Baylis and Stevenson, 1998), changes in climatic conditions leading to wider distribution of tse-tse (Onyiah, 1997), drug resistance (Greerts and Holmes, 1998) and poor acceptance of trypanotolerant animals as means of control (Kamuanga et al., 2001). In Nigeria for example, increased risk of trypanosomosis in animals has been associated with prevalent tsetse infestation including the high lands of Jos, Mambilla and Obudu Plateaux previously known to be tsetse free (Onyiah, 1997). Onyiah (1997) also postulated that if trypanosomosis is controlled or eradicated, tsetse infested areas could support additional 2.5 to 3.2 times the current estimated livestock's population. The continent wide tsetse eradication plan through the Pan-African Tsetse and Trypanosomiasis Eradication Campaign (PATTEC) of the African Union which focuses largely on the use of sterile insect technique commenced since year 2000 (Kabayo, 2004). The shortcomings of this initiative have been described (Bourn, 2002; Shaw, 2002).

For many years, the decreasing efficacy of available drugs and the difficulty of sustaining tsetse control have increased the imperative need to enhance trypanotolerance through selective breeding either within breeds or through cross breeding (d'leteren et al., 1998; Almeida, 1999).

Trypanotolerance has been described as the relative capacity of an animal to control the development of the trypanosome parasite and to limit its pathological effects, the most prominent of which is anaemia (d'leteren et al., 1998; Naessens et al., 2002). According to d'leteren et al. (1999), packed cell volume in particular and parasitaemia, the two principal indicators of trypanotolerance are strongly correlated with animal performance especially, post weaning growth, reproductive performance and overall cow productivity.

They suggested the use of more sensitive trypanosome diagnostic technique such as detecting trypanosome antigens for characterization of parasite growth. Although evidences suggest that trypanotolerance is a relative rather than an absolute trait, and may be affected by nutritional status and stress of work as well as concurrent infections (Seck et al., 2002), certain breeds of ruminants are found able to resist trypanosomosis more than others. This is characterized by ability of such breeds to live in tsetse infested areas.

In West Africa, shorter breeds of cattle; N'Dama and Muturu, and West African Dwarf (WAD) sheep and goats (Murray et al., 1981) are known to exhibit different levels of trypanotolerance, while not much is known about the tolerance status of many other animal species. Similarly, trypanotolerance has been described in Cape buffaloes (Black et al., 2001). According to Food and Agriculture Organization (1987), trypanotolerant cattle are found in 19 countries of West and Central Africa. This constitutes a significant minority of over all susceptible cattle breeds and numbers at risk of trypanosomosis. This makes research on identification of mechanisms involved in trypanotolerance and utilization of such findings in enhancing trypanoresistance of susceptible livestock imperative. We recently described trypanotolerance traits in *T. congolense* infected young Nigerian puppies based on resistance to development of anaemia, parasitaemia control and progressive increase in body weight through out the eight week observation period (Abenga et al., 2005a;b)

Trypanotolerance is a complex mechanism involving factors which are not yet fully known while current results of research into the various factors involved in trypanotolerance remains inconclusive.

HAEMOPOIETIC FACTORS

According to Naessens et al. (2002), two mechanisms are involved in natural resistance to African trypasomosis in cattle, namely; an innate mechanism that controls parasite growth and another involving haemopoietic system that is able to limit anaemia. Logan-Henfrey et al. (1999) reported that the bone marrow response is a key determinant factor of trypanotolerance in cattle as it determines the animal's capacity for haematopoietic cell regeneration and control of anemia. This was supported by light and electron microscopic studies of sequential biopsies of bone marrow of *T. congolense* infected animals which showed key differences between trypanotolerant N'Dama and trypanosusceptible Boran Cattle. This was further supported by some beneficial effects of macrophage activation in the bone marrow (which had to do with enhanced haematopoiesis, parasite clearance and antigen processing) which was found to be greater in N'Dama than in Boran, enabling the N'Dama to

resist infection better. Esievo et al. (1982) demonstrated that the cleavage of erythrocyte sialic acid of cattle infected with *T. congolense* rendered them more proned to phagocytosis by the mononuclear phagocyte system and development of anemia. However there was return to normality of erythrocyte surface sialic acid 15 days after infection followed by improvement of anaemia. They suggested that there was accelerated replacement of sialic acid on the erythrocyte surface by the enzyme, sialytransferase known to be in the calf thyroid glands. The role of sialytransferase in trypanotolerance has not yet been reported. Sialytransferasce might play a role in trypanotolerance as increased activities of this enzyme might lead to more efficient replacement of sialic acid on the erythocyte surface of trypanosome-infected animals as soon as they are being removed, thereby preventing the development of anaemia. Molecular characterization of this enzyme may offer clues for enhancing its activities in other animal species to prevent the development of anaemia, a cardinal pathological feature and cause of death in animals suffering from African trypanosomosis.

FACTORS DETERMINING PARASITE CONTROL

Trypanosome parasite control in trypanotolerance has been associated with two factors (Wang et al., 1999); 1. compliment dependent and clone specific lytic activities, and 2. compliment-independent trypanocidal activities that are not restricted to trypanosome clones and species. Similarly, Black et al. (1999) demonstrated anti-trypanosomal activites in the sera obtained from trypanotolerant Cape buffalo, giraffe and greater kudu resulting in inhibition of replication of *T. brucei.* Also serum xanthine oxidase, serum catalase and trypanosome specific immune response have been reported to play roles of regulation of the level of parasitaemia in the Cape buffalo (Black et al., 2001). According to Wang et al. (2000), the trypanocidal activities of serum xanthine oxidase in the Cape buffalo arises from H_2O_2 generated by this enzyme during hypoxanthine and xanthine catabolism. They showed that xanthine oxidase dependent trypanocidal activities in the Cape buffalo (Black et al., 2001) serum was also elicited by purine nucleotides, nucleotides and bases even though xanthine oxides did not catabolise these purines.

Further studies characterizing these enzymes in both trypanotolerant and trypanosusceptible animals may define their exact roles in trypanotolerance and provide clues for enhancing their activities to control the development of trypanosome parasites and parasitaemia in susceptible animals. In our observation of trypanotolerance in the local puppies, similar trypanolytic activities were believed to have been responsible for maintenance of very low parasitaemia through out the eight weeks observation period (Abenga et al., 2005a).

Naessens et al. (2002) while comparing immune responses between trypanotolerant and trypanosusceptible cattle observed some differences in antibody response, complement level and cytokine expression, but were not sure whether these differences are the causes of resistance to trypanosomosis. Earlier, Taylor et al. (1996) observed that *T. congolense* infected N'Dama had significantly more variable surface glycoprotein (VSG)-specific IgG in blood than trypanosusceptible Boran cattle during infections. Furthermore, the peripheral blood mononuclear cell populations in N'Dama cattle contained a higher percentage of surface IgM-positive B-cells prior to and throughout infection than were found in the blood of Boran. Also during infection, N'Dama cattle had more circulating lymphocytes that could be activated *in vitro* to undergo differentiation into IgM and IgG-secreting cells. Nevertheless, the roles of superior antibody mediated destruction of trypanosome in trypanotolerance remains doubtful (Williams et al., 1996). Ogunsanmi et al. (2001) on their part observed a possible correlation between plasma lipid levels and trypanotolerance or susceptibility between trypanotolerant N'Dama and trypanosusceptible white Fulani cattle suggesting that plasma lipids might play roles in trypanosome growth, differentiation, and pathology of disease.

GENETIC FACTORS

Trypanotolerance has been described as a genetically determined complex mechanism involving factors which are not yet well known (Naessens et al., 2002). Over the last decade, molecular based studies at the International Livestock Research Institute have identified genomic regions controlling trypanotolerance in mice and cattle (Iraqi et al., 2001; Hanotte, 2003). In mice, many of the genes lying within these genomic regions (Quantitative trait Loci, QTL) have been identified leading the way to better identification of genes controlling trypanotolerance (Kemp et al., 1997). According to Hanotte et al. (2003), the use of this molecular technique has led to the definition of sixteen phenotype traits describing anaemia body weigh and parasitaemia. These authors observed that a genome-wide scan based on 477 markers revealed ten trypanotolerant QTL on mice chromosomes. They suggested that selection for trypanotolerance within a F_2 cross between N'Dama and Boran cattle could produce a synthetic breed with higher trypanotolerance levels than currently exists in the parental breeds (Hanotte et al., 2003).

Towards this direction, Koudande et al. (2002) conducted a marker-associated introgression to transfer trypanotolerance QTL from a donor mouse strain into a recipient mouse strain which revealed that introgressed mice showed better survival time to challenge than the recipient mice. However none of those mice reached the survival level of donor mice. According to Hanotte et al., (2003), in many cases, similar genes lying within the

genomic regions in trypanotolerant N'Dama were surprisingly found in Kenyan Boran cattle but did not display trypanotolerance. Berthier et al. (2003) concluded that, even though the gene- based ability called trypanotolerance results from various biological mechanisms under multigenic control, the methodologies used so far have not succeeded in identifying the complete pool of genes involved in trypanotolerance. According to Berthier et al. (2003), identification of the genes involved in trypanotolerance will however allow the setting up of specific micro-array sets for further metabolic and pharmacological studies and the design of field marker-assisted selection by introgression programmes.

PROSPECTS FOR INCREASING TRYPANORESIS-TANCE

According to d'leteren et al. (1999), preliminary genetic parameters available provide evidence that trypanotolerance is not just a breed characteristic but is also a heritable trait within the N'Dama population. Furthermore, the genetic variation identified within the N'Dama breed has opened new opportunities for improved productivity through selection for trypanotole-rance. Further to understanding the mechanisms underlying trypanotolerance, the exploitation of resistance traits lies on further characterization of these traits in the field and their practical measurements. As chemotherapy and chemoprophylaxis remains the major methods of control practiced besides tsetse trapping, and strategic animal movements, trypanotolerance has been identified as a more sustainable approach to controlling animal trypanosomosis (Gbodjo et al., 2001; Maichomo et al., 2001). However further field studies may require intergrating components that will improve acceptability of trypanotolerant breeds in the husbandry practices of trypanosomosis endemic countries (Kamuanga et al., 2001; Machomo et al., 2001; Tano et al., 2001).

It is concluded that whereas bone marrow responses may play roles in the control of anaemia in trypanotolerance, the roles of serum trypanolytic factors such as xanthine oxidase and serum catalase in control of trypanosome parasite development in trypanotolerance need further investigation. Similarly, further genomic studies on local breeds of sheep and goats, pigs and dogs may further identify the genes controlling trypanotolerance. Although current methodologies in molecular characterization of trypanotolerance genes in animals have not succeeded in identifying the complete pool of genes involved in trypanotolerance, it raises hope for producing synthetic breeds of animals with higher trypanotolerance level than currently exists in N'Dama, and improving the tolerance levels of susceptible animals through improved animal breeding systems.

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