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Review article

Combatting African Animal Trypanosomiasis (AAT) in livestock: The potential role of trypanotolerance

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ABSTRACT

African Animal Trypanosomiasis (AAT) is endemic in at least 37 of the 54 countries in Africa. It is estimated to cause direct and indirect losses to the livestock production industry in excess of US$ 4.5 billion per annum. A century of intervention has yielded limited success, owing largely to the extraordinary complexity of the host-parasite interaction. Trypanotolerance, which refers to the inherent ability of some African livestock breeds, notably Djallonke sheep, N'Dama cattle and West African Dwarf goats, to withstand a trypanosomiasis challenge and still remain productive without any form of therapy, is an economically sustainable option for combatting this disease. Yet trypanotolerance has not been adequately exploited in the fight against AAT. In this review, we describe new insights into the genetic basis of trypanotolerance and discuss the potential of exploring this phenomenon as an integral part of the solution for AAT, particularly, in the context of African animal production systems.

Contents

1. Introduction

African trypanosomiasis is a chronic debilitating disease caused by extracellular flagellate trypanosome protozoans (*Trypanosoma* species) and is spread mainly by the infected Tsetse fly vector (Diptera: Glossinidae) (Bruce, 1915; Hill et al., 2005; Brun et al., 2010; Mony and Matthews, 2015). The disease affects a wide range of mammalian species including humans (Matovu et al., 2001; Seck et al., 2010; Jha et al., 2015; Mwai et al., 2015). The three main trypanosome species endemic to Africa are *Trypanosoma vivax* (Dutonella) and *Trypanosoma congolense* (Nanomonas) that mainly infect livestock, and *Trypanosoma brucei* (Trypanozoon) which infects both humans and animals (Nakayima et al., 2012; Bezie et al., 2014; Kato et al., 2015). *T. brucei* has three subspecies of which two, *T. b. gambiense*, and *T. b. rhodesiense* infect humans, whereas the third, *T. b. brucei* infects domestic and wild animals (Welburn et al., 2001, 2009; Sima et al., 2011; Munday et al., 2015). The distribution of the tsetse fly (*Glossina* spp.) vector correlates closely with the prevalence of trypanosome parasites in the 10 million km^2 prevalence zone, thereby facilitating the entrenchment of the disease (Black and Seed, 2002). Trypanosome parasites invade the host's lymphatic system, the blood circulation, and eventually migrate to the brain to cause a broad range

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of pathologies, most commonly severe anaemia, weight loss, abortion, and cachexia. It can kill the host if left untreated (Matovu et al., 2001; Sima et al., 2011; Stijlemans et al., 2015), and indeed millions of trypanosomiasis related deaths are recorded in livestock each year (Smetko et al., 2015). Other symptoms that have been reported for African animal trypanosomiasis (AAT) include infertility, sleeping disorders, emaciation, pica, splenomegaly, paralysis, neuroendocrine dysfunctions and coma (Courtin et al., 2008; Steverding, 2008).

For several decades, AAT has been considered a neglected tropical disease and as such, remains endemic in 37 of 54 African countries. The affected areas cover approximately 10 million km^2 of arable land mass, and AAT has been shown to significantly reduce productivity in over 150 million cattle and 260 million sheep and goats (Jahnke et al., 1988; Baker, 1995; Leigh et al., 2014; Nyimba et al., 2015). AAT has a very significant combined economic and health burden in this sub-Saharan African (SSA) region (Shaw, 2009; Habila et al., 2012; Namangala, 2012). The disease also has an additional impact on crop agriculture, human settlement and welfare, as approximately 7 million km^2 of the region is rendered unsuitable for mixed crop-livestock farming systems (Peregrine, 1994; Dagnachew et al., 2015). AAT is estimated to cause annual losses of more than US$ 4.5 billion dollars through direct and indirect agricultural production losses (Sanni et al., 2013; Leigh et al., 2014; Dagnachew and Bezie, 2015). It is not surprising that as a direct consequence of the confounding effects of AAT on the general development of SSA, that 21 of the countries for which Trypanosomiasis is endemic are deemed to be amongst the world's 25 poorest countries (Shaw, 2009), with 32 considered highly indebted (IAEA, 2002).

Over several decades, the use of just a few therapeutic drugs for AAT that have limited efficacy against the parasites, but which are highly toxic to the host, has fueled the widespread emergence of drug resistance across the region (Matovu et al., 2001; Delespaux and de Koning, 2007; Delespaux et al., 2008). The continued lack of a suitable vaccine for the disease has also facilitated an over-reliance on these drugs (Tsegaye et al., 2015). Furthermore, ongoing efforts directed at controlling the Tsetse fly vector in SSA have been largely ineffectual (Holmes, 1997; Goossens et al., 1999; Hendrickx et al., 2004; Torr and Vale, 2015). These factors, coupled with persistent political instability and armed conflicts have ensured that AAT persists across the region (Geerts et al., 2001; Brun et al., 2010).

Certain African livestock breeds such as Djallonke sheep and Taurine cattle, which entered Africa from the near east around 5000 BCE and 7000 BCE respectively, have developed innate tolerance to AAT, probably as a result of natural selection pressures (Dolan, 1987; Naessens, 2006; Muigai and Hanotte, 2013). The innate ability of these livestock breeds to survive and remain productive under AAT challenge, with very low mortality and without the use of trypanocidal drugs, is referred to as trypanotolerance. To illustrate the potential relevance of trypanotolerant breeds in SSA, Fig. 1 indicates the geographical distribution of three important trypanotolerant breeds of livestock within the Tsetse fly – AAT region of Africa. Trypanotolerance has been described as an economical and sustainable option for combating AAT (Murray et al., 1982; Goossens et al., 1997; Geerts et al., 2009; Namangala, 2012). If systematically implemented as a control strategy, utilizing trypanotolerance could have a major positive effect on long-term food security for the region (Osaer et al., 1994). In this review, we detail the key challenges remaining after a century of intervention against AAT, and the new insights on the genetics and mechanisms of trypanotolerance. Finally, we discuss the potential benefit of identifying the genetic mechanisms of trypanotolerance and harnessing livestock trypanotolerance through introgression within the context of SSA livestock systems.

2. Century of intervention against AAT

The history of intervention programs for African trypanosomiasis involves the contributions of parasitologists, zoologists, entomologists, veterinarians and clinicians. However, with regards to AAT the landmark events are the findings of Bruce and Evans in the last decade of the 19th century (Bruce, 1915; Cox, 2004). Between 1891 and 1898, Evans identified *T. evansi* in equine spp. and Bruce identified *T. brucei* in cattle (Cox, 2004). In 1909, Bruce also identified the Tsetse fly as the vector transmitting trypanosome parasites (Bruce, 1915). These significant findings marked the beginning of attempts to combat AAT using a variety of measures, and the next 100 years was spent trying to eradicate this disease, with little success (Steverding, 2008). Throughout the 20th century, there were several attempts to control AAT through controlling the transmitting Tsetse fly vector. These control methods included; the sterile insect release technique, the destruction of fly habitat, the use of Tsetse traps, the use of insecticide-treated livestock, and coordinated mass spraying of insecticide (Doyle et al., 1984; Holmes, 1997; Hendrickx et al., 2004; Hill et al., 2005; Torr and Vale, 2015). These interventions yielded limited positive outcomes against AAT, but have often been associated with negative environmental consequences including insecticide pollution of water bodies and deforestation (Holmes, 1997; Goossens et al., 1999; Hendrickx et al., 2004; Torr and Vale, 2015). Other attempts at curbing AAT through targeting the parasite using anti-AAT drugs have not produced the expected results due to the rapid development of trypanocidal resistance (Kaufmann et al., 1992; Alsford et al., 2013). In 2008, 17 SSA countries reported veterinary trypanocidal drug resistance problems, and by early 2015 this number had risen to 21 countries (Delespaux et al., 2008; Tsegaye et al., 2015). This resistance was expedited in part by the reliance on predominantly three drugs for treating AAT over 50 years (Peregrine and Mamman, 1993; Geerts et al., 2001; Delespaux et al., 2008; Munday et al., 2015). Development of resistance and cross-resistance of trypanosomes to these drugs was further expedited as these drugs have similar chemical compositions (Peregrine, 1994). Furthermore, these three AAT drugs have high host toxicity, and have shown limited efficacy (Peregrine and Mamman, 1993; Matovu et al., 2001; Steverding, 2015). Other factors contributing towards drug resistance include the high degree of re-infection rates among treated livestock, and significant levels of misuse of trypanocides by farmers as a consequence of the deregulation and privatization of veterinary services (Geerts et al., 2001). In 2008, a report indicated that, out of an estimated 35 million doses of veterinary trypanocidal drugs administered, diminazene aceturate, isomethamidium chloride and ethidium bromide accounted for 33%, 40% and 26% respectively (Delespaux et al., 2008). Peregrine and Mamman (1993) reviewed the causes and mechanisms for parasite resistance to each of the drugs used against AAT. Drug resistance continues to interfere with effective therapeutic management of AAT, and is reported to be responsible for many widespread outbreaks of Trypanosomiasis, in different parts of the region, that did not respond to standard chemotherapeutic regimens (Holmes, 1997; Mamoudou et al., 2008).

The hope of developing an effective vaccine based on the surface glycoprotein antigens of trypanosomes remains particularly elusive due to the complexity of the parasite's antigenic repertoire (McCulloch et al., 1997; Hill et al., 2005). Horn (2014), Manna et al. (2014) and Taylor and Rudenko (2006) have provided comprehensive reviews on the mechanisms of trypanosome antigenic variation. Although an increased understanding of the structure and mechanism of this antigenic variation of trypanosome parasites has occurred over the past 40 years, to date no vaccine is available (Manna et al., 2014; McCulloch and Field, 2015; Mony and Matthews, 2015). These factors are the main reasons why most