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Invited review

Bovine trypanotolerance: A natural ability to prevent severe anaemia and haemophagocytic syndrome?

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Abstract

Trypanotolerance is the capacity of certain West-African, taurine breeds of cattle to remain productive and gain weight after trypanosome infection. Laboratory studies, comparing *Trypanosoma congolense* infections in trypanotolerant N'Dama cattle (*Bos taurus*) and in more susceptible Boran cattle (*Bos indicus*), confirmed the field observations. Experiments using haemopoietic chimeric twins, composed of a tolerant and a susceptible co-twin, and T cell depletion studies suggested that trypanotolerance is composed of two independent traits. The first is a better capacity to control parasitaemia and is not mediated by haemopoietic cells, T lymphocytes or antibodies. The second is a better capacity to limit anaemia development and is mediated by haemopoietic cells, but not by T lymphocytes or antibodies. Weight gain was linked to the latter mechanism, implying that anaemia control is more important for survival and productivity than parasite control. Anemia is a marker for a more complex pathology which resembles human haemophagocytic syndrome: hepatosplenomegaly, pancytopenia and a large number of hyperactivated phagocytosing macrophages in bone marrow, liver and other tissues. Thus, mortality and morbidity in trypanosome-infected cattle are primarily due to self-inflicted damage by disproportionate immune and/or innate responses. These features of bovine trypanotolerance differ greatly from those in murine models. In mice, resistance is a matter of trypanosome control dependent on acquired immunity. However, a model of anaemia development can be established using C57BL/6J mice. As in cattle, the induction of anaemia was independent of T cells but its development differed with different trypanosome strains. Identification of the molecular pathways that lead to anaemia and haemophagocytosis should allow us to design new strategies to control disease.

Keywords: Trypanosomiasis; Trypanotolerance; Anemia; Haemophagocytic syndrome; Cattle; Murine models; Tumor necrosis factor alpha

1. African trypanosomes

While other pathogens evade innate and adaptive responses in the plasma by hiding in a host cell, African trypanosomes are unique for being able to multiply and survive in the blood of their mammalian host. Trypanosomes elude antibody attack by sporadically varying their surface glycoprotein, forcing the host to mount a new cycle of antibody production each time a new variant appears. In this way, the parasite manages to survive and increase its chances of transmission by tsetse or biting flies. Unfortunately for the host, the disease often leads to a fatal outcome.

Not all mammalian hosts are equally susceptible. For example, *Trypanosoma brucei brucei* is known to infect cattle and mice, but not humans. A trypanolytic factor in human serum, apoL-I in high density lipoprotein (Vanhamme and Pays, 2004), is lethal for *T. b. brucei*, but not for the related parasite *Trypanosoma brucei rhodesiense* which has adapted to a life in the blood of its human host. Further, not all trypanosome strains living in the host's blood are invariably lethal, and the disease severity is strain dependent. In Europe and North America, the parasite *Trypanosoma theileri* occurs in a high percentage of otherwise healthy cattle and appears in blood cell cultures, but as it does not cause pathology (Verloo et al., 2000) is not the object of control.

There exists a variety of disease patterns associated with different host–trypanosome combinations. Patterns of susceptibility to infection and disease between trypanosome strains and different mammalian hosts may help us identify mechanisms that lead to higher resistance and potentially allow the design of new control measures.

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2. Bovine trypanosomosis

African trypanosomosis in livestock is a serious hindrance to development and reduction of poverty. Estimates of the cost to consumers and producers on the African continent reach US$ 1 billion (Kristjanson et al., 1999). The main parasites that cause disease in livestock are tsetse-transmitted *Trypanosoma congolense* and *Trypanosoma vivax* and to a minor extent *T. brucei*. Their distribution is restricted to Africa, although *T. vivax* has crossed the Atlantic and spreads in South America via mechanical transmission by biting flies. *Trypanosoma evansi* is also transmitted by biting flies and infects a wide range of livestock, including camels and buffalo in parts of Asia. Cattle are also an epidemiologically important reservoir for the human-infective parasite *T. b. rhodesiense* (Hide et al., 1996; Welburn et al., 2001; Njiru et al., 2004).

During the bite of an infected tsetse fly, metacyclic trypanosome forms are deposited in the skin of the mammalian host. An immune reaction to the metacyclic parasites causes a huge swelling in the skin, known as a chancre, and triggers the enlargement of the local draining lymph node. Metacyclics differentiate into bloodstream forms, migrate to the blood and cause a systemic infection. The most consistent clinical features in livestock are intermittent fever and anaemia. There is a general leukopenia, enlarged spleen and liver, and loss of weight. Chronically infected animals lose appetite, become lethargic and emaciated, and die usually of congestive heart failure.

3. Cerebral infections in cattle

Both *T. congolense* and *T. vivax* are intravascular parasites, while the *T. brucei* ssp. and *T. evansi* can leave the blood vessels and invade solid tissues (Losos and Ikede, 1972). *Trypanosoma congolense* show a preference for microvascular sites, where they will occur in higher densities and may even bind to endothelial cells (Banks, 1978). They contribute to pathology by provoking dilation of the microvasculature, compromising capillary circulation and impairing nutrient and metabolite exchange. Because *T. congolense* and *T. vivax* do not leave the circulation, cerebral infection is not a major clinical feature in cattle infections, but it has been reported with *T. brucei*. About half of all cattle infected with *T. b. rhodesiense* developed fatal CNS disease, which is comparable with that found in man (Wellde et al., 1989). Further *T. b. brucei* has been reported to cause CNS abnormalities and can be found in CSF (Losos and Ikede, 1972; Morrison et al., 1983). Although figures are not available, the frequency of CNS involvement seems to be lower for *T. b. brucei* than for *T. b. rhodesiense*, and may depend on the particular strain. No cerebral infections have been observed with monospecific infections with *T. congolense* or *T. vivax* in cattle (Losos and Ikede, 1972; Masake et al., 1984) but a high frequency of CNS involvement was observed in concurrent infections (Masake et al., 1984). These authors suggested that *T. congolense*, because of its potential to bind microvascular walls (Banks, 1978), may partially damage the endothelial barrier either mechanically or through inflammatory responses, allowing *T. brucei* to cross into the CNS. Most isolates from the CSF of multiply-infected cattle were *T. brucei*, but in one case *T. congolense* was recovered. The isolation of *T. congolense* from brain tissue of a multiply infected cow, was probably the result of a similar mixed infection (Haase et al., 1981). *T. vivax* is able to cross the blood barrier in goats and has also been found in the eye of infected goats and cattle, causing corneal cloudiness (Ilemobade and Schilhorn van Veen, 1974; Whitelaw et al., 1988). More recently, clear evidence for cerebral infections in cattle has been observed in an outbreak of surra, caused by *T. evansi* (Tuntasuvan et al., 1997). Even *T. theileri*, which is considered a non-pathogenic parasite, was reported in the CSF of a cow with encephalitis (Braun et al., 2002).

The evidence available so far suggests that *T. brucei* strains, and in particular the subspecies *T. b. rhodesiense,* constituted the major cerebral infections in cattle. The presence of trypanosomes in immunoprotected tissues such as brain and eyes presents a problem for therapy since they are protected from drugs that do not cross the blood–brain barrier (Jennings et al., 1979; Whitelaw et al., 1988), and potentially develop reactive encephalitis (Jennings et al., 1993). The relative frequencies of cerebral infections in tolerant and susceptible cattle has not been investigated.

4. Trypanotolerance

Cattle of taurine origin were first introduced in Africa around 6000 BC. From their origin of domestication in the Near East, taurine cattle spread through Egypt and the North African coast and expanded westward until they encountered the tsetse belt, which prevented further migration. Millennia of selection in tsetse-infested areas allowed some of these cattle breeds to develop a certain degree of ‘reduced susceptibility’ to trypanosomosis. It is possible that genes conferring this tolerance entered the population through cross breeding with an ancient population of African cattle, whose existence could be traced by DNA analysis in breeds from the continent (Hanotte et al., 2002). The term trypanotolerance was defined as the trait that confers the capacity to survive and remain productive after trypanosome infection (Murray et al., 1982).

Despite the rapid and wide distribution of zebu cattle (*Bos indicus*) over the African continent since their first introduction around 700 AD, taurine breeds predominate in areas of the tsetse belt. Early studies described that certain taurine breeds in West Africa could cope better in tsetse-infested areas (reviewed in Murray et al., 1982; Murray and Dexter, 1988). Under natural conditions of tsetse challenge, trypanotolerant cattle had lower mortality, lower trypanosome levels, less severe anaemia, superior weight gain and better reproductive performance than more susceptible indicine breeds. The breeds were tolerant to both *T. vivax* and *T. congolense*, with a higher degree of resistance to *T. vivax* (Murray et al., 1981, 1982; Mattioli et al., 1999). Field studies suggested that control of anaemia, but not parasitaemia, had a major effect on overall productivity (Trail et al., 1991a) and had a significant degree of heritability (Trail et al., 1991b).