Genetic Resistance to Parasites in Small Ruminants: from Knowledge to Implementation in the Tropics

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Abstract: The key for sustainability of tropical small ruminant farming systems is to search for a balance between the environment and the animal. It is in vain to avoid constraints in animal rearing and wiser to choose animals for their adaptations to these constraints. In this context, gastrointestinal nematode (GIN) infections are a major constraint in small ruminant production in the tropics. The strategy of pest eradication has evolved to a more logical manipulation of host parasite equilibrium in grazing systems by implementation of various actions. The genetic resistance of small ruminants to GIN is a part of this new approach. This review addresses the questions of the pertinence and feasibility of genetic selection in the context of the tropics. Then, with the background of the last 20 years of research, the strategies to adopt for the building of breeding schemes in the tropics are discussed.
Keywords: Genetic resistance; small ruminants; parasites; tropic; breeding

Introduction

One way to meet the challenge of feeding 9 billion people by 2050 is to rapidly improve productivity and resources utilization (*i.e.* efficiency) in livestock farming systems. Small ruminants participate in the subsistence of a large human population and provide tangible (cash, milk, meat, fiber and manure) and intangible benefits (prestige, saving, insurance, cultural and ceremonial purposes). The key for sustainability of tropical and extensive temperate small ruminant farming systems is to search for a balance between the environment (soil, fauna and flora), animals, and plant production. The restoration or preservation of such a trophic and ecological balance requires the implementation of innovative techniques. It is ineffective to avoid constraints in animal rearing and wiser to choose animals for their adaptations to these constraints. In this context, gastrointestinal nematode (GIN) infections in grazing small ruminants are the major pathogenic constraint worldwide (Over et al. (1992)). Estimates of economic losses realized in Australia and the United States, range into millions of dollars per year and concern all phases of production (Gibbs and Herd (1986); McLeod (1995)).

In developing countries, the most important parasite is *Haemonchus contortus* (Perry et al. (2002)). It has a major impact on subsistence of populations. In Guadeloupe, goat farm profit was reduced by 81% when parasite infections were no longer controlled by anthelmintics (Gunia et al. (2013a)). The GIN infection of Creole does during lactation leads to lower ADG of kids between 30 and 70 days of life, and lower weaning weight (Mandonnet et al. (2005)). The risk of dying from strongylosis after weaning is hence increased (Mandonnet et al. (2003)). GIN infections cause a 20% loss of yearling body weight in Creole kids compared to a potential of 17.5 kg on average (Tesfamicael et al. (2012)).

Today worldwide there is a massive rise of anthelmintic resistant GIN (Kaplan, 2004). In addition, the use of anthelmintics is counter to the legitimate consumer demand for chemical free animal products; their use in rural communities is further complicated by a dearth of veterinary services and the high relative cost of drugs. In recent years, the strategy of pest eradication has evolved towards a more agroecological approach whose objective is to restore the equilibrium between host and parasite by implementation of various actions. The genetic resistance of small ruminants to GIN infections is part of this new approach and plays a major role. In this review, we successively address the questions of the pertinence and the feasibility of genetic selection in the context of the tropics. Then, with the background of the last 20 years of research of our team in this field we discuss the question of the strategies to adopt for building breeding schemes in tropics.

Genetic selection: a solution?

Until 8-10,000 years ago, ruminants had evolved in equilibrium with their parasite populations. Mammal domestication by humans broke up this natural balance (Mignon-Grasteau et al. (2005)). Indeed, the animals were herded on limited surface areas which significantly altered the epidemiology of gastrointestinal parasites (Thamsborg et al. (1996)). The animal keeper gradually entered into a patttern of increasing flock production. According to the theory of resource allocation (Beilharz et al. (1993)), in the absence of compensatory food intake, selection effort on these production traits resulted in a reallocation of food resources and in a genetic depression of the other traits such as reproduction and adaptation to the environment (Menendez-Buxadera and Mandonnet (2006)). Thus parasites were favoured while host defenses were reduced. However, the impact was not the same for all hosts. There is individual variability in the resistance of animals in a flock. The parasite relies on a very small number of susceptible animals to quickly complete its cycle (Herbert and Isham (2000)) and produce a large number of propagules to colonize the pasture. Grazing ruminants are then constantly exposed to natural challenge by GIN, especially in tropics where no seasonal break occurs in GIN development. Nowadays, a unique solution for controlling GIN infections in small ruminants is no more realistic. Three main strategies of research have been developed.

- The first, as a short-term strategy, is the **reduction of host contact with infective larvae though flock management**. For gastrointestinal nematode

infections in ruminants, a reduced stocking rate has been proven to be one of the most efficient ways of diluting the parasitic risk (Mahieu (2013)) although the relationship between the stocking rate and the worm burden was shown to be non-linear (Saul (1996)). A dilution strategy can be developed by grazing animals of different resistance/ susceptibility status and/or more or less permissive to small ruminant GIN, in the same pasture, simultaneously or alternatively (Mahieu et al. (1997)). A compromise should be made between herbage quality and infection risk. It has been suggested that other semi-industrial techniques such as nematophagous fungi (Chandrawathani et al. (2002)) and coprophagous fauna (d'Alexis et al. (2009)) could be used to reduce larval contamination on pasture but they are not adapted to low input systems.

- A second middle-term strategy, which consists of **extending the efficiency of synthetic anthelminthic molecules,** can be implemented though targeted selective treatment and/or the use of phytotherapeutic drugs. The choice of targeted selective treatment (TST, FAMACHA© for example) relies on the assumption that some animals are more infected than others. The value of TST strategy is highly dependent on the climatic environment, the general management of animals, and the nematode fauna. Moreover, it requires additional labor which limits feasibility even if there could be a return by the reduction of cost of treatments. Finding new therapeutical resources or restoring old ones relies on traditional pharmacopea issued from local ethnoveterinary knowledge. Some identified phytotherapeutic drugs remain an important source of natural anthelminthic materials against GIN infections in small ruminants exploited by small farmers in different parts of the world (Hammond et al. (1997); Akhtar et al. (2000); Githiori et al. (2006)).
- Finally, long term strategy is **enhancing the ability of the host** to tolerate the negative effects of the worms (resilience) and eventually to respond to the parasites (resistance) from complementarity and/or genetic selection as vaccines do not seem to be finalized yet. Feed complementarity is particularly interesting for those nutrients which are the limiting factors of the diet (*i.e.* generally proteins). Several studies have aimed to define the optimal time or animals to target the distribution of extra proteins in order to maximise the potential benefits (Bambou et al. (2011)). The use of **genetic selection** of ruminants for traits of resistance to GIN infection has been presented as the "ultimate tool in sustainable parasite control" (Waller and Thamsborg (2004)).

In the end, it is the integration of several of these solutions which could lead to rebalance of the host-parasite relationships (Jackson and Miller (2006); Mahieu et al. (2009)).

We will focus now on sustainable genetic tools for improving host resistance (not as the unique solution but rather in combination with other integrated control methods). The genetic solution, which is the focus of numerous scientific teams worldwide, consists of mimicking what natural selection has done for centuries at a faster rate. The adaptation of the GIN to their resistant host should not be ignored; nevertheless the polygenic nature of host resistance would probably exert a lower and more complex selection pressure on worm populations than methods aimed at eradicating parasitic populations with anthelmintics. In their report to FAO, Bishop et al. (2003) developed a SWOT (strengths, weaknesses, opportunities, threats) analysis of selection for resistance to GIN in small ruminants in tropics. The main benefit pointed out was the sustainability of the method (genetic change is permanently acquired). However weaknesses were the complex infrastructures required and the long term inclusion of resistance/resilience traits in the breeding goal.

Genetic selection: a realistic method?

Abundant knowledge has been accumulated on this topic since 80's. Early programs to examine and to understand the mechanisms underlying the genetics of resistance were initiated in Australia (Woolaston et al. (1991)) and New Zealand (Watson et al. (1986)) as sheep there were intensively exposed to parasitism and anthelmintic resistance.

Evidence of genetic variation between and within sheep and goat breeds. In the tropics, more precisely in developing countries of the tropics, less intensive management (multi-purpose breeding, less artificial environmental intervention) together with the utilization of indigenous breeds adapted to their environment has permitted the preservation of genotypes conferring resistance to GIN infections. In sheep, numerous studies comparing local and commercial breeds either natural or experimental infections with GIN showed a better capacity of local breeds from humid areas to express a resistant/resilient phenotype (lower faecal eggs count (FEC), parasite burden and packed cell volume (PCV) reduction). More generally, hair sheep express higher resistance than wool sheep (Baker and Gray (2003)). Local breeds from South America, the Caribbean and Asia at different physiological stages (*i.e.* growing lambs, adult male and female around parturition), such as the Santa Ines, Crioula lanada, Criollo, Blackbelly, Florida native and Garole breeds, showed a higher level of resistance against GIN compared with Ile de France, Corriedale, Suffolk, Romane, Rambouillet and Decanni breeds respectively (Amarante et al. (2004); Rocha et al. (2004); Bricarello et al. (2002) (2004); Alba-Hurtado et al. (2010); Courtney et al. (1984); Nimbkar et al. (2003)). Some studies compare goat breeds in the tropics (de la Chevrotière et al. (2011)). Generally, specialized breeds are not able to express their genetic potential of production under harsh environments due to their higher nutritional requirements (Hoste et al. (2001)).

There are also numerous studies showing within breed variability for resistance criteria (FEC, worm burden), immune response criteria (eosinophilia, immunoglogulins), and resilience criteria (anemia,

serum pepsinogen concentration, growth rate, required drenching frequency). In sheep, Safari et al. (2005) calculated the weighted mean of FEC heritability estimates in the literature (0.27). In goats, heritability of resistance appears about one-half that in sheep (Baker et al. (2001); Chiejina and Behnke (2011); Rout et al. (2011); Costa et al. (2000); Mandonnet et al. (2001)). Some studies even conclude an absence of genetic variability in goats (Woolaston et al. (1992)). Strong genetic correlations were estimated whatever the species, between resistance to different GIN species (*H.contortus vs. Trichostrongylus colubriformis*: Gruner et al. (2004); experimental *H.contortus* infection *vs.* mixed natural infection at pasture: Bambou et al. (2010)) suggesting non specific genetic control of resistance, at least partially. Genetic correlations between FEC and body weight vary from favorable negative values to unfavorable positive values (Safari et al. (2005); Baker et al. (2001); Gunia et al. (2011)). This variation may be due to interactions between host genetic resistance and the environment (Laurenson et al. (2012)). In Creole kids, increasing genetic variability was assessed between 3 and 11 month of age with decreasing maternal genetic effects with age. A positive genetic correlation was estimated between resistance of growing kids and periparturient rise of does (Mandonnet et al. (2006)). Otherwise, neutral relationships were shown between fertility, litter size, milking value and FEC while the genetic correlation was slightly favorable between body weight and FEC (Gunia et al. (2011)).

Several studies using diverse approaches, breeds and nematode species have been published, and many Quantitative trait loci (QTL) associated with resistance to GIN in small ruminants have been detected on more than 20 chromosomal regions, as reviewed by Dominik (2005) and Bishop and Morris (2007). Some of these QTL were detected near candidate genes such as interferon-gamma (Coltman et al. (2001); Davies et al. (2006)) or the MHC region (Boloorma et al. (2010)). The first genome scan for GIN resistance in goats was undertaken in Creole breed (de la Chevrotière et al. (2012)) identifying 13 QTL for resistance, resilience and immune criteria. The main conclusion of these studies is that most significant QTL effects tend to be scattered throughout the genome. So resistance to GIN is probably driven by numerous genes with small effects and few playing a key role (Bishop (2012)). This genomic information accumulates but remains difficult to exploit by professionals.

All the above presented results make obvious the feasibility of selection for resistance and resilience to GIN infections in small ruminants in the tropics. Moreover, the local tropical breeds in comparison with the commercial ones provide an opportunity to identify genes that significantly impact the expression of resistance against GIN (Piedrafita et al. (2010)). In addition, the different applications of genomics help researchers to better understand the genetic mechanisms leading to disease resistance (Goddard and Hayes (2009)).

Underlying mechanisms: The richness of the ovine-caprine comparison. The mechanisms underlying the genetic resistance against GIN are well documented in sheep, particularly in commercial breeds. The response against gastrointestinal nematodes is associated with proliferation of mucosal mast cells, globule leukocytes, and circulating and tissue eosinophils. This response also involves production of parasite-specific immunoglobulin A (IgA), IgG1 and IgE (Shaw et al. (1998)). More recently, it has been shown that proteins of the lectin-family (carbohydrate binding proteins) play a key role in the immune response to GIN, suggesting the importance of the innate immune response which has not been sufficiently studied in the past (French et al. (2008); Robinson et al. (2010a)).

Strong evidence for a close association between the genetic resistance and the immune response was showed in Merino lambs. The CD4+ T helper cells have been found to be essential for the genetic control of the development of immunity against *H. contortus* (Gill et al. (1993)). Numerous studies aimed at investigating the immune mechanisms involved in genetic resistance have compared local more resistant tropical breeds to commercial more susceptible breeds. Inflammatory cell counts and parasite-specific IgA were inversely associated with *H. contortus* worm burden and FEC, however, similar mean values of inflammatory cells and IgA were found in the resistant Santa Ines and in the susceptible INRA401, Suffolk and Ile de France breeds of sheep (Amarante et al. (2005); Lacroux et al. (2006)). Limited differences in eosinophil and globule leucocytes counts were observed between resistant Crioula and susceptible Corriedale breeds (Bricarello et al. (2004)). Differences between resistant and susceptible breeds in the kinetics of the cytokine expression showed resistant sheep breeds had quicker up-regulation of several cytokines than susceptible sheep breeds. The IL-5 gene over-expression was shown to remain high in the resistant Black Belly lambs during a *H. contortus* infection, while it was down regulated earlier in INRA 401 susceptible lambs (Lacroux et al. (2006)).

The feeding behaviour of goats as browsers has allowed them to avoid infective L3 ingestion at pasture, contrary to sheep which are grazers. The co-evolution of these two hosts with GIN was qualitatively and quantitatively deeply different (Mirkena et al. (2010)). It is hypothesised that the mechanisms involved in GIN control in goats compared to sheep would be also qualitatively and quantitatively different. A few studies have investigated the goat immune response to *Teladorsagia circumcincta*, *Trichostrongylus colubriformis* and *H. contortus* infections (Huntley et al. (1995); Fakae et al. (1999); Perez et al. (2001); Macaldowie et al. (2003)). The immune cell populations observed in the digestive mucosa were identical to those observed in sheep. However, results suggest that the correlation between the intensity of the cell infiltration and a decreased worm burden was less evident in goats compared with sheep (Hoste et al. (2008)). Moreover, the ability of dairy goats to control challenge infections was lower than that generally observed in sheep, which suggested that the immunologic memory after drenching does not last as long (Chartier and Hoste (1997); Hoste and Chartier (1998)). To our knowledge,

the mechanisms involved in genetic resistance of goats against GIN have been investigated only in Creole goats infected with *H. contortus*. It has been shown that in animals previously infected by *H. contortus*, a degree of protection occurred and the phenotypic and genetic segregation in resistant and susceptible animals were related neither to the humoral (*i.e.* IgA and IgE) immune response nor to the circulating activated sub-populations of LTCD8+ and LTCD4+ (Bambou et al. (2008); Bambou et al. (2009a)). In this breed, the expression of the resistance mechanisms appeared after a second infection since no difference in FEC is observed between resistant and susceptible indexed kids after a primary infection. This result is consistent with studies showing that the level of a secondary infection of kids with *H. contortus* was lower after a primary infection (Bambou et al. (2009b)), and GIN infections in young animals during post-weaning increase the efficiency of the protective immune response at the adult stage (Bambou et al. (2010)). More recently, globule leukocyte infiltration was found to be higher in resistant Creole kids compared with susceptible ones, but no differences were observed in the eosinophil and mononuclear cell infiltration. Altogether, these results suggest that the resistant mechanisms in goats may differ from those described in sheep because the relative importance of the innate and adaptive immune responses seems different in these two species. Nevertheless, all these data were obtained on a limited number of experimentally infected animals and should be considered with caution.

Which strategies to impact?

Necessity to identify biomarkers to implement synthetic criteria? How to choose the "good" phenotype for "sustainable" breeding schemes? Most of the time, selection is based on the phenotyping of relevant traits such as zootechnical performance, FEC, and measures of anaemia and blood eosinophilia under conditions of either natural or experimental nematode infection. Despite numerous studies aimed at investigating the mechanisms involved in genetic resistance, a standardized biological parameter indicative of GIN resistance or susceptibility has not yet been identified. Indeed, most studies have been confined due to: i) a high inter-individual variability and, ii) the impossibility of monitoring kinetics of local cellular changes and genes expression patterns with time of infection. The forthcoming challenges for the scientific community will be to better characterize this response and to understand how it may influence expression of the resistant/susceptible status. However, it is crucial to take into account the fact that the objective is to understand the complex cross-talk between two organisms: the host and the parasite. Thus, it is probably more pertinent to stress on dynamic of the host responses rather than to target single time point analysis during the course of the infection, as done in the past. Few studies attempting to monitor the host response on live animals during an experimental GIN infection have been realized (Pernthaner et al. (2005); Robinson et al. (2010b)). Today by our point of view, it seems that all the ingredients are available to conduct further experiments while compare local and commercial breeds of goats and sheep using advanced high-throughput tools (i.e. transcriptomic, proteomic, metabolomic). The real added value will come from the data analysis. An integrative biology approach will probably help to open new avenues for the characterization of a biomarker profiles associated with the genetic resistance.

Necessity to build adapted breeding program. Different attempts have been made worldwide to develop adapted breeding stock in both temperate and tropical conditions. Overall, results obtained from various programs in both sheep and goats have repeatedly shown that genetic selection of responding animals, after several generations, lead to substantial reductions in FEC and pasture contamination and, consequently, to modulation of the dynamics of infection (Vagenas et al. (2002); Bishop and Morris (2007); Jacquiet et al. (2009)). In Guadeloupe, Blaes et al. (2010) observed a decrease of 32% for FEC in periparturient Creole does that were 0.5 genetic standard deviations from the average on their resistance index. This resulted in a 16% benefit in flock productivity at 70 days of lactation.

Generally, the choice of a breeding strategy depends on the available knowledge of genetic variability in indigenous breeds and behaviour of exotic breeds in harsh environments (Alexandre and Mandonnet (2005)). One policy is to postulate that no selection organisation is viable under traditional environment in the tropics and that genetic improvement can only be introduced via exotic sires (Juvenal-Castillo and Omar-Garcia (2001)). This method is easy to implement, but its results are uncertain and non-sustainable. Good experiments have been reported (improvement of liveweight at 3 and 6 months of age in local kids in India through Boer crossbreeding, Nimbkar et al. (2000)) but bad ones as well (in Kenya, East African and Galla goats were tolerant to infection with *Trypanosoma congolense* while Saanen goats and their crosses suffered severely and had a high mortality rate, (Griffin and Allonby (1979)). A second method is to propose selection within a local breed. It is an appropriate strategy when management can only be improved marginally and when crossbred goats are unlikely to perform well (Peacock (1996)). In this case, strong emphasis must be put on selection for performance characteristics and on maintaining adaptation (disease resistance, heat tolerance, etc.).

This second strategy is the option supported by INRA, farmers' organisations and extension services in Guadeloupe for the improvement of Creole goats (Gunia et al. (2013a,b)). A deterministic bio-economic model was developed to calculate the economic values based on describing of the profit of a Guadeloupean goat farm. To ensure a balanced selection outcome, the breeding objective included two production traits, live weight (BW11) and dressing percentage (DP) at 11 months (the mating or selling age), one reproduction trait, fertility (FER), and two traits to assess animal response to parasite infection: PCV and FEC. The economic values were 7.69€ per kg for BW11, 1.38€

per % for FER, 3.53€ per % for DP and $3x10^{-4}$€ per % for PCV. The maximum weighting for FEC was -18.85€ per log(eggs/gram). The breeding program, accounting for the overall breeding goal and a selection index including all traits, gave annual selection responses of 800 g for BW, 3.75% for FER, 0.08% for DP, −0.005 ln(eggs/g) for FEC, and 0.28% for PCV. The expected selection responses for BW and DP in this breeding program were reduced by 2% and 6%, respectively, compared with a breeding program not accounting for FEC and PCV. This can be considered as a first step in genetic upgrading. The improved local does can be further used in crossbreeding with exotic bucks in the best managed farms.

Because it is probably difficult to implement industry-wide or governmental breeding schemes in many parts of the tropics, centralized nucleus breeding schemes (Bondoc et al. (1989); Peacock (1996)) and village-based or community-based breeding schemes (Gizaw et al. (2009)) have been suggested to be a sustainable alternative in harsh environments. There are examples of commercial programmes where the selection for resistance to GINs is promoted (WormBoss, http://www.wormboss.com.au, in Australia, Guicheha et al. (2007) in Kenya, Gunia et al. (2013b) in Guadeloupe). The use of molecular markers which followed sheep and goat genome sequencing and the rapid improvement of high throughput genotyping and sequencing will potentially modify this reality in the future (Pinard-Van der Laan and Gay (2007)) as the genomic revolution gives new perspectives for researchers to increase the efficiency of selection.

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