Selective criteria for resistance to gastrointestinal nematodes in sheep

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Abstract

Breeding represents the effort of mankind to constantly improve living beings for its own benefit. This is how breeds were created and many were chosen for their productive qualities. However, efficiency in one direction often leads to reduced performance in another. Increasing the profit from milk, meet or wool may influence other parameters like the ability of the individual animal to cope with disease. Gastrointestinal nematode parasitism is one of the most important issues that should be addressed in sheep farming. It causes significant economic loss worldwide that cannot be covered by extensive livestock systems. The problem is exacerbated by the continuous spread of anthelmintic resistance. Integrated sustainable strategies are being recommended in the struggle to find effective solutions to this question. One of the possible answers can be selection of sheep on the trait resistance/resilience to gastrointestinal nematodes.

Key words: resistance, gastrointestinal nematodes, selection, sheep

Селективни критерии за резистентност към стомашно-чревни нематоди по овцете

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Резюме

Развъждането представлява процес на целенасочено подобряване на живите организми в полза на човечеството. Така са били затвърдени определени продуктивни качества и са възникнали породите. Селекцията с цел повишаване на добива от мляко, месо и вълна може да доведе до промени в други показатели като, например, способността на индивида да се справя със заболявания. Стомашно-чревните нематодози представляват един от най-важните проблеми в овцевъдството, който причинява сериозни икономически загуби в световен мащаб и води до понижена рентабилност при екстензивен тип на животновъдство. Проблемът се задълбочава поради възникването на антихелминтна резистентност. Предложени са редица интегративни устойчиви практики за разрешаването на този въпрос. Един от възможните подходи е селекция на овце по белега резистентност/устойчивост на стомашно-чревни нематоди.

Ключови думи: резистентност, стомашно-чревни нематоди, селекция, овце

Introduction

Gastrointestinal nematodes (GIN) of sheep have a major economic impact globally. According to a ranking system of animal diseases helminthic infections were identified as the top reason of economic loss in developing countries. Statistical analysis showed that the annual treatment cost for *Haemonchus contortus* alone reach 26 million USD in Kenya, 46 million USD in South Africa and 103 million USD in India (Periasamy et al., 2014). Interestingly the same holds true in the European context (Bishop, 2009), where the cost of ovine GIN infections in the UK was estimated on 99 million € per year (Morgan et al., 2013).

Parasitism leads to direct losses from costly anthelmintic treatment and decreased production due to emaciation or mortality (McRae et al., 2014). Performance of infected sheep is negatively influenced compared to healthy individuals as notified by percentage distribution: 85% for weight gain, 90% for wool and 78% for milk yield (Mavrot et al., 2015). Increased parasite burden is correlated to reduction in weight gain in meet breeds (Ilangopathy et al., 2019) which can be attributed to reduced food intake and food conversion efficiency (Jas et al., 2017). Wool production is also negatively influenced (Liu et al., 2003; Southcott et al., 2006) especially in the case of chronic infection. Daily milk yield can be decreased predominantly during the first lactation (Alberti et al., 2012).

This question about the control of GIN became highly relevant with the emergence of anthelmintic resistance (AR) that continues to spread worldwide (Roeber et al., 2013). The term is described as a decrease or loss of effect in the response to treatment by a previously susceptible population (Coles, 2006; Fleming et al., 2006). It can be manifested as a heritable decline in the efficacy of a drug that leads to the requirement of more frequent administration (Shalaby, 2013). Factors that can influence the process include the species involved, host reaction, drug treatment, on-farm control management, environment conditions (Coles, 2005). Frequent or continuous use of the same group of anthelmintic, sub-optimal dosing, prophylactic mass treatments are all mentioned as possible reasons predisposing to resistance (Shalaby, 2013).

Resistance It has arisen to all the major families of anthelmintics. The future viability and profitability of the entire sheep industry is threatened (Waller, 1999) as costs for treatment are constantly rising while drug efficacy is decreasing. It is increasingly recognized that dependency on chemotherapeutic control should be minimized to keep at least some drugs effective and available for critical situations (Ploeger et al., 2016).

Talking about anthelmintic resistance in sheep it should be noted that the term generally pertains to gastrointestinal nematodes belonging to the order Strongylida and predominantly the Trychostrongylidae family which are the most potent and economically important infective agents in small ruminant livestock production systems (Hamie, 2018).). Infections from mixed agents are common and pose a greater treat for the host compared to monospecific diseases (Roeber et al., 2013). Haemonchus, Teladorsagia and Trichostrongylus are repeatedly reported as resistant to different anthelmintic groups with multiple drug-resistant populations already present (Papadopoulos et al., 2012).

Traditional disease control strategies often fail to cope in dynamic situations such as the widespread of anthelmintic resistance in ovine gastrointestinal nematodes. Several programs have been lounged to investigate the possibilities offered by integrative control strategies, namely the European Union funded projects PAPASOL and GLOWORM and the UK initiative "SCOPS" (Sustainable Control of Parasites in Sheep). Among recommendations discussed attention is drawn to breeding for resistance as a steady long-term approach for reducing the impact of worms on sheep industry. FAO's Animal Health Service, together with its Regional Offices and "The Working Group on Parasite Resistance" (WGPR) established in 1997, have made resistance management an important component of its program.

The purpose of this article is to summarize the current knowledge about breeding for resistance to gastrointestinal nematodes of sheep with emphasis on conventional methods and recent innovations. Scientific experience for using certain selection traits is widely discussed. Molecular methods are presented as a valuable alternative to traditional approaches with the ability to discover the genetic basis of resistance and incorporate it for standard diagnostics in the near future.

Materials and Methods

A systematic search was conducted utilizing several web databases such as PubMed, NCBI, ScienceDirect, ResearchGate, SpringerLink, Google Scholar. Multiple key words were used to search for relevant articles including "sheep", "breed", "genetics" "gastrointestinal nematodes", "anthelmintic", "resistance", "breeding", "selection traits", "genetics", "inheritance". Data was also identified from citations provided within articles peer-reviewed original publications, conference papers, and PhD theses. A total of 83 articles related to GINs, AR and breeding for resistance in sheep were finally included in this review.

Europe and Bulgaria – where do we stand?

Livestock farming is central to the sustainability of rural communities with sheep population estimated at 101 million in the European Union (Morgan et al., 2013). Small ruminant production systems are predominantly based on pasture and consequently parasitic diseases are observed frequently. Strains of nematodes that are resistant to anthelmintics have already been documented in several European countries including the United Kingdom (Sargison et al., 2007; Abbott et al., 2012), Ireland (Keane et al., 2014), France (Geurden et al., 2014; Cazajous et al., 2018), Germany (Voigt et al., 2012), Nederland (Borgsteede et al., 1991; Ploeger and Everts, 2018), Denmark (Peña-Espinoza et al., 2014), Spain (Alvarez-Sánchez et al., 2006), Italy (Geurden et al., 2014), Czech Republic (Vernerova et al., 2009), Slovakia (Dolinská et al., 2014), Lithuania (Kupčinskas, 2017), Greece (Geurden et al., 2014), Turkey (Köse et al., 2007).

The sheep industry in Bulgaria comprises of predominantly small-scaled farms keeping on average less than 500 to 1000 animals that are bred under grazing conditions during most of the year. Husbandry conditions can be described as poor to average. Seasonal outbreaks of GIN infections are expected during spring and autumn months (Kamburov et al., 1994). Radev et al. (2012) reported that prevalence was high in winter and early spring in semi-mountain areas of Central Northern Bulgaria with peak levels until the beginning of June, a visible decrease in summer and steady increase in autumn. A study from the South-Eastern part of the country supported this epidemiological data and documented the following distribution on frequency of GIN: Teladorsagia 25.3%, Chabertia 21.3%, Haemonchus 19.4%, Trichostrongylus 14.4%, Oesophagostomum 7.8%, Nematodirus 5.8%, Bunostomum 4.1%, Cooperia spp. 1.9% (Iliev, 2019). Invasion by GIN was registered in 87% of herds. However, the importance of AR as a threat is still not recognized in Bulgaria. Resistance to levamisole was first described by Zhelyazkov et al. (1998) and later by Iliev et al. (2013). Resistance to benzimidazoles was identified in 2 out of 13 sheep farms in South-Eastern Bulgaria (Iliev et al., 2014). It is possible that the issue is underestimated due to lack of understanding from owners and insufficient scientific involvement. Nevertheless strategies to reduce the potential effects of AR should be urgently incorporated in parasite control programs. One of the promising and sustainable approaches is breeding for disease resistance that is able to result in sheep flocks less susceptible to GIN.

The genetic basis of resistance

Resistance to parasites and pathogens has a significant additive genetic component (Smith et al., 1999) with rapid genetic progress demonstrated in both research and commercial flocks (McRae et al., 2014). It is generally assumed that the genetic basis of resistance is polygenic with many genes responsible for the trait to be expressed. The issue is going to be discussed in detail in the part dedicated to genomic studies.

Breed and within breed variations

The level of resistance varies among breeds and individuals within breeds. Adaptation as a result of natural selection has led to the ability to withstand continuous disease pressure (Bishop, 2009). Indigenous sheep breeds like Red Maasai, Garole, Gulf Coast Native, Rhon and Barbados Black Belly were found to have relatively increased resistance against gastrointestinal nematodes. Interest to local breeds is constantly rising as they are better adapted to environmental conditions and serve as a valuable pool of resistance genes. In the context of Bulgaria special attention should be paid to the Karakachan and other local sheep breeds. Within-breed genetic variation has also been proven in sheep populations such as Merino, Romney, Scottish Blackface, feral Soay sheep (Periasamy et al., 2014). It is explained by the individual differences in immune response that enhance the ability to withstand GIN infestation.

Resistance/tolerance/resilience – several terms to be explained

Resistance can be defined as the ability of the host to exert some degree of control over the pathogen life cycle (Bishop and Stear, 2003). It comprises host mechanisms to resist infection such as immune response, difference in allel frequencies, lack of certain genes or receptors. The trait is continuous and heritable. It is acquired, not innate. A positive breeding effect can be observed in adults that have been exposed to infection rather than lambs (Gruner and Lantier, 1995). On the population level it benefits the individual as well as the group.

Tolerance is characterized by the reduction of pathogen impact on host performance without necessarily affecting pathogen burden (Doeschl-Wilson et al., 2012). Host is infected but suffers little adverse effects. Increased tolerance equals greater fitness as pathogen load increases. The trait depends on disease prevalence, which makes it difficult for estimation separately from resistance (Bishop, 2012).

The selective value of resilience relies on the productivity of an animal in the face of infection (Bishop and Woolliams, 2014). It refers to the ability of an animal to maintain performance irrespective of pathogen burden (Doeschl-Wilson et al., 2012). Resilience appears to be far less heritable than resistance with criteria difficult to measure. Furthermore, it is suggested that breeding for resistance leads to increase in resilience as well (Albers et al., 1987).

Resistant animals mount an immune response to reduce or eliminate parasites from the gastrointestinal tract. Resilient animals remain immunologically inactive with little effect on their production capacity. On the opposite, susceptible animals are characterized by reduced productivity (Tibbo and Haile, 2009).

Many authors propose that selection should be focused on reducing the transmission of infection (i.e. resistance) rather than reducing the clinical signs (resilience/tolerance). Resistance influence the establishment of infective larvae, decrease the rate and speed of development into the adult stage, reduce survival of worms and fecundity of females (Gruner and Lantier, 1995). Nevertheless, resilience or maintenance of productivity during infection can also possess its benefits.

Selection criteria for resistance/resilience to GIN in sheep

Identification of appropriate indicator traits for estimating the impact of infection on host have been proposed. These should be easy to apply in the field, repeatable, heritable and correlated with the breeding goal (Bishop, 2009). Heritability is defined as the proportion of phenotypic difference among individuals within a population that is attributable to genetic variation (Falconer and MacKay, 1996). Therefore, heritability estimates are able to predict what percentage or ratio of variation in a given trait depends on genetic or environmental factors. Repeatability measures the degree to which variation within individuals contributes to total variation in a population (Boake, 1989). Statistical analysis on repeatability is usually utilized to set the upper limit of heritability (Dohm, 2002).

Among many criteria that have been discussed in scientific literature feacal egg count (FEC) and packed cell volume (PCV) have proven to be suitable under a variety of conditions with FEC given preference as it can also indicate rates of pasture contamination (Bishop, 2009).

Fecal egg count (FEC)

Enhanced natural ability to prevent establishment of larval stages is one of the main factors for development of host resistance to nematodes. Such parameters are not actually measurable and consequently nematode-resistance has usually been defined in terms of low fecal nematode egg counts (FEC) (Douch et al., 1996; Lobo et al., 2009). This indicator trait has been shown to be highly effective in breeding for worm resistance (Woolaston, 1992; Greeff et al., 2009) when implemented on the individual level as it allows for the quantification of parasite burden (Valilou et al., 2015).

FEC is the most common method for the diagnosis of gastrointestinal nematode infections of sheep (Ward et al., 1997; Roepstorff and Nansen, 1998; Cringoli et al., 2010). Various methods have been developed, including the direct centrifugal flotation method, the Stoll dilution technique, the McMaster method, the Wisconsin flotation method, etc. Numerous modifications of these methods are described and most institutions use their own protocol of the original technique (Roeber et al., 2013).

Computer simulation models have shown that selection for host resistance based on the trait "low fecal egg count" remains stable over a short period that can extend to 20 years. This is supported by field studies where parasites failed to adapt to host immune mechanisms (McRae et al., 2014). Selection for resistance is regarded to be successful if it can achieve reduction in egg output and decrease in pasture larval contamination with subsequent fall in larval challenge (Bishop and Stear, 2003).

Heritability as measured by FEC was summarized by Smith et al. (1999) – data from different studies suggest ranges between 0.13–0.07 and 0.53–0.15 for domestic sheep. The heritability indicates the genetic potential of a trait to be passed to generations. Progress in resistance can be documented by a positive correlation in parasite load between parents and offspring. Therefore, selecting animals with the lowest FEC is expected to increase host resistance to parasites (Zvinorova et al., 2016).

Divergent breeding of Romney sheep reached 11-fold difference between low FEC lines compared to high FEC lines (Morris et al., 2000). A reduction of 69% in FEC following genetic selection was reported by Eady et al. (2003) in an experimental infection with *Haemonchus contortus* in Merino sheep.

Lambs from flocks selected for low FEC developed stronger acquired resistance with reduced number of nematode eggs in feces and diminished worm burdens. Resistant ewes showed lower FECs during the periparturient period and their lambs had lower FECs at weaning (Abbott et al., 2012).

Resistant animals selected on the basis of FEC were found to be more profitable in comparison to non-selected animals (Greeff et al., 2009). Variation in the rate at which individuals lose weight with increasing strongyle FEC can be viewed as an important indicator for selection on tolerance (Hayward et al., 2014).

FEC as a selection trait is characterized by some practical limitations. Animals should be infected in order to determine the FEC value which can be difficult to access under production conditions (Valilou et al., 2015). Results are influenced by the level and composition of a natural nematode challenge as well as the expression of the immune response (Douch et al., 1996). Furthermore, the number of eggs shed by the host does not necessarily correlated with the parasite load (Alba-Hurtado and Muñoz-Guzmán, 2012).

When using FEC for selective breeding animals should be tested twice during the spring months because the worm activity and fecal egg counts will be higher. Following this approach animals with the best immunity can be identified. Measurement of FEC is more effective on rams rather than on ewes as their number is usually limited. Furthermore a sire selected for resistance is more likely to pass this trait to numerous offspring. Breeding values for FEC in rams allow for the establishment of sheep herds with increased worm resistance in Australia and New Zealand. The Rylington Merino has become the most worm resistant Merino flock in Australia and a major resource for genetic studies (Greeff et al., 2009).

Packed cell volume (PCV)

PCV presents a valuable parameter to be measured when estimating resistance to the blood-sucking nematode *Haemonchus contortus*. It is negatively correlated with FEC in infected sheep (El-Ashram et al., 2017). A study by Tsukahara et al. (2019) pointed that PCV decrease as FEC increase, and correlation coefficients indicate stronger relationships with natural than artificial infection.

PCV represents a useful indicator for selecting animals on resistance/resilience (Gauly and Erhardt, 2001) with heritability between 0.12 to 0.31 (e.g. Santa Ines sheep, composite of Dorset, Romney, Finn sheep). Values reported by Vanimisetti et al. (2004) approach this range: 0.29 to 0.49. Heritability after infection was estimated at 0.4 (Albers et al., 1987).

The FAMACHA system

The FAMACHA system was proposed as a practical method to estimate the clinical manifestation and need of treatment for Haemonchosis in South Africa. The abbreviation stands for the name of Dr Faffa Malan (FAffa MAlan CHArt) who originally started to work on the idea. It was further developed by vanWyk and Bath (2002). The color of the eye mucous membranes is matched to a chart of five categories with each corresponding to a definite anemia level and haematocrit range. The scoring is done against a standardized set of five colours ranging from red-pink (normal) to white (terminal anemia) (Malan et al., 2001). The FAMACHA system aims at improved resistance and/or resilience with the ultimate objective of producing animals that survive and produce without the necessity of deworming (Notter et al., 2017). Heritability of FAMACHA score was reported in the range from 0.06 ± 0.04 (low parasite challenge) to 0.24 ± 0.05 (high parasite challenge) (Tibbo and Haile, 2009). Therefore it can also be used as a selective trait in the case of *Haemonchus contortus*.

As long as the prevalence of gastrointestinal infections remain high the identification of low FEC, low FAMACHA eye score or high PCV mean that an animal is resistant or resilient (Tibbo and Haile, 2009).

Other selection criteria have been proposed such as weight gain, body condition score (BCS), dag score, eosinophil count, antibody level, ect. (Bishop, 2012) that are beyond the scope of this review.

Genomic studies

Disease resistance traits present an attractive target for genomic studies based on DNA selection markers. This can be achieved if major genes or quantitative trait loci (QTL) for resistance can be identified, or single nucleotide polymorphism (SNP) chip based genomic predictors of sufficient accuracy developed (Bishop and Woolliams, 2014). Variation in SNP profiles between breeds is expected on the basis of random mutation, natural selection and genetic drift during periods of geographic isolation (Malek, 2009).

QTL mapping studies for parasite resistance in sheep were initiated using microsatellite markers. Several genome-wide association studies (GWAS) relying on the detection of genome-wide significant SNPs were also published (Becker et al, 2020; Al Kalaldeh et al., 2019; Atlija et al., 2016; Kim et al., 2015; Pickering et al., 2015). Another technique called regional heritability mapping (RHM) was suggested as a better option for the identification of genetic variation (Al Kalaldeh et al., 2019).

Candidate genes involved in innate and adaptive immune pathways were investigated to correlate results with resistance to parasites. These include genes that code for pattern recognition receptors (Toll like receptors (Thévenon, 2009), NOD like receptors, RIG I like receptors, C type Lectin binding receptors); cytokine genes (e.g. Interleukins, Interferons; IFN-γ genes as published by Coltman et al., 2001; Preston et al., 2014); ovine histocompatibility genes (Luffau et al., 1990; Schwaiger et al., 1995; Outteridge et al., 1996; Stear et al., 1997; Miller and Horohov, 2006; Preston et al., 2014; Valilou et al., 2015). The most promising QTLs were found in Ovis aries chromosomes (OAR) 3, in INFγ region, in OAR20 and in the major histocompatibility complex (MHC) region (Thévenon, 2009). It was observed that the highest concentration of QTLs associated with resistance to GIN belongs to chromosome 3 (16 QTLs) followed by chromosome 14 (7 QTLs) (Periasamy et al., 2014). Results from genome-wide association studies (GWAS) and regional heritability mapping (RHM) identified significant genomic regions on ovine chromosomes 2, 6, 18, and 24 (Al Kalaldeh et al., 2019). A genome-wide association study (GWAS) suggested QTL in OAR7 and OAR26 that were related to FEC (Pickering et al., 2015). Another study by Riggio et al. (2014) was able to identify loci underlying variation in nematode resistance in three European sheep populations on OAR1, 3, 4, 5, 7, 19, 20, and 24 with the most significant located on OAR20. However, it is still not clear if genes that control immune processes during the primary response to gastrointestinal nematodes are the same as those involved in subsequent infections (Dominik, 2005).

The question about the genetics of resistance to gastrointestinal nematodes is still not widely recognized among Bulgarian scientific society. An article by Dimitrova et al. (2013) mentions the issue in respect of its economic value. The polymorphism in sheep breeds was studied with emphasis on productive traits and the importance of marker-assisted selection (Hristova et al., 2012; Bozhilova-Sakova, 2017; Bozhilova et al., 2019; Gencheva, 2019).

Utilising QTL as a means of increasing genetic progress still lacks consistency. The lack of consensus overlap among reported QTLs represents an important obstacle for the identification of genetic markers that can be a reliable factor in sheep selection (Periasamy et al., 2014). Unless sufficient consistency in protocols, experimental materials and analysis approaches is reached the application of QTL as indicators of resistance is not practically possible (Dominik, 2005).

Results

The current review of selected literature results in the perception that classical criteria for breeding sheep on resistance to GIN are still widely accepted in contrast to innovative techniques. Despite future benefits of genomic selection there are obvious practical implications to its incorporation in extensive farming systems (Zvinorova et al., 2016). Therefore, selection for resistant hosts based on inexpensive easy to measure phenotypic markers such as FEC, PCV, FAMACHA though less specific can be instituted as sustainable control strategy on the field.

Discussion

Selection on resistance to GIN within a breed or the incorporation of resistant breeds represents a promising strategy for disease control and prevention. Breeds with unique genetics like many indigenous ones present a valuable source for conservation purposes (Malek, 2009). As gastrointestinal nematodes have become a major threat to sheep production it is mandatory to identify and protect resistant/tolerant breeds in their specific environment (Greeff et al., 2009).

More resistant individuals in the herd mean less larval contamination on the pasture and decreased risk for infection of lambs. It is estimated that eggs shed onto pasture will decrease by 4% per year under a selection program for both production and resistance traits (Johnson, 2012).

Advantages from selective breeding on resistance can be seen in lambs after 4- 5-months of age or more. Therefore programs should be concentrated in the production of ewes rather than animals that will go to the meat market soon after this age. The genetic improvement of herds is most efficient through breeding rams (Abbott et al., 2012) that significantly affect variables responsible for resistance (Luffau et al., 1990). Knowing the level of resistance in terms of FEC can be used to estimate the breeding value of sires and the probability in percentage to pass this trait to offspring. On the other hand, FEC in ram lambs can be utilized as a criterion for selecting replacement stock.

Another breeding strategy may rely on resilience. Selection on this trait may result in better performance under limited drenching; the progeny of such rams need fewer drench treatments than their non-resilient counterparts. Lambs from resilient rams have significantly less dags and higher weight gains under challenge compared to lambs from resistant or susceptible rams (Johnson, 2012). Resilience however, does not necessarily reduce FEC levels. Furthermore the process is slow, depends on the level of exposure to parasites and heritability is low (0.10–0.19) (Hamie, 2018).

The concept of hybrid vigor (heterosis) can also be utilized as crossbred animals tend to perform better and therefore possess increased ability for resilience to gastrointestinal nematodes (Johnson, 2012). Maintenance of heteregenous genetic populations allows for variation in response to disease outbreaks which is crucial to viability of livestock production systems (Jovanović et al., 2009).

Selection for resistance to gastrointestinal nematodes in the individual and group level results in permanent effects such as decreased worm burden, pasture contamination and reliance on anthelmintic drugs, enhanced health status and consequently increased production.

Conclusions

Breeding for resistance appears to be one of the most promising approaches with beneficial effects on animal health and welfare that is able to reduce the dependance on anthelmintic drugs as well as result in economic gain. It is a long term strategy that is going to bring livestock production systems to a new level in management and prophylaxis of gastrointestinal nematode infections.

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