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A key mechanism of pathogenesis in sheep infected with the nematode *Teladorsagia circumcincta*

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Abstract

Infection of sheep with the abomasal nematode *Teladorsagia circumcincta* can cause a relative protein deficiency and reduce growth rate in growing lambs. A key event appears to be the destruction of junctions between epithelial cells. If the infection is heavy or prolonged, this leads to increased mucus production, hyperplasia, decreased acid production, gastrinemia, inappetance and pepsinogenemia. The severity of the infection depends upon the extent of concurrent infection, the nutritional status of the host and genetically controlled variation in the ability to mount protective immune responses.

Keywords: Teladorsagia circumcincta, pathogenesis, sheep, parasitic diseases, parasitic nematodes

Introduction

Gastrointestinal nematode infections of livestock (especially cattle, goats and sheep) have always attracted considerable attention because of their economic importance and welfare implications (Holmes, 1987; McKellar, 1993; Sykes, 1994; Fox, 1997; Stear *et al*., 1997a, Coop and Kyriazakis, 2000; Simpson, 2000). There are additional reasons for studying these parasites. They have simple, direct life cycles (Urquhart *et al*., 1987) and they are superb models for nematode–host interactions (Grenfell *et al*., 1996; Stear *et al*., 1997a). They are also natural parasites. While natural host–parasite interactions can be more demanding to study than artificial models, they represent evolved relationships, whereas laboratory models may have unnatural responses or responses reflecting the limitation of the laboratory environment. Therefore natural systems appear more credible and the results may be more relevant to other natural host–parasite systems.

The accumulation of knowledge has been especially rapid over the last 10 years. While veterinary science often lags behind medical science, this is not true for parasitology. Our knowledge of the epidemiology (especially natural history and mathematical modeling), immunoparasitology (especially protective mechanisms), quantitative and molecular genetics of host resistance and the pathophysiology of gastrointestinal nematodes is at least comparable to that of any other host–parasite interaction.

The aim of this review is to discuss the mechanisms responsible for the pathophysiology of nematode infection, especially infections of sheep with the abomasal nematode *Teladorsagia circumcincta* (also known as *Ostertagia circumcincta*). This review will focus on this species because this is the dominant nematode in many temperate areas of the world, including the UK, and is an important component of parasitic gastroenteritis and reduced production efficiency. This review will not attempt to revisit areas that have been reviewed recently but will attempt to synthesize and extend our existing knowledge and to develop clear, coherent and consistent hypotheses to explain the interaction between sheep and *T. circumcincta*.

The pathological consequences of infection

A variety of studies have produced a consensus about pathogenesis following infection with *T. circumcincta*

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(Armour *et al*., 1966; Coop *et al*., 1982, 1985). Infection causes a relative protein deficiency. Convincing evidence that pathogenesis is largely a consequence of the induced relative protein deficiency is the demonstration that clinical signs can be prevented or reduced when animals are fed supplementary protein before and during infection (Coop *et al*., 1995).

The importance of supplementary feeding of sheep has also been demonstrated for *Haemonchus contortus* (Abbott *et al*., 1984, 1986, 1988; Wallace *et al*., 1999) as well as the small intestinal species *Trichostrongylus colubriformis* (Bown *et al*., 1991; Kambara *et al*., 1993; van Houtert *et al*., 1995; Kyriazakis *et al*., 1996) and *Nematodirus battus* (Israf *et al*., 1996). Interestingly, dietary supplementation with urea also enhances resistance and resilience to *T. colubriformis* (Knox and Steel, 1999) as well as *T. circumcincta* (Wallace *et al*., 1998; Stear *et al*., 2000a), presumably because bacteria in the rumen convert urea into amino acids and proteins that are subsequently digested by the host. This suggests that cheap sources of non-protein nitrogen could be used instead of expensive proteins to supplement diets.

The relative protein deficiency has four causes: (i) infected animals eat less; (ii) the protein that they do eat is digested less efficiently; (iii) host proteins are lost into the gastrointestinal tract due to breaches in the epithelial barrier; and (iv) infection increases protein demand as host protein is lost or diverted to immune and inflammatory responses.

Inappetance can account for much of the observed reduction in weight gain (Fox, 1997; Kyriazakis *et al*., 1998). A reduction in food intake is a strange response to a relative protein deficiency. However, inappetance (also known as anorexia) is a common response to a variety of infections, and one consequence of anorexia may be a reduction in the likelihood of subsequent reinfection (Kyriazakis *et al*., 1998).

There is considerable damage to the abomasal mucosa (McKellar, 1993). The cell junctions are broken, creating breaches in the epithelium. The mucosa is hyperplastic and many cells are dedifferentiated, mucosal pH rises and mucus production increases. The concentrations of gastrin and pepsinogen in the plasma increase while the concentrations of albumin and fructosamine decrease. This damage to the mucosal architecture often, but not always, produces a decrease in the apparent digestibility of the diet in infected compared with uninfected animals (Parkins *et al*., 1973; Coop and Holmes, 1996). Indeed, given the extensive damage to the mucosa, it is somewhat surprising that changes in apparent digestibility are not detected more readily, but this may relate to the severity of the infection (Parkins *et al*., 1973) as well as the difficulty of assessing digestibility (Parkins and Holmes, 1989).

There are also several changes reflecting the development of immunity. There is a considerable influx of mast cells, eosinophils, lymphocytes, plasma cells and globule leukocytes (Stear *et al*., 1995). Globule leukocytes represent discharged mast cells (Murray *et al*., 1968; Huntley *et al*., 1984).

In summary, the consequence of reduced food intake and possibly reduced digestibility coupled with increased protein loss through breaches in the epithelium (Holmes, 1987) and the diversion of protein to mucosal repair and immune responsiveness is relative protein deficiency. This relative protein deficiency is associated with reduced growth rate (Coop *et al*., 1982, 1985), poorer immune responses (Coop *et al*., 1995; Stear *et al*., 2000a) and, in some situations, death (Gulland *et al*., 1993).

Pathogenesis clearly differs among nematode species. Many of the pathological features are similar in abomasal infections (Holmes, 1987), and haemonchosis has been described as a protein-losing gastropathy exacerbated by anemia (Strain and Stear, 2001). The small intestinal species, such as *T. colubriformis*, obviously do not affect abomasal enzymes and hormones but they can cause relative protein deficiency. Coop and Kyriazakis (1999) have argued that the reduction in voluntary feed intake is the major consequence of infection with *T. circumcincta*, while the predominant effect of infection with *T. colubriformis* is the reduction in the efficiency of food utilization.

The influence of infection on production traits

One example of the influence of gastrointestinal nematode infection on weight gain comes from the study by Coop *et al*. (1982). In this trial, animals were kept inside and fed a defined diet over a 12-week period. Uninfected animals gained approximately 15 kg and animals infected daily with 1000, 3000 or 5000 larvae gained 13, 11 and 8 kg respectively. Interestingly, regular anthelmintic treatment of animals receiving 5000 larvae daily restored weight gain to only 10 kg. While the details differ among experiments, the general principles are widely held. Increasing levels of infection reduce weight gain and anthelmintic treatment restores part of the lost weight gain, but not to the values seen in uninfected animals.

An alternative means of assessing the importance of infection on weight gain under natural conditions is to estimate genetic correlations between weight gain or body weight and a trait that indicates infection status, such as fecal egg count. The genetic correlation describes relationships between level of infection and weight gain at the individual animal level, whereas experimental results such as those described above (Coop *et al*., 1982) summarize changes in the population mean after infection. To our knowledge, five such studies with predominantly *T. circumcincta* infection have been carried out. All studies estimated the genetic correlation between body weight and fecal egg count during

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natural exposure. A negative correlation is desirable, i.e. body weight should increase as egg counts decrease. One study in Scottish Blackface sheep estimated the genetic correlation at −0.8 (Bishop *et al*., 1996); a second in Polish Longwool sheep estimated the correlation at −0.6 (Bouix *et al*., 1998); a third in Scottish Blackface sheep estimated the correlation at −0.26 (Bishop and Stear, 2000); and a fourth in Scottish Texel sheep estimated the correlation at −0.13 (Bishop and Stear, 2001). A fifth study in feral sheep also produced negative genetic correlations between egg counts and body size (Coltman *et al*., 2001a). Whilst these correlations do apparently differ, modeling studies suggest that the size of the correlation will vary with the intensity of infection (Bishop and Stear, 1999). However, all these relationships are favorable. Together, they indicate that animals with lower egg counts grow more quickly and that variation among animals in resistance to predominantly *T. circumcincta* infection plays an important role in growth under conditions of natural challenge.

Somewhat surprisingly, the favorable genetic correlations of parasite resistance and growth found for predominantly *T. circumcincta* infections in Europe do not appear for predominantly *H. contortus* or *T. colubriformis* infections in Australia and New Zealand (Albers *et al*., 1987; Bisset *et al*., 1992; Douch *et al*., 1995; McEwan *et al*., 1995; Eady *et al*., 1998). Here the correlations tend to be neutral or unfavorable. The genetic correlations of wool production with parasite resistance are also unfavorable; as egg counts decrease, wool production also decreases (McEwan *et al*., 1995).

The different signs for the genetic correlations in Europe compared with Australia and New Zealand could reflect differences in management conditions, host breed or parasite species. One explanation for the negative genetic correlations between egg counts and production traits is that under some circumstances the immune response to gastrointestinal nematodes can have deleterious consequences for wool production and growth. The unfavorable genetic correlations of wool growth with resistance have been attributed to competition for cysteine between wool-producing cells and cells of the immune system (Miller *et al*., 1998). The unfavorable genetic correlations between egg counts and growth are considered later.

The influence of infection with *T. circumcincta* on growth rate also depends upon the nutritional status of the host (Coop *et al*., 1995; Stear *et al*., 2000a). As stated earlier, well-fed animals show very few, if any, clinical signs compared with animals on a normal diet (Coop and Kyriazakis, 1999). In addition, there may be compensatory protein absorption in the small intestine, but this will be affected by infection with small intestinal nematodes (Parkins and Holmes, 1989). Mixed nematode infections are likely to be more pathogenic than single-species infections for this reason.

Nematode infection can also adversely affect wool production, carcass composition and milk production (Parkins and Holmes, 1989). Nematode infection can decrease production but the severity of production losses varies with the intensity of infection, host nutrition, host immunity and the species composition of the infection (Sykes, 1994).

Pathogenesis depends on worm number and worm size

For a single animal, the observed fecal egg count reflects the number of nematodes present and the number of eggs produced by each worm (i.e. fecundity). Differences in fecal output could also influence the concentration of eggs in the feces, but the possible 2- to 4-fold variation in fecal output is relatively trivial compared with the large variation among animals in fecal egg counts. There is genetic variation in fecal egg count; the heritability of fecal egg count increases in lambs as they mature and is about 0.33 in 6- to 7-month-old animals (Bishop *et al*., 1996; Stear *et al*., 1997a). Therefore it is of interest to determine whether the genetic variation in fecal egg output is a consequence of genetic variation in the number of nematodes present in each sheep or genetic variation in the mean fecundity of the nematode population. Fecundity can be difficult to measure directly, but for *T. circumcincta* more fecund worms have more eggs *in utero* and are longer (Stear *et al*., 1995, 1997a); the association between the length of adult female *T. circumcincta* and egg production is very strong and consistent across both natural and deliberate infections (Stear and Bishop, 1999). Analysis from necropsy samples in 6- to 7-month-old lambs indicates that most of the genetic variation in fecal egg count is associated with differences in fecundity and worm length rather than differences in worm number (Stear *et al*., 1997a, b). In this study the majority of eggs produced and the majority of nematodes recovered were *T. circumcincta*. In particular, the heritability of worm length in adult female *T. circumcincta* was 0.62. This is very high and indicates that genetic variation in the host accounts for almost twice as much of the variation in mean worm length as all other sources of variation combined. In contrast, the heritability of worm number is only 0.14, which is not significantly different from zero. Therefore, either there is little genetic variation in worm number or the variation is too weak in comparison with other sources of variation to be detectable in a study of over 500 lambs.

The observation that genetic variation in fecal egg count is due largely or entirely to genetic variation in worm length suggests that the genetic correlation between growth and fecal egg count is due to the effect of worm size on lamb growth. Differences among sheep in worm length are also associated with differences in plasma pepsinogen concentration (Stear *et al*., 1999).

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Therefore, the severity of infection with *T. circumcincta* is associated with mean worm length as well as total worm number.

Nematode size and number also appear to affect pathogenicity for *H. contortus* (Strain and Stear, 2001), but detailed studies do not appear to be available for other species of sheep nematodes.

The influence of immune responses on pathogenesis

Several studies indicate that exposure to infection can influence growth rate or cause pathological changes even when very few larvae establish. These studies demonstrate pathological changes with very light infections and suggest that at least some pathological changes are a consequence of the host response to incoming larvae rather than a result of the infection process. McAnulty *et al*. (1982) demonstrated decreased growth during natural infection, even with regular anthelmintic treatment. Yakoob *et al.* (1983) showed pathophysiological changes in older immune ewes even though levels of establishment were very low; in particular, larval challenge led to increased plasma pepsinogen concentrations, increased albumin catabolism and increased losses of plasma protein into the gastrointestinal tract. Stear *et al.* (2000b) infected lambs over winter. In this protocol very few larvae managed to establish and most of those that did were inhibited as fourth-stage larvae. Even so, infected animals grew more slowly than uninfected controls. One possible explanation for these findings is that the immune response itself is responsible for at least part of the decrease in growth.

For *T. circumcincta*, the protective immune response appears multiphasic (Stear *et al*., 1997b). Very young animals are protected because most of their nutrients are obtained from suckling and they eat very little contaminated grass. Lambs imbibe maternal antibody with colostrum (Filmer and McClure, 1951). Maternal antibody may be protective, but this has yet to be seriously investigated. As lambs mature, grass forms an increasing part of their diet and if the grass is contaminated with infective larvae they will elaborate an immune response. Up to about 7 months of age, a major manifestation of immunity appears to be the IgA-mediated retardation and inhibition of worm growth and fecundity (Stear *et al*., 1995). During this period, resistant animals have lower egg counts, stronger IgA responses and grow more quickly.

Subsequently, sheep acquire the ability to regulate worm number, and this is associated with increased mucosal mast cell responses (Stear *et al*., 1995). Mast cell responses may prevent larval establishment or expel established adult parasites (Miller, 1996). Preliminary observations suggest that relatively resistant lambs more than 7 months of age grow more slowly than relatively susceptible lambs of the same age (Stear *et al*., 2000a).

Therefore, epidemiological studies suggest that some immune responses may reduce growth rate. The two major mechanisms of protective immunity to *T. circumcincta* are the IgA-mediated suppression of nematode growth and development and the mast cell-mediated regulation of nematode numbers. IgA-mediated suppression of nematode growth is unlikely to contribute to reduced growth rate, but mast cell-mediated responses may do so. Further enlightenment comes from the study of gastric ulceration.

Similarities with gastric ulceration

A comparison of the pathophysiology of gastric ulceration, especially enlarged fold gastritis, demonstrates considerable similarity with the pathophysiology of abomasal nematode infection (Scott, 1996). The features common to the two pathologies are disruption of cell junctions, increased mucus production, hyperplasia, decreased acid production, gastrinemia, inappetance and pepsinogenemia. The critical event in gastric ulceration is the disruption of cell junctions (Schubert, 1997). This breach in the mucosal barrier allows epithelial growth factor and transforming growth factor α to diffuse across the epithelium and bind to the epithelial growth factor receptor on the inner surface of epithelial cells. Binding to this receptor triggers increased secretion of mucus and decreased acid production, and increases cell division and migration (Playford, 1995). These are adaptive responses by the host to repair the damaged barrier and to minimize further damage. Acid secretion is normally stimulated by gastrin, which also promotes the proliferation and differentiation of gastric mucosal cells. A prolonged or severe decrease in acid secretion leads through normal, but poorly understood, homeostatic mechanisms to hypergastrinemia. Increased production of gastrin could also induce inappetance because of reduced gastric emptying (Fox *et al*., 1989) or through increased production of leptin (Bado *et al*., 1998). Inappetance could be a protective response to minimize food intake while the mucosa is being repaired. Decreased acid production also inhibits the autocatalytic conversion of pepsinogen into pepsin. The breakdown of the mucosal barrier would allow pepsinogen to diffuse back into the tissues; from there it flows into lymph and subsequently into the bloodstream (Baker *et al*., 1993). Similarly, other proteins at higher concentrations in the interstitial fluid would diffuse into the gastrointestinal tract, and this would lead to the observed protein losses and increases in protein turnover (Yakoob *et al*., 1983; Heath and Connon, 1991; Stear *et al*., 2001).

Therefore the pathophysiological consequences of infection with *T. circumcincta* may follow from widespread, repeated breaches in the mucosal barrier due to sustained parasite-induced insult. Additional support for this hypothesis comes from studies in cattle and rats. Murray *et al.* (1970) have shown that the tight junctions

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between epithelial cells are disrupted in bovine ostertagiasis. Scudamore *et al.* (1995) have shown that proteases produced by mast cells in rats are capable of destroying cell junctions. Mast cell degranulation and protease release could be triggered by the binding of parasite molecules to anaphylactic antibodies on the cell surface.

A simple unifying hypothesis

Together, these observations suggest a relatively simple hypothesis to account for much of the pathology following infection with *T. circumcincta*. This hypothesis also appears applicable to infection of cattle with the abomasal parasite *Ostertagia ostertagi* (Murray *et al.*, 1970), but the two species may differ in some details, such as the regulation of gastrin secretion (Fox, 1997). The hypothesis may also explain some of the pathology following *Haemonchus* infections of cattle and sheep, although here the pathology is exacerbated by anemia. The hypothesis is not relevant to infection with small intestinal nematodes, such as *Trichostrongylus colubriformis* and *Nematodirus battus*.

Following infection, the parasite releases molecules that trigger mast cell degranulation. Mast cell proteases then break down the nearby cell junctions. Epithelial growth factor and transforming growth factor α bind to epithelial growth factor receptor and trigger increased secretion of mucus, decreased acid production and increased cell division and migration. A heavy or sustained infection leads to hypergastrinemia, which produces inappetance. Pepsinogen diffuses into the interstitial fluid and from there into the lymph and subsequently into the bloodstream. The breakdown of cell junctions allows protein in the interstitial fluid to flow into the gastrointestinal tract. The reduction in protein concentration in the interstitial fluid causes a loss of protein from the lymph and ultimately from the blood.

A number of predictions can be made from this hypothesis. For example, parasite extracts could reproduce some of the pathology even in the absence of viable parasites. This has been shown by Eiler *et al.* (1981) in rats. In addition, the pathology caused by transplanted adult parasites should be similar to the pathology of natural infections. This has been shown by Scott (2000) following on from an earlier demonstration in cattle (McKellar *et al.*, 1986, 1987). Scott (1996) has also demonstrated the presence of epithelial growth factor and transforming growth factor α in abomasa from infected sheep.

However, a more interesting test of the validity of a hypothesis is not so much how it predicts the events it was constructed to explain but whether it clarifies other areas. One active area of research is the attempt to explain why growing lambs aged 3–6 months acquire immunity to gastrointestinal nematode infections more slowly than sheep older than 8 months (Coop *et al.*, 1995). Coop and Kyriazakis (1999) have proposed a framework hypothesis that suggests that the development of immunity is slow because the expression of immunity has a lower priority for resource allocation than growth. This framework has been developed to explain general patterns, and possibly the framework needs to be extended to consider each type of parasite and each relationship separately. For example, immunity to the small intestinal nematodes *N. battus* and *T. colubriformis* develops quite rapidly (Israf *et al.*, 1996; McClure *et al.*, 1998). In addition, the IgA-associated antifecundity responses to the abomasal nematodes *T. circumcincta* and *H. contortus* develop quite rapidly (Stear *et al.*, 1995; Strain and Stear, 2001). Therefore, perhaps the key issue that needs to be resolved—and this is consistent with the general framework of Coop and Kyriazakis (1999)—is why the mast cell responses that regulate worm numbers develop so slowly in the abomasum. One explanation that flows immediately from the hypothesis developed here is that natural selection is unable to promote the rapid development of strong mast cell responses in the abomasum because this would lead to lowered growth rates in growing lambs. Slow-growing lambs would suffer reduced viability and fitness compared with faster-growing contemporaries, hence this route would not be favored by natural selection.

Possible modifying influences on pathology

The hypothesis that a key event in pathogenesis following infection with *T. circumcincta* is breakdown in cell junctions is clear, coherent and consistent, it rests upon well-established pathophysiological mechanisms, and it is supported by the available evidence. However, there are a number of potential modifying influences. Further work is necessary to determine the relative contributions of these influences to the observed pathology, but these influences are plausible mediators of the observed effects. For example, the parasite might produce molecules that contribute to pathology (Simpson, 2000). Interestingly, adult *T. circumcincta* that were prevented from contacting the abomasal mucosa were still able to raise abomasal pH and, in some cases, to increase gastrin and pepsinogen secretion (Simpson *et al.*, 1999).

In addition, a wide variety of cytokines are produced following nematode infection. This area of research is most advanced in rodent models (Finkelman *et al.*, 1997; Grencis, 1997; Else and Finkelman, 1998) but similar results have been shown in sheep (Pernthaner *et al.*, 1997) and cattle (Gasbarre *et al.*, 2001). Some of these cytokines could contribute to the observed pathology. As well as epidermal growth factor and transforming growth factor α, mentioned already, other cytokines, including interleukin-1β, hepatocyte growth factor and tumour necrosis factor α, could inhibit gastric acid secre-

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tion (Beales, 2000). There are no experimental models of gastric nematode infection, but cytokine production in the stomach has been studied in *Helicobacter pylori* infection. Interleukin-1β may initiate much of the pathology in *H. pylori*-associated, enlarged fold gastritis (Lord *et al*., 1991; Harris *et al*., 1996; Yasunaga *et al*., 1997). Another cytokine, tumour necrosis factor α, is important in the intestinal pathology that develops in mice following infection with the nematode *Trichinella spiralis* (Lawrence *et al*., 2001).

Similarly, eosinophilia is a hallmark of parasitic infection (Stear *et al*., 2002), and Balic *et al*. (2000) have argued that eosinophils play a role in killing infective nematode larvae. Eosinophils could also contribute, either directly or indirectly through the release of cytokines, to the pathogenesis of nematode infection (Larsen *et al*., 1994; Behm and Ovington, 2000).

In addition, there is substantial genetic and non-genetic variation among individuals in resistance to *T. circumcincta* (Bishop *et al*., 1996; Stear *et al*., 1997a, b). Particular alleles within or around the major histocompatibility complex class II *DRB1* locus and the interferon γ locus are associated with resistance to infection (Schwaiger *et al*., 1995; Coltman *et al*., 2001b). Genetic variation among individuals could also explain individual variation in the severity of pathological effects (McEwan *et al*., 1992; Williamson *et al*., 1995; Bisset *et al*., 2001).

Conclusion

Infection with *T. circumcincta* can cause a relative protein deficiency and reduce growth rate in growing lambs. The key event appears to be the destruction of cell junctions by mast cell proteases. If the infection is sufficiently severe, this leads inexorably to the typical features of the infection, including increased mucus production, hyperplasia, decreased acid production, gastrinemia, inappetance and pepsinogenemia. The severity of the infection depends upon the extent of concurrent infection, the nutritional status of the host and genetically controlled variation in the ability to mount protective immune responses.

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