



Review

Manipulative parasites in the world of veterinary science: Implications for epidemiology and pathology

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ARTICLE INFO

Article history:

Accepted 24 January 2009

Keywords:

Parasite manipulation

Host behaviour

Transmission

*Diplostomum spathaceum**Echinococcus* spp.*Toxoplasma gondii*

ABSTRACT

One of the most complex and least understood transmission strategies displayed by pathogenic parasites is that of manipulation of host behaviour. A wide variety of parasites alter their host's behaviour, including species of medical and veterinary importance, such as *Diplostomum spathaceum*, *Echinococcus* spp. and *Toxoplasma gondii*. The manipulative ability of these parasites has implications for pathology and transmission dynamics. Domestic animals are hosts for manipulative pathogens, either by being the target host and acquiring the parasite as a result of vector-host manipulation, or by having their behaviour changed by manipulative parasites. This review uses several well-known pathogens to demonstrate how host manipulation by parasites is potentially important in epidemiology.

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Introduction

Parasites face considerable odds against the successful completion of their life cycle, since most hosts represent isolated and patchy resources that are capable of self-defence. This is especially true for parasite species that rely on a vector host coming in contact with or being eaten by a specific target host in which the parasite must continue its development (Choisy et al., 2003; Parker et al., 2003; Poulin, 2007). The parasite and its host must be at the right place at the right time to be transmitted to the next appropriate host. As a result, in some situations, natural selection has favoured parasites capable of manipulating their host's behaviour.

Parasites may use chemical secretions or other means to alter a variety of host behaviours in a way that benefits the parasites by increasing their chances of transmission to the next host (Moore, 2002; Thomas et al., 2005; Poulin, 2007). Some of these examples involve changes in host phenotype, including the acquisition of new behaviours, and they provide strong evidence for the concept of the extended phenotype, i.e. genes in one organism having phenotypic expression in another organism (Dawkins, 1982).

Here, we provide an overview of ways in which parasites can alter some aspects of their host's behaviour to increase their own transmission success. In particular, we highlight some parasites of veterinary significance that are known to alter host behaviour, demonstrating that host manipulation is tightly linked to the parasite's epidemiology.

Classical examples of parasitic 'manipulation'

The scientific literature contains many reports of modified behaviours in parasitised animals. Three spined sticklebacks harbouring the larval cestode *Schistocephalus solidus* swim closer to the water surface and become less aware of the presence of predatory birds that serve as the parasite's definitive hosts (DHs) (Barber et al., 2004). Rodents infested by the nematode *Trichinella spiralis* or the protozoan *Sarcocystis cernae* are less wary of predators, thus facilitating the parasites' transmission to DHs (Rau, 1983; Hoogenboom and Dijkstra, 1987).

In some cases, completely new behaviours are observed in infested hosts. For instance, an orb-weaving spider infested by a parasitic wasp larva builds an unusual web designed to protect the emerging larva after the host spider's death (Eberhard, 2000). Another parasitic wasp induces its caterpillar host to remain near the parasite after the latter emerges from its body, thus protecting the pupating wasps from potential predators by acting as a 'bodyguard' (Grosman et al., 2008).

Ants infested by a nematode that must be transmitted to fruit-eating birds not only look like fruit, by developing a swollen, red abdomen, but also 'behave' like fruits, perching among berries of similar colour, with the abdomen held in an elevated position, motionless, waiting for predation by birds (Yanoviak et al., 2008).

Nematomorphs (hairworms) and mermithid nematode larvae are parasitic and develop inside terrestrial arthropods, but must reach the aquatic environment in which the adult worms live after maturation. They induce their arthropod hosts to commit 'suicide' by forcing them to seek and jump into water (Thomas et al., 2002,

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2003; Penney and Bennett, 2006). Again, such manipulation involves the sudden appearance of new host behaviours induced by the parasite for its own needs (Thomas et al., 2003; Biron et al., 2005).

Clearly, many parasite species are capable of manipulating their hosts' behaviour in natural systems. However, domestic animals can also be affected by manipulative parasites, either as target hosts or manipulated vector hosts. Rabies is one of the best examples of a pathogen that manipulates the behaviour of the host. The virus infects the central nervous system (CNS) of mammals, particularly regions of the brain controlling aggressive and social behaviours, and the salivary glands. Infected hosts may display aggression, which facilitates transmission of infection through biting (Klein, 2003). Although the fatal outcome of rabies forces the pathogen into a permanent search for new hosts, rabies-induced behavioural changes has ensured the transmission, survival and spread of this pathogen across time, space and host species with extraordinary efficacy.

Parasites of veterinary importance

Dicrocoelium dendriticum

The trematode *D. dendriticum* is present worldwide and is distributed throughout Europe, Asia, North Africa and America (Otranto and Traversa, 2002). Although the pathogenicity of *D. dendriticum* is usually low, dicrocoelosis can lead to weight loss and reduced milk production in domestic ruminants and can sometimes be fatal (Otranto and Traversa, 2002). Reports of the disease are increasing, mostly due to the development of anthelmintic resistance and the geographical expansion of *D. dendriticum* (Otranto and Traversa, 2002; Goater and Colwell, 2007).

D. dendriticum is transmitted to ruminants, including domestic cattle and sheep, when they accidentally ingest infested ants along with their plant food. The parasite larvae induces their insect hosts to climb to the tips of grass blades and remain there, anchored by their mandibles, awaiting ingestion by a grazing herbivore (Carney, 1969; Roming et al., 1980).

Diplostomum spathaceum

The common digenean eye fluke *D. spathaceum* has a complex three host life cycle including lymnaeid snails, fish and fish-eating birds, such as grebes and cormorants (Crowden and Broom, 1980; Karvonen et al., 2004a). Free-swimming cercariae, produced through asexual multiplication within the snail and released into the water, must find a fish, which they penetrate through the gills or skin. They migrate through tissues to the lens of the eye, where they develop into long-lived metacercariae. The cycle is completed when the fish host, along with its metacercariae, is eaten by the DH, a bird.

By lodging themselves in the host's eyes, metacercariae induce cataracts due to mechanical destruction of the lens and metabolic products excreted by the parasites, thus reducing the host's vision (Karvonen et al., 2004b; Seppälä et al., 2004). *D. spathaceum* infestation in fish is also associated with changes in host behaviour, such as increased activity, migration towards the surface of the water and lack of responsiveness to visual stimuli, although swimming ability is unaffected (Crowden and Broom, 1980; Brassard et al., 1982; Seppälä et al., 2004). Thus, by injuring important sensory organs, *D. spathaceum* is able to alter fundamental fish anti-predator mechanisms, such as crypsis and shoaling behaviour, in a way that is likely to increase the vulnerability of the intermediate host (IH) to predation by the DHs (Krause and Ruxton, 2002; Seppälä et al., 2005, 2006, 2008).

D. spathaceum is a globally distributed parasite that infests a large number of fish species, with high prevalence and intensities recorded in some hosts (Crowden and Broom, 1980; Moody and Gatén, 1982; McKeown and Irwin, 1997; Valtonen and Gibson, 1997; Karvonen et al., 2004b). While pathological effects of diplostomiasis have seldom been documented in wild fish, partly because heavily infested individuals are removed from the population through predation (Pennycuik, 1971), *D. spathaceum* epizootics can be serious in captive fish, particularly farmed salmonids, such as rainbow trout (*Oncorhynchus mykiss*; Betterton, 1974).

Since *D. spathaceum* cercariae are not actively host seeking and are often patchily distributed, behavioural avoidance of these sources of infestation is the prime defence mechanism displayed by fish hosts (Karvonen et al., 2004c). Captive housing of fish for research, display and large-scale aquaculture is likely, because of spatial confinement and artificially high densities, to constrain fish avoidance behaviours (Barber, 2007). As a result of high and continuous exposure to parasite larvae, *D. spathaceum* frequently is found in large numbers in farmed fish and may cause welfare problems. Anecdotally, rainbow trout heavily infested by *D. spathaceum* are not responsive to anglers' lures, which reduces their suitability for recreational fishing (Moody and Gatén, 1982).

Echinococcus spp.

Hydatid disease (echinococcosis) is due to infestation with cysts (metacestodes) of the cestode parasite *Echinococcus* spp. (Lymbery and Thompson, 1996). These parasites have a life cycle with two hosts, both mammals. The DHs are carnivores, in which the adult cestodes inhabit the small intestine. Eggs are released in the faeces and are accidentally ingested by an IH, in which they hatch and develop into hydatid cysts in the lungs, liver and other internal organs. The DH becomes infested when preying on an infested IH.

Several *Echinococcus* spp. are currently recognised, although numerous intraspecific genetic strains exist (Jenkins et al., 2005). *Echinococcus* spp. have a narrow range of DHs, mainly domestic and wild canids, but a wide geographical distribution, being virtually present on every continent (Eckert and Thompson, 1997). Their metacestodes are generally less host-specific than those of other taeniids and can develop in a wide range of herbivores and omnivores, including humans and, of particular veterinary concern, sheep, cattle and horses (Lymbery and Thompson, 1996; Eckert and Thompson, 1997).

E. granulosus and *E. multilocularis* are the most important species in term of public health implications and geographical distribution (Eckert et al., 2000; Jenkins et al., 2005; Schweiger et al., 2007; Gottstein and Hemphill, 2008). *E. granulosus* infests predominantly domestic animals, with dogs as DHs and mainly sheep as IHs, but is also infectious for humans (Eckert and Thompson, 1997). *E. granulosus* and *E. multilocularis* are responsible for cystic and alveolar echinococcosis, respectively, both resulting, through asexual reproduction, in increasingly large and abundant cysts that eventually become debilitating, if not lethal (Jenkins et al., 2005; Thompson, 2008). Infested IHs may thus become more vulnerable to predators, including the DH of the parasite (Ewald, 1995).

The hypothesis that echinococcosis could increase host vulnerability to predation came from an anecdotal incident reported by Crisler (1956), in which a caribou cow (*Rangifer tarandus*) failed to escape from wolves. Postmortem examination revealed that its lungs were infested with several large cysts of *E. granulosus*. In moose (*Alces alces*), a large proportion of hydatid cysts are found in the lungs and severe infestations reduce the endurance of animals trying to escape from grey wolves (*Canis lupus*), one of the DHs of *E. granulosus* (Messier et al., 1989). Wolves and other carnivores selectively prey on weaker animals and moose with cystic

hydatid disease may be more vulnerable to predation (Messier et al., 1989; Joly and Messier, 2004). However, no study to date has empirically shown the direct link between hydatid infestation, increased predation risk and increased transmission rates for the parasite.

Internal organs, including the lungs, are often among the first to be eaten by large carnivores, such as wolves (Joly and Messier, 2004). Therefore, it is possible that selection has favoured the location of parasite cysts at these sites to ensure rapid consumption by the DHs rather than to enhance transmission probability. Nevertheless, the pathological effects of echinococcosis do modify the escape behaviour of its IHs in a way that could increase predation and parasite transmission.

Toxoplasma gondii

Alterations in host behaviour following parasitic infection are sometimes exactly what we would expect to see if the host was to start acting in ways that benefit parasite transmission (Poulin, 2007). This is shown by the modifications in host behaviour induced by *T. gondii* and how they may influence the parasite's transmission to the DH.

T. gondii is a widespread intracellular protozoan capable of infecting all endothermic vertebrates. The parasite has a complex life cycle in which Felidae, mostly cats, are the DHs. Oocysts released in host faeces are persistent in the environment and can remain infectious for more than a year (Webster, 1994a). During that time, they must be ingested by another host, either directly by a cat, in which the parasite invades intestinal cells, matures and sexually produces new oocysts, or by an IH.

Although a wide range of endotherms (rodents, birds or humans) can be infected, wild rodents are the natural IHs of *T. gondii* (Berdoy et al., 2000). In the acute phase of infection, the parasite penetrates the intestine, undergoes asexual reproduction and enters macrophages and is transported to preferred encystment sites. The parasite then forms resistant cysts in various organs of its IHs, most commonly the brain (Berdoy et al., 1995); these cysts can persist for the life of an infected host (Webster, 2001). The parasite completes its life cycle when a cat consumes an infected host.

Although *T. gondii* does not need its DH to survive and can be maintained over time in IH populations by congenital transmission, cannibalism or interspecific predation, its infectivity increases after each episode of sexual reproduction (Webster, 1994a, 2001). Since sexual reproduction of *T. gondii* can be accomplished only in the DH, the parasite is ultimately dependent upon predation of infected animals by cats. As a result, there might be strong selective pressures for transmission to the DH and, therefore, on the parasite to evolve mechanisms to enhance the transmission rate from IHs to cats (Berdoy et al., 2000; Webster, 2001; Webster et al., 2006).

Latent toxoplasmosis has long been considered to produce inapparent infections in immunocompetent hosts (Webster et al., 1994, 2006; Kankova et al., 2007). However, recent studies have shown that chronic *T. gondii* infection can induce modifications in the behaviour of infected hosts. In rodents, *T. gondii* causes increased levels of activity, along with decreases in neophobic (i.e. fear of novelty) and anxiety behaviours, all of which could potentially enhance transmission to DHs (Webster, 1994b; Webster et al., 1994; Gonzalez et al., 2007). Since *T. gondii* mostly invades and encysts in the brain of its IHs, behavioural alterations (i.e. increased activity and loss of neophobia) observed in infected wild rats were initially attributed to encephalitis (Webster, 1994b; Skalova et al., 2006). However, other directly transmitted brain parasites (i.e. parasites that do not rely on the predation of the host) of wild rats do not appear to induce changes in behaviour (Webster, 1994b).

Rats are strongly neophobic and display a strong innate aversive reaction to cat odour, even after several hundred generations with

no exposure to the predator (Berdoy et al., 2000; Webster, 2001; Vyas et al., 2007b). Such anti-predator behaviour is an obvious obstacle against *T. gondii* transmission and could be a prime target for parasite manipulation. *T. gondii* infected rats not only lose their innate aversive reaction to cat odour, but appear to be specifically attracted to the odour, even though other behavioural traits, such as social status and mating success, are unaltered (Webster, 1994b; Berdoy et al., 1995, 2000; Vyas et al., 2007a,b; Lamberton et al., 2008).

While these studies provide convincing evidence that *T. gondii* is capable of manipulating the behaviour of its IHs, two fundamental questions remain unanswered. First, actual predation rates by the appropriate DH on infected and uninfected rats in the wild are currently unknown and require further investigation (Berdoy et al., 2000; Webster, 2001). Testing the real link between host manipulation and increased transmission (i.e. increased predation) in the wild is a cornerstone of the manipulation hypothesis (Poulin, 1995). Secondly, the mechanisms by which *T. gondii* affects the CNS of its host and achieves such behavioural manipulation have yet to be elucidated (Webster, 2001, 2007). The harmful effects of latent toxoplasmosis on human health and behaviour include meningoencephalitis, personality changes, decreased intelligence quotient, reduced psychomotor performance and neuropsychiatric disorders, such as schizophrenia (Webster et al., 2006; Flegr, 2007).

Secretion of chemicals by *T. gondii* and/or manipulation of neurotransmitter secretion are likely to be required to induce alterations in behaviour, since the physical presence of cysts in the brain is unlikely to be sufficient to cause such complex and specific changes in IH innate behaviours (Carruthers and Suzuki, 2007; Vyas et al., 2007b). Hosts infected with *T. gondii* exhibit changes in expression of dopaminergic and anxiogenic brain receptors, in levels of neurotransmitters, such as dopamine, and in concentrations of noradrenaline (norepinephrine) and testosterone (Skalova et al., 2006; Flegr, 2007; Webster, 2007; Flegr et al., 2008).

Although the effects of toxoplasmosis on the brain have been investigated in detail, the pathways by which *T. gondii* manipulates host behaviour remain unclear. For example, preferential invasion sites of different strains of *T. gondii* in the brain could also affect the severity of the disease (Klein, 2003; Carruthers and Suzuki, 2007; Gonzalez et al., 2007; Vyas et al., 2007a). In addition, the outcome of infection is strongly influenced by both parasite and host properties; in humans and laboratory rodents, different genetic strains of *T. gondii* may vary in virulence (Carruthers and Suzuki, 2007; Webster, 2007). A combination of neurochemical and behavioural studies, controlling for both host and parasite genetic strains, are still essential to our understanding of the physiological mechanisms underlying *T. gondii*-induced alterations in animal behaviour (Skalova et al., 2006).

Conclusions

Since van Dobben (1952) reported that fish harbouring larvae of the cestode *Ligula intestinalis* were significantly more likely to be captured by cormorants (their DHs) than uninfected counterparts, it has been suspected that parasites could manipulate their hosts. Since then, examples of parasite-induced modifications of host behaviour have been documented in a wide range of parasite-host associations, including species of medical and veterinary importance. Some diseases, such as rabies and echinococcosis, are of concern due to their recent re-emergence, wide spatial distribution and human health implications.

Parasite-induced alterations are often considered to be adaptive parasitic manipulations that increase the transmission rates of the pathogens. However, the mechanisms, particularly neurological pathways, underlying these behavioural changes are only now

coming to light (Thomas et al., 2003). How a pathogen alters its host's phenotype remains a central topic in parasite-induced behavioural manipulation. Understanding such mechanisms is vital for solving fundamental evolutionary questions. Moreover, understanding parasite transmission strategies is also at the heart of applied aspects of parasitology, such as the treatment of associated disease.

The use of proteomics to study the proteins produced by manipulative parasites and the associated host behavioural alterations offers new opportunities for the study of manipulation by parasites (Biron et al., 2005; Thomas et al., 2005). Future studies would therefore benefit from a focus on the molecular cross-talk, particularly the neurochemical pathways, between hosts and their manipulative parasites.

Conflict of interest statement

None of the authors of this paper has a financial or personal relationship with other people or organisations that could inappropriately influence or bias the content of the paper.

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