Review

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

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17   **Abstract**

18   One of the most complex and least understood transmission strategies displayed by

19   pathogenic parasites is that of manipulation of host behaviour. A wide variety of pathogens

20   alter their host's behaviour, including species of medical and veterinary importance, such as

21   *Diplostomum spathaceum*, *Echinococcus* spp. and *Toxoplasma gondii*. The manipulative

22   ability of these parasites has implications for pathology and transmission dynamics. Domestic

23   animals are hosts for manipulative pathogens, either by being the target host and acquiring the

24   parasite as a result of vector-host manipulation, or by having their behaviour changed by

25   manipulative parasites. This review uses several well-known pathogens to demonstrate how

26   host manipulation by parasites is potentially important in epidemiology.

27

28   *Keywords*: Parasite manipulation; Host behaviour; Transmission; *Diplostomum spathaceum*;

29   *Echinococcus* spp.; *Toxoplasma gondii*

30

31 **Introduction**

32   Parasites face considerable odds against the successful completion of their life cycle, since

33 most hosts represent isolated and patchy resources that are capable of self-defence. This is

34 especially true for parasite species that rely on a vector host coming in contact with or being

35 eaten by a specific target host in which the parasite must continue its development (Choisy et

36 al., 2003; Parker et al., 2003; Poulin, 2007). The parasite and its host must be at the right

37 place at the right time to be transmitted to the next appropriate host. As a result, in some

38 situations, natural selection has favoured parasites capable of manipulating their host's

39 behaviour.

40

41   Parasites may use chemical secretions or other means to alter a variety of host behaviours

42 in a way that benefits the parasites by increasing their chances of transmission to the next host

43 (Moore, 2002; Thomas et al., 2005; Poulin, 2007). Some of these examples involve changes

44 in host phenotype, including the acquisition of new behaviours, and they provide strong

45 evidence for the concept of the extended phenotype, i.e. genes in one organism having

46 phenotypic expression in another organism (Dawkins, 1982).

47

48   Here, we provide an overview of ways in which parasites can alter some aspects of their

49 host's behaviour to increase their own transmission success. In particular, we highlight some

50 parasites of veterinary significance that are known to alter host behaviour, demonstrating that

51 host manipulation is tightly linked to the parasite's epidemiology.

52

53 **Classical examples of parasitic 'manipulation'**

54   The scientific literature contains many reports of modified behaviours in parasitised

55 animals. Three spined sticklebacks harbouring the larval cestode *Schistocephalus solidus*

56 swim closer to the water surface and become less aware of the presence of predatory birds

57 that serve as the parasite's definitive hosts (DHs) (Barber et al., 2004). Rodents infested by

58 the nematode *Trichinella spiralis* or the protozoan *Sarcocystis cernae* are less wary of

59 predators, thus facilitating the parasites' transmission to DHs (Rau, 1983; Hoogenboom and

60 Dijkstra, 1987).

61

62   In some cases, completely new behaviours are observed in infested hosts. For instance, an

63 orb-weaving spider infested by a parasitic wasp larva builds an unusual web designed to

64 protect the emerging larva after the host spider's death (Eberhard, 2000). Another parasitic

65 wasp induces its caterpillar host to remain near the parasite after the latter emerges from its

66 body, thus protecting the pupating wasps from potential predators by acting as a 'bodyguard'

67 (Grosman et al., 2008).

68

69   Ants infested by a nematode that must be transmitted to fruit-eating birds not only look

70 like fruit, by developing a swollen, red abdomen, but also 'behave' like fruits, perching

71 among berries of similar colour, with the abdomen held in an elevated position, motionless,

72 waiting for predation by birds (Yanoviak et al., 2008).

73

74   Nematomorphs (hairworms) and mermithid nematode larvae are parasitic and develop

75 inside terrestrial arthropods, but must reach the aquatic environment in which the adult worms

76 live after maturation. They induce their arthropod hosts to commit 'suicide' by forcing them

77 to seek and jump into water (Thomas et al., 2002, 2003; Penney and Bennett, 2006). Again,

78 such manipulation involves the sudden appearance of new host behaviours induced by the

79 parasite for its own needs (Thomas et al., 2003; Biron et al., 2005).

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4

81   Clearly, many parasite species are capable of manipulating their hosts' behaviour in

82   natural systems. However, domestic animals can also be affected by manipulative parasites,

83   either as target hosts or manipulated vector hosts. Rabies is one of the best examples of a

84   pathogen that manipulates the behaviour of the host. The virus infects the central nervous

85   system (CNS) of mammals, particularly regions of the brain controlling aggressive and social

86   behaviours, and the salivary glands. Infected hosts may display aggression, which facilitates

87   transmission of infection through biting (Klein, 2003). Although the fatal outcome of rabies

88   forces the pathogen into a permanent search for new hosts, rabies-induced behavioural

89   changes has ensured the transmission, survival and spread of this pathogen across time, space

90   and host species with extraordinary efficacy.

91

92   **Parasites of veterinary importance**

93   *Dicrocoelium dendriticum*

94   The trematode *Dicrocoelium dendriticum* is present worldwide and is distributed

95   throughout Europe, Asia, North Africa and America (Otranto and Traversa, 2002). Although

96   the pathogenicity of *D. dendriticum* is usually low, dicrocoelosis can lead to weight loss and

97   reduced milk production in domestic ruminants and can sometimes be fatal (Otranto and

98   Traversa, 2002). Reports of the disease are increasing, mostly due to the development of

99   anthelminthic resistance and the geographical expansion of *D. dendriticum* (Otranto and

100   Traversa, 2002; Goater and Colwell, 2007).

101

102   *D. dendriticum* is transmitted to ruminants, including domestic cattle and sheep, when

103   they accidentally ingest infested ants along with their plant food. The parasite larva induces

104   its insect host to climb to the tip of grass blades and remain there, anchored by its mandibles,

105   awaiting ingestion by a grazing herbivore (Carney, 1969; Roming et al., 1980).

107 *Diplostomum spathaceum*

108   The common digenean eye fluke *Diplostomum spathaceum* has a complex three host life

109 cycle including lymnaeid snails, fish and fish-eating birds, such as grebes and cormorants

110 (Crowden and Broom, 1980; Karvonen et al., 2004a). Free-swimming cercariae, produced

111 through asexual multiplication within the snail and released into the water, must find a fish,

112 which they penetrate through the gills or skin. They migrate through tissues to the lens of the

113 eye, where they develop into long-lived metacercariae. The cycle is completed when the fish

114 host, along with its metacercariae, is eaten by the DH, a bird.

115

116   By lodging themselves in the host's eyes, metacercariae induce cataracts due to

117 mechanical destruction of the lens and metabolic products excreted by the parasites, thus

118 reducing the host's vision (Karvonen et al., 2004b; Seppälä et al., 2004). *D. spathaceum*

119 infestation in fish is also associated with changes in host behaviour, such as increased activity,

120 migration towards the surface of the water and lack of responsiveness to visual stimuli,

121 although swimming ability is unaffected (Crowden and Broom, 1980; Brassard et al., 1982;

122 Seppälä et al., 2004). Thus, by injuring important sensory organs, *D. spathaceum* is able to

123 alter fundamental fish anti-predator mechanisms, such as crypsis and shoaling behaviour, in a

124 way that is likely to increase the vulnerability of the intermediate host (IH) to predation by the

125 DHs (Krause and Ruxton, 2002; Seppälä et al., 2005, 2006, 2008).

126

127   *D. spathaceum* is a globally distributed parasite that infests a large number of fish species,

128 with high prevalence and intensities recorded in some hosts (Crowden and Broom, 1980;

129 Moody and Gaten, 1982; McKeown and Irwin, 1997; Valtonen and Gibson, 1997; Karvonen

130 et al., 2004b). While pathological effects of diplostomiasis have seldom been documented in

6

131   wild fish, partly because heavily infested individuals are removed from the population

132   through predation (Pennycuick, 1971), *D. spathaceum* epizootics can be very serious in

133   captive fish, particularly farmed salmonids, such as rainbow trout (*Oncorhynchus mykiss*;

134   Betterton, 1974).

135

136   Since *D. spathaceum* cercariae are not actively host seeking and are often patchily

137   distributed, behavioural avoidance of these sources of infestation is the prime defence

138   mechanism displayed by fish hosts (Karvonen et al., 2004c). Captive housing of fish for

139   research, display and large-scale aquaculture is likely, because of spatial confinement and

140   artificially high densities, to constrain fish avoidance behaviours (Barber, 2007). As a result

141   of high and continuous exposure to parasite larvae, *D. spathaceum* frequently is found in large

142   numbers in farmed fish and may cause welfare problems. Anecdotally, rainbow trout heavily

143   infested by *D. spathaceum* are not responsive to anglers' lures, which reduces their suitability

144   for recreational fishing (Moody and Gaten, 1982).

145

146   *Echinococcus* spp.

147   Hydatid disease (echinococcosis) is due to infestation with cysts (metacestodes) of the

148   cestode parasite *Echinococcus* spp. (Lymbery and Thompson, 1996). These parasites have a

149   life cycle with two hosts, both mammals. The DHs are carnivores, in which the adult cestodes

150   inhabit the small intestine. Eggs released in the faeces and are accidentally ingested by an IH,

151   in which they hatch and develop into hydatid cysts in the lungs, liver and other internal

152   organs. The DH becomes infested when preying on an infested IH.

153

154   Several *Echinococcus* spp. are currently recognised, although numerous intraspecific

155   genetic strains exist (Jenkins et al., 2005). *Echinococcus* spp. have a narrow range of DHs,

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156 mainly domestic and wild canids, but a wide geographical distribution, being virtually present

157 on every continent (Eckert and Thompson, 1997). Their metacestodes are generally less host-

158 specific than those of other taeniids and can develop in a wide range of herbivores and

159 omnivores, including humans and, of particular veterinary concern, sheep, cattle and horses

160 (Lymbery and Thompson, 1996; Eckert and Thompson, 1997).

161

162 *E. granulosus* and *E. multilocularis* are the most important species in term of public health

163 implications and geographical distribution (Eckert et al., 2000; Jenkins et al., 2005; Schweiger

164 et al., 2007; Gottstein and Hemphill, 2008). *E. granulosus* infests almost exclusively domestic

165 animals, with dogs as DHs and predominantly sheep as IHs, but is also infectious for humans

166 (Eckert and Thompson, 1997). *E. granulosus* and *E. multilocularis* are responsible for cystic

167 and alveolar echinococcosis, respectively, both resulting, through asexual reproduction, in

168 increasingly large and abundant cysts that eventually become debilitating, if not lethal

169 (Jenkins et al., 2005; Thompson, 2008). Infested IHs may thus become more vulnerable to

170 predators, including the DH of the parasite (Ewald, 1995).

171

172 The hypothesis that echinococcosis could increase host vulnerability to predation came

173 from an anecdotal incident reported by Crisler (1956), in which a caribou cow (*Rangifer*

174 *tarandus*) failed to escape from wolves. Postmortem examination revealed that its lungs were

175 infested with several large cysts of *E. granulosus*. In moose (*Alces alces*), a large proportion

176 of hydatid cysts are found in the lungs and severe infestations reduce the endurance of

177 animals trying to escape from grey wolves (*Canis lupus*), one of the DHs of *E. granulosus*

178 (Messier et al., 1989). Wolves and other carnivores selectively prey on weaker animals and

179 moose with cystic hydatid disease may be more vulnerable to predation (Messier et al., 1989;

180 Joly and Messier, 2004). However, no study to date has empirically shown the direct link

181   between hydatid infestation, increased predation risk and increased transmission rates for the

182   parasite.

183

184   Internal organs, including the lungs, are often among the first to be eaten by large

185   carnivores, such as wolves (Joly and Messier, 2004). Therefore, it is possible that selection

186   has favoured the location of parasite cysts at these sites to ensure rapid consumption by the

187   DHs rather than to enhance transmission probability. Nevertheless, the pathological effects of

188   echinococcosis do modify the escape behaviour of its IHs in a way that could increase

189   predation and parasite transmission.

190

191   *Toxoplasma gondii*

192   Alterations in host behaviour following parasitic infection are sometimes exactly what we

193   would expect to see if the host was to start acting in ways that benefit parasite transmission

194   (Poulin, 2007). This is shown by the modifications in host behaviour induced by *Toxoplasma*

195   *gondii* and how they may influence the parasite's transmission to the DH.

196

197   *T. gondii* is a widespread intracellular protozoan capable of infecting all endothermic

198   vertebrates. The parasite has a complex life cycle in which Felidae, mostly cats, are the DHs.

199   Oocysts released in host faeces are persistent in the environment and can remain infectious for

200   more than a year (Webster, 1994a). During that time, they must be ingested by another host,

201   either directly by a cat, in which the parasite invades intestinal cells, matures and sexually

202   produces new oocysts, or by an IH.

203

204   Although a wide range of endotherms (rodents, birds or humans) can be infected, wild

205   rodents are the natural IHs of *T. gondii* (Berdoy et al., 2000). In the acute phase of infection,

206   the parasite penetrates the intestine, undergoes asexual reproduction and enters macrophages

207   and is transported to preferred encystment sites. The parasite then forms resistant cysts in

208   various organs of its IHs, most commonly the brain (Berdoy et al., 1995); these cysts can

209   persist for the life of an infected host (Webster, 2001). The parasite completes its life cycle

210   when a cat consumes an infected host.

211

212   Although *T. gondii* does not need its DH to survive and can be maintained over time in IH

213   populations by congenital transmission, cannibalism or interspecific predation, its infectivity

214   increases after each episode of sexual reproduction (Webster, 1994a, 2001). Since sexual

215   reproduction of *T. gondii* can be accomplished only in the DH, the parasite is ultimately

216   dependent upon predation of infected prey by cats. As a result, there might be strong selective

217   pressures for transmission to the DH and, therefore, on the parasite to evolve mechanisms to

218   enhance the transmission rate from IHs to cats (Berdoy et al., 2000; Webster, 2001; Webster

219   et al., 2006).

220

221   Latent toxoplasmosis has long been considered to produce inapparent infections in

222   immunocompetent hosts (Webster et al., 1994, 2006; Kankova et al., 2007). However, recent

223   studies have shown that chronic *T. gondii* infection can induce modifications in the behaviour

224   of infected hosts. In rodents, *T. gondii* causes increased levels of activity, along with

225   decreases in neophobic (i.e. fear of novelty) and anxiety behaviours, all of which could

226   potentially enhance transmission to DHs (Webster, 1994b; Webster et al., 1994, Gonzalez et

227   al., 2007). Since *T. gondii* mostly invades and encysts in the brain of its IHs, behavioural

228   alterations (i.e. increased activity and lost of neophobia) observed in infected wild rats were

229   initially attributed to encephalitis (Webster, 1994b; Skallova et al., 2006). However, other

230   directly transmitted brain parasites (i.e. parasites that do not rely on the predation of the host)

231   of wild rats do not appear to induce changes in behaviour (Webster, 1994b).

232

233   Rats are strongly neophobic and display a strong innate aversive reaction to cat odour,

234   even after several hundred generations with no exposition to the predator (Berdoy et al., 2000;

235   Webster, 2001; Vyas et al., 2007b). Such anti-predator behaviour is an obvious obstacle

236   against *T. gondii* transmission and could be a prime target for parasite manipulation. *T. gondii*

237   infected rats not only lose their innate aversive reaction to cat odour, but appear to be

238   specifically attracted to the odour, even though other behavioural traits, such as social status

239   and mating success, are unaltered (Webster, 1994b; Berdoy et al., 1995, 2000; Vyas et al.,

240   2007a, b; Lamberton et al., 2008).

241

242   While these studies provide convincing evidence that *T. gondii* is capable of manipulating

243   the behaviour of its IHs, two fundamental questions remain unanswered. First, actual

244   predation rates by the appropriate DH on infected and uninfected rats in the wild are currently

245   unknown and require further investigation (Berdoy et al., 2000; Webster, 2001). Testing the

246   real link between host manipulation and increased transmission (i.e. increased predation) in

247   the wild is a cornerstone of the manipulation hypothesis (Poulin, 1995). Secondly, the

248   mechanisms by which *T. gondii* affects the CNS of its host and achieves such behavioural

249   manipulation have yet to be elucidated (Webster, 2001, 2007). The harmful effects of latent

250   toxoplasmosis on human health and behaviour include meningoencephalitis, personality

251   changes, decreased intelligence quotient, reduced psychomotor performance and

252   neuropsychiatric disorders, such as schizophrenia (Webster et al., 2006; Flegr, 2007).

253

254   Secretion of chemicals by *T. gondii* and/or manipulation of neurotransmitter secretion are

255   likely to be required to induce alterations in behaviour, since the physical presence of cysts in

256   the brain is unlikely to be sufficient to cause such complex and specific changes in IH innate

257   behaviours (Carruthers and Suzuki, 2007; Vyas et al., 2007b). Hosts infected with *T. gondii*

258   exhibit changes in expression of dopaminergic and anxiogenic brain receptors, in levels of

259   neurotransmitters, such as dopamine, and in concentrations of noradrenaline (norepinephrine)

260   and testosterone (Skallova et al., 2006; Flegr, 2007; Webster, 2007; Flegr et al., 2008).

261

262   Although the effects of toxoplasmosis on the brain have been investigated in detail, the

263   pathways by which *T. gondii* manipulates host behaviour remain unclear. For example,

264   preferential invasion sites of different strains of *T. gondii* in the brain could also affect the

265   severity of the disease (Klein, 2003; Carruthers and Suzuki, 2007; Gonzalez et al., 2007; Vyas

266   et al., 2007a). In addition, the outcome of infection is strongly influenced by both parasite and

267   host properties; in humans and laboratory rodents, different genetic strains of *T. gondii* may

268   vary in virulence (Carruthers and Suzuki, 2007; Webster, 2007). A combination of

269   neurochemical and behavioural studies, controlling for both host and parasite genetic strains,

270   are still essential to our understanding of the physiological mechanisms underlying *T. gondii*-

271   induced alterations in animal behaviour (Skallova et al., 2006).

272

273   **Conclusions**

274   Since van Dobben (1952) reported that fish harbouring larvae of the cestode *Ligula*

275   *intestinalis* were significantly more likely to be captured by cormorants (their DHs) than

276   uninfected counterparts, it has been suspected that parasites could manipulate their hosts.

277   Since then, examples of parasite-induced modifications of host behaviour have been

278   documented in a wide range of parasite-host associations, including species of medical and

279   veterinary importance. Some diseases, such as rabies and echinococcosis, are of concern due

280   to their recent re-emergence, wide spatial distribution and human health implications.

281

282   Parasite-induced alterations are often considered to be adaptive parasitic manipulations

283   that increase the transmission rates of the pathogens. However, the mechanisms, particularly

284   neurological pathways, underlying these behavioural changes are only now coming to light

285   (Thomas et al., 2003). How a pathogen alters its host's phenotype remains a central topic in

286   parasite-induced behavioural manipulation. Understanding such mechanisms is vital for

287   solving fundamental evolutionary questions. Moreover, understanding parasite transmission

288   strategies is also at the heart of applied aspects of parasitology, such as the treatment of

289   associated disease.

290

291   The use of proteomics to study the proteins produced by manipulative parasites and the

292   associated host behavioural alterations offers new opportunities for the study of manipulation

293   by parasites (Biron et al., 2005, Thomas et al., 2005). Future studies would therefore benefit

294   from a focus on the molecular cross-talk, particularly the neurochemical pathways, between

295   hosts and their manipulative parasites.

296

297   **Conflict of interest statement**

298   None of the authors of this paper has a financial or personal relationship with other

299   people or organisations that could inappropriately influence or bias the content of the paper.

300

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