CellPress

Making the best of a bad situation: host partial resistance and bypass of behavioral manipulation by parasites?

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With few exceptions, parasitic manipulation dramatically reduces host fitness. That said, evidence of host resistance to behavior-manipulating parasites is scarce. Here, we suggest that the evolution of partial resistance, as well as bypass, to manipulation (PRM and BPM, respectively) represents new, seldom-explored options for parasitized hosts. Natural selection could favor hosts that partially resist certain manipulative dimensions to postpone their death and perform additional reproductive episodes (PRM). Alternatively, manipulated hosts may express novel traits that do not alter the manipulation *per se* but that alleviate its detrimental fitness consequences (BPM). If effective, PRM and BPM have many implications for the ecology and evolution of hosts and their parasites, especially the evolution of multidimensional manipulations.

Behavioral manipulation by trophically transmitted parasite

The suggestion that a parasite can manipulate host phenotypes permeates science fiction and horror literature, but it is now a well-established concept in the study of animal behavior [1–4]. Although historically of interest to mainly parasitologists and evolutionary biologists, parasite manipulation of host behavior is gaining attention given the potential impacts of this transmission strategy on several areas of conservation, economic, or medical sciences [5]. Briefly, trophically transmitted parasites, from several phylogenically distinct taxa, have been shown to manipulate the phenotype (morphology, behavior, physiology, etc.) of their intermediate host to increase the probability of transmission to their final host [1,3]. Thomas *et al.* [6] recognized that manipulated hosts may have several phenotypic traits altered when parasitized (a phenomenon known as multidimensional manipulation), which can significantly increase the transmission and/or survival of the parasite ([6–9], but see [10]). For instance, trophically transmitted parasites can enhance the probability of transmission to their definitive hosts by simultaneously altering both the color and behavior of their intermediate host [2,11]. Although multidimensionality in host manipulation has received attention only recently [6,10,12], it seems to be the rule rather than the exception [13]. Here, we propose the following hypothesis: that under certain conditions, hosts will be favored to express subtle defensive behaviors that alleviate the cost of manipulation. In many systems, infected hosts engage behavioral defenses against parasites. For instance, self-medication, kin-selected suicide, and changes in thermal preferences are only a few of many behavioral strategies that can benefit the parasitized host at the expense of the parasite [2]. However, the influence of the host is rarely considered in the context of behavioral manipulation ([14,15], but see [16,17]). Given that the end result of behavioral manipulation by trophically transmitted parasites, whether single or multidimensional, is host death (because intermediate hosts are eaten by final hosts), it is advantageous for hosts to evolve strategies to avoid or resist infection in the first place.

Not all observed altered host phenotypes are necessarily extensions of the parasite genotype [18]. Indeed, hosts are not passive and there is likely a host dimension within the observed phenotypic changes associated with manipulation. Specifically, we suggest here that hosts infected by manipulative parasites, when they cannot fully resist manipulation, have themselves evolved ways of mitigating fitness impacts through PRM and/or BPM. Here, we aim to: (i) examine specific host resistance mechanisms that may evolve in response to behavioral manipulation; (ii) provide

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Keywords: manipulation; parasites; phenotype; resistance.

1471-4922/
 http://dx.doi.org/10.1016/j.pt.2015.05.007

conditions under which hosts can evolve PRM and BPM; and (iii) discuss the consequences of behavioral manipulation and the evolution of PRM and BPM for host–parasite coevolution.

What are PRM and BPM?

Hosts can use a range of strategies to defend themselves against parasites and pathogens: namely, avoidance, resistance, and tolerance [2,19–21]. Briefly, avoidance behavior reduces contact with pathogens, whereas resistance minimizes the success of a parasite by preventing its establishment or inhibiting its growth (i.e., parasite burden). By contrast, a tolerant host, although susceptible, acts to minimize the fitness effects of infection, without directly affecting parasite fitness [22]. A trade-off between tolerance and resistance can exist [23–25].

We introduce here the new concepts of PRM and BPM to describe the reduction of the deleterious fitness effects of parasites that manipulate host behavior. Depending on the nature and architecture of multidimensional manipulations (i.e., number of dimensions involved, their level of interdependence, and their respective contribution to parasite transmission), we propose that natural selection should favor hosts that express partial resistance to certain dimensions (i.e., PRM), and/or that add host dimensions in the manipulated phenotype to alleviate the fitness consequences of the parasite-induced dimensions (i.e., BPM). When complete resistance is too costly for the host, PRM may be the optimal level based upon costs and benefits; it can theoretically concern one or few dimensions in a multidimensional manipulation or the only dimension in a simple manipulation. BPM may take on the same appearance as tolerance (since it neither changes nor opposes resistance to manipulation); however, there is a cost for the parasite (while that is not the case for tolerance) to circumvent novel host responses that reduce transmission probabilities. By relying on PRM and/or BPM, parasitized hosts could substantially postpone their death and/or castration. Selective pressures on the host could be high for exerting PRM and BPM when either allows parasitized hosts to perform reproductive episodes. In fact, when the benefit:cost ratio of PRM and/or BPM exceeds that of displaying no form of opposition, these options should be advantageous for manipulated hosts. From the parasite perspective, when preventing host PRM comes with increased energetic cost to the parasite, it is less advantageous for the parasite to keep complete its manipulative effort to counteract PRM. Similarly, depending on the costs of preventing manipulated hosts from displaying protective behaviors, selection could also be low on the parasite to prevent the evolution of BPM. Thus, although currently unexplored, PRM and BPM theoretically represent two options for host species to reduce the deleterious fitness effects of behavior-manipulating parasites.

Potential examples of PRM and BPM

PRM may manifest through physiological mechanisms that increase variability or decrease intensity of the parasitic manipulation, which in turn lead to an increase in the reproductive opportunities of the host. Recently, Franceschi *et al.* [26] reported that amphipod (*Gammarus pulex* L. 1758) hosts from four naturally infected populations were significantly less sensitive to parasite-induced behavioral changes following experimental infection by the acanthocephalan *Pomphorhynchus laevis* (Müller 1776) compared with hosts from a naïve population, where the parasite does not naturally occur. In this amphipod, the acanthocephalan induces numerous behavioral alterations, such as reversal in phototaxis behavior, change in drift behavior, and reversal in antipredator behavior. Hosts from the different naturally infected populations all had a similar level of behavioral sensitivity to parasites. Nevertheless, the hosts from the naive population were more manipulated. The difference in manipulation intensity between naïve hosts and those with coevolving parasites suggests that PRM can evolve, but the reproductive gains of such mechanisms have not yet been quantified.

BPM may occur in two ways. First, it could be expressed in the form of novel host behaviors that reduce the efficiency of the parasitic manipulation (i.e., instantaneous transmission probability) and ultimately increase host reproductive opportunities before transmission and host death. These behaviors could be state dependent, solely expressed in infected hosts and similar to fecundity compensation following infection by castrating parasites [27,28], once the parasitic manipulation has been initiated. As long as the cost of resistance is less than the benefit, such a trait can be selected, state dependent or not. For trophically transmitted parasites that bring their intermediate hosts into novel habitats, such behaviors could include shifts in microhabitat preference, whereby hosts select sites in the novel environments where they are less conspicuous to predators. Thus, despite the manipulation exerted by the parasite to increase host vulnerability to predators, hosts capable of such adjustments would benefit from a reduction in predation pressure and presumably increased reproductive opportunities. There are several biological systems in which such a hypothesis could be tested; for example, the association between the amphipod *Gammarus insensibilis* (Stock 1966) and its manipulative trematode *Microphallus papillorobustus* (Rankin 1940). When a *M. papillorobustus* larva (metacercaria) encysts in the brain of *G. insensibilis*, it causes dramatic changes in the responses of the amphipod to environmental stimuli; contrary to uninfected amphipods that are benthic, manipulated amphipods inhabit the water–air interface and cling to floating vegetation, which facilitates parasite transmission to its avian final host [29,30]. Thus, infected gammarids typically live at the surface of the water, while uninfected individuals inhabit the bottom [31]. However, parasitized amphipods within their natural habitat can exploit two types of seagrass (*Zostera*), one that is maroon and the other green. Parasitized hosts could select to cling to the seagrass on which they are the least conspicuous to predators, thereby reducing or delaying parasite transmission. Another type of BPM could involve the formation of aggregates of infected individuals. Within the same amphipod–trematode association described above, by forming aggregates, infected amphipods would benefit from a dilution effect that reduces the risk of predation [32,33] while increasing mating opportunities. Here, the formation of