



Integrating Concepts of Physiological and Behavioral Resistance to Parasites

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Conceptual parallels between physiological and behavioral forms of resistance to parasites have led to the development of terminology like “the behavioral immune system” to refer to behaviors that combat parasites. I extend this metaphor by applying findings from research on physiological resistance to generate predictions for the ecology and evolution of behavioral resistance (here, synonymous with avoidance). In certain cases, behavioral resistance may follow similar evolutionary dynamics to physiological resistance. However, more research on the nature of the costs of behavioral resistance is needed, including how parasite transmission mode may be a key determinant of these costs. In addition, “acquiring” behavioral resistance may require specific mechanisms separate from classical forms of conditioning, due to constraints on timing of host learning processes and parasite incubation periods. Given existing literature, behavioral resistance to infectious disease seems more likely to be innate than acquired within the lifetime of an individual, raising new questions about how individual experience could shape anti-parasite behaviors. This review provides a framework for using existing literature on physiological resistance to generate predictions for behavioral resistance, and highlights several important directions for future research based on this comparison.

Keywords: associative learning, behavioral immune system, evolution, host–parasite interactions, parasite avoidance

INTRODUCTION

Behavior establishes the first interface at which animal hosts and parasites interact (Moore, 2002). Given the parallels between physiological and behavioral forms of resistance to parasites, the concept of the “behavioral immune system” has emerged: the cognitive and behavioral mechanisms for avoiding infectious agents and their cues (Schaller and Duncan, 2007; Schaller and Park, 2011). In other words, through behavioral means, hosts can prevent establishment of parasites analogously to physiological resistance strategies. Does this analogy predict that behavioral resistance should follow the evolutionary and ecological patterns of innate and/or acquired forms of physiological resistance? Although behavioral resistance can also encompass strategies for controlling parasite growth, recovery from infection, and tolerance of infection (Moore, 2002; Hart, 2011; Hawley et al., 2011; Adelman and Hawley, 2017; Townsend et al., 2020), in this review, I explore the parallels

between behavioral avoidance of infection and physiological resistance, highlighting potential limitations of acquiring behavioral resistance through individual experience.

DISTINGUISHING PHYSIOLOGICAL AND BEHAVIORAL FORMS OF PARASITE RESISTANCE

First, I establish definitions of physiological and behavioral resistance within the broader framework of host resistance to parasites. I use the term “parasite” for all infectious agents, including micro-organisms usually referred to as “pathogens.” Infection of a host by a parasite occurs through a multi-step process that can be broken down into two general steps: (1) contact between host and parasite (host exposure) and (2) establishment of parasite infection in or on the host (host susceptibility) (Combes, 2001; Hall et al., 2017). Exactly how contact is defined will depend upon the transmission mode of the parasite: for a vector-transmitted parasite, it could be the vector biting the host; for a sexually transmitted parasite, it could be deposition of the parasite into the reproductive tract during mating. The host has resistance to the parasite if it can interfere with at least one of these two broad steps along the parasite’s path from the previous host. Correspondingly, this two-step process generates two broad categories of resistance: (1) pre-contact resistance, sometimes called “avoidance,” which prevents or reduces likelihood of the initial host-parasite contact, and (2) post-contact resistance, which, given contact between host and parasite, interferes with the establishment of parasite infection.

Behavioral and physiological resistance roughly map onto, but do not exactly match, pre- and post-contact resistance. Indeed, behaviors are one form of pre-contact resistance, commonly conceptualized as an avoidance response of animals to a cue of parasite risk (Curtis, 2014). However, pre-contact resistance is not achieved only through behavioral responses: e.g., for pollinator-transmitted parasites of plants, earlier flowering can function as pre-contact resistance (Biere and Antonovics, 1996). Similarly, post-contact resistance does not have to be physiological: e.g., many ectotherms will raise their body temperatures by seeking warm environments to fight parasite infections with a “behavioral fever” (Kluger, 1979). Other behavioral forms of post-contact resistance include grooming (Mooring et al., 2004; Akinyi et al., 2013) and self-medication (Clayton and Wolfe, 1993). Although I do not discuss them thoroughly here, these forms of post-contact behavioral resistance might be expected to have many similarities to post-contact physiological resistance. For the sake of simplicity and drawing connections to the previous literature, I will limit the scope of “behavioral resistance” in this review to pre-contact behavioral resistance, and “physiological resistance” to post-contact physiological resistance.

To compare these two forms of resistance, I also distinguish between innate and acquired physiological resistance, a distinction mostly relevant to vertebrates. Innate resistance refers to the mechanisms that detect and defend against parasites that are present throughout the lifetime of an

individual (Beutler, 2004). Acquired resistance refers to the ability to gain resistance in subsequent exposures to a parasite following recovery from an initial exposure, sometimes termed “immunological memory” (Bonilla and Oettgen, 2010). Here, I investigate whether delineating innate and acquired resistance is a useful paradigm to apply to behavior.

EVOLUTION OF INNATE BEHAVIORAL RESISTANCE

Corresponding to innate forms of physiological resistance, behaviors for parasite resistance may be innate and shaped heavily by evolutionary forces. Evidence suggests that parasite avoidance behavior is under the control of genes and therefore likely to evolve. In a knockout experiment in laboratory mice (*Mus musculus*), the oxytocin gene was identified as a central component of the olfactory mechanism female mice used to avoid parasitized males (Kavaliers et al., 2005a). Domestic sheep (*Ovis aries*, Perendale lines) artificially selected for physiological resistance to parasites also avoided parasites in their grazing behavior (Hutchings et al., 2007). In addition, parasite avoidance behavior has been experimentally evolved in *Caenorhabditis elegans* in response to a bacterial parasite, *Serratia marcescens* (Penley and Morran, 2018).

Despite evidence of genetic variation in parasite avoidance behaviors, little is known about the forces that drive their evolution (i.e., allele frequency change). A rich literature has considered theoretical aspects of ecological feedbacks on the evolution of physiological resistance (e.g., Antonovics and Thrall, 1994; Boots and Haraguchi, 1999; Boots et al., 2009). Capturing dynamics of the evolution of physiological resistance involves considering the nature and magnitude of the costs of resistance, and how evolutionary processes are affected by the numbers of hosts and pathogens, in addition to changes in allele frequencies (Antonovics and Thrall, 1994; Boots and Haraguchi, 1999). Identically to models of physiological resistance, theory predicts that if behavioral resistance to a directly transmitted parasite is assumed to carry a fixed cost, resistance is more likely to evolve when costs are low, and resistant and susceptible genotypes can exist in a stable polymorphism under certain conditions (Amoroso and Antonovics, 2020).

However, because behavioral resistance commonly acts before contact between the host and the parasite, the costs of resistance may depend on the transmission mode of the parasite, which defines a contact between the host and the parasite. For example, if social interactions are assumed to be beneficial but also carry a risk of parasite transmission, resistant hosts pay a cost of losing these social interactions, and behavioral resistance (avoidance of conspecifics) is much less likely to evolve (Amoroso and Antonovics, 2020). These conclusions depend on the assumption that the parasite is contact-transmitted, because the costs and benefits of resistance are a function of the host’s social behavior. In a social host, resistance could even function as groups avoiding other groups, with costs allocated or shared among group members. Under different transmission modes, the costs

could take different forms: e.g., hypothetically, locomotion costs of avoiding habitats with high risk of environmentally transmitted parasites, or reproductive costs of missed mating opportunities when avoiding sexually transmitted parasites. To better understand how behavioral resistance to parasites could evolve, future work will need to conceptualize and measure the associated costs, which may be unique to different parasite transmission modes.

The genetics of coevolution between hosts and parasites have been intensively studied in terms of physiological resistance, generating predictions for coevolutionary dynamics of behavioral resistance. For example, the gene-for-gene model of resistance was originally developed to explain cases in which a plant host's resistance to infection and a parasite's ability to cause disease were each determined by a single genetic locus (Flor, 1956; Frank, 1993). Similar to gene-for-gene dynamics, the host could detect and behaviorally avoid a specific elicitor produced by the parasite, and parasites could evade detection by losing that elicitor. A gene-for-gene model could possibly govern coevolution between *C. elegans*, in which the gene controlling lawn-leaving (avoidance) behavior has been identified (Peng et al., 2018), and its bacterial parasite *Bacillus thuringiensis*, in which the gene has been identified that governs production of a toxin that *C. elegans* detects (Nakad et al., 2016). However, the coevolutionary dynamics of these traits have not yet been examined. In addition, theoretical assessments of coevolutionary processes in mate choice have suggested that avoidance behaviors can influence virulence evolution in sexually transmitted parasites (Ashby and Boots, 2015; Ashby, 2020), and similar predictions could follow for the coevolutionary dynamics of other host avoidance behaviors and parasite transmission modes.

Although hosts could respond to specific cues produced by the parasite, they might instead respond to general cues: a behavioral equivalent to the concept of broad spectrum resistance in plants (e.g., Ke et al., 2017), or cross-immunity of a host to multiple strains of a parasite (Haraguchi and Sasaki, 1997). Parasites are likely to be impossible for hosts to detect directly (Hart, 2011), and therefore selection may be based on detectable yet indirect cues: for example, avoiding feces (Sarabian and MacIntosh, 2015; Amoroso et al., 2017), detecting general signs of disease in conspecifics (Curtis et al., 2004; Paciência et al., 2019), or swatting away insect vectors (Hart and Hart, 1994). If evolved resistance behaviors are general, they could confer resistance to multiple parasites transmitted through the same route, similar to the broader protections offered by the innate immune system. In this way, coevolutionary dynamics between a host and one of its parasites could have ramifications for other parasites transmitted via the same route, possibly resulting in diffuse coevolution (Iwao and Rausher, 1997).

ACQUIRED BEHAVIORAL RESISTANCE

In addition to innate forms of resistance, behaviors for resisting parasites might be acquired in the course of an

individual's lifetime, analogous to immunological memory. Evidence supports that animals can learn to avoid predators (reviewed in Griffin et al., 2000), raising the possibility that prior experience of infection with a parasite could induce a novel aversion to the conditions of exposure to that parasite. Classical conditioning research suggests that animals can reliably associate two things when they are separated by a very short time delay, on the order of seconds (Perin, 1943; Renner, 1964). Meanwhile, for most parasites, the incubation period—the time lag between a host being exposed to a parasite and the onset of clinical signs of infection—is on the order of days (Lessler et al., 2009; Azman et al., 2013; Lee et al., 2013; Rudolph et al., 2014). On the short end of this spectrum are parasites with incubation periods of 12 h (e.g., influenza B) (Lessler et al., 2009), and as short as 4 h for some foodborne illnesses (Eley, 1992). Thus, the onset of experienced signs of infection typically occurs too late relative to exposure for a host to associate the two events via classical forms of conditioning, making it exceedingly difficult for hosts to learn to avoid parasite exposure.

However, at least two exceptions exist to the expectation that parasite avoidance is unlikely to be acquired. First, association between exposure to parasites and infection signs would be possible when the host can perceive the parasite's attacks simultaneously with exposure, similar to conditions for learning predator avoidance, such as large, conspicuous ectoparasites like biting flies, whose bites are painful. A series of experiments have shown that both laboratory mice and deer mice (*Peromyscus maniculatus*), upon naïve exposure to biting flies, will avoid the flies by burrowing into the bedding of their cages (Kavaliers et al., 2001, 2003, 2005b). On subsequent exposures, the mice will burrow even if the flies' biting mouthparts have been removed: evidence of a learned avoidance response (Kavaliers et al., 2001). Mice can also learn through observation to avoid the flies with mouthparts removed, without any prior experience of being bitten (Kavaliers et al., 2001, 2003, 2005b). If such avoidance can be learned, it could also have downstream effects on the vector-borne parasites that these conspicuous ectoparasites transmit. It is important to note that in addition to being detectable, a parasite must also induce experienced negative effects (e.g., pain, other clinical signs) in temporal proximity to the infestation (e.g., fly bite). For example, although rock pigeons (*Columba livia*) could detect lice in their feathers, prior experience did not improve rate or efficacy of preening (Villa et al., 2016). The authors suggest that the relatively low virulence and lack of immediate negative fitness effects of lice could explain the absence of a "priming" effect (Villa et al., 2016).

A second exception is a phenomenon called "conditioned taste aversion," the association of taste and odor with gastrointestinal distress such as nausea or vomiting, which can take place over a delay of hours, longer than observed in traditional operant conditioning. In an experiment, an hour or more after ingesting flavored water, mice were injected with a toxin that induced gastric disturbances. On subsequent trials, the mice reliably avoided the flavored water, even after just

TABLE 1 | Several key contrasts between physiological and behavioral resistance.

Physiological resistance	Behavioral resistance
Primarily interferes with infection processes <i>after</i> contact between the host and the parasite	Primarily interferes with transmission processes <i>before</i> contact between the host and the parasite
Resistance cost often modeled as fixed	Costs may be fixed, social, or some other form that depends on parasite transmission mode
Detection of parasite likely to be on a specific basis	Detection of parasite may commonly be based on general indicators
Can be acquired in the lifetime of an individual	Less likely to be acquired within an individual's lifetime, though learning may shape aspects of behavioral resistance
Individual-level trait	Could function at the group level; groups may avoid other groups

The "Behavioral resistance" column offers future directions for research on this topic.

one experience (Garcia et al., 1966). This phenomenon has since been confirmed in a wide variety of animals, over delays commonly ranging from 1 to 7 h, and up to 24 h (Lin et al., 2017)—long enough to encompass some shorter incubation periods of parasites. Conditioned taste aversion has been extended to associations between specific flavors or odors and digestive discomfort induced specifically by parasite infection. For example, *Drosophila melanogaster* avoided smells present when they ingested a virulent bacterial parasite (Babin et al., 2014), and *Rattus norvegicus domestica* became averse to ingesting flavors following injection with third-stage nematode larvae (Keymer et al., 1983). Taste-conditioned avoidance of parasites has also been demonstrated in *C. elegans* with lawn-leaving assays (Zhang et al., 2005), and has been suggested to be heritable for multiple generations (Moore et al., 2019). Whether learned avoidance behaviors can be transmitted across generations in other host–parasite systems analogously to maternal transmission of antibodies (Grindstaff et al., 2003) deserves further research.

In humans, the improbability of individual learning as an effective strategy for parasite avoidance is underscored by the misattributions of the cause of infectious diseases prior to wide acceptance of germ theory. For example, the widespread belief in the miasma theory of disease—that diseases are acquired through inhaling “bad air”—as recently as the late 19th Century (Halliday, 2001) suggests that for most of our evolutionary history, humans could not reliably associate the particulars of our exposures to infectious agents with symptoms that ensued after a delay. However, human social learning and communication have since proven effective at coordinating widespread avoidance behaviors, including strategies such as hygiene and social distancing (Curtis, 2014; Townsend et al., 2020).

The literature reviewed here suggests that most host behavioral resistance strategies are likely to be innate, rather than acquired through past experience. Furthermore, given the constraints of classical learning processes and typical incubation periods of parasites, not only could acquiring behavioral avoidance of parasites be ineffective, but reliance on learning may lead to incorrect associations between harmless stimuli and experienced signs of infection. Some specialized learning processes, such as imprinting, have even been suggested to cause maladaptive attraction to conspecifics displaying signs of infection with directly transmitted parasites

(Stephenson and Reynolds, 2016). Although aversion to parasites is only likely to be acquired in specific circumstances, prior experience could still influence the contexts in which individuals perform behavioral resistance strategies, e.g., if animals associate an innately aversive cue of parasite risk with a specific individual or habitat. Thus, even if behavioral resistance is unlikely to be acquired analogously to immunological memory, future research should consider what role individual experience could play in shaping behavioral resistance.

DISCUSSION

The examples discussed here illustrate that extending the analogy of the “behavioral immune system” can be a useful framework to generate predictions about behavioral resistance to parasites, but should be applied cautiously and with attention to the biology of the processes involved (Table 1). A rich literature on physiological resistance to parasites has investigated the population genetics and numerical dynamics that lead to the evolution of different forms of resistance (Boots and Bowers, 2004; Boots et al., 2009). Given that little is known about the specific processes that generate changes in frequency of alleles for behavioral resistance to parasites, expectations from theoretical and empirical research on physiological resistance are a useful starting point from which to advance. This review suggests that evolutionary dynamics of behavioral resistance may be predicted reasonably well by physiological resistance theory under certain assumptions. But more empirical research on the evolutionary dynamics of behavioral resistance is needed, especially on the costs, and the possibility that they may vary with parasite transmission mode. On the other hand, only in particular circumstances it is likely that behavioral resistance to a parasite would be acquired newly in the lifetime of an individual, a major departure from processes of acquired physiological resistance. If behavioral resistance is primarily an innate, evolved response to parasites, understanding the evolutionary—and coevolutionary—processes that have generated behavioral resistance, and whether general principles govern these processes should be central aims in future studies of host behavioral responses to parasites.

I have considered behavioral and physiological resistance separately here, but behavioral resistance precedes physiological resistance in the course of a host's interaction with a single parasite; thus, these two forms of resistance are not independent. Physiological and behavioral resistance are expected to interact with one another. For example, they made trade off, with individuals balancing investment in immune and behavioral defenses (Zylberberg et al., 2013; Zylberberg, 2014). Together, behavioral and physiological resistance constitute a step-wise infection process, in which multiple sequential steps are required (Hall et al., 2017). Not only is a two-step process likely to lead to unique infection genetics, but genes for functionally independent resistance traits can become linked when they are jointly affected by coevolutionary processes (Fenton et al., 2009, 2012). Behavioral and physiological resistance evolution might be expected to interact in many ways, an exciting open direction for future investigation.

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Conflict of Interest: The author declares that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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