Review Article

HOST BEHAVIORAL MANIPULATIONS BY PATHOGEN INFECTION

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Abstract

Scientists have discovered that pathogens have the ability to change the behavior of the hosts through various mechanisms. Behavior changes by host-pathogen interactions can help the pathogen spread and reproduce more effectively. Pathogens can affect their host's behavior, physiology, and gene expression, leading to increased aggression, suicidal tendencies, or deformities. *Toxoplasma gondii* can make infected hosts more prone to risk-taking behavior and aggression, leading to a lack of aversion to cat odor and an increased risk of car accidents. Rabies can also influence the biting habits of infected animals, making it more likely that the virus will be transmitted through saliva. Some parasites, such as the Gordian worm, *Cordyceps fungi*, *Mermis* nematode, and *Dicrocoelium dendriticum*, can even manipulate their hosts into committing suicide. Other parasites, such as *Riveiroia* spp. and *Leucochloridium* spp., can cause physical deformities in their hosts, making them more vulnerable to predators. Despite the previous research, there remains significant uncertainty surrounding host-pathogen interactions. Reviewing host behavior manipulations by pathogens is a critical and fascinating medical and psychological science area.

Keywords: Host-pathogen interactions, Behavior manipulation, Physical deformity, Suicidal tendencies

Introduction

The host-pathogen interactions are an evolutionary struggle that has persisted through millions of years (Thomas et al., 2005). Pathogens, from bacteria and viruses to parasites and fungi, have successfully developed impressive survival strategies to infect and transmit to their host organisms. Significantly, parasites often alter their hosts' behavior to benefit the parasite or its offspring (Libersat et al., 2009). The manipulation involves a complex interplay between pathogen-derived molecules and host cellular machinery, resulting in host behavior, physiology, and gene expression alterations. Some infectious agents may affect the central nervous system (CNS) of the host, which leads to altered host behaviors such as phototaxis, locomotion, behavioral fevers, foraging behavior, reproduction, and various social interactions, to name only a few (Libersat et al., 2009; Moore, 2002; Thomas et al., 2002; Zimmer, 2001). Some pathogens manipulate the immune or endocrine system or the metabolism of the host (Hueffer et al., 2017; Libersat et al., 2009). The changes enhance host-to-host transmission, ensure the parasite or its propagules are released in an appropriate location, or increase parasite survival (Biron et al., 2005). Our main three focuses are: first, host manipulation leading to becoming aggressive, which includes *Toxoplasma gondii*, and second, host manipulation leading to suicide, which provides for *Gordian worm*, *Cordyceps fungi, Mermis nematode,* and *Dicrocoelium dendriticum*. This review explores the fascinating strategies of host manipulation by pathogens (Table 1). It highlights fundamental mechanisms employed by diverse pathogens and provides a comprehensive overview of pathogens' skills to manipulate host biology to their advantage.

MAIN TEXT

HOST MANIPULATION LEADING TO BECOME AGGRESSIVE

Toxoplasma gondii is a protozoan parasite that can invade the vital organs of its host. In the chronic stage of infection, *Toxoplasma* encysts in the brain and remains for the host's life. These tissue cysts can be distributed in brain regions such as the olfactory bulb, hippocampus, and amygdala (Berenreiterova et al., 2011). The abnormal behavior changes observed in infected hosts may be related to the anatomic localization of tissue cysts (Berenreiterova et al., 2011). *T. gondii* has been observed to subvert rodents' inborn behavior of avoiding cat urine odor into attraction to the odor (Vyas et al., 2007; Abdulai-Saiku et al., 2021). This alteration in behavior is accompanied by lower neophobia, better capability, risk-tolerance, impulsive decision-making, and conspicuous sexual advertisements. In male rats, increased testosterone levels caused by the infection affect methylation levels, leading to overexpression of AVP and a loss of fear (Tong et al., 2019). In contrast, female rats experience increased oxytocin levels, leading to improved maternal care and a higher probability of offspring survival. However, this comes at the cost of resources or time for subsequent pregnancies (Abdulai-Saiku et al., 2021). In both male and female rat populations, the behavioral change increases the probability of being predated since they no longer fear the predator's odor. Humans are also prone to behavioral manipulation by *Toxoplasma*. Studies have suggested that the parasite's manipulative or pathogenic activities in the brain can lead to prolonged reaction time, impaired motor performance, and changes in personality profiles (Flegr et al., 2002; Havlíček et al., 2001; Gohardehi et al., 2018). These changes may increase the risk of traffic accidents, with 5 out of 9 studies reporting a significant relationship between *Toxoplasma* infection and traffic accidents.

Rabies is a deadly disease that causes significant changes in behavior and neurological disorders, often leading to human fatalities (Hueffer et al., 2017). Despite its severity, our understanding of the viral mechanism is limited, and it continues to claim over 500,000 lives each year (Hueffer et al., 2017). Biting is the most effective means of transmitting the disease, and the virus can manipulate the brain areas that regulate aggression to increase its transmission (Rupprecht et al., 2002). The virus resides in the brain and induces behavior modifications like aggression, paralysis, and difficulty breathing (Rupprecht et al., 2002; Hueffer et al., 2017).

Recent studies have suggested that the rabies virus can affect the way infected cell function, specifically in altering neuronal function (Ladogana et al., 1994; Iwata et al., 1999) or inhibiting nicotinic acetylcholine receptors present in the central nervous system (Hueffer et al., 2017). The virus targets specific brain areas, such as the brainstem, thalamus, basal ganglia, and spinal cord. As a result, it is unlikely that the virus is directly manipulating aggression through infected neurons (Hemachudha et al., 2002). Therefore, further analysis of the evidence is required to understand the relationship between the virus and its host.

Hemachudha et al. (2002) suggest that immune responses generated by the host cause increased aggression in some rabies victims. They postulate that infection of the brainstem triggers the production of cytokines by the host's immune system, which then alters the functioning of limbic system structures responsible for controlling aggression (Hemachudha et al., 2002). Moreover, the increased aggression observed in some rabies victims is likely due to a host-generated immunopathology. This is supported by the fact that similar changes in behavior occur in other neurological disorders (both infectious and non-infectious) and are not exclusive to rabies (Hemachudha et al., 2002). This rare behavioral change in neurological patients is likely caused by immune-generated destruction of the CNS (e.g., inflammation, Bechter, 2001). In rabies, an individual host's physiological responses to the virus may be crucial in determining whether the virus can manipulate the host.

HOST MANIPULATION LEADING TO SUICIDE

Grasshoppers and crickets infected by Gordian worms exhibit abnormal suicidal behavior for the aquatic larva to return to the water from the terrestrial host (Libersat et al., 2009; Biron et al., 2005). The hosts display behavior not usually found within their repertoire and seek water, jumping in to favor the parasite (Libersat et al., 2009; Thomas et al., 2002). Once the parasite reaches maturity, infected crickets seek out water and willingly commit suicide by drowning. Researchers hypothesize that the larvae produce chemicals directly affecting the host's brain, which may also hold for other parasitic species. Evidence suggests that the worm releases chemicals that disrupt the geotactic sense of its terrestrial host, prompting it to jump into the water and allowing the mature parasite (Biron et al., 2005). When infected by the Mermis nematode, land insects are induced to jump into water, aiding in the spread of the nematode. This is similar to the suicidal behavior of Gordian worms (Maeyama et al., 1994).
Cordyceps fungi create chemicals that impact the navigation ability of their ant hosts (Hughes et al., 2011). The process starts when the fungus spores attach to the ant's cuticle and travel through the tracheae into the body (Moore et al., 2006). The fungal mycelia feed on the ant's organs, excluding important ones, and produce specific, unknown chemicals that prompt the ant to climb

to the top of a tree or plant and bite down on a leaf or leaf stalk. Eventually, the fungus consumes the ant's brain when it's ready to sporulate, causing the ant's death (Moore et al., 2006). The fungus's fruiting bodies protrude from the cuticle and release spore capsules that detonate, spreading spores throughout the area and infecting other ants to begin a new cycle (Moore et al., 2006).

The lancet liver fluke, known as *Dicrocoelium dendriticum*, manipulates an ant's navigational abilities, compelling it to climb to the top of a blade of grass (Libersat et al., 2009). As the final host, cows consume these ants and the grass they are on. Ants, the second intermediate host, then ingest these slime balls and lancet flukes, enabling the parasites to enter their gut and wander through their body in the hemocoel. The ants climb to the tip of the grass, where the cow consumes them during the night. If the ants aren't eaten, they return to the ground as if nothing had occurred and repeat the behavior the next night (Moore et al., 1995).

HOST DEFORMITIES BY PARASITE INFECTION

Ribeiroia spp. causes abnormal formation or growth of limbs in frogs, leading to hindered host movement. Two theories attempt to explain how invading *Ribeiroia* spp. cercariae causes improper limb development. The first theory suggests that the parasites mechanically disrupt the arrangement of growing limb cells, which leads to abnormal limb formation or even duplication (Johnson et al., 1999). The second theory suggests that *Ribeiroia* actively produces a compound that interferes with a retinoid-sensitive signaling pathway, stimulating or inhibiting continued limb growth (Maden, 1996).

The snails infected with pulsating brood sacs displayed different behaviors than their uninfected counterparts (Wesolowska et al., 2013). They moved further, positioned themselves in more exposed and well-lit areas, and climbed higher up the vegetation. These changes in behavior could benefit the parasites by making them more visible and accessible to their eventual hosts. As a result, they discovered that *L. paradoxum* sporocysts modified the physical appearance of their intermediate *S. putris* hosts and altered their behavior (Wesolowska et al., 2013).

Table 1. Various manipulations of Host behavior by pathogen infection

Pathogens	Host Behavior Manipulation	References
Toxoplasma gondii	Mice infected with toxoplasmosis lose their natural aversion to cat urine, making them vulnerable to predators.	Vyas et al., 2006
Gordian worm	The host - mantis - exhibits suicidal behavior which is searching for water and diving into it.	Thomas et al., 2002
Cordyceps fungi	The host ant loses navigational sense and stays still after climbing a tree or branch. When the fungus inside the ant becomes mature, it eats up the ant's brain, killing it.	Moore et al., 2007
Mermis nematode	Infected ants show suicidal behavior by looking for water and diving into it	Biron et al., 2005
Dicrocoelium dendriticum	The *Dendriticum* overtakes the ant's navigational senses, making it climb up the tip of the grass only during the nighttime.	Moore et al., 2007
Riveiroia spp.	It causes abnormal formation or growth of limbs in frogs, leading to hindered host movement.	Johnson et al., 2003

Leucochloridium spp.	Infected snails exhibit pulsating broodsacs which makes them more visible to their predators.	Wesolowska et al., 2013

Conclusion

In this review paper, we explore the various pathogen strategies used to manipulate the behavior of their hosts. These tactics can range from simple alterations in behavior to even causing the host to take their own life. However, this is only a glimpse into the intricate interactions between hosts and pathogens, which can harm or benefit one or both parties. As humans, we are a part of this community, and it is essential that we understand our role within it. This understanding will help us better predict what will happen when we encounter new species that interact with us. In the case of new contagious diseases such as COVID-19 and Monkeypox, we must observe physical behaviors and conduct research on psychological manipulation.

Acknowledgment

I would like to thank Daniel Jung for his guidance and encouragement during the process of this review paper.

Statement of Competing Interests

The authors have no competing interests.

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