Schizophrenia Bulletin vol. 33 no. 3 pp. 752–756, 2007
doi:10.1093/schbul/sbl073
Advance Access publication on January 11, 2007

The Effect of *Toxoplasma gondii* on Animal Behavior: Playing Cat and Mouse

Joanne P. Webster[1,2]

[2]Department of Infectious Disease Epidemiology, Imperial College Faculty of Medicine, St Mary's Hospital Campus, Norfolk Place, London, UK

A convincing body of evidence now exists to indicate that the ubiquitous protozoan *Toxoplasma gondii* can cause permanent behavioral changes in its host, even as a consequence of adult-acquired latent infection. Such behavioral alterations appear to be the product of strong selective pressures for the parasite to enhance transmission from its intermediate host reservoir, primarily rodent, to its feline definitive host, wherein sexual reproduction can occur and the life cycle completed. This article reviews evidence of behavioral alterations in animal hosts and considers what these may elucidate about the potential mechanisms involved and what implications such alterations could have on animal and human health.

Key words: rodents/parasite/behavior/schizophrenia

Introduction

The intracellular apicomplexan protozoan *Toxoplasma gondii* is found worldwide and in an exceptionally broad host range, making it one of the most "successful" protozoan parasites on earth.[1] Prevalence levels vary widely, depending on exposure, but may surpass 50% in dogs, rabbits, and sea otters; 60% in mice, rats, and wild birds; and 70% in cats, bears, deer, and humans.[2–5] Serological studies have also identified infection rates of 50% or higher in domestic chickens, geese, cattle, goats, pigs, and sheep, with the animals themselves usually being asymptomatic. A study of meat samples in stores in the United Kingdom reported that up to 38% were infected with *T. gondii*,[6] and studies in the United States have demonstrated that such tissue cysts can be viable, although prevalence may be very low.[7]

The transmission of *T. gondii* is also facilitated by its ability to modify its host's behavior. As specified by the "manipulation hypothesis," certain parasites can alter host behavior for their own selective benefit. Classic examples concern transmission through the food chain, where a parasite is immature in an intermediate host, that must be eaten by a predatory definitive host before the parasite can reach maturity and complete its life cycle. The parasite thus manipulates the behavior of its intermediate host so as to enhance its transmission to the definitive host. *Toxoplasma gondii* provides a convincing example of such a manipulatory parasite. Members of the cat family (*Felidae*) are the only definitive hosts, within which the parasites undergo full gametogenesis and mating within the intestinal epithelium, culminating in the generation of oocysts that are shed in the cat's feces.[8] These oocysts are highly infectious and extremely stable in the environment.

If oocysts are ingested by an intermediate host, such as a wild rodent, or another secondary host, such as a human or domestic animal, the parasite undergoes asexual reproduction, characterized by rapidly dividing tachyzoites and the more slowly dividing bradyzoites, that can encyst in the brain, heart, and other tissues, where they remain, potentially for the host's lifetime.[9,10] Transmission back to the feline definitive host occurs when a naive cat ingests bradyzoite-infected tissue through predation or consumption of contaminated meat. Because sexual reproduction of *T. gondii* can be accomplished only in felines, there are strong selective pressures on the parasite to evolve mechanisms to enhance transmission from the intermediate host to the definitive feline host and thereby complete its life cycle. The predilection of *T. gondii* for the brain of its intermediate host places it in a privileged position to cause such manipulation.[11] A convincing body of evidence now exists to indicate that *T. gondii* can achieve such manipulation.

Evidence From Rodent Models

Initial studies observed that laboratory mice inoculated with *T. gondii* showed significantly diminished learning capacity and memory in double-training maze experiments compared with their uninfected counterparts.[12,13] While any disruption to normal behavior in such prey species may be predicted to influence predation rate, a more specific method for *T. gondii* would be to increase intermediate host activity, because cats are immediately

[1]To whom correspondence should be addressed; tel: +44 (0)2075943636, fax: +44 (0)2074023927, e-mail: joanne.webster@imperial.ac.uk.

attracted to moving and exposed objects and show little interest, or cannot see, stationary ones. A series of studies thus investigated the potential effect of postnatal and congenital toxoplasmosis on laboratory mouse activity and exploratory behavior by recording each individual's entry into marked squares on a cage floor, Y-shaped maze and/or on running wheels.[14–17] Infected mice were found to be more active than their uninfected counterparts. Likewise, infected mice showed a preference for more exposed or novel areas of apparatus and spent significantly less time grooming, a typical "displacement activity," before investigating such novel areas than did their uninfected counterparts. Such selective effects appeared to exclude explanations of behavioral abnormalities in terms of lowered motivation or general debility, because these could not be expected to produce consistently increased levels of one behavioral category consistent with decreases in other categories. A more likely explanation was that *T. gondii*–infected mice interact with their environment and novel stimulation arising from it in a different way than uninfected mice.

Initial studies with laboratory rats found that, while learning capacity was also reduced in some individuals, this was much milder and rarer than that observed for laboratory mice.[12,13] Potential explanations for these differences were related to the higher infection rate of *T. gondii* in the brains of mice than rats during latent toxoplasmosis and the formers' increased potential for severe morbidity during the acute phase of infection. Indeed, while the general health and behavior of laboratory rats usually appear unaffected by infection, laboratory mice often show signs of acute infection and have been observed to run in circles and have their heads bent to one side.[12,13,18] It has thus been proposed that experiments with more resistant animals, such as rats, provide a better model in which to study the potential manipulatory activity of *T. gondii*, particularly in terms of their generalizability to other species such as humans.[18]

In accordance with this, Webster and colleagues performed a series of studies on the potential impact of *T. gondii* on rat behavior. In contrast to the artificiality of most laboratory-based experiments, particular attention was paid to testing each hypothesis using wild or wild hybrid rats maintained under naturalist habitats and/or social conditions. In an initial study, the activity levels of both wild-trapped rats with a range of directly and indirectly transmitted naturally occurring parasite loads and purpose-bred wild/laboratory hybrid rats with experimentally induced parasite loads were investigated.[19] Replication using each of these combinations controlled for a number of potential biases such as, eg, generalized encephalitis due to artificial parasite inoculation, differences in past parasitic histories, and/or inherent behavioral differences between laboratory and wild rats. Moreover, inclusion of additional comparative observations of rats infected with a range of other directly transmitted parasites (such as *Leptospira spp.*) provided reliable controls to test for any generalized response to parasitism per se. Because the other directly transmitted parasites do not require a definitive host in order to complete their life cycle, they would not be predicted to increase host activity levels, because any increase in predation rate would result in death of both host and parasite.[20]

Toxoplasma gondii–infected rats were found to be significantly more active than their uninfected counterparts. In contrast, the activity levels of wild and hybrid rats, either naturally or artificially infected with the variety of other direct life cycle parasites, were not altered.[19] The effect of *T. gondii* on the neophobic (fear of novelty) response in rats was also examined.[21,22] Wild rats are among the most innately neophobic mammals known and react to novel stimuli with extreme caution and often with total avoidance[23]; it is this neophobia that makes wild rats so notoriously difficult to control through trapping and poisoning.[20] The reactions of wild and hybrid rats to a range of novel, in particular food-related, stimuli, together with their propensity to be caught in live traps, was observed. *Toxoplasma gondii*–infected rats were found to be significantly less neophobic toward each of the novel stimuli presented, relative to their uninfected counterparts, while there were again no differences in neophobic behavior between rats infected or uninfected with the directly transmitted parasites.[21,22]

Subsequent studies took the concept that *T. gondii* can alter innate behavior further by examining whether *T. gondii* affects a rat's perception of cat predation risk.[24,25] The response to cat odor was chosen as a measure because this is known to elicit strong innate aversion, even among laboratory rodents following several hundred generations of passage. While uninfected rats showed a strong aversion to areas with cat odor (but not to, eg, rabbit odors), a proportion of infected rats showed not simply a reduction in their cat-aversion areas but actually a preference for cat-treated areas. These results suggested a significant divergence in the perceived response to cat predation, where uninfected rats show a significant and innate avoidance of cat-scented areas while infected rats show a significant, potentially suicidal, preference for cat-treated areas.

The next experiment drew on the demonstration that many antipsychotic drugs commonly used in the treatment of schizophrenia inhibit the replication of *T. gondii* tachyzoites in cell culture.[25,26] Such observations provided support for the hypothesis that the antipsychotic and mood-stabilizing activity of some medications may be achieved, or at least augmented, through their inhibition of *T. gondii* replication and/or invasion in infected individuals. Moreover, they led to the prediction that such medications could also inhibit the behavioral effects of *T. gondii* in rats. To test this, 4 groups of rats were infected with *T. gondii* and then treated, respectively, with haloperidol, valproic acid (both of which were

shown to be highly effective inhibitors of *T. gondii* in cell culture), pyrimethamine with dapsone (a standard anti–*T. gondii* agent), and water. Without drug treatment, the infected rats demonstrated the same suicidal feline attraction and altered behavior described above. Following treatment, however, such behavior was significantly reduced, in order of decreasing efficacy, by haloperidol, pyrimethamine with dapsone, and valproic acid. Moreover, fluorescence staining of tissue sections throughout the brains at postmortem indicated that the frequencies of *T. gondii*–exposed animals showing immunohistochemically positive neurons and glial cells were reduced following drug treatment, especially with haloperidol. Furthermore, certain *T. gondii*–exposed rats treated with haloperidol failed to seroconvert from IgM to IgG, while all the other treated rats did so.[25]

Potential Mechanisms

The mechanism of action by which *T. gondii* alters rodent behavior is unknown. Histopathological, immunological, and/or neuromodulatory changes are all potential candidates. While gross pathology alone is unlikely to account for the observed changes in the majority of cases, because other behavioral characteristics are left intact,[18,21] multifocular lesions and/or histopathological changes in the cyst-containing regions of the brain have been observed. These include inflammatory granulomatous changes of perivascular areas, progressive deposition of necrotic material, and subsequent vesicular occlusion and sclerosis.[11] Indication of potential immunological involvement has also been suggested because, even in relatively resistant strains of mice, latent toxoplasmosis can be accompanied by permanently increased levels of mRNA of cytokines TNF-alpha and IL-10.[27] Moreover, it is plausible that the local immune response in the brain required to keep *T. gondii* dormant may alter cytokine levels that could then subsequently influence neuromodulator levels.[28]

Neuromodulation may represent an ideal mechanism whereby *T. gondii* can influence, at least in part, the expression of host behavior. Studies investigating the neurological basis of anxiety, which often use the reaction of potential prey to cat stimuli as a model, have found that blocking the normally anxiogenic *N*-methyl-D-aspartic acid receptors in the amygdala, and/or provision of serotonin (5-HT) antagonists, causes rats to approach cat odors "fearlessly,"[29,30] in much the same way that *T. gondii*–infected rats do.[24,25] Moreover, significant differences in levels of homovanillic acid, norepipephrine, and in particular, dopamine have been observed between *T. gondii*–infected and uninfected mice[31]; all are substances that mediate, among others, locomotor activity, mood, learning, memory, and cerebral blood flow. Furthermore, in the aforementioned experimental studies,[25] the antipsychotic drug haloperidol is a known dopamine D2 antagonist that may explain its superior therapeutic impact in normalizing the behavior of infected individuals through a combination of its ability to inhibit *T. gondii* replication and also to reduce, directly and indirectly, dopamine levels; in contrast, the actions of valproic acid and pyrimothamine with dapsone may be antiparasitic alone.

Future Directions

In terms of future directions for research, together with further mechanistic studies, it will be important to elucidate why any effects of *T. gondii* on behaviur differ between host species and individuals. Potential host factors may relate to inherent differences in individual genetic predisposition, the state of the immune system, the time of exposure (eg, period of pregnancy, prenatal or postnatal, juvenile or adult initial *T. gondii* exposure), the duration of infection (eg, humans live longer than the average rodent intermediate host), and, perhaps, the parts of the brain affected. Exciting new opportunities in this latter area may be through the use of novel bioluminescence-based imaging systems that allow noninvasive, real-time examination of the in vivo growth, dissemination, spatiotemporal distribution, and reactivation of *T. gondii* in living animals, together with monitoring of the efficacy of anti–*T. gondii* therapy.[32] However, for detection of parasites in any tissues or specific central nervous system areas of interest, such techniques still need to be used in association with histopathology, because such bioluminescence imaging systems are currently much less sensitive than plaque assays or PCR.

Potential parasite-related factors include the source of infection, especially whether it is oocyst or tissue cyst ingestion. At present, data are insufficient to draw meaningful conclusions about how these 2 routes impact disease outcome. The *T. gondii* exposure dose, and if a single or multiple exposure, is also likely to be important. Likewise, the potential interaction between *T. gondii* and coinfecting pathogen species may turn out to be important, particularly coinfection with other neurotropic agents such as cytomegalovirus.[28] Finally, it seems plausible that the genotypes of the *T. gondii* strains may play a role in the comparative impact of this parasite on host behavior between species and individuals. *Toxoplasma gondii* is composed of 3 major genotypes, Types I, II, and III (94% of all isolates), that have emerged as the dominant strains worldwide.[1] Type II strains are the most common in nature and have been isolated from a wide variety of intermediate hosts, although it is critical to point out that sampling has been largely biased toward parasites recovered from symptomatic humans and domestic animals; hence little is known about what strains are responsible for the majority of animal or human infections, particularly those with no apparent disease.[1] Preliminary evidence using the aforementioned bioluminescent image tracking suggests that different *T. gondii*

genotypes disseminate differently in the brain and show different profiles in reactivation and recrudescence.[33] Moreover, evidence from both humans and laboratory mice indicates that different strains of *T. gondii* may be responsible for different disease manifestations.[1]

Evidence of a role for atypical genotypes in cases with more severe host morbidity has been suggested by recent data on a new genotype observed in sea otters.[34] Miller and colleagues[35] genotyped *T. gondii* isolates from California sea otters with toxoplasmic encephalitis and observed that whereas 40% were infected with the common zoonotic Type II strain, 60% were infected with a genotype, now designated as Type X, that possessed novel alleles at 3 genetic loci different from the alleles found in Types I–III. A statistically significant spatial cluster of Type X–infected otters was also detected in the same location identified as a high-risk site for sea otter mortality in previous studies.[36,37] Otters with moderate to severe *T. gondii* encephalitis were observed to be 3.7 times more likely to be attacked by sharks than otters without encephalitis,[36] suggesting that they may exhibit aberrant behavior, similar to findings in infected rodents described previously.[19,22,24] It may therefore be suspected that *T. gondii*–associated neurological dysfunction or behavioral alterations, though of no adaptive advantage to the parasite, might cause otters to be less able to evade attacks, or even to attract shark's attention through their abnormal movements.[36] With increasingly sensitive means for determining strain type available, it is likely that correlations between strain type and disease outcome will become more numerous and more precise.

Conclusions

In summary, extensive studies carried out under different experimental conditions suggest that *T. gondii* changes the behavior of rodents so as to make them more likely to be predated on by cats, the parasite's definitive host. Additional studies have demonstrated that the behavioral change induced by *T. gondii* can be partially reversed by treatment with some antipsychotic and mood-stabilizer medications. While much further research is certainly required, particularly in terms of elucidating the potential mechanisms and/or genotypes involved within and between host species, the observations to date suggest possible new avenues for the treatment of *T. gondii* infections and, insofar as *T. gondii* is etiologically important in schizophrenia, new avenues for the treatment of schizophrenia.

Acknowledgments

I am very grateful to Robert Yolken and Fuller Torrey for inviting this review and to Fuller Torrey, Poppy Lamberton, James Rudge, Manuel Berdoy, and 2 anonymous referees for comments on the text.

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