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**RK Anish**
Senior Research Fellow, Centre For Advanced Studies in Animal Genetics and Breeding, College of Veterinary and Animal Sciences, Mannuthy, Thrissur, Kerala, India

**Corresponding Author:**
**RK Anish**
Senior Research Fellow, Centre For Advanced Studies in Animal Genetics and Breeding, College of Veterinary and Animal Sciences, Mannuthy, Thrissur, Kerala, India

# Protozoan manipulations in behaviour of hosts

## RK Anish

**Abstract**
Parasite manipulation can be either direct or indirect. Indirect manipulation is the most frequent method used by behavior-altering parasites, while the direct approach is far less common. Direct manipulation is when the parasite itself affects the host and induces a behavioral response, by creating neuroactive compounds that stimulate a response in the host's central nervous system, a method mostly practiced by parasites that reside within the CNS. Parasites can also indirectly affect the behavior of their hosts by disturbing their metabolism, development, or immunity. Parasitic castrators drastically modify their hosts' metabolism and reproduction, sometimes by secreting castrating hormones, changing their behavior and physiology to benefit the parasite. They may alter hosts' behaviors in ways that increase their likelihood of transmission, resulting in the parasite's release at appropriate sites, which increase parasite survival or increase the host's likelihood of being infected with more parasites.

**Keywords:** Parasite manipulations, behavior- altering parasites, host, central nervous system, neuroactive compounds, parasitic castrators

## Introduction
Some parasites directly or indirectly interact with host nervous systems, leading to a change in host behaviour (Moore, 2002) [10]. Such interactions occurred early in host/parasite evolution. In some cases, the change in host behaviour enhances parasitic transmission (Klein, 2004) [9].

## Modification Mechanisms
Parasites appear to use at least three broadly defined mechanisms (omitting destruction of sensory structures and/or muscles): (1) psycho-neuro- immunological mechanisms, (2) neuro mechanisms and (3) genomic- and proteomic-based mechanisms. (Hart, 2003) [8].

## Psycho Neuro Immunological Mechanisms
The immune system releases factors (e.g. cytokines) that alter neural function, resulting in co-ordinated changes in behaviour. These factors induce 'sickness behaviour', a suite of changes in motivational state (decreased propensity for reproduction) that is thought to help the animal recover from infection (Barnard and Behenke, 1990) [3].
Cytokines can induce these shifts in behaviour because neurons have receptors for them in specific brain areas. By changing the amount, type or relative ratio of cytokines that the immune system releases, a parasite could produce robust and reliable changes in host behaviour. Parasites that alter host behaviour by inducing the host to secrete immune-derived compounds would be expected to produce a form of sickness behaviour in their host, only more extreme or distorted in order to enhance parasitic transmission (Adamec *et al.*, 1999) [1].

## Neuro Mechanisms
Although parasites have impressive abilities for infesting specific organs and subsections of organs within a host, their ability to selectively attack specific brain regions is modest. Parasites do not limit their attack to only those brain areas controlling specific behaviours. For example, *Toxoplasma gondi* intracellular cysts are found in most areas of the brain, not just in those areas thought to be involved in the response to cat odour. If parasites infest wide regions of the brain, the odds are good that at least one parasite will hit neural areas crucial for the targeted host behaviours (Berdoy *et al.*, 1995) [6, 7].

## Behavioural Modification in Mice in Toxoplasma Infection (Evidence from Rodent Models)
Initial studies observed that laboratory mice inoculated with *Toxoplasma gondii* showed

significantly diminished learning capacity and memory in double-training maze experiments compared with their uninfected counterparts. Cats are 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. 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 in the unexposed areas of the apparatus. Several studies have investigated the innate fear of laboratory rodents toward cat odours. These studies have delineated a neuroanatomical circuit comprising the medial hypothalamic zone and associated forebrain structures. These forebrain inputs correspond to those emanating from the ventral hippocampus and septum on one hand (septo hippocampal pathway) and the medial and baso- lateral amygdala on the other (amygdalar pathway). Interestingly, the medial amygdala, basolateral amygdala, and ventral hippocampus, implicated above in mediating innate fear to predators, are also important for conditioned or learned fear and unconditioned anxiety. Furthermore, behaviours pertaining to both anxiety and learned fear appear related to those pertaining to innate defensive reactions against predators (such as the aversion to cat urine among rodents). However, the density of cysts in the medial and basolateral amygdale is almost double that in other structures like hippocampus, olfactory bulbs, and prefrontal cortex. This supports the case of a subtle tropism. Interestingly, the amygdala is widely interconnected with a variety of different brain regions. Hence, a subtle tropism to the amygdale does have the potential to influence innate fear via specific modulation of relevant pathways (Berdoy and Macdonald, 1995) [6, 7].

Toxoplasma infection also causes neuromodulatory changes (e.g.,in the noradrenergic and dopaminergic systems). Hence, alteration of neuromodulation also provides an important avenue for such behavioral manipulation. The enigma with this scenario is how specificity is achieved as a consequence of broad neurobiological alteration. It has been postulated that Toxoplasma has some degree of causal relation to schizophrenia. This postulate rests on the positive relationships between the prevalence of Toxoplasma antibodies and the development of schizophrenia (Berdoy and Macdonald, 1991) [5].

**Behavioural Modification in Rat in Toxoplasma Infection**

Male rats are more aggressive than females, because they have a high circulating testosterone, thus this aggressiveness increase the susceptibility to the parasite. Despite the advantage of high testosterone concentration on reproductive success, testosterone- dependent aggression (i. e. inter-make aggression) increases exposure to the parasite and may underlie the increased prevalence of infections among males as compared with females. Testosterone production by the host or by parasite can alter the behavior of host and finally facilitate growth of parasite (Klein, 2004) [9].

Several studies showed that the infection of parasite can alter the innate behavior and memory capacity in rats. Uninfected rats showed a strong aversion to the areas with cat odour, while infected rats show a significant, potentially suicidal preference to the cat areas (Webster, 2007) [13].

**Behavioural Modification in Final Host in Toxoplasma Infection**

The clinical picture of schizophrenia in Toxoplasma- infected animals differs from that of Toxoplasma-free animals. For example, the decrease in gray matter density in the brain occurs only in Toxoplasma- infected animals and the same is true for gender differences in the onset of schizophrenia – on average, a 3-year delay of the onset of the disease exists only in Toxoplasma- infected subjects (Berdoy, 1994) [4].

Toxoplasma-infected schizophrenic animals express more severe positive symptoms of the psychiatric disease (more frequent or intense hallucinations, delusions) than Toxoplasma-free subjects (Poulin, 2010) [11].

**Fatal Attraction Phenomenon**

Fatal attraction phenomenon, i.e. change their native, inborn fear of the odor of cats into an attraction to this odor. The infected mice and rats visit more often and stay longer in places containing the odor of cat urine. Conversely, they are not attracted by the odor of urine of other species (Vyas, 2007) [12].

The Fatal attraction phenomenon was observed only in females of Balb/c mice while a decrease in preference for novel food was observed only in male mice. Infected female mice expressed higher activity in open field test while infected males showed lower activity. A gene expression study revealed that Toxoplasma infection altered the expression of genes involved in the development of the forebrain, neurogenesis, and sensory and motor coordination in females, while in male mice, infection led mainly to modulation of genes associated with olfactory function (Berdoy *et al.*, 1995) [6, 7].

Large Toxoplasma strain specific differences were also observed in the concentration of various neurotransmitters in the brains of artificially infected animals, suggesting that Type I strains of Toxoplasma probably express the strongest manipulative activity. It is not clear yet, which of the Toxoplasma-associated behavioral changes are products of manipulative activity of the parasite aimed to increase the probability of the transmission in latent phase of infection, and which are the product of other manipulative activities of parasite, e.g. of the down- regulation of the host immune functions, and which are just transient side-effects of passed acute infection (Barnard and Behenke, 1990) [3].

**Behavioural Modification in Mosquito**

Plasmodium parasites can alter mosquito behaviour. These changes depend on the developmental stage of the parasite, with evidence for reduced foraging and feeding during the pre-infectious oocyst stage of infection and increased foraging and feeding during the infectious sporozoite stage. Risky feeding associated activities during the non infectious stage and increased probing and feeding at the infectious stage increases the overall likelihood of transmission. Decreased biting persistence of female mosquitoes on a human host when infected with oocysts and increased biting persistence when infected with sporozoites. Small proportion of mosquito population is actually responsible for transmission. A 20% reduction in feeding associated mortality during the pre-infectious stage could increase the relative force of malaria infection by 60% (Hart, 2003) [8].

Infected mosquitoes have less salivary apyrase (a platelet inhibitor). Consequently, these mosquitoes spend more time feeding, probe more often, are more persistent in biting and feed more often than uninfected mosquitoes. These changes in behaviour are likely to increase the risk of infected mosquitoes being detected and killed while feeding. Plasmodium infection elicits the transcriptional activation of at least six different immune markers in the human malaria vector *Anopheles gambiae*, particularly when parasites are invading the midgut and salivary glands. Mosquito ovary size is reduced and protein content gets depleted (Anderson, 1999) [2].

## Conclusion

To summarise, behaviour modification occurs by Psycho neuro immunological and neuro mechanisms. Apart from intermediate hosts, definitive hosts are also manipulated in behaviour as in the case of *Toxoplasma* infection (Decrease in gray matter density in the brain, Schizoprenia and suicidal tendency). Lab animals with high level of infection respond differently compared to that with low level of infection. To conclude, behavioural modification facilitate transmission of protozoa to complete its life cycle.

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