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REVIEW

Toxoplasma gondii: host–parasite interaction and behavior manipulation

Rodrigo Costa da Silva · Helio Langoni

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Abstract *Toxoplasma gondii* is an obligate intracellular parasite that causes different lesions in men and other warm-blooded animals. Humoral and cellular immune response of the host against the parasite keeps the protozoan in a latent stage, and clinical disease ensues when immunological response is compromised. Brain parasitism benefits the parasite causing behavioral changes in the host, not only in animals but also in humans. Schizophrenia and epilepsy are two neurological disorders that have recently been reported to affect humans coinfected with *T. gondii*. Further studies based on host–parasite interaction in several wild or domestic warm-blooded species are still necessary in order to better understand parasitism and behavioral changes caused by *T. gondii*.

Introduction

Toxoplasmosis is an anthropozoonosis of warm-blooded hosts caused by the obligate intracellular parasite *Toxoplasma gondii*. Economic impact because of the disease is considerable, once the parasite infects several livestock species, such as sheep and goats. Moreover, it has an important public health impact, because toxoplasmosis is transmitted from infected animals to men via contaminated food. Brain and muscles are the main tissues affected, and the most severe signs are observed in cases of brain parasitism. It is an opportunistic infection and a risk for newborns—causing fetal damage in humans—and for people showing any degree of immunodeficiency, such as carriers HIV or other immunocompromising conditions (Tenter et al. 2000; Suzuki 2002a; Henriquez et al. 2009). This infection has a considerable impact on human and animal lives because the quality of life of the hosts is deeply affected when the central nervous system (CNS) is involved, not to mention the paramount importance of the disease in economic, medical, and veterinary terms (Luft and Remington 1986).

R. C. da Silva (✉) · H. Langoni
Department of Veterinary Hygiene and Animal Science (DHVSP),
College of Veterinary Medicine and Animal Science (FMVZ),
São Paulo State University (UNESP),
Campus of Botucatu,
Botucatu, São Paulo, Brazil
e-mail: silva_rcd@yahoo.com.br

Immunity to toxoplasmosis

The host resistance to *T. gondii* infection is guaranteed for gamma-interferon (IFN-γ) cytokine action, preventing the colonization of many organs and the reactivation of tissue cysts present in the brain. This cytokine is produced by macrophages, dendritic cells, neutrophils, natural killer (NK) cells, lymphocytes T CD8+ and T CD4+, and induce the production of other cytokines, mainly interleukin (IL)-12. NK cells are stimulated by IL-12 to produce IFN-γ, while the alpha-tumoral necrotic factor (TNF-α), IL-1, and IL-15 potentialized the effects of IL-12 in NK cells, stimulating the macrophages with the liberation of high levels of nitric oxide (NO), with microbicidal and microbiostatic effects, beyond of potent antiproliferative effects at the lymphocytic cells, limiting the tachyzoites replication before the T cells arrived, and directing to the development of an adequate response for T helper 1 (Th1) effector cells. Macrophages, NK cells, dendritic cells, and neutrophils answer to the infection releasing IL-12, TNF-α, and IFN-γ. NO emerges as an important regulatory molecule involved on the minimization of the immunopathological alterations induced by the parasite (Suzuki 2002a).

The microglia cells are important effector cells involved in the protector mechanisms mediated for the inducible nitric oxide synthase (iNOS) enzyme. The activation of these cells, mediated by IFN-γ, in collaboration with authocrine TNF-α consists in one of the mechanisms of resistance of the brain against *T. gondii*. However, it is known that the TNF-α and iNOS expression is not enough to prevent the toxoplasmic encephalitis in the absence of IFN-γ (Lüder et al. 1999; Maubon et al. 2008).

The dendritic cells are the major productors of IL-12 among the mononuclear cells of the brain, producing IFN-γ for T cells in the brain. In the other side, almost 85% neutrophils present IL-12 intracellular stock. The fast infiltration of these at the local of the infection must develop an important function in the induction of protector Th1 immune response during the start of the infection (Suzuki 2002a).

The *T. gondii* acquired immunity is characterized for a strong CD4+ e CD8+ activity, because the parasite surface peptides present high immunogenicity. Thus, the acute stage of the infection is marked for elevated levels of IFN-γ and IL-12, as well as other pro-inflammatory cytokines as TNF-α, IL-6 and IL-1, and anti-inflammatory, IL-10 (Denkers and Gazzinelli 1998).

IFN-γ and TNF-α are important for the control of the tachyzoites replication during the acute and chronic stages, while IL-10 and IL-12 are highly important at the initial stage and less during the chronic stage (Suzuki 2002a).

Among the regulatory cytokines, IL-10, produced by Th2 lymphocytes, B cells, and macrophages, is the first one identified for its ability to inhibit the IFN-γ synthesis by Th1 lymphocytes and NK cells throughout of the inhibition of IL-12 synthesis, being an important inflammation modulator and considered a regulator of the immune response for the prevention of a pathology mediated for the immune response during the acute stage. IL-4 inhibits some functions of macrophages and potentializes the effect of IL-10 in macrophages. These effects are discussed. The presence of these cytokines can avoid the pathological alterations, acting on the prevention of the induction of an overpowered Th1 response induced for the parasite (IL-2, IFN-γ, and TNF-α), or the absence must be benefic for the survival of the host during the acute infection (Denkers and Gazzinelli 1998; Maubon et al. 2008). However, an adequate balance between pro- and anti-inflammatory is decisive to reach a necessary balance between parasite and host (Carruthers and Suzuki 2007; Maubon et al. 2008).

In the congenital infection, a high response of type 1 cytokines, pro-inflammatory, occurs, resulting in a fetal rejection and contributing to a spontaneous abortion during the acute toxoplasmosis in pregnancy. The transmission can occur with a noncontrolled replication of the parasite in fetal organs causing abortion, hydrocephaly or microcephaly, intracranial calcifications, deafness, retina damages, and mental retardation (Torrey and Yolken 2003).

Therefore, major problem is observed in patients with AIDS or receiving immunosuppressive therapy. The parasite reactivates the chronic infection causing multiple focal neurological lesions in CNS or encephalopathy. Concomitant to the depletion of CD4+ T cells, the decrease in the synthesis of IL-12 and Th0 differentiation to Th1 can be observed, causing the disease (Denkers and Gazzinelli 1998).

Parasitism

T. gondii has a heteroxenous life cycle, with cats and other felids as definitive hosts and other warm-blooded animals, such as humans, as intermediate hosts. The parasite has three infective forms: *tachyzoites*, found in bodily fluids during acute infection; *bradyzoites*, found inside tissue cysts during chronic infection; and *oocysts*, a resistant, immature form shed in the feces of felids (Tenter et al. 2000). Men and other animals become infected after ingesting oocysts in poorly washed produce, cysts in raw or undercooked meat, or after transplacental transmission of tachyzoites (Carruthers and Suzuki 2007).

Parasitism is a relationship in which the parasite benefits at the expense of the host. Efficient parasites are able to keep the host alive, because the death of the latter host means destruction of the former one. *T. gondii* is able to determine a delicate balance between parasitism and the immune response of the host. This point of equilibrium is intimately related to factors such as mode of infection, parasite strain, cytokine response, and host genes (Suzuki 2002a; Carruthers and Suzuki 2007).

In 60% of the cases, human toxoplasmosis is benign and asymptomatic (Sawadogo et al. 2005). Fifteen to 85% of the adult human population is chronically infected by *T. gondii*, depending on the geographical area, feeding habits, and contact with cats (Dubey and Beattie 1988; Flegr 2007). In the USA, 1,500,000 infections are estimated to occur annually, with 15% of them being asymptomatic.

After birth, humans get infected most of the times by the ingestion of sporulated oocysts found in the environment, or by the ingestion of tissue cysts in raw or undercooked meat of intermediate hosts. Variations in prevalence seem to be due to climatic and geographical factors, feeding habits, type of work, and cultural habits, indicating that there are several mechanisms of transmission (Dawson 2005).

Once inside the host, *T. gondii* has the ability to cross nonpermissive biological barriers. Tachyzoites cross the placental or intestinal epithelium using paracellular trans-migration and enter circulating cells such as macrophages and dendritic cells. They cross the blood-brain barrier and gain access to important sites in the brain. During

activation, rhoptries release a family of proteins essential for the invasion and protection of parasitophorous vacuoles. Approximately 10 days after infection, tachyzoites are differentiated into bradyzoites, which slowly replicate into cysts. These resistant forms are able to escape the immune system of the host as well as most therapeutic agents (Carruthers and Suzuki 2007; Maubon et al. 2008).

Brain parasitism

Tachyzoites may invade different types of nervous cells, such as neurons, astrocytes, and microglial cells in the brain, and Purkinje cells in the cerebellum. Intracerebral proliferation of *T. gondii* easily occurs in neurons and astrocytes, whereas activated microglial cells, highly phagocytic brain macrophages, efficiently restrain parasite growth and may function as important inhibitors of *T. gondii* spread in the CNS. These cells also induce the production of several cytokines that promote or suppress inflammatory responses (Lüder et al. 1999; Carruthers and Suzuki 2007). In this way, Lüder et al. (1999) found, in mice, 30% of microglial cells infected, whereas only 10% of neurons and astrocytes were invaded. Besides, parasites showed low replication rates, with only one or two degenerated parasites in 93% of the parasitophorous vacuoles.

Destruction of neural tissue caused by unrestricted replication of *T. gondii* tachyzoites is the key factor in the pathogenesis of toxoplasmosis reactivation in immunocompromised patients, an event of important consequences in toxoplasma encephalitis. Activated microglial cells have an important role in defense against infections of the CNS, inhibiting *T. gondii* replication by IFN-γ and NO nondependent mechanisms. Astrocytes, combining IFN-γ and IL-1, also inhibit *T. gondii* replication via NO production. IL-6 of macrophages reverts the inhibition caused by IFN-γ and IL-1 of astrocytes and microglial cells and may be involved in the mechanism of reactivation of the infection in AIDS patients (Luft and Remington 1986; Suzuki 2002b).

T. gondii effects in brain cells may be almost immediate. In 2 h of infection, almost half of the genes affected encode proteins associated with immune response. Thus, host cells generate a strong response in order to warn and activate the immune system against infection. Intracellular tachyzoites also manipulate several signs for transduction mechanisms involved in apoptosis, antimicrobial effector functions, and immune cell maturation (Carruthers and Suzuki 2007).

Behavioral changes

Animal behavior

Chronic infection is associated with behavioral changes, known as “host behavior manipulation” or “manipulation hypothesis”, which lead to longer survival of the parasite, in a way to complete its life cycle (Henriquez et al. 2009). For instance, infected rats are more prone to be predated by felids. Holliman (1997) and Webster et al. (2006) reported increased nonspecific movements and diminished specific movements, such as standing up and exploring new areas in mice. In unfamiliar environments, infected animals prefer more exposed areas. Therefore, altered behavior associated with toxoplasma infection is not a transient phenomenon observed during initial exposure to a new stimulus.

Although rats naturally present neophobic behavior and avoid new stimuli, animals infected with *T. gondii* are more active and show reduced neophobic behavior. They are also more trap prone, an unlikely event among wild rodents. Learning behavior is decreased when compared to that of mice (Holliman 1997; Lafferty 2006; Webster et al. 2006). Parasite manipulation also occurs among whales. Infected animals are not only less able to flee from attacks but also draw attention of sharks because of abnormal movements (Kreuder et al. 2003).

Cats are the most common predators of rats and mice and are quickly attracted to moving preys. Due to the increased activity of infected rodents, they are more easily predated by cats, and the life cycle of the parasite may be completed by transmission from the secondary to the primary host, conferring a selective advantage to *T. gondii*. Behavioral changes may occur due to the release of metabolites from parasite cysts in the brain, causing inflammation and encephalitis. Cysts may also have a direct effect on the CNS, mainly on the limbic system. Concentration of certain neurotransmitters, such as norepinephrine and dopamine, are altered, movements increased, and learning ability and attention span reduced when animals are acclimatized to the new environment (Holliman 1997).

In rats, fears of new scents, sounds, or images, such as those produced by a predator, are decreased. In both rats and mice, behavioral changes are associated with increased predation (Holliman 1997). Cat urine and body odors strongly evoke innate defensive responses in rats (Dielenberg and McGregor, 2001). In infected rats, the innate aversion of these animals for cat urine is blocked and the odor becomes an attracting factor. Infected rats also seem to have altered baseline anxiety levels (Berdoy et al. 2000; Vyas et al. 2007a).

Behavioral manipulation of the intermediate host is necessary for the parasite to complete its life cycle. Medial amygdala, basolateral amygdala, and ventral hippocampus are important areas of the brain involved with conditioned or learned fear (defense behaviors) and nonconditioned anxiety. These areas show cyst density twice as great as that of nonamygdala areas (Vyas et al. 2007a, b). Increased nonconditioned fear is associated with changes in neurotransmitters of the amygdala and in hormones involved in stress regulation (Vyas et al. 2007a).

The greatest difficulty in the manipulation of host behavior is related to the consumption of energy and metabolites. Most cases of behavioral manipulation are dependent on active secretion of chemical mediators; only the physical presence of parasite in the brain or eyes is not enough to cause behavioral changes. Besides, mortality of parasites during invasion of the host is high (Vyas et al. 2007b).

Parasite invasion and replication may be controlled by the association of chemotherapeutic drugs of synergistic effect. Much has been discussed in relation to pyrimethamin treatment. In the absence of folinic acid, the substance causes neuron demyelinization, preventing the passage of nervous impulses. Demyelinization is even more severe in the presence of immunosuppressive diseases, such as AIDS or cancer in humans, distemper in dogs, feline leukemia, and feline immunodeficiency in cats, among other infections. In these cases, treating *T. gondii* infection would be more beneficial to the parasite than to the host.

Human behavior

In humans, congenital toxoplasmosis may reduce brain function and has been estimated to be responsible for more than 9% of intellectual disability cases in some regions (Caiaffa et al. 1993). Besides, in chronic infections, men become more jealous, more introspective, easily bored, show reduced psychomotor activity and reaction times, are emotionally unstable, suspicious, have short temper, low self-esteem, and disregard social rules (Flegr and Havlícek 1999). Moreover, were more prone to guilt and showed group dependency when compared with infected women, who show greater self-esteem, are more intelligent, aware, cordial, participative, amicable, attentive to others, rigid, loyal and self-sufficient, respect social rules, are sentimental, socially precise, and affective (Flegr et al. 2000; Lafferty 2006). Both infected women and men are significantly more anxious than noninfected subjects (Flegr 2007).

Loss of psychomotor performance observed in mice was also seen in infected humans. Concentration was quickly lost (Havlícek et al. 2001; Flegr 2007). Besides, effects of cerebral damage caused by *T. gondii* were significantly associated with traffic accidents in the Czech Republic by Flegr et al. (2002). These authors reported that the risk for car accidents was 2.65 times greater in infected individuals, no matter if they were drivers or passengers. The risk increased with the duration of the infection. In Turkey, Yereli et al. (2006) observed IgG titers in 24.32% of the subjects analyzed and IgM titers in 3.24% of them, compared with 6.48% and 0.54% in the control subjects, respectively. Thus, besides being an economic problem, asymptomatic acquired toxoplasmosis represents a serious and underestimated public health problem.

Cultural influences are completely related to regional habits. The world today is divided into three major cultural groups, the Occident, the Asian, and the African continent. Feeding habits, worshiping of animals, ancient cultures, among other habits, directly interfere in the transmission of the protozoan and contribute for its prevalence and incidence (Lafferty 2006).

Recent estimates indicate that 1/50 of the North American population shows some level of immunodeficiency, a fact that greatly contributes to the susceptibility to opportunistic diseases. This population includes pregnant women, senior citizens over 65 years of age, cancer and transplant patients, and HIV carriers. These individuals are at risk of acquiring toxoplasmosis or of reactivating chronic infections, as observed by Palm et al. (2008), who detected tachyzoites in the lumbar cerebrospinal fluid of AIDS patients. Reactivation of the infection may lead to the death of these patients, once they lack specific immunity.

Schizophrenia or epilepsy

The publishing, in 1896, of a *Scientific American* editorial called “Is insanity due to a microbe?” was the starting point of discussions on the infectious etiology of schizophrenia (Torrey et al. 2007). The relationship between toxoplasmosis and schizophrenia has been known for more than 50 years. Several other agents, including viruses (influenza type A, rubella), encephalitis and meningitis-causing bacteria, and protozoans (*Plasmodium*—malaria; *Trypanosoma*—sleeping sickness; *T. gondii*) have been cited. However, details are still lacking (Torrey et al. 2007; Vyas et al. 2007a; Maubon et al. 2008).

Currently, individuals with schizophrenia show an increased prevalence of antibodies against *T. gondii* (Dickerson et al. 2007; Mortensen et al. 2007; Torrey et al. 2007; Henriquez et al. 2009). As tachyzoites induce more pronounced cytokines responses than bradyzoites, tachyzoite proliferation in the brain may lead to schizophrenia. Besides, clinical signs of schizophrenia also start to be observed together with toxoplasma chorioretinitis, which begins to appear around 20–30 years of age (Carruthers and Suzuki 2007).

The relationship between *T. gondii* and schizophrenia is based on injuries caused by the parasite on astrocytes. Astrocytes are involved in the synthesis of kynuremic acid (KYNA), a kynuramine metabolite produced after tryptophan degradation by the reaction between indoleamine 2,3-dioxigenase and tryptophan dioxigenase (TDO). When kynuremic acid reaches levels greater than the endogenous concentrations in brain, it is inhibited by nicotine acetylcholine receptors. However, KYNA is significantly increased in the brain of schizophrenic patients. Astrocyte activation in toxoplasma infection increases KYNA pro-

duction in the brain. This effect is greater in subjects that have high TDO activity in the brain, such as those who have genetic predisposition to schizophrenia. Increased KYNA levels in the brain cause or contribute for excessive inhibition of glutamine and nicotine neurotransmitter receptors, an effect that is believed to cause the cognitive impairment observed in schizophrenic patients (Schwarcz and Hunter 2007).

According to serological evidence, comanifestation schizophrenia/toxoplasmosis seems to be more common in women than in men. However, there are no significant differences in relation to age, race, or even clinical and demographical characteristics. Besides, mortality rates among schizophrenic subjects infected with *T. gondii* are five times greater (Dickerson et al. 2007) than in uninfected subjects. Patients generally show hydrocephaly, illusions and hallucinations, increased size of ventricles, and cognitive impairment, as well as other kinds of psychosis (Torrey and Yolken 2003).

Mortensen et al. (2007) observed that the risk of showing antibodies IgG against *T. gondii* is 2.61 (1.00–6.82) times greater in mothers that developed symptoms of schizophrenia and that this risk is 1.79 (1.01–3.15) times greater in babies born from schizophrenic mothers. These results are further supported by the possibility that the child may be exposed to *T. gondii* after birth, mainly when seropositive mothers have feeding habits that may lead to food poisoning, or by contact with cats.

Torrey et al. (2007) analyzed 42 studies in the MEDLINE database involving 17 countries and five decades (1953–2006) and demonstrated that the risk of presenting antibody titers against *T. gondii* is 2.73 (2.10–3.60) times greater in schizophrenic patients. Most genetic studies show lower risks, and the evidence presented by Torrey et al. (2007) suggests that *T. gondii* has a role in a wide number of cases of schizophrenia.

Nowadays, drugs used in schizophrenia treatment (valproic acid—Dekapene®, Valpakine®; haloperidol—Haldol®; with action equivalent to that of trimetropim) are successfully applied in the treatment of chronic toxoplasmosis, with excellent effects on the inhibition of *T. gondii* replication. Other discussions involve the relationship between toxoplasmosis and epilepsy. The mechanisms of action of the parasite and the origin of many brain disorders have to better understood in order to achieve improved clinical and therapeutic results (Torrey and Yolken 2003; Torrey et al. 2007; Maubon et al. 2008), once antibodies anti-*T. gondii* were found in 59% (Stommel et al. 2001) and 52% (Yazar et al. 2003) of epilepsy patients.

New studies are still necessary to elucidate the critical points in the pathogenesis and the risks both for epilepsy and schizophrenia. However, new research fields may be opened by studies involving other agents such as *Neospora caninum* and *Hammondi hammondi*, Apicomplexa, which have a very close relationship with *T. gondii* and may produce cross reactions in some diagnostic tests (Torrey and Yolken 2003).

Concluding remarks

Toxoplasmosis is an opportunistic disease both in humans and in animals. It uses its heteroxenous cycle to manipulate the behavior of the intermediate hosts and complete its life cycle. The brain is therefore the preferred tissue for the parasite and even with local immunity induced by cellular and humoral responses, mediated by pro- and anti-inflammatory cytokines, the host–parasite relationship is unbalanced in some immunologically compromised or very young patients.

Behavioral changes are also observed in humans, such as high predisposition to accidents, and are linked to other diseases that affect the CNS, such as schizophrenia and epilepsy. *T. gondii* is worldwide distributed and is able to manipulate the behavior and profile of several hosts.

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