Toxoplasma gondii: Model Manipulating by the Host Behaviour

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ABSTRACT

Toxoplasma gondii is an obligate intracellular parasite. Its life cycle includes two hosts, intermediate host (Mice, Rats, Birds, and Mammalians) and definitive host (feline family) which may be intermediate host, also. Toxoplasma infection exhibited variable consequences ranging from aborted to hard infections, in addition to modifications cytokines, change gene expression, and behaviour alterations.

Alteration of behaviour mechanism includes stimulating a special immune response, a change in the rate of concentration of many neurotransmitters, and a change in the concentration of some important hormones, in addition to many genetic modifications.

Many researches have established the association between Toxoplasma infection and various behaviour of the intermediate host. On the other hand, many studies regret the presence of such a relationship. Comparing the results of both studies, it can be said that the parasite infection has a clear role in the emergence of many behavior disorders that may sometimes reach schizophrenia, where the interaction of the parasite presence with the strength of the immune response and the effect of it on the concentration of neurotransmitters and some other hormones have confirmed their occurrence as confirmed the occurrence of pathological effect.

Keywords: Toxoplasma gondii; Parasite – host interaction; Dopamine; Behaviour disorder.
INTRODUCTION

Parasites, especially those that live in two hosts, are interested in finding the suitable method for their transmission between these hosts, the most notable of these methods is to modify the behaviour of the intermediate host, these changes constitute the color, environment, or the host way of living which makes it easy prey for predators (definitive host) (Luong et al., 2014). Changing the behaviour of the intermediate host may be intended to provide protection for the immature parasite stages (Maure et al., 2013).

There are several examples of parasite alter of the host's behaviour, for instance, Plasmodium falciparum changes the appetite of Anopheles mosquitoes to prefer feeding over nectar rather than feeding on blood to ensure that the largest amount of sugar is obtained ensuring the maturity of the parasite, while the desire to consume blood increases only when this phase has matured and tends to pass to the other host (Nyasembe et al., 2014). Horsehair worms make its host, Leucochloridium paradoxum, tend to opened and lighted places, finally, it has to drop into the water to facilitate the exit of the worm (Ponton et al., 2011).

Toxoplasma gondii can change the behaviour of an infected mouse to become more aggressive and less fearful of the cat (the definitive host) (Boillat et al., 2020), there are reports that the infection with T.gondii is responsible for schizophrenia and the craving for crime in humans (Lindová et al., 2011). Although the acute infection of the parasite is asymptomatic, the chronic stage of the infection reveals change in behaviour (Webster et al., 2013), many researches have been suggested relation between Toxoplasma and schizophrenia, in addition to, increasing of psychiatric disorders including suicide attempts when rates of exposure to Toxoplasma increase (Okusaga et al., 2011), self-directed violence (Pedersen et al., 2012), bipolar disorder (Dickerson et al., 2014), general anxiety disorders (Markovitz et al., 2015) anxiety and depressive disorder (Alvarado-Esquível et al., 2016), obsessive-compulsive disorder (Flegr and Horacek, 2017), psychotic-like symptoms (Lindgren et al., 2018), mixed and Autism (Flegr and Horacek, 2018).

The type and severity of the disorder may be related to the location of the damage in the brain, as well as the genetic readiness of the host and the parasite strain (Lindová et al., 2011). For example, type I cannot form a cyst in the tissues or cause latent infection in the laboratory but can cause abortion, inflammatory impacts, and maybe schizophrenia (Suzuki, 2012).

Mechanisms of Behaviour Manipulation

Parasites use different mechanisms to change the host behaviour in a method that serves their survival and the continuation of the life cycle, generally, there are two ways to manipulate the behaviour: direct and indirect (Maure et al., 2013), the first being by the parasite’s interference in producing special substances that change metabolism, Thus the host behaviour, the second is induced the immune system or hormonal-nervous system to reduce or increase the production of exciting substances, thus change the internal environment of the host body (Lindová et al., 2011).

Parasites always target the central nervous system, either by targeting the neurons themselves (Cabral et al., 2016) or inducing the immune system to stimulate the production of special substances that modify behaviour. In any case, methods of manipulating behaviour are by an immunological route or by modifying some neurotransmitters or by changing levels of Some of the important hormones, especially the sex hormones and testosterone (Madlaina et al., 2020).

Neuron Disruption

Neurons, in the brain, are the main target cell for T. gondii during central nervous system (CNS) infection, encysted bradyzoite-stage parasites are restricted to neurons (Cabral et al., 2016), it is known that, the infection hardness and the mass of cyst are determinant in the severity of the behaviour changes of infected mice (Madlaina et al., 2020).

Infection of T. gondii drives to the destruction of dendrites and axons structural complexity, primarily in the hippocampus and neocortex (Parlog et al., 2014). Moreover, the synaptic protein
composition and synaptophysin were altered, especially, with a down-regulation of compounds of glutamatergic signaling as a consequence of the inflammatory milieu (Lang et al., 2018). "increased release of brain-derived neurotrophic factor (BDNF) and reversal of memory impairment due to down-regulation of pro-inflammatory myeloid cell activity via the type 2 cytokine IL-4 produced by T cells" (Derecki et al., 2010), express receptors for multiple neurotransmitters such as GABA, dopamine, or glutamate by microglia cells (Kuhn et al., 2014).

Finally, neuronal cell will die via apoptosis or necrosis and to motor dysfunction and "cognitive by the action of interleukins (IL)-6 or IL-1β and tumor necrosis factor (TNF)" (Stojakovic et al., 2017).

Modification of Neurotransmitters
Neurons in the rat brain have sensory neurons that express olfactory sensory receptors that characterize the smells of predators (Hiro et al., 2016) and produce signals that travel to the amygdala or ventromedial hypothalamus (VMH) that mediate the behaviour al response (Dewan et al., 2013). Although the role of this region of the brain in the process of selection is controversial (Lindová et al., 2011), the effect of modifying the levels of some neurotransmitters in altering behaviour remains intuitive. Assumptions of modifying behaviour by changing levels of neurotransmitters assume three reasons: The first is to increase the level of neurotransmitters by the host itself, the second is the parasite’s intervention in changing these levels, and the third is because the inflammatory response is the cause of this modification (Pérez-Gómez et al., 2015).

Modification of Neurotransmitters by Host
Alsaady et al., noted that elevating dopamine levels may be to decrease the DBH expression (in noradrenergic) that gives a potential evidence for various modification notes with infection in this neurotransmitter (Johnson and Koshy, 2020). Filiano et al., showed "inhibition of neurotransmitter gamma aminobutyric acid (GABA) by Interferon-γ (IFN-γ), a crucial cytokine type 1, instance, thereby affecting neuronal connectivity and social behaviour" (Filiano et al., 2016), also IFN-γ-inducible enzymes: tryptophan dioxygenase (TDO) and indoleamine-2,3-dioxygenase (IDO) accelerated tryptophan depletion (McConkey et al., 2013), decreasing of tryptophan level generates the accumulation of some harmful metabolites, particularly kynurenic acid (KYNA), an antagonist of N-methyl-D-aspartate- (NMDA) and nicotinic receptors (Campbell et al., 2014).

Modification of Neurotransmitters by Parasite
The capacity of T. gondii to pass the biological barriers is the main reason of the parasite progress (Harker et al., 2015). In a study, Du et al. suggested that "degradation of proteasomal by parasite rhoptry protein, T. gondii bends the NF-κB pathway that causes p65 ubiquitination" (Du et al., 2014). In another study, assumed that "T. gondii changes lysine acetylation in astrocytes" (Bouchut et al., 2015). After there, bradyzoite cyst produces much of dopamine that can transmit into surrounding tissues (Prandovszky et al., 2011). Interestingly, T. gondii genome contains two tyrosine hydroxylase genes (AAH1 and AAH2) that could convert tyrosine to L-dopa (Johnson and Koshy, 2020).

Alter Concentration of Hormones
Alsaady et al., found suppressing of the noradrenergic system with decreasing of norepinephrine (NE) levels in vitro in neural cells of infected animals as rat and in infected human brain (Alsaady et al., 2019 ; Johnson and Koshy, 2020), as well, increased of neuroactive metabolites levels which may disturb glutamatergic and dopaminergic and stimulates tryptophan degradation due to cytokine-mediated activation of indoleamine-2,3-dioxygenase (IDO) (Alsaady et al., 2019) and reduce the amount of serotonin[36]. As well as, a very active of genes expression Drd1 and Drd2 to dopamine receptor in mice with high cyst burden (Lindová et al., 2011).
T. gondii elevates Testosterone concentration in patients (Madlaina et al., 2020), just male (Johnson and Koshy, 2020). Giltay et al. explained that "Testosterone able to relieve depression and anxiety, and actives Pure thinking", decreasing of this hormone levels were noted also in female with anxiety and depressive disorders (Giltay et al., 2012), "increase the expression of Testosterone receptors in the testes which regulates the synthesis of testosterone" (Lim et al., 2013).

**Immunity Reaction**

The overexpression level of interferon-gamma (IFN-\(\gamma\)), interleukin-12b (IL-12b), tumor necrosis factor (TNF) [6] and IL-12/IL-23" (Hiro et al., 2016), interleukin (IL)-6, or IL-1\(\beta\) (Habbas et al., 2015), as well as, the nitric oxide synthase locates downstream effector of IFN-\(\gamma\), therefor the higher production of (Nos2) can lead to neuronal toxicity also, through nitrosative and oxidative stress, instead of protection against the parasite (Lindová et al., 2011).

The parasite attempts to balance the slow multiplication and excessive virulence by modifying some host immune mechanisms, especially dense granule family (GRA) members (Olias et al., 2016), by the analytical action of ASP5 by the cologne system in the parasite (Curt-Varesano et al., 2016).

**Genomic Modification**

**Modification of Host Genes:**

Several phenomena of gene modification occur after Toxoplasma infection including modification of many cytokines, and increasing their concentration (Abdul-Lateef et al., 2012), dopamine receptor gene and dense granule family (GRA) inhibition were inhibition (Lindová et al., 2011), "gene expression down-regulation of dopamine -hydroxylase (DBH) (encoding enzyme that produces norepinephrine from dopamine) and observed down regulation in infected brain tissue and in vitro , with a significant difference in male" (Donley et al., 2016).

Chronic T. gondii infection Genetic control the resistance and susceptibility in the brain of both mice and humans was formed, such as, the Ld gene in mice which is located in the D region of the major histocompatibility complex (H-2). In humans, HLA-DQ3 is a genetic marker of susceptibility in congenitally infected infants and AIDS patients, whereas DQ1 is a genetic marker of resistance. Because the Ld gene in mice and the HLA-DQ genes in humans are part of the major histocompatibility complex that regulates the immune responses (Donley et al., 2016).

**Modification of Parasite Genes**

T. gondii secrets effector molecules that modulate the host gene expression (Adamo and Webster, 2013; Fond et al., 2013) or cause post-translational modification such as protein residues acetylation in glial cells and neurons (Bouchut et al., 2015). Qing Tao and his colleagues indicated the presence of 14 antigens that contributed to the parasite invasion and metabolism, and confirmed the hypothesis that say that the calmodulin (CaM) antigen is important in the pathogenesis of the parasite and destroy the host neuron cells (Qing et al., 2014). It is possible that the action of these antigens is indirect by triggering an immune response that affects dopamine concentrations (Flegr, 2007). Other studies have indicated the parasite's ability to modify genes that stimulate host cells to rest cell cycle at the M and G2 stages (Brunet et al., 2008; Molestina et al., 2008). Some studies Overexpression of ASP5 gene (protoanalytic GRA) (Lim et al., 2013), and tyrosine hydroxylase AAH1 and AAH2 that Increase L-dopamine level(Johnson and Koshy, 2020). Finally, several studies confirmed relationship between parasite and the development of infection with the strain, (Xiao et al., 2018) as it indicated the association of the strain II with a number of schizophrenia cases and a host behavioral modulation (Carruthers and Suzuki, 2018).
DISCUSSION

Although many studies have attempted to correlate infection with *T. gondii* and manipulation of behaviour after infection (Ling *et al.*, 2011; Okusaga *et al.*, 2011; Del Grande *et al.*, 2017), there is still no conclusive evidence that alters in behaviour caused by parasite infection only (Dickerson *et al.*, 2018), there are many conditions that may cause behaviour modification such as environmental conditions (Sih *et al.*, 2004), and genetic predisposition in people (Bell, 2005), in addition to the parasite strain (Torrey *et al.*, 2007).

All immune, genetic, hormonal and other variations represent a natural reaction to the parasite's entry into the host (Boillat *et al.*, 2020), the parasite has many ways to stimulate the immune system or inhibit it to survive the parasite (Okusaga *et al.*, 2011), for example, the parasite is trying to transform to the latent phase (bradyzoite) after reaching the central nervous system (Cabral *et al.*, 2016), the presence of the latent phase and the chain of the immune response towards it lead to necrosis or death of neurons, the reason for their occurrence may be due to the influence of these cells by the substances produced by the parasite, as well as, by the lack of food and oxygen resulting from disturbances in the blood vessels, or perhaps necrosis. The result in the cells and brain tissue that they are affected by the case-specific enzymes of the protein present in the white blood cells, especially the rates that increase their infiltration as a response to inflammatory reactions in the cerebellum, as well as some immune reactions, and if they are protective, they may cause necrosis or cells death by macrophages and mononucleosis (Fischer *et al.*, 1997).

Many alterations occur at the level of neurotransmitters after the chronic infection of the parasite, as many studies have indicated a high concentration of dopamine after infection (AL-Hadad *et al.*, 2019), the reason may be attributed to defects in the metabolism of catecholamine (Martynowicz *et al.*, 2019), or due to the parasite has two important enzymes, phenylalanine hydroxylase and tyrosine hydroxylase, which together act to increase the level of dopamine by stimulating the metabolism of phenylalanine and tyrosine (Prandovszky *et al.*, 2011).

*T. gondii* can synthesize the sphingolipids (Azzouz *et al.*, 2002), but they obtain phospholipids and fatty acids from the host or by salvage (Charron and Sibley, 2002), this may explain the downregulate that occurs in the metabolism of many compounds made from fats, such as arachidonic acid, steroids, and glycerophospholipid, which directly enter the functions of the neuron (Ma *et al.*, 2019), in addition to many other functions such as Antioxidants, apoptosis, and others (Farooqui *et al.*, 2000). Also, the products of the steroid hormone metabolites are identified as gamma-aminobutyric acid (GABA) receptor. Besides, GABA depends on arachidonic acid in its formation (Ma *et al.*, 2019).

The level rise of some sex hormones in the event of infection with the parasite may not be caused by the host only, but the parasite may get involved in this (Abdul-Lateef *et al.*, 2012), the increase in the progesterone hormone, for example, causes inhibition of NK cells, macrophage and T cells, and reduces the production of NO (McKay and Cidlowski, 1999), which survive the parasite (Lori *et al.*, 2002), and vice versa, weak immunity stimulates the increase of the hormone (Flegr, 2013), two hypotheses explain the increase testosterone hormone: the first assumes that the increase is a defensive process performed by the host when suppressing immunity, the second assumes that the parasite contributes to increasing the concentration of the hormone to resist the immune force and survive (Roberts *et al.*, 2001).

CONCLUSION

From all we see that, Toxoplasma, like other parasites, has the ways to survive and ensure transmission between hosts, thus, alter the host behaviour to serve the parasite. These changes include stimulating a moderate immune response, an altering in the level of neurotransmitters and some primary hormones, in addition to, modifying the gene expression of the host. The relationship between infection with the parasite and the feeling of hysterical outbursts of anger, abandonment of over-impulsion fear, in addition to neurological disorders such as bipolar disorder and the urge to
commit suicide. All these effects and their association with the infection confirm the parasite's association with host behavior disorders.

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المقوسة الغوندية نموذج التلاعب بسلوك المضيف

الملخص

المقوسة الغوندية طفيلي داخلي اجباري التطفل، تتضمن دورة حياته اثنين من المضيفين مضيف وسطى يشمل الفئران والجرذان والطيور والثديات ومضيف نهائي (عائلة السنوريات) وتشمل هذه الدورة اثنين من المضيفين. تنتشر المقوسة الغوندية في جميع أنحاء العالم وتشمل السلوك البيولوجي المناعي والجيني والكيميائي.

تتشكل النتائج من تكاثر أثر المقوسة الغوندية في تجاوز السلوك المضيف الانتهازي، حيث تؤدي المقوسة الغوندية إلى تغيرات في السلوك المضيف، حيث تتأثر النواقل العصبية والهرمونات وتتغير اهتمامات المضيف.

تتضمن آلية تغيير السلوك تفعيل استجابة مناعية خاصة ويعتمد على التأثير في تراكيز النواقل العصبية وتراكيز الهرمونات المهمة بالإضافة إلى تعديل العديد من الجينات.

على الرغم من أن الكثير من الدراسات أكدت أثر الاصابة بالمقوسة الغوندية في تجاوز سلوك المضيف المتوسطة، إلا أن هناك دراسات أخرى لا ترى ربطًا بين الاصابة بالطفيلي وتعويض السلوك المهمة، ومن منعك أن تحدث الآلات في ظل تعويض السلوك المهمة، حيث إن تداخل وجود الطفيلي مع قوة الاستجابة المناعية وتأثيره في تراكيز النواقل العصبية وتأثيره في التأثير في التفاعلات السلوكية قد أدى حدوثها كما أكد حدوث الأثر المناعي والتغذية النسيجية بسبب الطفيلي.

الكلمات الدالة: المقوسة الغوندية، تفاعلات الطفيلي- المضيف، اضطراب السلوك، دوامين.